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**BIOCHEMICAL ASSESSMENT OF THE PATHOPHYSIOLOGY
OF LIVER CANCER**

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BIOCHEMICAL ASSESSMENT OF THE PATHOPHYSIOLOGY OF LIVER CANCER

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June 2022

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ABSTRACT

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Master of Science in Chemistry

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Patients afflicted with HCC and cirrhosis of the liver show substantial changes in cell structure and metabolic problems. As a consequence of this study in 2021-2022, researchers were able to examine how these people' lipid metabolisms, micronutrients and chemical tests varied from one other and how this changed from their liver ailment. Agreement has been reached on a trial in Karbala with 55 healthy individuals, 14 patients with liver cancer and 53 with liver cirrhosis as well as 16 patients infected with viral hepatitis. A control group of 55 patients was also included. With viral cirrhosis and liver cancer, the metabolic nutritional profiles of patients have been changed, with major anomalies in triglyceride levels, cholesterol levels, protein levels, and iron levels in particular (ferritin). An additional metric is the hematocrit level, which is determined. Researchers think that patients with cirrhosis, regardless of whether they had hepatocellular carcinoma (HCC), had greater levels of the lipid biochemical markers C, L, and D than those without cirrhosis. Lipid metabolism is affected by the presence of viral hepatitis in this group. Other studies have shown a substantial connection between many pathologies of the liver, such as cirrhosis, hepatocellular carcinoma, malnutrition, and the hepatitis C virus.

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Keywords: Cancer, Liver, Alpha-fetoprotein, Matrix metalloproteinases, Tumor marker

ÖZET

KARACİĞER KANSERİNİN PATOFİZYOLOJİSİNİN BİYOKİMYASAL DEĞERLENDİRMESİ

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HCC ve karaciğer sirozundan mustarip hastalar, hücre yapısında ve metabolik problemlerde önemli değişiklikler gösterirler. 2021-2022'deki bu çalışmanın bir sonucu olarak, araştırmacılar bu insanların lipid metabolizmalarının, mikro besinlerin ve kimyasal testlerinin birbirinden nasıl değiştiğini ve bunun karaciğer rahatsızlıklarından nasıl değiştiğini inceleyebildiler. Kerbela'da 55 sağlıklı, 14 karaciğer kanserli, 53 sirozlu ve viral hepatitli 16 hasta üzerinde yapılan bir denemede anlaşılmaya varıldı. Ayrıca 55 kişilik bir kontrol grubu da dahil edildi. Viral siroz ve karaciğer kanseri ile hastaların metabolik beslenme profilleri değişmiştir, trigliserit seviyelerinde, kolesterol seviyelerinde, protein seviyelerinde ve özellikle demir seviyelerinde (ferritin) büyük anormallikler olmuştur. Ek bir ölçüm, belirlenen hematokrit seviyesidir. Araştırmacılar, hepatoselüler karsinom (HCC) olup olmadığına bakılmaksızın sirozlu hastaların sirozu olmayanlara göre C, L ve D lipid biyokimyasal belirteçlerinin daha yüksek seviyelerine sahip olduğunu düşünüyorlar. Bu grupta viral hepatitlerin varlığından lipid metabolizması etkilenir. Diğer çalışmalar, siroz, hepatoselüler karsinom, yetersiz beslenme ve hepatit C virüsü gibi karaciğerin birçok patolojisi arasında önemli bir bağlantı olduğunu göstermiştir.

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Anahtar Kelimeler: Kanser, Karaciğer, Alfa-fetoprotein, Matriks metalloproteinazlar, Tümör belirteci

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LIST OF SYMBOLS

%	Percent
±	Plus minus
°C	Degrees Celcium
µg	Migrogram
µL	Microliter
g	Gram
h	Hour
kg	Kilogram
mg	Miligram
mL	Mililitter



LIST OF ABBREVIATIONS

ADA	American Diabetes Association
AFP	Alpha-fetoprotein
BCLC	American Association for the Study of Liver Disease
BMI	Body mass index
CT	Computed tomography
ECL	Electrochemiluminescence
ECM	Extracellular matrix
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C Virus
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
MMP	Matrix metalloproteinases
MMPs	Matrix metalloproteinases
MOS	Median overall survival
MR	Magnetic resonance
NASH	Non-alcoholic hepatic steatosis
pRb	Tumor suppressor gene
TPA	Tripropylamine
US	Ultrasonography
VLDL	Very low-density lipoprotein
WHO	World health organization

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1. INTRODUCTION

Excessive carcinogen exposure that causes pathobiological damage in target cells and/or higher oncogenic susceptibility is the primary objective of biochemical and molecular epidemiology (Arias-Flórez *et al.* 2018). This expanding and multifaceted field of cancer research is advancing our understanding of cancer through the use of epidemiology and laboratory procedures, among other approaches. DNA damage may be utilized as an internal molecular dosimeter to monitor carcinogen exposure in the body since DNA is known to be a significant target for mutations and carcinogens. Carcinogen exposure may be detected in the body using DNA damage as an internal molecular dosimeter. Depending on how these carcinogens react with DNA, they may either connect directly to it and create adducts or they can cause more DNA damage indirectly, such as by the creation of ROS and aldehydes in the body's cellular membranes. DNA damage and DNA repair products in biological samples collected from persons who have been exposed to carcinogens may now be analyzed using extremely sensitive and precise techniques developed by scientists. These methods have been shown to be highly accurate. Individuals who have been treated to carcinogenic polycyclic aromatic hydrocarbons at their work location, for example, have been found to have DNA adducts in their cells and tissues, according to research. Aside from that, there have been reports of antibodies recognizing carcinogenic-DNA adducts being discovered in human serum. Recent discoveries in molecular genetics, such as the discovery of restriction fragment length polymorphism, have revealed that some people are predisposed to cancer due to an inherent susceptibility to it. As an instance, researchers are presently investigating whether previously observed higher lung cancer risk is due to uncommon alleles of the proto-oncogene Ha-ras. These approaches have the potential to improve the ability of biochemical and molecular epidemiology to predict disease risk for individuals rather than populations and to do so prior to the beginning of clinically manifest disease (Parizadeh *et al.* 2019).

1.1 Statement of Problem

Primary liver cancer, or hepatocellular carcinoma, is a cancer that begins in the liver. Liver tumors may arise from both primary and secondary causes (cancers that originate elsewhere in the body) (i.e. cancer that has spread to the liver from elsewhere, known as liver metastasis). Furthermore, the accumulating mutations caused by these signals have the potential to cause significant health problems (Sayiner *et al.* 2019). DNA mutations are important in the development of many cancers and can be induced by both hereditary and environmental causes. While genetics was among the most well-established causes of cancer, there are many additional elements involved. Hepatocellular carcinoma is generated by DNA damage that results in particular mutations (Cowppli-Bony *et al.* 2019).

In the elderly, hepatocellular carcinoma is the most common form of liver cancer and the most common cause of death. Heavy alcohol use and chronic hepatitis B and C viruses cause HCC. Infecting more than 500,000 individuals globally, it defies conventional chemotherapy and radiation treatment and kills its victims without mercy. In order to better understand how HCC operates and develop new methods for early detection and treatment, these research may be invaluable. There are numerous mutant genes in HCC, however their incidence is lower than well-known genes like TP53, CTNNB1, AXIN1, and CDKN2A. Only CTNNB1 mutations seem to induce malfunction in the majority of cases. Because of this, HCC mutations are difficult to treat. In the search for new therapy targets, regular epigenetic abnormalities might be considered. Common epigenetic disorders include global DNA hypomethylation, promoter methylation, aberrant non-coding RNA production, and dysregulated epigenetic regulatory genes like EZH2. Future research may help identify new HCC biomarkers and therapy targets (Puustinen *et al.* 2019).

1.2 The Importance of the Thesis

AFP tumor marker testing is a blood test that measures the levels of alpha-fetoprotein (AFP) in the bloodstream of healthy adult volunteers who have not been diagnosed with

cancer. There are a number of molecule tumor markers that are produced in the body, either as a result of cancer or as a result of cancerous cells. They are used to detect cancer in patients who have been diagnosed with it. The existence of liver cancer may be indicated by elevated levels of AFP (Li *et al.* 2019). Matrix metalloproteinases (MMPs) are a type of proteinase that degrades components of the extracellular matrix as well as a wide spectrum of non-matrix proteins. MMPs are found in a variety of tissues and organs. Tissue inhibitors of molecular motor proteins (MMPs) and Molecular Motor Proteins (MMPs) have been implicated in the pathogenesis of hepatic diseases. Therapeutic drugs might be developed by targeting the extracellular matrix (ECM) remodeling activities of MMPs, according to research (Gogna and Goyal 2018). There have been a number of studies that have related MMPs, as well as MMP tissue inhibitors, to the etiology of liver illnesses and other diseases (Benson *et al.* 2017).

Comprises several different conditions, such as the growing incidences of NASH and cirrhosis of the liver, as well as the basic steatosis that is often associated with it. When HCC is histologically verified, it means the cancer has been found in the liver cells itself. In order to reduce the amount of liver biopsies conducted on a regular basis, it is required to develop non-invasive diagnostic and screening methods. Among the most suitable techniques are those that can identify progressive fibrosis from steatosis and quantify the amount of steatosis present (Covey 2018). An excessive amount of dental plaque, severe gingival inflammation, and periodontal disease are all factors that will be explored in this study in order to determine their function in the development of early atherosclerosis lesions in women. In order to examine the carotid arteries in the neck, an ultrasound was performed. Periodontal disease has been reported to be the most significant independent predictor of the development of atherosclerotic disease in women, and it is also the most common (Qiu *et al.* 2020). They may be important in tumor growth in tissues where active neutrophils have penetrated due to the vast range of morphological and functional diversity they display. The majority of study has focused on understanding the physical variability of neutrophils; however, an increasing body of evidence indicates that neutrophils also exhibit functional variation, much of which is likely governed by the granule content of their granules (Kuo *et al.* 2015).

2. LITERATURE REVIEW

2.1 Introduction

In its simplest form, cancer is a problem with tissue growth control. There must be changes in the genes that regulate cell growth and differentiation in order for a normal cell to become a cancerous cell. Genetic mutations may range from the acquisition or loss of whole chromosomes to a single DNA nucleotide in one gene, depending on the specific mutation. These design alterations affect two primary categories of genes: transcriptional regulators and transcriptional repressors, both of which are involved in transcriptional regulation. The presence of oncogenes does not rule out the possibility that they are normal genes that have been overexpressed at an unacceptably high level, or that they are mutant genes with unique characteristics. This gene expression is associated with both the formation of cancer cells with a malignant nature and the growth of cancer cells without malignant characteristics. Genes known as tumor suppressors inhibit the growth, survival, and/or reproduction of cancer cells, among other properties. Tumor suppressor genes are commonly silenced as a result of genetic changes that contribute to the development of tumors. The majority of the time, mutations in numerous genes are required for a normal cell to progress to the stage of malignancy (Covey 2018).

In order to classify the numerous genetic modifications that can lead to the development of malignant cells, a complex classification scheme has been developed. Mutations and alterations in the nucleotide sequence of genomic DNA account for the overwhelming bulk of these modifications. Having an abnormally large number of chromosomes, or aneuploidy, is a kind mutation that is not a true change in the genetic code. Mistakes in mitosis may result in the loss or acquisition of one or more chromosomes, which can cause it (Benson *et al.* 2017). Deletion or gain of a whole chromosome is required for large-scale alterations. A small chromosomal region, which generally contains one or more oncogenes and adjacent genetic material, may amass many copies in a cell's lifetime (often 20 or more). It is known as translocation when two separate chromosomal regions fuse together improperly, most typically at a specific position on

the chromosome. Philadelphia chromosome, which is a translocation of chromosomes 9 and 22 that occurs in chronic myeloid leukemia and results in the BCR-abl fusion protein, an oncogenic tyrosine kinase, is an example of this (Kuo *et al.* 2015). There are several instances of small-scale alterations, including as point mutations, deletions, and inserts. Genes' promoters and coding sequences may include mutations that affect gene expression, whereas mutations in genes' promoters and coding sequences affect the function and stability of the protein products generated by those genes. It's possible that the integration of genomic material from a DNA virus or retrovirus disrupts one gene in a cell. Viral oncogenes may be produced in both the afflicted cell and its descendants as a consequence of this (Qiu *et al.* 2020).

2.2 Cancer Pathophysiology

The uncontrolled proliferation of cancer cells is the fundamental aberration that leads to the development of all types of cancer. Cancer cells multiply and divide out of control, infiltrating and spreading throughout normal organs and tissues before eventually spreading across the entire body. The accumulation of anomalies in various regulatory systems ultimately results in the loss of growth control, which results in the variations in cellular activity that distinguish cancer cells from normal cells (Kuo *et al.* 2015). According to current understanding, the development of cancer has always been regarded as a multi-step process that involves the mutation and selection of cells whose ability to multiply, survive, infiltrate, and spread gradually rises over time. It is believed that a genetic alteration that causes abnormal cell proliferation and the creation of a tumor cell population with a clonal origin, as described above, is responsible for the first phase in this process, which is known as tumor initiation. Another feature of tumor formation is the accumulation of mutations over time, which results in the so-called property of clonal selection, which is present throughout the duration of tumor development (Labadie *et al.* 2019). Cancer's pathogenesis is exceedingly complex, and it is difficult to understand. Pathologists are medical experts who are primarily concerned with the investigation of illness in all of its manifestations, regardless of the source of the sickness. In addition to the etiology and diagnosis of a disease, the pathophysiology of a disease, its mode of action, and its natural course, this includes the

natural history of the disease. The biochemical characteristics, course, and prognosis or outcome of the disease are all addressed by these professionals, as well as the treatment options available. The development of diagnostic techniques such as immunohistochemistry, flow cytometry, and molecular biology approaches to cancer has caused a significant change in the pathophysiology of malignancies and other challenging disorders (Adam and Kitano 2019).

2.2.1 Epigenetics

A branch of genetics known as epigenetics is the study of the control of gene expression by biochemical alterations in DNA structure that do not result from mutations. Non-mutational DNA modifications may lead to changes in gene expression, which is regarded to be the initial step in the progression of cancer. In most cases, oncogenes do not make any noise at all, for example, as a result of DNA methylation. In the absence of this methylation, oncogenes are produced in an aberrant manner, which can eventually result in the development of cancer. DNA methylation, acetylation of histone proteins that are linked to chromosomal DNA, and other epigenetic processes have been uncovered, among other things. HDAC inhibitors and DNA methyltransferase inhibitors, two classes of medicines with the potential to alter cancer cells' epigenetic signaling, may be used to this end (Chow and Chok 2019).

2.2.2 Oncogenes

There are numerous methods in which cancerous genes encourage the proliferation of cells. Many cells have the ability to create hormones, which operate as a "chemical messenger" between cells, promoting the process of mitosis. This is because the function of these hormonal is dependent on cell signaling from the receptor tissue or cells, which can be present in a variety of tissues and cells throughout the body. When a hormone receptor signaling event occurs in an infected cell, a signal is carried from the cell surface to the nucleus, where it has the ability to modify gene transcription at the nuclear level, resulting in a variety of consequences. For example, some oncogenes are components of or receptors for signal transduction systems, and hence influence the

body's response to hormone signals. Oncogenes often create mitogens or are engaged in DNA transcription during protein synthesis, which leads in the development of proteins and enzymes necessary for the generation of the products and biochemicals that cells utilize and interact with on a daily basis. DNA transcription, which is part of the process of protein synthesis, also involves oncogenes (Saraswat *et al.* 2014). proto-oncogene mutated genes may lead to increased protein synthesis or increased protein activity as a consequence of the aberrant expression and functioning of the proto-oncogenes in issue. It is at this point that the proto-oncogenes undergo a transformation into oncogenes, and the disturbance of the cell's normal balance of cell cycle regulation makes it possible for the cell to expand uncontrollably. Because they are essential for the body's growth, repair, & homeostasis to function properly, deleting proto-oncogenes from its genome would be ineffective in lowering cancer risk, even if it were technically possible. The growth signals become excessive when they are altered (Chan *et al.* 2019). It was one among the first oncogenes to be found and one of the most intensively studied in the field of cancer research. It is estimated that 20% to 30% of all human malignancies are caused by mutations in the Ras gene family, which includes H-Ras, N-Ras, and K-Ras. Researchers were astounded to discover that not only is the Raf gene present in the human genome, but it can also cause cancer in cell line cultures when it is ligated to an exciting control element. Raf was first discovered in the chromosome of the human cancer virus Harvey's sarcoma virus by scientists. In the development of cancer, Raf is a transcription factor that has been linked (Li *et al.* 2019).

2.2.3 Genetic changes

Genes influence the growth, maturation, and death of normal cells. The genome may be altered at a variety of levels. A single nucleotide of DNA, as well as whole chromosomes, may be acquired or lost. These alterations primarily affect two types of genes: transcription factors and transcriptional regulators. Oncogenes are carcinogenic genes. It's possible that they are normal genes that are overexpressed in cancer patients, or that they are normal genes that have been mutated. Both genes are connected to malignant tissue growth. Normal tumor suppressor genes halt cell division and kill damaged cells. Tumor suppressor genes are typically suppressed in cancer patients.

Genetic mutations are to blame for this. For a normal cell to become cancerous, mutations in a large number of genes are often required. Genome amplification Amplification of the genome is possible. Oncogenes and other genetic material are copied several times (often 20 or more) by a cell to become malignant (Bos 1989).

2.2.4 Point mutations

Point mutations are those that arise on a single nucleotide basis. The gene's promoter region, in particular, may have deletions and insertions due to a variety of reasons. In this case, the protein that is encoded by the gene in question is altered. When a retrovirus or a DNA virus is integrated into the genome, it is possible to damage a single gene, which may lead to oncogenes being created (Chang *et al.* 1982, Knudson 1971).

2.2.5 Translocation

When two distinct chromosomal regions fuse together improperly, which is generally at a specific position, translocation is still another mechanism that occurs. Chronic myeloid leukemia has been recognized to be caused by the translocation of two chromosomes (the Philadelphia chromosome and chromosome 22) which results in the BCR-abl fusion protein, which is an oncoprotein (Chang *et al.* 1982).

2.2.6 Tumors (tumor suppressor genes)

Cancer suppressor genes provide anti-proliferation signals and proteins that prevent cells from proliferating uncontrollably and causing tumors to spread. The most common kind of tumor suppressor in the human body seems to be transcriptional factors, which are triggered by cellular stress or DNA damage. As a consequence, DNA damage is commonly accompanied by symptoms such as floating genetic material. Enzymes and signaling pathways activated by DNA damage also activate cancer suppressor genes, which must be switched off during cell division in order to carry out DNA repair. If they do so, they will be able to prevent the spread of mutations to their offspring. It is

one among the most extensively studied tumor suppressor genes, triggered by a variety of cellular stresses, including hypoxia and UV radiation (Nikitaki *et al.* 2015).

It is yet unclear what role the protein plays as a tumor suppressor, despite the fact that mutation in the p53 gene are thought to be implicated in nearly half of all cancers, according to current estimates. p53 appears to have two separate activities in the cell: one is as a transcription factor in the nucleus, and the other is as a cytoplasm regulator of the cell cycle, cell division, and apoptosis in the cytoplasm, according to the current understanding of its function (Kantidze *et al.* 2016). According to Warburg's theory, cancer cells prefer to use glycolysis as an energy source, which serves as the foundation for his study. P53 is thought to be involved in the regulation of the transition from the respiratory to the glycolytic pathways, according to the latest studies (Matoba *et al.* 2006). The oncogene itself or the signal channel that activates it may be damaged by another kind of mutation, thus "turning it off." As a result, DNA repair is inevitably slowed or inhibited: When DNA damage is not repaired, it builds up and finally results in cancer (Knudson 1971).

In germ cells, cancer-causing mutations in tumor suppressor genes are passed on to future generations, increasing the risk of cancer diagnoses. These families have a greater prevalence of numerous malignancies and shorter latency periods than the rest of the general population. Each kind of tumor suppressor gene mutation is connected with a typical tumor form, with some mutations causing particular malignancies and others causing cancers of a different nature. type. Because of the manner that tumor suppressor mutations are handed down through families, it is possible for a member of the family to inherit both a defective and a normal copy of the tumor suppressor (Ferla *et al.* 2007). Li-Fraumeni syndrome is one example of a genetic condition that may cause melanomas and pancreatic cancer in people who inherit a defective p53 allele (so they are heterozygous for the mutated p53). Gene mutations in the APC gene, which have been connected to adenopolyposis colon cancer and adenocarcinoma, are also associated with retinoblastoma, in addition to Rb gene mutations. If untreated, adenopolyposis colon cancer may progress to colon cancer at a very early age in adolescents with hundreds of polyps in the colon. Finally, BRCA1 and BRCA2 gene

mutations have been linked to early-onset breast cancer development (Fodde and Smits 2002).

There were at least two separate mutational mechanisms involved in the formation of cancer, according to a theory proposed in 1971. According to Knudson's two-shot theory, only if and when a second mutation event occurs later in life will a genetic mutation in a tumor suppressor gene cause cancer. It is made inactive in the organism if the other allele of this tumor suppressor gene is inherited (Chow and Chok 2019). The presence of loss-of-function mutations in mutant oncogenes makes them dominant; on the other hand, the presence of gain-of-function mutations makes mutant tumor suppressors recessive. Oncogene function may be gained by mutations in just one copy of a proto-oncogene, but mutations in both copies of a given proto-oncogene are not sufficient to turn that gene into an onco-enabled oncogene in most circumstances (Knudson 1971). First, both copies of a tumor suppressor gene must have a loss of function mutation in order for that gene to become non-functional when it comes to loss-of-functional mutations. In theory, one mutant copy of the same tumor suppressor gene may make the other wild-type gene useless, however this has not been shown in any experiments. The dominant-negative impact has been seen in a large number of p53 mutations, and it is recognized as such (Hanahan and Weinberg 2000). According to Knudson's two-hit theory, a number of researchers have questioned its validity. However, certain tumor suppressor genes may cause cancer even while just one allele of a tumor suppressor gene is silenced. This condition is referring to as haploinsufficiency, and it has been proven through a variety of different experimental methods over the course of several decades. When compared to tumors induced by a two-hit mechanism, cancers caused by haploinsufficiency often manifest themselves at a later stage in the disease's progression (Bray et al. 2018, Knudson 1971).

2.2.7 Solid tumor parts

Solid tumors can be categorized into two types: malignant and nonmalignant, both the parenchyma and stroma play a role in cancer development. The parenchyma contains the tissues as well as the malignant cells, while the stroma is caused by the neoplastic

cells and is found throughout the body (Cholongitas *et al.* 2017). It is possible to discern a basal lamina on the surface of epithelial malignancies, which serves to separate tumor cell clusters from the surrounding stroma. The basal lamina, on the other hand, is frequently absent or only partially present, particularly at the sites of tumor invasion and invasion of the surrounding tissue. In part due to its location between tumor tissue and normal host tissues, the stroma plays an important role in the progression and proliferation of tumors. Noncancerous supporting components such as connective tissue, blood vessels, and inflammatory cells make up the stroma, which is present in substantial proportions and serves as a protective layer around the tumor. A stromal support is required for the progression of all solid tumors unless they grow to be larger than 2mm (Bhamidimarri *et al.* 2015). Furthermore, as part of their growth, malignant tumors have the ability to produce new blood vessels. It is composed of several different components, including blood vessels, that make up a tumor stroma. As has been said, interstitial connective tissue makes up the great majority of the tumor stroma, with blood vessels accounting for only a small proportion of the total tumor mass in many instances. The stroma comprises blood tissues and cells, as well as water and plasma proteins, and it also contains a range of inflammatory cells of varied types and numbers, which are distributed throughout the body. It's also worth noting that additional compounds, such as fibrinogen, fibronectin and various fibrinopeptides as well as fibroblasts are included in this list of molecules (Mantovani and Targher 2017).

2.3 Biology of Cancer Cells

When the various genetic abnormalities that contribute to cancer build over a lengthy period of time, this is known as carcinogenesis. The biological activity of pre-malignant cells gradually switches from that of normal cells to that of cancerous cells throughout this time period, as previously mentioned above. Precancerous tissue may have a distinct look when examined under a microscope. Increased cell division, variances in nucleus size and form, variations within cells' size and shape, loss of specific cellular features, and a reduction in tissue architecture are some of its distinguishing characteristics. A kind of excessive cell proliferation in premalignant cells that is distinguished by the loss of normal tissue organization in addition to the breakdown of

normal cell structure. A reversible increase in cell division brought on by an external trigger such as a hormone imbalance or prolonged inflammation should be separated from these early neoplastic alterations as cancer (Arzumanyan *et al.* 2013). Carcinoma in situ is the medical term for cases of extreme dysplasia. An uncontrolled growth of cells that hasn't gone beyond the site of origin or shown evidence of invasion into nearby tissues is known as a carcinoma in situ when the phrase "in situ" is translated from Latin to "in place". The cancer in situ may progress to invasive malignancy hence it is normally treated surgically if feasible (Sacco and Cohen 2015).

2.3.1 Clonal evolution

When the process of malignancy is viewed from an evolutionary perspective, it becomes easier to comprehend it. In the course of millions of years of biological development, cancer has only developed in a very small number of cases, which means that the metabolic changes in the cells that lead to cancer are incredibly rare. The vast majority of changes in cell metabolism that cause cells to expand uncontrolled result in the death of the cells involved in the transformation. It has been likened to biological evolution in that a few cells that have recently experienced genetic changes that improve their survival continue to multiply and gradually take over the majority of the tumor cells as cells with less favorable genetic alterations are superseded by cells with more favorable genetic changes. In scientific literature, this process is known as clonal evolution. Tumors, on the other hand, normally continue to grow in response to chemotherapy treatments, and in rare instances, aberrant cells may acquire resistance to certain anti-cancer medicines (Ralphs and Khan 2013, Khan *et al.* 2012).

2.3.2 Biological properties of cancer cells

According to Hanahan and Weinberg's article released in 2000, the following biological properties of malignant tumor cells are present: Uncontrolled growth happens as a result of the development of self-sufficiency in the production of growth signals (Catalyst *et al.* 2020). Uncontrolled growth is produced by a decrease in the sensitivity to anti-growth signals, which occurs as a result of aging. Inability to undergo apoptosis in

designed to facilitate for growth in the face of genetic errors and extrinsic anti-growth signals. Due to a lack of aging capacity, a population that is infinitely reproduced has arisen (immortality) Developing the ability to develop sustained angiogenesis, which allows the tumor to grow beyond the limits of passive nutrition transport. As an invasive carcinoma evolves, it gains the ability to infiltrate adjacent tissues, which is a trait that distinguishes it from other types of cancer. It is a classic property of cancerous tumors (carcinomas or others) that they have acquired the ability to spread to distant sites (Hanahan and Weinberg 2000).

2.3.3 Achieving these multiple milestones would be a very rare event without

Genetic errors are no longer repaired, resulting in an increase in the rate of mutation (genomics instability), which increases the advancement of all other modifications. These metabolic changes are typical in carcinomas; however, it is possible that other malignancies do not necessitate all of them in order to be effective. Even while leukocytes may invade tissues and spread to distant regions, these actions aren't necessary for leukemia to develop. Leukemia can grow without these activities. A mutation may or may not be present at any particular stage of development. Genomic instability, apoptosis avoidance, and enhanced angiogenesis all occur when a single gene encoding the P53 protein is silenced (Kew 2013).

2.3.4 Etiology

Hepatocellular carcinoma is a kind of cancer that may develop as a consequence of chronic liver illness, which can be brought on by a variety of risk factors. The advancement of hepatocellular carcinoma has been closely linked to infections with the hepatic damage B and C virus (HBV and HCV). There are several risk factors for liver cancer, including chronic hepatitis C (HCV) co-infection, alcohol intake and smoking, and the existence of chronic cirrhosis (HCV) co-infection (Gogna and Goyal 2018). Chronic hepatitis of any origin (e.g. hemochromatosis or alpha-1 antitrypsin deficiency) or cryptogenic cirrhosis, a kind of liver disease, are linked to an increased risk of HCC. Aflatoxin, blue-green algal toxin-tainted water, and betel nut intake have all been

associated to hepatocellular carcinoma, according to research. Consumption of ethanol and the metabolic syndrome have both been associated to an increased risk of liver cancer, with steatosis and other forms of liver damage ultimately leading to the development of liver cancer and other types of liver disease. The combination of statins and coffee has been shown to reduce the risk of developing hepatocellular carcinoma. Preventing the development of liver cancer by taking care of chronic hepatitis as well as controlling the metabolic syndrome, eliminating iron from the body, and abstaining from excessive alcohol use may all help. It is feasible to decrease the occurrence of hepatocellular carcinoma around the world with the use of the HBV vaccine and HCV screening procedures. Standards for HCC surveillance is advised for high-risk groups, and they varied from society to society/institution to institution. Every six to twelve months, regardless of whether or not alpha-fetoprotein (AFP) is present, they prescribe an ultrasound (US) (Tsochatzis *et al.* 2014).

2.3.5 Epidemiology

According to the World Malignancy Research Fund, HCC is the world's fifth-most frequent cancer and the second-leading cause of cancer mortality. Histologically proven chronic hepatitis virus B and C are the most prevalent causes of hepatocellular carcinoma, accounting for the large majority of cases. There has been an increase in the annual incidence rate of 3.1 percent in the United States, which is more than the previous year's increase of 2.2 percent. Compared to women, males have an incidence rate of 11.5 per 100,000 people, while women have an incidence rate of 3.9 per 100,000 people. Death rates from hepatocellular carcinoma increased by 2.8 percent in males and by 3.4 percent in women per year, according to the National Cancer Institute. Hepatocellular carcinoma that has been established by histology is most commonly observed in the older people after a lengthy history of chronic liver disease has been present. It is depending on the risk factor that produced the cancer that regional and racial/ethnic differences in hepatocellular carcinoma incidence are observed. It is estimated that HBV is more prevalent in the United States compared to HCV, with HCV accounting for 30% of all cases in the country. This is a five-fold rise in the

incidence of HCV among persons born between 1945 and 1965, which has resulted in a fivefold increase in liver cancer deaths (Jeong *et al.* 2012).

2.3.6 Pathophysiology

Hepatocellular carcinoma-related genes have been found by genome-wide observational research, which has led to the discovery of a significant number of previously unknown genes that are involved in the onset of these genetic processes. A key factor in the development of liver cancer tumors may be genomic instability, such as chromosomal or single nucleotide polymorphisms. Somatic recurrent mutations in cancer genes (e.g., TP53, CTNNB1, ARID1A, FGF) and signal transduction pathways (JAK/STAT, WntB/catenin, PI3K-AKT-mTOR) were shown to be important drivers of the disease's development as a consequence of these investigations. The genetic diversity of hepatocellular carcinoma means that no possible lead or targeted treatment has been found. Expression of the Ki-67 protein and mutation of the TP53 gene are classical number of factors have contributed of hepatocellular carcinoma that have been shown to be related with a poor prognosis on several occasions (Takeda *et al.* 2017). It is critical to distinguish between the fibrolamellar variation and tumor encapsulation, which reveals itself in younger persons and is the most serious pathological worry in this case. These tumors are more likely to be surgically resectable than conventional hepatocellular carcinoma, which mainly affects the elderly and chronically ill and has fewer than a quarter of resectable tumors. Additionally, they are less frequently associated with viral illness or cirrhosis, and they are associated with normal AFP levels, which indicates a better overall prognosis (McLarney *et al.* 1999).

2.3.7 Evaluation

Patients with symptoms suggestive hepatocellular carcinoma will be subjected to a general laboratory workup in order to be classified according to their risk of getting the condition, which will include liver biopsy. The severity of liver disease, which includes hypovolemia, hyperbilirubinemia, and hypoprothrombinemia, as well as the existence of pleural effusion and encephalopathy, will be assessed using the Child-Pugh grading

scale, which is used to classify liver illness. Throughout the surgery, the patient's health will be continuously examined. Diagnostic algorithms for solid liver damage have been developed by the American Association for the Study of Liver Injury (AASLD). These algorithms are based on a patient's tumor size on the liver. High-risk patients are often diagnosed utilizing contrast-enhanced dynamic magnetic resonance (MR) or four-stage tomography (CT) imaging, in addition to ultrasound surveillance (CT) (Benson *et al.* 2017). Repeated ultrasonic scans each three months should be performed on patients who have had an MRI scan and found no signs of hepatocellular cancer. (e.g., T2 signal intensity) or CT (e.g., T3 signal intensity) can be used to diagnose hepatocellular carcinoma in people at high risk of developing the disease. A biopsy is not necessary in these cases (eg, arterial enhancement with lavage). Hepatocellular carcinoma should be considered more likely if the level of alpha-fetoprotein (AFP) rises above 500 micrograms per milliliter of blood. Additionally, L3-agglutinin-reactive (AFP) & Desgamma-carboxy prothrombin are two other authorized tumor markers that are not regularly employed, in addition to AFP. When paired with AFP, these indicators may have a high positive predictive value of 90 percent, but they may be missed in as many as 9 percent of patients with hepatocellular carcinoma, according to the American Association for Cancer Research. Depending on whether the diagnosis is still in doubt, it may be required to do a biopsy. If hepatocellular carcinoma is found to be present, additional staging imaging with computed tomography (CT) will be performed to examine for metastases (Labadie *et al.* 2019). There have been a number of different prognostic management in patients for liver cancer proposed, but no specific strategy has been determined to be effective. More comprehensive evaluations of performance status rating (0, 1, 2, or greater than 2), constitutional signs according to Child-Pugh stage (A, B or C), and the Okuda methodology are all part of Barcelona Clinic Liver Cancer System's (four stages A to D) most widely used system (four stages A to D). Performance status rating (0, 1, 2, or higher than 2), constitutional symptoms according to the Child-Pugh stage are part of the Barcelona Clinic Liver Cancer System (four stages A to D) (four stages A to D). A tumor size of or less than 50%, clinically detectable ascites, albumin lower or higher than 3 mg/dL, and bilirubin below 3 mg/dL are all included in the Okuda criteria, according to the American Cancer Society, which assigns points positive found to correlate with stages I, II, and III in untreated patients

with MOS of 8.3, 2.0, and 0.7 months, respectively. A variety of treatments are available for patients at the Barcelona Clinic with liver cancer, including the following: liver cancer known as hepatocellular carcinoma (Bonthapally *et al.* 2015, Mokdad *et al.* 2015).

Patients with multinodular hepatocellular carcinoma who are asymptomatic and in the intermediate stage (B) may benefit from chemoembolization. It is possible to treat a symptomatic patient with advanced stage (C) of the Barcelona clinic liver cancer system who has vascular invasion and/or extra-hepatic dissemination and has retained liver function with chemotherapy in the Barcelona clinic setting. The Barcelona clinic liver cancer system recommends that patients with terminal D disease get systemic palliative care. For patients in the early stages (A and 0), resection or even liver transplantation may be an option, with 30 percent and 40 to 70 percent cure rates, respectively. To put it another way, the five-year survival rates for patients who have had complete resection for hepatocellular carcinoma are as follows: 55%, 37%, 37%. (33 percent). Updates were made to the TNM staging system in 2010. (16%) If the patient has advanced disease, the Italian Cancer of the Liver Program (CLIP) score can be used to predict survival, which adds up the points from each of the sub-scores (Child-Pugh stage, tumor morphology uni-nodular versus multi-nodular and less or greater than 50 percent extension, AFP less or greater than 400, and portal vein thrombosis present or absent) and assigns a survival risk category accordingly (Zhao *et al.* 2013).

2.4 Liver Cancer

Hepatocellular cancer (also known as primary liver cancer, primary hepatic malignancy, or hepatic carcinoma in situ) begins in the liver and spreads to other organs in the case of liver cancer (Parizadeh *et al.* 2019). There are two forms of liver cancer, primary and secondary, both of which begin in the liver and spread throughout the body (i.e. cancer that has spread to the liver from elsewhere, known as liver metastasis). hepatic tumors that spread to other organs are more prevalent than liver cancers itself, and liver cancer is now the most common form of cancer in the world (Benson *et al.* 2017).

2.4.1 Types

- Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma is the most common and most severe kind of liver cancer to arise. In Hepatocellular Carcinoma (HCC), a kind of cell known as hepatocytes grows abnormally, resulting in the formation of tumors ("hepat" and "hepato" are derived from the Greek word for liver). It is focused on a single liver cell that is believed to be at the core of the tumor. Most patients diagnosed with this type of cancer are over the aged of 50, and men are more likely than women to be diagnosed with the disease. It is possible for hepatocellular carcinoma to spread, and when this occurs, it frequently affects the lymph nodes and lungs in the nearby region (Parizadeh *et al.* 2019).

- Cholangiocarcinoma

This type of carcinoma, also known as bile duct cancer, originates in the tissues of the directly connecting the liver to the gallbladder as well as the gallbladder to the intestine, and it is the most common type of cancer in women. In the United States, it is the most frequent type of cancer (hepatic bile ducts). Cholangiocarcinoma can also form in the ducts of the liver, albeit this is a rare occurrence (intrahepatic ducts). By clicking on the links below, you can learn more about the anatomy of these organs. They grow slowly and do not spread for long periods of time despite the fact that the overwhelming majority of cholangiocarcinomas are adenocarcinomas (which means that they form in glandular tissue). There are few specific symptoms and the cancer may be confused for other liver disorders, which is why it is difficult to diagnose (such as hepatitis or cirrhosis). As a result, it is difficult to detect early on, and when it is discovered, it is usually at an advanced level. It is estimated that the average age of persons diagnosed with cholangiocarcinoma at the initial diagnosis is 65 years (Benson *et al.* 2017).

- Hepatoblastoma

Cancer of the liver that develops in children is known as hepatoblastoma. It is most commonly identified in babies between the ages of 14 and 24 months, and practically all patients are detected before the age of five years. Hepatoblastoma is the most common type of cancer in children under the age of five (Staib *et al.* 2003). This form of carcinoma can manifest itself in older children and adults, however it is extremely unusual in both groups of people. In this type of cancer, the uncontrolled proliferation (i.e., cell division that does not stop proliferating) of immature liver cells results in the development of the cancerous tumor (hepatocytes). In most cases, hepatoblastoma is found in a single location (unifocal), and it seldom spreads to other sections of the body (Matoba et al. 2006).

In livers damaged by hepatitis B and C, hemochromatosis (a genetic illness linked with excessive iron in the liver), and cirrhosis (cirrhotic liver disease), hepatocellular carcinoma is more prone to develop (cirrhosis is a disease in which there is too much iron in the liver). People with primary liver cancer are more likely to have cirrhosis, a liver disease usually caused by heavy alcohol use, than those without it. These infections, hepatitis C and hemochromatosis, may cause long-term liver damage in certain persons, as well as liver failure in other cases. Obesity and high lipid levels have previously been linked to liver cancer, according to previous research (Knudson 1971).

Primary liver cancer is the fourth largest cause of cancer-related mortality globally and the sixth most frequent cancer overall. So, in 2018, it affected 841,000 individuals and killed 782,000 people over the globe. Liver cancer is more common in people who live in regions where hepatitis B and C are common, such as Asia and sub-Saharan Africa. Prostate cancer affects males at a greater rate than women (Sayiner *et al.* 2019). People between the ages of 55 and 65 are the most likely to get the disease. When it comes to liver cancer, viral hepatitis B, C or alcohol abuse cirrhosis is the most common cause. Aflatoxin, non-alcoholic hyperlipidemia, and liver flukes are other possible causes. The most common kind of cancer is intrahepatic cholangiocarcinoma, which accounts for 80% of all occurrences (which accounts for 20 percent of all cases). Verification of the

diagnosis may be done by blood tests, medical imaging, and a tissue sample. Preventing liver cancer might be difficult due to the wide variety of factors that contribute to its development. The control of anthrax in agriculture and the treatment of obesity and diabetes are being addressed. Liver disease patients should be routinely checked for signs of illness (Covey 2018). If a patient has a history of chronic liver disease, they should get an ultrasound every six months to look for signs of hepatocellular carcinomas. Furthermore, since the phrase "liver cancer" encompasses a wide range of cancers, the signs and symptoms might differ widely. It is difficult to diagnose a patient with vague symptoms. Sweating, jaundice, stomach discomfort, weight loss, and liver enlargement are all signs of cholangiocarcinoma. According to the American Cancer Society (Arias-Flórez *et al.* 2018), signs of hepatocellular carcinoma include an abdominal mass, stomach discomfort, vomiting, anemia, back pain, jaundice, itching, weight loss, and fever. Treatment options include surgical intervention, targeted therapy, and radiation therapy. The use of ablation treatment, embolization therapy, or a liver transplant may be contemplated under certain conditions (Parizadeh *et al.* 2019).

2.4.2 Hepatitis C virus (HCV)

Hepatocellular carcinoma (HCC) and chronic liver disease are prevalent in Western countries, particularly the United States, with hepatitis C infection being the most common cause. Hepatitis C is particularly deadly because, unlike the hepatitis B, there is presently no vaccine available it against, making it an extremely severe condition to contract (Kuo *et al.* 2015).

- Excessive consumption of alcohol

For HCC in the United States, hepatitis C virus infection and alcohol-induced liver disease are the second and third most common risk factors, respectively.

- Geography

More than 80 percent of all Patients with cirrhosis are found in East Asia and Sub-Saharan Africa, respectively. Compared to other regions, the incidence rates in Europe and , and Australasia are considerably lower (Labadie *et al.* 2019). The incidence of HCC varies by ethnicity in the United States. Asians have a two-to-one incidence rate of HCC comparing to African Americans and a four-to-one increasing incidence compared to whites in the United States (Adam and Kitano 2019).

- Sex

A man's chance of developing liver cancer is three times greater than a woman's. Europe has the highest gap between male and female ratios, which can be seen in the following countries: Various levels of exposure to risk factors such as alcohol consumption, smoking, and contamination with either the hepatitis B virus (HBV) or the hepatitis B and c (HCV) are most likely responsible for the variance in prevalence (HCV). You may find out about HBV and HCV (Labadie *et al.* 2019)

- Age

According to the World Health Organization, high-risk colorectal cancer (HCC) is more common in adults over age of 75 in industrialised nations (such as United states and Canada) and in most Asian communities. According to the other side, the average age of African men with HCC ranges between 60 and 65 years old, and the amount of persons with HCC decreases as the population's age grows. African women are at their peak between the ages of 65 and 70, then after they begin to decrease in health and appearance (Adam and Kitano 2019).

- Hepatitis B virus (HBV)

People who have HBV have a 5 to 15-fold greater chance of developing HCC when compared with the general population, according to research. According to current estimates, patients with cirrhosis are responsible for between 70 and 90 percent of all HCCs linked to the presence of HBV. In addition to other factors, cirrhosis is a condition characterized by significant liver cirrhosis that can be caused by liver illnesses (such as hepatitis) and other ailments (Chow and Chok 2019). HBV is frequently transmitted from parents to children (vertical transmission) in areas with a high incidence of HCC; in areas with a low incidence of HCC, patients typically contract HBV through sexual contact and intravenous nourishment (horizontal transmission) (Chan *et al.* 2019).

- Obesity

According to the findings of a 16-year study done in the United States, people with a high mass index died of cancer at a rate that was five times greater than that of people with a low body mass index. Patient's who suffer from metabolic disorders are at a higher risk of acquiring liver cancer (Fodde and Smits 2002).

- Diabetic sugar

Studies conducted all over the world have shown a statistically significant association between diabetes as well as the development of HCC, according to the findings of numerous studies. The prevalence of overt diabetes in patients with cirrhosis is higher than the general population, and a larger percentage of them have high blood sugar (Hanahan and Weinberg 2000).

- The tobacco

There is yet no definitive explanation for the relationship between smoking and HCC. Results from several studies have been conflicting, with evidence of both negative and positive relationships between the two variables. Two studies conducted on women, however, discovered a positive association between smoked and breast cancer, showing that smoking could be a greater risk for women than for men (Bray *et al.* 2018).

- Exposure to aflatoxins

Among the several variations of mycotoxin produced from various groups of fungi, mycotoxins are among the most toxic and toxicant-producing compounds. When a fungus called *Aspergillus* grows on food that has been improperly maintained for an extended period of time, it produces aflatoxin, which is toxic. Aflatoxins have the potential to produce DNA abnormalities, notably those in the oncogene TP53, which is responsible for tumor suppression (p53). In addition to peanuts and tree nuts, aflatoxins can be found in a range of grains and oilseeds, as well as corn, wheat, and other grains and cereal grains (Bhamidimarri *et al.* 2015).

- Weightloss

Gastrointestinal discomfort and/or oedema in the abdomen Persons who are at increased risk of getting HCC should have a surveillance ultrasonography performed every six months, according to current recommendations. An ultrasound scan may reveal potentially life-threatening liver injury in a patient with cirrhosis of the liver, prompting the use of a CT scan or computer tomography imaging (MRI) to determine whether the anomaly (lesion) is HCC or not. If it is found that now the patient does not even have underlying cirrhosis, or if the therapy outcomes are ambiguous, a biopsy may be conducted (Arzumanyan *et al.* 2013).

- Staging and pathology report

Whenever it is suspected that a patient could be dealing from hepatocellular carcinoma, a tissue sample (biopsy) may be taken for further examination and analysis. After a biopsy has been performed, the specimen is delivered to a pathologist by the doctor who performed the biopsy (Ratovitski *et al.* 2001). The pathologist will examine the specimen. The pathologist examines the specimen at both the microscopic, after which a pathology report is generated and given to the attending physician for consideration. The look of the tissue, the makeup of the cells, and the presence or absence of sickness or normalcy are all discussed in depth in this study. The section diagnosis and detection contain a more in-depth discussion of pathology report interpretation. A variety of different staging methods have been used in the treatment of liver cancer. There are several ways of liver cancer staging available, but two of the most commonly used are the T/N/M approach and the Barcelona Hospital Liver Cancer Staging System (BCLC) (Catalyst *et al.* 2022).

- BCLC uses a four-step system

Patients with asymptomatic early tumors are included in this category (meaning they do not have symptoms).

Patients with asymptomatic multinodular HCC are classified as B. (still no symptoms, but now there are a handful of grapes versus a single grape as in stage A)

Patients who have symptomatic tumors and/or invasive tumors are classified as C.

Illness that is terminal. Treatment should be limited to symptomatic relief.

The T/N/M method assigns a severity level to cancer based on the size, location, and extent of the cancer's spread throughout the body. Find out more about the T/N/M staging system.

2.4.3 Tumor biology

- TP53

The p53 tumor gene, which is also responsible for regulation of cell division, regulates both apoptosis and cell division in cancer cells. In around half of all human cancers, a mutation in the gene encoding TP53 is discovered to be the cause. More than one study has found evidence that mutations in the p53 gene are associated with the development of colorectal cancer cell carcinoma (HCC) (Chan et al. 2019).

pRb

Tumor suppressor gene (pRb): This gene is responsible for the suppression of tumor growth. This protein, in combination with TP53, is responsible for the regulation of cell division. The alteration of the pRb pathway in HCC is comparable to that reported in other types of cancer (Li *et al.* 2019, Oren *et al.* 1999).

- Ras

In humans, the ras protein family is a collection of proteins that are involved in the process of cell division. Several Ras family inhibitors have been found to be inactivated in human HCC, indicating the role of Ras network signaling in the progression of the illness, according to a recent study. The NOTCH family of receptors is involved in the regulation of a variety of cellular functions, including proliferation, differentiation, & cell death (apoptosis) (Li *et al.* 2019, DeBaun and Tucker 1998). Translocations on the long reach (q) of chromosome 1 that induce hepatoblastoma have been associated to a variety of cancers, including ovarian cancer and breast cancer, among others. Hepatoblasts produce the NOTCH 2a protein, which delays the maturation of these cells. NOTCH 2a expression is associated with the differentiating of hepatoblasts into hepatocellular and bile cells throughout the process of liver development. A role for NOTCH 2 in the formation of hepatoblastoma is considered to be blocking the

differentiation of a group of hepatoblasts, according to this hypothesis (Bos 1989, Perduca *et al.* 2018).



3. MATERIALS AND METHODS

3.1 Materials

3.1.1 Patients

In this particular instance, analytic cross-sectional research was carried out. An interesting group of people took part in the experiment, including those who had developed cirrhosis of the liver but had no indication of HCC caused either by hepatitis C virus (HCV). HCV and HCC-related cirrhosis patients may be found in the Santa Casa Hospital Complex, a significant outpatient facility in southern Brazil that specializes in liver transplantation and liver sickness. Patients in the research had been tracked for an average of 18 years prior to the study's inception. Diabetics, frequent drinkers, patients with cirrhosis that was not caused by HCV, and patients who were co-infected with the human immunodeficiency virus (HIV) all had to be excluded from participation in the study. Prior to being enrolled into the study, patients were not allowed to have any gastrointestinal issues for six months.

3.1.2 Blood collection

It is planned to collect baseline information from patients prior to enrolling them in the trial. In a vacutainer, the blood will be collected, and the serum will be isolated from the blood plasma before being used.

The study groups were as the following Figure 3.1:

- Group A included 55 Patient without any disease (Control group).
- Group B 53 Patient with liver cirrhosis without HCC disease.
- Group C 14 Patient with HCV-related cirrhosis patients and HCC.
- Group D 16 Patient with HCC disease.

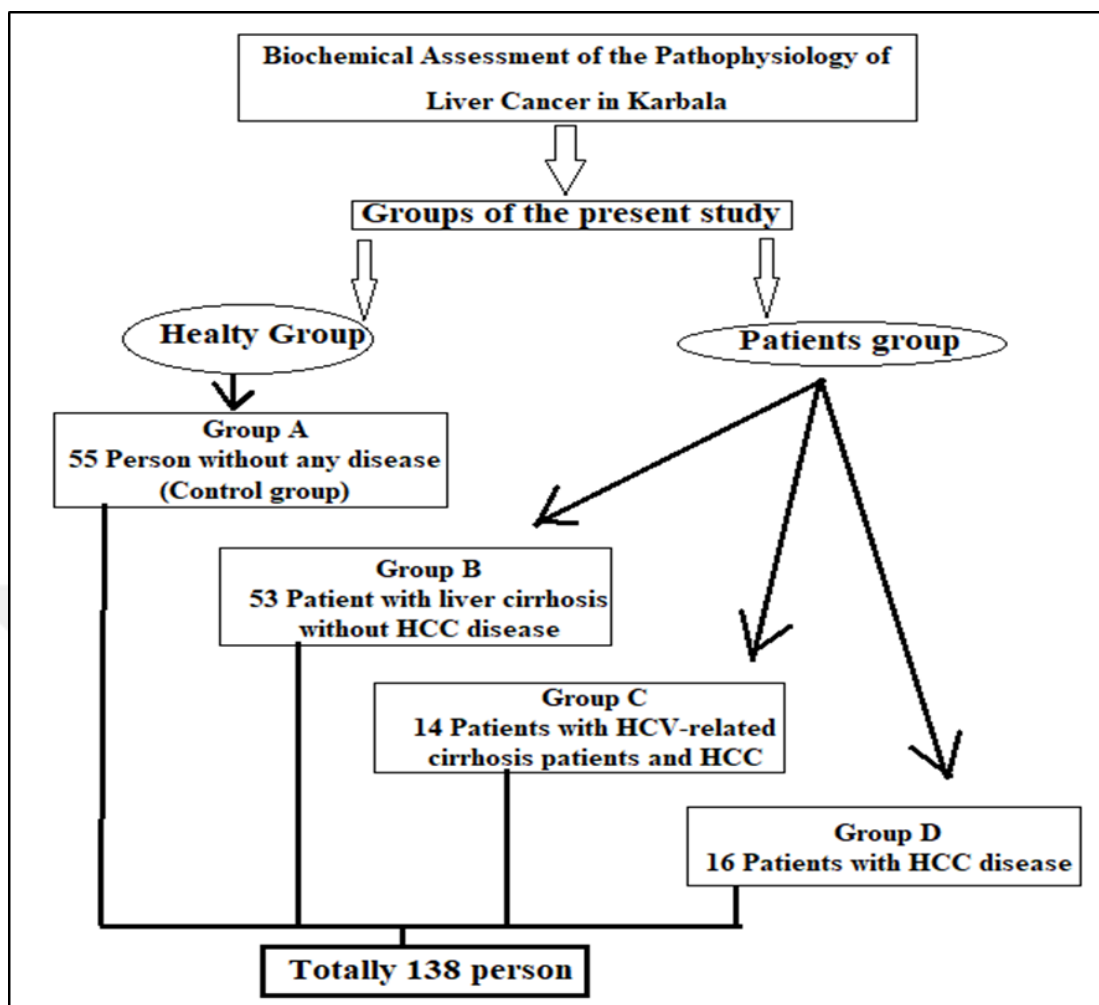


Figure 3.1 Main groups of the current study

3.2 Methods

3.2.1 General roles for the patient's selection

It was determined whether or not ascites was present by interviewing patients and collecting their demographic data (such as age, gender, and BMI). We ran a total of 14 tests in the lab: blood glucose, HDL cholesterol, triglyceride levels, total protein, albumin, creatine and uric acid levels as well as ferritin, hematocrit and hemoglobin concentrations. According to the Barcelona Clinic Liver Cancer Group (BCLC) and the American Association for the Study of Liver Disease (AASLD), the patient had been diagnosed with liver cancer (AASLD criteria). Before taking part in the trial, all

volunteers were required to sign a permission form and submit it to the ethical committee of the KARBLA Hospital Complex for approval.

Principles:

COBAS e411

The detail is the Roche Diagnostic Cobas e411 Immunoassay Device that is the ideal choice when it comes to immunoassay analysis, it is a completely automated, random access, software-controlled system with a high degree of automation. You can use three different test principles: a competitive principle for the detection of extremely small samples, a sandwich principle (in one or two steps) for the detection of larger samples (such as antibodies), and the bridging principle for the detection of antibodies present in a sample when using this system. The electrochemiluminescence (ECL) technology built into the instrument allows the cobas e411 to automate the immunoassay reaction procedure. Electrochemical oxidation refers to the formation of highly reactive species on the electrode surface as a consequence of the interaction of stable precursors with highly reactive species (ECL). Light is created as a byproduct of the interaction between two highly reactive molecules. An ECL immunoassay was constructed using ruthenium [II]-tris(bipyridyl)[Ru(bpy)] complexes, tripropylamine (TPA) complexes, and tripropylamine (TPA) in combination with tripropylamine (TPA). This stage is responsible for the generation of the final chemiluminescent product. In order for the chemiluminescent processes to occur, voltage must be applied to the immunological complexes that are bound to the streptavidin-coated microparticles for a period of time, after which the processes must be allowed to continue for an extended amount of time.

SYSMEX XP 300

In addition to being an automated 3-part imbalance haematology analyser, the Sysmex XP-300 is an excellent alternative for laboratories that require durable, dependable service even while producing high-quality diagnostic results. There is an enhanced 3-

part division of white blood cells, including a neutrophil count, in addition to the basic blood count (CBC). As a result, it gives information that is more therapeutically valuable.

Regarding the most fundamental and routine haematology tests, the XP-300 makes use of proven technology to provide outstanding quality in analytical performance, with a special emphasis on dependability and improved repeatability for the tests. RBC, WBC, and PLT are presented on the screen in addition to the measurement parameters related with each of these variables.

3.3 Statistical Analysis

ANOVA one way and Pearson tests were performed in order to determine whether or not there was a correlation between qualitative variables. A modified residual test was also done if it was deemed essential. it was decided to use the student t-test to compare the means of two different independent samples, it was considered significant when the p-value was less than 0.05.

4. RESULTS AND DISCUSSION

4.1 Results

Table 4.1 summarizes the characteristics of the samples used in this study. In group A, B, C, and D, there were indications that the rate of disease and the transformation of the disease from hepatitis C to liver cancer were greater at age, while in the HCC group the disease increased in the average age of 61 years, there was no Effect of weight, but the effect of the disease on the patient's weight towards a decrease. Patients in the HCC group had a significantly lower body mass ($P = 0.027$) than those in the control group. There is no statistically significant relationship between BMI and the presence of ascites.

Table 4.1 The following is a sample of the qualities

Variables	Group A	Group B	Group C	Group D	P-value
	Mean $\pm$ SD N = 55	Mean $\pm$ SD N = 53	Mean $\pm$ SD N = 14	Mean $\pm$ SD N = 16	
Male	34 (61.81)	30 (56.60)	9 (64.28)	11 (68.75)	
Female	21 (38.18)	23 (43.39)	5 (35.71)	5 (31.25)	
Age (years)	41.684 $\pm$ 9.638	48.274 $\pm$ 12.85	53.361 $\pm$ 14.954	61.038 $\pm$ 7.639	0.035
Weight	78.473 $\pm$ 11.64	83.583 $\pm$ 15.107	76.847 $\pm$ 8.206	69.859 $\pm$ 11.074	0.042
BMI	26.164 $\pm$ 5.073	29.584 $\pm$ 10.462	25.856 $\pm$ 9.238	23.581 $\pm$ 4.395	0.027
				08 (25.8)	

As indicated in Figure 4.1 ($P = 0.837$), serum blood glucose levels were found to be considerably higher than normal in both groups and there was no difference in mean values between the studied groups. In addition, there was no difference in the average values between the two groups that were examined.

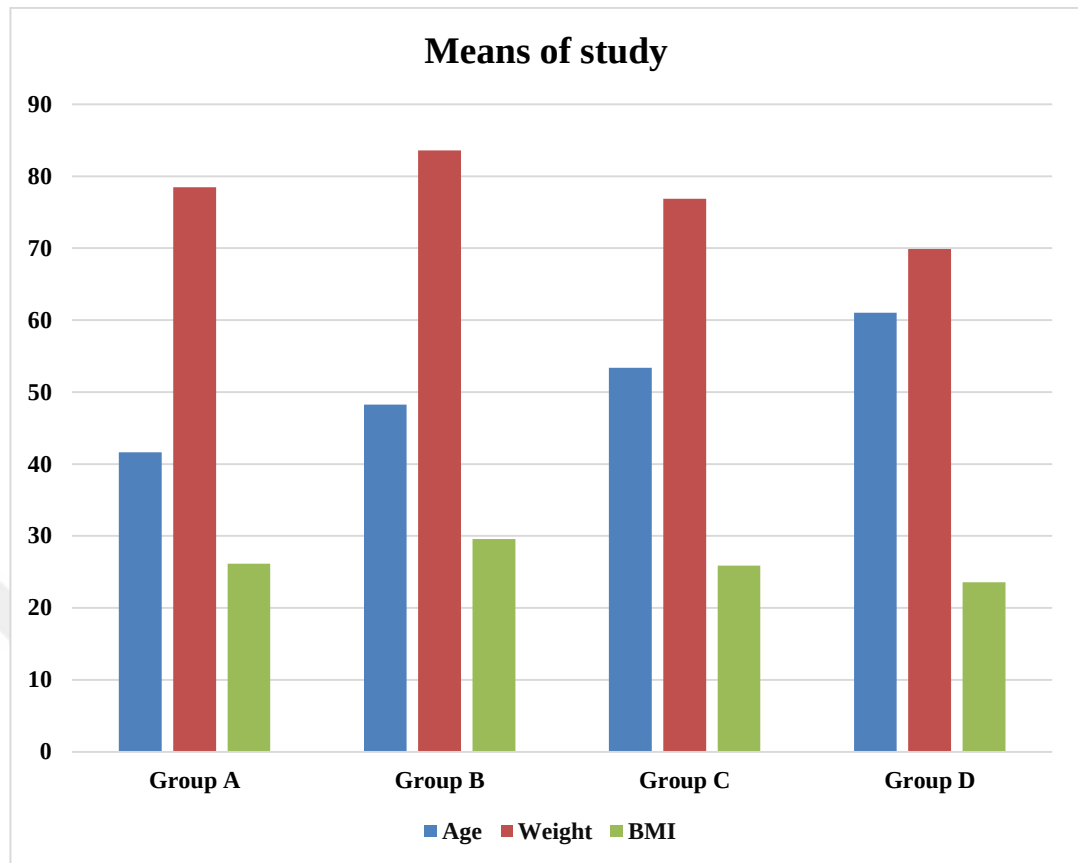


Figure 4.1 The mean of age, weight, and BMI for all studied groups

4.2 Examining Normal Levels for Glucose and Lipid Profile Indicators

Regarding serum blood glucose, it was discovered that they were significantly low than normal fourth in groups Table 4.2 ($P = 0.846$) and that there was no difference between the mean values between the analyzed groups. In addition, it was discovered that there was no difference in the mean values between both the analyzed groups. Regarding total cholesterol, it was discovered that they were significantly higher than normal between the four groups Figure 4.2 ($P = 0.031$) and that there was a difference between the mean values between the analyzed groups at compared to controls group. Regarding triglyceride, HDL, LDL and VLDL it was discovered that they were a non-significantly between the three groups Table 4.2 ($P = 0.746, 0.127, 0.335$ and 0.085 respectively) when compared to control group, and that there was a no difference between the mean values.

Table 4.2 Comparative analysis of biochemical nutritional indicators based on reference values

Variables	Group A	Group B	Group C	Group D	P-value
	Mean $\pm$ SD N = 55	Mean $\pm$ SD N = 53	Mean $\pm$ SD N= 14	Mean $\pm$ SD N = 16	
Glucose	82.638 $\pm$ 17.738	90.748 $\pm$ 18.378	78.638 $\pm$ 25.854	73.644 $\pm$ 22.848	0.846
T. cholesterol	168.854 $\pm$ 22.637	174.74 $\pm$ 27.058	139.84 $\pm$ 19.604	148.53 $\pm$ 29.759	0.031
Triglycerides	115.648 $\pm$ 13.953	109.74 $\pm$ 24.950	97.648 $\pm$ 18.405	103.80 $\pm$ 14.648	0.746
HDL	55.965 $\pm$ 10.901	47.648 $\pm$ 13.065	58.850 $\pm$ 11.070	41.075 $\pm$ 9.583	0.127
LDL	98.587 $\pm$ 26.964	113.68 $\pm$ 19.068	98.774 $\pm$ 12.275	107.74 $\pm$ 15.759	0.335
VLDL	27.547 $\pm$ 5.049	23.583 $\pm$ 6.880	26.851 $\pm$ 9.002	28.228 $\pm$ 8.017	0.085

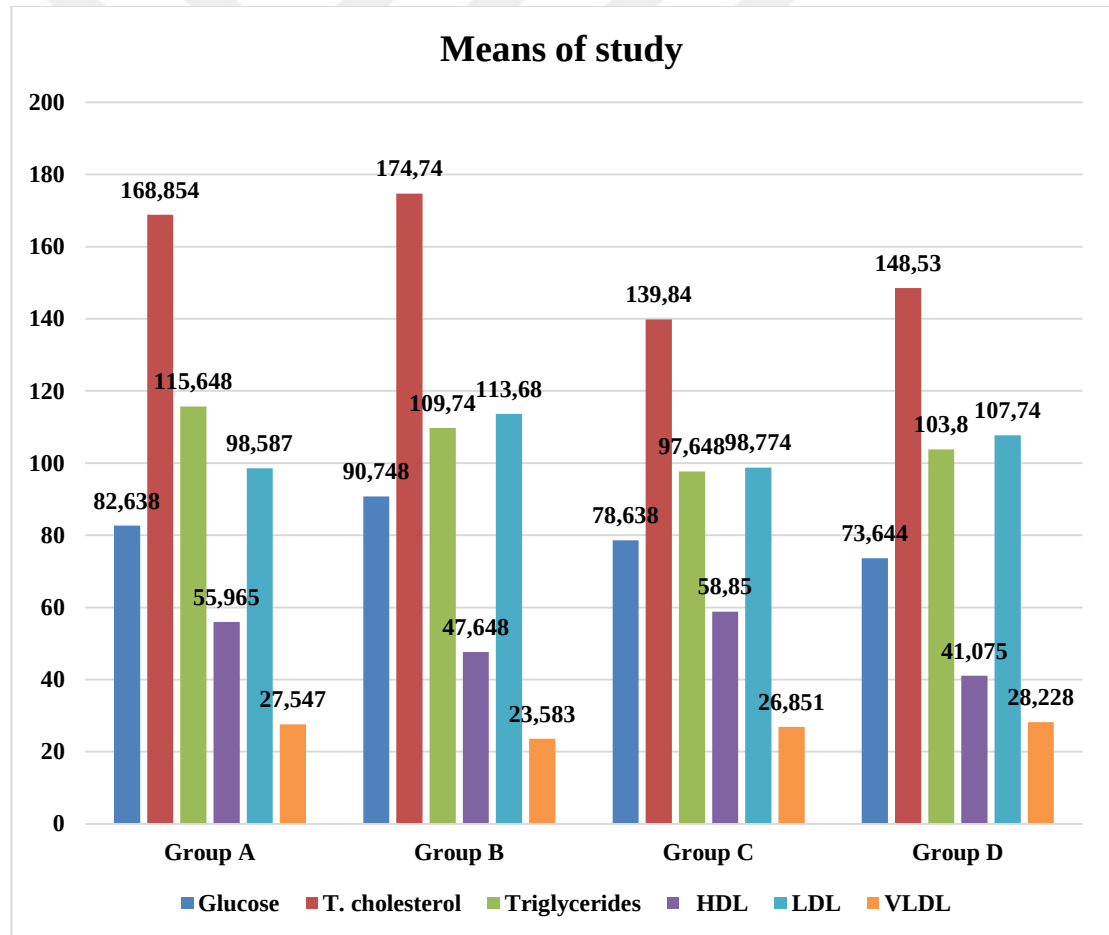


Figure 4.2 Means of glucose, T. cholesterol, triglycerides, HDL, LDL, and VLDL for all studied groups

4.3 Examining Normal Levels for T. proteins(g/L), Albumin (g/dL), Blood urea Creatinine, Ferritin (µg/L) and Transferrin saturation (mcg/dL) Indicators

Regarding T. proteins (g/L), Albumin (g/dL) and Ferritin (µg/L), it was discovered that they were significantly higher in three groups Table 4.3 (P = 0.041, 0.046 and 0.048 respectively) and that there was difference between the mean values between the analyzed groups when compared to control group. Regarding Blood urea and Creatinine, it was discovered that they were a non-significantly between the three groups Figure 4.3 (P = 0.094 and 0.355 respectively) when compared to control group, and that there was a no difference between the groups.

Table 4.3 Testing for differences between groups in biochemical nutritional indicators by comparing results to the mean

Variables	Group A	Group B	Group C	Group D	P-value
	Mean ± SD N = 55	Mean ± SD N = 53	Mean ± SD N= 14	Mean ± SD N = 16	
T. proteins (g/L)	63.759 ± 17.582	92.675 ± 24.743	83.850 ± 22.75	92.060 ± 27.860	0.041
Albumin (g/dL)	4.856 ± 1.795	3.859 ± 0.684	5.874 ± 1.960	5.964 ± 1.995	0.046
Blood urea	33.754 ± 10.678	41.758 ± 11.758	36.749 ± 8.695	39.789 ± 12.117	0.094
Creatinine	0.956 ± 0.160	1.046 ± 0.647	1.696 ± 0.960	1.471 ± 0.992	0.355
Ferritin (µg/L)	86.784 ± 16.749	177.85 ± 21.754	184.80 ± 28.895	115.86 ± 35.965	0.048
Transferrin saturation (mcg/dL)	254.76 ± 42.784	269.08 ± 36.758	248.86 ± 31.860	292.75 ± 44.894	0.050

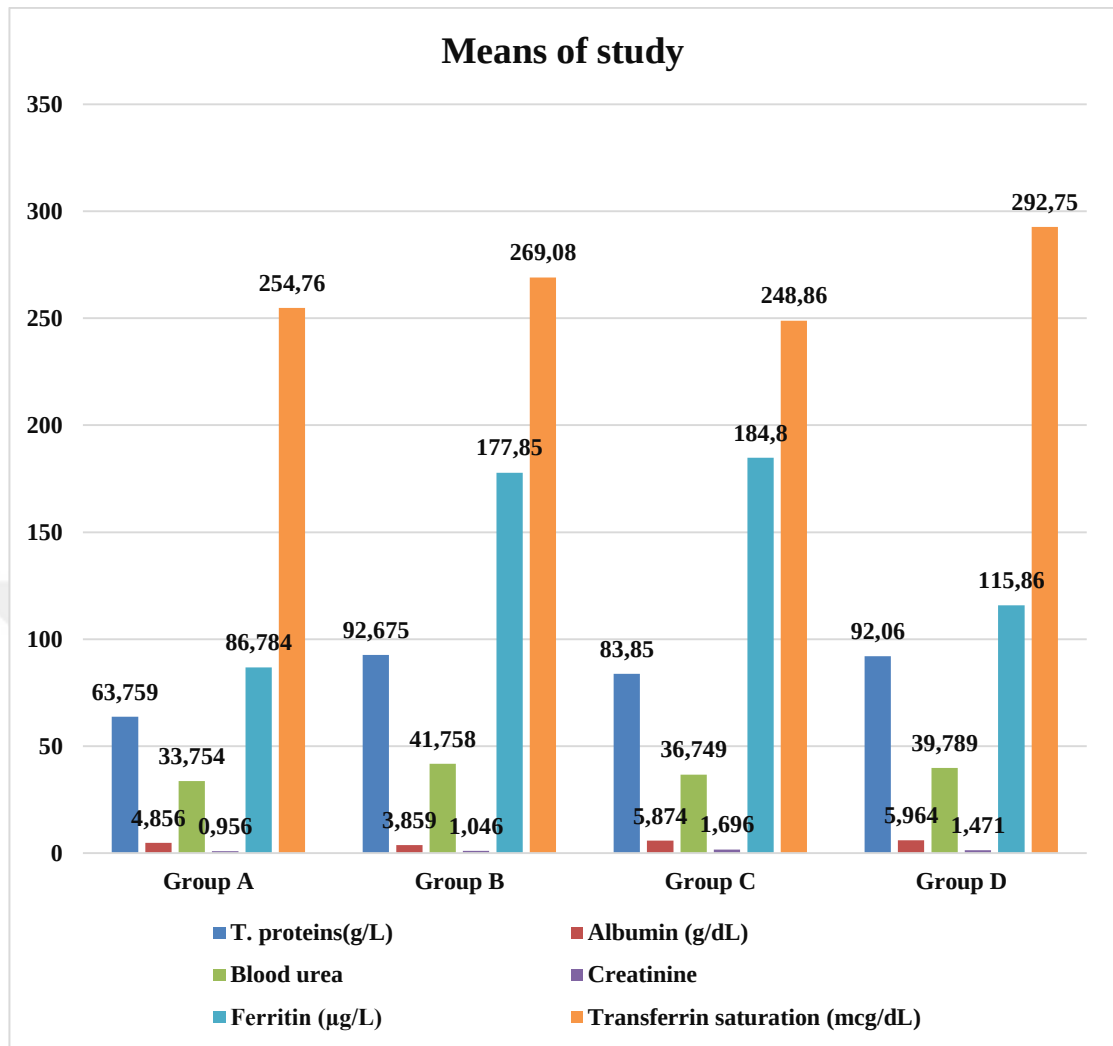


Figure 4.3 Levels for T. proteins (g/L), albumin (g/dL), blood urea creatinine, ferritin (µg/L) and transferrin saturation (mcg/dL) indicators

4.4 Examining Normal Levels for GOT, GPT, ALP(IU/L), TSB and PCV Indicators

Regarding GOT, GPT, ALP(IU/L) and TSB in same study, it was discovered that they were significantly higher in three groups Table 4.4 ($P = 0.001$, 0.003 , 0.001 and 0.036 respectively) and that there was difference between the mean values between the analyzed groups when compared to control group. Regarding PCV, it was discovered that they were a non-significantly between the three groups Figure 4.4 ($P = 0.066$) when compared to control group, and that there was a no difference between the groups.

Table 4.4 Normal ranges for biochemical nutritional indicators, and comparisons across groups investigated

Variables	Group A	Group B	Group C	Group D	P-value
	Mean $\pm$ SD N = 55	Mean $\pm$ SD N = 53	Mean $\pm$ SD N= 14	Mean $\pm$ SD N = 16	
GOT	13.748 $\pm$ 1.494	183.754 $\pm$ 32.759	848.72 $\pm$ 68.371	1047.74 $\pm$ 148.85	0.001
GPT	9.703 $\pm$ 3.740	264.85 $\pm$ 48.839	925.956 $\pm$ 136.84	1473.73 $\pm$ 1162.84	0.003
ALP (IU/L)	47.840 $\pm$ 8.946	195.860 $\pm$ 28.850	213.79 $\pm$ 31.748	211.74 $\pm$ 36.804	0.001
TSB	0.930 $\pm$ 0.074	1.957 $\pm$ 0.483	3.648 $\pm$ 1.648	4.578 $\pm$ 1.937	0.036
PCV	38.748 $\pm$ 10.997	36.684 $\pm$ 9.953	34.670 $\pm$ 10.473	30.953 $\pm$ 12.373	0.066

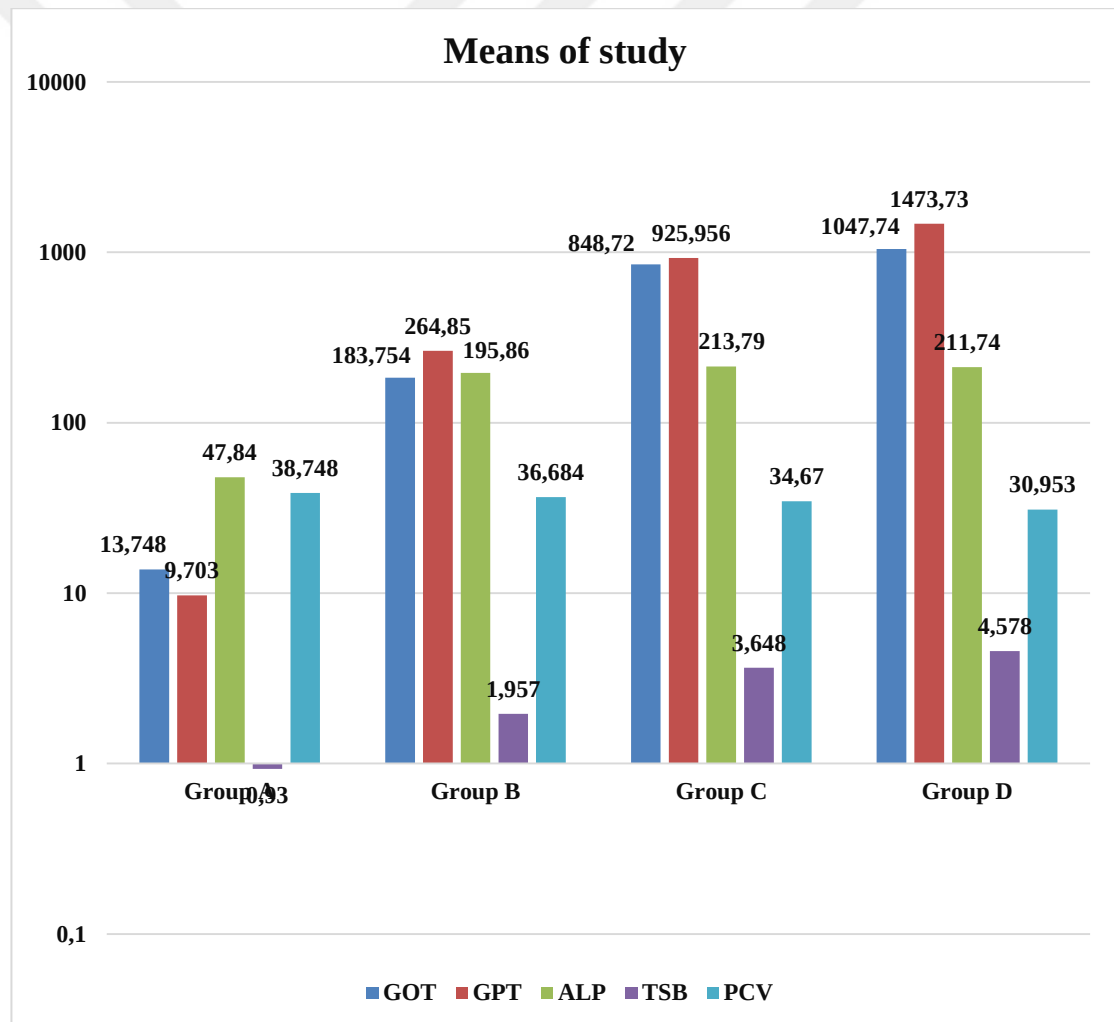


Figure 4.4 Results for the levels for GOT, GPT, ALP (IU/L), TSB, and PCV indicators

4.5 Evaluation of Biochemical Markers Based on Mean correlation with HCV

The evaluation of biochemical markers based on mean correlation with HCV have shown clearly in Table 4.5.

Table 4.5 The correlation between biochemical parameters and HCV disease severity in each study group

Variables	<i>r</i>	P-value
HCV-Age	0.463 [*]	<0.05
HCV-Weight	0.052	> 0.05
HCV-BMI	0.047	> 0.05
HCV-Glucose	0.153	> 0.05
HCV-T. cholesterol	0.74 [*]	<0.05
HCV-Triglycerides	0.437 [*]	<0.05
HCV-HDL	0.537	> 0.05
HCV-LDL	0.023	> 0.05
HCV-VLDL	0.094	> 0.05
HCV-T. proteins(g/L)	0.537 [*]	<0.05
HCV-Albumin (g/dL)	0.527 [*]	<0.05
HCV-Blood urea	0.637	> 0.05
HCV-Creatinine	0.583	> 0.05
HCV-Ferritin (μg/L)	0.473 [*]	<0.05
HCV-Transferrin saturation (mcg/dL)	0.362 [*]	<0.05
HCV-GOT	0.853 ^{**}	<0.05
HCV-GPT	0.748 ^{**}	<0.05
HCV-ALP(IU/L)	0.647 ^{**}	<0.05
HCV-TSB	0.842 ^{**}	<0.05
HCV-PCV	0.053	> 0.05
Using the median or the median and standard deviation to describe (percentiles 25-75)		

The study concluded that viral hepatitis is one of the multiple causes of malnutrition in individuals with cirrhosis, which results from the development of viral hepatitis, especially those who suffer from cirrhosis. It is possible that this disease is related to enteropathy caused by protein loss, metabolic disorder, or persistent restrictive dietary methods that these patients are forced into. Patients in both groups C and D showed lower cholesterol and HDL than those in the control group. The research found that the mean serum levels in group D were considerably lower than those in group C, indicating that viral hepatitis progresses into liver cancer. Ferritin levels in patients with chronic HCV were greater than those in the cirrhosis group compared to the control group, according to the current findings for all analyzed groups. This research found a statistically significant difference between the mean values of HCC and Group B. There were no statistically significant differences in the PCV concentrations between the patient groups, and there were no statistically significant variations in the concentrations between the groups. An ALP (IU/L) test was shown to be particularly effective in distinguishing across groups of patients. Both patients in this research were obese, which made it more difficult to examine dietary factors in this group.

A common occurrence is the development of metabolic diseases, such as insulin resistance and alterations in glucose metabolism. proteins because of increased demand and lower absorption, which is combined with decreased hepatic production. Due to increased lipolysis and lipid oxidation (Wang *et al.* 2014), fat can also contribute to the development of malnutrition. Hypermetabolism, which happens in 16 to 34 % of patients with chronic liver disease and is associated with malnutrition, can also occur in patients with chronic liver disease (Jeong *et al.* 2012, Wang *et al.* 2014).

Among patients with liver cirrhosis, malnutrition has long been associated with worse clinical progression and more severe complications, as research has shown. There are a variety of problems that can arise, including ascites, hepatic encephalopathy and infection, liver syndrome, and diabetes, among others. In conformity with the results of various research (Adam and Kitano 2019, Mantovani and Targher 2017, Takeda *et al.* 2017, Wang *et al.* 2014), it is a health risk for both short and long-term health problems, as well as mortality.

The presence of liver cirrhosis was shown to be the most common in both groups of patients who underwent testing. That data was collected from patients in an outpatient environment, when stable people are examined, is the most plausible explanation in this study. HCC patients tend to be younger and male, which is in line with prior studies, according to a new study published in JAMA Oncology (Labadie *et al.* 2019, Adam and Kitano 2019).

Those who have CI, for example, are more likely than others to acquire diabetes and insulin resistance, as well as a higher risk of getting HCC than those who do not have the disease, according to recent research. Chronic HCV infection is connected with the development of diabetes mellitus, however the mechanisms with which this is associated are yet unknown (Razumilava and Gores 2013). Similarly, to prior reports, the current study confirms these findings, with more than half of patients in both study groups having elevated glucose levels.

There has been a documented favorable association between the CTP score and serum lipid levels in patients with liver cirrhosis, indicating that this parameter may be beneficial in predicting the prognosis of patients with liver cirrhosis (Matoba *et al.* 2006). Fat tissue loss in patients with malignant neoplasms results in an increase in serum triglycerides, glycerol, and free fatty acids. This is symptomatic of a condition of lipolysis and a decrease in the production of new lipids in the peripheral circulation (Dai *et al.* 2017). Low triglyceride and total serum cholesterol levels are also associated with the development of HCC, with a negative relationship observed between tumor size and total serum cholesterol levels (Matoba *et al.* 2006, Knudson 1971). According to some study, persons with liver cirrhosis (Chow and Chok 2019) and HCC (Matoba *et al.* 2006) had lower levels of total cholesterol and high-density lipoprotein (HDL) cholesterol in their blood. According to the same line of reasoning, higher triglyceride levels have been recorded in this population (Dai *et al.* 2017). Specifically, the outcomes of this study revealed that total cholesterol levels in the CI group were found to be adversely connected to CTP score, whereas HDL cholesterol levels in the HCC group were shown to be negatively and significantly related to CTP score. The serum triglyceride levels of the vast majority of patients in both groups were normal, with the

mean values in the CI group being lower than in the other. Patients with HCC have seen a variety of outcomes, all of which have shown a drop in their triglyceride and total cholesterol (Matoba *et al.* 2006, Fodde and Smits 2002).

Inequalities based on race and food preferences are prevalent. There have been a plethora of hypotheses advanced to explain the variations in lipid metabolism seen between research. In order to identify the prognostic significance of lipids in patients with cirrhosis of the liver, studies have been conducted on these patients, and it has been revealed that lower serum lipid levels are associated with more acute liver failure as well as higher mortality rates (Chow and Chok 2019, Du *et al.* 2017).

According to the findings of the protein metabolism study, some authors have concluded that albumin levels are negatively and significantly related to CTP scores, as well as to morbidity and mortality tables (Bray *et al.* 2018, Ralphs and Khan 2013), whereas others have concluded that albumin levels in CTP-A patients are comparable to those of the reference norm (Bray *et al.* 2018). Patients with a higher TNM classification (malignant tumor classification) (Balogh *et al.* 2016) were found to have higher blood uric acid levels, and there was a positive relationship between serum urea levels and mortality in patients with cirrhosis (Arias-Flórez *et al.* 2018, Hanahan and Weinberg 2000), respectively. There is also a positive relationship between albumin score and CTP in both the CI and CI groups, as well as a positive relationship between uric acid categorization and BCLC, as well as modifications due to a range of non-nutritional factors in the CI group. When it comes to persons suffering from liver cirrhosis, elevated serum protein values are strongly associated with increased morbidity and mortality. In the presence of hepatic encephalopathy, serum albumin and creatine levels fall, making them suitable for use as non-food-dependent indicators of nutritional status. According to the researchers, this result was expected and has little to do with the nutritional analysis of individuals with liver cirrhosis, which they conducted.

According to one possible explanation, the facts that iron absorption by ferritin receptors in hepatocellular carcinoma is higher than it is in normal liver (Catalyst *et al.* 2022), which shows the presence of ferritin in HCC, is one possible cause.

Furthermore, it has been established that hematocrit is inversely related to the CTP score. Hemotocrit is unaffected by hepatic metabolism, although this is not the case under situations of severe hypertension and splenomegaly, as well as gastrointestinal bleeding [Jeong *et al.* 2012, Takeda *et al.* 2017).

The hemotocrit levels were found to be inversely related to the severity of cirrhosis as determined by the CTP score. Patients with CI and HCC had lower levels of hematocrit in their blood, as well as a negative relationship between CTP and BCLC levels, according to the findings of the current study. Findings from the present research reveal a number of biochemical indicators that may be used to identify individuals with more advanced liver disease, such as total cholesterol (total cholesterol), creatine (creatine), uric acid (uric acid), transferrin saturation, and hematocrit (total hemoglobin). C is what it is, whether or not it has HCC groups. No other choice exists. When compared to C without HCC, C with HCC may result in higher alterations to the evaluation of iron metabolism tests (hematocrit and ferritin levels) and lipid different metabolic tests (HDL cholesterol, triglycerides) than CI without HCC. When compared to CI without HCC, CI with HCC may lead to higher alterations in the assessment of lipid metabolism tests (Catalyst *et al.* 2022, Wang *et al.* 2014).

5. CONCLUSIONS

Viral hepatitis is one of the many reasons of malnutrition in people with cirrhosis, particularly those with cirrhosis, according to a research published in the journal *Pediatrics*. Possible causes include protein loss, metabolic imbalance and prolonged restricted dietary techniques that these individuals are subjected to, which may be the root cause of this condition. Compared to the patients in the control group, patients in groups C and D had lower levels of cholesterol and HDL fats. The research shows that when viral hepatitis evolves into liver cancer, the mean serum levels in group D were considerably lower than those in group C. Ferritin levels in patients with chronic HCV were greater than those in the cirrhosis group compared to the control group, according to the current findings for all analyzed groups. This research found a statistically significant difference between the mean values of HCC and Group B. There were no statistically significant differences in the PCV concentrations between the patient groups, and there were no statistically significant variations in the concentrations between the groups. An ALP (IU/L) test was shown to be particularly effective in distinguishing across groups of patients. Both patients in this research were obese, which made it more difficult to examine dietary factors in this group.

REFERENCES

- Adam, R. and Kitano, Y. 2019. Multidisciplinary approach of liver metastases from colorectal cancer. *Annals of Gastroenterological Surgery*., 3(1): 50-56.
- Arias-Flórez, J. S., Martínez-Delgado, A. M., Alarcón-Tarazona, M. L., Insuasty-Enriquez, J. S. and Díaz-Martínez, L. A. 2018. Conventional serum tumor markers in liver cancer. Retrospective analysis of 118 patients. *Revista Medica. De. Chile*., 146(12): 1422-1428.
- Arzumanyan, A., Reis, H. M. and Feitelson, M. A. 2013. Pathogenic mechanisms in HBV-and HCV-associated hepatocellular carcinoma. *Nature Reviews Cancer*., 13(2): 123-135.
- Balogh, J., Victor III, D., Asham, E. H., Burroughs, S. G., Boktour, M., Saharia, A. and Monsour Jr, H. P. 2016. Hepatocellular carcinoma: a review. *Journal of Hepatocellular Carcinoma*., 3: 41.
- Benson III, A. B., D'Angelica, M. I., Abbott, D. E., Abrams, T. A., Alberts, S. R., Saenz, D. A. and Darlow, S. 2017. Hepatobiliary cancers, version 1.2017: featured updates to the NCCN guidelines. *Journal of the National Comprehensive Cancer Network: JNCCN*., 15(5): 563.
- Bhamidimarri, K. R., Roth, D., Guerra, G., Levy, C. and Martin, P. 2015. Preliminary experience of direct acting antiviral therapy in hepatitis C infected kidney transplant recipients, who received grafts from hepatitis C positive or negative donors. In *Hepatology. NJUSA*., 62(111): 776A-776A.
- Bonthapally, V., Yang, H., Ayyagari, R., Tan, R. D., Cai, S., Wu, E. and Huebner, D. 2015. Brentuximab vedotin compared with other therapies in relapsed/refractory Hodgkin lymphoma post autologous stem cell transplant: median overall survival meta-analysis. *Current Medical Research and Opinion*., 31(7): 1377-1389.
- Bos, J. L. 1989. Ras oncogenes in human cancer: a review. *Cancer research*., 49(17): 4682-4689.
- Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A. and Jemal, A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*., 68(6): 394-424.

- Catalyst, N. E., Knowledge, N. E., Resident, N. E. and Healer, N. E. 2022. Learning/CME. *N. Engl. J. Med.*, 386: 488-490.
- Chan, K. M., Wu, T. H., Cheng, C. H., Lee, C. F., Wu, T. J., Chou, H. S. and Lee, W. C. 2019. Implementation of sorafenib treatment for advanced hepatocellular carcinoma: an illustration of current practice in Taiwan. *Cancer Management and Research.*, 11: 1013.
- Chang, E. H., Furth, M. E., Scolnick, E. M. and Lowy, D. R. 1982. Tumorigenic transformation of mammalian cells induced by a normal human gene homologous to the oncogene of Harvey murine sarcoma virus. *Nature.*, 297(5866): 479-483.
- Cholongitas, E., Pipili, C. and Papatheodoridis, G. V. 2017. Interferon-free regimens in patients with hepatitis C infection and renal dysfunction or kidney transplantation. *World Journal of Hepatology.*, 9(4): 180.
- Chow, F. C. and Chok, K. S. 2019. Colorectal liver metastases: An update on multidisciplinary approach. *World Journal of Hepatology.*, 11(2): 150.
- Covey, A. M. 2018. Hepatocellular carcinoma: updates to screening and diagnosis. *Journal of the National Comprehensive Cancer Network.*, 16(5S): 663-665.
- Cowppli-Bony, A., Colonna, M., Ligier, K., Jooste, V., Defossez, G. and Monnereau, A. 2019. Descriptive epidemiology of cancer in metropolitan France: Incidence, survival and prevalence. *Bulletin du Cancer.*, 106(7-8): 617-634.
- Dai, Y., Huang, K., Zhang, B., Zhu, L. and Xu, W. 2017. Aflatoxin B1-induced epigenetic alterations: An overview. *Food and Chemical Toxicology.*, 109: 683-689.
- DeBaun, M. R. and Tucker, M. A. 1998. Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry. *The Journal of Pediatrics.*, 132(3): 398-400.
- Di Tommaso, L., Sangiovanni, A., Borzio, M., Park, Y. N., Farinati, F. and Roncalli, M. 2013. Advanced precancerous lesions in the liver. *Best Practice & Research Clinical Gastroenterology.*, 27(2): 269-284.
- Du, X., Hidayat, K. and Shi, B. M. 2017. Abdominal obesity and gastroesophageal cancer risk: systematic review and meta-analysis of prospective studies. *Bioscience Reports.*, 37: 3.

- Ferla, R., Calo, V., Cascio, S., Rinaldi, G., Badalamenti, G., Carreca, I. and Russo, A. 2007. Founder mutations in BRCA1 and BRCA2 genes. *Annals of Oncology.*, 18: vi93-vi98.
- Fodde, R. and Smits, R. 2002. A matter of dosage. *Science.*, 298(5594): 761-763.
- Gogna, S. and Goyal, P. 2018. Recent Strategies and Paradigm Shift in Management of Hepatic Metastasis from Colorectal Cancer. *Indian Journal of Surgical Oncology.*, 9(4): 456-460.
- Half, E., Bercovich, D. and Rozen, P. 2009. Familial adenomatous polyposis. *Orphanet Journal of Rare Diseases.*, 4(1): 1-23.
- Hanahan, D. and Weinberg, R. A. 2000. The hallmarks of cancer. *cell*, 100. *Transpl. Immunol.*, 5: 179-183.
- Jeong, S. W., Jang, J. Y. and Chung, R. T. 2012. Hepatitis C virus and hepatocarcinogenesis. *Clinical and Molecular Hepatology.*, 18(4): 347.
- Kantidze, O. L., Velichko, A. K., Luzhin, A. V. and Razin, S. V. 2016. Heat stress-induced DNA damage. *Acta Naturae.*, 8(29): 75-78.
- Kew, M. C. 2013. Hepatitis viruses (other than hepatitis B and C viruses) as causes of hepatocellular carcinoma: an update. *Journal of Viral Hepatitis.*, 20(3): 149-157.
- Khan, S. A., Davidson, B. R., Goldin, R. D., Heaton, N., Karani, J., Pereira, S. P. and Wasan, H. 2012. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut.*, 61(12): 1657-1669.
- Knudson, A. G. 1971. Mutation and cancer: statistical study of retinoblastoma. *Proceedings of the National Academy of Sciences.*, 68(4): 820-823.
- Kuo, K. L., Stenehjem, D., Albright, F., Ray, S. and Brixner, D. 2015. Treatment patterns and outcomes in patients with hepatocellular carcinoma stratified by stage-guided treatment categories. *Journal of the National Comprehensive Cancer Network.*, 13(8): 987-994.
- Labadie, K. P., Schaub, S. K., Khorsand, D., Johnson, G., Apisarnthanarax, S. and Park, J. O. 2019. Multidisciplinary approach for multifocal, bilobar hepatocellular carcinoma: A case report and literature review. *World Journal of Hepatology.*, 11(1): 119.

- Li, J., Cai, H., Li, H., Liu, Y., Wang, Y., Shi, Y. and Wang, D. 2019. Combined inhibition of sonic Hedgehog signaling and histone deacetylase is an effective treatment for liver cancer. *Oncology Reports.*, 41(3): 1991-1997.
- Malkin, D., Li, F. P., Strong, L. C., Fraumeni Jr, J. F., Nelson, C. E., Kim, D. H. and Friend, S. H. 1990. Germ line p53 mutations in a familial syndrome of breast cancer, sarcomas, and other neoplasms. *Science.*, 250(4985): 1233-1238.
- Mantovani, A. and Targher, G. 2017. Type 2 diabetes mellitus and risk of hepatocellular carcinoma: spotlight on nonalcoholic fatty liver disease. *Annals of Translational Medicine.*, 5: 13.
- Matoba, S., Kang, J. G., Patino, W. D., Wragg, A., Boehm, M., Gavrilova, O. Hwang, P. M. 2006. p53 regulates mitochondrial respiration. *Science.*, 312(5780): 1650-1653.
- McLarney, J. K., Rucker, P. T., Bender, G. N., Goodman, Z. D., Kashitani, N. and Ros, P. R. 1999. From the Archives of the AFIP: Fibrolamellar Carcinoma of the Liver: Radiologic-Pathologic Correlation. *Radiographics.*, 19(2): 453-471.
- Mokdad, A. A., Singal, A. G. and Yopp, A. C. 2015. Liver cancer. *Jama.*, 314(24): 2701-2701.
- Nikitaki, Z., Hellweg, C. E., Georgakilas, A. G. and Ravanat, J. L. 2015. Stress-induced DNA damage biomarkers: applications and limitations. *Frontiers in Chemistry.*, 3: 35.
- Oda, T., Tsuda, H., Scarpa, A., Sakamoto, M. and Hirohashi, S. 1992. p53 gene mutation spectrum in hepatocellular carcinoma. *Cancer Research.*, 52 (22): 6358-6364.
- Oren, M. and Rotter, V. 1999. Introduction: p53-the first twenty years. *Cellular and Molecular Life Sciences CMLS.*, 55(1): 9-11.
- Parizadeh, S. M., Jafarzadeh-Esfehani, R., Ghandehari, M., Goldani, F., Parizadeh, S. M., Hassanian, S. M. and Avan, A. 2019. MicroRNAs as potential diagnostic and prognostic biomarkers in hepatocellular carcinoma. *Current Drug Targets.*, 20(11): 1129-1140.
- Perduca, V., Omichessan, H., Baglietto, L. and Severi, G. 2018. Mutational and epigenetic signatures in cancer tissue linked to environmental exposures and lifestyle. *Current Opinion in Oncology.*, 30(1): 61-67.

- Puustinen, L., Barner-Rasmussen, N., Pukkala, E. and Färkkilä, M. 2019. Incidence, prevalence, and causes of death of patients with autoimmune hepatitis: A nationwide register-based cohort study in Finland. *Digestive and Liver Disease.*, 51(9): 1294-1299.
- Qiu, X., Li, M., Wu, L., Xin, Y., Mu, S., Li, T. and Song, K. 2020. Severe Fatigue is an Important Factor in the Prognosis of Patients with Advanced Hepatocellular Carcinoma Treated with Sorafenib. *Cancer Management and Research.*, 12: 7983.
- Ralphs, S. and Khan, S. A. 2013. The role of the hepatitis viruses in cholangiocarcinoma. *Journal of Viral Hepatitis.*, 20(5): 297-305.
- Ratovitski, E. A., Patturajan, M., Hibi, K., Trink, B., Yamaguchi, K. and Sidransky, D. 2001. p53 associates with and targets $\Delta Np63$ into a protein degradation pathway. *Proceedings of the National Academy of Sciences.*, 98(4): 1817-1822.
- Razumilava, N. and Gores, G. J. 2013. Classification, diagnosis, and management of cholangiocarcinoma. *Clinical Gastroenterology and Hepatology.*, 11 (1): 13-21.
- Sacco, A. G. and Cohen, E. E. 2015. Current treatment options for recurrent or metastatic head and neck squamous cell carcinoma. *Journal of Clinical Oncology.*, 33(29): 3305-3313.
- Saraswat, V. A., Pandey, G. and Shetty, S. 2014. Treatment algorithms for managing hepatocellular carcinoma. *Journal of Clinical and Experimental Hepatology.*, 4: S80-S89.
- Sayiner, M., Golabi, P. and Younossi, Z. M. 2019. Disease burden of hepatocellular carcinoma: a global perspective. *Digestive Diseases and Sciences.*, 64(4): 910-917.
- Staib, F., Perwez Hussain, S., Hofseth, L. J., Wang, X. W. and Harris, C. C. 2003. TP53 and liver carcinogenesis. *Human Mutation.*, 21(3): 201-216.
- Takeda, H., Takai, A., Inuzuka, T. and Marusawa, H. 2017. Genetic basis of hepatitis virus-associated hepatocellular carcinoma: linkage between infection, inflammation, and tumorigenesis. *Journal of Gastroenterology.*, 52(1): 26-38.
- Tsochatzis, E. A., Bosch, J. and Burroughs, A. K. 2014. Liver cirrhosis. *The Lancet.*, 383(9930): 1749-1761.
- Wang, W., Lin, P., Sun, B., Zhang, S., Cai, W., Han, C., ... & Zhao, X. (2014). Epithelial-mesenchymal transition regulated by EphA2 contributes to

vasculogenic mimicry formation of head and neck squamous cell carcinoma. *BioMed research international*., 8: 4.

Zhao, W. C., Fan, L. F., Yang, N., Zhang, H. B., Chen, B. D. and Yang, G. S. 2013. Preoperative predictors of microvascular invasion in multinodular hepatocellular carcinoma. *European Journal of Surgical Oncology (EJSO)*., 39(8): 858-864.



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