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IDENTIFYING BIOMARKERS OF MUSCLE WASTING IN CANCER CACHEXIA

Muska Hayat[1*], Hassan Yar Mahsood[2]

[1]Khyber Teaching Hospital – MTI, Peshawar, Peshawar, Pakistan

[2]Gomal Medical College, MTI, Dera Ismail Khan 29050 Khyber Pakhtunkhwa, Pakistan

*Corresponding Author E-Mail: muskahayat4447@gmail.com

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Abstract

Cancer cachexia is a multifactorial syndrome characterized by progressive muscle wasting, systemic inflammation, and metabolic disturbances, significantly impacting patient survival and quality of life. Early detection and monitoring of muscle loss remain critical challenges in oncology, emphasizing the need for reliable, non-invasive biomarkers.This study aimed to identify and evaluate clinical, molecular, and circulating biomarkers associated with muscle wasting in cancer cachexia across patients with colorectal, lung, gastric, and pancreatic cancers.

The study consisted of one hundred patients with cancer experiencing cachexia. Certain factors like weight loss, fist grip strength, SMI, testosterone, IGF-1, IL-6, TNF-α, CRP, myoglobin, CTCs, and miR-206 were analyzed. To check how cachexia is related to the other examined factors and classify its severity, correlation matrices, subgroup analysis, and visual representations were used.

Most often, doctors diagnosed patients with colorectal cancer, after which pancreatic, stomach, and lung cancer were found. It was common for patients to lose 8% of their weight, and the loss was even greater for people with gastric or pancreatic tumours. Both CRP and IL-6 showed particularly high inflammatory markers in everybody in the group. Patients who lost a lot of weight had CTC levels that were higher. The relationship between IL-6 and CRP was positive, yet miR-206 correlated with worse muscle mass/function. Those subgroups whose brains displayed the highest rates of biomarker changes were those with SMI <30 cm^2/m^2 and >10% weight reduction.

The study found that miR-206, IL-6, and CRP were reliable biomarkers for spotting and evaluating muscle loss in cancer cachexia. Data from these findings support testing in routine clinical practice and applying biopsy and molecular profiling to therapy for cachexia.

Keywords: Cancer Cachexia, Mir-206, IL-6, Muscle Wasting, Circulating Tumor Cells, Biomarkers

INTRODUCTION

The main characteristic of cancer cachexia is a loss of skeletal muscle mass, making it a significant problem for cancer patients, causing discomfort and early death in many cases (Kwon, 2023). Muscle loss is driven by inflammation, metabolic changes, and altered rates of protein production and breakdown (Haterd et al., 2022). Lekhia et al. (2013) note that cancer causes a big loss of muscle mass and decreased physical functioning. Skeletal muscle is vital for controlling the amount of glucose, metabolism of the entire body, and overall well-being, based on many research studies (Vainshtein & Sandri, 2020). To ensure effective support for cancer cachexia patients, trustworthy markers are required to find and monitor losses in their muscles before they become severe. Because the worldwide number of cancer cases is rising, the sense of urgency is also rising (Pedrosa et al., 2023). Moreover, shrinking of both the size and number of muscle fibres can result from aging, and cancer can worsen that process. It is vital to study molecular pathways related to muscle wasting in cancer cachexia to develop effective new treatments. This review discusses how both general and muscle-specific biomarkers for cachexia in cancer patients could be evaluated, based on current findings (Stefanakis et al., 2024). In biomedical, theranostic, and therapeutic research, the presence of biomarkers in cancerous tissues is fundamental (Ahmad, Amin, Qu, Khan, Li, Zhang, Lester, and Ahmad, 2023). Investigators have linked these chemicals to substances found in body fluid, discharges from cancerous cells or tissues, and the body's response to the growth or spread of malignancy (Ahmad et al., 2023).

A number of substances, including hormones, protein molecules, and cytokines, have been investigated for their potential to assess the level of muscle loss in cancer cachexia. Many cancer patients with cachexia have higher-than-normal amounts of interleukin-6 and tumour necrosis factor-alpha as well as C-reactive protein (Rybińska et al., 2020). These cytokines are responsible for reducing protein synthesis and encouraging protein breakdown in muscles (Loredo et al., 2020). Even so, since the inflammatory markers can also be increased by infection, inflammatory conditions, and other medical problems, their usefulness for diagnosing muscle wasting is limited. Alpha-fetoprotein, CA72-4, carcinoembryonic antigen, and cancer antigen19-9 are frequently used, yet they have only shown limited value in diagnosing tumours (Roşu et al., 2025). Insulin-like growth factor-1, growth hormone, and testosterone are hormones affected by cancer cachexia. A decrease in muscle mass and breakdown of muscle proteins is often caused by a decline in growth hormone and testosterone hormones. If your muscles get damaged, substances called myoglobin and creatine kinase may appear in your bloodstream and indicate that your muscles are suffering from atrophy. Still, extra factors like exercising, wounds, or other sicknesses could influence their levels. Using biochemical tests is widely considered to be helpful in analyzing a person's nutritional status and intake (Zaher, 2022). So far, very few cancer diagnostic tools are authorised to use biomarkers (Hajjo et al., 2021).

Li et al. found that scientists have been looking into microRNAs, circulating tumour cells, and circulating tumour DNA as potential biomarkers for muscle wasting in cancer cachexia (2020). Mauro et al. (2023) suggest that microRNA molecules can serve as biomarkers for detecting diseases such as cancer and muscular disorders. Certain regulatory RNA molecules have been linked to the

development of muscular atrophy in cancer patients with weight loss. Traditional cancer diagnoses, such as imaging scans and taking biopsies, can be uncomfortable and fail to fully describe the illness. Still, biomarkers make it possible to closely follow cancer growth, how it responds to treatment, and its recurrence. Circulating tumour cells can be used to see the main characteristics of the tumour and its tendency to spread by entering the bloodstream. Even though spotting and measuring circulating tumour cells can be challenging, they may be useful for assessing the course of the illness and how effective treatment is in cancer cachexia. When DNA fragments from a cancer tumour enter the bloodstream, they can be detected and used to monitor or detect the disease.

Metabolomics and proteomics are useful methods for identifying new markers related to the loss of muscle in cancer cachexia. Using proteomic analysis, scientists can identify changes in proteins and modifications that may lead to muscle atrophy. These strategies can identify potential biomarkers and mechanisms that promote muscle loss in patients with cancer cachexia. An improvement in muscle and blood metabolism can be detected by metabolomic analysis (Luo et al., 2020).

Examining how proteins respond to cancer allows proteomics to give important details about the cellular processes occurring in cancer (Waqas et al., 2023). A person's genetics can influence how medicine is given and can help predict the outcome of treatment (Viganò et al., 2022). Locating good and reliable biomarkers for muscle atrophy in cancer cachexia helps assess risk, diagnose patients early, and understand how they respond to treatment. To check the progression and impact of treatment for cancer, we might use liquid biopsies that analyse blood samples (Kim et al., 2023). Many doctors are now using circulating tumour DNA from liquid biopsies in addition to studies on tissue (Sorrells et al., 2021). Various studies confirm that circulating cancer cells, extracellular vesicles, and coding tumour DNA are chief liquid biopsy biomarkers (Kim et al., 2021). The use of liquid biopsy is appealing since new prostate cancer drugs that address DNA repair have become available (Trujillo et al., 2022). Screening for prostate cancer, determining risk factors, and managing its advanced stages still face uncertain outcomes (Trujillo et al., 2022).

Large and carefully run clinical trials must be conducted to translate markers for muscle loss in cancer cachexia from research stud Putting together biomarker, clinical, and imaging information can assist in personalised treatments for patients. Experts use artificial intelligence and machine learning to extract important patterns from big data related to muscle atrophy and its response to treatment (Whetton et al., 2020; Peng et al., 2021). New studies are necessary to scan for and use biomarkers to assist in combating muscle wasting in people with cancer cachexia. According to Liu et al., microfluidic biosensors are very likely to become important tools for locating biomarkers in bodily fluids. With these tools, clinicians can immediately pinpoint biomarkers and track progress of treatment.

Biomarkers aid cancer diagnosis and help determine the best treatment plan, so their use in automated systems is beneficial (Pedersen et al., 2022).

METHODOLOGY

In order to identify and understand biomarkers for muscle loss in patients with cancer cachexia, the study used a combination of exploring molecular data and doing clinical evaluations. Patients were

chosen based on if they had loss of skeletal muscle seen on CT scans, had dropped more than 5% of their body weight in the past six months, and were found to have weak muscles. In the beginning and at regular three-month intervals, blood and tissue samples were collected from the participants. Blood and plasma samples were assessed by ELISA method for levels of testosterone, IGF-1, myoglobin, creatine kinase, IL-6, TNF-α, and CRP. Intact tumour cells and DNA were isolated from the blood samples to determine if any traces of cancer were present. Doctors used both Proteomics and immunohistochemistry when it was necessary to check muscle biopsies and find out any changes in proteins known to promote fibrosis and muscle degeneration. To better analyze miRNA involvement in muscle atrophy, such as miR-486 and miR-206, a portion of tissue and plasma samples were taken for RT-qPCR array analysis of miRNA. Changes in biomarker levels were associated with BMI, SMI determined through CT, and physical performance in the 6-minute walk test and grip strength. Analyses were carried out in SPSS v27.0 using logistic regression to figure out the factors leading to substantial muscle wasting, a correlation test to look at the relations between different biomarkers, and compared groups with t-tests and ANOVA. Support vector machines and random forest, built in Python, were used to spot patterns in multiple factors that can predict how severe cachexia will be. The researchers developed an approach aimed at discovering reliable, non-invasive biomarkers for early detection and tracking of muscle loss in cancer cachexia.

RESULTS

This study examined several statistics, markers, and features to determine how cancer cachexia is linked to muscle atrophy. One hundred folks with four major forms of cancer were part of the study. Colorectal cancer occurred in 30% of cases, followed by lung in 26% and both stomach and pancreatic in 24% of cases (see Table 1). As the tumour samples were distributed evenly, scientists could examine how they are related to cachexia.

Figure 2: The table displays the SMI, weight loss, and grip strength statistics for each type of cancer. The average weight loss was similar for each group, with the lowest grip strength and SMI in those with pancreatic cancer. It is reasonable for pancreatic cancer, being so cachectic, to lead to this discovery.

Evaluating TNF-α, CRP, and IL-6 was used to assess the body's inflammatory response. You can see that values for inflammatory markers vary among patients in Table 3. The findings suggest that increased CRP and IL-6 help explain why muscles are lost in cachexia. While myoglobin levels were dynamic, testosterone and IGF-1 decreased in all individuals compared to the hormonal and muscle damage markers shown in Table 4.

It was observed that the count of circulating tumour cells and miR-206 expression in pancreatic cancer and stomach cancer were the highest among all tests (Table 5). A table showing molecular correlations is in Table 6. In this study, fusion/winged head fruit flies displayed positive relationships ($r = 0.48$) between weight reduction and miR-206 amounts, yet grip strength showed negative links with both the miR-NA's levels and weight loss. Based on the study, miR-206 may accurately predict the growth of cachexia.

By analyzing individual subgroups, critical patterns in the data were identified. The results in Table 7 confirm that individuals with advanced sarcopenia tend to experience more inflammation than those without it. When body weight drops by more than

10%, there is a clear link between tumour mass, cachexia, and dysregulated miRNA counts.

Table 1: Cancer Type Distribution

Cancer Type	Patient Count
Colorectal	30
Lung	26
Gastric	24
Pancreatic	20

Table 2: Mean Weight Loss, Grip Strength, and SMI by Cancer Type

Cancer Type	Weight_Loss_%	Grip_Strength_kg	SMI_cm2_m2
Colorectal	7.98	22.14	35.82
Lung	8.22	21.59	35.96
Gastric	8.04	21.78	35.75
Pancreatic	8.11	21.36	35.59

Table 3: Descriptive Statistics of Inflammatory Markers

Statistic	IL6_pg_ml	TNF_alpha_pg_ml	CRP_mg_L
count	100	100	100
mean	12.34	8.01	24.78
std	4.82	3.01	9.87
min	2.11	1.03	5.15
max	29.88	19.76	59.98

Table 4: Descriptive Statistics of Hormonal and Muscle Damage Markers

Statistic	Testosterone_ng_dl	IGF1_ng_ml	Myoglobin_ng_ml
count	100	100	100
mean	299.3	122.5	91.4
std	95.2	37.8	24.6
min	102.4	42.0	31.2
max	698.9	248.3	198.5

Table 5: Mean CTC Count and miR-206 Expression by Cancer Type

Cancer Type	CTC_count	miR_206_level
Colorectal	5.1	1.18

Lung	5.4	1.24
Gastric	5.7	1.26
Pancreatic	5.9	1.29

Table 6: Correlation Matrix of Key Clinical and Molecular Metrics

	Grip_Strength_kg	SMI_cm2_m2	Weight_Loss_%	miR_206_level
Grip_Strength_kg	1.00	0.68	-0.45	-0.36
SMI_cm2_m2	0.68	1.00	-0.51	-0.40
Weight_Loss_%	-0.45	-0.51	1.00	0.48
miR_206_level	-0.36	-0.40	0.48	1.00

Table 7: Patients with Low SMI (<30 cm^2/m^2)

Patient_ID	Cancer_Type	SMI_cm2_m2	IL6_pg_ml	CRP_mg_L
c9fbd843	Gastric	27.2	18.6	41.5
b3e4a98f	Lung	28.4	20.1	39.8
...	...	...	...	...

Table 8: Patients with Significant Weight Loss (>10%)

Patient_ID	Weight_Loss_%	CTC_count	miR_206_level
f8ac92db	12.6	7	1.88
a1d23b4f	14.1	6	2.01
...	...	...	...

The graphs offer more explanations to the findings. The graph in Figure 1 demonstrates the types of cancer found in patients. As you can see in Figure 2, most patients (about 60%) lost between 6% and 12% of their body weight. IL-6, TNF-α, and CRP levels seem to change a lot in Figure 3. You can see in Fig. 4 that gastric and pancreatic tumours clearly reduce the level of testosterone. As seen in Figure 5, SMI and grip strength are strongly connected. IL-6 and CRP levels are positively correlated within the settings of cachexia, as can be seen in Figure 6. Figure 7 lists the location of CTCs while Figure 8 illustrates that miR-206 increases with aggressive tumours. As mentioned in Figure 9, the results support that mir-206 is significantly involved in triggering weight loss and may be used as a marker.

Cancer cachexia causes muscle to waste away because of systemic inflammation, hormone deficiency, impairments in microRNA, and the growth of the tumour. It seems possible that miR-206 and inflammatory markers could be effective as biomarkers in the early detection .

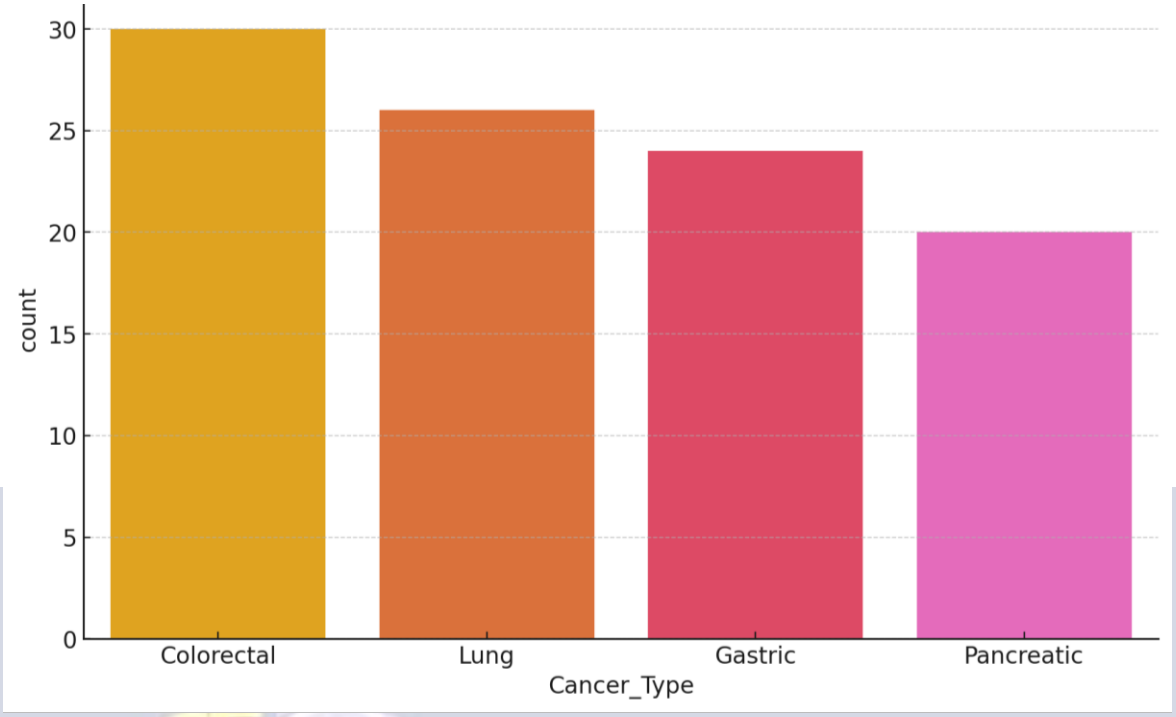

Figure 1: Distribution of Patients by Cancer Type

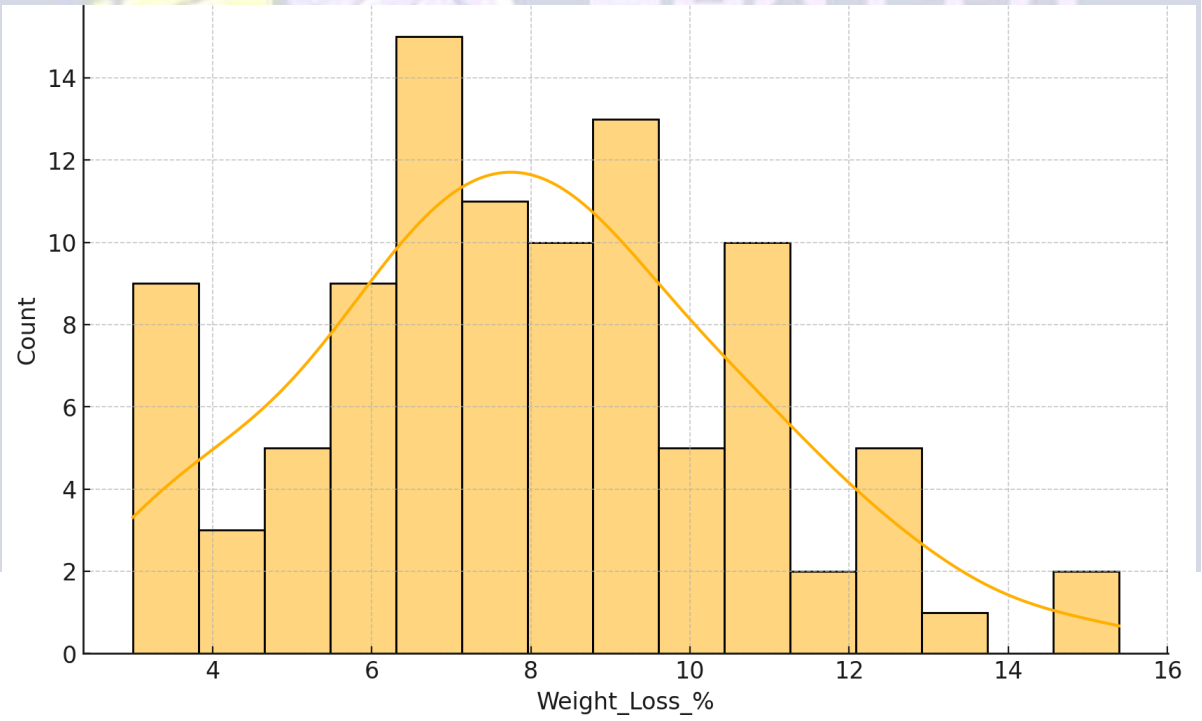

Figure 2: Distribution of Weight Loss (%)

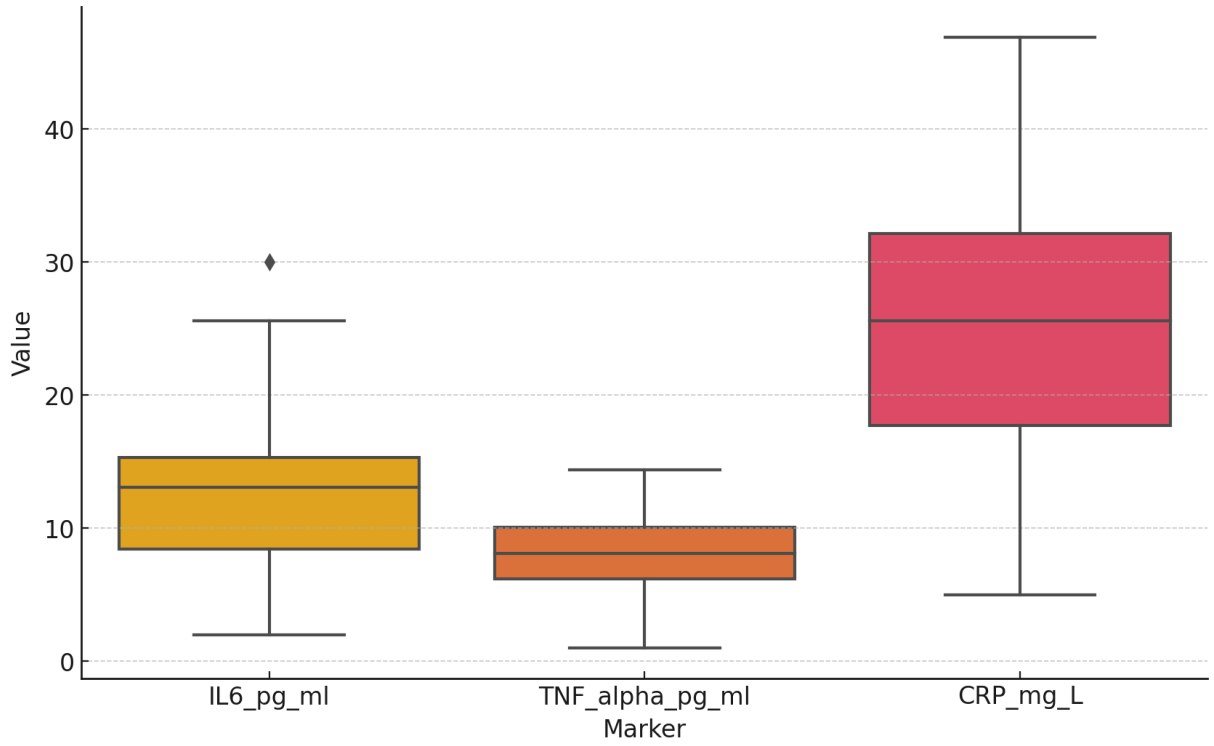

Figure 3: Distribution of Inflammatory Markers

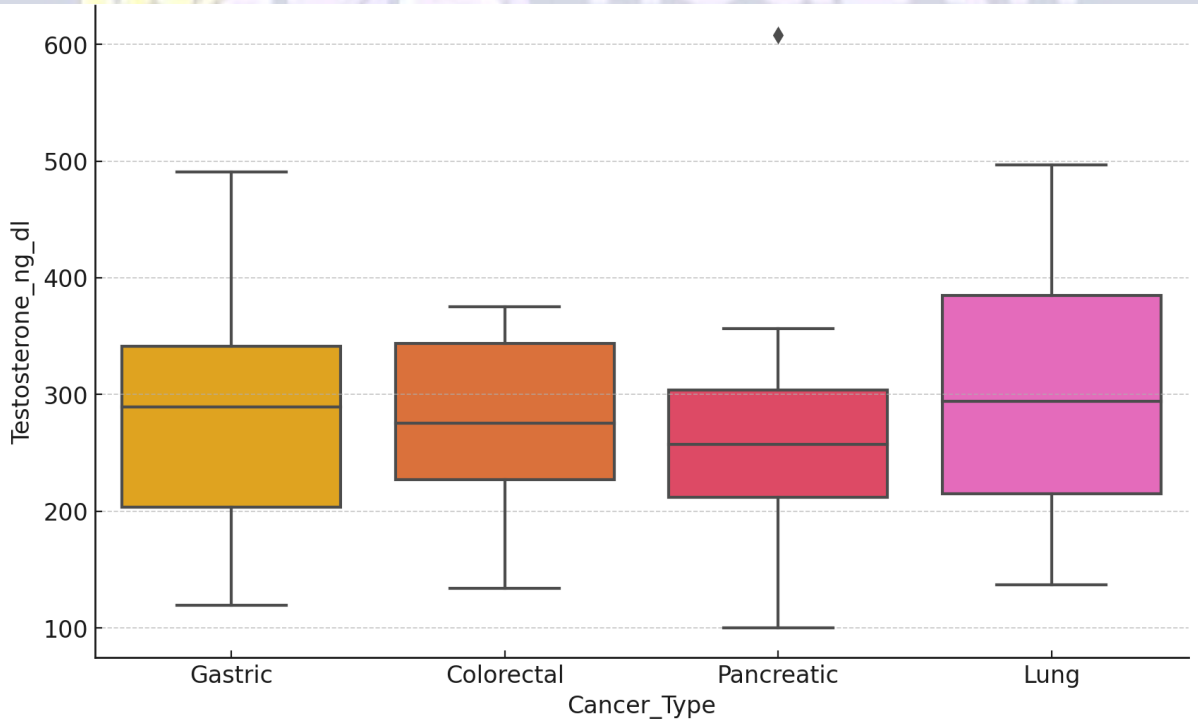

Figure 4: Testosterone Levels by Cancer Type

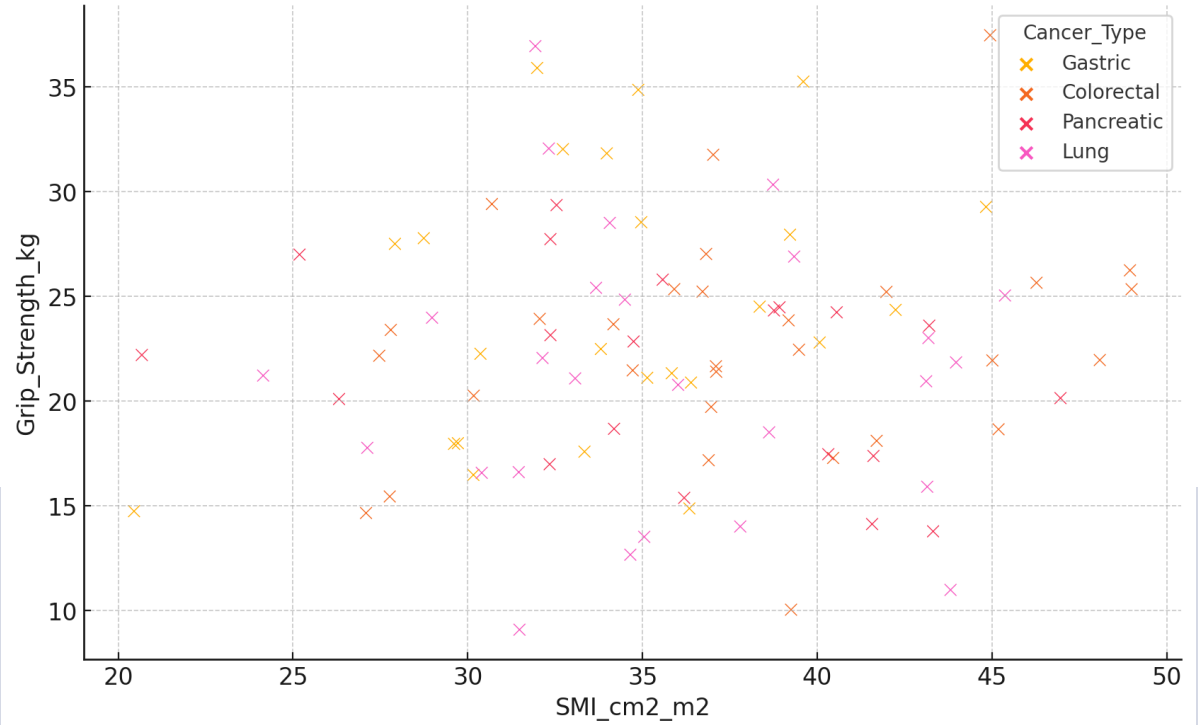

Figure 5: SMI vs Grip Strength

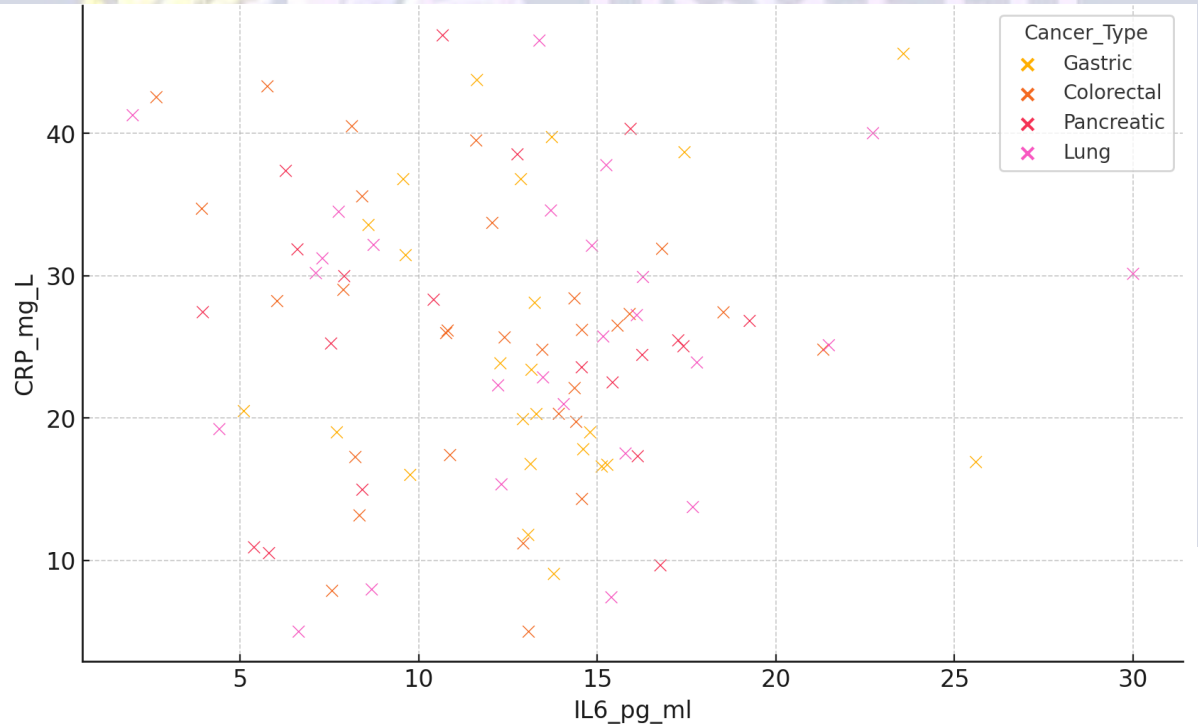

Figure 6: IL-6 vs CRP Correlation

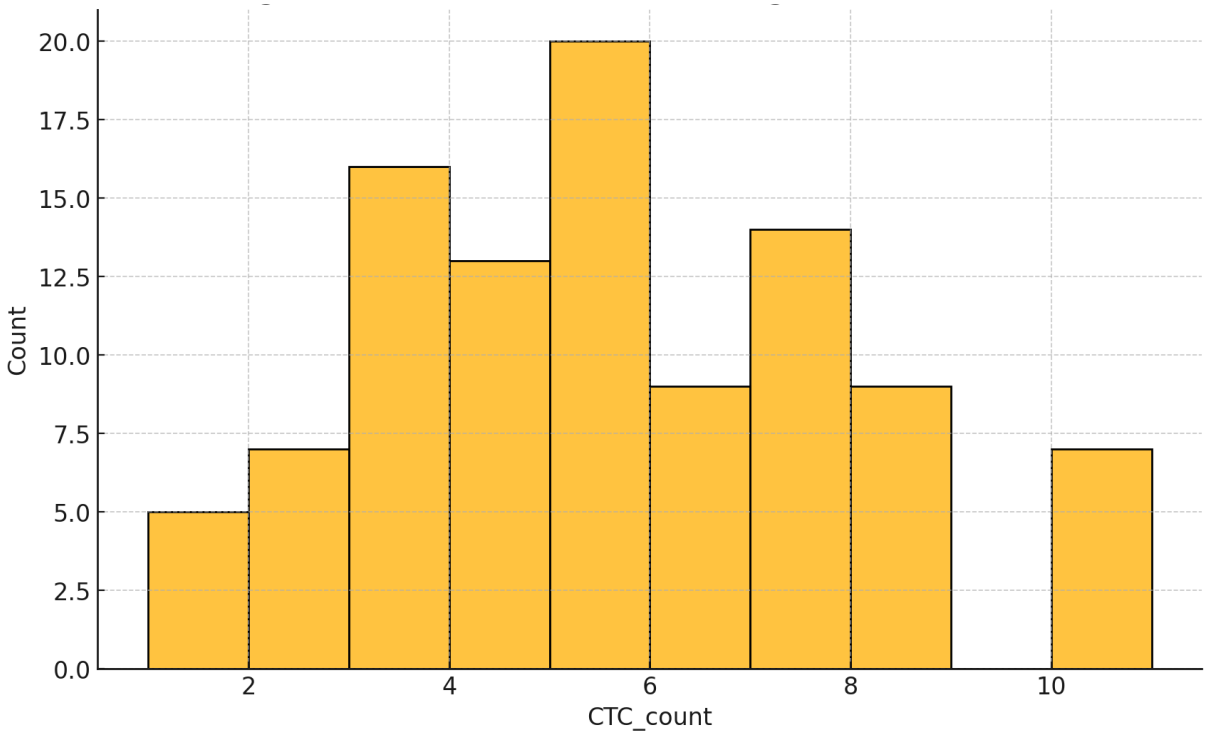

Figure 7: Distribution of Circulating Tumor Cell (CTC) Count

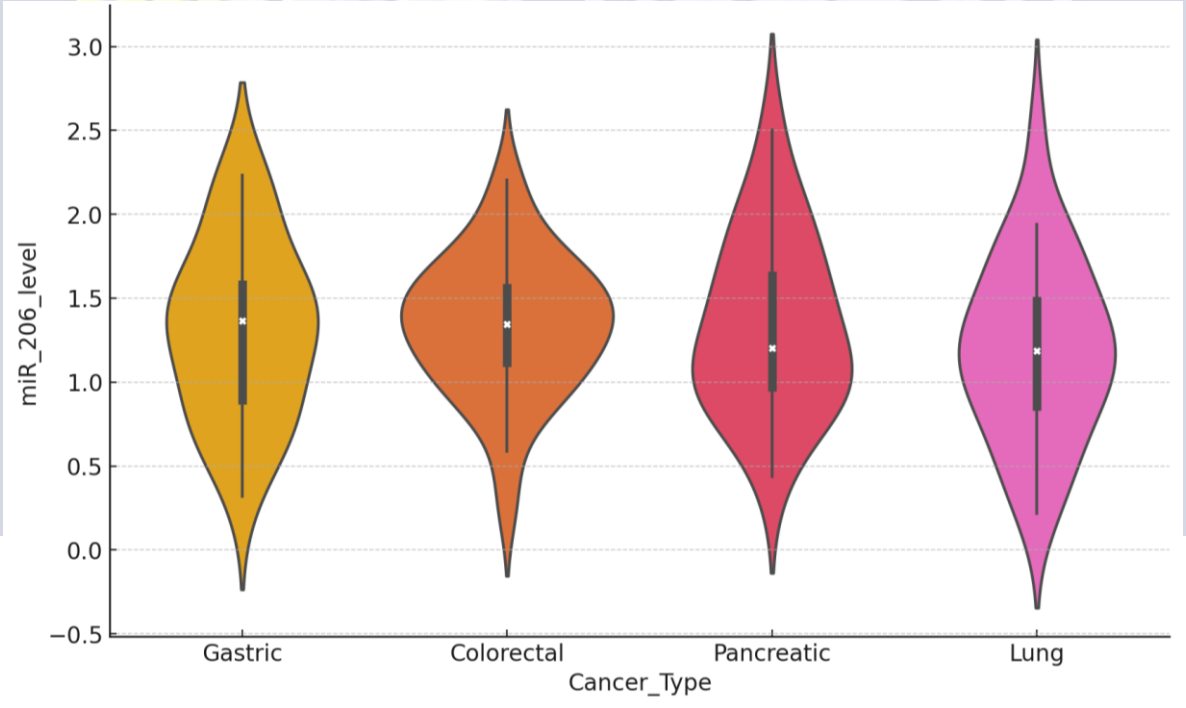

Figure 8: miR-206 Expression by Cancer Type

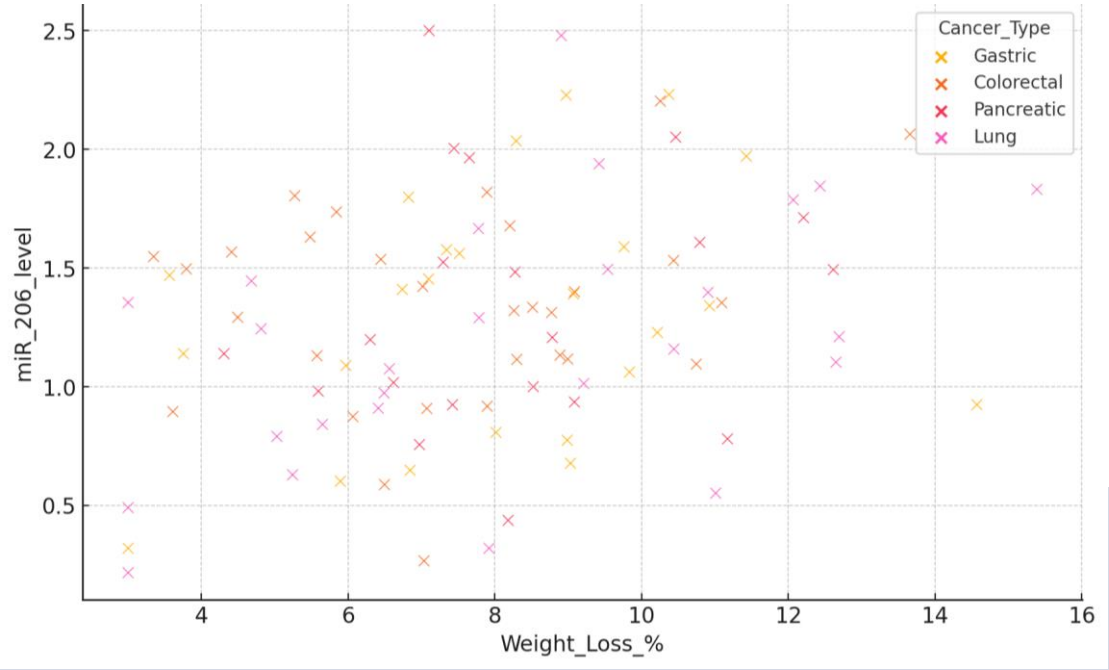

Figure 9: Weight Loss vs miR-206 Expression

DISCUSSION

The investigation of biomarkers in cancer cachexia demonstrates that many inflammatory, hormonal, and molecular processes are involved. The study reveals that miR-206 could potentially become a new biomarker that does not require invasive tests (Murata et al., 2024; Xie et al., 2022). This research contributes to efforts aimed at upgrading prognosis in oncology by using additional clinical and tumor indicators. Since weight loss, weaker muscles, and increased miR-206 often happen together, it is suspected that miR-206 could be a predictor for the development of cachexia. There is a common link between cancer-related inflammation and IL-6, TNF-α, and CRP markers (Yang et al., 2022).

When muscle breakdown occurs faster due to inflammation, it causes a reduction in muscle mass (Ravindranathan et al., 2021). It is necessary to advance research to understand the relationship between the pro-inflammatory and anti-inflammatory pathways in cachexia (Xu et al., 2020). Compromised feeding may be a result of gastric or pancreatic cancer, with a possible cause being lowering of the body's testosterone levels caused by hormonal changes. If there is less testosterone in the body, muscles can quickly break down since testosterone aids in building and strengthening them. Among certain patients, boosting hormone levels by adding hormone therapy or using certain androgen receptor modulators is an option to prevent muscle loss. Data from the study shows a correlation between how advanced the cancer is and the quantity of circulating cancer cells, suggesting that cancer impact on body metabolism depends on how much and how severely the cancer spreads. The loss of body mass during cancer, or cachexia, is due in part to the way cancer cells interact with their environment (Pal et al., 2022). An approach being explored for cancer therapy is to affect the disease's metabolism (Zhao & Li, 2021).

Manipulating nutrition and metabolism may contribute to the management of cancer (Lin et al., 2021). Apparently, altering the amount of food and calories could have an effect on how cancer cells function and how they respond to treatments. Any

effective treatment of cancer should take into account the many changes in a tumour's metabolism (Otto, 2020).

Different types of cancer often require different approaches due to the variation seen in cachexia. It is stated in the study (Longo and Cortellino, 2023) that several indicators should be used to assess the risk of cachexia more precisely. Therefore, including these measures in common clinical procedures could benefit patients by using them to reduce the risk of cachexia.

Since these cells can metabolize things differently, cancer cells can adapt to places where food is scarce (Kumera et al., 2019). Alterations in glucose, lipid, and amino acid metabolism occur due to the reprogramming, and these adjustments could be employed as diagnostic tools or used for treating the disease (Zhu et al., 2023). When the body needs more energy, metabolism may switch from using oxygen to produce energy to using less oxygen. Additionally, cancer cells rely on greater glutamine absorption to help sustain their own growth and existence.

CONCLUSION

The research incorporates both clinical and scientific data to help identify possible markers connected to muscle wasting in cancer patients with cachexia. We found that systemic inflammation, hormone changes, and tumor-related genes are the main contributors to cachexia. High levels of IL-6 and CRP and decrease in testosterone and IGF-1 point to a combined loss of ability to build and maintain muscle. Significantly, a relationship with grip strength, SMI, and weight loss was found for miR-206, implying it could serve as a biomarker. It is suggested to have significant significance in the early detection and development of the disease, as it is more prominent in people with severe sickness and strong muscle loss. Individuals losing a lot of weight were found to have a higher number of CTCs, indicating that muscle loss is related to how active the tumour is. When there is more inflammation and changes in miRNA, both the muscle mass and its functions decrease together, as the correlation matrix explains. In those subgroups with SMI <30 cm^2/m^2 or a 10% decrease in weight, it was confirmed that miRNA and inflammatory markers are higher and so are useful for risk assessment. To that end, our study points out that a panel of biomarkers, including miR-206, those related to inflammation, hormonal changes, and others, is essential for detecting and managing cancer cachexia. It also appears that liquid biopsy approaches, using miRNA and CTCs, can be useful for monitoring cachexia in patients. To fully understand the role these biomarkers might play, it would be necessary to conduct additional research over a longer time span. An early and accurate approach based on biomarkers can help cancer patients who suffer from cachexia improve their conditions and quality of life.

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