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# Asam amino rantai cabang terhadap status gizi, dan perubahan metabolik pada penyakit hati: Sebuah tinjauan sistematis

*Amino acids on nutritional status and metabolic changes in liver disease: A systematic review*

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Poltekkes Kemenkes Aceh

Carissa Wityadarda[1*], Ester Hanantika Immanuella[2], Fernando Diaz Ndopo[3], Teresa Ester[4], Sarah Damayanti[5], Yuli Berliana[6]

## Abstract

**Background:** Liver diseases such as non-alcoholic fatty liver disease (NAFLD) and cirrhosis are influenced by factors like viral infections, alcohol, immune dysfunction, genetic predisposition, and metabolic factors. Branched-chain amino acids (BCAAs)—leucine, isoleucine, and valine—are vital for protein metabolism and liver function. The role of BCAAs in liver disease and metabolic changes requires further study.
**Objectives:** To evaluate the role of BCAAs in nutritional status and metabolic changes in liver disease through a systematic review.
**Methods:** A systematic review was conducted following the PRISMA protocol. Literature was searched on Google Scholar for publications from 2019 to 2024. Studies were selected based on inclusion and exclusion criteria. Descriptive analysis summarized the findings, and statistical tests evaluated the relationship between BCAA consumption or supplementation and liver disease progression.
**Results:** Eight studies met the inclusion criteria. High BCAA consumption was associated with an increased risk of NAFLD (OR = 1,32, p < 0,001). In contrast, BCAA supplementation improved MELD and CP scores in cirrhotic patients. Elevated BCAA levels were also linked to a higher risk of type 2 diabetes (OR = 1,60, 95% CI = 1,14-2,23, p = 0,006).
**Conclusions:** BCAA supplementation may help slow cirrhosis progression and improve sarcopenia and liver function. However, its use should be tailored to avoid adverse effects. More research is needed to explore long-term effects on liver disease.

**Keywords**
Branched-chain amino acids, nutritional status, obesity, and liver

## Abstrak

**Latar belakang:** Penyakit hati seperti non-alcoholic fatty liver disease (NAFLD) dan sirosis dipengaruhi oleh berbagai faktor, termasuk infeksi virus, konsumsi alkohol, disfungsi imun, predisposisi genetik, dan faktor metabolik. BCAA (leusin, isoleusin, dan valin) merupakan nutrisi penting yang berperan dalam metabolisme protein dan fungsi hati. Peran BCAA dalam status gizi dan perubahan metabolik pada penyakit hati masih memerlukan kajian lebih lanjut.
**Tujuan:** Penelitian ini bertujuan untuk mengevaluasi peran BCAA dalam status gizi serta dampaknya terhadap perubahan metabolik pada penyakit hati melalui tinjauan sistematis.
**Metode:** Tinjauan sistematis dilakukan dengan mengikuti protokol PRISMA. Pencarian literatur dilakukan melalui Google Scholar untuk publikasi tahun 2019 hingga 2024. Studi dipilih berdasarkan kriteria inklusi dan eksklusi. Analisis deskriptif digunakan untuk merangkum temuan, dan uji statistik dilakukan untuk mengevaluasi hubungan antara konsumsi atau suplementasi BCAA dan perkembangan penyakit hati

[1] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: carissaadriana92@gmail.com
[2] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: esterhana.2608@gmail.com
[3] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: fernandodiaz149a@gmail.com
[4] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: teresaesk247@gmail.com
[5] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: siregarsarah1234@gmail.com
[6] Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: yuliberlianasimanjuntak20@gmail.com

**Penulis Koresponding**
**Carissa Wityadarda**: Program Studi Gizi, Fakultas Ilmu Kesehatan, Universitas Santo Borromeus, Provinsi Jawa Barat, Indonesia. E-mail: carissaadriana92@gmail.com

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**Hasil:** Delapan artikel memenuhi kriteria inklusi. Asupan BCAA yang tinggi dikaitkan dengan peningkatan risiko NAFLD (OR = 1,32, p < 0,001). Sebaliknya, suplementasi BCAA ditemukan meningkatkan skor MELD dan CP pada pasien sirosis. Kadar BCAA yang tinggi juga dikaitkan dengan peningkatan risiko diabetes tipe 2 (OR = 1,60, 95% CI = 1,14–2,23, p = 0,006).
**Kesimpulan:** Suplementasi BCAA dapat memperlambat progresi sirosis, meningkatkan fungsi otot, dan fungsi hati. Namun, penggunaannya harus disesuaikan untuk menghindari efek samping. Penelitian lebih lanjut diperlukan untuk memahami efek jangka panjang BCAA pada penyakit hati.

**Kata Kunci**
Asam amino rantai cabang, status gizi, obesitas, dan hati

## Introduction

Liver diseases, including hepatitis, cirrhosis, and liver cancer, are among the primary contributors to global morbidity and mortality due to viral infections, alcohol consumption, and metabolic conditions such as nonalcoholic fatty liver disease (NAFLD) (Devarbhavi et al., 2023). NAFLD affects 25% of the world's population and is the leading cause of chronic liver disease prevalent in several countries (Younossi et al., 2023). Obesity and insulin resistance are key contributors to its development, which may progress into hepatocellular carcinoma (HCC), cirrhosis, and fibrosis (HCC) (Guo et al., 2022).

Additionally. Obesity is associated with alterations in branched- chain amino acids (BCAAs) metabolism, which contribute to metabolic dysfunction and liver disease progression (Lischka et al., 2021) Liver cirrhosis is characterized by progressive fibrosis, which leads to severe complications such as portal hypertension, ascites, and hepatic encephalopathy (Silaban et al., 2020). The WHO reports that 310,000 deaths from cirrhosis occur each year, making it the fifth leading cause of death worldwide (Setiawan et al., 2022).

The nutritional status of individuals with liver disease is often compromised. Malnutrition, characterized by protein- energy wasting and muscle loss (sarcopenia), is common in advanced liver disease and worsens prognosis (Lai et al., 2021). Dietary strategies are key to mitigating the impact of liver disease, one of which is the administration of branched-chain amino acids (BCAAs), such as valine, isoleucine, and leucine, are key to mitigating the impact of liver diseases. BCAAs contribute to protein synthesis, energy production, and liver tissue regeneration. Patients with cirrhosis often experience BCAA deficiency, which increases their risk of developing sarcopenia, hepatic encephalopathy, and liver failure (Dimou et al., 2022). Deficiency in BCAAs can exacerbate sarcopenia, hepatic encephalopathy, and liver failure, highlighting the importance of BCAA supplementation in nutritional therapy (Ismaiel et al., 2022).

Nevertheless, elevated BCAA levels may contribute to insulin resistance, NAFLD, and type 2 diabetes as well as trigger inflammation in the liver. In liver transplant patients, increased BCAA levels may contribute to a heightened risk of metabolic complications (Böhler et al., 2022). The mechanism involves activation of the mTOR pathway, which plays a role in energy metabolism and protein synthesis but, when excessively activated, can also promote insulin resistance and liver inflammation (Wali et al., 2021).

Furthermore, the Covid-19 pandemic has exacerbated lifestyle risk factors, such as reduced physical activity and increased consumption of processed foods, leading to higher rates of obesity and NAFLD globally (López-González et al., 2022). These changes highlight an urgent need to reassess nutritional interventions targeting both metabolic and liver health in the post-pandemic era.

Therefore, this systematic review aims to evaluate the complex relationship between BCAA supplementation, nutritional status, obesity, and liver disease progression. Understanding these interactions is crucial for developing evidence-based nutritional strategies to manage and prevent liver- related complications effectively.

## Methods

This literature review was conducted using the Google Scholar search engine with the aim of examining the relationship between branched-chain amino acids (BCAAs) and liver disease, including their impact on patients' nutritional status and related metabolic alterations. The inclusion criteria were peer-reviewed articles published between 2019 - 2024 that explored the role of BCAAs in liver disease, assessed nutritional status, or examined metabolic changes. Both experimental and observational studies were included, while studies focusing specifically on healthy human subjects were excluded. Additional exclusion criteria comprised studies published before 2019, studies conducted on animals, articles that did not address BCAAs or liver-related issues, and paid-access articles.

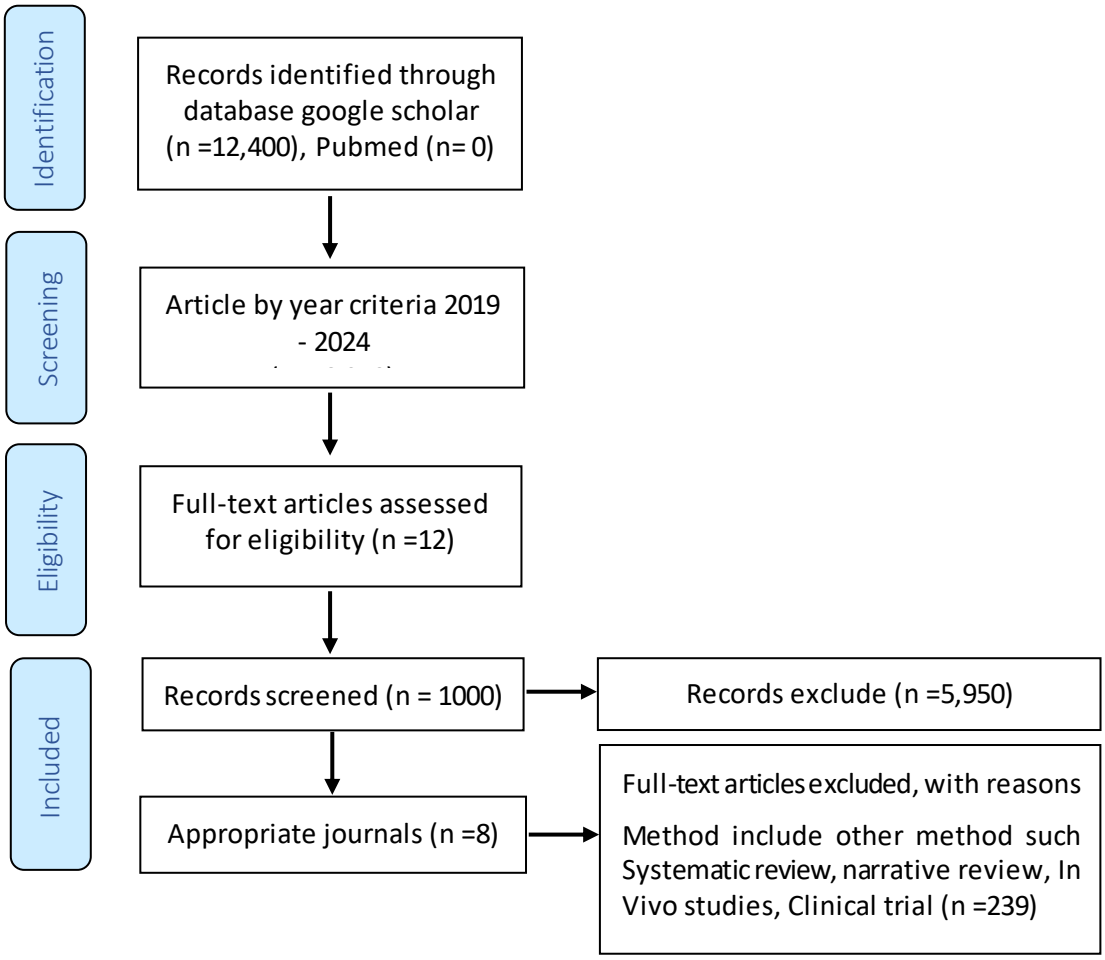


**Figure 1.** Preferred Reporting Items for Systematic Riviews (PRISMA) chart for systematic reviews

## Result

A literature search through Google Scholar yielded 12.400 articles. After filtering by publication year (2019-2024), 6.950 articles, leaving 1.000 articles for further examination. After full text evaluation, 239 articles were excluded for using inappropriate methods such as systematic review, in vivo studies, as well as clinical trials on healthy subjects. Finally, eight studies met the inclusion criteria and were analyzed in this review. The study selection flowchart can be seen in figure 1.

From the eight studies analyzed, several important findings were obtained. High BCAA consumption was associated with an increased risk of NAFLD (OR = 1,32; 95% CI: 1,17 – 1,49; p < 0,001). Park et al. (2020) reported that BCAA supplementation in cirrhotic patients with Child-Pugh score of 8-10 for six months resulted in significant improvements in MELD and CP score (HR = 0,389;95% CI: 0,221-0,684; < 0,001) (Mokhtari et al., 2022; Park et al., 2020).

High plasma BCAA levels were associated with an increased risk of type 2 diabetes post liver transplantation (OR =1,60; 95% CI: 1,14-2,23; p=0,006). BCAA supplementation in alcoholic cirrhosis and cirrhosis patients with sarcopenia improved muscle mass, muscle strength, and nutritional status such as MAC and BMI (OR = 0,823; 95% CI: 0,72-1,445; p = 0,007) (Böhler et al., 2022a; Khruomo et al., 2020; Singh Tejavath et al., 2021).

Feeding with oral nutritional supplements (ONS) enriched with HMB and BCAAs increased Fischer's ratio and decreased the incidence of MHE (p< 0,05). Higher protein intake, particularly from plant sources was associated with a reduced risk of mortality in patients with liver cirrhosis (HR = 0,7;95% CI 0,5-9,9; p < 0,05). Consumption of BCAA-containing sports drinks did not significantly improve sprint performance, but increased blood glucose levels after exercise (p < 0,05) (Daftari et al., 2023; Espina et al., 2021; Farra, 2023).

Overall, BCAAs play a role in improving nutritional status and liver function in cirrhotic patients, but excessive consumption may increase the risk of metabolic complications such as NAFLD and type 2 diabetes.

**Table 1** Studies included in the systematic review

| Writer | Subject | Research Population | Duration of Study | Title | Method | Results |
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| Mokhtari. E (Mokhtari et al., 2022) | Nutrition | 225 newly diagnosed NAFLD cases, 450 controls | Not Specified | Relationship between dietary amino acids and risk of nonalcoholic fatty liver disease among Iranian adults: a case-control study | Case-control study; Diet assessment using 168-item FFQ | A higher intake of total amino acids (OR: 1,25, 95% CI: 1,10-1,43, p<0,001), the intake of branched-chain amino acids (OR: 1,32, 95% CI: 1,17–1,49, p<0,001) and essential amino acids (OR: 1,21, 95% CI: 1,06–1,38, p=0,004) have been linked to a higher of NAFLD. Conversely, a higher consumption of glutamic acid (OR: 0,87, 95% CI: 0,77-0,98, p=0,022) appears to reduce the likelihood of developing NAFLD. |
| Jung Gil Park et al (Park et al., 2020) | Influence of BCAA Supplementation in End-Stage Liver Disease | Patients with liver cirrhosis with a Child-Pugh score of 8 to 10 | 6 months (24 months follow-up) | Effects of Branched Chain Amino Acid (BCAA) Supplementation on the Progression of Advanced Liver Disease | A longitudinal observational cohort study was carried out in 13 healthcare institutions in Korea. Participants were assigned to either the BCAA group, receiving a daily dose of 12,45 g of BCAA granules, or the control group. the study assessed their progress by measuring MELD and CP scores, along with serum albumin and bilirubin levels. | In the BCAA group, MELD and CP scores showed significant improvement over time, whereas the control group showed no significant variations in serum BCAA concentrations, serum albumin or bilirubin levels throughout the study. However, event-free survival was markedly higher in the BCAA group. (HR = 0,389, 95% CI = 0,221-0,684, p < 0,001). |
| Vikie-oKhruomo al (Khruomo et al., 2020) | Compensated Alcoholic Cirrhosis of the Liver | 116 Compensated Alcoholic Liver Cirrhosis Patients over the age of 18 years | September 2017 - August 2019 | The role of oral supplementation of branched-chain amino acids on the outcome of compensated alcoholic | Cross-sectional study, routine blood tests, oral BCAA supplementation (6g per sachet) daily for 3 months | A statistically significant improvement was observed in mid-arm circumference (MAC), body mass index (BMI), and triceps skinfold thickness measurement, along with increases in Serum bilirubin, hepatic enzymes, prothrombin time-international normalized ratio (PT-INR), and plasma |

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| | | | | cirrhosis of the liver | | albumin. Serum creatinine and platelet count. The CP (Child-Pugh) score was significantly improved, indicating better liver function and prognosis. The cross-sectional study design allowed for the observation of these effects at a specific time point, demonstrating the impact of BCAA supplements on liver disease severity. |
| Arun Singh Tejavath (Singh Tejavath et al., 2021). | Cirrhotic patients with sarcopenia | Sarcopenic patients with liver cirrhosis | 24 weeks | Impact of Branched-Chain Amino Acids on Muscle Mass, Muscle Strength, Physical Performance, Combined Survival, and Maintenance of Laboratory Changes in Liver Function and Prognostic Markers in Sarcopenia Liver Cirrhosis Patients (BCAAS Study): A Randomized Clinical Trial | A randomized, controlled, open-label study with a two-arm parallel group design | 1. Significant Improvement in Sarcopenia Parameters: There was a marked improvement in the various parameters used to measure sarcopenia.<br>2. Improved Muscle Strength: Participants showed a significant increase in muscle strength. 3. Improved Muscle Function: Participants' muscle function also improved significantly.<br>4. Increased Muscle Mass: The study noted an increase in muscle mass among the participants.<br>5. Fewer Cirrhosis-Related Complications: Participants experienced fewer cirrhosis-related complications.<br>6. Improved Prognostic Markers: Prognostic markers showed improvement, which had a positive impact on the patient's long-term prospects.<br>7. OR: 0,823 (95% CI: 0,72 – 1,445), *p*=0,007. The BCAA group showed a reduced risk of cirrhosis-related complications compared to the L-ALB group. |
| Marco Bohler et al (Böhler et al., 2022a) | Branched-chain amino acids and metabolic complications | Liver transplant recipients (336 patients) | Cross-section analysis | Branched-Chain Amino Acids are associated with metabolic complications in liver transplant recipients. | This cross-sectional research analyzed data from the Transplant lines biobank and cohort studies. BCAA concentrations were assessed using nuclear magnetic | Higher plasma BCAA concentrations have been linked to an increased incidence of recurrent type 2 Diabetes (T2D) and metabolic syndrome (MetS). MetS: An increase of one standard deviation in BCAA levels was linked to an adjusted odds ratio (OR) of 1,68 (95% CI: 1,18-2,20, *P* = 0,003). T2D: A similar increase in BCAA levels was correlated with an adjusted odds ratio (OR) of 1,60 |

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| | | | | resonance (NMR) spectroscopy. while patient information was obtained from electronic medical records. | (95% CI: 1,14-2,23, *P* = 0,006). Additionally, regardless of age, gender, time since liver transplantation, metabolic syndrome (MetS) , and other immunosuppressive drugs, the use of the mTOR inhibitor sirolimus was significantly associated with higher levels of BCAAs (adjusted *P* = 0,002). |
| Silvia Espina (Espina et al., 2021) | Modification of Amino Acid Composition via Oral Nutrition Supplements. | 43 people with cirrhosis and malnutrition | 12 weeks | Amino Acid Profile in Malnourished Patients with Liver Cirrhosis and its Modification by Oral Nutritional Supplements: Implications for Minimal Liver Encephalopathy | Participants in this randomized, double-blind, placebo-controlled study were assigned to receive either 220 mL of Ensure® Plus Advance (HMB group) or Ensure® Plus High Protein (HP group) twice daily. | HMB is a metabolite designed to increase fasting plasma concentrations of valine, leucine, phenylalanine, tryptophan, and branched-chain amino acids (BCAAs). HMB and BCAAs increase the Fischer ratio without affecting the fasting plasma glutamine (Gln) level or baseline ratios. Minimal Hepatic Encephalopathy (MHE) is associated with reduced plasma concentrations of neurotoxic amines, lower BCAA levels, and a decreased Fischer ratio, along with an increased Gln/Glu ratio. In contrast, Oral Nutritional Supplements (ONS) enriched with HMB were shown to enhance the Fischer ratio without altering fasting plasma Gln levels or baseline ratios. |
| Ghazal Daftari (Daftari et al., 2023) | Cirrhosis | 166 outpatient cirrhosis patients | 2016 - 2022 | Dietary protein intake and mortality among survivors of liver cirrhosis: a prospective cohort study | A cohort study categorized dietary protein intake into three groups (tertiles). Statistical analyses utilizing the Cox proportional hazards regression model and ANOVA were conducted to estimate hazard ratios (HR) with 95% confidence intervals (CI), and the chi-square test. Participants were monitored | A higher protein intake, particularly from dairy and plant-based sources, was linked to a reduced risk of cirrhosis-related mortality (HR) of 0,7 was observed (95% CI: 0,5–0,9). Conversely, insufficient protein consumption was linked to adverse clinical outcomes and elevated mortality risk in cirrhotic patients, (HR: 1,5, 95% CI: 1,2–1,8). |

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| | | | | until April 30, 2022. | |
| Saro Farra (Farra, 2023) | D. Investigating the ergogenicity of BioSteel High Performance Sports Drink (B-HPSD) | 11 experienced cyclists | Not specified | Acute consumption of sports drinks containing branched-chain amino acids and vitamin B-6 does not improve sprinting performance, but increases blood glucose after exercise. | MSE trials with consumption of B-HPSD or placebo, measuring power output, heart rate, perceived exertion rating, blood lactate, and glucose levels. | BCAA supplementation has been demonstrated to enhance muscular strength, promote muscle growth, and improve physical function in patients with cirrhosis. Additionally, BCAAs contribute to increased blood albumin levels by supporting the production and release of albumin in hepatocytes. They also exhibit anti-catabolic properties that enhance total protein absorption.<br>Heart Rate (HR) Results:<br>Sprint 1: Placebo 161 ± 10 bpm, B-HPSD 162 ± 11 bpm<br>Sprint 2: Placebo 168 ± 9 bpm, B-HPSD 168 ± 10 bpm<br>Sprint 3: Placebo 171 ± 8 bpm, B-HPSD 172 ± 9 bpm<br>Sprint 4: Placebo 172 ± 8 bpm, B-HPSD 174 ± 8 bpm<br>Sprint 5: Placebo 174 ± 7 bpm, B-HPSD 175 ± 8 bpm |

## Discussion

Branched-Chain Amino Acids (BCAAs) include leucine, isoleucine, and valine, are essential amino acids that play an important role in protein synthesis, energy production and nitrogen metabolism. As the body is unable to synthesize BCAAs endogenously, BCAAs intake must be obtained through dietary consumption. Under normal physiological conditions, the primary metabolism of BCAAs occurs in skeletal muscle through the action of the enzyme branched-chain α- keto acid dehydrogenase (BCKDH), which converts BCAAs into branched-chain keto acids (BCKAs) before undergoing further metabolism in the liver. However, in individuals with chronic liver disease, BCKDH activity is decreased, leading to the accumulation of BCAAs in the bloodstream, potentially contributing to insulin resistance and impaired lipid metabolism (Lo et al., 2022; Reifenberg & Zimmer, 2024).

Moreover, the gut microbiota is critically involved in the metabolism of BCAAs. An imbalance in the gut microbiota, known as gut dysbiosis, can worsen liver dysfunction by enhancing inflammatory responses and promoting insulin resistance, both of which are major contributors to the development of non-alcoholic fatty liver disease (NAFLD) This evidence emphasizes that, in addition to muscle and liver metabolism, the interactions between the gut and other organs are essential considerations when investigating the systemic impact Of BCAAs (Guo et al., 2022).

Several studies have demonstrated a link between excessive BCAA intake and a heightened risk of developing NAFLD, particularly among individuals with insulin resistance and obesity. Higher BCAA consumption was significantly associated with an increased likelihood of NAFLD (OR = 1,32, $p < 0,001$). Supporting these findings. Showed that leucine-induced activation of the Mtorc1 pathway could promote lipogenesis and impair insulin signaling, thereby exacerbating hepatic fat accumulation and insulin resistance. Similarly, elevated BCAA concentrations in liver transplant recipients were linked to a greater risk of developing type 2 diabetes (OR = 1,60, 95% Cl: 1,14- 2,23, $p = 0,006$), underscoring the broad metabolic consequences of systemic BCAA accumulation (Böhler et al., 2022; Gojda & Cahova, 2021; Mokhtari et al., 2022).

Nevertheless, the findings regarding BCAA supplementation are not entirely consistent across studies. Observed that supplementation with HMB, a metabolite of leucine, elevated BCAA levels without increasing ammonia concentration and even reduced the incidence of minimal hepatic encephalopathy (HME) in malnourished cirrhotic patients. Similarly, BCAA supplementation led to improvements in MELD and Child-Pugh scores among patients with severe cirrhosis, in addition, reported that BCAA supplementation contributed to increases in muscle mass and overall clinical improvement in individuals with cirrhosis (Khruomo et al., 2020; Park et al., 2020; Singh Tejavath et al., 2021).

The discrepancy in results may stem from differences in the populations studied. Some studies included individuals with obesity, insulin resistance, and those who had undergone liver transplants, all of whom already experienced impairment in the BCAA metabolic pathway. In these cases, excessive BCAA intakefurther worsened metabolic dysfunction. In contrast, studies focusing on malnourished cirrhotic patients who had BCAA deficiency and compromised protein synthesis. In these individuals, BCAA supplementation.

Resulted in clinical improvement. Additionally, factors such as the form of BCAA administration (pure supplements vs. natural foods), dosage, duration of intervention, and the participants' baseline metabolic conditions play a significant role in determining the overall outcome (Böhler et al., 2022a; Espina et al., 2021; Mokhtari et al., 2022; Park et al., 2020).

The practical implications of these findings are crucial for clinical practice and nutrition education. For individuals who are obese or have insulin resistance, it is essential to educate them about limiting BCAA intake, particularly from high-dose supplements and fatty animal-based foods. On the other hand, for patients with liver cirrhosis and malnutrition, BCAA supplementation can be a vital component of a nutritional approach to enhance nutritional status, prevent sarcopenia, and improve overall prognosis. Hospital policies should consider evaluating metabolic status before prescribing BCAA supplementation, and nutrition education programs should tailor recommendations according to the patient's specific condition.

Moreover, the origin of BCAAs plays a significant role. Consumption of plant-based proteins rich in BCAAs, such as those from beans and soybeans, was associated with a lower risk of mortality in cirrhotic patients (HR = 0,38, 95% CI: 0,2 -1,1, p-trend = 0,045). In contrast, a higher intake of animal-based protein was liked to an increased mortality risk (HR = 3,8, 95% CI: 1,7-8,2, p-trend = 0,035). These findings highlight the importance of encouraging the inclusion of plant-based protein sources in the diets of patients with liver disease (Daftari et al., 2023).

In addition, consuming BCAA containing sports drinks did not lead to a significant improvement in athletic performance. However, it did result in improved blood glucose levels following exercise. This suggests that, while the effects of BCAAs on physical performance may be limited, they could provide notable metabolic benefits, especially in terms of regulating glucose balance. Nevertheless, it is important to note that individuals with liver disease have different metabolic processes compared to healthy individuals, so these results cannot be directly applied to that population without further specific research (Farra, 2023).

BCAAs can be sourced from both plant-based and animal-based foods. Plant-derived products such as soy, quinoa, tempeh, and chickpeas not only provide BCAAs but also offer additional benefits such as fiber, vitamins and antioxidants, which may aid in reducing oxidative stress and inflammation. On the other hand, consuming fatty animal-based sources is often linked to higher insulin resistance and the progression of non-alcoholic fatty liver disease (NAFLD). While BCAA supplements can quickly improve nutritional status, especially in cases of severe malnutrition, caution is needed with prolonged or high-dose use, as this may exacerbate metabolic disorders without proper monitoring (Yanti et al., 2021).

## Conclusion

Branched-Chain Amino Acids (BCAAs)- leucine, isoleucine and valine- play a dual role in liver health: as nutritional therapy in liver cirrhosis and as risk factors in the development of non-alcoholic fatty liver disease (NAFLD). In patients with liver cirrhosis, BCAA supplementation can improve insulin resistance, preserve muscle mass, and enhance quality of life. However, in individuals with NAFLD, excessive BCAA consumption could potentially worsen glucose metabolism and increase the risk of insulin resistance.

These findings emphasize the importance of a tailored approach in BCAA supplementation, considering the individual clinical condition. Therefore, it is recommended to conduct a comprehensive evaluation before initiating BCAA supplementation, including assessments of metabolic status and liver function.

Further research is needed to with other macronutrients, as well as their impact on liver health in the Indonesian population. This study will provide deeper insights to formulate appropriate nutritional recommendations to prevent and effectively manage NAFLD.

## Conflict of Interest

The author states that there are no conflicts of interest with respect to this precise audit. No proficient or individual connections affected the study plan, information collection, investigation, or elucidation.

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