Thesis

Sarcopenia in liver cirrhosis
retrospective outcome analysis

Submitted by

Jakob Schwarzl

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Dr. med. univ. Stefan Fürst

and

Univ. Prof.^{in} Priv.-Doz.^{in} Dr.^{in} med. univ. Vanessa Stadlbauer-Köllner, MBA

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I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in essays, articles, dissertations, books and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

Graz, am 28.07.2024 *Jakob Schwarzl m.p.*

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Zusammenfassung

Hintergrund und Zielsetzung: Der Verlust von Muskelkraft, Muskelmasse und Muskelfunktion, Sarkopenie genannt, ist ein häufig auftretendes Problem in unserer Gesellschaft. Besonders häufig davon betroffen sind chronisch kranke Patient*innen. Eine der häufigsten Begleiterkrankungen der Leberzirrhose ist Sarkopenie. Das Ziel dieser Arbeit ist zu analysieren, ob ein Zusammenhang zwischen Sarkopenie und Mortalität bei Patient*innen mit Leberzirrhose besteht. Zusätzlich wird überprüft, ob Komplikationen der Leberzirrhose häufiger bei Patient*innen mit Sarkopenie auftreten.

Material und Methode: Es wurden retrospektiv die Daten von 118 Patient*innen mit Leberzirrhose und 60 Patient*innen ohne Zirrhose (Kontrollgruppe) der Abteilung für Gastroenterologie und Hepatologie analysiert. Aus den Krankenakten der Patient*innen wurden folgende Daten erhoben: Alter, Geschlecht, Größe, Gewicht, BMI, Sterbedatum (falls vorhanden) inklusive Sterbeursache, Status der Leberzirrhose, Status der Sarkopenie und das Auftreten von Komplikationen (Aszites, hepatische Enzephalopathie, spontan bakterielle Peritonitis, Ikterus, gastrointestinale Blutung, Portalvenenthrombose, Infektionen, akute Nierenschädigung, hepatozelluläres Karzinom).

Ergebnisse: 118 von 178 Patien*innen wiesen eine Leberzirrhose auf. 58 Patient*innen waren sarkopen, 67 präsarkopen und 53 Patient*innen wiesen keine Sarkopenie auf. Im gesamten Patientenkollektiv zeigte sich unabhängig voneinander eine signifikant erhöhte Mortalität durch Leberzirrhose ($p<0.001$) und Sarkopenie ($p=0.001$). Ein signifikanter Anstieg der Sterblichkeit von Patient*innen mit Leberzirrhose durch Sarkopenie konnte jedoch nicht festgestellt werden ($p=0.074$). Ebenfalls zeigte sich keine Signifikanz in den unterschiedlichen Geschlechtergruppen (Männer: $p=0.057$; Frauen: $p=1.000$). Im Gegensatz dazu zeigte sich in der Gruppe über 65 Lebensjahre ein signifikanter Unterschied in der Mortalität zwischen Zirrhose-Patient*innen mit und ohne Sarkopenie ($p=0.010$). Bei der Analyse der Komplikationen der Leberzirrhose zeigte sich, dass Portalvenenthrombosen signifikant häufiger bei Patient*innen mit Sarkopenie aufgetreten sind ($p=0.035$). Hier zeigte sich ebenfalls, dass vor allem Männer betroffen waren (9 Männer, 1 Frau, $p=0.448$). Gastrointestinale Blutungen traten signifikant häufiger bei Frauen auf ($p=0.045$). Im gesamten Patientenkollektiv konnte gezeigt werden, dass Infektionen ($p=0.020$) neben Portalvenenthrombosen ($p=0.001$) signifikant häufiger auftreten, wenn Patient*innen eine Sarkopenie aufweisen.

Schlussfolgerung: Sarkopenie ist eine häufige Begleiterkrankung der Leberzirrhose. Während sich im gesamten Patientenkollektiv eine gesteigerte Mortalität durch Sarkopenie feststellen lassen konnte, zeigte sich bei Patient*innen mit Leberzirrhose nur ein Trend in Richtung einer erhöhten Sterblichkeitsrate. Insbesondere im gesteigerten Alter hatte Sarkopenie einen signifikanten Einfluss auf die Mortalität bei Leberzirrhose. Ebenso konnte in dieser Arbeit gezeigt werden, dass Sarkopenie einen Einfluss auf die Häufigkeit von Leberzirrhose-spezifischen Komplikationen nimmt. Dies deckt sich mit bereits durchgeführten Studien, die sich ebenfalls mit der Interaktion zwischen Sarkopenie und Leberzirrhose beschäftigten. Diese Ergebnisse zeigen, dass ein frühzeitiges Screening von Patient*innen mit Leberzirrhose auf Sarkopenie sinnvoll ist, um Patient*innen in frühen Stadien zu identifizieren und therapieren.

Abstract

Introduction: The loss of muscle strength, muscle mass, and muscle function, known as sarcopenia, is a common problem in our society. Chronically ill patients are particularly frequently affected. Sarcopenia is one of the most common concomitant diseases of liver cirrhosis. This work aims to analyse whether there is a correlation between sarcopenia and mortality in patients with liver cirrhosis. In addition, it is examined whether complications of liver cirrhosis occur more frequently in patients with sarcopenia.

Material and methods: The data of 118 patients with liver cirrhosis and 60 patients without cirrhosis (control group) from the Department of Gastroenterology and Hepatology were analyzed retrospectively. The following data was collected from the patient's medical records: Age, sex, height, weight, BMI, date of death (if available) including cause of death, status of liver cirrhosis, status of sarcopenia and the occurrence of complications (ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, jaundice, gastrointestinal bleeding, portal vein thrombosis, infections, acute kidney injury, hepatocellular carcinoma).

Results: 118 of 178 patients had liver cirrhosis. 58 patients were sarcopenic, 67 were presarcopenic, and 53 patients had no sarcopenia. In the entire patient collective, there was a significant increase in mortality due to liver cirrhosis ($p<0.001$) and sarcopenia ($p=0.001$). However, a significant increase in mortality in patients with liver cirrhosis due to sarcopenia could not be determined ($p=0.074$). There was also no significance in the different sex groups (men: $p=0.057$; women: $p=1.000$). In contrast, there was a significant difference in mortality between cirrhosis patients with and without sarcopenia in patients over the age of 65 ($p=0.010$). The analysis of complications of liver cirrhosis showed that portal vein thrombosis occurred significantly more frequently in patients with sarcopenia ($p=0.035$). It turned out that men were particularly affected (male: 9; female; 1; $p=0.448$). Gastrointestinal bleeding occurred significantly more frequently in women ($p=0.045$). In the entire patient population, it was shown that infections ($p=0.020$) and portal vein thrombosis ($p=0.001$) occur significantly more frequently in patients with sarcopenia.

Conclusion: Sarcopenia is a common concomitant disease of liver cirrhosis. While increased mortality due to sarcopenia was found in the entire patient population, there was only a trend towards an increased mortality rate in patients with liver cirrhosis. Sarcopenia had a significant impact on mortality in older patients with cirrhosis. This study also showed that sarcopenia influences the frequency of liver cirrhosis-specific complications. This is in line with previous studies that also looked at the interaction between sarcopenia and liver

cirrhosis. These results show that early screening of patients with liver cirrhosis for sarcopenia makes sense in order to identify and treat patients in the early stages.

Publications created during thesis

The data collected as part of this thesis was also used for the following work:

Haller, R; Fürst, S; Woltsche, J; Gulden, L; Schwarzl, J; Traub, J; Feldbacher, N; Aliwa, B; Madl, T; Fauler, G; Horvath, A; Stadlbauer, V
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Haller, R; Fürst, S; Woltsche, J; Gulden, L; Schwarzl, J; Traub, J; Feldbacher, N; Aliwa, B; Madl, T; Fauler, G; Horvath, A; Stadlbauer, V
Intestinal Permeability in liver cirrhosis
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Doctoral Day 2023; FEB 9, 2023; GRAZ, AUSTRIA. 2023. [Poster]

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Malnutrition in liver cirrhosis: can screening tools predict outcome?
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Acute kidney injury in liver cirrhosis: Combining microbiome and metabolome in the search for biomarkers.
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S. Fürst, J. Traub, J. Schwarzl, J. Woltsche, L. Gulden, A. Horvath, V. Stadlbauer-Köllner;
Validation of an easy-to-use malnutrition screening in cirrhosis to predict outcome.
EASL Congress; JUN 5 - 8, 2024, MILAN, ITALY [Poster]

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Abbreviations

AKI	Acute kidney injury
ALT	Alanine transaminase
AST	Aspartate transaminase
AWGS	Asian Working Group for Sarcopenia
BCAA	Branched-Chain Amino Acids
BIA	Bioelectrical impedance analysis
CRP	C reactive Protein
CT	Computed tomography
DEXA	Dual-energy X-ray absorptiometry
DNS	Deoxyribonucleic acid
EASL	European Association for the Study of the Liver
ESPEN	European Society for Enteral and Parenteral Nutrition
EWGSOP	European Working Group on Sarcopenia in Older People
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HE	Hepatic encephalopathy
HR	Hazard ratio
HRS	Hepatorenal syndrome
IGF-1	Insulin-like growth factor 1
IL	Interleukin
INR	International normalised ratio
IWGS	International Working Group on Sarcopenia
MASH	Metabolic dysfunction-associated steatohepatitis
MCP-1	Monocyte chemoattractant protein-1
MELD	Model of End-Stage Liver Disease
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds Ratio
RAAS	Renin-Angiotensin-Aldosteron-system
RONS	Reactive Oxygen and Nitrogen Species
SARM	Selektiv Androgen Receptor Modulator

SBP	Spontaneous bacterial peritonitis
SD	Standard Deviation
SMI	Skeletal muscle index
SPPB	Short Physical Performance Battery
TIPS	Transjugular intrahepatic portosystemic shunt
TNF-α	Tumour necrosis factor α

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Introduction

1.1 Sarcopenia

1.1.1 Definition

Sarcopenia is a generalised disease of the musculoskeletal system that primarily affects the elderly population. However, it can also occur in younger people. (Cruz-Jentoft, Bahat et al. 2019)

The term sarcopenia was first described in 1989 by the American physician Dr. Irwin H. Rosenberg. It comprises the following two words: “sarx” = flesh and “penia” = loss. (Rosenberg, 1989)

The increase in age is responsible for an increasing loss of tissue and organ function. Age is also accompanied by reduced muscle mass and, consequently, reduced muscle function. From age 50, muscle mass decreases by 1-2% per year; from age 65, this process accelerates enormously. The European Working Group on Sarcopenia in Older People (EWGSOP) first described this phenomenon in 2010 as “a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death”. (Cruz-Jentoft, Baeyens et al., 2010) According to the 2010 definition, decreased muscle mass and either reduced grip strength or slow gait speed represent sarcopenia. In 2018, the EWGSOP redefined sarcopenia. Since then, decreased muscle strength is used as the primary parameter because it has the highest predictive value in terms of muscle function. A diagnosis for sarcopenia can be made when there is decreased muscle strength and either decreased muscle mass or muscle function. Sarcopenia is considered severe if all three, namely muscle strength, mass, and function, are decreased. (Cruz-Jentoft, Bahat et al., 2019) Stadlbauer, Traub et al were able to show that sarcopenia is diagnosed less frequently in patients with liver cirrhosis with the new definition from 2019 compared to the definition from 2010. It was shown that muscle strength is maintained longer in patients with liver cirrhosis, where muscle mass is already reduced. (Traub, Bergheim et al., 2020)

1. Low muscle strength

2. Low muscle quantity or quality
3. Low physical performance
Probable sarcopenia is identified by Criterion 1.
Diagnosis is confirmed by additional documentation of Criterion 2.

If Criterion 1, 2 and 3 are all met, sarcopenia is considered severe.

Figure 1: 2018 operational definition of sarcopenia (Cruz-Jentoft, Bahat et al. 2019)

1.1.2 Prevalence

The prevalence of sarcopenia is not easy to determine because there are different definitions of sarcopenia. In the systematic review by Nascimento PR et al., the prevalence varies from 5% (according to the EWGSOP definition) to 17% (according to the IWGS definition). If all patients from different definitions are combined, a prevalence of approximately 10% is obtained, according to Nascimento PR et al. However, the prevalence of sarcopenia increases in different groups of patients. For example, it is about 18% in patients with diabetes mellitus and about 66% in patients with inoperable oesophagal carcinoma. Likewise, the prevalence is increased in patients with renal and liver diseases and carcinoma patients. (Yuan, Larsson, 2023)

1.1.3 Diagnosis

Diagnosing sarcopenia is often difficult as there are different definitions of sarcopenia. The most commonly used definition is that of EWGSOP. It recommends the following diagnostic algorithm:

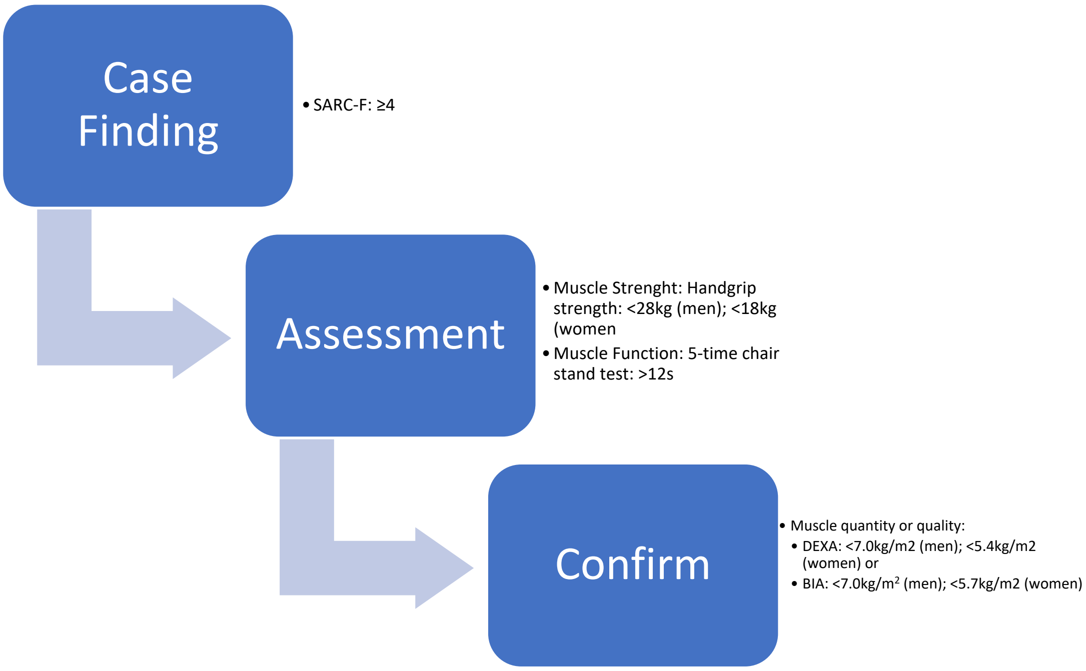

Figure 2: EWGSOP diagnostic algorithm (Cruz-Jentoft, Bahat et al. 2019)

The EWGSOP recommends using the SARC-F questionnaire for clinical practice, which is designed to screen out individuals with probable sarcopenia. Grip strength or chair stand test is used to detect low muscle strength. Muscle mass is measured in the clinical setting using dual-energy X-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA) methods. Muscle mass can also be assessed by measuring the skeletal muscle index (SMI) at the third lumbar level (L3) in computed tomography (CT) or magnetic resonance imaging (MRI). Measurements such as the 4-meter gait speed or a 400-meter-walk test are recommended to test the physical performance aspect. This helps especially in assessing the severity of the disease. (Cruz-Jentoft, Bahat et al., 2019)

The SARC-F questionnaire has been developed to detect changes in health status associated with sarcopenia. It comprises five different items. Muscle strength, walking aids, climbing stairs, getting up from a chair and falls are queried. A maximum of 10 points can be achieved, so 2 points can be assigned to each component. 0 means best, 10 worst.

Muscle strength is measured by how difficult it is for individuals to lift or carry 10 pounds (0 = easy; 1 = medium; 2 = very difficult or impossible).

The walking aid item is checked by asking the individuals about the use of assistive devices. Also assessed is whether the person can walk independently across a room (0 = no difficulty; 1 = somewhat difficult; 2 = very difficult or impossible).

Stair climbing is assessed by asking patients how difficult it is to climb ten steps (0 = no difficulty; 1 = somewhat difficult; 2 = very difficult or impossible).

The ability to get up from a chair or a bed is asked. The need for assistive devices is also considered (0 = no difficulty; 1 = somewhat difficult; 2 = very difficult or impossible).

If there has been no fall in the last year, this is scored 0. If there are 1-3 falls, 1 point is calculated; if there are more than four falls, 2. (Malmstrom, Theodore K., Miller et al., 2016)

Values above 4 indicate the presence of sarcopenia and are associated with a worse outcome. (Malmstrom, Theodore K., PhD, Morley, John E., MB, BCh, 2013)

As mentioned above, CT, MRI, DEXA or BIA are suitable for the examination of muscle mass and muscle quality. The CT is often used to quantify muscle mass. For this purpose, the skeletal muscle index (SMI) is calculated at the third lumbar vertebral body level. The limit values here are $<50\ cm^2/m^2$ for men and $<39\ cm^2/m^2$ for women. (Dhaliwal, Armstrong, 2020) MRI can be used to calculate the fat infiltration in the muscle. However, since this is a very expensive examination, it is not performed in the clinical setting but in research. DEXA can also be used to assess body composition, in which the patient is exposed to a low dose of radiation. Since this is also costly, it is not performed as a routine examination. In everyday clinical practice, BIA has become the accepted method. It is easy to perform, inexpensive and radiation-free. BIA is used to visualise fat-free mass and muscle mass. The disadvantage of BIA is that it can measure incorrect results due to the patient's hydration state and edema or ascites. (Malafarina, Úriz-Otano et al. 2012) However, the Asian

Working Group for Sarcopenia (AWGS) does not recommend using home BIAs, but rather DEXA or multifrequency BIAs.

As measured by DEXA, cutoff values for low muscle mass in sarcopenia are <7.0 kg/m^2 in men and <5.4 kg/m^2 in women. If BIA is used, the value changes to <7.0 kg/m^2 in men and <5.7 kg/m^2 in women.

For muscle strength assessment, handgrip strength is checked. Here, values below 28 kg in men and below 18 kg in women indicate insufficient muscle strength.

Several different tests have been developed to assess muscle function. In addition to the 400-meter walk test mentioned above, the Short Physical Performance Battery (SPPB), gait speed, 5-time chair stand test, 6-minute walk test, and stair-climb power test are also used. The AWGS recommends using the SPPB, the 6-minute walk test, or the 5-time chair stand test. The cutoff value for gait speed is <1.0 m/s. For the SPPB score, values ≤9, for the 5-time chair stand test, values >12 seconds are signs of low muscle function. (Chen, Woo et al., 2020)

1.1.4 Pathogenesis

The pathogenesis of sarcopenia is multifactorial and is influenced by many age-related factors.

In particular, neuromuscular degeneration plays an important role. Atrophy of muscle fibers, decreased number of alpha motor units from the spinal cord and accumulation of fat in the muscle are signs of this. With age, irreversible neuron loss occurs, leading to denervation. This results in muscle fibers no longer being involved in contraction. To compensate for this, proteins and chemotactic signals are sent out to lead to re-innervation. However, this mechanism fails with age. In addition, Schwann-cells become impaired and lead to ineffective re-innervation.

The connection between muscle and nerve, the neuromuscular junction, influences the development of sarcopenia. It consists of the presynaptic motor nerve terminal, the intrasynaptic basal lamina and postsynaptic the muscle fiber and membrane. With age, the nerve terminal area and the number of folds in the muscle membrane decrease. Furthermore, the mitochondria number is decreased here with consequent oxidative damage and decreased release of neurotransmitters during depolarisation. (Liguori, Russo et al., 2018)

A change in hormone balance also plays a role in the development of sarcopenia. In particular, the levels of sex hormones such as testosterone or dehydroepiandrosterone, growth hormones and IGF-1 decrease with age. Low testosterone levels have the consequence of decreasing muscle mass and bone density. As a result, there is an increased risk of falls and fractures. Reductions in growth factors and IGF-1 lead to an increase in visceral adipose tissue and also decreased bone density. This effect is further enhanced by increased cortisol levels with age. The anabolic effect of insulin is inhibited by an increasing resistance of skeletal muscles to the hormone. Responsible for this is a chronic inflammatory stage in older people, which is massively intensified by being overweight. (Liguori, Russo et al., 2018)

The process of the chronic inflammatory stage is caused by an increase in inflammatory parameters. These include the tumor necrosis factor-α (TNF-α), the c-reactive protein (CRP) and interleukin (IL) 1 and 6. The consequence is sarcopenia due to anabolic resistance due to activation of the ubiquitin protease system and, as mentioned above, low IGF-1 levels. This effect is amplified by chronic oxidative stress in old age with permanent activation of the immune system. This mutual interaction between the activation of the immune system and ageing is also called "oxi-inflamm-aging". In skeletal muscle, large amounts of reactive species of nitrogen and oxygen (RONS) are produced due to the high oxygen demand. In sarcopenia, this production is significantly increased, which can be attributed to mitochondrial dysfunction and DNS damage. A consequence of increased RONS production is proteolysis with a decrease in muscle mass, lower synaptic acetylcholine release, decreased number of fibers at the neuromuscular junctions, and changes in actin and myostatin structures. (Liguori, Russo et al., 2018)

An important role is also played by a change in behaviour in old age. At the same time, there is a change in food intake and reduced physical activity. Reasons for this can be dementia, depression and loss of appetite due to reduced sense of taste. (Liguori, Russo et al., 2018)

The loss of muscle strength precedes the loss of muscle mass. Already, after ten days of bed rest, you lose, on average, one kilogram of muscle mass, and the muscle strength of the quadriceps is already lost by 9% in the first five days. (Tournadre, Vial et al., 2019)

1.1.5 Consequences

The consequences of sarcopenia are dreadful. Sarcopenia is associated with an increased risk of short- and long-term mortality, a reduced overall survival rate, more frequent and more severe complications, longer hospital stays and more frequent postoperative infections. In addition, the risk of disease progression due to sarcopenia increases in patients with liver disease, patients with chronic obstructive pulmonary disease have an increased risk of osteoporosis. Patients with coronary heart disease have a higher risk of severe cardiovascular

consequences due to sarcopenia. (Yuan, Larsson, 2023) Sarcopenia is shown to have a negative impact on osteoporosis, fall frequency, quality of life, and metabolism. In addition, it leads to an increased risk of metabolic syndrome, dyslipidemia, and immunosuppression. Mortality is increased 3.7 times due to a reduction in muscle mass and function. Falls occur twice as often and need long-term care more frequently. (Tournadre, Vial et al., 2019)
A meta-analysis showed that patients with liver cirrhosis have a 2-fold increase in mortality with sarcopenia. The 1-, 3-, and 5-year survival rates for cirrhosis patients with sarcopenia were 76.6%, 64.3%, and 45.3%, respectively, and 93.4%, 82.0%, and 74.2% for cirrhosis patients without sarcopenia. Especially male patients, patients with alcohol-induced liver cirrhosis and advanced stages of cirrhosis are affected by sarcopenia. (Tantai, Liu et al., 2022)

1.1.6 Treatment

In treating sarcopenia, exercise and adequate nutrition play an essential role. People who move more in everyday life have a lower risk of developing sarcopenia. This includes climbing stairs, dancing, walking or doing housework. Bedriddenness, on the other hand, leads to rapid muscle loss, especially in older people. (Morley, J. E., 2008) One hour of physical activity per day is thought to reduce the risk of sarcopenia in nursing home residents by 60%. (Landi, Liperoti et al., 2012)
An adequate intake of proteins can lead to an increase in muscle mass and muscle function. In particular, leucine-enriched essential amino acids (whey protein) should enhance this effect. In addition to proteins, vitamin D should be supplemented. This, in combination, leads to increased muscle mass and better results when climbing stairs. Vitamin D alone leads to an increase in muscle strength without a simultaneous increase in muscle mass. The result is a reduction in the number of falls. Thus, vitamin D shows the highest therapeutic effectiveness compared to other drugs. (Morley, John E., 2016)
In old age, it is important to increase protein intake. An amount of protein of 1.1 g/kg (body weight) per day is recommended. The contraindication for this is renal insufficiency. Besides protein, creatine could also affect muscle growth. However, since studies have shown controversial results in older people, supplementation of creatine is not recommended. (Keller, 2019)
The therapy of sarcopenia using drugs is controversial. One therapeutic approach for men is the use of testosterone. The application of testosterone can achieve an increase in muscle strength and muscle mass. There is an additional hypertrophy of muscle fibers and an

increase in lean body mass. (Keller, 2019) The effect of testosterone is dose-dependent. Low dosages lead to an increase in muscle mass and a decrease in fat due to increased protein synthesis; at higher dosages, muscle strength also increases. Walking distance was shown to improve in patients with heart failure. Testosterone also increases bone density, which is often reduced in patients with sarcopenia. (Morley, John E., 2016) However, the side effects of testosterone limit their use enormously. They include enlargement of the prostate with an increased risk of prostate cancer, gynecomastia, sleep apnea, polycythemia, fluid retention, allergic reactions, and nausea. Mood is also affected; the consequence is an increased risk of depression.

Another option is the use of SARMs, selective androgen receptor modulators, which, however, have shown no advantage compared to testosterone. (Keller, 2019) A reduced testosterone level can be detected in up to 90% of men with liver cirrhosis. It has been shown that mortality is increased in this patient group. (Sinclair, Grossmann et al., 2015) Low testosterone levels in patients with liver diseases also lead to sarcopenia, reduced strength, infections and more rapid hepatic decompensation requiring liver transplantation. However, clinical studies on testosterone supplementation have not shown any significant improvement in cirrhosis complications or mortality rates. Likewise, no significant increase in the incidence of hepatocellular carcinoma, hospitalisation rates or mortality rates was shown by testosterone supplementation. (Deng, Mallepally et al., 2021)

The influence of myostatin on muscle is an important aspect of research into the treatment of sarcopenia. Myostatin is produced primarily in skeletal muscle cells, inhibiting the growth and differentiation of muscle cells. Decreased function of myostatin thus leads to an increase in muscle mass. In animal models, insufficiency of myostatin was shown to lead to longer life expectancy in mice. Agents such as Stamulumab, Landogrozumab, Trevogrumab and others have been developed to obtain this desired effect. Their efficacy and safety are part of today's research. (Kwak, Kwon, 2019)

The use of growth hormone is also controversial. An increase in muscle mass without an increase in strength has been noticed in older individuals, but with significant side effects such as gynecomastia or carpal tunnel syndrome. Growth hormone leads to an increase in IGF-1, which can lead to muscle and joint pain, hyperglycemia, and edema. Too low or too high levels of IGF-1 also increase cardiovascular risk. (Morley, John E., 2016) In addition, growth hormone could be a risk factor for the development of Hodgkin's lymphoma. (Brotto, Abreu, 2012) Thus, the use of growth hormone is not recommended. (Keller, 2019)

Other drugs that are currently not approved for the treatment of sarcopenia but which could bring a positive therapeutic effect are Bimagrumab, Allopurinol or Statins. (Keller, 2019)
In summary, adequate exercise and diet are the most important methods for treating sarcopenia. (Morley, John E. 2016) An umbrella review of systematic reviews and meta-analyses showed that vitamin D significantly affects muscle strength and performance, especially in women with low vitamin D levels (<25 nmol/l). In men with low testosterone levels (<200-300 ng/dl), testosterone supplementation led to a significant increase in muscle mass and a slight increase in muscle strength and performance. Only rare and mild side effects were observed here. (De Spiegeleer, Beckwée et al., 2018)

1.2 Liver cirrhosis

In this chapter, liver cirrhosis is described in general terms. The connection between sarcopenia and liver cirrhosis is explained in Chapter 1.3.

1.2.1 Definition

Liver cirrhosis is the result of a chronic liver disease with long-term inflammation of the liver. Chronic inflammation leads to liver fibrosis, which is characterised by a remodelling process of the liver parenchyma. Regenerative hepatic nodules replace the normal liver architecture. This can lead to liver failure. The duration of this process can vary widely, ranging from weeks to decades. Chronic inflammation does not lead to cirrhosis in all patients. (Ginès, Krag et al., 2021)
Damage to the liver, which leads to inflammation and fibrosis, can have various causes. Increased alcohol consumption and the hepatitis C virus are the leading causes of cirrhosis in industrialised countries. Obesity, in combination with metabolic dysfunction-associated steatohepatitis (MASH), also plays a role in the development of cirrhosis. Other common causes include autoimmune hepatitis, hepatitis B, hepatitis D, and primary biliary cirrhosis. (Pinzani, Rosselli et al., 2011)
Cirrhosis occurs in both low- and high-income countries and is associated with high mortality and morbidity. Worldwide, it is the 14th leading cause of death. Focusing here on central Europe, cirrhosis is the 4th leading cause of death and is responsible for 5,500 liver transplants per year. (Tsochatzis, Emmanuel A., Bosch et al., 2014)

1.2.2 Epidemiology and mortality

Estimating the prevalence of liver cirrhosis is difficult to perform because the early stages are usually asymptomatic and thus undiagnosed. A French screening program reported an

estimated prevalence of 0.3%. The annual incidence ranges from 15.3 to 132.6 cases per 100,000 persons. (Tsochatzis, Emmanuel A., Bosch et al., 2014)
Improvements in antiviral therapy against the hepatitis C virus have significantly improved the prognosis in patients with hepatitis C cirrhosis. Another benefit of antiviral treatment is that patients on medication for hepatitis C are less likely to develop cirrhosis. Conversely, the incidence of hepatitis C is steadily increasing. The incidence of acute hepatitis C has doubled (0.3 to 0.7 cases per 100,000), which can be attributed to increasing intravenous drug use.
A particularly marked increase can be seen in patients with alcohol-related cirrhosis. Although this occurs primarily in older patients, an increasing number of younger patients are presenting to hospitals with decompensated cirrhosis. Mortality among patients aged 25 to 34 years increased by 200% from 2009 to 2016. Patients with alcohol-related cirrhosis tend to have more frequent decompensations, leading to increased health resource needs and mortality. (Baki, Tapper, 2019) Alcohol-related liver disease affects 75 million people worldwide due to alcohol consumption. (Ginès, Krag et al., 2021)
In addition to alcohol-related cirrhosis, non-alcoholic steatohepatitis is also playing an increasingly important role, which can also be explained by an increased incidence of diabetes mellitus and obesity. By 2030, non-alcoholic steatohepatitis is predicted to increase by 63%. In contrast to other chronic liver diseases, this disease mainly affects young patients. The majority of affected patients are asymptomatic. The risk for symptom development and, thus, decompensation is between 5-7% per year, rising to 58% after ten years. This depends strongly on the causative disease of liver cirrhosis. (Baki, Tapper, 2019)
Mortality in cirrhosis depends on the type of liver disease and sex. In men, hepatitis B accounted for 31.5%, alcohol-related liver disease for 27.3%, hepatitis C for 25.5%, MASH for 7.7%, and other causes for 8% of deaths. In women, hepatitis C is the leading cause of death at 26%, followed by hepatitis B at 24%, alcohol-related cirrhosis at 20.6%, other causes at 17%, and MASH at 11.3%. (Ginès, Krag et al., 2021)

1.2.3 Diagnosis

In the early stages of compensated cirrhosis, patients are asymptomatic. In the course, symptoms such as fatigue, weight loss, and weakness may occur. With clinical decompensation, complications such as ascites, jaundice and hepatic encephalopathy are observed.

A thorough physical examination of the patient is essential to avoid overlooking signs of impaired liver function. Starting with the head, these include fetor hepaticus (a sweetish mouth odor resulting from an increased concentration of dimethyl sulfides), jaundice, enlargement of the parotid gland, and spider nevi. The trunk may show gynecomastia, ascites, caput medusae, splenomegaly, or hemorrhages. On the hands, thickening of the fingertips, palmar erythema, Terry nails, or clustered Dupuytren's contracture can be found. The lower extremity should be checked for erythema and petechiae. In addition to physical examination, laboratory values may indicate liver damage. In cirrhosis, expect low albumin (<3.5 g/dL), thrombocytopenia (<160 platelets/10^3 µL), AST to ALT ratio above 1, increase in bilirubin, and prolonged prothrombin time. (Smith, Baumgartner et al., 2019)
By means of sonography, MRI or CT, imaging may reveal signs of liver cirrhosis. These include an irregular liver surface or decreased liver size. A combination of abnormal imaging and evidence of decreased liver function are sufficient for a diagnosis of cirrhosis. In rare cases, liver biopsy is necessary, which can determine the aetiology of cirrhosis in uncertain cases. In addition to the percutaneous approach, a transjugular approach is possible, allowing hepatic-vein pressure gradient measurement. (Tsochatzis, Emmanuel A., Bosch et al., 2014)
If evidence of liver cirrhosis is present, further tests should be performed to determine the aetiology of cirrhosis. In addition to the imaging mentioned above, serologies for viral hepatitis, ferritin, and transferrin saturation should be checked. If MASH is suspected, lipid levels and HbA1C should be assessed. Antinuclear antibody determination should also be performed if autoimmune hepatitis is suspected.
Another method that can detect liver fibrosis and cirrhosis is transient elastography. This method can determine liver stiffness by measuring the velocity of low-frequency ultrasound waves propagating in the liver. This method has a sensitivity of 81% and a specificity of 88%. Transient elastography can be performed on an outpatient basis and is increasingly replacing biopsy as the method of choice for determining fibrosis. The disadvantage, however, is that false results may occur in patients with obesity, ascites, massive alcohol consumption, and extrahepatic cholestasis. (Smith, Baumgartner et al., 2019)

1.2.4 Pathogenesis

Liver cirrhosis has many different etiologies. In addition to viral cirrhosis due to hepatitis B, hepatitis C or hepatitis D, alcohol consumption and hereditary diseases such as hemochromatosis, Wilson's disease, α1-antitrypsin deficiency and cystic fibrosis play a role. Autoimmune diseases such as autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, or biliary drainage diseases such as biliary atresia are also triggering factors. Vascular diseases such as Budd-Chiari syndrome, veno-occlusive disease, or Fontan-associated liver disease may also contribute to the formation of cirrhosis. The use of medications such as methotrexate, amiodarone, methyldopa, or vitamin A also affects the liver. (Ginès, Krag et al., 2021)

Aetiology of cirrhosis	
Viral	- Hepatits B - Hepatitis C - Hepatitis D
Alcohol	
Metabolic and genetic	- Non-alcoholic fatty liver disease - Haemochromatosis - Wilson's disease - α1-antitrypsin deficiency - Cystic fibrosis
Autoimmune	- Autoimmune hepatitis - Primary biliary cholangitis - Primary sclerosing cholangitis
Biliary	- Biliary atresia
Vascular	- Budd-Chiari syndrom - Veno-occlusice disease - Fontan-associated liver disease
Drug-related	- Methotrexate - Amiodarone - Methyldopa - Vitamin A

Figure 3: Aetiology of cirrhosis (Ginès, Krag et al., 2021)

The above aetiologies result in liver tissue damage and continuous accumulation of fibrillar extracellular matrix accompanied by chronic activity of the wound healing process and degradation and remodeling processes resulting in chronic tissue damage. If the degradation is subjected to this process, fibrosis results. Liver cirrhosis is an advanced stage of fibrosis, which can lead to liver failure. Cirrhosis results in the formation of regenerative liver parenchymal nodules with angioarchitectural changes. The individual nodules are separated from each other by connective tissue septa. The cause of liver damage is responsible for a different course of fibrosis development. The development depends mainly on the site of liver tissue damage and the concentration of profibrogenic factors. Furthermore, there are other mechanisms leading to fibrosis. These can be divided into three groups: a chronic activation of the wound healing response, oxidative stress, and epithelial-mesenchymal interactions.

Based on the different courses of fibrosis formation, a conclusion can be drawn about the aetiology of liver injury. One example shows that portal-central septa are signs of chronic viral hepatitis. Alcohol-related cirrhosis and MASH show intercellular fibrosis and accumulation of fibrillar matrix around sinusoids.

Another role in the development of liver cirrhosis is played by hepatic stellate cells. These are activated and transformed into myofibroblasts. In addition to hepatic stellate cells, other cells affect fibrosis formation. They include fibroblasts and myofibroblasts of the portal tract, myofibroblasts in the centrilobular vein area, and smooth muscle cells of the vessel walls. "Fibrocytes", stem cells from bone marrow, are freely circulating cells and are involved in liver fibrosis.

The consequence of chronic tissue damage is oxidative stress, which leads to increased formation of critical genes and thus free radicals, promoting the progression of fibrosis. This occurs through the activation of profibrogenic genes, which include procollagen type 1, tissue inhibitor of metallopeptidase 1, and MCP-1.

The environment of the liver also plays an important role in the development of cirrhosis. Additionally, immune cells and macrophages that regulate fibrosis formation, liver stiffness, and the gut microbiota influence liver tissue. Periods of hypoxia and the anaerobic, pro-inflammatory environment also promote fibrosis. Bacterial translocation was shown to lead to chronic liver injury, especially in MASH. This translocation results from dysbiosis with increased intestinal permeability and reduced immunological competence with consequent migration of bacteria from the intestine to other structures. (Pinzani, 2015)

1.2.5 Complications

1.2.5.1 Ascites

An increase in abdominal circumference combined with abdominal discomfort is observed in ascites. It can be divided into three stages: Grade 1, mild ascites, which does not yet present clinical symptoms, but is already visible on ultrasound; Grade 2, moderate ascites, characterised by an increase in abdominal girth; Grade 3, severe ascites, with a marked increase in abdominal girth. Furthermore, ascites is divided into uncomplicated or complicated/refractory. (Ginès, Krag et al., 2021) In untreated cirrhosis, the risk of developing ascites after ten years is 60%. At the same time, the occurrence of ascites means the decompensation of liver cirrhosis, which also decreases the probability of survival. Thus, the 5-year survival rate without ascites is 80%, whereas it drops to 50% in the presence of ascites. (Wong, 2012) Therefore, liver transplantation should be considered when ascites occurs. The development of ascites in liver cirrhosis is multifactorial. On the one hand, portal hypertension plays an important role; on the other hand, arterial vasodilation and neurohumoral activity occur. Portal hypertension is responsible for increased hydrostatic pressure in the hepatic sinusoids. This promotes the transudation of fluid. Due to arterial vasodilation, there is decreased renal sodium excretion and, consequently, water retention with an increase in extracellular fluid volume. This activates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. This leads to renal vasoconstriction and sodium retention with ascites and edema. The cause of arterial vasodilation in portal hypertension is explained by increased formation of vasodilators, impaired smooth muscle cell function in response to vasoconstrictive signals, and neurohumoral signals from the liver to the brain, but is not fully understood. (Julie, Bendtsen et al., 2015)

1.2.5.2 Portal hypertension

The earliest complication is portal hypertension. It results from increased intrahepatic resistance, which is a consequence of fibrotic remodelling and endothelial dysfunction with intrahepatic vasoconstriction. Vascular shunts between arterial and venous vessels within the liver also play a role. Portal pressure can be measured indirectly by the hepatic venous pressure gradient. Values between 3-5 mmHg are the norm, while a pressure above 10 mmHg indicates decompensation of liver cirrhosis. This significantly increases the risk of developing varicose veins. (Pinzani, Rosselli et al., 2011) Variceal hemorrhage is an absolute medical emergency. The mortality rate is 20% after six weeks. Bleeding due to portal hypertension can also occur chronically in the context of gastropathy, enteropathy or colopathy and manifest as anemia. (Ginès, Krag et al., 2021)

1.2.5.3 Hepatic encephalopathy

Cognitive, psychiatric, and psychomotor disorders may occur in the setting of liver cirrhosis. These indicate a worse prognosis with a reduced quality of life and an increased risk of mortality. Likewise, hepatic encephalopathy reduces the priority for liver transplantation. Causes of hepatic encephalopathy may include acute liver failure or portosystemic shunt in addition to chronic cirrhosis. (Butterworth, 2019) It can be divided into four grades. Grades 0 and 1 are classified as "covert", and grades 2, 3, and 4 as "overt". Grade 0 and 1 are not noticeable in the clinical examination, yet these stages already reduce the patient's quality of life. They can be diagnosed by the psychometric hepatic encephalopathy score. Patients with hepatic encephalopathy grades 2 to 4 show a neuropsychiatric impairment, which can already be detected clinically. Grade 2 includes lethargy, mild temporal and spatial disorientation, striking behaviour, personality changes, and asterixis. Grade 3 is characterised by somnolence, increasing disorientation and confusion, and bizarre behaviour. If the patient is in a coma that cannot be awakened by external stimuli, it is referred to as grade 4. Grades 0 and 1 are observed in 30-45% of patients with cirrhosis. (Ginès, Krag et al., 2021)

1.2.5.4 Acute kidney injury

Acute renal failure may have multiple aetiologies in liver cirrhosis. Prerenal acute kidney injury (AKI) may be induced by a decrease in blood volume. This reduction may occur in the setting of gastrointestinal bleeding or when diuretics are taken. Exposure to nephrotoxic drugs such as NSAIDs, aminoglycosides, or contrast agents also promotes renal damage. It is important to note that cirrhotic patients usually have a hyperdynamic circulatory state, which is particularly susceptible to fluctuations in blood volume. This hyperdynamic circulation occurs in patients with cirrhosis due to progressive vasodilation, which leads, for example, to spider nevi and a high pulse pressure in the nail bed. (Garcia-Tsao, Parikh et al., 2008) Hepatorenal syndrome (HRS), a condition in which kidney function is impaired due to chronic liver disease, can be divided into two types: type 1 and type 2. Increased peripheral blood flow to the viscera is suspected, which leads to peripheral vasoconstriction. In addition, vasodilatory substances such as nitric oxide, prostacyclin or carbon monoxide are produced in hepatocytes and stellate cells. When liver cells are destroyed as part of liver disease, these substances are released, resulting in increased arterial vasodilation. This lowers the mean arterial pressure and activates the sympathetic nervous system with the release of noradrenaline, angiotensin two and antidiuretic hormone with the aim of maintaining constant renal blood flow. As liver disease progresses, vascular resistance drops to such an extent that sufficient organ perfusion can no longer be maintained. (Gupta, Bhurwal et al., 2021) 30-50% of patients with decompensated cirrhosis develop acute renal failure. (Ginès, Krag et al. 2021) Acute renal failure can be divided into the following stages:

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥26.4 µmol/L) or increase to more than or equal to 150% to 200% (1.5-fold to 2-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2	Increase in serum creatinine to more than 200% to 300% (>2-fold to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3*	Increase in serum creatinine to more than 300% (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL [≥354 µmol/L] with an acute increase of at least 0.5 mg/dL [44 µmol/L])	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours
	*Any patient requiring renal replacement therapy is, by definition, at a stage 3.	

Table 1: Classification/Staging System for Acute Kidney Injury (AKI) (Garcia-Tsao, Parikh et al., 2008)

1.2.5.5 Bacterial infections

Bacterial infections in patients with cirrhosis often occur in combination with other complications of liver disease and are a consequence of the immune dysfunction associated with cirrhosis. They may also be causative of other sequelae, such as gastrointestinal bleeding, hepatic encephalopathy, or renal failure. The occurrence of infection leads to frequent hospital admissions and a reduction in patients' quality of life.

(Jalan, Fernandez et al., 2014) Furthermore, the risk of sepsis increases by a factor of two-six and the mortality rate by a factor of four in contrast to persons without liver disease. Thus, bacterial infection is one of the most important causes of death in cirrhotic patients. The most common infections are urinary tract infection and spontaneous bacterial peritonitis, followed by pneumonia, skin and soft tissue infections, and bacteremia.

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascites without an intra-abdominal source of infection that can be treated surgically. Symptoms include nausea, vomiting, and abdominal pain, but very nonspecific symptoms or asymptomatic courses may be observed. Paracentesis should be performed for diagnosis, as well as a neutrophil count and culture of the ascites. In-hospital mortality of SBP is approximately 20%. (Ginès, Krag et al., 2021) Gram-negative bacteria, which originate from the intestine, are detected in the majority of patients. Gram-positive bacteria are frequently found in hospitalised patients. Multi-resistant germs are becoming increasingly common here. Early detection and treatment of the infection are of enormous importance to improve the prognosis for patients with infections. (Jalan, Fernandez et al., 2014)

1.2.5.6 Frailty and sarcopenia

The relationship between liver cirrhosis and sarcopenia is described in Chapter 1.3. Frailty is a syndrome in which physiological, psychological and social factors play a role. Patients are particularly vulnerable to changes in their environment. They have an increased risk of falls, a shorter life expectancy and more frequent hospital visits. The transition to the need for long-term care is the end state here. Older adults are particularly affected. Fried et al. described frailty with the following attributes: shrinkage, weakness, exhaustion, slowness, and low activity. If only one or two points apply to a person, it is called a preliminary stage of frailty. It is striking that patients with liver disease have an increased incidence of a preliminary stage of frailty. Since this condition is still reversible, early diagnosis and intervention are important. The difference between sarcopenia and frailty is that in sarcopenia, purely muscle quality is assessed, whereas in frailty, other factors, such as psychological aspects, are considered. (Nishikawa, Fukunishi et al., 2021)

1.2.5.7 Portal vein thrombosis

The occurrence of portal venous thrombosis is associated with the severity of liver cirrhosis. While the prevalence is 10% in patients with compensated cirrhosis, it increases to 26% in patients requiring liver transplantation. Damage to the liver results in a decrease in both anticoagulant and procoagulant factors. Von Willebrand factor and coagulation factor VIII are increased. In combination with a decrease in the flow velocity in the portal vein, the risk of thrombosis thus increases. (Ginès, Krag et al., 2021) Symptoms of portal vein thrombosis vary widely, with some patients being asymptomatic while others present with a life-threatening condition. The thrombus may resolve spontaneously or spread further proximally or distally. Intestinal infarction due to the spread of the thrombus into the superior mesenteric vein is a complication that can be rapidly fatal. In addition, the risk of bleeding is higher in patients with portal vein thrombosis compared to cirrhotic patients without portal vein thrombosis. Thus, the exclusion of esophageal varices is of great importance. First-line therapy is anticoagulation, which aims to prevent the further spread of the thrombus. Other treatment options include thrombectomy and transjugular intrahepatic portosystemic shunts (TIPS). (Tsochatzis, E. A., Senzolo et al., 2010)

1.2.5.8 Hepatocellular carcinoma

Liver cirrhosis is one of the leading causes of the occurrence of hepatocellular carcinoma. It occurs most frequently in liver cirrhosis due to hepatitis C, followed by hereditary hemochromatosis. Here, the incidence ranges from 17 to 30%. In patients with cirrhosis due to hepatitis B, the 5-year incidence in Europe is 10%. Hepatocellular carcinoma is even less common in patients with alcohol-related cirrhosis. The incidence here is 8%. It is recommended that patients with liver cirrhosis be screened for hepatocellular carcinoma at least once a year. (Schuppan, Afdhal, 2008) The treatment of hepatocellular carcinoma is complex. Patients with hepatocellular carcinoma are divided into five stages according to the BCLC classification (0, A, B, C, D). (Attwa, El-Etreby, 2015) Depending on the stage, different treatment modalities are recommended, the following diagram describes the various treatment options:

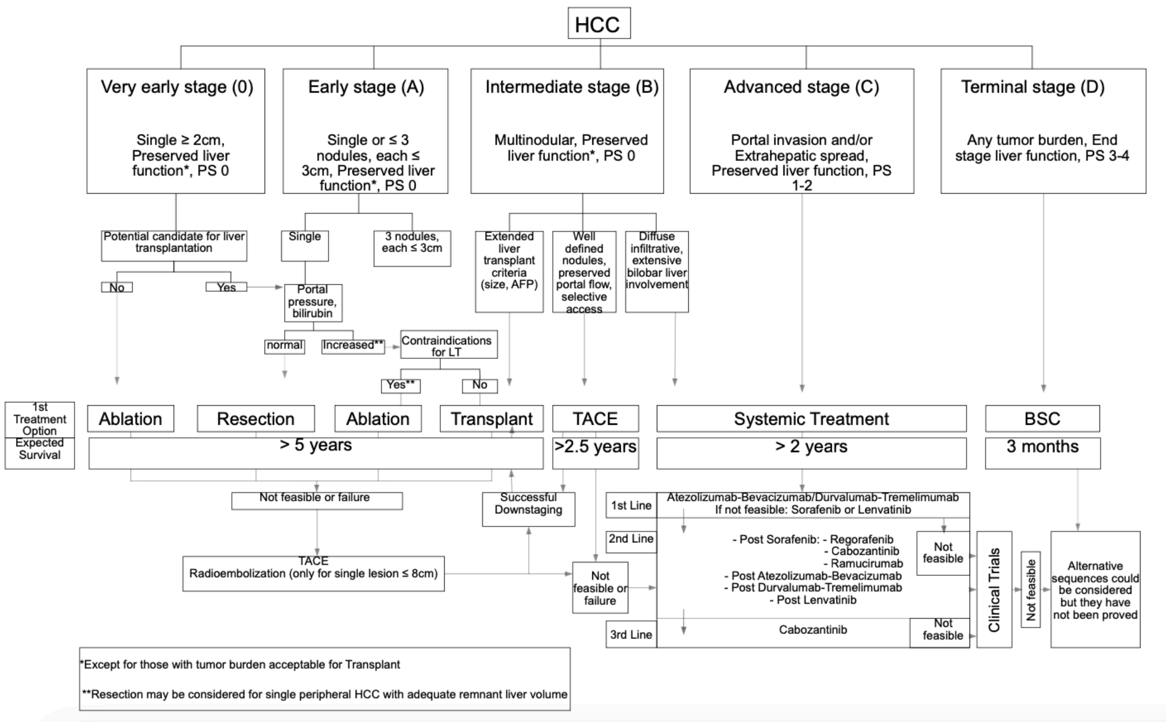

Figure 4: BCLC staging and treatment strategy in 2022. *(Reig, Forner et al., 2022)*

A therapeutic option for hepatocellular carcinoma in patients with liver cirrhosis is liver transplantation. Here, according to the Milan criteria, there should be a maximum of one tumor with a maximum diameter of 5 cm or a maximum of three tumors with diameters up to 3 cm. (Schuppan, Afdhal, 2008)

1.2.6 Treatment

The goals of therapy for liver cirrhosis are to eliminate the trigger of the disease, prevent decompensation, screen for liver carcinoma and esophageal varices, prevent further complications, and, if necessary, consider the possibility of liver transplantation. If complications occur, the priority is to treat them. In case of portal hypertension and consequent variceal formation, prophylaxis against variceal bleeding must be performed. Beta-blockers are used medicinally, and interventional variceal band ligation is possible. It has been shown that non-selective beta-blockers reduce the risk of decompensation in patients with portal hypertension in liver cirrhosis, as this mainly prevents ascites. If ascites occurs, paracentesis must be performed in all patients to exclude spontaneous bacterial peritonitis. Malnutrition also plays a major role in patients with liver cirrhosis. Energy intake should be 35 kcal/kg per day, and protein intake should be between 1.2-1.5 g/kg to counteract sarcopenia and frailty. Alcohol and nicotine should be avoided. In addition, vaccination against the hepatitis A virus, hepatitis B virus, influenza and pneumococcus is recommended.

In the case of decompensation, the treatment of complications is the priority. The final therapy is liver transplantation. (Ginès, Krag et al., 2021)

1.3 Relationship between sarcopenia and liver cirrhosis

Sarcopenia is one of the most common comorbidities associated with liver disease. It is estimated that between 30-70% of individuals with liver cirrhosis also have sarcopenia. The cause of sarcopenia in liver cirrhosis is not yet fully understood. From studies, it can be observed that there is an association between sarcopenia and mortality, poorer outcomes after liver transplantation, longer hospital stays, and other complications. In addition, as mentioned above, the treatment of sarcopenia is complicated. (Bojko, 2019)

1.3.1 Cause of sarcopenia in liver cirrhosis

Liver cirrhosis has a marked influence on the development of sarcopenia. The causes are again very different. In addition to reduced food intake, early satiety due to ascites, increased catabolic state and impaired gastrointestinal passage play a central role. Alcohol, which is often the cause of liver cirrhosis, also influences the development of sarcopenia. (Fox, Stenning et al., 2022)

1.3.1.1 Malnutrition

Patients with liver cirrhosis are often affected by reduced energy and protein intake. Studies show that there is a 13-34% reduction in energy intake. This may be caused by decreased gastric motility and relaxation due to portal hypertension. Ascites, which is often found in liver cirrhosis, additionally leads to a premature feeling of satiety. Furthermore, the senses of taste and smell are impaired in old age, which can also lead to reduced food intake. Patients with liver cirrhosis showed increased levels of the hormone ghrelin, which physiologically stimulates appetite. However, this effect cannot be observed in cirrhosis.(Traub, Reiss et al., 2021) The hepatocytes in liver cirrhosis are no longer able to form, store or degrade glycogen. As a result, the consumption of amino acids for gluconeogenesis increases, and a ketogenic metabolic state occurs, promoting the breakdown of skeletal muscle and reducing fat stores. (Bojko, 2019) To counteract this, the European Society for Enteral and Parenteral Nutrition (ESPEN) recommends an increased energy intake of 35-40 kcal/kg/d and an amino acid intake of 1.2-1.5 g/kg/d. (Fox, Stenning et al., 2022) This can be achieved by eating in the late evening or at night since the switch to ketogenic metabolism occurs mainly at night. (Bojko, 2019)

Furthermore, increased inflammatory markers such as TNF-α lead to nausea and loss of appetite. A disturbance of fat absorption can be promoted by pancreatic insufficiency and reduced bile flow. As a result, fat-soluble vitamins can be absorbed more poorly. (Bojko, 2019) Serum levels of the anorexigenic hormone leptin are also increased in patients with liver cirrhosis. The effect of the increased leptin level is early satiety. (Meyer, Bannert et al., 2020)

1.3.1.2 Hormonal alteration

As mentioned above, testosterone and growth hormone, among others, play an important role in the development of sarcopenia. Growth hormone from the pituitary gland stimulates the production of IGF-1, which is mainly produced in the liver. In liver cirrhosis, this process is impaired due to decreased liver function. This results in a change in the hypothalamic-pituitary axis. This also affects the hypothalamic-pituitary-gonadal axis, which influences testosterone production. Low testosterone levels worsen the prognosis in patients with liver cirrhosis. In addition, the production of steroid hormone-binding globulin increases, resulting in increased testosterone in bound form and thus reduced bioavailability. Another factor in patients with liver cirrhosis that favors the progression of sarcopenia is increased peripheral androgen aromatisation with decreased anabolic effect. (Fox, Stenning et al., 2022)

1.3.1.3 Inflammation

Liver cirrhosis is a chronic process that promotes inflammation and thus leads to the release of cytokines. This is due to an alteration of the gut microbiome with disruption of gut barrier function. TNF-α, IL-1 and IL-6 are increasingly produced as a result of bacterial translocation due to the reduced intestinal barrier and the resulting increased intestinal permeability. (Fox, Stenning et al., 2022) The cytokines lead to increased muscle autophagy via the ubiquitin-proteasome pathway. In addition, they lead to increased resting energy expenditure with an increased requirement for proteins. (Bojko, 2019)

This pro-inflammatory process also has the effect of altering bile acid metabolism. Intestinal bacteria can thus proliferate and lead to a disturbance in the absorption of nutrients, especially fat-soluble vitamins such as vitamin D. The influence on the immune system and the resulting bacterial overgrowth of the intestine can lead to endotoxemia with the risk of bacterial peritonitis. (Fox, Stenning et al., 2022) This is indicated by an increased concentration of bacterial lipopolysaccharides in the blood. (Meyer, Bannert et al., 2020)

1.3.1.4 Intestinal malabsorption and maldigestion

Malabsorption in liver cirrhosis has many different causes. These range from pancreatic insufficiency, cholestasis, and drug-induced diarrhea. Long-term alcohol consumption, which is often causative of cirrhosis, exacerbates the effect of pancreatic insufficiency and leads to decreased nutrient absorption and alteration of the gut microbiome. Cholestasis results in decreased bile in the intestine and increased toxic bile acid in the liver. It is also increased in systemic circulation. Malabsorption of fat and fat-soluble vitamins results from impaired bile acid secretion. A deficiency of fat-soluble vitamins is often found in patients with liver cirrhosis.

Another effect that influences the malabsorption of mainly fat and fat-soluble vitamins is the bacterial overgrowth of the small intestine described above. Patients suffer from diarrhea, abdominal pain and flatulence. (Meyer, Bannert et al., 2020)

1.3.2 Treatment of sarcopenia in liver cirrhosis

The treatment of sarcopenia in patients with liver cirrhosis starts at several points. These include dietary and lifestyle interventions, physical training and appropriate pharmacological therapy. (Dhaliwal, Armstrong, 2020)

In terms of nutrition, it is essential for sarcopenic patients with liver cirrhosis to consume sufficient sources of energy and protein. They should consume 35-40 kcal/kg body weight per day. The protein intake should be 1.2-1.5 g/kg body weight per day. The European Association for the Study of the Liver (EASL) also recommends BCAA supplementation of 0.25 g/kg/d for patients with advanced liver cirrhosis. (Fox, Stenning et al., 2022) These BCAAs include valine, leucine and isoleucine. They act as substrates in energy production and protein synthesis, leading to ammonia detoxification in the muscles. Meta-analyses have shown that BCAA supplementation can increase muscle mass but not muscle strength. However, muscle strength could also be improved with simultaneous physical activity. The effect of Vit-D supplementation and other dietary supplements in sarcopenic patients with liver cirrhosis has not yet been sufficiently investigated. (Ebadi, Burra et al., 2023)

Lifestyle adjustments also appear to be helpful. Alcohol and nicotine should be avoided. Mental well-being and a good quality of sleep are also important. (Dhaliwal, Armstrong, 2020)

Physical training should be performed at a moderate intensity and consist of a combination of aerobic training (3x/week) and resistance exercises (2x/week). (Dhaliwal, Armstrong, 2020) Aerobic training is said to improve muscle capacity, while resistance training is said to improve muscle mass. An optimal dietary supplement for physical exercise to improve skeletal muscles has not yet been found. (Fox, Stenning et al., 2022)

The pharmacological treatment of sarcopenia in patients with liver cirrhosis is part of current research. The focus is on lowering ammonia levels, hormone treatments and micronutrient supplementation including vitamin D. (Dhaliwal, Armstrong, 2020)

Combined therapy with Rifaximin and L-ornithine-L-aspartate increased skeletal muscle mass in hyperammonemia in preclinical models by decreasing intramuscular myostatin and proinflammatory cytokine levels. Rifaximin, in combination with L-carnitine, increased the effect of L-carnitine and thus resulted in less muscle wasting in cirrhotic rats.

Patients with cirrhosis have low levels of anabolic hormones such as IGF-1 and testosterone. An increase in muscle mass in male patients with cirrhosis and low testosterone levels was achieved by intramuscular administration of testosterone. The administration of IGF-1 showed varying results in clinical studies. Thus, the safety and efficacy of hormone replacement therapies in patients with liver cirrhosis need to be further investigated. (Ebadi, Burra et al., 2023)

The myokine myostatin plays a central role in muscle metabolism. Its upregulation leads to muscle atrophy. This process plays an important role in many chronic diseases, including liver cirrhosis. Hyperammonemia or a reduction in IGF-1 or testosterone in cirrhosis leads to activation of myostatin. Therapies with monoclonal antibodies, such as Landogrozumab or Bimagrumab, which act directly on myostatin, are part of current research. (Ebadi, Burra et al., 2023)

It has been shown that a reduction in portal hypertension through a TIPS demonstrably improves nutritional status and muscle mass. Lower blood ammonia levels were also found after the implantation of a TIPS. (Ebadi, Burra et al., 2023) Beta-blockers also reduce portal hypertension and increase intestinal motility, reducing the risk of infection in patients with liver cirrhosis. They have already been used in the treatment of cachexia in patients with heart failure, in some cases with good results. They could, therefore, also be used to treat sarcopenia. (Fox, Stenning et al., 2022)

1.4 Aim of the work

This work addresses the question of whether there is a relationship between mortality and sarcopenia in patients with liver cirrhosis. This question is of enormous importance because if there is a correlation, this has a major impact on patients with liver cirrhosis. Thus, if sarcopenia is diagnosed, it could be counteracted at an early stage with treatment such as a high-protein diet and exercise training. Likewise, screening for sarcopenia or frailty could be performed when liver cirrhosis is diagnosed, and common risk scores could be improved by adding these items. Additionally, whether the presence of sarcopenia favors complications of cirrhosis was reviewed.

2 Material and methods

The data of this retrospective analysis comes from 178 patients of the Department of Gastroenterology and Hepatology of the University Hospital Graz. The research ethics committee of the Medical University of Graz (EK29-280 ex 16/17) and the ethics committees of the participating hospitals approved this study. Furthermore, the study was registered at clinicaltrials.gov (NCT03080129). The data were collected from the hospital information system "openMEDOCS" between May and July 2022. The following persons participated in the data collection: Dr. med. univ. Stefan Fürst, Dr. med. univ. Lukas Gulden, Johannes Woltsche and Jakob Schwarzl.

2.1 Patient Inclusion and Exclusion criteria

The data used for this analysis were obtained from a prospective cohort study of liver cirrhosis patients with sarcopenia. Inclusion criteria include hospitalised men and women aged 18 years and older, who gave written informed consent, with clinical, radiological or histological evidence of liver cirrhosis.

Exclusion criteria are hepatic encephalopathy of grade 2 or higher and/or other cognitive impairments that prevent informed consent. Furthermore, patients with hepatocellular carcinoma stage C and D, according to BCLC, treatment with ursodeoxycholic acid (UDCA) or the intake of probiotics or antibiotics were excluded.

The inclusion criteria for the control group include male and female patients over the age of 18 with written informed consent who presented to the Department of Gastroenterology and Hepatology at the same time. This included patients without liver cirrhosis who were diagnosed with the following diseases: chronic kidney disease, osteoporosis, pancreatitis, hypertension, hypercholesterolemia, hashimoto thyroiditis, diabetes mellitus type 2, thrombocytopenia, chronic obstructive pulmonary disease, portal hypertension, ascites, reflux esophagitis, splenomegaly and appendicitis. Exclusion criteria for the control group are the presence of liver cirrhosis, illnesses that prevent consent and the use of probiotics and/or antibiotics.

2.2 Data collection

The following parameters were considered in the data collection:

- Personal information: date of birth, sex (male/female), age (at time of inclusion), height, weight, BMI
- Date of inclusion, last patient contact (last documented contact in a hospital)
- Date of death and cause of death (if available).

- Liver cirrhosis (yes/no), if liver cirrhosis was present, the cause was ascertained (alcohol, NASH, HCV, others)
- Sarcopenia (no sarcopenia/presarcopenia/sarcopenia (according to the EWGSOP 2010 guidelines))
- Complications of cirrhosis:
  - Ascites: Developed after inclusion (yes/no), date of diagnosis of newly developed ascites, ascites already presents at inclusion (yes/no), renal function impairment with ascites (yes/no), ascites before observation period (yes/no)
  - Hepatic encephalopathy: Developed after inclusion (yes/no), date of diagnosis of new hepatic encephalopathy, severity of newly developed hepatic encephalopathy (West Haven criteria), hepatic encephalopathy already presents at inclusion (yes/no), renal function impairment in hepatic encephalopathy (yes/no), hepatic encephalopathy before observation period (yes/no)
  - Spontaneous bacterial peritonitis: developed after inclusion (yes/no), date of diagnosis of new spontaneous bacterial peritonitis, causative agent of spontaneous bacterial peritonitis, spontaneous bacterial peritonitis already presents at inclusion (yes/no), renal function impairment in spontaneous bacterial peritonitis (yes/no), spontaneous bacterial peritonitis before observation period (yes/no)
  - Jaundice: developed after inclusion (yes/no), date of diagnosis of newly developed jaundice, jaundice already present at inclusion (yes/no), renal function impairment with jaundice (yes/no), jaundice before observation period (yes/no)
  - Gastrointestinal hemorrhage: developed after inclusion (yes/no), date of diagnosis of new-onset gastrointestinal hemorrhage, location of hemorrhage, gastrointestinal hemorrhage already presents at inclusion (yes/no), renal function impairment in gastrointestinal hemorrhage (yes/no), gastrointestinal hemorrhage before observation period (yes/no)
  - Portal vein thrombosis: Developed after inclusion (yes/no), Date of diagnosis of newly developed portal vein thrombosis, Portal vein thrombosis already present at inclusion (yes/no), Renal function impairment with portal vein

thrombosis (yes/no), Portal vein thrombosis before observation period (yes/no))

- Infections: Serious infection (need for hospitalisation and antibiotics) after inclusion (yes/no), date of diagnosis of newly developed infection, focus of infection, infectious pathogen, infection already present at inclusion (yes/no), renal function impairment with infection (yes/no), infection before observation period (yes/no)
- Acute renal failure: developed after inclusion (yes/no), date of diagnosis of new-onset acute renal failure, renal function impairment (GFR < 90ml/min) already present at inclusion (yes/no), cause of acute renal failure, acute renal failure before observation period (yes/no)
- Hepatocellular carcinoma: Developed after inclusion (yes/no), date of initial diagnosis, staging at initial diagnosis (Barcelona Clinic Liver Cancer Staging), hepatocellular carcinoma already presents at inclusion (yes/no), renal function impairment in hepatocellular carcinoma (yes/no), occurrence of recurrence (yes/no).

Acute renal failure is defined by an increase in creatinine of 0.3 mg/dl within 48 hours or greater than 50% from baseline. Subsequently, the collected data were transferred to the program "SPSS" for statistical analysis.

2.3 Statistical data analysis

The statistical data analysis took place with the help of the program “SPSS”. For this purpose, all collected data were first entered into an Excel spreadsheet and then uploaded into the statistical program “SPSS Statistics 28”.

The influence of sarcopenia on the mortality rate in liver cirrhosis patients was analysed using cross-tabulations and the Pearson Chi-square test. The Fisher exact test was used if the requirements for the Pearson Chi-square test were not met. For this purpose, all stages of sarcopenia were first compared with each other, then non-sarcopenic and presarcopenic patients were combined in further analyses due to approximately equal mortality rates and compared with sarcopenic patients. Age and sex were also considered. Kaplan-Meier curves and the Log-Rank test were used to perform survival time analyses.

To examine the influence of sarcopenia on the incidence of complications of liver cirrhosis, cross-tabulations and the Pearson chi-square test were also used to demonstrate possible significance. In all analyses, a p-value less than 0.05 is considered statistically significant.

3 Results

3.1 Demographics of the patient population

The patient cohort comprises a total of 178 patients, 118 of whom have liver cirrhosis and 60 of whom are in the control group. The table below describes the group of patients with liver cirrhosis based on their demographics:

Characteristics	*Cirrhosis group*	*Control group*	*P-values*
Number	118	60	
Male (%); Female (%)	88 (74.6); 30 (25,4)	33 (55); 27 (45)	<0.01
Median age in years (SD)	62.1; (11.2)	57.5; (14.4)	<0.05
***Stages of sarcopenia**:*			
No sarcopenia; (%)	38; (65.5)	20; (34.5)	<0.01
Presarcopenia; (%)	38; (56.7)	29; (43.3)	not significant
Sarcopenia; (%)	24; (68.6)	11; (31.4)	<0.01
Weight in kg; (SD)	80.7; (15.9)	72.2; (15.3)	<0.01
Height in cm; (SD)	172.6; (9.4)	171.05; (8.8)	not significant
BMI; (SD)	27.1; (5)	24.5; (4.2)	<0.01
Child-Pugh-Score			
A; (%)	52; (44.1)	-	
B, (%)	45; (38.1)	-	
C; (%)	21; (17.8)	-	

Table 2: Demographics of the patient population, comparison between patients with liver cirrhosis and the control group

In the entire patient population, 53 patients are considered sarcopenic, 67 patients are presarcopenic, and 58 have no sarcopenia. The following table describes the patient groups according to their sarcopenia stage:

Characteristics	*Sarcopenia*	*Presarcopenia*	*No sarcopenia*	*P-values*
Number; (%)	53	67	58	
Male (%); Female (%)	40 (75.5); 13 (24.5)	46 (68.7); 21 (31.3)	35 (60.3); 23 (39.7)	not significant
Median age in years (SD)	64.8; (10.7)	58; (13.4)	59.5; (12.2)	<0.05
Stages of Cirrhosis				<0.05
Liver cirrhosis; (%)	42; (35.6)	38; (32.2)	38; (32.2)	
Control group; (%)	11; (18.3)	29; (48.3)	20; (33.3)	
Weight in kg; (SD)	76; (17.2)	74.7; (14.5)	83.1; (16.1)	<0.01
Height in cm; (SD)	172.1; (8.1)	174.7; (8.7)	169; (10)	<0.01
BMI; (SD)	25.5; (4.9)	24.4; (3.5)	29; (4.9)	<0.01

Table 3: Demographics of the patient collective based on the sarcopenia stage

3.1.1 Causes of liver cirrhosis

The cause of liver cirrhosis in this patient population varies. Alcohol is the cause of liver cirrhosis in 67 individuals, MASH in 22 individuals, and hepatitis C virus in 19 individuals. The cause is unclear in 10 individuals.

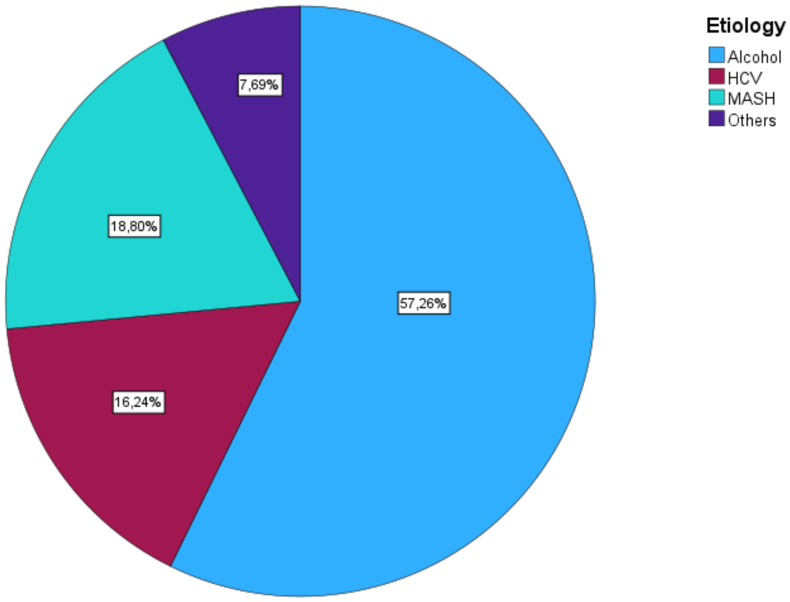

Figure 5: Distribution of the aetiology of liver cirrhosis

3.2 Mortality rates of the entire patient population

It was found that the mortality rate in patients with liver cirrhosis was significantly higher than in the control group (Pearson Chi-square test: $p<0.001$). There is also a significantly longer survival in patients without cirrhosis (Log-Rank test: $p<0.001$)

	No death	*Death*	*Total*
Control group	51 (85%)	9 (15%)	60
cirrhosis	58 (49%)	60 (51%)	118
Total	109	69	178

Table 4: Cross tabulation to show the mortality of liver cirrhosis in the entire patient population

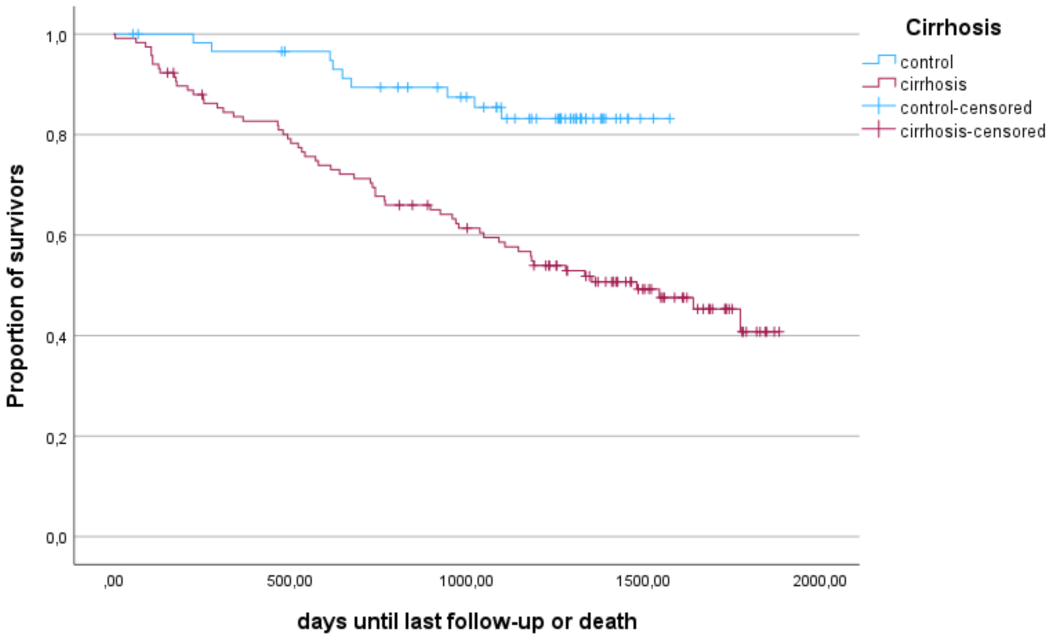

Figure 6: Survival rate between liver cirrhosis patients and the control group

The following cross table shows the mortality of patients depending on their stage of sarcopenia (Pearson Chi-square test: p=0.006)

	No death	*Death*	*Total*
No sarcopenia	41 (71%)	17 (29%)	58
Presarcopenia	45 (67%)	22 (33%)	67
Sarcopenia	23 (43%)	30 (57%)	53
Total	109	69	178

Table 5: Cross table for analyzing mortality depending on the stage of sarcopenia

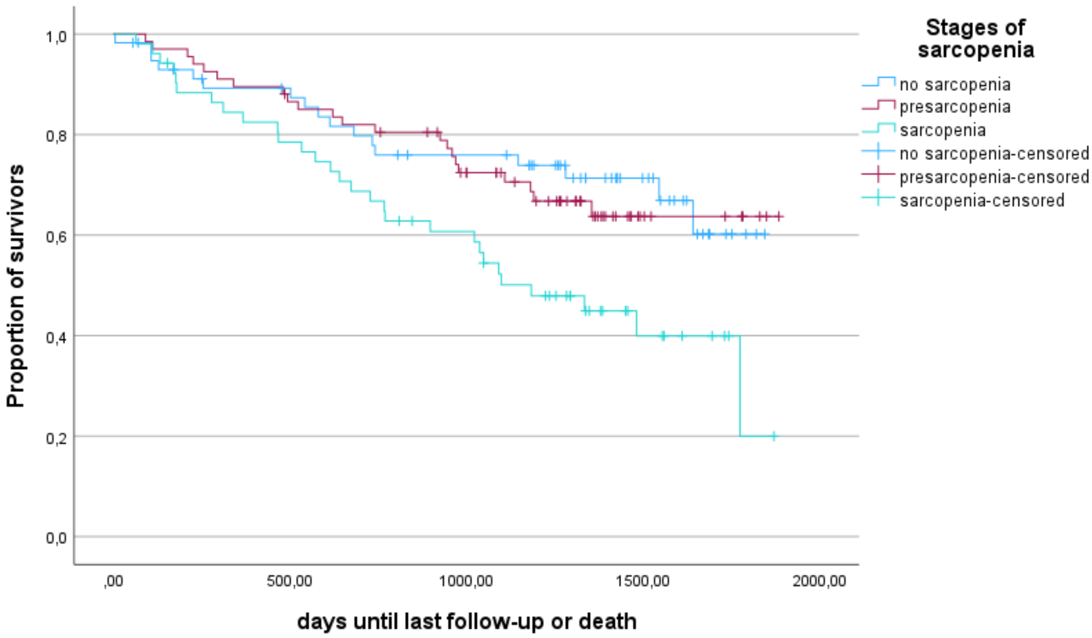

Figure 7: Survival rate of patients depending on their stage of sarcopenia

It has been shown that survival is significantly shorter in patients with sarcopenia (Log-Rank test: p=0.013).

It can be seen that the survival rates of patients without sarcopenia and patients with presarcopenia are approximately the same in the entire cohort.

If patients without sarcopenia and presarcopenic patients are combined and compared with sarcopenic patients, a significant difference in the mortality rate can be observed (Pearson Chi-square test: p=0.001).

	No death	*Death*	*Total*
No sarcopenia + presarcopenia	86 (79%)	23 (21%)	109
Sarcopenia	39 (57%)	30 (43%)	69
Total	125	53	178

Table 6: Cross tabulation to analyse mortality rates between patients without saropenia and presarcopenia compared to sarcopenic patients

The survival time analysis also shows a significant difference in survival time between patients without sarcopenia and presarcopenia compared to patients with sarcopenia in the entire cohort (Log-Rank test: p=0.003):

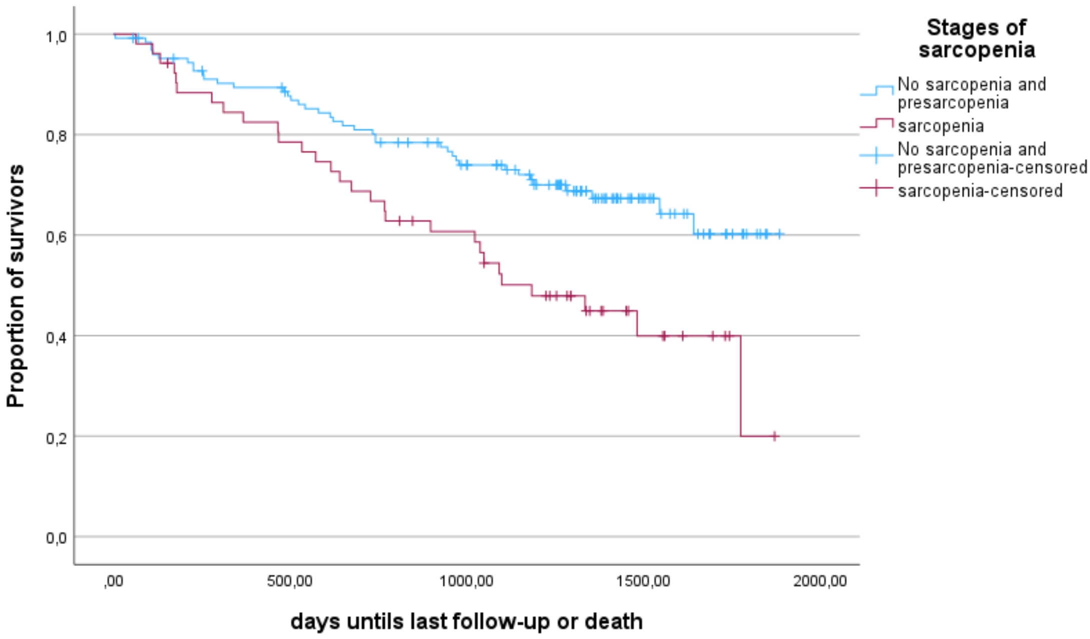

Figure 8: Survival time analysis in patients without sarcopenia and presarcopenia compared to patients with sarcopenia

To determine the influence of sarcopenia on patients without liver cirrhosis, the mortality rate of the control group without and with sarcopenia is shown in the following cross-tabulation. There is a significantly higher mortality rate in patients with sarcopenia (Fisher-exact test: p=0.045).

	No death	Death	Total
No sarcopenia and presarcopenia	44 (90%)	5 (10%)	49
Sarcopenia	7 (64%)	4 (36%)	11
Total	51	9	60

Table 7: Mortality rate of the control group in patients with and without sarcopenia

3.3 Does sarcopenia have an impact on the mortality rate in liver cirrhosis?

In our observation period, 16 out of 38 patients with liver cirrhosis but without sarcopenia, 18 out of 28 patients with presarcopenia and 26 out of 42 patients with sarcopenia died. In absolute figures, this shows an increased mortality rate in patients with sarcopenia.

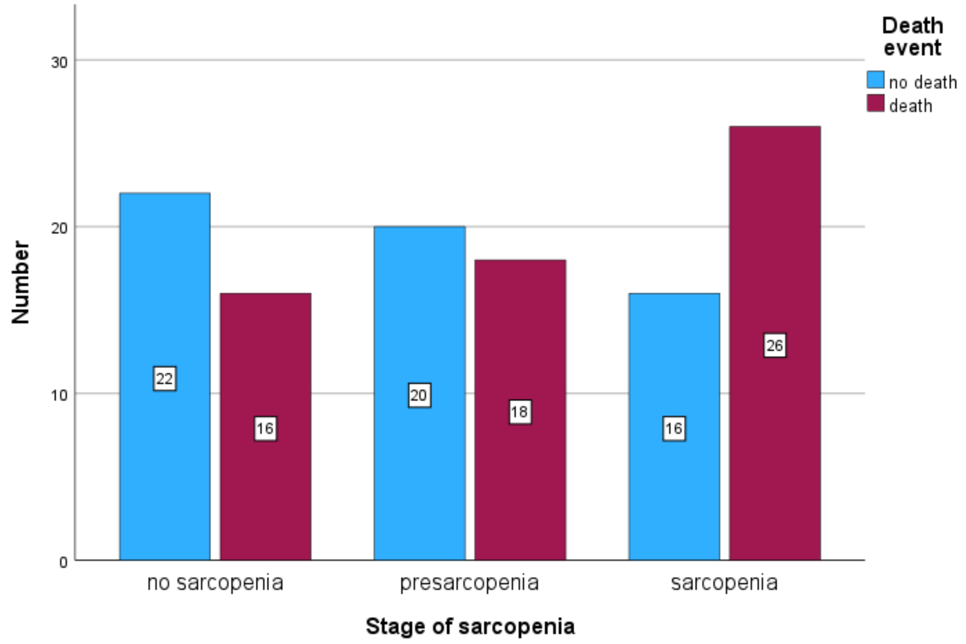

Figure 9: Mortality of liver cirrhosis patients depending on their sarcopenia stage

The following table shows the mortality rates in liver cirrhosis patients depending on the stage of sarcopenia. No significant difference was found (Pearson Chi-square test: p=0.183).

	No death	*Death*	*Total*
No sarcopenia	22 (58%)	16 (42%)	38
Presarcopenia	20 (53%)	18 (47%)	38
Sarcopenia	16 (38%)	26 (62%)	42
Total	58	60	118

Table 8: Mortality rates in patients with liver cirrhosis depending on their stage of sarcopenia

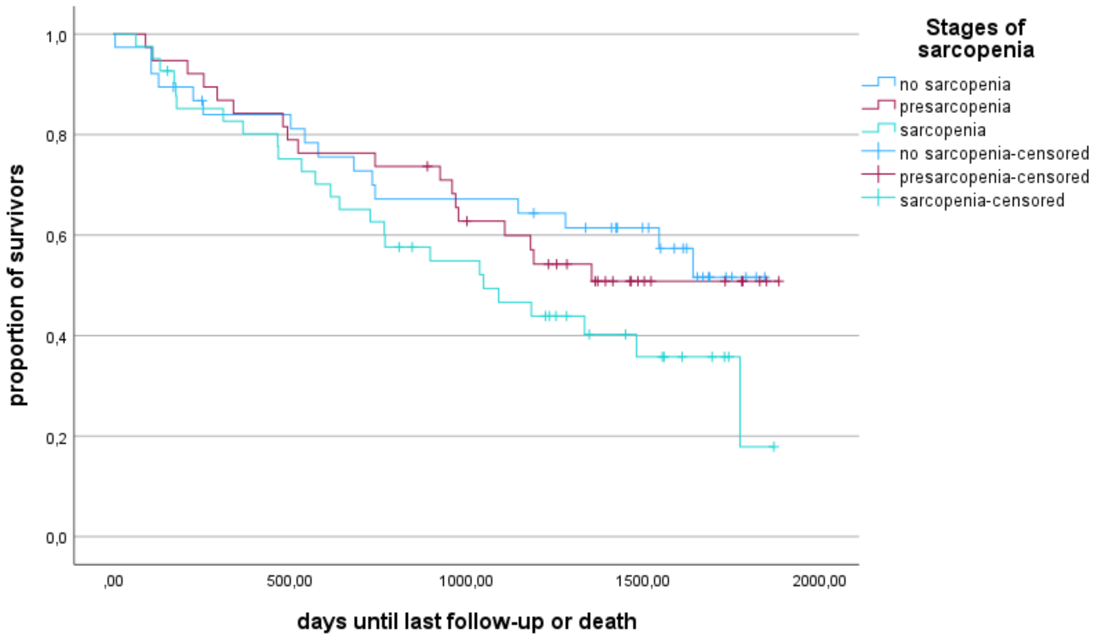

Figure 10: Survival rate of liver cirrhosis patients depending on their stage of sarcopenia

As the survival rate in patients without sarcopenia and patients with presarcopenia is approximately the same, these were combined and compared with sarcopenic patients. No significant difference in mortality was found (Pearson Chi-square test: p=0.074).

	No death	Death	Total
No sarcopenia and presarcopenia	42 (55%)	34 (45%)	76
Sarcopenia	16 (38%)	26 (62%)	42
Total	58	60	118

Figure 11: Mortality rate between patients without sarcopenia and presarcopenia compared with sarcopenic patients

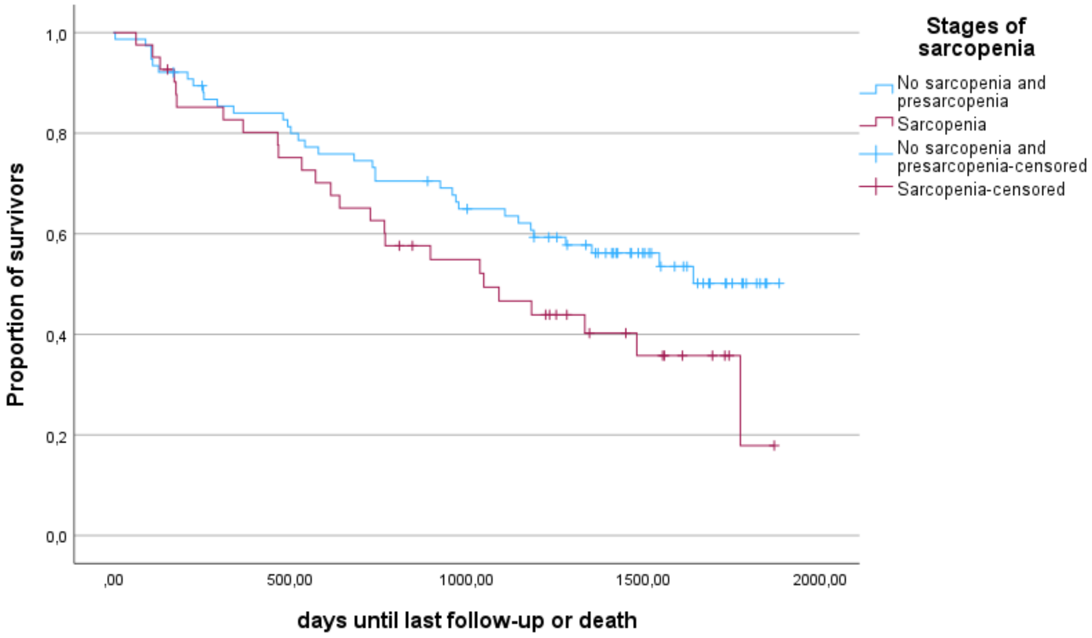

Figure 12: Survival rate in liver cirrhosis patients between patients without sarcopenia and presarcopenia compared to patients with sarcopenia

The survival time analysis also shows no significant difference (Log-Rank test: p=0.069).

3.4 The influence of age and sex on the mortality rate

The following cross-tabulation shows the mortality of men with liver cirrhosis depending on their sarcopenia stage. There is no significant difference in the mortality rate for men (Pearson Chi-square test: p=0.057).

	No death	Death	Total
No sarcopenia and presarcopenia	28 (70%)	12 (30%)	40
Sarcopenia	24 (50%)	24 (50%)	48
Total	52	36	88

Table 9: Mortality rate of male patients with liver cirrhosis as a function of sarcopenia

The following table shows mortality in women with liver cirrhosis. No significant difference was found here either (Fisher-exact test: p=1.000).

	No death	Death	Total
No sarcopenia and presarcopenia	14 (78%)	4 (22%)	18
Sarcopenia	10 (83%)	2 (17%)	12
Total	24	6	30

Table 10: Mortality rate of female patients with liver cirrhosis as a function of sarcopenia

In order to examine the influence of age on mortality in patients with liver cirrhosis depending on the stage of sarcopenia, the patients were divided into two age groups (under 65 years and over 65 years).

In cirrhotic patients under 65 years of age, no significant difference in the mortality rate depending on sarcopenia was found (Pearson Chi-square test: p=0.605).

	No death	*Death*	*Total*
No sarcopenia and presarcopenia	27 (69%)	12 (31%)	39
Sarcopenia	21 (75%)	7 (25%)	28
Total	48	19	67

Table 11: Mortality rate of patients under 65 years with liver cirrhosis as a function of sarcopenia

In cirrhotic patients over 65 years of age, significantly more patients with sarcopenia than without sarcopenia died (Fisher-exact test: p=0.010).

	No death	*Death*	*Total*
No sarcopenia and presarcopenia	15 (79%)	4 (21%)	19
Sarcopenia	13 (41%)	19 (59%)	32
Total	28	23	51

Table 12: Mortality rate of patients over 65 years with liver cirrhosis as a function of sarcopenia

3.5 Does sarcopenia affect potential complications of liver cirrhosis?

A comparison was made to determine whether there was a difference in the incidence of complications in patients with cirrhosis and with or without sarcopenia. For this reason, cirrhosis patients without sarcopenia and presarcopenia were combined and compared with sarcopenic patients.

3.5.1 Ascites

Overall, ascites occurred 37 of 76 times in individuals without sarcopenia during the observation period, whereas it occurred 18 of 42 times in individuals with sarcopenia. Therefore, it can be seen that sarcopenia has no influence on the occurrence of ascites (Pearson Chi-square test: p=0.543). There is also no influence of sex on the occurrence of ascites (male: 48%; female: 43%; Pearson Chi-square test: p=0.677).

	No Ascites	*Ascites*	*Total*
No sarcopenia and presarcopenia	39 (51%)	37 (49%)	76
Sarcopenia	24 (57%)	18 (43%)	42
Total	63	55	118

Table 13: Cross tabulation of the frequency of ascites in liver cirrhosis between patients with and without sarcopenia

3.5.2 Hepatic Encephalopathy

In the group of patients with liver cirrhosis but without sarcopenia, 25 out of 76 subjects developed hepatic encephalopathy, while in individuals with sarcopenia, 5 out of 42 subjects had hepatic encephalopathy. This shows that hepatic encephalopathy is significantly less common in patients with sarcopenia (Pearson Chi-square test: p=0.012). There is no influence of sex on the occurrence of hepatic encephalopathy (male: 23%; female: 33%; Pearson Chi-square test: p=0.249)

	No HE	*HE*	*Total*
No sarcopenia and presarcopenia	51 (67%)	25 (33%)	76
Sarcopenia	37 (89%)	5 (11%)	42
Total	88	30	118

Table 14: Cross tabulation of the frequency of hepatic encephalopathy in liver cirrhosis between patients with and without sarcopenia

3.5.3 Jaundice

Cirrhotic patients without sarcopenia developed jaundice in 36 out of 76 cases, while individuals with sarcopenia developed jaundice 19 out of 42 times. This suggests that in this patient population, sarcopenia does not affect the incidence of jaundice (Pearson Chi-square test: p=0.824). Again, sex does not make a significant difference (male: 43%; female: 57%; Pearson Chi-square test: p=0.201).

	No Jaundice	*Jaundice*	*Total*
No sarcopenia and presarcopenia	40 (53%)	36 (47%)	76
Sarcopenia	23 (55%)	19 (45%)	42
Total	63	55	118

Table 15: Cross tabulation of the frequency of jaundice in liver cirrhosis between patients with and without sarcopenia

3.5.4 Gastrointestinal hemorrhage

Gastrointestinal bleeding occurred at least once in 18 of 76 subjects without sarcopenia and 6 of 42 subjects with sarcopenia (Pearson Chi-square test: p=0.225). However, it is striking that an above-average number of women (10 out of 20, 50%) were affected. In contrast, approximately 18% of men were impacted. It was found that significantly more women were affected (male: 16%; female: 33%; Pearson Chi-square test: p=0.041).

	No gastrointestinal bleeding	*Gastrointestinal bleeding*	*Total*
No sarcopenia and presarcopenia	58 (76%)	18 (24%)	76
Sarcopenia	36 (86%)	6 (14%)	42
Total	94	24	118

Table 16: Cross tabulation of the frequency of gastrointestinal hemorrhage in liver cirrhosis between patients with and without sarcopenia

3.5.5 Spontaneous bacterial peritonitis

4 out of 42 persons with sarcopenia suffered from spontaneous bacterial peritonitis at least once, while in the group with patients without sarcopenia, it was 4 patients out of 76. There is no significant difference in occurrence (Fisher-exact test: p=0.448). It is noticeable that of the total of 8 people, 7 were male (male: 8%; female: 3%; Fisher exact test: p=0.677).

	No SBP	*SBP*	*Total*

No sarcopenia and presarcopenia	72 (95%)	4 (5%)	76
Sarcopenia	38 (90%)	4 (10%)	42
Total	110	8	118

Table 17: Cross tabulation of the frequency of spontaneous bacterial peritonitis in liver cirrhosis between patients with and without sarcopenia

3.5.6 Portal vein thrombosis

Overall, it is notable here that portal vein thrombosis occurred primarily in sarcopenic patients. In 76 individuals without sarcopenia, there were 3 cases of portal vein thrombosis, while in patients with sarcopenia, there were 7 cases in 42 participants. There is, thus, a significant association between the occurrence of PVT and the presence of sarcopenia (Fisher exact test: p=0.035). Also noticeable is that 9 out of 10 portal vein thromboses occurred in men (male: 10%; female: 3%; Fischer-exact test: p=0.448).

	No portal vein thrombosis	*Portal vein thrombosis*	*Total*
No sarcopenia and presarcopenia	73 (96%)	3 (4%)	76
Sarcopenia	35 (83%)	7 (17%)	42
Total	108	10	118

Table 18: Cross tabulation of the frequency of portal vein thrombosis in liver cirrhosis between patients with and without sarcopenia

3.5.7 Infection

Infections occurred frequently in the patient population, with 72 individuals (61%) having an infection at least once. Pneumonia and urinary tract infections were the most common. 44 of 76 persons without sarcopenia and 28 of 42 patients with sarcopenia had an infection at least once. Thus, there was no significant difference (Pearson Chi-square test: p=0.350). Also, the sex of the patients does not play a role in the occurrence of an infection (male: 61%; female: 60%; Pearson Chi-square test: p=0.895).

	No infection	*Infection*	*Total*
No sarcopenia and presarcopenia	32 (42%)	44 (58%)	76
Sarcopenia	14 (33%)	28 (67%)	42
Total	46	72	118

Table 19: Cross tabulation of the frequency of infection in liver cirrhosis between patients with and without sarcopenia

3.5.8 Acute kidney injury

Acute kidney injury occurred in 51 of 76 subjects without sarcopenia, whereas 24 of 42 patients with sarcopenia were affected. Thus, in this patient population, sarcopenia did not influence the occurrence of acute kidney injury (Pearson Chi-square test: p=0.282). Also, no differences can be found between men and women (male: 64%; female: 63%; Pearson Chi-square test: p=0.976).

	No acute kidney injury	*Acute kidney injury*	*Total*
No Sarcopenia and presarcopenia	25 (33%)	51 (67%)	76
Sarcopenia	18 (43%)	24 (57%)	42
Total	43	75	118

Table 20: Cross tabulation of the frequency of acute kidney injury in liver cirrhosis between patients with and without sarcopenia

3.5.9 Hepatocellular carcinoma

In the group of patients without sarcopenia, one person developed hepatocellular carcinoma (HCC), while in the group with sarcopenia, it was 2 persons. Due to the low number of cases, a statistical analysis is not used here.

	No HCC	*HCC*	*Total*
No Sarcopenia and presarcopenia	75 (99%)	1 (1%)	76
Sarcopenia	40 (95%)	2 (5%)	42
Total	115	3	118

Table 21: Cross tabulation of the frequency of hepatocellular carcinoma in liver cirrhosis between patients with and without sarcopenia

3.5.10 Complications in total patient collective

The frequency of complications was also reviewed for the entire patient population. Thus, all 178 patients are now analysed. Patients without sarcopenia and pre-sarcopenia together were compared against sarcopenic patients.

A cross-tabulation and Pearson chi-square test were performed for the following variables: Ascites (Pearson Chi-square test: p=0.171), hepatic encephalopathy (Pearson Chi-square test: p=0.163), spontaneous bacterial peritonitis (Fisher exact test: p=0.240), jaundice (Pearson Chi-square test: p=0.152), gastrointestinal hemorrhage (Pearson Chi-square test: p=0.834), portal vein thrombosis (Fisher exact test: p=0.003; OR=7.230; 1.837-28.458), infection (Pearson Chi-square test: p=0.020; OR=2.169; 1.123-4.191), acute kidney injury (Pearson Chi-square test: p=0.280), and hepatocellular carcinoma (Fisher exact test: p=0.211).

Thus, there is a significant difference in the incidence of portal vein thrombosis and infection complications between patients with and without sarcopenia.

In addition, the control group (patients without liver cirrhosis) is checked for the occurrence of complications. The results are as follows: Ascites (Pearson Chi-square test: p=0.002), hepatic encephalopathy (Fisher exact test: 0.183), jaundice (Fisher exact test: p=0.039), gastrointestinal bleeding (Fisher exact test: p=0. 183), portal vein thrombosis (Fisher exact test: p=0.183), infections (Pearson Chi-square test: p=0.083) and AKI (Fisher exact test: p=0.031).

This showed that ascites, jaundice and AKI occurred more frequently in patients without liver cirrhosis but with sarcopenia.

4 Discussion.

The research question addressed in this thesis is: Does sarcopenia influence mortality in patients with liver cirrhosis?

In this study, we were able to show that mortality in the entire patient group was significantly increased by liver cirrhosis ($p<0.001$). The diagnosis of "sarcopenia" also had a significant influence on mortality in the overall collective ($p=0.001$) and on the survival of patients without liver cirrhosis (control group) ($p=0.045$).

However, in the liver cirrhosis group, only a trend towards higher mortality could be found in patients with sarcopenia ($p=0.074$). Likewise, no significant difference in the mortality rate was found between liver cirrhosis patients with sarcopenia and without sarcopenia, divided into both sexes. Nevertheless, a significant increase in mortality due to sarcopenia was observed in cirrhotic patients over the age of 65 years ($p=0.010$).

Furthermore, we investigated whether complications of liver cirrhosis were significantly more frequent in liver cirrhosis patients with sarcopenia. As a result, it was shown that portal vein thrombosis ($p=0.035$) occurs significantly more frequently in liver cirrhosis patients with sarcopenia than in patients without sarcopenia. In addition, gastrointestinal bleeding occurred significantly more frequently in women ($p=0.041$), but overall, there was no significant difference in frequency. However, contrary to expectations, hepatic encephalopathy was significantly less common in patients with sarcopenia than in patients without sarcopenia ($p=0.012$). Within the patient collective, it could be shown that portal vein thrombosis ($p=0.001$) and infections ($p=0.020$) occurred significantly more often in sarcopenic patients than in non-sarcopenic patients.

Several studies have already investigated the association between sarcopenia and liver cirrhosis. For instance, Carey, Lai et al. studied mortality in 396 patients who were on the waiting list for liver transplantation. The most common cause of cirrhosis was HCV, followed by alcohol and MASH. The median follow-up was 8.8 months, and 112 patients died within the waiting period. However, among the patients who died, it was shown that they had a significantly lower skeletal muscle index (SMI) compared with those who survived (45.6 cm^2/m^2 vs. 48.5 cm^2/m^2; <0.001). Cutoff points at which there is a significant difference in survival are 50 cm^2/m^2 in men and 39 cm^2/m^2 in women. They also showed that men with sarcopenia had a 70% increased risk, and women with sarcopenia had a 182% increased risk of dying within the waiting list period. (Carey, Lai et al., 2017)

Van Vugt, Buettner et al. looked at the relationship between sarcopenia and hospital costs with patients on the waiting list for liver transplantation. They showed that the average cost of liver transplantation in patients with sarcopenia was 11,294 euros, while the average cost in patients without sarcopenia was 6,878 euros (p=0.008). Thus, they showed that an improvement in skeletal muscle mass could reduce hospital costs. This cost difference would also warrant further research on the treatment of sarcopenia in liver cirrhosis. (van Vugt, Buettner et al., 2018)

Montano-Loza, Meza-Junco et al. studied the effects of sarcopenia on time after a liver transplantation. Their study included 248 patients with an average age of 55 years, of whom 169 were male (68%). The most common cause of cirrhosis was HCV (51%), followed by alcohol (19%), autoimmune liver disease (15%), HBV (8%), and other aetiologies (7%). In total, 112 individuals (45%) were sarcopenic. The average life span after liver transplantation was 117 (SD: 17) months in sarcopenic patients and 146 (SD: 20) months in non-sarcopenic patients (p=0.4). In addition, they demonstrated that the average hospitalisation time was 40 (SD: 4) days with sarcopenic patients after liver transplantation and 23 (SD: 3) days with non-sarcopenic patients (p=0.005). Additionally, sarcopenic patients had a bacterial infection within 90 days after liver transplantation in 26% of cases and non-sarcopenic patients in 15% of cases (p=0.04). However, higher mortality was not observed after liver transplantation. (Montano-Loza, Meza-Junco et al., 2014)

Kim, Kang et al. conducted a literature search on the influence of sarcopenia on liver cirrhosis in relation to mortality, complications and hospital duration, in which 20 relevant studies were filtered out of the original 388 studies. As a result, a total of 4,037 patients who were either awaiting a liver transplant or already undergoing one were analysed. The average age of the study participants was 54.78 years, and the prevalence of sarcopenia was 48.1% overall, 61.6% in men and 36% in women. They were able to show that the risk of dying with sarcopenia was 3.23 times higher than in the absence of sarcopenia. They also showed that mortality was 22% lower with higher muscle mass. A longer hospital stay and higher infection rates (a higher muscle mass reduces the risk by 47%) were also found in patients with sarcopenia. (Kim, Kang et al., 2017)

Tantai, Liu et al. were also able to show in a literature search with a total of 6,965 patients that sarcopenia has an influence on mortality in patients with liver cirrhosis. The 1-, 3-, and 5-year survival rates of patients with sarcopenia were 76.6%, 64.3%, and 45.3%, respectively, while with the absence of sarcopenia, these rates were 93.4%, 82.0%, and 74.2% (p <0.001). They also noted that the risk of death was increased in patients with liver cirrhosis (HR 2.30). (Tantai, Liu et al., 2022)

Other studies have also analysed the influence of sarcopenia on the frequency of complications of liver cirrhosis. For example, in a prospective study, Topan, Sporea et al. showed the frequency of complications of liver cirrhosis in sarcopenic patients. For this purpose, 201 patients (63.2% male) with liver cirrhosis, with an average age of 61.64 years, were included in the study. 57.2% of the subjects also had sarcopenia classified according to EWGSOP2. As a result, they were able to show that there is a significant influence of sarcopenia on the incidence of portal hypertension, hepatocellular carcinoma and infections. They also found that sarcopenia increased the risk of ascites (3.78 times), urinary tract infections (4.83 times), and spontaneous peritonitis (2.49 times). The 6-month and 1-year survival rates in patients with sarcopenia were also significantly reduced ($p<0.0001$). In addition, pulmonary infections and upper gastrointestinal bleeding were higher in patients with sarcopenia compared to patients without sarcopenia, but no significance was found. (Topan, Sporea et al., 2021)

Chang, Chen et al. showed in a meta-analysis, in which six studies with a total of 1,795 patients were included, that sarcopenia is associated with an increased risk of hepatic encephalopathy (OR: 2.74, 95% CI: 1.87-4.01). However, an increased serum ammonia level was not found in patients with sarcopenia. One reason could be that the ammonia level was only reported in two of the total six studies, and therefore, the number of patients analysed was lower. (Chang, Chen et al., 2019)

Xiao, Dai et al. showed in a study of 271 patients with liver cirrhosis (hepatitis B as the leading cause), 75 of whom were sarcopenic, that sarcopenia leads to higher hospital costs, an increased risk of spontaneous bacterial peritonitis, ascites, hepatic encephalopathy and electrolyte disturbances ($p <0.05$). (Xiao, Dai et al., 2023)

The following table summarises the results of the above studies:

Author/Year	Study Population	Outcome Associated with Sarcopenia
Carey et al., 2017	396 patients, median age: 58 years, 70% male, North America	Men: 70% increased risk of death Women: 182% increased risk of death
Van Vugt et al., 2018	224 patients, median age: 56 years, 66,5% male	Increased costs for the healthcare system

Montano-Loza et al., 2014	248 patients, median age of transplantation: 55 years, 68% male, Canada	Longer hospital stay and increased bacterial infections after liver transplantation
Kim et al., 2017	4,037 patients, median age: 54.78 years, Korea, Japan, America, Italy, France, Canada	Increased risk of death (3.23 times), longer hospital stays, higher infection rates
Tantai et al., 2022	6,965 patients, median age: 50-68.3 years among the included studies, Asian and non-Asian	Increased 1-, 3-, and 5-year mortality rates
Topan et al., 2021	201 patients, median age: 61.65 years, 63.2% male, Romania	Increased risk for portal hypertension, hepatocellular carcinoma, infections, ascites, urinary tract infections and spontaneous peritonitis Reduced survival rates
Chang et al., 2019	1,795 patients, median age: 56-69 years among the included studies, 68% male	Increased risk of hepatic encephalopathy
Xiao et al., 2023	271 patients, 67.5% male, China	Higher hospital costs, increased risk of spontaneous bacterial peritonitis, ascites, hepatic encephalopathy and electrolyte disturbances

Table 22: Various studies analysing the influence of sarcopenia on liver cirrhosis and their results

One explanation for the more frequent occurrence of infections in the context of sarcopenia could be a low-grade chronic inflammation associated with age, which is referred to as inflammatory ageing. With age, there is a decreased adaptability of the innate immune system, characterised by increased levels of proinflammatory cytokines, such as IL-6, TNF-α, and CRP. In addition, the disruption of the skeletal muscle leads to chronic inflammatory reactions, which have a negative effect on the muscle and lead to a vicious cycle. (Pan, Xie et al., 2021)

The cause of the more frequent occurrence of portal vein thrombosis in patients with sarcopenia is still poorly understood. One reason could be that sarcopenia and reduced muscle mass are associated with conditions (e.g., tumor diseases) that promote thrombus formation. Another factor could be that patients with sarcopenia often exhibit low physical activity, bedriddenness, and immobility, which are also factors that promote thrombus formation. (Karakousis, Gourgoulianis et al., 2024)

Another important question is whether sarcopenia influences the outcome after liver transplantation.

Kalafateli, Mantzoukis et al. investigated this question in 2017. In their study of 232 patients (mean age: 53 years, 162 (69.8%) male) after liver transplantation, they assessed the infection rates, need for intensive care, need for ventilation, and 1-year mortality. Within the study, the leading cause of liver cirrhosis was hepatitis C (29.3%), followed by alcohol (23.7%). Overall, 93% of patients were still alive one year after liver transplantation. Additionally, the study found that infections were significantly more common after transplantation due to malnutrition (OR: 6.55; 95% CI: 1.99-21.5). They also analysed 1-year mortality, finding that sarcopenia (identified by low L3-psoas muscle index) had a significant impact (OR: 0.996; 95% CI: 0.992-0.999). In addition, the age and sex of the patients and their nutritional status (determined using the Royal Free Hospital Global Assessment) had no influence. This showed that sarcopenia has an impact on the prognosis after liver transplantation. (Kalafateli, Mantzoukis et al., 2017)

Kumar, Benjamin et al. also dealt with this topic in a study of 115 recipients of liver transplantation. They defined sarcopenia in men with an SMI (cm^2/m^2) of < 52.4 and in women < 38.5; 47% of the female patients had sarcopenia. The most common cause of liver cirrhosis, with 53%, was alcohol. Sarcopenia also had a significant influence on postoperative complications such as sepsis (p=0.001), neurological complications (p=0.04), duration of intensive care (p=0.024), and time to ambulation (p=0.001). Nevertheless, the two groups' 90-day mortality was similar (p=0.63). However, it was noted that preoperative sarcopenia also had a significant impact on the prevalence of acute kidney injury and intraoperative blood loss. (Kumar, Benjamin et al., 2020)

These studies all show that sarcopenia influences the prognosis of patients before and after liver transplantation. Therefore, it is necessary to identify sarcopenia in liver cirrhosis patients and to intervene at an early stage.

The Model of End Stage Liver Disease Score (MELDNa score) is most commonly used to determine the prognosis of patients with liver cirrhosis. Using total bilirubin, creatine, INR and sodium values, the risk of death within the first 90 days postoperatively is calculated very accurately. However, the score does not consider the influence of muscle wasting and malnutrition, which is often found in patients with end-stage liver cirrhosis. For this reason, Lai, Covinsky et al. developed a frailty index as part of a study, which included grip strength, balance and stool position. In a study of 536 liver cirrhosis patients, they used the scores to predict a 3-month mortality rate on the waiting list. The concordance statistic was 0.8 for the MELDNa score and 0.76 for the frailty index. However, when the two scores were combined, a value of 0.82 was found, meaning the predictive power of the score for mortality on a waiting list could be improved. (Lai, Covinsky et al., 2017)

4.1.1 Limitation and Conclusion

One limitation of this study is the relatively small number of study participants. Thus, it was often impossible to determine a significant influence in several analyses despite the difference in absolute numbers due to the small number of participants. A further limiting factor was the retrospective data collection via the electronic patient records "openMEDOCS", as the presence of these complications is very dependent on the examiners at the time and their documentation, particularly in the analysis of complications under the points hepatic encephalopathy and ascites. Therefore, the data was collected in routine clinical practice and not systemically.

Nevertheless, this study showed that hepatic encephalopathy occurs significantly less frequently in patients with sarcopenia, which contradicts current studies. However, this result could be due to documentation bias in the data collection.

In summary, no significant difference in mortality in liver cirrhosis was found in this study between patients with and without sarcopenia. However, differences could be shown in absolute numbers and certain patient groups. Therefore, it is important to investigate further the influence of sarcopenia on liver cirrhosis in larger studies with more participants. Malnutrition and sarcopenia should also be implemented in existing risk scores for the mortality of liver cirrhosis patients on the waiting list for transplantation. This will ensure early diagnosis of sarcopenia, allowing treatment to be initiated. Furthermore, as it has been shown that non-sarcopenic and presarcopenic patients have similar mortality rates, presarcopenic patients should already be identified and treated to prevent further progression of the disease. As the risk of complications after liver transplantation is also increased in patients with sarcopenia, patients who are on the waiting list for a liver transplant should be screened for sarcopenia preoperatively and treated if necessary.

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