Aus dem Comprehensive Cancer Center
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Evaluation of Body Weight and Body Composition in Patients with Metastatic Colorectal Cancer or SARS-CoV-2 Infection

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Zusammenfassung (Deutsch):

Körpergewicht und Körperzusammensetzung können sich auf verschiedene Behandlungsergebnisse auswirken. Ziel dieser Dissertation ist es, die Auswirkungen von Körpergewicht und Körperzusammensetzung in Patienten mit metastasiertem kolorektalkarzinom (engl. *metastatic colorectal cancer*; mCRC) und SARS-CoV-2-Infektion zu untersuchen. Insbesondere liegt der Schwerpunkt auf der Auswirkung von Körpergewicht und Skelettmuskelmasse vor Einleitung einer Chemotherapie sowie deren Entwicklung drei Monate hiernach bei Patienten mit mCRC. Bei Patienten mit COVID-19-Infektion wird die Fettgewebekompartimenten untersucht.

Der Körpergewichtsverlust wird als negativer prognostischer Faktor für das Überleben bei Patienten mit malignen Erkrankungen angesehen. Entsprechend wurde das Körpergewicht während der Behandlung im Rahmen der FIRE-3-Studie nachträglich bewertet. Diese randomisierte Phase III Studie untersuchte mit FOLFIRI (Folinsäure, Fluorouracil und Irinotecan) eine Standard-Erstlinienchemotherapie zusammen mit Cetuximab oder Bevacizumab bei mCRC Patienten mit RAS-WT-Tumoren (d.h., Wildtyp in KRAS- und NRAS Exone 2-4). Um mit den Wirksamkeitsendpunkten und den Nebenwirkungen der Behandlung zu korrelieren, wurden die Patienten nach klinisch signifikantem frühem Gewichtsverlust (engl. early weight loss; EWL) im dritten Monat ≥ 5% und < 5% eingeteilt.

Univariate und multivariate logistische Regressionen wurden verwendet, um Einflussfaktoren auf EWL zu bewerten. Hier zeigte sich nur das Patientenalter ≥ 65 Jahre als unabhängig prädiktiv für das Auftreten von EWL (Odds Ratio (OR) = 2,37; 95% Konfidenzintervall (CI) = 1,16-5,04; P = 0,021). Das Alter war der einzige signifikante Prädiktor für die EWL und folgt einer linearen Beziehung (P = 0,016). EWL zeigte sich signifikant korreliert mit Nebenwirkungen unter Therapie: Durchfall, Ödemen, Müdigkeit, Übelkeit und Erbrechen. Darüber hinaus ergab eine multivariate Analyse, dass EWL ein unabhängiger ein schlechteres Gesamtüberleben (OS) (32,4 vs. 21,1 Monate, P = 0,0032) sowie progressionsfreie Überleben (PFS) (11,8 vs. 9,0 Monate, P = 0,003) prädizieren vermochte.

Zusammenfassend erscheint EWL ≥ 5% nach drei Monaten Therapie bei Patienten mit mCRC ein Prädiktor für Patientenüberleben und Nebenwirkungen unter Behandlung. Klinische Ernährungsberater und Onkologen sollten hierauf besonderes Augenmerk legen. Insbesondere bei geriatrischen Patienten mit mCRC besteht das Risiko für einen signifikanten Gewichtsverlust unter Therapie.

Da sich die Ernährungsbewertung von einer einfachen anthropometrischen Messung des Körpergewichts zu spezifischen Bewertungen der Körperzusammensetzung entwickelte, bewerteten wir ebenfalls den Skelettmuskelindex (SMI) und teilten die untersuchten Dickdarmkarzinompatienten entsprechend einem geschlechtsspezifischen Schwellenwert zur Definition von Sarkopenie ein. Hierfür wurde retrospektiv die entsprechende CT-Bildgebung ausgewertet. Es zeigte sich, dass der SMI der Patienten zu Therapiebeginn keine signifikante Korrelation mit Gesamtüberleben aufwies (28,1 vs. 27,1 Monate, P = 0,12) oder Progressions-freiem Überleben (10,5 vs. 10,4 Monate, P = 0,33). Bei Patienten mit Sarkopenie trat jedoch eine höhere Inzidenz von unerwünschten Ereignissen unter Behandlung auf, einschließlich Hämatotoxizität. Schließlich bewerteten wir die Veränderungen von SMI (engl. skelettal muscle change; SMC). Patienten mit einem SMI-Verlust > 5% und einem SMI-Gewinn > 5% hatten keinen signifikanten Unterschied im Gesamtüberleben. Daher betrachteten wir diese gemeinsam und fanden einen signifikanten Unterschied zu denjenigen Patienten, deren SMI in Grenzen von -5% bis 5% stabil blieb. Patienten mit einer extremeren Veränderung des SMIs zeigten ein signifikant vermindertes Gesamtüberleben (Hazard Ratio (HR) = 1,99; 95% CI = 1,32-2,99; P = 0,00092). Die prognostische Eigenschaft eines stabilen SMI zeigte sich hierbei in einer multivariate Cox-Regressionsanalyse als signifikant unabhängig von weiteren relevanten Prognosefaktoren sowie auch von Körpergewichtsverlusst (EWL).

Die Körperzusammensetzung kann auch eine Rolle bei den Ergebnissen von Patienten mit chronischen und infektiösen Krankheiten spielen. Beispielsweise ist bekannt, dass höhere Mengen an Fettgewebe ein Risikofaktor für schwere Erkrankungen bei COVID-19 Patienten sind. Unsere Studie umfasste 58 Patienten, bei denen COVID-19 diagnostiziert wurde, und führte eine Analyse der Körperzusammensetzung unter Verwendung der Thorax-Computertomographie am 12. Level der Brustwirbelsäule durch. Wir analysierten den Einfluss von Fettgewebekompartimenten (viszerales Fettgewebe (VAT), subkutanes Fettgewebe (SAT), epikardiales Fettgewebe (EAT), Leberfett) und anthropometrischen Parametern wie dem Verhältnis von Taille zu Körpergröße (WtHR) auf den Grad von systematischer Entzündung und ihre Korrelationen mit der Notwendigkeit einer invasiven mechanischen Beatmung (IMV). Unsere Studie legt nahe, dass WtHR, VAT und Leberfett stark mit der Notwendigkeit von IMV verbunden sind und überlegene Parameter sind, die die Notwendigkeit von IMV im Vergleich zum Body-Mass-Index (BMI). WtHR, VAT, EAT und Leberfett sind bei COVID-19 Patienten mit höheren Interleukin-6-Grundwerten (IL-6) assoziiert, was auf einen möglichen Zusammenhang zwischen einer mit Fettleibigkeit verbundenen Entzündung

und einer übermäßigen Immunantwort nach einer COVID-19-Infektion hinweist. Diese Studie legte nahe, dass mit Fettleibigkeit verbundene systemische Inflammation eine wichtige Rolle bei den durch SARC-CoV-2 ausgelösten Entzündungsreaktionen spielen könnten.

Abstract (English):

Body weight and body composition can influence treatment outcomes. Therefore, the aim of this dissertation is to explore the effects of body weight and body composition on outcomes in patients with metastatic colorectal cancer (mCRC) and SARS-CoV-2 infection. Specifically, the focus is on effect of body weight and sarcopenia and percentage of change of skeletal muscle index from baseline to month 3 among patients with mCRC undergoing therapy, as well as adipose tissue distribution among patients with COVID-19 infection.

Body weight loss is frequently regarded as negatively related to outcomes in patients with malignancies. Therefore, in this retrospective analysis we evaluated body weight during the first six months of treatment within FIRE-3 trial. The randomized phase III study evaluated standard first-line chemotherapy FOLFIRI (folinic acid, fluorouracil and irinotecan) together with cetuximab or bevacizumab in mCRC patients with RAS wild-type tumors (i.e. wild-type in KRAS and NRAS exons 2-4) (1). To correlate with efficacy end points and treatment side effects, patients were divided into two groups based on clinically significant early weight loss (EWL) ≥ 5% and < 5% at month 3.

Univariate and multivariate logistic regressions were applied to evaluate predictors for EWL. Here, only patient age ≥ 65 independently predicted the occurrence of EWL (odds ratio (OR) = 2.37; 95% confidence interval (CI) = 1.16-5.04; P = 0.021). Of note, patient age exhibited a linear effect on log-odds ratio regarding the occurrence of EWL (P = 0.016). EWL was furthermore significantly correlated with the incident frequencies of diarrhoea, oedema, fatigue, nausea, and vomiting. Furthermore, a multivariate analysis indicated EWL to be an independent negative prognostic factor for overall survival (OS) (32.4 vs. 21.1 months, P = 0.0032) and progression free survival (PFS) (11.8 vs. 9.0 months, P = 0.003). In summary, EWL ≥ 5% after 3 months of treatment in mCRC patients is a predictor for patients' outcomes and treatment related adverse events. Clinical dietitians and oncologists need to pay attention to patients with EWL ≥ 5%. Particularly in geriatric patients with mCRC, early preventative measures for weight maintenance are advised.

As guidelines recommend when possible, to augment the simple anthropometric measurements used in nutritional screening and assessment with specific evaluations of body composition (2, 3), change of skeletal muscle index (SMI) using computed tomography scans and divided mCRC patients into two groups according to their sex specific SMI before initiating therapy (sarcopenia vs. no sarcopenia) were evaluated. It is shown that the SMI of the patients at the start of therapy had no significant correlation with OS (28.1 vs. 27.1 months, P = 0.12) or PFS (10.5 vs. 10.4 months, P = 0.33). However, patients

with sarcopenia experienced higher incidence of post treatment adverse events including hematotoxicity. Then, the change of SMI (SMC) on survival were evaluated. Patients with SMI loss > 5% and SMI gain > 5% had no significant difference on OS. Thus, we merged the groups with SMI loss > 5% and SMI gain > 5% into absolute SMC > 5% and found that it is an independent prognostic parameter for OS compared to patients with stable SMC (absolute SMC $\leq$ 5%) (hazard ratio (HR) = 1.99; 95% CI = 1.32-2.99; P = 0.00092). Hereafter, the prognostic property of a stable SMC is shown in a multivariate Cox regression analysis to be significantly independent of other relevant prognostic factors as well as EWL.

Body composition can also play a vital role in the outcomes of patients with chronic and infectious diseases and should therefore be considered as a possible assessment parameter. For example, higher amount of adipose tissues is known to be risk factor for severe disease in COVID-19 patients (4). We conducted a body composition analysis on 58 patients diagnosed with COVID-19. We analyzed the impact of adipose tissue compartments (visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), epicardial adipose tissue (EAT), liver fat) and anthropometric parameters like waist to height ratio (WtHR) on the degree of systematic inflammation and their correlations with necessity of invasive mechanical ventilation (IMV). To this end, we evaluated the available computed tomography scans, accordingly. Our study suggested that WtHR, VAT and liver fat are strongly associated with necessity of IMV and are superior parameters that strongly predict necessity of IMV compared with body mass index (BMI). WtHR, VAT, EAT, and liver fat are associated higher levels of baseline IL-6 in COVID-19 patients, indicating a possible association between obesity-associated inflammation and excessive immune response upon COVID-19 infection. The low-grade inflammatory status caused by metabolism alterations is known as meta-flammation. This study suggested that obesity associated meta-inflammation might play an important role in the SARC-CoV-2 triggered inflammatory responses.

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- ACE2	angiotensin-converting enzyme 2
- AE	adverse event
- AIC	Akaike information criterion
- ARDS	acute respiratory distress syndrome
- AUC	area under the curve
- BIA	bioelectrical impedance analysis
- BMI	body mass index
- BSA	body surface area
- CEA	carcinoembryonic antigen
- CI	confidence interval
- COPD	chronic obstructive pulmonary disease
- COVID-19	coronavirus disease 19
- CR	complete response
- CRC	colorectal cancer
- CRP	C-reactive protein
- CSA	cross-sectional area
- CT	computed tomography
- CTCAE	Common Terminology Criteria for Adverse Events
- DLT	dose-limiting toxicity
- DXA	dual-energy X-ray absorptiometry
- EAT	epicardial adipose tissue
- ECOG	Eastern Cooperative Oncology Group
- EWGSOP2	European Working Group on Sarcopenia in Older People
- EWL	early weight loss
- FFAs	free fatty acids
- FiO_2	fraction of inspired oxygen
- 5-FU	fluorouracil
- GLIM	Global Leadership Initiative on Malnutrition

- HIV	human immunodeficiency virus
- HR	hazard ratio
- HU	Hounsfield units
- ICU	intensive care unit
- IL-1β	interleukin-1β
- IL-6	interleukin-6
- IMV	invasive mechanical ventilation
- LBM	lean body mass
- LDH	lactate dehydrogenase
- LLD	liver limited disease
- L3	third lumbar vertebra
- mCRC	metastatic colorectal cancer
- MRI	magnetic resonance imaging
- OR	odds ratio
- OS	overall survival
- PaO_2	partial pressure of oxygen
- PCT	procalcitonin
- PFS	progression free survival
- PG-SGA	Patient-Generated Subjective Global Assessment
- PR	partial response
- ROC	receiver operating characteristic
- ROIs	regions of interests
- RT-PCR	real-time reverse transcriptase polymerase chain reaction
- SD	stable disease
- SAT	subcutaneous adipose tissue
- SIV	simian immunodeficiency virus
- SMC	change of skeletal muscle index
- SMI	skeletal muscle index
- SML	skeletal muscle loss

- SMM	skeletal muscle mass
- SOFA	Sequential Organ Failure Assessment
- TH12	12th thoracic vertebrae
- TNF-α	tumor necrosis factor-α
- VAT	visceral adipose tissue
- vs.	versus
- VSR	visceral to subcutaneous adipose tissue area ratio
- WC	change of weight
- WHO	world health organization
- WtHR	waist to height ratio

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1. Introduction

1.1 General introduction

Weight is an important anthropometric parameter. Body composition is the proportion of fat tissue and non-fat tissue, including muscle, bones, and organs and is in additional an increasing more recognized anthropometric and clinical parameter (5). Weight loss and sarcopenia influence human health through affecting the nutritional status, quality of life, treatment outcomes, and overall well-being (6). These two anthropometric parameters flow into the Global Leadership Initiative on Malnutrition (GLIM) for nutritional assessment (7). GLIM recommends the diagnosis of malnutrition with at least one phenotypic criterion (nonvolitional weight loss, low body mass index (BMI), and decreased muscle mass), and one etiologic criteria (reduced food intake/ assimilation and disease burden/inflammation) (Figure 1) (7).

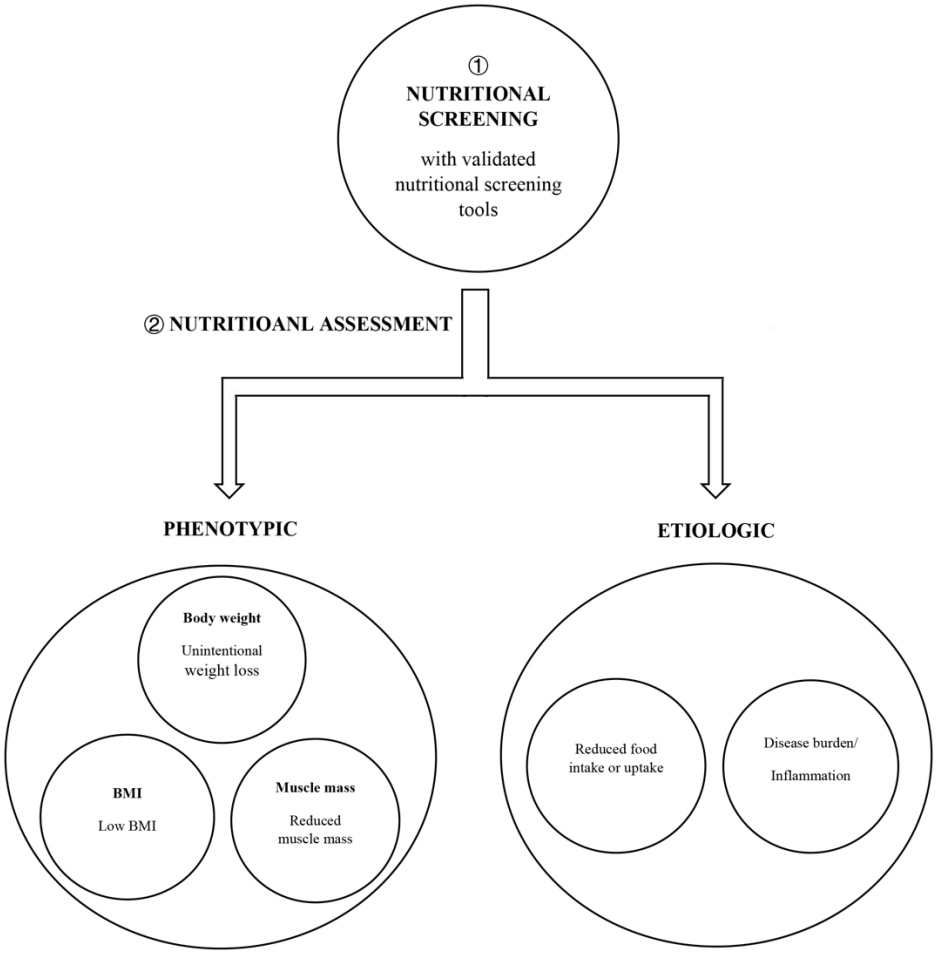


Figure 1. This figure was adapted from the GLIM diagnostic scheme of malnutrition. Abbreviation: GLIM = Global Leadership Initiative on Malnutrition.

Cancer patients represent a vulnerable population for body composition and weight related complications (6, 8). A common recommendation for cancer patients is the simple importance of recording the patient's body weight from the time they are first diagnosed with cancer and to follow the evolution of body weight as patients proceed through all aspects of care. This recommendation is based, in part, on the fact that weight loss is a negative predictor in patients with malignancies, which leads not only to more complications during antineoplastic treatment, but also to possible treatment interruptions as it makes patients more vulnerable and less able to tolerate the treatment. Furthermore, when patients lose weight, it is probable that they also lose muscle mass (9-11). Patients with low muscle mass (skeletal muscle index (SMI) < 52.4 cm^2/m^2 for men and < 38.5 cm^2/m^2 for women) and muscle function are diagnosed as sarcopenic, regardless of their weight (12). During the past decade, more clinical studies focused on the evaluation of sarcopenia and found that it indicated disease severity as negative prognostic factors especially in cancer patients (13-17).

While weight and sarcopenia contribute to worse outcomes among patients with malignant diseases, adipose tissue has been associated with the severity of infectious diseases (18). This association is also important for understanding the influence of body composition on treatment outcomes in patients infected with the coronavirus disease 19 (COVID-19) (19-22). However, as the novel COVID-19 is still developing and spreading at a rapid rate, treatment priorities and methods need to be developed rapidly. Therefore, almost all studies to date use the BMI to predict severity of the disease and predict the necessity of invasive mechanical ventilation (IMV). However, BMI alone does not reflect adipose tissue compartments, such as visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), epicardial adipose tissue (EAT), and liver fat. As COVID-19 is still not fully understood it could therefore contribute useful insights to gain a deeper understanding of how body composition may affect and predict outcomes among this patient population.

The aim of my doctoral thesis, therefore, was to add new insights into this research area. The focus of the thesis will remain on the prognostic relevance of EWL and baseline sarcopenia and change of SMI (SMC) on survival and adverse events (AEs) in metastatic colorectal cancer (mCRC) patients, and the correlation of adipose tissue compartments with respiratory failure and its association with inflammation in COVID-19 patients was analyzed.

1.1.1 Associations between body weight and survival in mCRC patients

Colorectal cancer (CRC) is the world's second most common cancer in females and the third most common cancer in males (23). The 5-year survival rate declines to 12% for mCRC patients (24). Loss of body weight before and during antineoplastic treatment is commonly observed in patients with malignancies and is frequently negatively correlated with survival and AEs (25, 26). Studies suggested that weight loss during chemotherapy causes an inferior survival in lung cancer patients (27) and gastrointestinal cancers (28). Treatment side effects, particularly in the gastrointestinal tract, can lead to significant weight loss, and are known to impair physical performance, and can subsequently result in a continuous deterioration of the patient's overall state and well-being (29). However, to the best of our knowledge, no studies have yet evaluated the effect of weight loss on survival and AEs in patients with RAS wild-type mCRC during the targeted first-line treatment. Previous studies that have been identified did not evaluate the longitudinal evolution of weight loss and focus on the importance of EWL. Therefore, retrospective analysis of the FIRE-3 study enabled the investigation of the evolution of weight loss from baseline to month 6 during the targeted first-line treatment. For this purpose, EWL was defined in accordance with previous publications. The most common cut-off point for EWL $\geq$ 5% from previous publications designates this cut-off point as an acceptable parameter indicating malnutrition (10, 30-33).

Weight loss $\geq$ 5% in the last six months is defined as cancer cachexia according to international consensus (34). Cachexia is correlated with complications of cancer therapies (35). Cancer patients with cachexia experience a reduced quality of life, overall well-being, and these patients are known to present an increased burden to health care systems (35). According to a systematic review investigating prevalence of cachexia in cancer patients in USA and the European Union (EU), around 37% patients are at risk of developing cachexia in all types of cancer (36). For CRC patients, the risk of developing cachexia is reported to be 50% (36). For patients with liver and pancreatic cancer, the risk has been reported to reach 90% (36). Until now, no effective treatment is available to reverse cancer cachexia and no medicine is approved to cure it (35). Therefore, prevention is the only effective method of reducing risk. To this purpose, recognition of cancer patients' weight loss in time gives nutritionists and oncologists more time to find causes and seek interventions as early as possible. Thus, patients have more chance to be treated at proactively before or at the start of weight loss. Cancer treatment may affect patients' eating habits and the ability to the nutrients. Thus, a personalized professional dietary counseling delivered through a qualified dietitian specializing in cancer should be available to cancer patients before, during and after cancer treatment (10, 11).

1.1.2 Associations between sarcopenia and survival and pharmacokinetics in mCRC patients

Sarcopenia is a term that used to define loss of skeletal muscle mass (SMM) and strength for geriatric patients (2, 37). Over time, the term has become more generalized term and is used to broadly describe skeletal muscle disorder with increased likelihood of AEs, with low muscle strength rather than low SMM as a principal determinant (3, 38). According to the guidelines most recently published by European Working Group on Sarcopenia in Older People (EWGSOP2) in 2019, probable sarcopenia is identified by low muscle strength (3). Diagnosis is confirmed by further reduced muscle quantity or low quality (2). If reduced muscle strength, quantity/quality and low physical performance are identified, severe sarcopenia is assumed (2). Muscle mass can be reported as SMM or SMI. SMI is normalized by dividing the cross-sectional area (CSA) of SMM by the square of the patient's height in meters (SMM/height^2) (12).

Sarcopenia is also considered to be a potential biomarker for survival and mortality in CRC patients. Sarcopenia is known to also contribute to cancer surgery complications and dose-limiting toxicity (DLT) during systemic anticancer therapy. Many chemotherapy treatments doses are calculated by body surface area (BSA) developed from DLT testing trials. Yet, some cancer patients still experience AEs due to inaccuracy of doses (39). Sarcopenia was found to affect the pharmacokinetics of different drugs including anti-cancer drugs (40). A study evaluated the pharmacokinetics (including clearance and volume of distribution) of fluorouracil (5-FU) in 34 CRC patients with different body compositions suggested that the pharmacokinetics of 5-FU are better predicted by fat free mass than by BSA (40). Sarcopenic patients had significantly higher health care costs during hospitalization than those without sarcopenia. Reported sarcopenia prevalence in the geriatric population ranges from 18.6% to 22.6% in elderly women and 23.6% to 26.8% in elderly men (41, 42). For patients older than 80 years old, its prevalence is even higher, and is reported to be 31.0% for females and 52.9% for males, respectively (41). For CRC patients undergoing surgery, the prevalence of pre-operative sarcopenia is reported to be even higher, with 40.6-51.8% for females and 48.2-59.4% for males (43).

Sarcopenia has gained interest as a possible independent prognostic factor for patients with different diseases. Focusing specifically on CRC patients, a low SMI at recruitment was not correlated with survival for mCRC patients during chemotherapy (44). However, loss of SMI ≥ 9% at month 3 after receiving chemotherapy was independently associated with a patient's outcome when adjusted for other clinical relevant parameters (hazard ratio (HR) = 4.47; 95% confidence interval (CI) = 2.21-9.05; $P < 0.001$) (45). A retrospec-

tive study of 300 mCRC patients during first-line palliative systematic treatment of chemotherapy capecitabine + oxaliplatin + bevacizumab (CAPOX-B) demonstrated that loss of SMI was associated with tumor response (46). Patients with stable disease (SD) lost 2.48% more SMI compared to patients with partial response (PR) or complete response (CR) after 6 cycles of chemotherapy (46). A prospective randomized phase 3 CAIRO3 study of 450 mCRC patients showed that SMI may be influenced by the intensity of systemic treatment regimens and thus can be reversed (47). A retrospective study of the same CAIRO3 study also found that during subsequently less intensive maintenance capecitabine + bevacizumab (CAP-B) or observation, SMI recovered to its pre-treatment levels (48). Finally, after receiving more intensive treatment CAPOX-B, they further lost SMI. In a large-scale observational study with 3262 men and women diagnosed with stages I to III CRC, sarcopenic patients had the highest overall and CRC-specific mortality rates (49). In another prospective study among 650 patients undergoing surgery for CRC, sarcopenia was calculated to be predictive parameter for overall survival (OS) in multivariate analysis (HR = 1.50, P = 0.031) (43).

1.1.3 Hyperinflammation in patients with severe COVID-19

On the opposite side of the spectrum, distribution of muscle and fat can also affect clinical outcomes (50). Therefore, it is also interesting to examine how body fat distribution can affect the outcomes of new and emerging diseases. The clinical course of pandemic COVID-19 which began in December of 2019 is so far highly heterogeneous. According to world health organization (WHO), most patients infected with COVID-19 will experience mild or moderate symptoms. Yet, other patients are more at risk. It is suggested that up to 15% developed into acute respiratory distress syndrome (ARDS) (51, 52). Around 5% patients are estimated to fall critically ill and need intensive care, including IMV (53, 54). Several risk factors for severe courses have been identified, such as age, gender, D-dimer level, and the presence of cardiovascular, metabolic and/or pulmonary comorbidities (53, 55). A retrospective study of 191 COVID-19 patients from Wuhan, China- where the outbreak was originally identified suggested that age, a higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer > 1 µg/mL were potential parameters to discriminate patients with poor prognosis at an early stage (53). Another study showed a correlation of persistently elevated inflammatory markers with ARDS (56).

The cytokine cascade which is caused by a severe COVID-19 infection describes an overproduction of inflammatory cytokines and is a hallmark feature associated with severe outcomes (57). Among these different cytokines, interleukin-6 (IL-6) seems to be of

crucial importance and is not only correlated with severity of COVID-19 but also with influenza (58, 59). A recent study identified the risk factors associated with the need of IMV for COVID-19 patients and found that IL-6 and C-reactive protein (CRP) are highly predictive of the need of IMV (60). Other inflammatory markers also increased during the course of a COVIE-19 infection include ferritin, procalcitonin (PCT) and lactate dehydrogenase (LDH) (51, 53, 61). In fact, maximal IL-6 levels during the course of COVID-19 predicted the respiratory failure with the highest accuracy, followed by CRP level (IL-6: area under the curve (AUC) = 0.97, 95% CI = 0.93-1.0; CRP: AUC = 0.86, 95% CI = 0.74-0.98) (60). When a level of maximal IL-6 concentration of 80 pg/mL and higher was reached, the median time to IMV was 1.5 days ranging from 0 to 4 days (60). When a level of maximal CRP level of 97 mg/L was reached, the median time to IMV ranged from 0 to 4 days (60). Furthermore, an association of increased inflammatory markers and survival in COVID-19 patients is considered to be an indicator of a high-risk phenotype.

COVID-19 associated meta-inflammation was defined by a retrospective cohort study as CRP level > 150 mg/L or doubling within 24 hours from > 50 mg/L, or a ferritin level > 1500 µg/L (62). The criteria of COVID-associated hyperinflammation significantly correlated with the risk of next-day IMV or death (62). For patients in the high-risk inflammatory phenotypes, the adverse outcomes could be ameliorated through modulation of hyperinflammatory responses (63-66). Several clinical trials evaluated the effects of anti-IL-6-receptor monoclonal antibodies including sarilumab, tocilizumab and the anti-IL-6 monoclonal antibody siltuximab in COVID-19 patients. There is to date only unpublished studies available describing the efficacy of siltuximab. These studies suggest that the 30-day mortality rate was much lower in patients in the siltuximab group compared to patients in the control group (HR = 0.462, 95% CI = 0.221-0.965, P = 0.0399) (67). A prospective, open-label study investigated the efficacy of tocilizumab with 63 hospitalized COVID-19 patients of severe cases (68). Following administration of tocilizumab, the mean ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (PaO_2/FiO_2 ratio) improved from 152 ± 53 at randomization to 283.73 ± 115.9 at day 7 and 302.2 ± 126 at day 14 ($P < 0.05$) (68). Inflammatory markers including CRP, ferritin, and D-dimer levels declined. No moderate to severe AEs were reported. However, this trial had known limitations and it did not describe a control group. Future randomized controlled trials in patients with severe COVID-19 are therefore in need to validate the benefit of IL-6 antibodies (68).

1.1.4 Adipose tissue compartments and outcomes in COVID-19 patients

Hospitalized COVID-19 patients have shown a high prevalence of obesity. However, this data is not always consistent. A Spanish study which included 48 COVID-19 patients with admission to intensive care unit (ICU) suggested that most common comorbidity identified was obesity (48 %) (69). Similarly, a large-scale population-based study indicated that among 1482 patients hospitalized with COVID-19, almost half (48.3%) were obese (70). In contrast, a Chinese study with 383 COVID-19 patients suggested that 10.7% were obese at admission (71). A study evaluating 3611 fatal COVID-19 cases from Brazil, and comparing them to 23188 fatal COVID-19 cases from Italy found the prevalence of obesity ranges from 4.6% in Brazil to 12.1% in Italy (72).

Nevertheless, recent data strongly supports the theory that overweight and obese patients are at high risk during a COVID-19 infection (73-77). The mechanisms that are postulated to increase risk are considered plausible. SARS-CoV-2 not only directly attacks the epithelial cells but can also induce inflammatory responses and cytokine release syndrome. Obesity contributes thus enhances the hyperinflammatory immune responses and ARDS development through the release of pro-inflammatory cytokines including IL-6, interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) (73, 78). When adipose tissue expands, they release inflammatory markers in the whole body and causes an overaction on part of the immune system (79). The excessive reaction of the immune system, in turn, causes damage to healthy tissues (80, 81).

Even though young COVID-19 patients are at lower risk of developing severe COVID-19, obese patients have been shown to be 2 times more likely to need acute care and 1.8 times more likely to receive critical care, than non-obese patients (73). Obese patients are also thought to be at a higher risk to develop pulmonary embolisms (0.7% of obese patients vs. 0.3% of the control population, $P < 0.0001$) (82). Abnormal coagulation results, especially elevated D-dimmer (2.12 vs. 0.61 ug/mL, $P < 0.001$) and FDP results (7.6 vs. 4.0 ug/mL, $P < 0.001$), are common in non-survivors compared to survivors (82). Obesity leads to restrictive pulmonary damage as it causes mechanical compressions on the lungs, diaphragm and chest cavity (83). In a few studies, obese patients with influenza were shown not only to have higher risk of developing into severe cases, but they were also shown to shed the virus for a longer period than the lean patients (84, 85).

Almost all previous studies presented here base the evaluation of obesity on BMI only and do not reflect adipose tissue distribution. While it may be the quickest and easiest method to determine obesity, there are recognized limitations of using BMI in assessing

obesity. Furthermore, the ratio of body fat to BMI changes across age, sex, ethnicity, and body condition (86-88). For example, a well-trained patient with a large amount of muscle mass may be considered obese using the BMI method alone. However, as the effects of muscle and adipose tissues distribution and amount affects health status, a simple calculation of BMI would not consider such a case. Furthermore, adipose tissue, particularly VAT, contributes to systematic inflammatory processes as it has endocrine functions and secretes multiple humoral factors including adipokines and cytokines (19). The enlarged VAT could therefore be regarded as vital organ. Among patients with human immunodeficiency virus (HIV) and simian immunodeficiency virus (SIV) infection diseased VAT is postulated to be a reservoir of virus leading to elevated virus loads (89, 90). Even though the coronavirus was detected only at low levels in the blood (91), it cannot yet be excluded that the virus's high affinity to its receptor angiotensin-converting enzyme 2 (ACE2) affects hematogenous spread to the adipose tissues (92). This theory can be supported by the fact that the ACE2 gene expression was higher in VAT than in SAT (93) and supports the notion that the virus might spread to the adjuvant VAT from infected organs - for example VAT may facilitate the spread from lungs to intrathoracic fat (92). The effect of SAT on inflammatory responses is heterogeneous as it is composed of deep and superficial depots with distinct metabolic effects (94). EAT covers 80% of the heart's surface (95). EAT correlates with VAT and with metabolic high risk situations and its changes upon obesity treatment (95). EAT is considered to be anatomically and functionally related to blood supply vessels. This is the reason that dysfunctional EAT is considered to be among the risk factors for cardiovascular diseases and, therefore, a potential therapeutic target (96). Liver fat content has also been shown to be an independent risk factor for metabolic morbidities in males (97).

Issues related to the association of adipose tissue distribution patterns with the increased morbidity and mortality in COVID-19 are essential. However, associations of adipose tissue compartments as well as anthropometric data with markers of inflammation in severe cases of COVID-19 have not been reported so far. Thus, we sought to analyze anthropometric data and adipose tissue distribution between COVID-19 patients with or without the necessity of IMV. Simultaneously, we incorporated a comprehensive analysis of the majority of immune-metabolically relevant adipose tissue sites such as VAT, SAT, EAT, as well as liver fat content using thoracic computed tomography (CT) scans. For the anthropometric analysis we chose to use waist circumference and waist to height ratio (WtHR) because these are known markers of obesity (98, 99). The goal was to use these parameters to identify an easy-to-use risk stratification platform for COVID-19 patients without the need of further diagnostics or enlargement of irradiation fields.

1.1.5 Relationship of sarcopenia and adipose tissue

There is a lack of consensus in the literature about how adipose tissue and sarcopenia are related. Prado et. al proposed that sarcopenic obese patients, in which severe obesity and sarcopenia occur at the same time, are associated with poorer functional status than obese patients without sarcopenia (12). However, B. C. Boer et al. found no association between sarcopenic obesity and OS after 1- and 3-years in CRC patients undergoing open colon resection ($P \geq 0.068$) (100).

The lack of consensus could be caused by the confounding factor that, throughout the aging process, adipose tissue is known to shift away from subcutaneous to visceral adipose and intramuscular areas (101). Beyond ectopic adiposity, impaired adipose tissue resulted in elevation of free fatty acids (FFAs), a common feature of many metabolic disorders. The most detrimental FFA is saturated FFA (101), which induces insulin resistance and inflammation. Evidence suggests that a correlation existed between chronic inflammation and skeletal muscle atrophy (102). For example, an analysis based on 336 community-dwelling elderly people (aged 59–70 years) in the UK suggested that higher inflammatory level (CRP) was associated with lower and accelerated decrease of muscle strength over time (103). An increased IL-8 level was also associated with higher risk of sarcopenia. These findings support that theory that the aging process may compound the problem of sarcopenia (103). Skeletal muscle loss (SML), with increasing intramuscular adipose tissue, leads to synthesis and pro-inflammatory adipokines secretions and decrease of myokines (104). The coexistence of sarcopenia and obesity could induce inflammatory microenvironment, consequently, impair immune function, accelerate muscle wasting and increase mortality risk (102). A retrospective study of 162 advanced pancreatic cancer patients proved that patients with SML ≥ 10% and high visceral fat before chemotherapy have a poor prognosis in both univariate and multivariate analysis (105). In a postoperative study of 533 mCRC patients during palliative systematic treatment, SML, irrespective of loss of BMI, was a potential marker for disease progression (106).

Nowadays, body composition including muscle and adipose tissue can be assessed with various imaging techniques. Visceral to subcutaneous adipose tissue area ratio (VSR) has been reported to be a predictive factor for inferior survival in different cancer types, including hepatocellular carcinoma, metastatic melanoma, and esophageal squamous cell carcinoma (107-109). However, the interaction of adipose tissue and muscle and the mechanisms by which sarcopenia and obese could affect adversely cancer survival is not yet fully illustrated. More clinical studies are necessary to investigate the relationship

of alterations of muscle and fat and the impact of its interaction on survival and AEs in patients with malignancies.

1.2 Aim of the thesis and outline

In consideration of the growing interest of malnutrition and sarcopenia in mCRC patients and the role of adipose tissue compartments in triggering the inflammatory responses, this thesis aims to understand the prognostic relevance of weight loss and body composition on treatment outcomes and mortality in mCRC patients and individuals infected with COVID-19 using CT scans. The focus of my thesis is the effect of EWL and baseline sarcopenia and percentage of change of skeletal muscle index from baseline to month 3 among patients with mCRC undergoing therapy on survival and adverse events, as well as impact of adipose tissue distribution on the degree of systematic inflammation and their correlations with necessity of IMV among patients with COVID-19 infection.

2. Patients and Methods

2.1 Study design and population

To gain a deeper insight into the impact of weight and body composition, datasets were derived from two databases: the randomized phase III trial FIRE-3 (AIO KRK-0306) (1) and the COVID-19 registry of the LMU University Hospital Munich (CORKUM, Trial ID: DRKS000212259) (110). FIRE-3 (NCT00433927) was a prospective, multicenter, open-label phase III study (1) comparing efficacy and safety of standard chemotherapy FOLFIRI combined with cetuximab/bevacizumab as first-line therapy of unresectable mCRC patients. Only patients with KRAS exon 2 wild-type tumors (N = 592) were recruited in the FIRE-3 study. 400 patients with RAS wild type in KRAS and NRAS exons 2-4 tumors were evaluated in a post-hoc analysis (111). Patients with all RAS wild type with available baseline and follow-up body weight data were recruited. Patients were divided into clinically significant EWL ≥ 5% and < 5% groups at month 3 (10, 30-33).

The following patient and therapy information from the collective comprising 326 patients was considered for the weight loss analyses:

- Gender of patients
- Age of patients
- Treatment: Cetuximab vs. Bevacizumab
- Type of primary tumor: colon vs. rectum
- Eastern Cooperative Oncology Group (ECOG) performance status: 0 vs. 1, 2
- Number of metastatic sites: 1, ≥ 2
- BMI (kg/m^2)
- Primary sidedness: left, right.
- Alkaline phosphatase (IU/L)
- Leucocyte (/L)
- Site of primary tumor: colon, rectum, colon and rectum
- Metastasis in liver
- Metastasis in lymph nodes
- Metastasis in peritoneum
- Body weight during the course of treatment

In the second analysis within the FIRE-3 study, patients' baseline SMI were evaluated with abdominal CT scans. Patients were divided into groups separating sarcopenic patients from patients with no sarcopenia according to sex-specific cut-offs defined as SMI

< 52.4 cm^2 /m^2 for men and SMI < 38.5 cm^2/m^2 for women (12). Using these cut-off values, the number of patients with a defined sarcopenia status at baseline was 334 (83.5%). We then focused on the cohort with SMI values at both baseline and 3 months after initiating treatment (N = 220) and evaluated the impact of SMC on survival.

The COVID-19 register of the University of Munich Clinic (CORKUM) was founded at the beginning of the coronavirus pandemic. In this cohort study, patients with COVID-19 infection and control patients are recruited to collect comprehensive clinical data and samples. CORKUM represents the central platform on the LMU campus and for COVID-19 related research and is intended to enable the scientific discussion of the pandemic. Anonymized data was thus systematically collected from patients who agreed to be part of the CORKUM. Within this framework, we performed a retrospective analysis of COVID-19 patients in the CORKUM project between 29 February 2020 and 6 May 2020. A positive result on real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay with nasal and pharyngeal specimens was used to confirm the diagnosis of COVID-19. We recruited only patients with confirmed laboratory diagnosis of COVID-19. Patients without thoracic CT scans were excluded from our study as we need thoracic CT scans for body composition analyses. In total, 58 patients met these criteria. Patients' baseline characteristics, including their pre-existing comorbidities hypertension, chronic obstructive pulmonary disease (COPD), chronic heart disease, chronic kidney disease, and diabetes laboratory parameters CRP, IL-6, LDH, creatine, troponin were extracted from their medical records. Patients were grouped according to necessity of IMV.

2.2 EWL definition

EWL was defined as percentage of body weight change from baseline to month 3. The parameter EWL was only evaluated among participants in the FIRE Study. For the CORKUM cohort this endpoint (EWL at month 3) was not considered relevant due to a shorter time frame of the COVID-19 disease process. In our exploratory analysis of the FIRE-3 study, patients were grouped according to weight loss into two groups: weight loss ≥ 5% and weight loss < 5% after 3 months of treatment. We used this cut-off as it is widely accepted in previous clinical trials and in nutritional guidelines as an early indicator for malnutrition (10, 30-32, 112-114).

2.3 Evaluation of sarcopenia

Muscle quality or quantity can be measured by various techniques, with CT being the gold standard for estimation muscle quality/quantity in clinical research (115). It is routinely applied as non-invasive imaging techniques for diagnosis, staging, surveillance of recurrence and assessment (3, 116), which could be used additionally to evaluate sarcopenia without any further burden or cost for patients (117). Using CT analysis to measure evolutions of body composition enables accurate evaluations of body tissues and the ability to assess both changes of specific muscle mass and muscle quality (116). Abdominal CT is also a routine test for patients with mCRC, so patients do not need to be exposed to any additional radiation to evaluate sarcopenia. Skeletal muscle area was assessed with Slice-O-Matic software (version 5.0, Tomovision, Canada). The structures of those muscle areas were quantified derived from pre-established thresholds of Hounsfield unit (HU) range of -29 to 150 for skeletal muscle tissue (13). The third lumbar vertebra (L3) is often used as a standard landmark, as it appears to correlate best with whole-body muscle mass and adipose tissue (45, 118). The L3 region areas include the abdominal wall, psoas muscle, autochthonous back muscles, quadratus lumborum muscles, SAT, and VAT.

Cut-off point of low levels of SMI estimated by CT defining sarcopenia is still controversial. EWGSOP2 does not recommend a specific cut-off point. However, Prado CM et al. defined the sex specific cut-offs for SMI at L3 level associated with mortality established by optimum stratification (12). In this study, sarcopenia is defined according to gender specific cut-offs defined as SMI < 52.4 cm^2/m^2 for men and SMI < 38.5 cm^2/m^2 for women (12). These sex-specific cut-offs were chosen as they were widely used and validated in many large-scale clinical trials (119-125). Abdominal CT slices of mCRC patients with sarcopenia or without sarcopenia are illustrated in Figure 2 and Figure 3. The SMI values at baseline and 3 months after treatment were evaluated. The percentage of SMC from baseline to month 3 is denoted as:

$$\frac{SMI_{month\ 3}\text{-}SMI_{baseline}}{SMI_{baseline}} \times 100\%$$

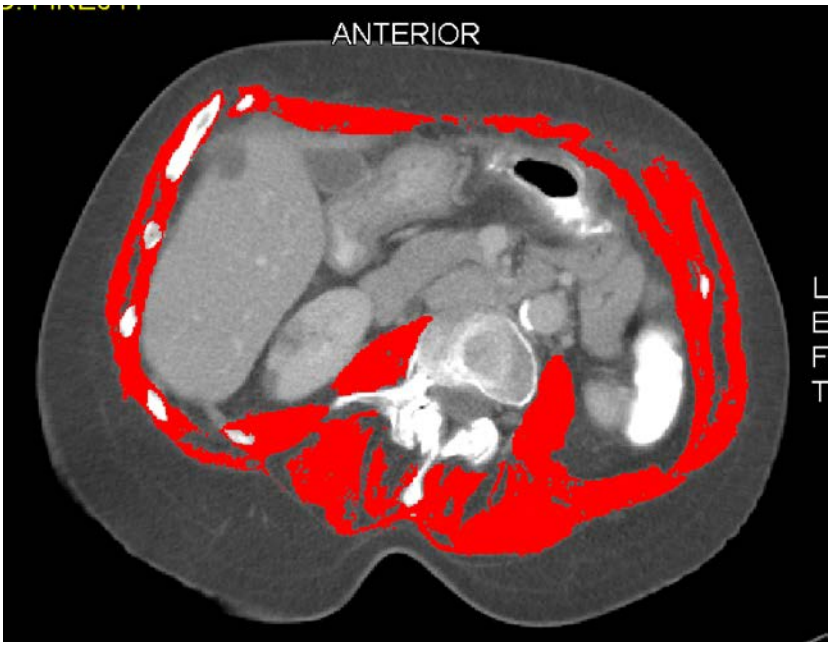


Figure 2. Patients with sarcopenia. SMM = 99.64 cm^2, height = 160 cm, SMI = 38.92 cm^2/m^2.

Abbreviations: SMM = skeletal muscle mass, SMI = skeletal muscle index.

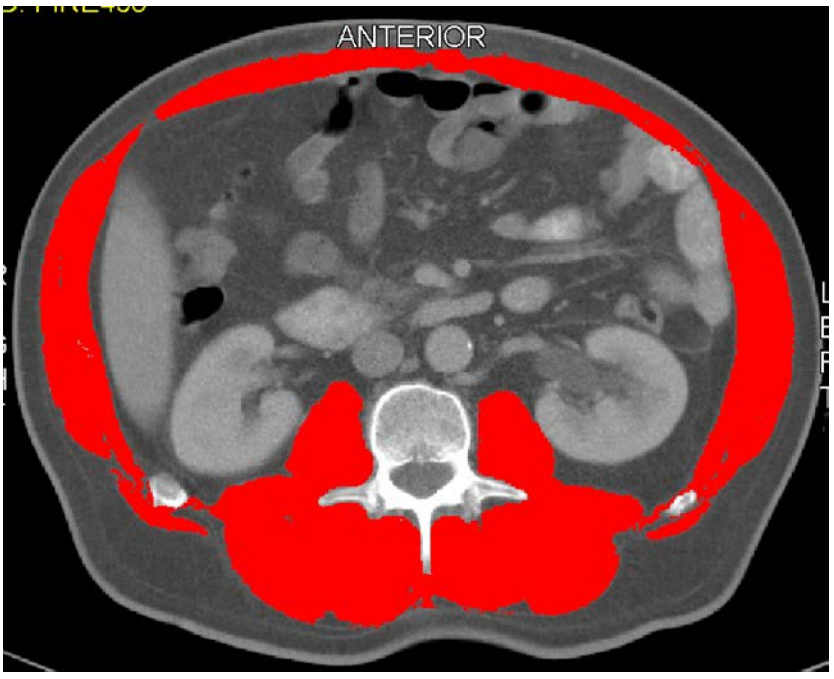


Figure 3. Patients without sarcopenia. SMM = 199.4 cm^2, height = 178 cm, SMI = 62.93 cm^2/m^2.

Abbreviations: SMM = skeletal muscle mass, SMI = skeletal muscle index.

2.4 Adipose tissue compartments and anthropometric data analyses

Chest CT scans taken at the day of recruitment, two weeks before or after diagnosis were evaluated, depending on which CT scan was closest to the day of diagnosis. We evaluated the adipose tissue compartments, including VAT, SAT, EAT and fatty contents of both the liver and spleen using CT scans with Slice-O-Matic software (version 5.0, Tomovision, Canada). The areas of VAT, SAT, and the average deterioration of several randomly selected regions of interests (ROIs) of both the liver and spleen were evaluated at the 12^{th} thoracic vertebrae (TH12) level. The EAT was measured at bottom, middle (the 4-chamber view) and top (left main coronary artery view) of the heart and calculated as the average of the three EAT areas in the three selected slices. Pre-defined HU ranges were used as followed: -190 to -30 HU for SAT and EAT, -150 to -50 for VAT, liver, and spleen. Figure 4 shows the original CT scan at TH12. Assessment of anthropometric measures like waist circumference was evaluated at TH12 using chest CT with ImageJ. Figure 5 shows the evaluation of wait circumference with ImageJ (version 2.0.0). Figure 6 illustrates the semi-automated segmentation of VAT, SAT, liver, and spleen at TH12 using Slice-O-Matic. Figure 7 shows the original slices and semi-automatic of EAT at bottom, middle (the 4-chamber view) and top (left main coronary view) of the heart using Slice-O-Matic.

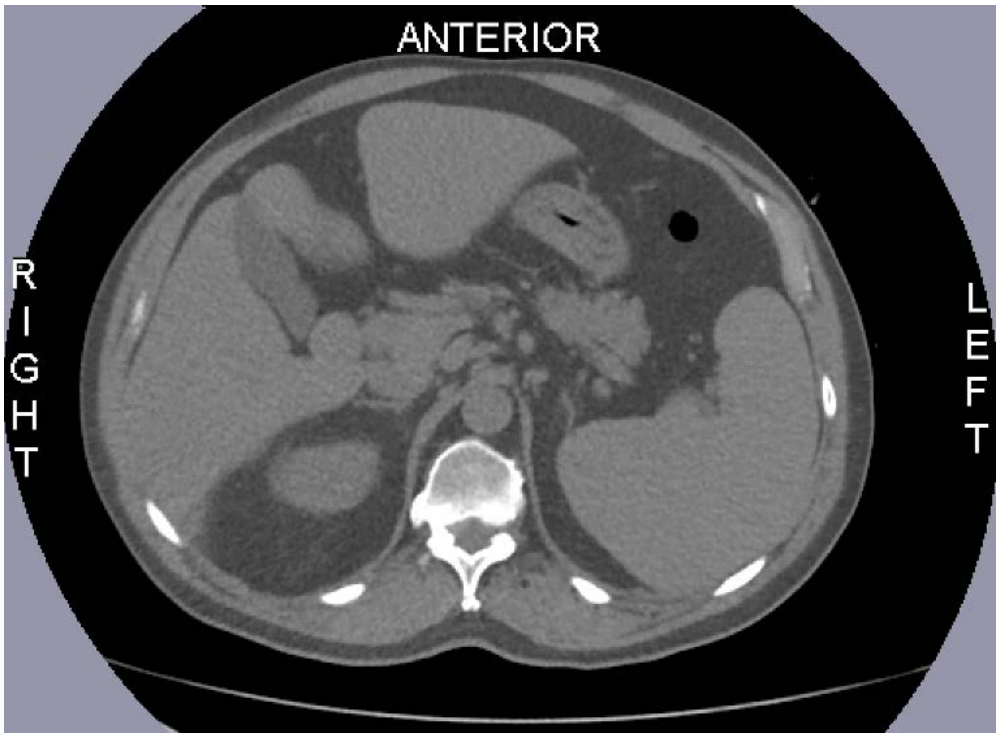


Figure 4. Original CT scan at TH12.

Abbreviations: CT = computed tomography, TH12 = 12th thoracic vertebrae.

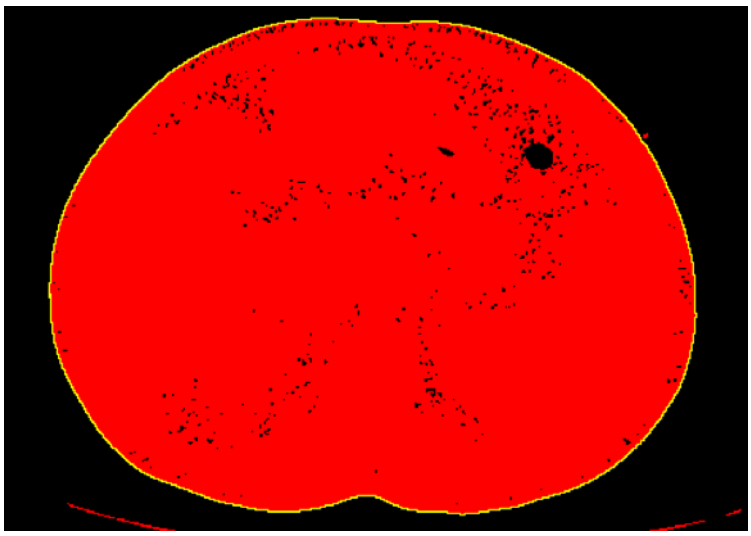


Figure 5. Evaluation of waist circumference at TH12 with ImageJ.

Abbreviation: TH12 = 12th thoracic vertebrae.

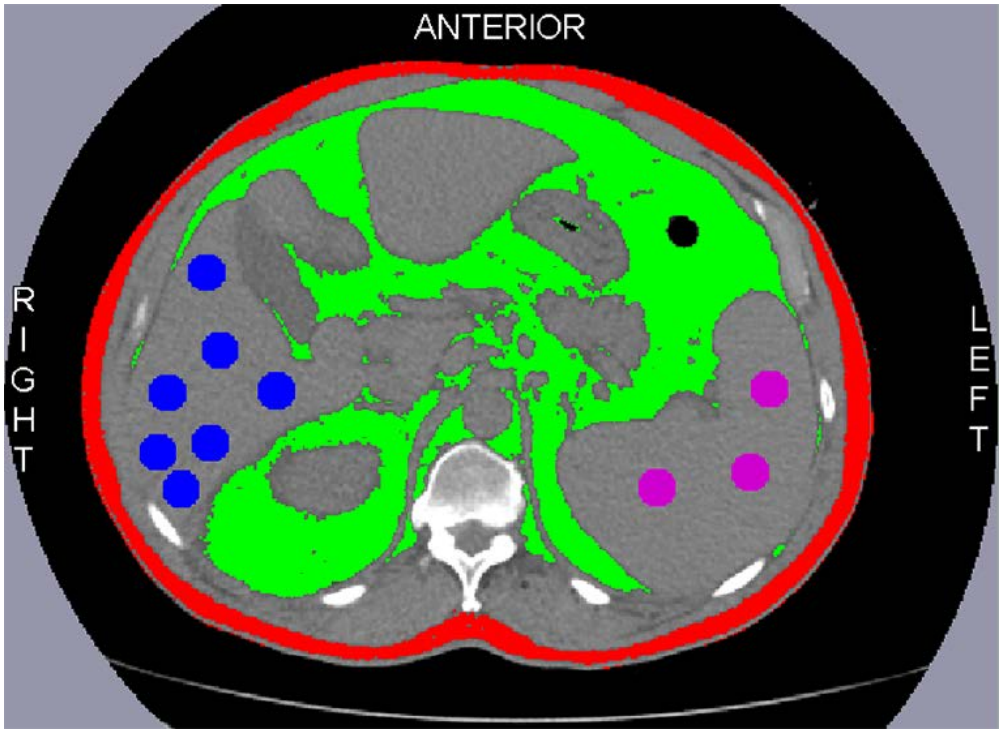


Figure 6. Semi-automated segmentation of VAT, SAT, liver, and spleen at TH12 using Slice-O-Matic. Red zone represents SAT. Green zone represents VAT. Blue regions are ROIs of liver and pink regions are ROIs of spleen.

Abbreviations: VAT = visceral adipose tissue, SAT = subcutaneous adipose tissue, TH12 = 12th thoracic vertebrae, ROIs = regions of interests.

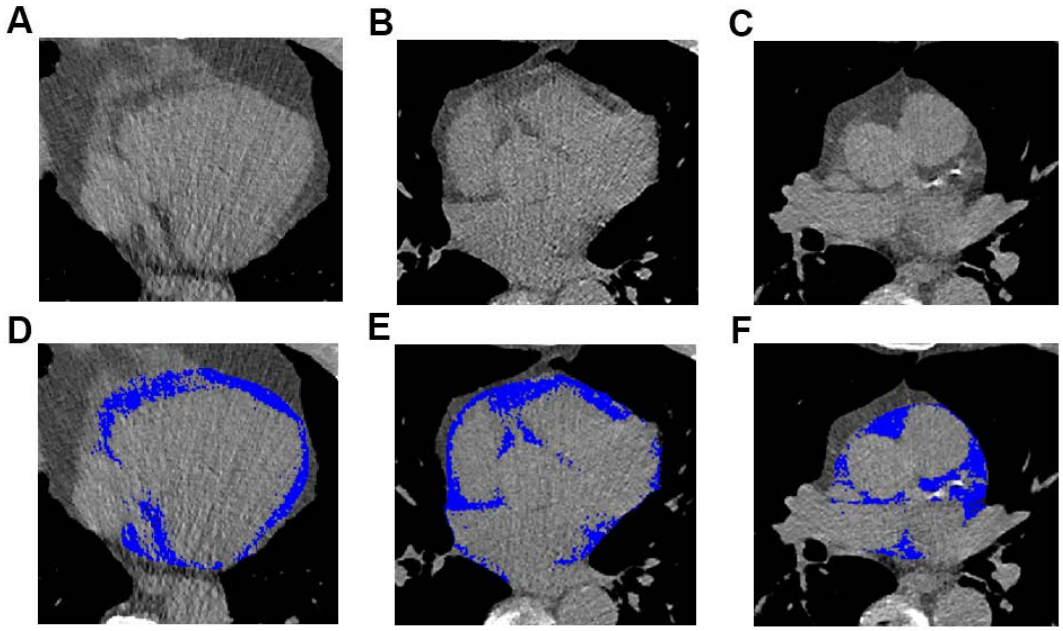


Figure 7. Original CT scans (A-C) and the semi-automatic (D-F) of EAT at bottom, middle (the 4-chamber view) and top (left main coronary view) of the heart using Slice-O-Matic. The blue regions illustrate the EAT.

Abbreviation: EAT = epicardial adipose tissue.

2.5 Statistical analyses

Statistical analyses for weight loss in the FIRE-3 study were performed using R (version 3.6.1). In this retrospective analysis of weight loss, patients were grouped into two cohorts weight loss ≥ 5% and weight loss < 5% after 3 months of treatment. Using Fisher exact tests, we compared the patients' baseline characteristics between two cohorts weight loss ≥ 5% and weight loss < 5%. Only patients with available body weight data after 3 months of treatment were included. We further explored the possible predictors for EWL using univariate and multivariate logistic regression analyses. A penalized logistic regression spline was fitted to explore the functional relationship between weight loss and age. AEs were monitored and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) throughout the treatment period during the original FIRE-3 study. In this study, the number of patients experiencing at least one AE in each EWL group were compared using Fisher's exact tests. Progression free survival (PFS) and OS were displayed as Kaplan-Meier curves and compared with log-rank tests. Considering the potential guarantee-time bias, we calculated PFS and OS from month 3 onwards. Median survival times using corresponding 95% CIs were computed. Univariate and multivariate Cox proportional hazards models were then used to calculate the HRs and corresponding 95% CIs of all indicators influencing survival. Multivariate Cox proportional hazards regression models were fitted to adjust the effect of weight loss during treatment for potentially prognostic covariates: age, sex, ECOG performance status, liver limited disease (LLD), baseline carcinoembryonic antigen (CEA), primary tumor side, number of metastatic sites and treatment. Finally linear mixed effect models were fitted to analyze the mean evolution of weight over time. Data were validated by a statistician.

Statistical analyses for baseline SMI and SMC in the FIRE-3 study were performed using R (version 3.6.1). Patients were grouped according to previous published sex-specific cut-offs into sarcopenia group and no sarcopenia group at baseline. Patients' baseline characteristics were compared within two groups (12). Kaplan-Meier curves and log-rank tests were applied to determine the impact of baseline sarcopenia on PFS and OS, followed by univariate and multivariate Cox proportional hazards models for HRs and 95% CIs of all prognostic parameters. AEs were compared within two groups. We also evaluated the impact of SMC on survival. The functional relationship between SMC and OS log hazard rate looks quadratic. The curve has also minimal value at about 0 suggesting that patients with maximal survival are patients with a steady SMI. To investigate this assumption, different models were developed and compared with consideration of the Akaike information criterion (AIC). A simpler model with binary versions of SMC and change of weight (WC) was developed and selected. An extreme percentage of WC in

weight is defined as a percentage of WC in absolute value greater than 2.5%. An extreme percentage of SMC is defined as a percentage of SMC in absolute value greater than 5%. The Fisher's exact test was applied to compare the relationship between SMC and WC and the association between the two variables and treatment arm. Univariate and multivariate Cox proportional hazards models were conducted to evaluate the influence of the 2 variables on OS. Data were validated by a statistician.

Statistical analyses for the CORKUM cohort were performed using GraphPad Prism 6.0 (GraphPad Software, Inc.). Patients' baseline characteristics, body composition and serum inflammatory parameters were compared with the Mann Whitney test for continuous variables, and the Fisher's exact test and Chi-squared test for categorical variables. Continuous variables are reported as median and range if not stated otherwise. The AUC and the 95% CI of the receiver operating characteristic (ROC) analysis were computed using the predicted probability for the need of IMV. Pearson correlation analyses were used to measure the relationship between two continuous variables. $P < 0.05$ was considered significant for all analyses.

3. Results

3.1 The implications of weight loss on side effects and outcomes of patients with metastatic colorectal cancer

3.1.1 Patients' characteristics and study design

Baseline weight data were available for all 400 patients with RAS-WT tumors within the FIRE-3 study (100%). To control for guarantee-time bias, we considered only mCRC patients who had completed ≥ 3 months of treatment. Patient inclusion and exclusion criteria for the retrospective study of FIRE-3 cohort are shown in Figure 8. Weight data after 3 months of systemic treatment were available for 326 patients (81.5%). Patients were unevenly distributed when grouped according to the criteria set for EWL < 5% (N = 279, 85.6%) and ≥ 5% (N = 47, 14.4%) after 3 months of systemic treatment. Within each weight loss group, baseline characteristics were analyzed (Table 1). Here, EWL ≥ 5% was significantly associated with age ≥ 65 years (P = 0.011). Further, patients exhibiting EWL ≥ 5% appeared to have less hepatic metastasis at baseline (P = 0.014) (Table 1).

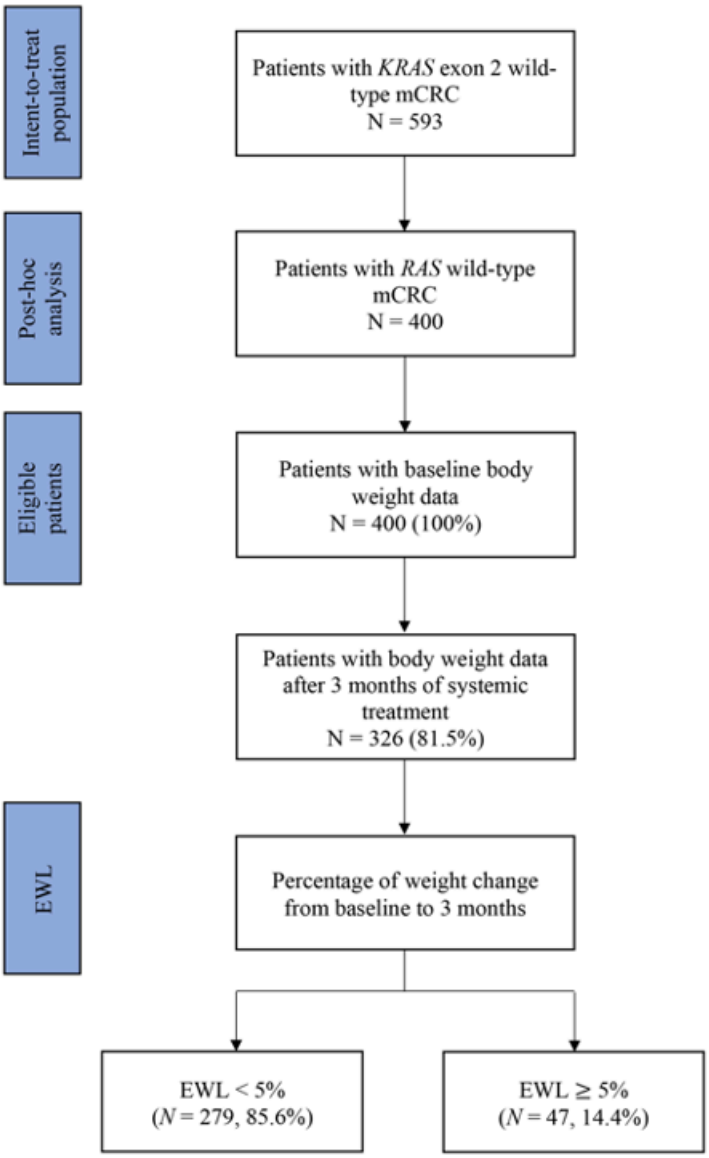


Figure 8. Patient inclusion and exclusion criteria for the retrospective study of FIRE-3 cohort.

Abbreviations: EWL = early weight loss, mCRC = metastatic colorectal cancer.

Table 1. Baseline characteristics within each weight loss group

Baseline characteristics	**Weight loss < 5% (n=279)**	**Weight loss ≥ 5% (n=47)**	***P* value**
Treatment			0.75
Cetuximab	133 (47.7 %)	21 (44.7 %)	
Bevacizumab	146 (52.3 %)	26 (55.3 %)	
Sex			1
Male	202 (72.4 %)	34 (72.3 %)	
Female	77 (27.6 %)	13 (27.7 %)	
Age (years)			**0.011**
< 65	147 (52.7 %)	15 (31.9 %)	
≥ 65	132 (47.3 %)	32 (68.1 %)	
ECOG performance status			0.43
0	157 (56.3 %)	23 (48.9 %)	
1,2	122 (43.7 %)	24 (51.1 %)	
Number of metastatic sites			0.057
1	125 (45 %)	14 (29.8%)	
≥ 2	153 (55 %)	33 (70.2%)	
Missing	1 (0.4 %)	0 (0 %)	
BMI (kg/m²)			0.16
< 30	231 (83.1 %)	35 (74.5 %)	
≥ 30	47 (16.9 %)	12 (25.5 %)	
Missing	1 (0.4 %)	0 (0 %)	
Primary sidedness			1
Left	217 (78.6 %)	36 (78.3 %)	
Right	59 (21.4 %)	10 (21.7 %)	
Missing	3 (1.1 %)	1 (2.1 %)	
Alkaline phosphatase (IU/L)			0.46
< 300	241 (88.9 %)	39 (84.8 %)	
≥ 300	30 (11.1 %)	7 (15.2 %)	
Missing	8 (2.9 %)	1 (2.1 %)	
Leucocyte (/L)			0.87
< 8×10^9	160 (58.2 %)	28 (60.9 %)	
≥ 8×10^9	115 (41.8 %)	18 (39.1 %)	
Missing	4 (1.4 %)	1 (2.1 %)	
Site of primary tumor			0.27
Colon	178 (63.8 %)	24 (51.1 %)	
Rectum	90 (32.3 %)	22 (46.8 %)	
Colon and rectum	10 (3.6 %)	1 (2.1 %)	
Unknown	1 (0.4 %)	0 (0 %)	
Metastasis in liver			**0.014**
Yes	243 (87.1 %)	34 (72.3 %)	
No	36 (12.9 %)	13 (27.7 %)	

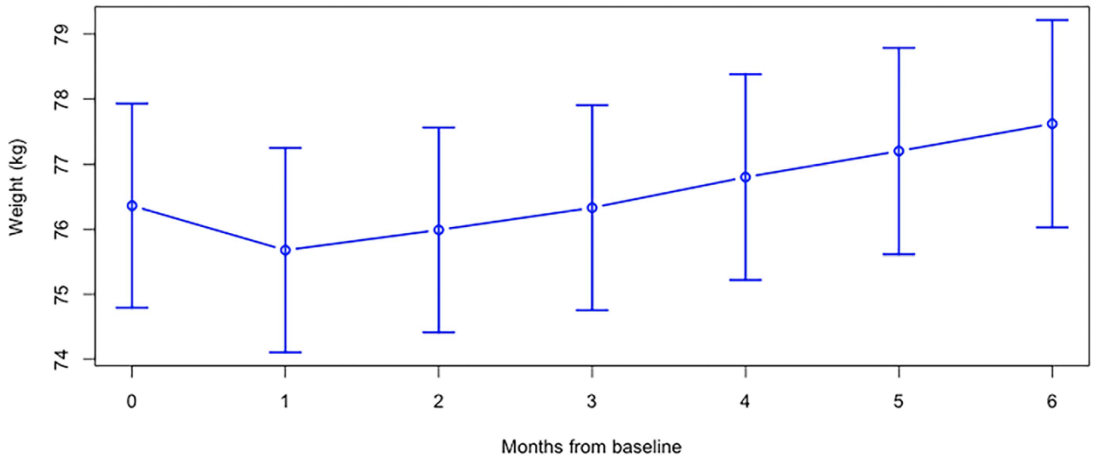
Metastasis in lung			0.87
Yes	102 (36.6 %)	18 (38.3 %)	
No	177 (63.4 %)	29 (61.7 %)	
Metastasis in lymph nodes			0.32
Yes	96 (34.4 %)	20 (42.6 %)	
No	183 (65.6 %)	27 (57.4 %)	
Metastasis in peritoneum			0.077
Yes	19 (6.8 %)	7 (14.9 %)	
No	260 (93.2 %)	40 (85.1 %)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group, BMI = body mass index.

3.1.2 Evolution of body weight and body weight change over time among patients with metastatic disease

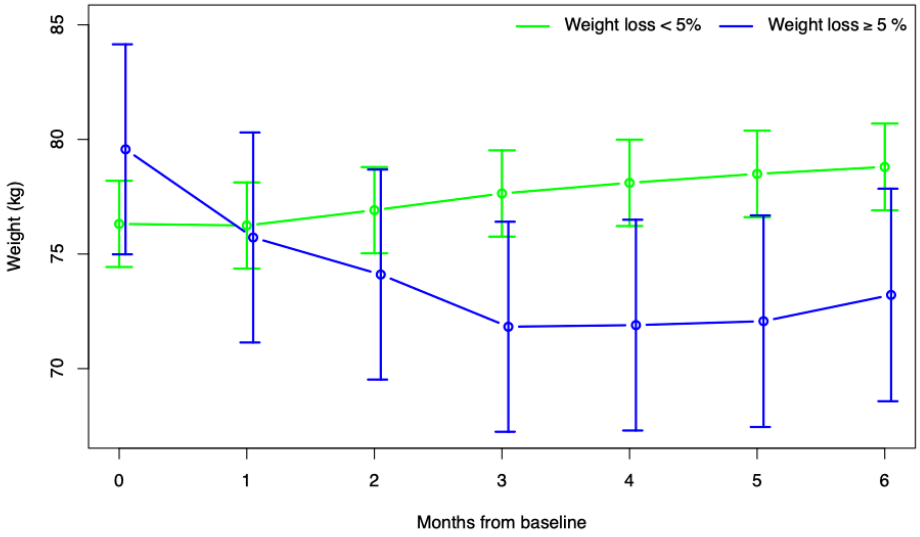
During the first month of treatment, patients lost an average of 0.7 kg of initial body weight (Figure 9). From month 1 to month 6, the evolution of weight seems to be linear with an average gain of 0.38 kg per month.

Patients with an EWL ≥ 5% at month 3 of treatment experienced a greater average weight loss from baseline to month 1 than patients with EWL < 5% (weight loss: 3.9 vs. 0.1 kg, difference: 3.8, 95% CI = 2.8-4.8, P < 0.001). From baseline to month 3, patients with EWL < 5% in fact gained an average of 1.3 kg of initial body weight compared to baseline, while patients with EWL ≥ 5%, in contrast, lost an average of 7.8 kg (95% CI = 6.8-8.7, P < 0.001). The difference between the two groups was 9.1 kg from baseline to month 3 (95% CI = 8-10.1, P < 0.001) (Figure 10). The evolution of weight change among the two groups according to gender and age are shown in Figure 11 and Figure 12.



Month 0 (n=400)	Month 1 (n=374)	Month 2 (n=352)	Month 3 (n=326)	Month 4 (n=283)	Month 5 (n=248)	Month 6 (n=208)
76.4 (74.8-77.9)	75.7 (74.1-77.2)	76 (74.4-77.6)	76.3 (74.8-77.9)	76.8 (75.2-78.4)	77.2 (75.6-78.8)	77.6 (76-79.2)

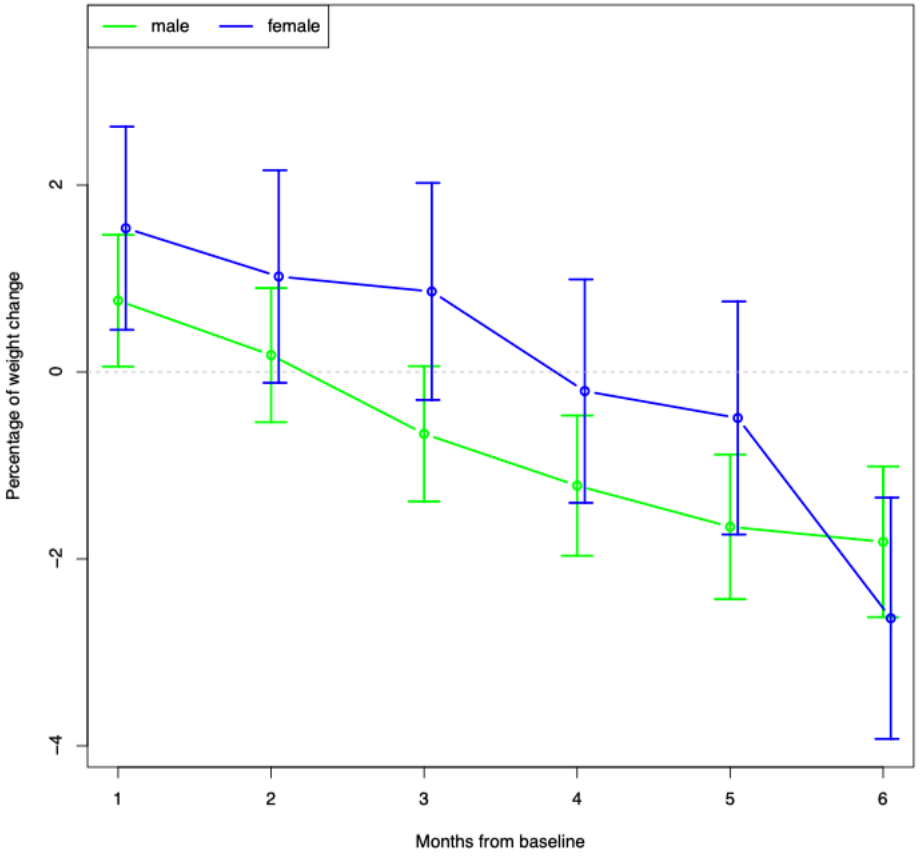
Figure 9. Representation of the mean evolution of weight with 95% CI over time (from baseline to month 6). N = 400.



Population fitted values with 95% confidence interval:

	Month 0	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
Weight loss $> 5\%$	n=279	n=279	n=279	n=279	n=246	n=218	n=184
	76.3 (74.4-78.2)	76.2 (74.4-78.1)	76.9 (75-78.8)	77.6 (75.8-79.5)	78.1 (76.2-80)	78.5 (76.6-80.4)	78.8 (76.9-80.7)
Weight loss $\geq 5\%$	n=47	n=47	n=47	n=47	n=37	n=30	n=24
	79.6 (75-84.2)	75.7 (71.1-80.3)	74.1 (69.5-78.7)	71.8 (67.2-76.4)	71.9 (67.3-76.5)	72.1 (67.5-76.7)	73.2 (68.6-77.9)

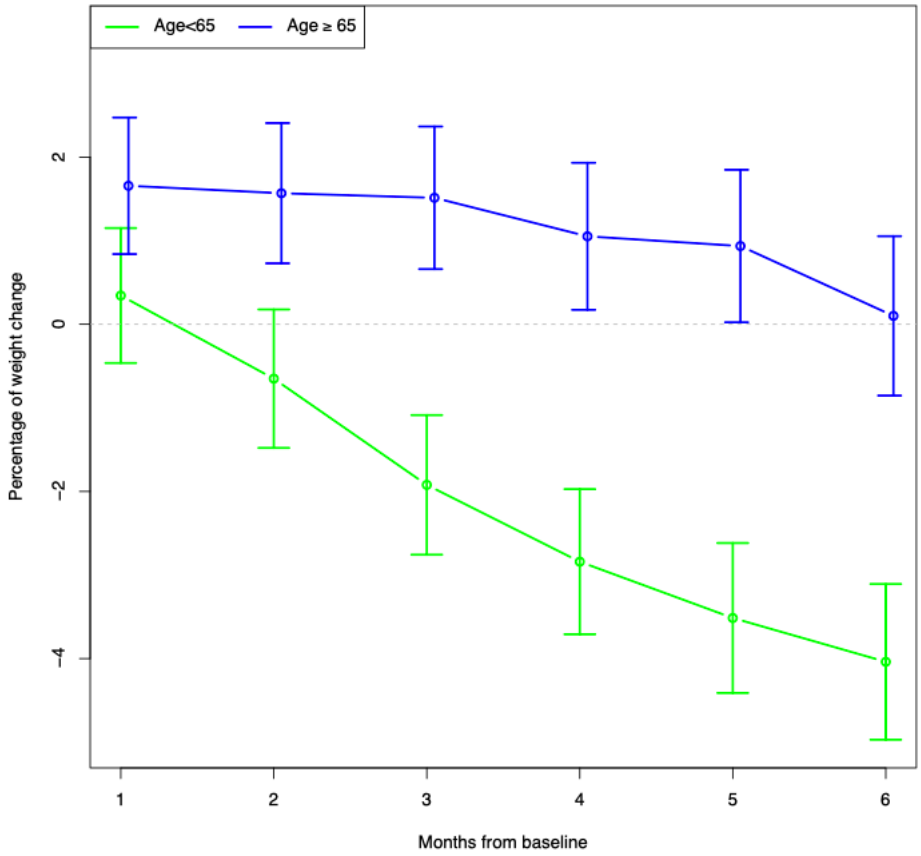
Figure 10. Representation of the mean evolution of weight with 95% CI over time (from baseline to month 6) according to weight group at month 3. N = 326.



Population fitted values with 95% confidence interval:

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
male	n=259	n=240	n=231	n=194	n=168	n=140
	0.76	0.18	-0.66	-1.22	-1.66	-1.82
	(0.06-1.47)	(-0.54-0.9)	(-1.39-0.06)	(-1.97–0.47)	(-2.43–0.88)	(-2.62–1.01)
female	n=109	n=90	n=82	n=72	n=60	n=52
	1.54	1.02	0.86	-0.2	-0.49	-2.63
	(0.45-2.63)	(-0.12-2.16)	(-0.3-2.02)	(-1.4-0.99)	(-1.74-0.76)	(-3.93–1.34)

Figure 11. Representation of the mean evolution of weight with 95% CI over time (from baseline to month 6) according to gender. N = 368.



Population fitted values with 95% confidence interval:

	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
age< 65	n=186	n=166	n=161	n=134	n=116	n=99
	0.34	-0.65	-1.92	-2.84	-3.51	-4.04
	(-0.46-1.15)	(-1.48-0.18)	(-2.76–1.09)	(-3.71–1.97)	(-4.41–2.62)	(-4.97–3.11)
age ≥ 65	n=182	n=164	n=152	n=132	n=112	n=93
	1.66	1.57	1.51	1.05	0.94	0.1
	(0.84-2.47)	(0.73-2.41)	(0.66-2.37)	(0.17-1.93)	(0.02-1.85)	(-0.85-1.05)

Figure 12. Representation of the mean evolution of weight with 95% CI over time (from baseline to month 6) according to age. N = 368.

3.1.3 Prediction of early weight loss among patients with metastatic disease

Univariate and multivariate logistic regressions were used to evaluate predictive factors for EWL. Here, only patient age ≥ 65 independently predicted the occurrence of EWL (OR = 2.37; 95% CI = 1.16-5.04; P = 0.021) (Figure 13A). Of note, patient's age exhibited a linear effect on log-odds ratio regarding the occurrence of EWL (P = 0.016) (Figure 13B).

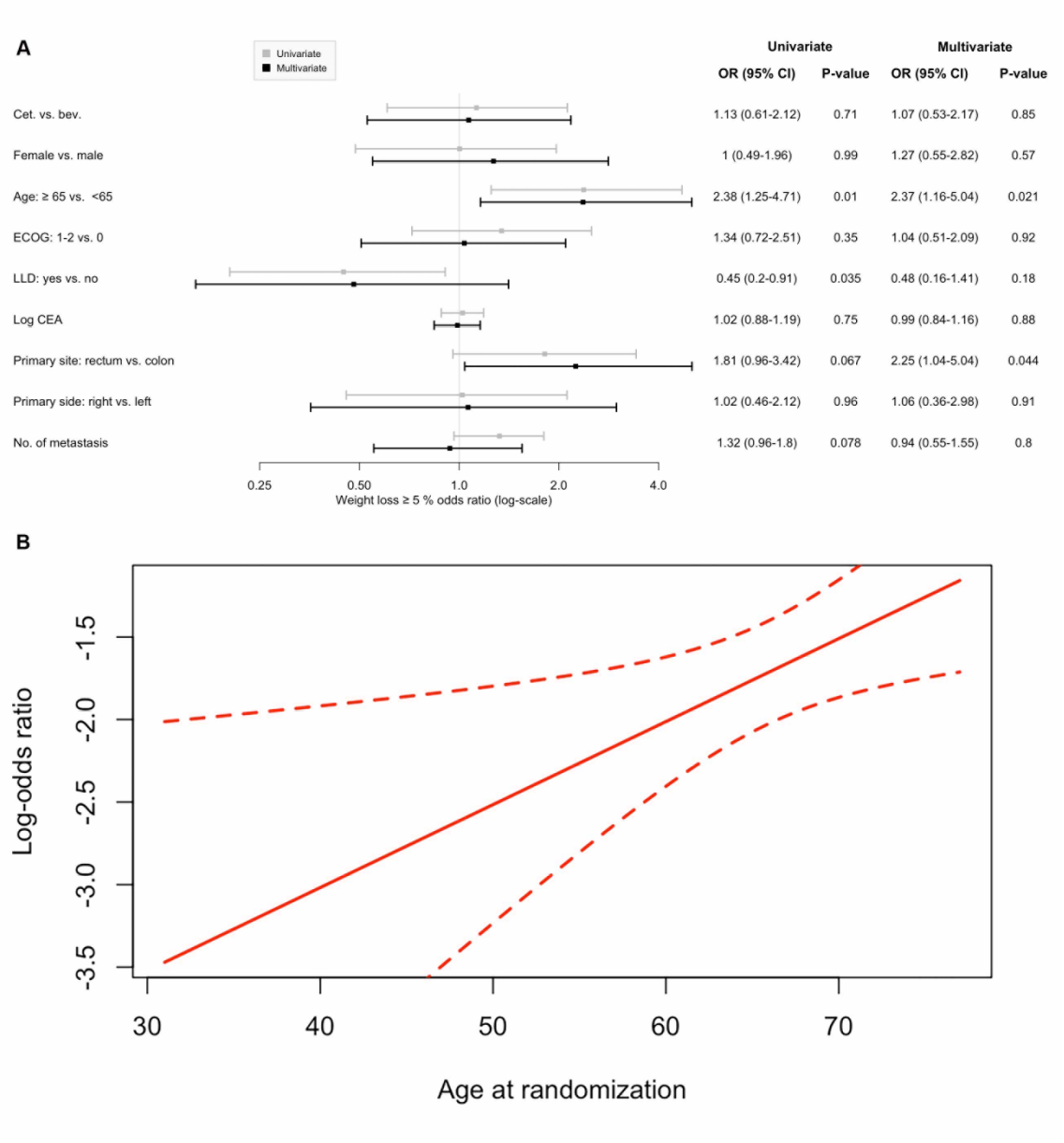


Figure 13. A. Univariate and multivariate logistic regression analysis of weight loss prediction. B. Impact of age on weight loss. N = 326.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

3.1.4 Adverse events (AEs)

Among all patients with available body weight data, the number of patients receiving full 3 months of treatment was 307 (93.9%). Only these patients were evaluated to allow for comparison of AE rates.

A significant relationship between EWL and following side effects after 3 months of treatment was observed: diarrhoea, oedema, fatigue, nausea, and vomiting (Table 2). Of note, comparable results were observed for side effects after one month of treatment (Table 3). From baseline to month 1, EWL was associated with a higher risk of diarrhoea, oedema, and fatigue (Table 3).

Table 2. Treatment related adverse events in two weight groups at month 3.

	Weight loss < 5% (N=265)		Weight loss ≥ 5% (N=42)		
	Any grade	Grade 3-4	Any grade	Grade 3-4	*P* value
Diarrhoea	123 (46.4)	13 (4.9)	32 (76.2)	6 (14.3)	**0.00039**
Oedema (e.g., peripheral)	16 (6)	0 (0)	7 (16.7)	0 (0)	**0.025**
Fatigue (asthenia, lethargy)	113 (42.6)	0 (0)	25 (59.5)	1 (2.4)	**0.046**
Hematotoxicity	238 (89.8)	36 (13.6)	38 (90.5)	14 (33.3)	1
Hypertension	63 (23.8)	15 (5.7)	7 (16.7)	0 (0)	0.43
Infection	78 (29.4)	7 (2.6)	18 (42.9)	2 (4.8)	0.11
Liver toxicity	150 (56.6)	10 (3.8)	29 (69)	3 (7.1)	0.18
Mucositis/stomatitis	85 (32.1)	7 (2.6)	18 (42.9)	3 (7.1)	0.22
Nausea	121 (45.7)	5 (1.9)	27 (64.3)	3 (7.1)	**0.03**
Neurotoxicity	59 (22.3)	0 (0)	14 (33.3)	1 (2.4)	0.12
Obstipation	58 (21.9)	1 (0.4)	9 (21.4)	0 (0)	1
Pain	101 (38.1)	4 (1.5)	19 (45.2)	3 (7.1)	0.4
Vomiting	39 (14.7)	4 (1.5)	14 (33.3)	0 (0)	**0.0069**

Table 3. Treatment related adverse events in two weight groups at month 1.

	Weight loss < 5% (N=279)		Weight loss ≥ 5% (N=47)		
	Any grade	Grade 3-4	Any grade	Grade 3-4	*P* value
Diarrhoea	85 (30.5)	8 (2.9)	27 (57.4)	2 (4.3)	**0.00073**
Oedema (e.g., peripheral)	6 (2.2)	0 (0)	7 (14.9)	2 (4.3)	**0.00074**
Fatigue (asthenia, lethargy)	72 (25.8)	0 (0)	20 (42.6)	0 (0)	**0.023**
Hematotoxicity	218 (78.1)	22 (7.9)	36 (76.6)	9 (19.1)	0.85
Hypertension	44 (15.8)	13 (4.7)	4 (8.5)	0 (0)	0.27
Infection	32 (11.5)	1 (0.4)	10 (21.3)	2 (4.3)	0.095
Liver toxicity	135 (48.4)	11 (3.9)	30 (63.8)	3 (6.4)	0.059
Mucositis/stomatitis	43 (15.4)	4 (1.4)	11 (23.4)	0 (0)	0.2
Nausea	93 (33.3)	3 (1.1)	20 (42.6)	3 (6.4)	0.25
Neurotoxicity	35 (12.5)	0 (0)	8 (17)	0 (0)	0.48
Obstipation	39 (14)	0 (0)	5 (10.6)	0 (0)	0.65
Pain	59 (21.1)	2 (0.7)	10 (21.3)	2 (4.3)	1
Vomiting	26 (9.3)	1 (0.4)	8 (17)	1 (2.1)	0.12

3.1.5 The prognostic relevance of weight loss among patients with metastatic disease

In Kaplan-Meier analyses, a prognostic relevance of EWL on OS and PFS was observed. Patients with EWL ≥ 5% exhibited an inferior OS and PFS compared to patients with EWL < 5% (OS: 21.1 vs. 32.4 months, P = 0.00084, Figure 14B; PFS: 9.0 vs. 11.8 months, P = 0.0022, Figure 15). Here, EWL independently predicted OS and PFS in patients with *RAS*-WT mCRC (HR for OS = 1.64, 95% CI = 1.13-2.38, P = 0.0098, Figure 14A; HR for PFS = 1.72, 95% CI = 1.18-2.5, P = 0.0048, Figure 16). Univariate and multivariate logistic regression analysis showed that EWL was not significantly associated with overall response rate (ORR) (HR = 0.5, 95% CI = 0.21-1.24, P = 0.12, Figure 17).

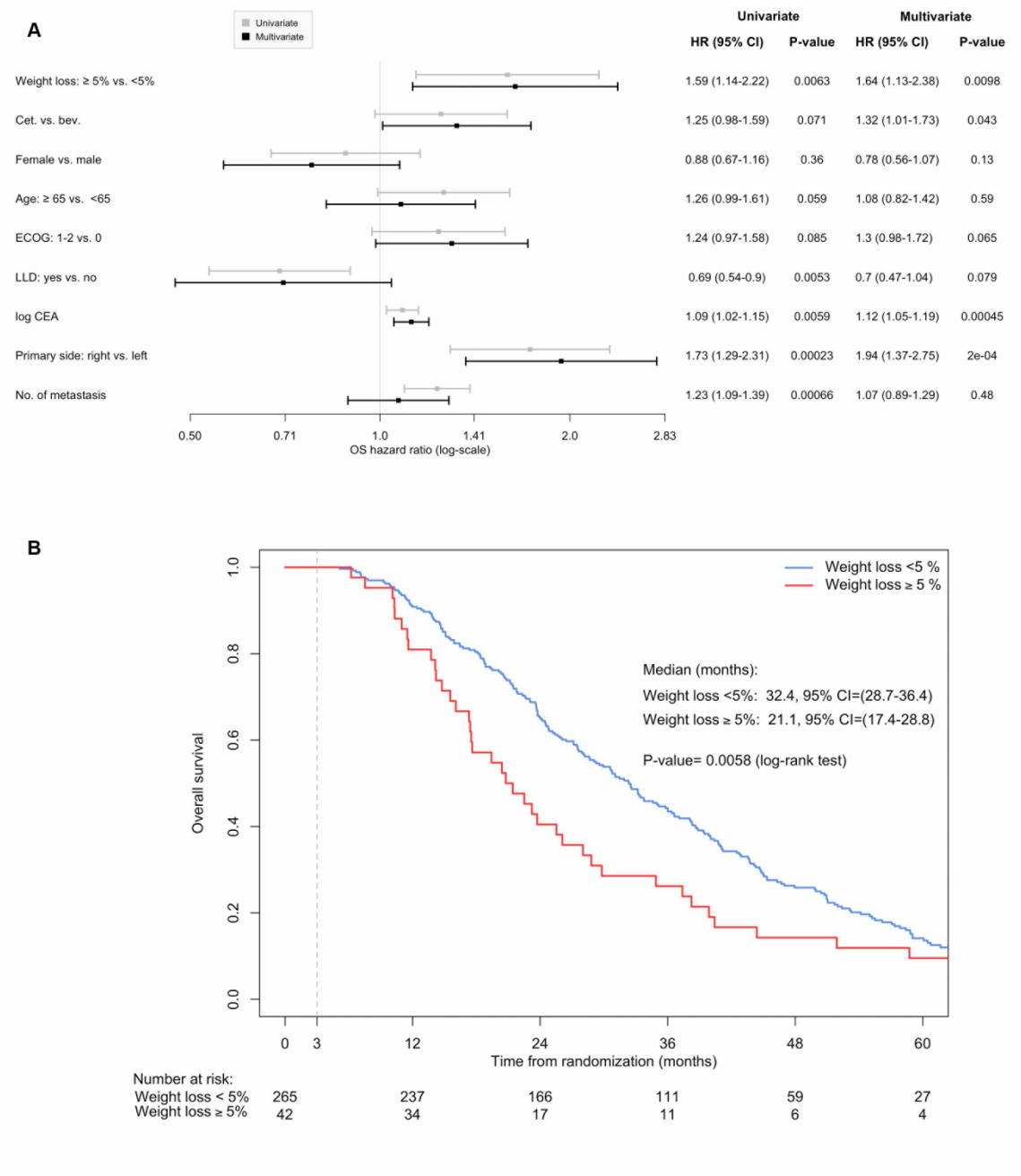


Figure 14. Impact of weight loss on OS after 3 months. N = 326. N = 47 for patients with weight loss ≥ 5% and N = 279 for patients with weight loss < 5%. A. Evaluation of independent prognostic factors for OS after 3 months using Cox regression analysis. B. Kaplan-Meier plot.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

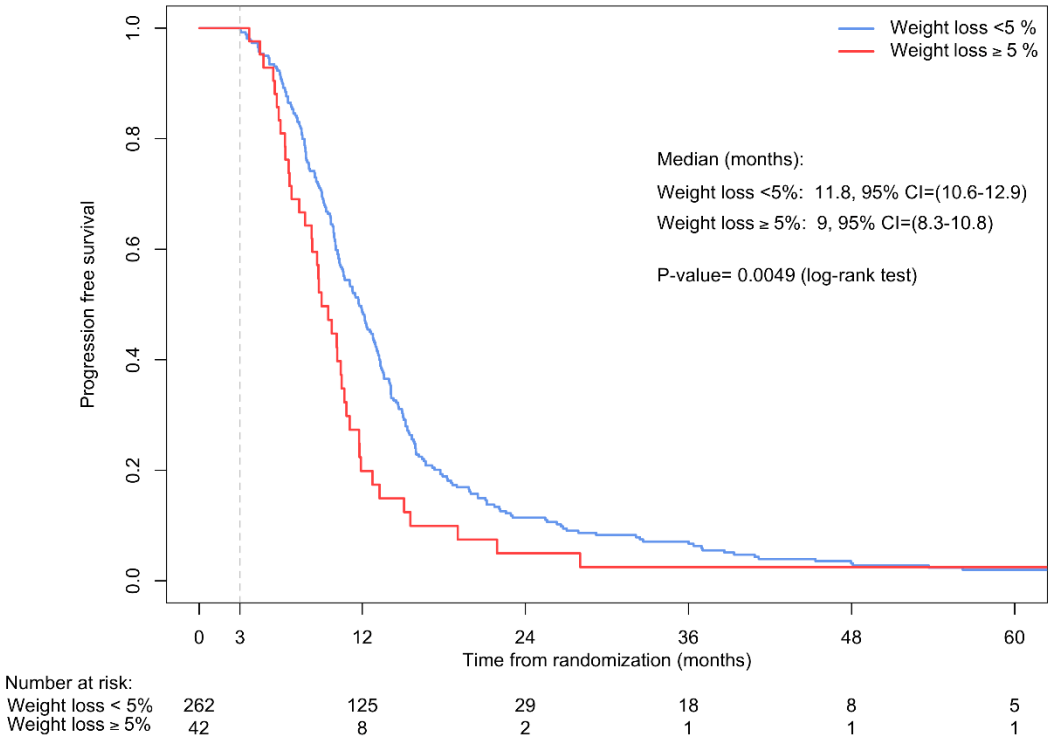


Figure 15. Kaplan-Meier curve of PFS after 3 months. N = 326. N = 47 for patients with weight loss ≥ 5% and N = 279 for patients with weight loss < 5%.

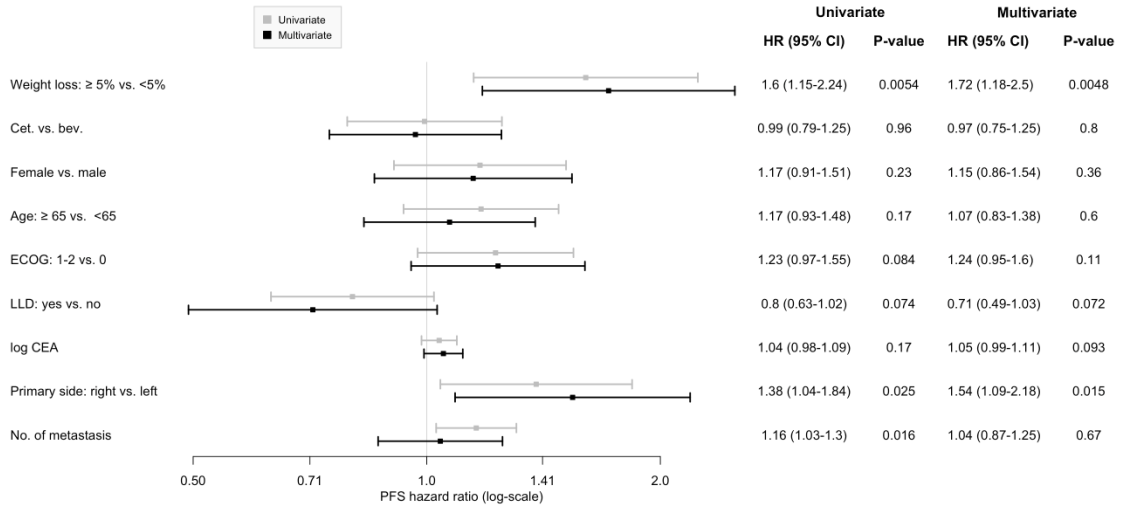


Figure 16. Evaluation of independent prognostic factors for PFS after 3 month using Cox regression analysis. N = 326.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

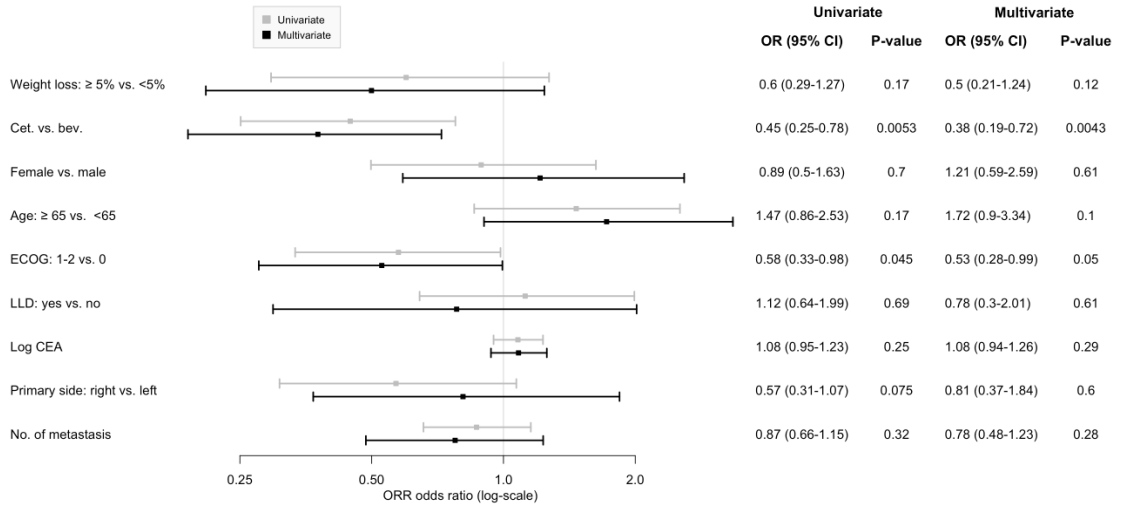


Figure 17. Univariate and multivariate logistic regression analysis of overall response rate prediction. N = 326.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

3.1.6 The predictive relevance of weight loss

To evaluate the relevance of EWL to predict a treatment benefit of FOLFIRI plus either bevacizumab or cetuximab, we compared EWL subgroups within each treatment arm. Here, no formal interaction of treatment arm with EWL could be detected (P = 0.65) (Figure 18).

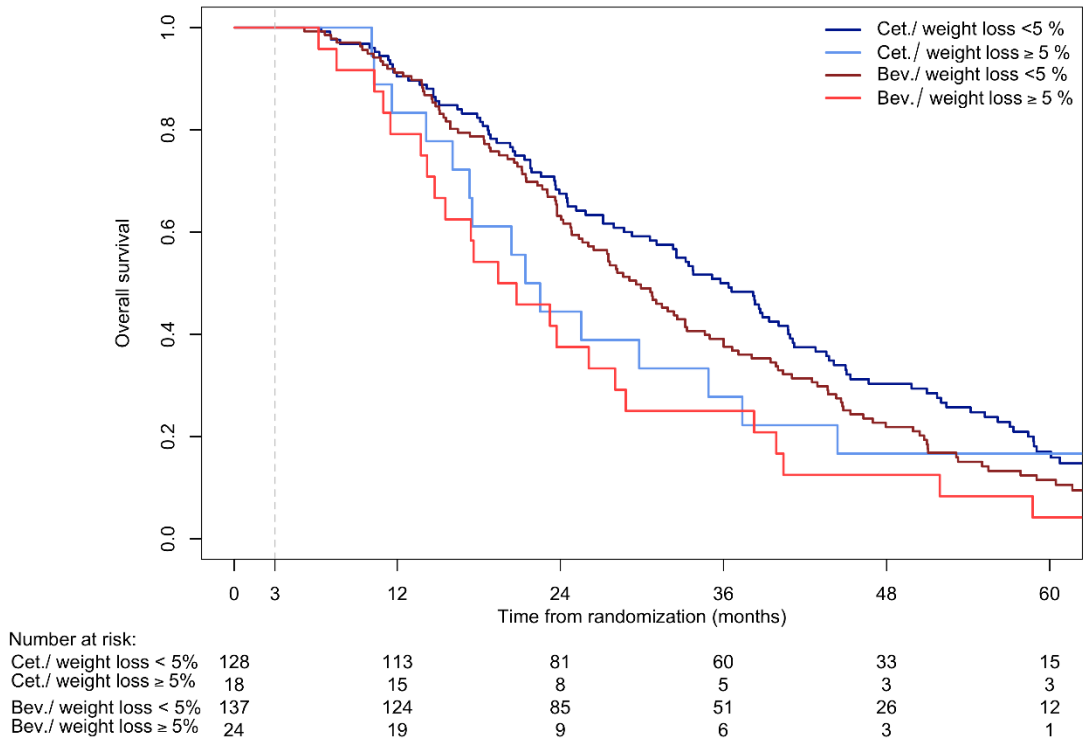


Figure 18. Impact of weight loss and treatment of either cetuximab or bevacizumab on OS after 3 months. N = 326.

Abbreviation: OS = overall survival.

3.2 The implication of sarcopenia on side effects and outcomes of patients with metastatic colorectal cancer

3.2.1 Patients' baseline characteristics

The number of patients with a defined baseline sarcopenia status at baseline with RAS-WT tumors within the FIRE-3 study was 334 (83.5%) and the distribution among the two groups was more normal. The CONSORT flow diagram is shown in Figure 19. Patients were grouped according to sex-specific cut-offs defined as SMI < 52.4 cm^2 /m^2 for men and SMI < 38.5 cm^2/m^2 for women (12) into sarcopenia group (N = 204, 61.1%) and no sarcopenia group (N = 130, 38.9%) at baseline. Within each group, baseline characteristics were analyzed (Table 4).

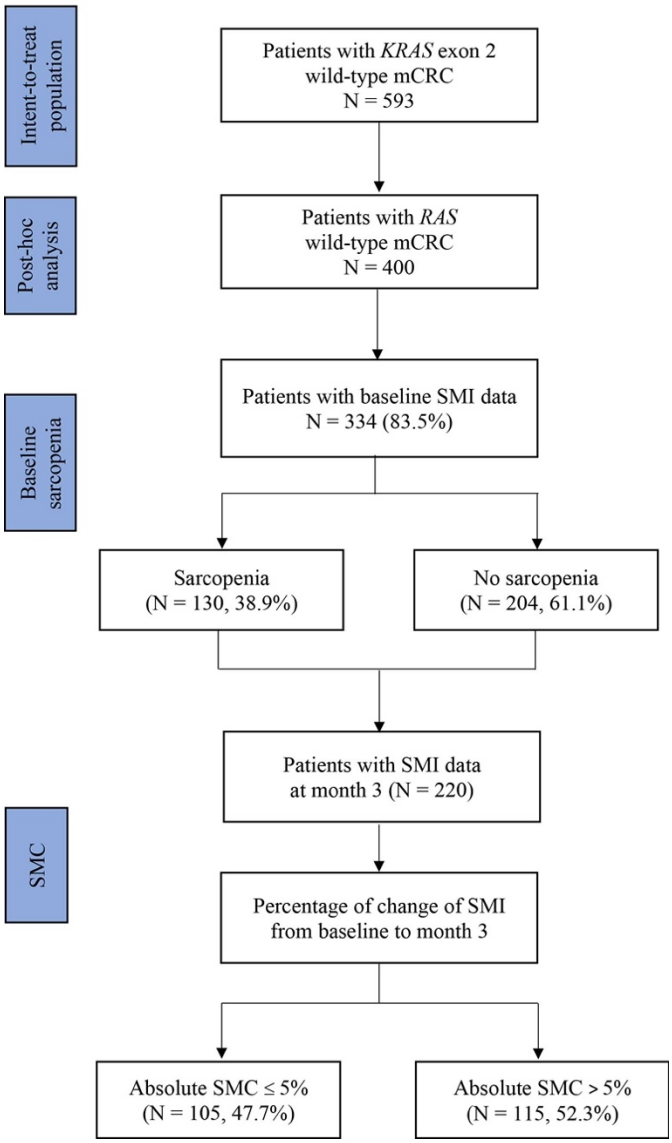


Figure 19. Study patient flow diagram.

Abbreviations: mCRC = metastatic colorectal cancer, SMI = skeletal muscle index, SMC = change of SMI.

Table 4. Baseline characteristics in patients with a defined sarcopenia status

Baseline characteristics	No sarcopenia (n=130)	Sarcopenia (n=204)	P value
Treatment			0.26
Cetuximab	58 (44.6 %)	105 (51.5 %)	
Bevacizumab	72 (55.4 %)	99 (48.5 %)	
Sex			0.22
Male	86 (66.2 %)	149 (73 %)	
Female	44 (33.8 %)	55 (27 %)	
Age (years)			**0.0051**
< 65	76 (58.5 %)	87 (42.6 %)	
≥ 65	54 (41.5 %)	117 (57.4 %)	
ECOG performance status			**0.0097**
0	81 (62.3 %)	97 (47.5 %)	
1,2	49 (37.7 %)	107 (52.5 %)	
Number of metastatic sites			0.26
1	60 (46.9 %)	82 (40.4 %)	
≥ 2	68 (53.1 %)	121 (59.6 %)	
Missing	2 (1.5 %)	1 (0.5 %)	
BMI (kg/m²)			**<0.00001**
< 30	91 (70.5 %)	184 (90.2 %)	
≥ 30	38 (29.5 %)	20 (9.8 %)	
Missing	1 (0.8 %)	0 (0 %)	
Primary sidedness			**0.0023**
Left	90 (70.3 %)	170 (84.6 %)	
Right	38 (29.7 %)	31 (15.4 %)	
Missing	2 (1.5 %)	3 (1.5 %)	
Alkaline phosphatase (IU/L)			0.31
< 300	113 (89.7 %)	168 (85.3 %)	
≥ 300	13 (10.3 %)	29 (14.7 %)	
Missing	4 (3.1 %)	7 (3.4 %)	
Leucocyte (/L)			**0.039**
< 8×10^9	80 (63.5 %)	103 (51.2 %)	
≥ 8×10^9	46 (36.5 %)	98 (48.8 %)	
Missing	4 (3.1 %)	3 (1.5 %)	
Site of primary tumor			0.07
Colon	86 (66.2 %)	115 (56.4 %)	
Rectum	41 (31.5 %)	79 (38.7 %)	
Colon and rectum	2 (1.5 %)	10 (4.9 %)	
Unknown	1 (0.8 %)	0 (0 %)	
Metastasis in liver			0.29
Yes	105 (80.8 %)	174 (85.3 %)	
No	25 (19.2 %)	30 (14.7 %)	
Metastasis in lung			0.062

Yes	39 (30 %)	83 (40.7 %)	
No	91 (70 %)	121 (59.3 %)	
Metastasis in lymph nodes			0.91
Yes	46 (35.4 %)	70 (34.3 %)	
No	84 (64.6 %)	134 (65.7 %)	
Metastasis in peritoneum			1
Yes	11 (8.5 %)	17 (8.3 %)	
No	119 (91.5 %)	187 (91.7 %)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group, BMI = body mass index.

3.2.2 The prognostic relevance of baseline sarcopenia

We evaluated the impact of sarcopenia on PFS and OS among 334 patients with RAS-WT tumors (334 out of 400, 83.5%) within the FIRE-3 trial. In Kaplan-Meier analyses, no prognostic relevance of sarcopenia on PFS and OS was observed. Univariate and multivariate logistic regression analysis showed that sarcopenia was not significantly associated with PFS (10.5 vs. 10.4 months, HR = 1.12, 95% CI = 0.89-1.41, P = 0.33, Figure 20) or OS (28.1 VS. 27.1 months, HR = 1.21, 95% CI = 0.95-1.53, P = 0.12, Figure 21).

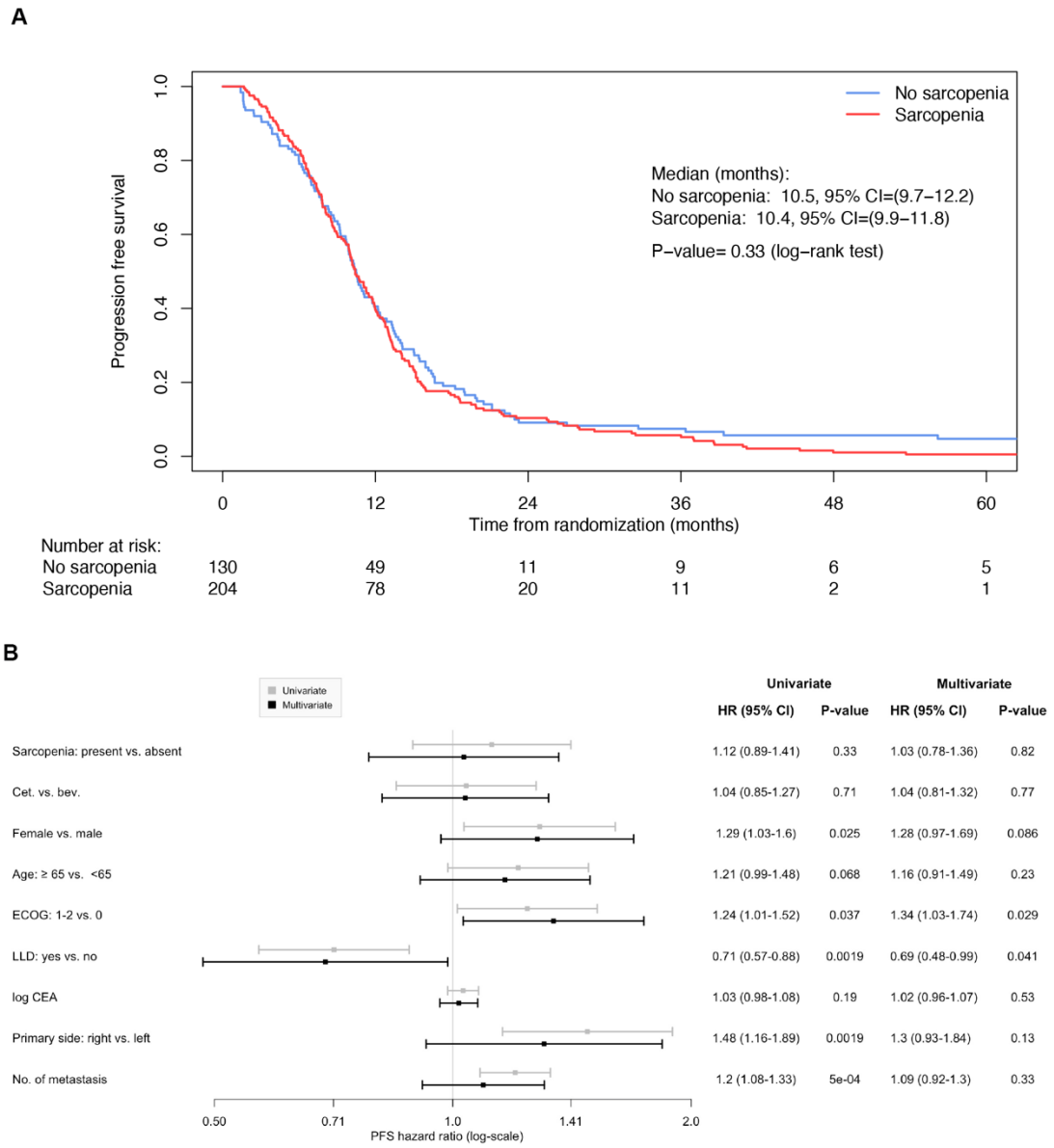


Figure 20. Impact of baseline sarcopenia on PFS. N = 334. A. Kaplan-Meier curve, B. Evaluation of independent prognostic factors for PFS using Cox regression analysis.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

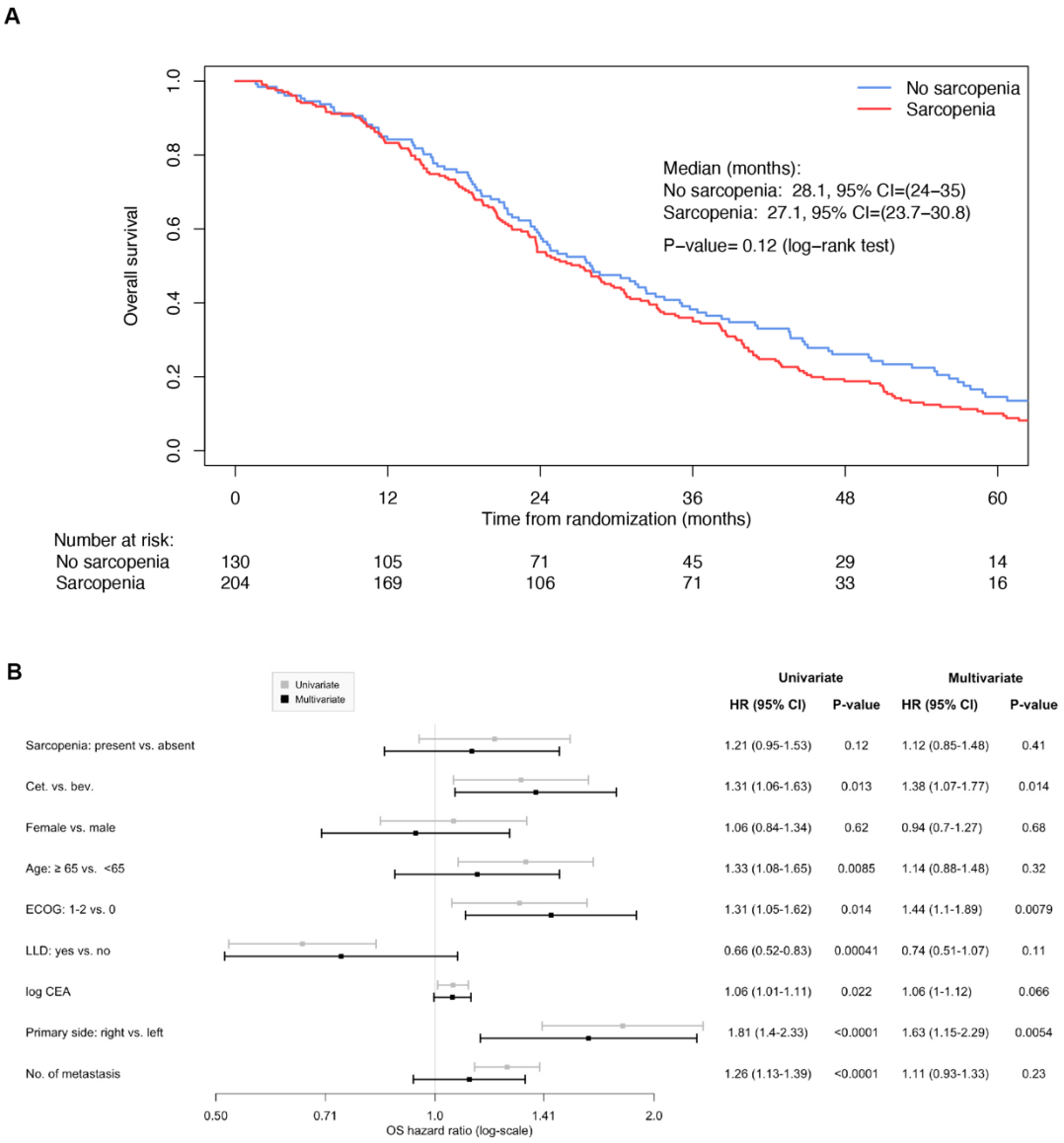


Figure 21. Impact of baseline sarcopenia on OS. N = 334. A. Kaplan-Meier curve, B. Evaluation of independent prognostic factors for OS using Cox regression analysis.

Abbreviations: LLD = liver limited disease, ECOG = Eastern Cooperative Oncology Group, CEA = carcinoembryonic antigen.

3.2.3 Impact of baseline sarcopenia on adverse events (AEs)

The number of patients with a baseline sarcopenia status according to the designation cut-off points was 334 (83.5%). Among these patients, the impact of baseline sarcopenia status on AEs was explored. A significant relationship between baseline sarcopenia status and hematotoxicity after one month of treatment was observed (Table 5).

Table 5. Impact of baseline sarcopenia status on treatment related adverse events.

	No sarcopenia (N=130)		Sarcopenia (N=204)		
	Any grade	Grade 3-4	Any grade	Grade 3-4	*P* value
Diarrhoea	53 (40.8)	3 (2.3)	70 (34.3)	10 (4.9)	0.25
Oedema (e.g., peripheral)	5 (3.8)	2 (1.5)	10 (4.9)	1 (0.5)	0.79
Fatigue (asthenia, lethargy)	37 (28.5)	0 (0)	61 (29.9)	0 (0)	0.81
Hematotoxicity	93 (71.5)	13 (10)	166 (81.4)	21 (10.3)	**0.044**
Hypertension	20 (15.4)	8 (6.2)	29 (14.2)	5 (2.5)	0.75
Infection	15 (11.5)	2 (1.5)	32 (15.7)	3 (1.5)	0.33
Liver toxicity	56 (43.1)	2 (1.5)	109 (53.4)	15 (7.4)	0.073
Mucositis/stomatitis	19 (14.6)	1 (0.8)	38 (18.6)	4 (2)	0.37
Nausea	41 (31.5)	1 (0.8)	72 (35.3)	4 (2)	0.55
Neurotoxicity	13 (10)	1 (0.8)	30 (14.7)	1 (0.5)	0.24
Obstipation	14 (10.8)	2 (1.5)	28 (13.7)	0 (0)	0.5
Pain	35 (26.9)	3 (2.3)	47 (23)	4 (2)	0.44
Vomiting	13 (10)	1 (0.8)	25 (12.3)	0 (0)	0.6

3.2.4 Prognostic relevance of change of skeletal muscle index (SMC) on OS

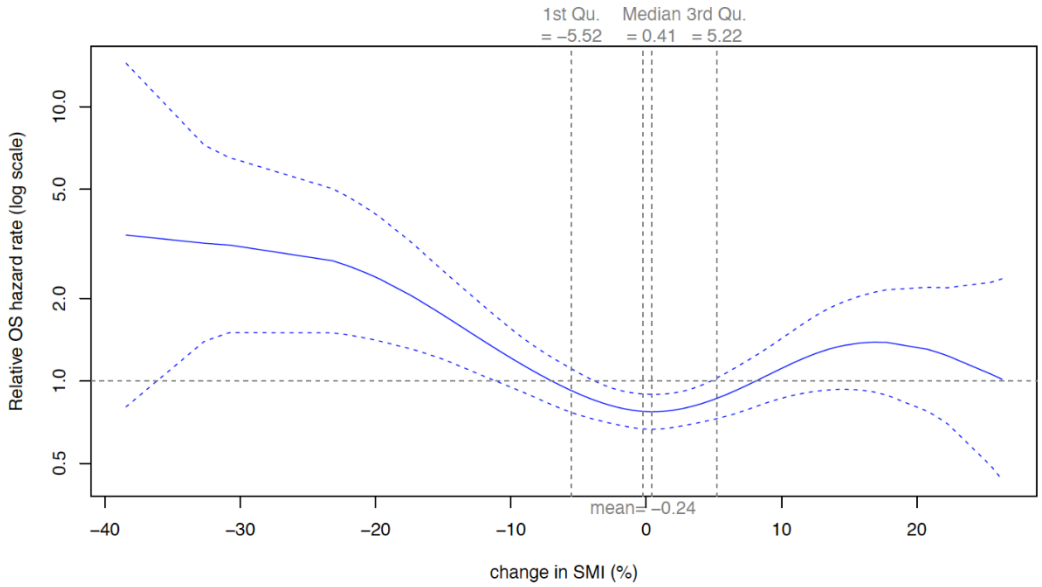


Figure 22. Impact of SMC on relative OS log hazard rate.

Abbreviations: SMI = skeletal muscle index, SMC = change of SMI, OS = overall survival.

The impact of SMC on OS log hazard rate appears to follow quadratic relationship, with minimal value at about 0 indicating that patients with longest survival are those with stable SMI (Figure 22).

Patients were divided into SMC stable (absolute SMC ≤ 5%), SMI gain (SMI gain > 5%) and SMI loss (SMI loss > 5%) groups. Patients with stable SMC had better OS compared to patients with SMI gain or SMI loss (Figure 23). The 2 slopes (SMI gain and SMI loss) absolute values are not significantly different (P = 0.13). Then, we merged patients with SMI gain and SMI loss into absolute SMC > 5% group and evaluated its impact on OS compared to absolute SMC ≤ 5%. To identify influencing factors leading to SMI gain with potential impact on outcome, an experienced radiologist checked part of patients within FIRE-3 study (N = 20) and found that our patients did not have edema, thus ruled out that edema impacted the survival within our study.

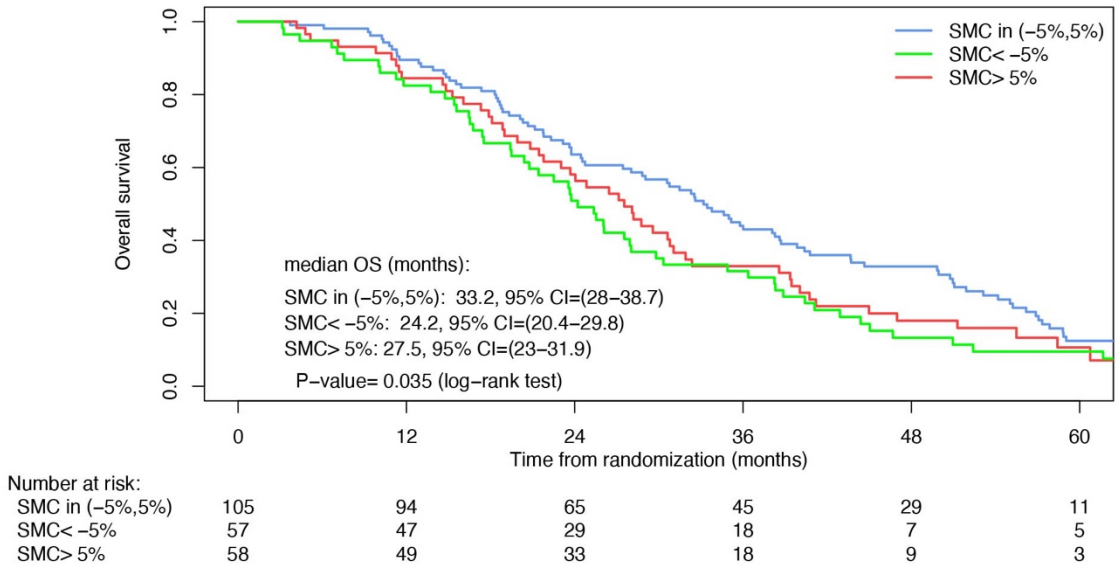


Figure 23. Impact of SMC on OS after 3 months with patients grouped into SMC stable, SMI gain and SMI loss. N = 220. N (absolute SMC ≤ 5%) = 105, N (SMC > 5%) = 58, N (SMC < -5%) = 57.

Abbreviations: SMI = skeletal muscle index, SMC = change of SMI, OS = overall survival.

The number of patients with an extreme percentage of change, i.e. absolute SMC > 5% is 115 (52.3%). The number of patients with a percentage of change ≤ 5% is 105 (47.7%). In Kaplan-Meier analysis, patients with SMC > 5% exhibited an inferior OS compared to patients with SMC ≤ 5% (P = 0.013) (Figure 24).

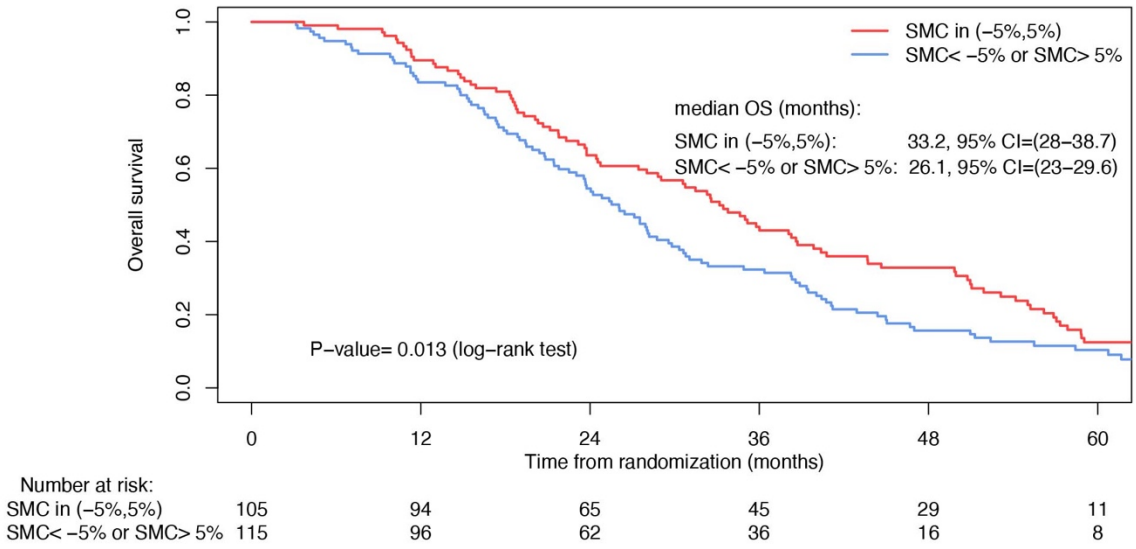


Figure 24. Impact of SMC on OS after 3 months with patients divided into absolute SMC > 5% and absolute SMC ≤ 5% groups. N = 220. N (absolute SMC ≤ 5%) = 105, N (absolute SMC > 5%) = 115.

Abbreviations: SMC = change of skeletal muscle index, OS = overall survival.

3.2.5 Relationship between percentage of change in weight (WC) and percentage of change in SMI (SMC)

WC alone did not indicate the detailed body composition. Thus, we evaluated the relationship of SMC and WC and found that patients with an extreme change in weight have more chances to have an extreme change in SMI (P = 0.015) (Figure 25).

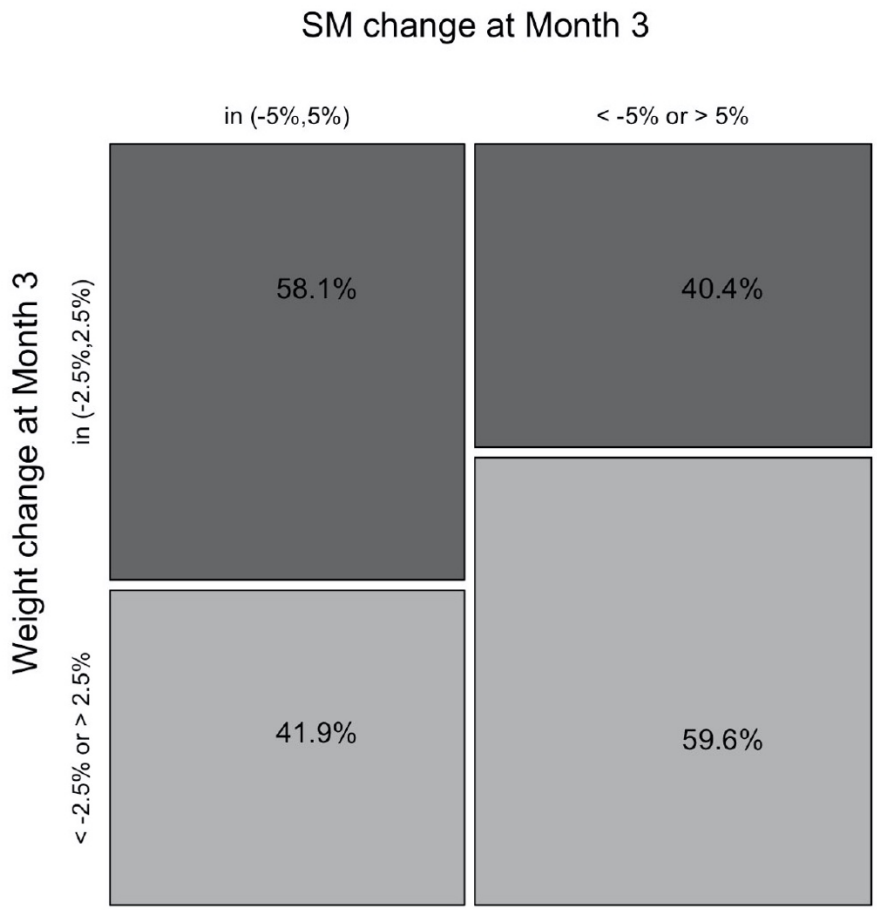


Figure 25. Percentage of patients with weight change at month 3 and SM change at month 3. N = 197.

Abbreviation: SM = skeletal muscle.

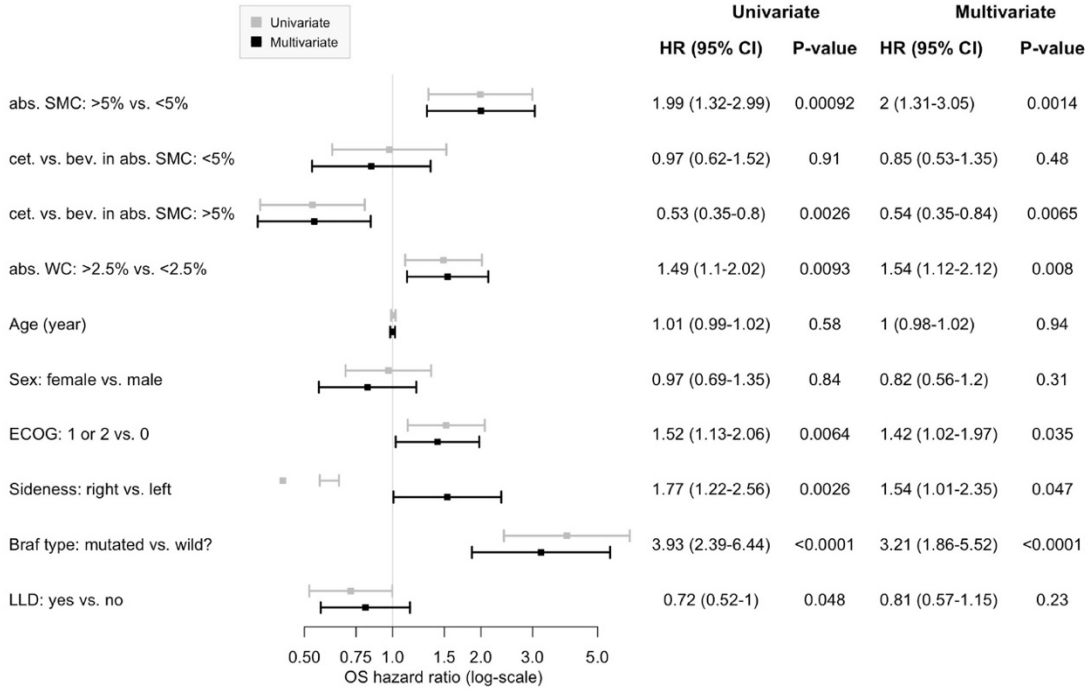


Figure 26. Univariate and multivariate Cox proportional hazards models for HRs and 95% CIs of all prognostic parameters including absolute SMC and WC. N = 220.

Abbreviations: HR = hazard ratio, CI = confidence interval, SMC = change of skeletal muscle index, WC = change of weight, ECOG = Eastern Cooperative Oncology Group, LLD = liver limited disease.

In addition, there is no evidence that the effect of an extreme percentage of change in weight on OS depends on the effect of an extreme percentage of change in SMI (P = 0.45). The SMC and WC are both independent predictive parameters for OS (Figure 26).

Univariate and multivariate proportional hazards models showed that absolute SMC at month 3 > 5% was an independent prognostic factor for OS (HR = 1.99, 95% CI = 1.32-2.99, P = 0.00092, Figure 26) considering other predictors including WC.

3.3 Analysis of adipose distribution patterns in hospitalized COVID-19 patients

3.3.1 Patients' characteristics

Among the CORKUM cohort we screened clinical records of 75 patients consecutively admitted to our medical center between February to May 2020. Based on data availability and completeness, 58 patient records were included into the analysis (Figure 27).

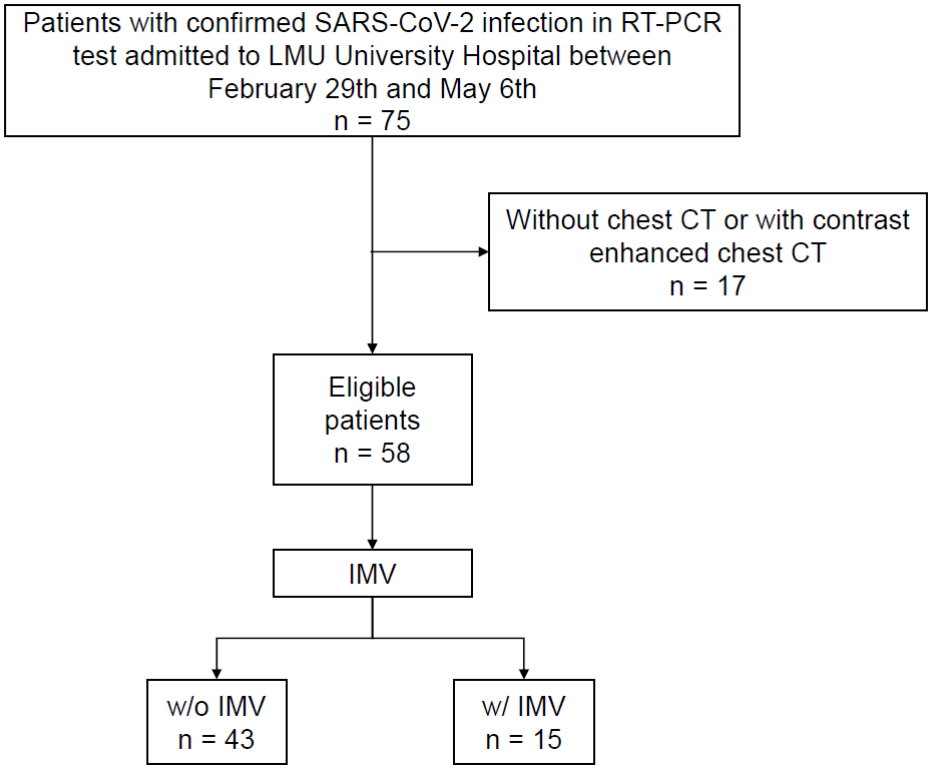


Figure 27. Patient inclusion and exclusion criteria for the retrospective study cohorts.

Abbreviations: IMV = invasive mechanical ventilation, RT-PCR = real-time PCR, w/o = with/without.

We then subdivided the entire cohort in two groups according to the need of IMV. The median age of the entire patient cohort was 63 years (range 32 to 91 years) without relevant differences between patients with IMV and without IMV. A total of 27.6% of all patients were female. A higher proportion of patients among the COVID-19 patients without IMV were female (non-IMV: 32.6% vs. IMV: 13.3%, P = 0.19). Within the entire patient cohort 56.9% had none of the considered comorbidities, 31% had one and 12% had at least a combination of two or more of the considered comorbidities. The number of comorbidities was similarly distributed between patients with, and patients without the need of IMV (P = 0.39). Although diabetes was more prevalent in COVID-19 patients

with IMV (IMV: 26.7% vs. non-IMV: 14%), the overall distribution of pre-existing comorbidities was similar between groups (P = 0.75). As laboratory surrogates for the considered pre-existing comorbidities we compared creatinine and high-sensitive troponin levels. We found increased levels of creatinine and troponin in the serum of COVID-19 patients that needed IMV at the time point of admission (creatinine: IMV: 1.1 (0.8-2.1) mg/dl vs. non-IMV: 0.9 (0.4-6.0) mg/dl; troponin: IMV: 0.02 (0-0.04) ng/ml vs. non-IMV: 0 (0-0.18) ng/ml). However, median levels of creatinine were still within (creatinine < 1.2 mg/dl) and for troponin barely past (troponin < 0.018 ng/ml) our institutional upper limits.

Table 6. Patient characteristics within CORKUM cohort

Characteristics	Invasive mechanical ventilation			P value [A]
	All patients (N = 58)	No (N = 43)	Yes (N = 15)	
Age, median (range) [years]	63 (32-91)	61 (31-91)	64 (47-82)	0.66
30-50 years	13 (22.4)	12 (27.9)	1 (6.7)	0.13
51-70 years	27 (46.6)	17 (39.5)	10 (66.7)	
> 71 years	18 (31)	14 (32.6)	4 (26.7)	
Females	16 (27.6)	14 (32.6)	2 (13.3)	0.19
Comorbidities				
None	33 (56.9)	24 (55.8)	9 (60)	0.39
1 comorbidity	18 (31)	15 (34.9)	3 (20)	
≥ 2 comorbidities	7 (12)	4 (9.3)	3 (20)	
Diabetes	10 (27.2)	6 (14)	4 (26.7)	0.75
Coronary heart disease	13 (22.4)	10 (23.3)	3 (20)	
COPD	5 (8.6)	4 (9.3)	1 (6.7)	
Chronic kidney disease	5 (8.6)	4 (9.3)	1 (6.7)	
Serum parameters				
Creatine, median (range) [mg/dL]	0.95 (0.4-6.0)	0.9 (0.4-60)	1.1 (0.8-2.1)	**0.006**
Troponin, median (range) [ng/mL]	0 (0-0.18)	0 (0-0.18)	0.02 (0-0.04)	**0.002**

All values are shown in number (percent) if not stated otherwise. [A] P-values were calculated either by Mann Whitney test, Fisher's exact test or Chi-square test if appropriate.

Abbreviations: COPD = chronic obstructive pulmonary disease.

3.3.2 Baseline inflammation parameters, anthropometric data, and body composition measurements

We analyzed routine serum laboratory parameters in all patients upon hospital admission. Similarly to previously published data, the median serum concentrations of proinflammatory markers CRP (IMV: 7.8 (2.1-15.2) mg/l vs. non-IMV: 1.9 (0.1-32.3) mg/l, P = 0.0008) and IL-6 (IMV: 129 (34.8-233) pg/ml vs. non-IMV: 23.4 (1.5-122) pg/ml, P <

0.0001) were increased in patients with a severe clinical course. LDH concentrations were also significantly increased in patients that were dependent on IMV (IMV: 439 (252-733) U/ml vs. non-IMV: 258 (153-619) U/ml, P = 0.0002). Mean NLR was higher among patients with IMV but did not reach significance level (IMV: 5.8 (2.5-20.4) vs. non-IMV: 3.5 (0.9-19.1), P = 0.057).

Anthropometric characterization of the two groups revealed a median BMI of the overall cohort of 25.7 kg/m², with increased relative numbers of obese patients within the IMV group (IMV: 6 (40%) vs. non-IMV: 7 (16.7 %), P = 0.77). In comparison, COVID-19 patients with IMV had a higher median BMI (IMV: 27.8 (20.4-45.8) kg/m² vs. non-IMV: 24.8 (17.7-38.5) kg/m², P = 0.032). Furthermore, the CT-derived anthropometric and body composition measurements revealed strong differences between these groups for the waist circumference (IMV: 111.2 (103.2-150.4) cm vs. non-IMV: 103.4 (77.7-134) cm, P = 0.0026), the WtHR (IMV: 0.66 (0.57-0.8) vs. non-IMV: 0.59 (0.47-0.71), P = 0.0006) and the amount of VAT (IMV: 133.4 (64.7-300.3) cm² vs. non-IMV: 84.6 (7-237.2) cm², P = 0.0047), but not for SAT or EAT. COVID-19 patients who required IMV also had higher amounts of hepatic fat as indicated by a lower radiation attenuation and correspondingly lower HU values (IMV: 45 (28.6-57) HU vs. non-IMV: 48.6 (31.3-61.2) HU, P = 0.0044). As a control, we also analyzed splenic tissue attenuation which revealed no differences between the two groups (Table 7).

Table 7. Proinflammatory markers, anthropometric data and adipose tissue compartments compared between the two groups.

Characteristics	Invasive mechanical ventilation			P value [A]
	All patients (N = 58)	No (N = 43)	Yes (N = 15)	
Proinflammatory markers				
CRP [mg/L]	2.9 (0.1-32.3)	1.9 (0.1-32.3)	7.8 (2.1-15.2)	**0.0008**
Interleukin-6 [pg/mL]	29.8 (1.5-233)	23.4 (1.5-122)	129 (34.8-233)	**<0.0001**
NLR [rel.]	4.3 (0.9-20.4)	3.5 (0.9-19.1)	5.8 (2.5-20.4)	0.057
LDH [U/mL]	276 (153-733)	258 (153-619)	439 (252-733)	**0.0002**
Anthropometric data				
BMI [kg/m^2]	25.7 (17.7-45.8)	24.8 (17.7-38.5)	27.8 (20.4-45.8)	**0.032**
BMI ≥ 30, number (percent) [kg/m^2]	13 (22.8%)	7 (16.7%)	6 (40%)	
Waist circumference [B] [cm]	107.5 (77.7-150.4)	103.4 (77.7-134)	111.2 (103.2-150.4)	**0.0026**
WtHR [B] [rel.]	0.61 (0.47-0.8)	0.59 (0.47-0.71)	0.66 (0.57-0.8)	**0.0006**
Body fat composition				
SAT [cm^2]	97 (8.5-383.6)	92.9 (8.5-383.6)	118 (40.8-343.7)	0.07
VAT [cm^2]	88.9 (7-300.3)	84.6 (7-237.2)	133.4 (64.7-300.3)	0.0047
EAT [cm^2]	12.3 (3.4-32.3)	11.9 (3.4-30.7)	13.2 (5.9-32.3)	0.084
Liver fat content [HU]	46.7 (28.6-61.2)	48.6 (31.3-61.2)	45 (28.6-57)	0.0044
Spleen [HU]	44.4 (29-55.1)	44.4 (29-55.1)	45.7 (31.2-54.8)	0.984

All values are shown in median (range) if not stated otherwise. [A] P-values were calculated either by Mann Whitney test or Fisher's exact test as appropriate. [B] CT-derived waist measurements (see Methods for further information).

Abbreviations: BMI = body mass index, CRP = C-reactive protein, LDH = lactate dehydrogenase, NLR = neutrophil to lymphocyte ratio, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, WtHR = waist-to-height-ratio.

3.3.3 WtHR, VAT and liver fat are superior to BMI, SAT and EAT in predicting the need of IMV among patients with COVID-19 infection

The quality of a diagnostic tests based on the anthropometric data and body composition analyses for predicting the need of IMV in COVID-19 patients were determined by ROC analyses (Figure 28). Analysis of the anthropometric data showed that WtHR was superior to BMI with a higher AUC for prediction of a severe clinical course of COVID-19 (BMI: AUC = 0.69 ± 0.08, 95% CI = 0.53-0.85, P = 0.03; WtHR: AUC = 0.79 ± 0.06, 95% CI = 0.67-0.91, P = 0.0009). An analysis of the adipose tissue compartments showed a good discrimination for VAT and liver fat with remarkably similar values (VAT: AUC = 0.74 ± 0.07, 95% CI = 0.6-0.88, P = 0.05; Liver fat: AUC = 0.74 ± 0.07, 95% CI = 0.6-0.89, P = 0.05) and a missing discrimination for predicting the need of IMV based on SAT and EAT (Table 8).

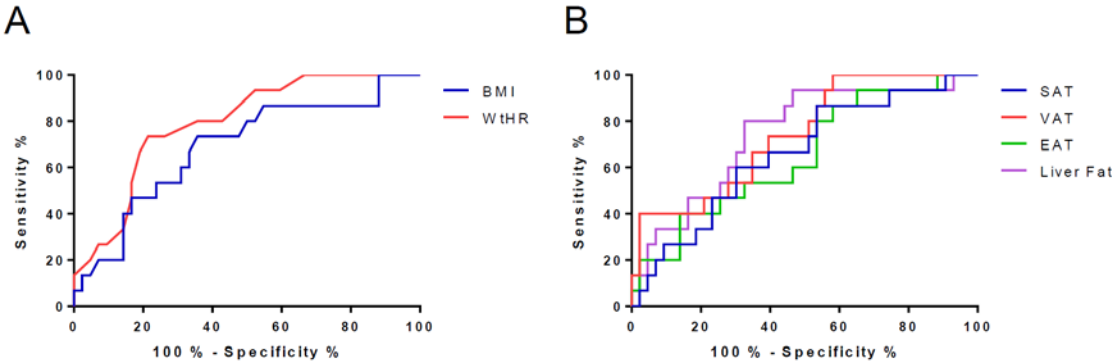


Figure 28. Receiver Operating Characteristic (ROC) curves for prediction of a severe clinical course of COVID-19 based on anthropometric data and body fat composition. For each of the anthropometric (BMI, WtHR) and body composition measurements (Liver fat, SAT, VAT, EAT) parameters ROC analyses were performed. **A** ROC curves for BMI and WtHR, N (non-IMV) = 42, N (IMV) = 15. **B** ROC curves for liver fat, SAT, VAT and EAT, N (non-IMV) = 43, N (IMV) = 15.

Abbreviations: BMI = body mass index, WtHR = waist-to-height-ratio, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue.

Table 8. ROC characteristics.

	ROC Characteristics		
	AUC	Std	95% CI
Anthropometric data			
WtHR	0.79	0.06	0.67-0.91
BMI	0.69	0.08	0.53-0.85
Body fat composition			
VAT	0.74	0.07	0.6-0.88
Liver fat	0.74	0.07	0.6-0.89
SAT	0.66	0.08	0.5-0.82
EAT	0.65	0.08	0.49-0.80

Abbreviations: 95% CI = 95% confidence interval, AUC = area under the curve, BMI = body mass index, Std = standard deviation, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, WtHR = waist-to-height-ratio.

3.3.4 WtHR and a higher amount of metabolically high-risk adipose tissue sites correlate with IL-6 and LDH, but not with CRP and NLR

To investigate the pathogenetic link between adipose tissue distribution with a severe clinical course among patients with COVID-19, we correlated the anthropometric data and the CT-derived adipose tissue compartments with the adverse biomarkers CRP, IL-6, NLR and LDH (60, 126-130). Notably, there was a positive correlation between WtHR and the pro-inflammatory cytokine IL-6 (coefficient: 0.4, P = 0.003), but not between BMI and IL-6 (coefficient: 0.18, P = 0.2). The metabolically high-risk adipose compartments VAT, EAT, and liver fat correlated with increased IL-6 levels (VAT: coefficient: 0.4, P = 0.002; EAT: coefficient: 0.31, P = 0.02; liver fat: coefficient: -0.36, P = 0.006), whereas SAT did not (coefficient: 0.12, P = 0.37, Figure 29). Correlation analyses between body composition data and CRP or NLR were not significant (Figure 30). We repeated the correlation analyses with LDH as an indicator for tissue damage. Here, we found significant correlations for all the investigated anthropometric data (BMI: coefficient: 0.44, P = 0.0007; WtHR: coefficient: 0.47, P = 0.0003) and adipose tissue compartments except EAT (SAT: coefficient: 0.41, P = 0.002; VAT: coefficient: 0.26, P = 0.049; liver fat: coefficient: -0.26, P = 0.047). There were no correlations between splenic tissue attenuation and any of the adverse biomarkers.

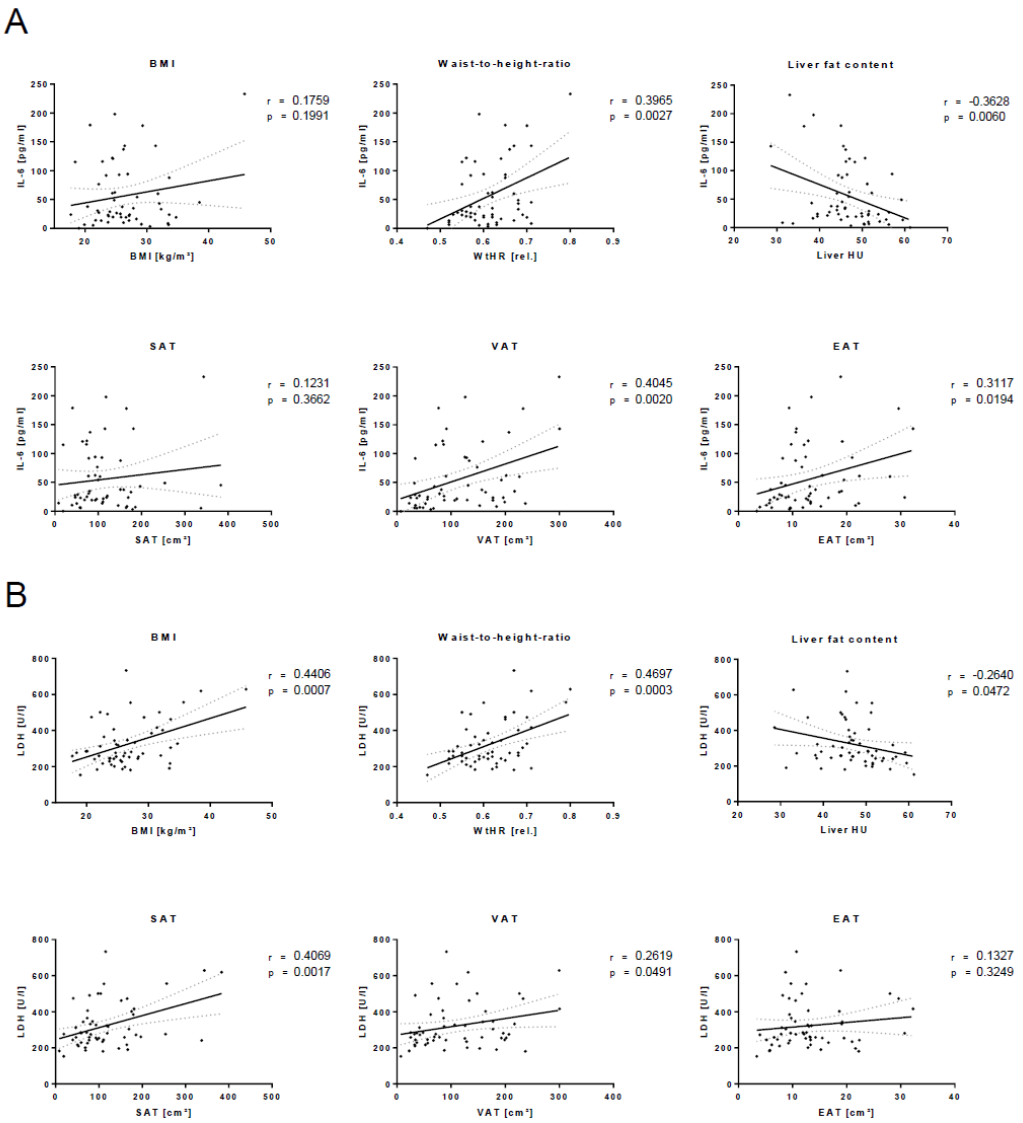


Figure 29. BMI, WtHR and metabolically high-risk adipose tissue compartments correlate with IL-6 and LDH. Each of the anthropometric data (BMI, WtHR) and adipose tissue compartments (Liver fat content, SAT, VAT, EAT) were correlated with IL-6 and LDH. Points display single measurements at admission. Linear regression is shown as continuous line with the 95% CI as dotted lines. Values for correlation coefficient r and p-values are displayed on the right side of each graph.

A WtHR and metabolically high-risk adipose tissue (VAT, EAT, liver fat) significantly correlate with increased levels of pro-inflammatory IL-6, but not BMI and SAT. N = 55.

B BMI, WtHR, Liver fat, SAT, and VAT correlate with increased levels of LDH as an indicator for tissue damage and cell turn-over, N = 56.

Abbreviations: BMI = body mass index, IL-6 = interleukin 6, LDH = lactate dehydrogenase, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, WtHR = waist-to-height-ratio.

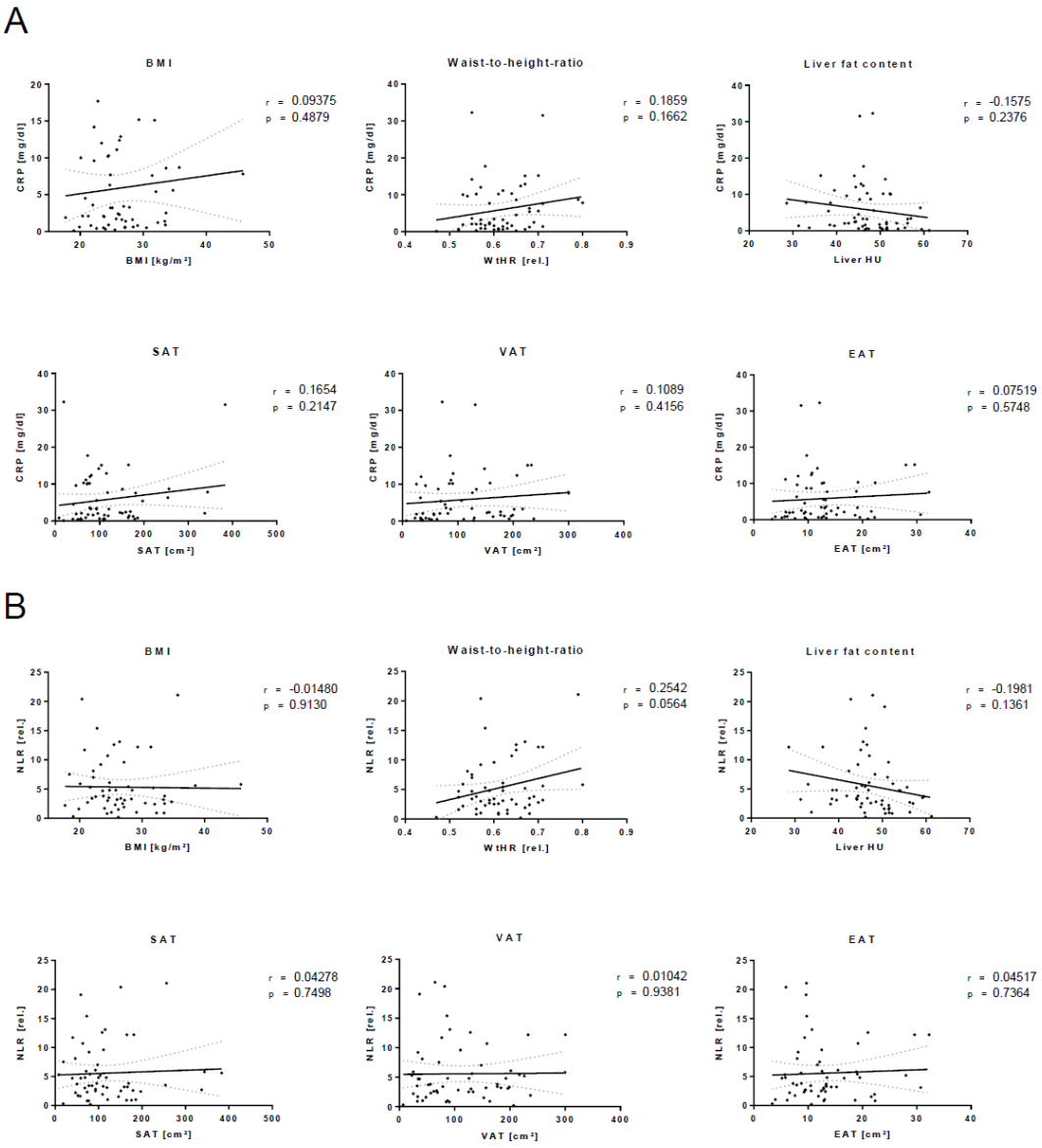


Figure 30. Body composition measurements do not correlate with CRP or NLR. Anthropometric data (BMI, WtHR) and each adipose tissue compartment (Liver fat content, SAT, VAT, EAT) were correlated with CRP and NLR. Points display single measurements at admission. Linear regression is shown as continuous line with the 95% CI as dotted lines. Values for correlation coefficient r and p-values are displayed on the right side of each graph.

A Correlations with CRP, N = 56. **B** Correlations with NLR, N = 56.

Abbreviations: BMI = body mass index, CRP = c-reactive protein, NLR = neutrophil-to-lymphocyte ratio, S/V/EAT = subcutaneous/visceral/epicardial adipose tissue, WtHR = waist-to-height-ratio.

4. Discussion

4.1 Discussion of the methods

4.1.1 “Conservative” nutritional risk assessment and body composition analyses in clinical practice

Nutritional risk indices help clinicians and nutritionists to better assess a risk of developing malnutrition. However, most of the commonly used “conservative” nutritional risk screening tools such as the nutrition risk assessment (NRS-2002) (131) and malnutrition universal screening tool (MUST) (132) assess the inadequate dietary intake as well as disease severity with consideration of BMI rather than using precise assessments of body composition. Alternative anthropometric parameters include body weight, BMI, skinfold thickness measurements, waist circumference, waist–hip ratio and waist to height ratio (WtHR). As BMI alone cannot account for fat and muscle distribution and amounts, a patient with large muscle mass may skew results. For these reasons, it may be postulated that a complete nutrition risk assessment performed in routine care should include one or more of the other anthropometric measurements available as well as body composition evaluation using CT. Several, more time consuming, yet more precise techniques are available to assess body composition clinical trials. These include CT as gold standard (133), and magnetic resonance imaging (MRI), ultrasound, dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA).

4.1.2 Computed tomography (CT)

CT is the gold standard for measurement of muscle mass recommended by EWGSOP2 (133). Many commercial software programs are available to evaluate body composition. Among them, Slice-O-Matic is a semiautomated software for assessing the body composition. It allows the user to select the area through painting with a virtual brush with a user-defined HU threshold. Studies showed that Slice-O-Matic software had a high agreement with in-house programs, which operates on a Sun workstation based on UNIX software for the adipose tissue assessment (134). It should be considered that using CT scans to evaluate body composition brings additional radiation exposure. However, for patients diagnosed with cancer, CT is a routine test for diagnosis, follow up on treatment effects and surveillance. Patients with infectious disease such as COVID-19 also undergo CT exams upon admission in order to strengthen the laboratory diagnoses and surveillance. In such cases they present a precise measurement that can be analyzed in clinical trials with no extra radiation exposure. Body composition analyses with segmentation of a single CT scan can take around 15 minutes per patient, which make the evaluations in large scale clinical trials time consuming (135). Thus, development of a

fully automated evaluation of body composition with CT scans is needed for researchers and clinicians to fully utilize the potential of such measurement. Novel algorithms invented to automatically assess body composition with high accuracy are emerging. For example, a deep learning–based, fully automated system for body composition analyses was developed (136). The intraclass correlation coefficients of the algorithm and manual assessments in evaluation of VAT, SAT and muscle volumes reached 0.998, 0.999 and 0.991, respectively (136).

Nonetheless the compartmental analysis performed using CT scans cannot be equaled to that obtained with other measurements available. For example, EAT is important to analyze in addition to simple weight and height data as it has been shown to associate with many risk factors and also plays an important role in the disease progress of inflammation and cardiovascular disease (137, 138). It is also important to note that the pericardium is sometimes barely seen in the CT scans so that EAT measurements rely on the skilled researchers with experience of cardiac anatomy and imaging.

CT scans for body composition is feasible in majority of patients with solid tumors and patients with infectious disease that have undergone CT scans as a part of diagnoses and surveillance. Due to their accuracy body analysis, CT scan is still considered to be the gold standard.

4.1.3 Other methods for body composition analyses

MRI can be used to measure body composition with high precision and is considered to be precise (139). However, MRI does not provide information of tissue density like the CT does, and semiautomated assessments of body composition with MRI takes more time. Ultrasound, DXA and BIA can be used to evaluate body composition as well (140-148). However, they cannot be regarded as the gold standard as each method has its limitations, such as inaccuracy, time-consuming or easy to be affected by the environment or the individuals' health condition (139, 149, 150).

4.2 Discussion of the results

4.2.1 Clinical implications of EWL

Our analysis of the FIRE-3 trial suggests that EWL ≥ 5% at month 3 was related to shorter PFS, OS and more side effects. These findings are supported by other literature (25-29) and thus stress the importance to further evaluations regarding the impact of patients' weight status during anti-neoplastic treatment. Previous studies looking at cancer patients classified as undernourished or high risk for undernutrition show controversial results regarding nutritional interventions. For example, a study by Uster A. et al from 2013 did not show any benefit from nutritional therapy in terms of nutritional status, physical performance, and/or quality of life (151). However, some other well-designed trials contradict these results. Further studies reveal a possible reason for the contradictive results (152-158). For example, Santarpia L. et al found that for cancer patients in the late disease stage, the catabolic process could not be reversible through nutritional interventions (159). EFFORT trail demonstrates that for 2028 patients at nutritional risk, nutritional support improved patients' survival and reduced hospitalization associated complications (160). In another trial, patients were recruited at an earlier stage in the catabolic process and treated with a nutrition and exercise program or given usual care (161). Results showed that the multimodal intervention was better than the usual care for reducing effects of nutrition-related symptoms, specifically regarding nausea and vomiting and also for protein intake (161). However, this study failed to show an improvement in overall quality of life (161). In contrast, these studies suggested that it is necessary to define the specific patients' group and interventions that could lead to profound effects (161). Thus, we performed our analysis evaluating the impact of EWL ≥ 5% at month 3 on clinical outcomes and side effects in mCRC patients. As far as we known, our study is the first to evaluate the impact of EWL within a randomized phase III study of standard first-line chemotherapy FOLFIRI with cetuximab or bevacizumab in RAS-WT mCRC patients.

Cachexia is defined as weight loss of ≥ 5% within 6 months (162) and it is difficult to reverse cachexia in cancer patients. Cachexia thus remains a clinical challenge with increased mortality and greater side effects. Our study defined weight loss at month 3 as a negative prognostic factor, earlier than the definition of at which point cachexia begins.

Our examination of the evolution of body weight during the first six months of treatment within the FIRE-3 study provides insights to support the idea of early identification of weight loss. In fact, when considering the total cohort, we found that patients lost on average, the most weight during the first month of treatment (an average of 0.7 kg),

whereas patients slowly recovered hereafter with a weight gain of average 0.38 kg per month (Figure 9). In contrast patients with EWL ≥ 5% further showed an average maximum weight loss 1.1kg per month during first six months of treatment (Figure 10). Of note, a patient's age at randomization (≥ 65 years) was the only baseline parameter that seemed to predict occurrence of EWL ≥ 5% with an OR of 2.37 in linear relationship analysis (P = 0.016), which indicated that elderly patients are at the highest risk of developing EWL. Elderly patients tend to lose more weight, in part due to changes of the metabolic state but also due to physical factors such as taste and dental status, or difficulty with food preparation and acquisition (163). These factors may come together to complicate elderly patients' nutrition status and therefore should be closely monitored.

Next, we examined consequences of EWL and found that patients exhibiting EWL ≥ 5% were at higher risk for the development of the following AEs: fatigue, diarrhoea, nausea/vomiting, and oedema. Here, our results are consistent with a previous study, which indicates that especially gastrointestinal symptoms, such as nausea and vomiting, significantly correlated with weight loss (164) and may point to the etiology of such weight loss. Thus, gastrointestinal symptoms, fatigue and oedema should be included in early nutritional evaluations and changes should be monitored. One internationally validated screening tool, the Patient Generated Subjective Global Assessment does include these parameters and the answers influence the extent of the identified nutrition risk. Therefore, in absence of body composition analysis this may present a more precise tool for identifying EWL during routine care (165-170).

We then evaluated the association of EWL ≥ 5% with patient outcomes. Here, we found a significant difference in OS between the two subgroups of 11.3 months favoring patients with EWL < 5% (32.4 vs. 21.1 months, HR = 1.64; 95% CI = 1.13-2.38; P = 0.0098). Further, EWL impacted PFS with a median difference of 2.8 months between the two subgroups (11.8 vs. 9.0 months, HR = 1.72; 95% CI = 1.18-2.5; P = 0.0048). Both results remained significant in multivariate analysis after adjusting for treatment and further prognostic parameters, such as primary tumor sidedness, baseline CEA and ECOG (all P < 0.05). Of note, no significant association of EWL and ORR was observed, most probably reflecting the disadvantages of this parameter in the assessment of targeted first-line treatment in mCRC patients (1, 171, 172).

Finally, we found that EWL ≥ 5% did not predict a treatment benefit when comparing FOLFIRI/cetuximab with FOLFIRI/bevacizumab. Here, no significant interaction between treatment arm and EWL was observed (P = 0.65).

As far as we know, this study is the first detailed analysis of the evolution of body weight during modern targeted first-line treatment among RAS-WT mCRC patients. Here, we identified elderly mCRC patients (age ≥ 65 years) being at highest risk of weight loss. In line with previous publications in the field of mCRC and various other tumor entities, weight loss was identified as risk factor for frequent AEs during first-line treatment, especially gastrointestinal symptoms as well as fatigue and oedema. Further, EWL ≥ 5% was associated with inferior patient survival.

These results indicate that weight maintenance during treatment should become a clinical priority. Methods to prevent further weight loss, such as early and etiology based nutrition interventions should be incorporated into the cancer care from the point of diagnosis (173). All cancer patients should have access to nutritional counselling during treatment provided by specially trained and qualified clinical dietitians (10, 173, 174). In tandem physicians and nurses who are specialized in nutrition care, dietitians, are uniquely qualified to discuss strategies to preserve body weight and stress its significance. Additionally, clinicians should stress the importance of weight management in patients with mCRC, especially among elderly patients who appear to be at the highest risk. These results are consistent with current ESPEN guidelines, which recommend that patients maintain weight during the course of their cancer care and strive for a healthy body weight through the course of the cancer continuum (10, 11).

Weight loss is accompanied by dynamic changes of muscle and adipose tissue. It is widely cited that around one fourth weight loss can be traced back to muscle loss (175). Loss of muscle, in turn, is a feature of cancer cachexia that is correlated with decreased survival and a greater number and severity of AEs (176). In conclusion EWL is an essential component that should be routinely assessed during the course of treatment when regarding risk of undernutrition.

4.2.2 Clinical implications of research about sarcopenia status in mCRC patients

Body composition describes detailed distribution of fat and muscle and is likely to be a predictor of chemotherapy pharmacokinetics (177-179). Weight loss alone may be an important factor to consider, yet in this context, the importance of body composition should also be considered. In our analysis regarding the presence and frequency of sarcopenia among patients within the FIRE-3 cohort, results were in accordance with previous publications (44). The results show that baseline sarcopenia status did not have statistically significant impact on survival in mCRC patients (PFS: 10.5 vs. 10.4 months, HR = 1.12, 95% CI = 0.89-1.41, P = 0.33; OS 28.1 vs. 27.1 months, HR = 1.21, 95% CI

= 0.95-1.53, P = 0.12). Patients' baseline characteristics between sarcopenia and no sarcopenia groups were not balanced and evenly distributed due to its retrospective nature. More patients without sarcopenia had primary right sided tumor compared with patients in the sarcopenic group (29.7 % vs. 15.4 %, P = 0.0023). This may be explained as right sided tumors have been shown to be a greater negative prognostic factor in mCRC patients. As our previous results regarding the evolution of body weight and EWL, the change of sarcopenia status from baseline to month 3 (SMC) may be more important than the initial status. In fact, the evolution of sarcopenia throughout the course of therapy may impact survival. Blauwhoff-Buskermolen and colleagues categorized SMC into tertiles and found that when mCRC patients lost more than 9% of SMI (lowest tertile) after 3 months of chemotherapy, they had worse OS (HR = 4.47, 95% CI = 2.21-9.05, P < 0.001) (45). The loss of muscle mass suggested that patients were less able to tolerate the treatment in order to gain survival benefit. In our first analysis regarding EWL, we have indicated that cancer patients should maintain body weight during treatment. However, this alone may not be sufficient. Thus, instead of only focusing on the baseline sarcopenia status, we evaluated further impact of SMC at month 3 on OS and its association with weight change.

We found that impact of SMC on OS log hazard rate follows a quadratic relationship. Patients with SMI loss > 5% and SMI gain > 5% group were not significantly different (P = 0.13). Thus, we merged the SMI loss > 5% and SMI gain > 5% into absolute SMC > 5% group and found it to be an independent prognostic factor for OS. It is in accordance with previous study that patients with SMI loss had an inferior survival. However, in our analysis, patients with SM gain > 5% also suffered from shorter survival. One possible explanation could be that increased SMI were not purely hypertrophy but probably due to edema-induced swelling (180, 181). The changes in SMM might impact dosing (39, 178, 182). In addition, muscle quality also has impact on survival in cancer patients (183, 184). Low muscle attenuation may also suggest adipose tissue infiltrated into muscle, known as myosteatosis, which indicates an impaired muscle quality and loss of muscle strength (185). Previous studies illustrated the negative impact of low muscle quality on survival in CRC patients (100, 186-188). Some patients tend to have lower muscle quality albeit higher muscle quantity (183, 184). Our study did not evaluate the impact of muscle quality on survival, nor did we evaluated patients' muscle strength, thus further prospective studies with a comprehensive evaluation of muscle status are needed to validate our results. We looked at HU from 20 patients and did not find hints for edema. Further evaluations are ongoing to elucidate the quadratic relation.

EWL appears to be an independent prognostic factor for OS, as our first study showed. However, EWL has its inherent limitations, as it is only anthropometric parameter and do not indicated further detailed information of body composition. SMC might add more information. It appears to be vital to know how proportions of muscle changed when patients lost or gained weight. We illustrated the patterns of SMC when patients experienced WC and found that patients with extreme WC have more chances to have an extreme SMC (P = 0.015). However, univariate and multivariate analysis showed that both SMC and WC were both independent prognostic factors for OS (SMC: HR = 1.99, 95% CI = 1.32-2.99, P = 0.00092, WC: HR = 1.49, 95% CI = 1.1-2.02, P = 0.0093). There is no evidence that treatment effect on OS could depend on percentage of SMC (P = 0.46). The effect of treatment on OS is only statistically significant among patients with an extreme SMC (P = 0.0026). It is recommended from our analysis that more precise nutritional and exercises recommendations should be provided to cancer patients to preserve the body weight and muscle. Further studies evaluating defined nutritional and exercise programs are on the way, such as the INTEGRATION study.

We also found that baseline sarcopenia status was associated with higher incidence of hematotoxicity after patients receiving one month of treatment (81.4 vs. 71.5%, P = 0.044). Sarcopenia may influence the absorption, distribution, metabolism and excretion process (178). Thus, sarcopenic patients might be found to undergo greater toxicity during chemotherapy (189). In stage II and III CRC patients (N = 533) treated with FOLFOX (Folic acid, FU and oxaliplatin), sarcopenic patients presented with higher incidence of DLT and had twice the risk for dose reduction on FOLFOX than patients without sarcopenia when adjusted with sex, age and tumor stage (OR = 2.28, 95% CI = 1.19-4.36, P = 0.01) (189). Low SMM was found to be associated with serious AEs and thus had a reduced treatment tolerability of sorafenib treatment in patients with hepatocellular carcinoma (190). Patients with low SMM are less likely to receive subsequent sorafenib treatment than patients without low SMM (190).

4.2.3 Clinical implications of research about adipose tissue in COVID-19 patients

On the other side of the spectrum of malnutrition, body composition and fat distribution may play a role in the outcome of obese patients with infectious disease (191). In fact, obese patients are known to have metabolic disturbances, as well as an altered immune response and often present with chronic low-grade inflammation (192). These factors, in turn, contribute to an altered clinical course among obese patients (193). For example, obese patients with influenza (defined as BMI $\geq$ 30 kg/m^2 in adults) are known to shed

the virus for a longer period than non-obese patients, which leads to a longer disease course as well as a higher chance of spreading the disease (85, 194). Obesity has similarly been proved to be a risk factor for severe cases of COVID-19 (20, 195, 196). However, most previous studies defined obesity only on hand the BMI and did not take body fat compartments into consideration (195, 196). Our study suggested the prognostic relevance of WtHR, VAT and liver fat regarding the necessity of IMV and the correlation was stronger than BMI (WtHR: AUC = 0.79 ± 0.06, 95% CI = 0.67-0.91, P = 0.0009; liver fat: AUC = 0.74 ± 0.07, 95% CI = 0.6-0.89, P = 0.05; VAT: AUC = 0.74 ± 0.07, 95% CI = 0.6-0.88, P = 0.05; BMI: AUC = 0.69 ± 0.08, 95% CI = 0.53-0.85, P = 0.03). This was consistent with a previous meta-analysis, which showed that adipose tissue distributions and WtHR were superior to BMI in predicting the risk of cardiometabolic disease. ROC curves were used to further investigate the prognostic relevance of these parameters. It is identified that WtHR, VAT and liver fat are superior to BMI, SAT and EAT in predicting the necessity of IMV. Thus, our study suggested that WtHR and adipose tissue compartments can more accurately predict necessity of IMV than BMI alone and this factor should be considered in further research.

Additionally, severe cases of COVID-19 had different inflammatory profiles compared with mild cases (197). Patients with severe COVID-19 infection defined by the need for IMV showed increased levels of IL-6 and CRP (60). The cytokine cascade caused by acute severe COVID-19 infection, and its downstream IL-6 activation is a hallmark of the progression from COVID-19 pneumonia to excessive inflammation and ARDS (57). Increased levels of VAT and liver fat are also associated with specific proinflammatory cytokines. Specific cytokines such as IL-6, TNF-α and IL-1β (198, 199) are thought to exert these effects through infiltration of cytokine secreting immune cells (200). This is the first study evaluating the correlations of anthropometric data as well as adipose tissue compartments with inflammatory biomarkers in severe cases of COVID-19. Our study reveals a strong association regarding the combination of metabolically high-risk adipose tissue sites (VAT, EAT and liver fat) and WtHR with baseline IL-6 concentrations, which may indicate a possible link between obesity-associated meta-inflammation and the excessive immune responses upon COVID-19 infection.

4.2.4 Limitations of our study

One of the limitations of our study is its retrospective nature. The patient number in our cohort gradually decreased due to discontinuation of treatment. Patients' dietary behaviours, psychosocial situations or environmental influences that could promote weight changes were not recorded. Nor was data available as to who received a nutrition intervention and who did not. Further, baseline data was available for all patients, but follow-up weight data was only available for a fraction of patients at month 3 (326 out of 400, 81.5%) on survival. In consideration of guarantee-time-bias as the potential confounding factor for efficacy, we performed a landmark analysis to rule out that EWL merely indicated treatment duration. Further prospective study with consideration of dose intensity is needed to validate our results.

The limitations of our sarcopenia analysis include that our results regarding the baseline sarcopenic status might be confounded by an imbalance of baseline characteristics. Our results regarding SMC are based on a sample size of 220. Our study did not consider the impact of muscle quality and muscle strength on survival. Thus, our results need to be validated in a large-scale prospective study with consideration of muscle strength, muscle quality and muscle quantity.

The limitations of our study investigating the correlations of adipose distribution patterns with inflammation and respiratory failure in hospitalized COVID-19 patients include its retrospective, single-center design and the small sample size. Additionally, a large part of our cohort was males, making it difficult to assess gender related differences. Thus, results of the present study need to be validated in a larger patient cohort from multiple treatment centers and assessed for gender related differences. This would also allow for a conclusive multivariate analysis of the detected body composition effects and might lead to the development of a body composition-based risk score for COVID-19 patients which could possibly then be used for similar infectious diseases.

4.3 Conclusion

In conclusion, our data suggests that EWL ≥ 5% from baseline to month 3 is an independent prognostic biomarker for survival and AEs in RAS-WT mCRC patients receiving standard first-line targeted therapy. Of note, age is significantly correlated with occurrence of weight loss. Therefore, early detection of weight loss needs to be considered as an integral part of clinical assessments and appropriate etiology-based nutrition interventions focusing on weight maintenance should be initiated for all mCRC patients from baseline and throughout treatment. Such early preventative measures targeted at weight maintenance are especially important among elderly patients.

Baseline sarcopenia status did not have impact on PFS or OS in RAS-WT mCRC patients receiving first-line targeted therapy according to our data. Nonetheless, patients with sarcopenia seemed to have a higher incidence of AEs, such as hematotoxicity after they received one month of treatment. EWL is an important prognostic parameter for OS. However, it has its inherent limitations of not illustrating detailed information about changes of body composition. Thus, we further evaluated the impact of SMC on survival and found it follows a quadratic relationship. Patients with SMI gain > 5% and SMI loss > 5% did not significantly differ regarding OS. Patients with absolute SMC > 5% had an inferior OS than patients with stable SMC (absolute SMC ≤ 5%). The additional analyses of SMC added additional information apart from EWL, albeit it is still not fully understood why both SMI gain and loss impact on survival negatively in a comparable matter. Further studies are necessary to unravel associations and validate this parameter for prospective evaluation.

CT-derived measurements, anthropometric parameters such as WtHR, and metabolically high-risk adipose tissues distribution appear to be superior to BMI in predicting the necessity of IMV in COVID-19 patients. These measurements can be semiautomatically performed using thoracic CT images and do not bring patients additional radiation exposure. Lastly, the correlation between metabolically high-risk adipose tissue compartments and baseline IL-6 serum levels indicate that obesity-associated meta-inflammation might play a vital role in hyperinflammation during the ARDS development in COVID-19 patients.

5. Future perspectives

5.1 Association of body composition and weight among patients with metastatic disease

For this thesis, the impact of EWL, as well as baseline sarcopenia status and its changes on survival and side effects in mCRC patients were evaluated. The findings indicate that further research should attempt to differentiate the role of body composition in the progression of disease. Ideally the development of a combined marker incorporating muscle strength, muscle quantity and/or quality, adipose tissue and change of body weight could be explored. As males tend to be more muscular than females (201), gender differences should be considered regarding the treatment benefit and side effects. Different age groups should also be considered as potential subgroups since age-related muscle loss could confound results (202). Furthermore, attention should be paid to specific groups who may be more vulnerable to suffer from an extreme SMC during treatment to gain the best treatment benefit. In this context, the effect of early and preventive interventions aimed at weight and muscle stabilization that are initiated at the time of diagnosis need to be evaluated in well-defined patient population.

5.2 Association of adipose tissue compartmental distribution with survival and side effects in patients with metastatic disease

In this thesis, data illustrated the association between adipose tissue compartments and necessity of IMV in patients with COVID-19. Specifically, a correlation of VAT, EAT and liver fat with markers of inflammation could be illustrated. As obesity is known to induce chronic inflammation in adipose tissue (203), which stimulates cancer progression (204), an evaluation of the association of fat tissue with survival and side effects in mCRC patients within the randomized phase III trial FIRE-3 could present the next step. The hypothesis is that mCRC patients exhibiting obesity and/or increased VAT and liver fat have worse survival and higher frequencies of AEs.

5.3 The AEs behind the etiology of EWL and nutritional supports as interventions

In the thesis, the prognostic relevance of EWL and baseline sarcopenia in patients with mCRC and adipose tissue compartments in patients with COVID-19 infection were

demonstrated. There is already a validate tool, the Patient-Generated Subjective Global Assessment (PG-SGA), that can measure all aspects of GLIM criteria (205), both etiologic and phenotypic assessments. However, we discovered that EWL as one phenotypic aspect of GLIM diagnostic scheme of malnutrition could be of significance in predicting survival and side effects in cancer patients. We would like to discover which AEs are perhaps behind the etiology of the EWL and if they can be treated with nutrition support.

These three further studies would enable us to further understand the proportions of changes of body composition and weight and how they affected survival and AEs in mCRC patients undergoing targeted treatment as well as the potential nutritional interventions for reserving muscle and weight.

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Appendix A:

Table 1. Comparison of baseline characteristics with ITT population within FIRE-3 study

Baseline characteristics	**Weight loss cohort (n=326)**	**Rest of the ITT population (n=409)**	***P* value**
Treatment			0.1
Cetuximab	154 (47.2 %)	219 (53.5 %)	
Bevacizumab	172 (52.8 %)	190 (46.5 %)	
Sex			0.017
Male	236 (72.4 %)	262 (64.1 %)	
Female	90 (27.6 %)	147 (35.9 %)	
Age (years)			0.55
< 65	162 (49.7 %)	194 (47.4 %)	
≥ 65	164 (50.3 %)	215 (52.6 %)	
ECOG performance status			0.33
0	180 (55.2 %)	211 (51.6 %)	
1, 2	146 (44.8 %)	198 (48.4 %)	
Number of metastatic sites			0.6
1	139 (42.8 %)	165 (40.7 %)	
≥ 2	186 (57.2 %)	240 (59.3 %)	
Missing	1 (0.3 %)	4 (1 %)	
BMI (kg/m²)			0.35
< 30	266 (81.8 %)	323 (79 %)	
≥ 30	59 (18.2 %)	86 (21 %)	
Missing	1 (0.3 %)	0 (0 %)	
Primary sidedness			0.22
Left	253 (78.6 %)	302 (74.6 %)	
Right	69 (21.4 %)	103 (25.4 %)	
Missing	4 (1.2 %)	4 (1 %)	
Alkaline phosphatase (IU/L)			0.73
< 300	280 (88.3 %)	345 (87.3 %)	
≥ 300	37 (11.7 %)	50 (12.7 %)	
Missing	9 (2.8 %)	14 (3.4 %)	
Leucocyte (/L)			0.13
< 8×10^9	188 (58.6 %)	211 (52.8 %)	
≥ 8×10^9	133 (41.4 %)	189 (47.2 %)	
Missing	5 (1.5 %)	9 (2.2 %)	
Site of primary tumor			0.52
Colon	202 (62 %)	236 (57.7 %)	
Rectum	112 (34.4 %)	161 (39.4 %)	
Colon and rectum	11 (3.4 %)	11 (2.7 %)	
Unknown	1 (0.3 %)	1 (0.2 %)	

Metastasis in liver			0.0085
Yes	277 (85 %)	315 (77 %)	
No	49 (15 %)	94 (23 %)	
Metastasis in lung			0.11
Yes	120 (36.8 %)	175 (42.8 %)	
No	206 (63.2 %)	234 (57.2 %)	
Metastasis in lymph nodes			0.35
Yes	116 (35.6 %)	131 (32 %)	
No	210 (64.4 %)	278 (68 %)	
Metastasis in peritoneum			0.78
Yes	26 (8 %)	30 (7.3 %)	
No	300 (92 %)	379 (92.7 %)	

Abbreviations: ITT = intention to treat, ECOG = Eastern Cooperative Oncology Group, BMI = body mass index.

Appendix B:

Table 2. Comparison of baseline characteristics with *RAS*-WT population within FIRE-3 study

Baseline characteristics	Cohort with available body weight data (n=326)	RAS-WT population (n=400)
Treatment		
Cetuximab	154 (47.2 %)	199 (49.8 %)
Bevacizumab	172 (52.8 %)	201 (50.3 %)
Sex		
Male	236 (72.4 %)	279 (69.8 %)
Female	90 (27.6 %)	121 (30.3 %)
Age (years)		
< 65	162 (49.7 %)	194 (48.5 %)
≥ 65	164 (50.3 %)	206 (51.5 %)
ECOG performance status		
0	180 (55.2 %)	216 (54.0 %)
1, 2	146 (44.8 %)	184 (46.0 %)
Number of metastatic sites		
< 2	139 (42.8 %)	167 (41.8 %)
≥ 2	186 (57.2 %)	230 (57.5 %)
Missing	1 (0.3 %)	3 (0.8 %)
BMI (kg/m²)		
< 30	266 (81.8 %)	324 (81.0 %)
≥ 30	59 (18.2 %)	75 (18.8 %)
Missing	1 (0.3 %)	1 (0.3 %)
Primary sideness		
Left	253 (78.6 %)	306 (76.5 %)
Right	69 (21.4 %)	88 (22.0 %)
Missing	4 (1.2 %)	6 (1.5 %)
Alkaline phosphatase (IU/L)		
< 300	280 (88.3 %)	339 (84.8 %)
≥ 300	37 (11.7 %)	49 (12.3 %)
Missing	9 (2.8 %)	12 (3.0 %)
Leucocyte (/L)		
< 8	188 (58.6 %)	224 (56.0 %)
≥ 8	133 (41.4 %)	168 (42.0 %)
Missing	5 (1.5 %)	8 (2.0 %)
Site of primary tumor		
Colon	202 (62 %)	245 (61.3 %)
Rectum	112 (34.4 %)	140 (35.0 %)
Colon + Rectum	11 (3.4 %)	14 (3.5 %)
Missing	1 (0.3 %)	1 (0.3 %)
Metastasis in liver		

Yes	277 (85 %)	333 (83.3 %)
No	49 (15 %)	67 (16.8 %)
Metastasis in lung		
Yes	120 (36.8 %)	148 (37.0 %)
No	206 (63.2 %)	252 (63.0 %)
Metastasis in lymph node		
Yes	116 (35.6 %)	141 (35.3 %)
No	210 (64.4 %)	259 (64.8 %)
Metastasis in peritoneum		
Yes	26 (8 %)	34 (8.5 %)
No	300 (92 %)	366 (91.5 %)

Abbreviations: ECOG = Eastern Cooperative Oncology Group, BMI = body mass index.

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Affidavit

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I hereby declare, that the submitted thesis entitled:

Evaluation of Body Weight and Body Composition in Patients with Metastatic Colorectal Cancer or SARS-CoV-2 Infection
……

is my own work. I have only used the sources indicated and have not made unauthorized use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

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place, date

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