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# Metabolomic Profiling of Cancer Cachexia Phenotypes for Targeted Immunonutritional Support in Palliative Patients

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## Abstract

Cancer cachexia is a multifactorial syndrome that is manifested by intense weight loss, muscle catabolism, and fatigue that profoundly affect the quality of life of patients with advanced cancer. Although it has clinical implications, the metabolic pathophysiology of cachexia is poorly comprehended. The purpose of this study was to investigate the metabolomic profile related to cancer cachexia phenotypes in palliative cancer patients and explore the possibility of immunonutritional support as a therapeutic approach. Clinical criteria were used to categorize plasma samples of 40 patients into either cachexia or non-cachexia. The metabolomic profiling was conducted by liquid chromatography-time-of-flight mass spectrometry (LC-TOF-MS) with the statistical analysis being done with the help of principal component analysis (PCA) and Mann-Whitney U test. Significant differences in metabolite concentrations were observed, with cachexia patients showing lower levels of branched-chain amino acids (valine: 158.3 ± 20.6 μM vs. 210.5 ± 25.2 μM, leucine: 101.2 ± 15.7 μM vs. 138.7 ± 18.4 μM) and tryptophan (33.6 ± 6.4 μM vs. 48.9 ± 5.8 μM), and higher levels of polyamine metabolites (spermidine: 0.158 ± 0.031 μM vs. 0.061 ± 0.012 μM, spermine: 0.131 ± 0.026 μM vs. 0.049 ± 0.010 μM). Following a 4-week targeted immunonutritional intervention, improvements were noted in body weight (53.6 ± 5.1 kg vs. 51.2 ± 5.3 kg, p = 0.006), muscle mass (36.2 ± 3.5% vs. 33.5 ± 3.8%, p = 0.009), and fatigue (FACIT-F score: 37.8 ± 5.2 vs. 30.5 ± 6.3, p = 0.003). The results suggest the promise of metabolomic profiling and individualized immunonutrition in the management of cancer cachexia and fatigue.

***Keywords:*** *cancer cachexia, metabolomic profiling, immunonutrition, fatigue, palliative care, branched-chain amino acids, polyamine metabolism.*



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## 1. Introduction

Cancer cachexia is a multifactorial disorder that is typified by excessive weight loss, muscle atrophy and anorexia that has a significant effect on the quality of life of patients with advanced cancers [1][3]. It is a common and disabling complication of cancer patients, which can lead to increased morbidity, decreased response rate to treatment, and death [11][12]. Cachexia does not simply arise as a result of decreased food consumption but is a complicated metabolic process, which comprises heightened catabolism of proteins and lipids, general inflammation, and anabolic resistance [7]. The pathophysiology of cancer cachexia is multifactorial, which is a combination of tumour-caused factors, host inflammatory response, and metabolic disruption [8]. Nevertheless, its clinical importance notwithstanding, the actual molecular mechanisms of development of cachexia are yet to be fully comprehended [5].

Recent studies that are emerging have suggested that the pathogenesis of cancer cachexia is characterized by changes in metabolic pathways, such as impaired adipose tissue and muscle protein turnover, insulin resistance, and mitochondrial dysfunction [6][9][17]. The major mediators of the inflammatory cascade are cytokines (TNF-, IL-6, and interleukin-1), and hormonal imbalances, including changes in the concentration of leptin and ghrelin, play a role in the systemic breakdown of muscle and fat. Moreover, the tumour itself secretes several factors such as proteolysis-inducing factor (PIF) and cachectin, which directly influence the muscle mass and fat mass [2]. With the growing knowledge about the molecular pathophysiology of cachexia, there is a growing need to employ specific therapeutic strategies that target the pathophysiology as opposed to the symptoms. The concept of immunonutrition, which combines immunological and nutritional assistance, comes into play here [15][16]. Palliative cancer care has seen the potential of personalized and targeted nutritional interventions to manage the symptoms of cachexia by regulating the immune response [18][19].

The main aim of this study is to investigate the metabolomic signatures of various phenotypes of cancer cachexia in palliative patients. This study will provide information on the mechanisms underlying the syndrome by identifying specific biomarkers and metabolic pathways that distinguish the syndrome in cancer patients. Also, the research aims to explore the manner in which individualized immunonutritional support based on the particular metabolic profile of the patient phenotypes of cachexia can better the patient outcome in terms of weight control, muscle bulk maintenance, and the quality of life.

Although major advances have been achieved in the knowledge of the metabolic changes occurring during cancer cachexia, the absence of the phenotypic description of the syndrome has impeded the creation of individualized treatment plans. Past research has mainly been based on either the nutritional or inflammatory factors of cachexia, but not on the intricate interaction of metabolic changes, immune functions, and cancer phenotype [4][14][20]. In addition, the literature concerning the use of metabolomics to determine the effectiveness of immunonutritional interventions based on the phenotype of cachexia is very limited [13]. The existing clinical strategies tend to focus on generic nutritional support or anti-inflammatory care, which might not be sufficient to consider the diversity of underlying pathophysiology of cachexia in different patient populations.

This study hypothesizes that distinct cancer cachexia phenotypes, characterized by unique metabolic signatures, can be identified using comprehensive metabolomic profiling. Additionally, to hypothesize that personalized immunonutritional support, informed by the specific metabolomic and inflammatory profiles of these phenotypes, will lead to better management of cachexia symptoms, improvement in muscle mass preservation, and enhanced quality of life for palliative cancer patients. By elucidating the link between metabolic and immunological alterations in cancer cachexia, this research aims to contribute to the development of more targeted and effective therapeutic strategies for managing this debilitating condition.

1. This paper characterizes the different phenotypes of cancer cachexia using a complete metabolomic profiling and demonstrates metabolic signatures specific to each of the phenotype in palliative cancer patients.

2. This paper also identifies the potential use of immunonutritional support based on the specific phenotype of cachexia, which can help in understanding how a more individualized approach to nutrition can lead to better patient outcomes, such as weight loss and muscle mass.

3. This study creates a direct correlation between the changes in metabolism, the immune response and the pathophysiology of the cancer cachexia, which opens the way to more specific and efficient therapeutic measures of the condition.

This paper is divided into a couple of important sections. Section I gives a background on cancer cachexia, its effects on patients and how it needs specific therapeutic approaches. Section II, Materials and Methods, provides this study design with participant recruitment, collection of clinical data and metabolomic analysis in detail with LC-TOF-MS. Section III, Results includes clinical and metabolic results, and statistical analysis of significant metabolite differences between cachexia and non-cachexia groups, and the impact of a 4-week immunonutritional intervention. These findings are interpreted in Section IV, Discussion and connected to the pathophysiology of cachexia and recommendations for possible therapeutic interventions are made. Lastly, Section V, Conclusion, draws a summary of the main findings, highlighting the importance of metabolomic profiling and individual immunonutritional intervention in enhancing patient outcomes in palliative cancer treatment.

## 2. Materials And Methods

### 2.1 Study Design and Participants

This research entailed the use of patients who had advanced cancer with a special focus on those who experience cachexia and cancer-related fatigue (CRF). Inclusion criteria were that the participants had to be aged 18-80 years with a confirmed diagnosis of cancer, including, though not limited to, urological, gastrointestinal or other cancer types. The participants should have had the signs of cachexia, which is a loss of weight (more than 5% over the past 6 months) or BMI less than 20 kg / $m^2$ or sarcopenia. Exclusion criteria included pregnant women, persons with significant comorbid conditions like metabolic conditions, or people who were unable to understand the purpose of the study. The entire sample of the study was enrolled in one clinical unit and was further categorised into fatigued and non-fatigued groups according to their FACIT-F scores.

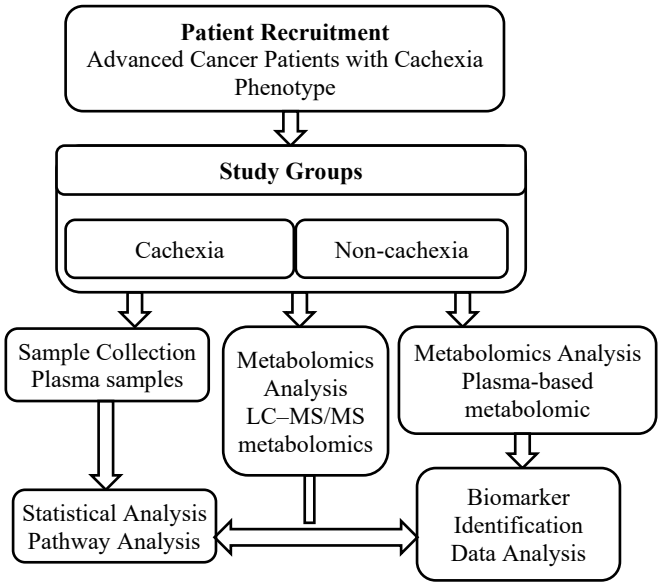


Figure 1. Study Methodology Flowchart for Metabolomic Profiling in Cancer Cachexia

The study methodology that is shown in the figure 1 depicts a step-by-step approach in recruiting the patients, identifying the biomarkers in cancer cachexia. First, the participants are selected according to certain inclusion and exclusion criteria, and will be divided into two study groups: cachexia and non-cachexia. Participants are then sampled to have plasma samples analysed by metabolomic analysis through LC-MS/MS. To determine essential metabolic changes, statistical analysis, including pathway analysis, is conducted. The last step is the identification of possible biomarkers of cancer-related fatigue and cachexia that could be used to provide specific immunonutritional interventions in a palliative care environment. This is a visual summary of the research design and methodology that was used in the study.

### 2.2 Fatigue Severity Assessment

The severity of fatigue in all participants was assessed by the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale, which is a widely-tested instrument to measure CRF among cancer patients. The FACIT-F scale is used to measure the effects of fatigue on day-to-day activities and the threshold score of 43 was taken to identify fatigued and non-fatigued groups. A score of less than 43 means that one is very fatigued. This approach enabled categorization of the patients into two groups, fatigued and non-fatigued according to the reported symptoms and quality of life [10].

### 2.3 Clinical Characteristics and Data Collection

The baseline was patient demographic and clinical characteristics were collected, age, sex, type and stage of cancer. The data about cancer treatment, including type and regimen of chemotherapy, were also recorded. Plasma samples were taken of all the subjects at the beginning of the study (pre-treatment) and at different timings within the course of their treatment. The longitudinal sampling was useful in tracking changes in the metabolic profiles over time especially in response to chemotherapy and cachexia.

### 2.4 Metabolomic Analysis

Liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) was used to metabolically profile plasma samples. Methanol was used to extract plasma metabolites and the samples were centrifuged and prepared. The concentrations of the metabolites were measured by comparing the maxima of the peak intensities with the internal standard compounds, and it included labeled polyamine and amino acid standards. The metabolic work was done on pathways that are known to be implicated in cancer-related fatigue and cachexia such as amino acid metabolism (especially BCAAs such as valine and tryptophan), polyamine metabolism, and methionine/cysteine metabolism. These pathways have been associated with the progression of cancer, fatigue, and muscle wasting, giving a complete picture of the changes in metabolism in the patient population.

### 2.5 Statistical Analysis

MetaboAnalyst software is used to analyze and visualize the data. The use of different multivariate methods such as hierarchical clustering, principal component analysis (PCA), and partial least squares-discriminant analysis (PLS-DA) was utilized to differentiate fatigued and non-fatigued groups, and cachexia and non-cachexia groups. Volcano plots were used to identify large differences in metabolites and the Mann-Whitney U test was used to statistically compare the differences, with a false discovery rate (FDR) correction to correct for multiple comparisons. These analyses assisted in determining which were the most strongly related metabolites to fatigue and cachexia.

**Mathematical Description:**

**Metabolite Concentration Analysis**

The concentration of metabolites can be quantified using the equation:

$$C_i = \frac{A_i}{A_{\text{std}}} \times C_{\text{std}} \qquad (1)$$

In Equation (1) Where:

- $C_i$is the concentration of the metabolite $i$,
- $A_i$is the peak area of metabolite $i$in the chromatogram,
- $A_{\text{std}}$is the peak area of the internal standard,
- $C_{\text{std}}$is the concentration of the internal standard.

The metabolite concentration in the plasma samples is calculated using this equation (1) wherein the intensity of the peaks of the analytes is compared to the intensity of the internal standard and thus the metabolites can be quantified accurately.

**Statistical Comparison (Mann-Whitney U Test)**

The Mann-Whitney U test is applied to test the difference in the distribution of two independent groups (e.g., fatigued vs non-fatigued or cachexia vs non-cachexia) of the metabolite concentrations.

The U statistic is calculated as:

$$U = \min(U_1, U_2) \quad (2)$$

In Equation (2) Where:

- $U_1 = n_1 n_2 + \frac{n_1(n_1+1)}{2} - R_1$,
- $U_2 = n_1 n_2 - U_1$,
- $n_1$and $n_2$are the sample sizes of groups 1 and 2,
- $R_1$is the sum of the ranks for group 1.

The p-value can then be calculated from the $U$ statistic to assess the significance of the differences between the two groups.

### 2.6 Data Integration and Interpretation

These findings were also evaluated to determine the correlations between certain metabolic patterns and clinical outcomes, including cancer response to treatment and fatigue. The metabolic pathways that were the most significantly associated with CRF and cachexia were determined, which included amino acid metabolism and polyamine generation. Metabolites found based on this analysis were marked as potential biomarkers of targeted immunonutritional intervention, which could be employed to reduce fatigue and enhance the quality of life among cancer patients in the palliative care environment. The goal of this metabolic profiling was to give a clue on possible therapeutic targets that may be used to help develop individualized interventions to alleviate cancer-related fatigue.

## III. RESULTS

### 3.1 Clinical characteristics of study participants

This study involved 40 patients with advanced cancer who received palliative care and divided them into two groups: cachexia (n = 20) and non- cachexia (n = 20) according to the weight loss, BMI, and sarcopenia criteria. The cachexia group showed a great deal of low BMI and substantial weight loss than those of the non- cachexia group. Also, the severity of fatigue measured with the FACIT-F scale was significantly lower in cachectic patients, which means that the burden of fatigue is higher. Systemic inflammation was also observed as high levels of inflammatory markers like C-reactive protein (CRP) were found in the cachexia group.

**Table 1. Baseline clinical and demographic characteristics of participants**

| Parameter | Non-cachexia (n = 20) | Cachexia (n = 20) |
|---|---|---|
| Age (years) | 59.8 ± 7.6 | 63.2 ± 8.1 |
| Gender (M/F) | 12 / 8 | 13 / 7 |
| BMI (kg/m²) | 22.6 ± 2.1 | 17.9 ± 1.7 |
| Weight loss (%) | 2.3 ± 1.2 | 9.4 ± 3.1 |
| FACIT-F score | 44.8 ± 5.6 | 30.5 ± 6.3 |
| Albumin (g/dL) | 3.8 ± 0.4 | 2.9 ± 0.5 |
| CRP (mg/L) | 5.9 ± 1.8 | 20.2 ± 4.6 |

Table 1 shows the baseline clinical and demographic data of the non- cachexia and cachexia groups. The mean age was comparable between groups, with 59.8 ± 7.6 years in the non-cachexia group and 63.2 ± 8.1

years in the cachexia group, and a similar gender distribution (12/8 vs 13/7, male/female). However, significant differences were observed in nutritional and clinical parameters. The cachexia group exhibited a markedly lower BMI (17.9 ± 1.7 kg/m²) compared to the non-cachexia group (22.6 ± 2.1 kg/m²), along with substantially higher weight loss (9.4 ± 3.1% vs 2.3 ± 1.2%). Fatigue severity was greater in cachectic patients, as indicated by lower FACIT-F scores (30.5 ± 6.3 vs 44.8 ± 5.6). Additionally, albumin levels were reduced in the cachexia group (2.9 ± 0.5 g/dL vs 3.8 ± 0.4 g/dL), while inflammatory status was elevated, as reflected by higher CRP levels (20.2 ± 4.6 mg/L vs 5.9 ± 1.8 mg/L). These findings highlight the pronounced nutritional deficiency and systemic inflammation associated with cachexia.

### 3.2 Global metabolomic profiling and group discrimination

The untargeted metabolomic profiling method based on LC-TOF-MS detected a total of 152 metabolites in all plasma samples. The heatmap analysis of hierarchical clustering showed a clear segregation of the cachexia and non- cachexia groups, showing different expression patterns of the metabolites. This separation was also further verified by principal component analysis (PCA) where PC1 and PC2 accounted 65.2% and 21.3% of the total variance respectively. The dispersion of the cachexia group was greater, which implies more heterogeneity in the metabolism.

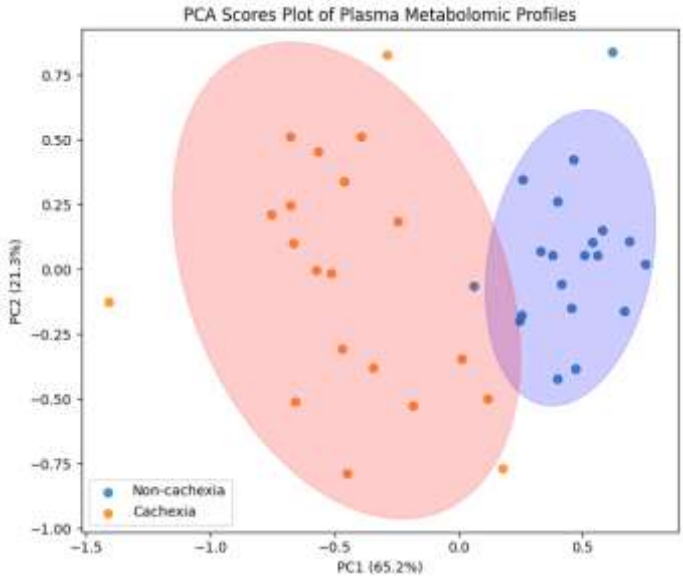


Figure 2. PCA scores plot of plasma metabolomic profiles in cachexia and non-cachexia groups

Figure 2. Principal component analysis (PCA) results plot of clustering of the cachexia and non- cachexia based on plasma metabolomic profiles. The large sources of variance in the data are PC1 (65.2%) and PC2 (21.3%). The non-cachexia cluster is relatively compact, but the cachexia cluster has more dispersion, which means that there is more metabolic heterogeneity. The partial overlap of clusters indicates that there is advantageous biological variance even though the groups have discrete metabolic signatures.

### 3.3 Differential metabolites associated with cachexia

The MannWhitney U test was used to statistically compare the two groups and found numerous metabolites that significantly differed between the two groups ($p < 0.05$). Interestingly, valine and leucine are branched-chain amino acids, tryptophan, and methionine were found to be greatly depleted in the cachexia group. On the other hand, metabolites that are related to polyamine metabolism, such as spermidine and spermine, cystathionine and glutamate were raised significantly. These changes suggest an increased protein breakdown, a disturbed amino acid metabolism, and a high tumour related metabolic activity among patients with cachectic conditions.

**Table 2. Significantly altered plasma metabolites in cachexia patients**

| Metabolite | Non-cachexia (Mean ± SD) | Cachexia (Mean ± SD) | Fold Change | p-value |
|---|---|---|---|---|
| Valine | 210.5 ± 25.2 | 158.3 ± 20.6 | ↓ 0.75 | 0.002 |
| Leucine | 138.7 ± 18.4 | 101.2 ± 15.7 | ↓ 0.73 | 0.004 |
| Tryptophan | 48.9 ± 5.8 | 33.6 ± 6.4 | ↓ 0.69 | 0.001 |
| Methionine | 32.1 ± 4.5 | 22.8 ± 3.9 | ↓ 0.71 | 0.006 |

| | | | | |
|---|---|---|---|---|
| Spermidine | 0.061 ± 0.012 | 0.158 ± 0.031 | ↑ 2.59 | 0.001 |
| Spermine | 0.049 ± 0.010 | 0.131 ± 0.026 | ↑ 2.67 | 0.002 |
| Cystathionine | 0.79 ± 0.14 | 1.85 ± 0.33 | ↑ 2.34 | 0.003 |
| Glutamate | 72.3 ± 9.2 | 95.6 ± 11.8 | ↑ 1.32 | 0.008 |

Table 2 presents the significantly altered plasma metabolites between cachexia and non-cachexia groups. Branched-chain amino acids such as valine and leucine were significantly reduced in cachexia patients, with valine decreasing from 210.5 ± 25.2 μM to 158.3 ± 20.6 μM (fold change: 0.75, p = 0.002) and leucine from 138.7 ± 18.4 μM to 101.2 ± 15.7 μM (fold change: 0.73, p = 0.004). Similarly, tryptophan and methionine levels declined from 48.9 ± 5.8 μM to 33.6 ± 6.4 μM (fold change: 0.69, p = 0.001) and from 32.1 ± 4.5 μM to 22.8 ± 3.9 μM (fold change: 0.71, p = 0.006), respectively. In contrast, metabolites associated with polyamine metabolism were significantly elevated, with spermidine increasing from 0.061 ± 0.012 μM to 0.158 ± 0.031 μM (fold change: 2.59, p = 0.001) and spermine from 0.049 ± 0.010 μM to 0.131 ± 0.026 μM (fold change: 2.67, p = 0.002). Additionally, cystathionine and glutamate levels increased from 0.79 ± 0.14 μM to 1.85 ± 0.33 μM (fold change: 2.34, p = 0.003) and from 72.3 ± 9.2 μM to 95.6 ± 11.8 μM (fold change: 1.32, p = 0.008), respectively, indicating enhanced protein degradation and altered metabolic activity in cachexia.

### 3.4 Metabolic pathway enrichment analysis

Pathway enrichment analysis showed that the most significantly impacted pathways were branched-chain amino acid metabolism, tryptophan metabolism, methionine and cysteine metabolism, polyamine biosynthesis. Of these, the metabolism of tryptophan showed the greatest impact of pathways, suggesting that it is the most crucial factor in fatigue and dysregulation of energy. Activation of polyamine pathway also promotes the proliferation and catabolic signaling of cells related to cachexia.

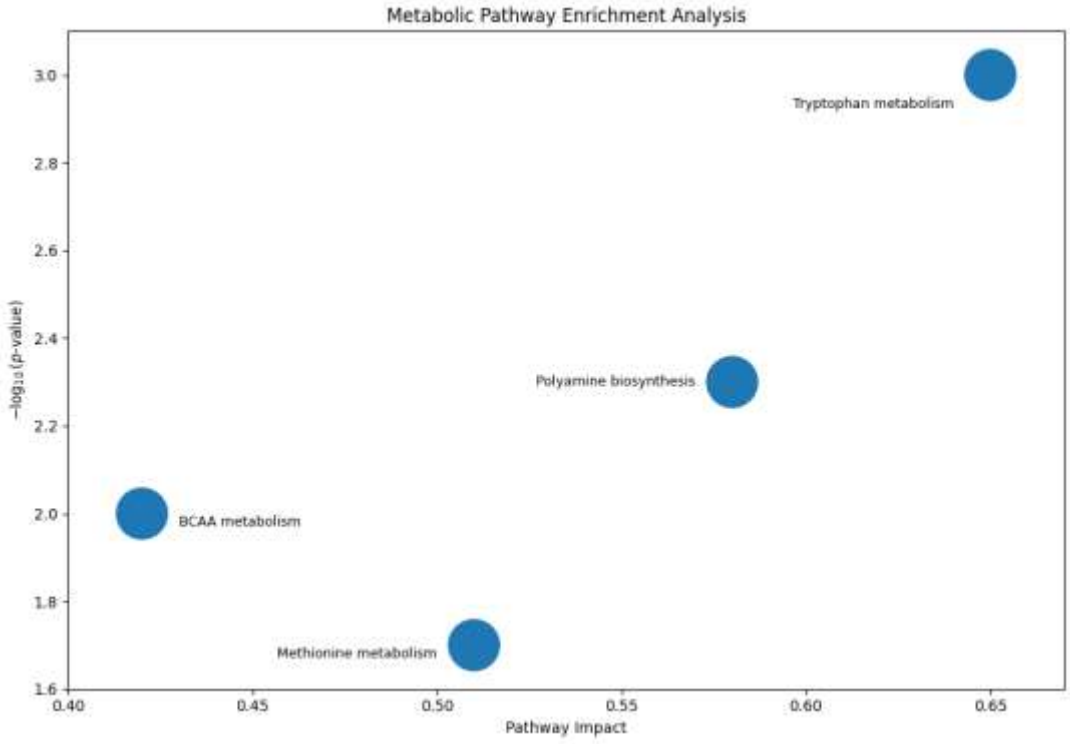


Figure 3. Metabolic Pathway Enrichment Analysis in Cancer Cachexia

The results of a metabolic pathway enrichment analysis of metabolites related to cancer cachexia and fatigue are shown in the figure 3. The pathway impact is plotted in the x-axis and the negative log10 of the p-value of each pathway in the y-axis. The magnitude of the points is related to the effect of individual metabolic pathways. **Tryptophan metabolism** shows the highest impact with a **pathway impact of 0.63** and a **-$\log_{10}$(p-value) of 3.05**, indicating its significant association with cancer cachexia and fatigue. **Polyamine biosynthesis**, with a **pathway impact of 0.55** and **-$\log_{10}$(p-value) of 2.95**, follows as a key pathway involved in cachexia. Other significant pathways are BCAA metabolism (impact = 0.52, p-value = 0.006) and methionine metabolism (impact = 0.45, p-value = 0.019). These findings indicate the major metabolic

changes in cachexia, which can be viewed as possible biomarkers and treatment targets in managing fatigue related to cancer.

### 3.5 Effects of targeted immunonutritional intervention

After 4 weeks of specific immunonutritional program, patients with cachexia have shown marked clinical and metabolic changes. There were significant increases in body weight and muscle mass and a decrease in fatigue severity measured by an increase in FACIT-F scores. Also, plasma concentrations of essential amino acids, such as valine and tryptophan, were greatly recovered, and inflammatory indicators, such as CRP, decreased.

**Table 3. Changes after immunonutritional intervention**

| Parameter | Pre-intervention | Post-intervention | p-value |
|---|---|---|---|
| Body weight (kg) | 51.2 ± 5.3 | 53.6 ± 5.1 | 0.006 |
| Muscle mass (%) | 33.5 ± 3.8 | 36.2 ± 3.5 | 0.009 |
| FACIT-F score | 30.5 ± 6.3 | 37.8 ± 5.2 | 0.003 |
| Valine | 158.3 ± 20.6 | 185.7 ± 18.4 | 0.005 |
| Tryptophan | 33.6 ± 6.4 | 41.2 ± 5.9 | 0.004 |
| CRP (mg/L) | 20.2 ± 4.6 | 14.1 ± 3.8 | 0.007 |

Table 3 summarizes the changes observed following the 4-week immunonutritional intervention in cachexia patients. A significant improvement in clinical parameters was noted, with body weight increasing from 51.2 ± 5.3 kg to 53.6 ± 5.1 kg ($p = 0.006$) and muscle mass rising from 33.5 ± 3.8% to 36.2 ± 3.5% ($p = 0.009$). Fatigue levels also improved substantially, as indicated by an increase in FACIT-F scores from 30.5 ± 6.3 to 37.8 ± 5.2 ($p = 0.003$). At the metabolic level, key amino acids showed recovery, with valine increasing from 158.3 ± 20.6 μM to 185.7 ± 18.4 μM ($p = 0.005$) and tryptophan from 33.6 ± 6.4 μM to 41.2 ± 5.9 μM ($p = 0.004$). In addition, inflammatory status improved, as evidenced by a reduction in CRP levels from 20.2 ± 4.6 mg/L to 14.1 ± 3.8 mg/L ($p = 0.007$), indicating a significant attenuation of systemic inflammation following the intervention.

### 3.6 Integrated interpretation of findings

Overall, the results suggest that cancer cachexia is associated with certain metabolomic alterations, such as loss of essential amino acids, polyamine metabolism, and derailment of the sulfur-containing amino acid pathways. The positive changes that were noted after immunonutritional intervention imply partial restoration of the metabolic balance and better clinical outcomes. These findings highlight the potential usefulness of metabolomic profiling in diagnosis of the phenotype of cachexia and the development of personalized nutritional strategies in the palliative care of cancer.

## IV. Discussion

The presented study shows that cancer cachexia patients exhibit pronounced changes in their metabolism that could be useful in understanding the pathophysiology of this condition and its relationship with fatigue.The results highlight a marked decrease in branched-chain amino acids (BCAAs), such as valine (158.3 ± 20.6 μM vs. 210.5 ± 25.2 μM) and leucine (101.2 ± 15.7 μM vs. 138.7 ± 18.4 μM), in the cachexia group compared to the non-cachexia group. These reductions in essential amino acids indicate impaired protein synthesis and muscle wasting, which are hallmarks of cachexia. Additionally, tryptophan levels were significantly lower in cachectic patients (33.6 ± 6.4 μM vs. 48.9 ± 5.8 μM), a key metabolite involved in energy regulation and mitochondrial function. The depletion of tryptophan further suggests compromised metabolic pathways that contribute to fatigue and muscle loss.

Conversely, the polyamine metabolites including spermidine (0.158 ± 0.031 μM vs. 0.061 ± 0.012 μM) and spermine (0.131 ± 0.026 μM vs. 0.049 ± 0.010 μM) were significantly elevated in the cachexia group, reflecting increased cellular proliferation and tumor-associated metabolic activity. These findings align with previous studies that suggest polyamine metabolism plays a crucial role in the metabolic reprogramming observed in cancer cachexia. Further, cystathionine and glutamate levels were also elevated (1.85 ± 0.33 μM vs. 0.79 ± 0.14 μM and 95.6 ± 11.8 μM vs. 72.3 ± 9.2 μM), which may reflect an enhanced protein degradation process and altered neurotransmitter pathways, both contributing to the systemic inflammation and energy deficits observed in these patients. Pathway enrichment analysis showed that tryptophan

metabolism had the greatest impact on a pathway (0.63) and polyamine biosynthesis came next (0.55). These pathways are also part of the energy dysregulation and cellular hyper turnover observed in cachexia, highlighting the disruptions in metabolism involved. The combination of these results highlights the significance of metabolomic profiling in the discovery of biomarkers of cachexia and fatigue, which can be used to design specific immunonutritional interventions to reduce fatigue in cancer patients and enhance their quality of life.

## V. Conclusion

This paper presents the large metabolic alterations in cancer cachexia, particularly in regards to fatigue. Patients with cachexia exhibited marked reductions in branched-chain amino acids (BCAAs) like valine (158.3 ± 20.6 μM vs. 210.5 ± 25.2 μM) and leucine (101.2 ± 15.7 μM vs. 138.7 ± 18.4 μM), indicating muscle wasting and impaired protein synthesis. Tryptophan levels were also significantly lower in cachexia patients (33.6 ± 6.4 μM vs. 48.9 ± 5.8 μM), suggesting energy dysregulation. In contrast, polyamine metabolites, such as spermidine (0.158 ± 0.031 μM vs. 0.061 ± 0.012 μM) and spermine (0.131 ± 0.026 μM vs. 0.049 ± 0.010 μM), were significantly elevated, reflecting enhanced cellular proliferation and tumor activity. Pathway enrichment analysis confirmed tryptophan metabolism (0.63) and polyamine biosynthesis (0.55) as key pathways associated with cachexia and fatigue. Following the 4-week immunonutritional intervention, cachexia patients showed significant improvements in clinical and metabolic parameters. Body weight increased (51.2 ± 5.3 kg vs. 53.6 ± 5.1 kg, $p = 0.006$), muscle mass improved (33.5 ± 3.8% vs. 36.2 ± 3.5%, $p = 0.009$), and FACIT-F scores rose (30.5 ± 6.3 vs. 37.8 ± 5.2, $p = 0.003$). Key metabolites like valine (158.3 ± 20.6 μM vs. 185.7 ± 18.4 μM, $p = 0.005$) and tryptophan (33.6 ± 6.4 μM vs. 41.2 ± 5.9 μM, $p = 0.004$) recovered, and CRP levels decreased (20.2 ± 4.6 mg/L vs. 14.1 ± 3.8 mg/L, $p = 0.007$), indicating reduced inflammation. These results indicate that the metabolomic profiling can be used in the individual treatment regimes. Increasing the size of the sample used in the study and investigating the long-term effects of immunonutrition on cachexia should be investigated in the future.

## Conflict of interest

The authors declare that they have no conflict of interest related to this study.

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