Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer

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Abstract

Background and aim   Co-morbidities and computerized tomography-measured muscle abnormalities are both common in cancer patients and independently adversely influence clinical outcomes. Muscle abnormalities are also evident in other diseases, such as diabetes and obesity. This study examined for the first time the association between co-morbidities and muscle abnormalities in patients diagnosed with colorectal cancer (CRC).
Methods   This cross-sectional study included 3051 non-metastatic patients with Stages I–III CRC. Muscle abnormalities, measured at diagnosis, were defined as low skeletal muscle mass index (SMI) or low skeletal muscle radiodensity (SMD) quantified using computerized tomography images using optimal stratification. Co-morbidities included in the Charlson index were ascertained. χ^2 tests were used to compare the prevalence of co-morbidities by the presence or absence of each muscle abnormality. Logistic regressions were performed to evaluate which co-morbidities predicted muscle abnormalities adjusting for age, sex, body mass index, weight change, cancer stage, cancer site, race/ethnicity, and smoking.
Results   Mean age was 63 years; 50% of patients were male. The prevalence of low SMI and low SMD were 43.1% and 30.2%, respectively. Co-morbidities examined were more prevalent in patients with low SMD than in those with normal SMD, and most remained independent predictors of low SMD after adjustment for covariates. Co-morbidities associated with higher odds of low SMD included myocardial infarction [odds ratio (OR) = 1.77, $P = 0.023$], congestive heart failure (OR = 3.27, $P < 0.001$), peripheral vascular disease (OR = 2.15, $P = 0.002$), diabetes with or without complications (OR = 1.61, $P = 0.008$; OR = 1.46, $P = 0.003$, respectively), and renal disease (OR = 2.21, $P < 0.001$). By contrast, only diabetes with complications was associated with lower odds of low SMI (OR = 0.64, $P = 0.007$).
Conclusions   Prevalence of muscle abnormalities was high in patients with non-metastatic CRC. Pre-existing co-morbidities were associated with low SMD, suggestive of a potential shared mechanism between fat infiltration into muscle and each of these co-morbidities.

Keywords   Muscle abnormalities; Charlson co-morbidities; CT imaging; Non-metastatic colorectal cancer

Introduction

Colorectal cancer (CRC) is a leading cause of cancer death in the United States.[1] As such, understanding the predictors of survival in CRC patients can aid the development of targeted interventions to decrease mortality, beyond cancer-specific care.

Co-morbidities are highly prevalent and adversely influence survival outcomes in patients with CRC and other cancer

types.[2,3] Muscle abnormalities, including low skeletal mass index (SMI, quantified as muscle cross-sectional area adjusted by height squared, cm^2/m^2) and low skeletal muscle radiodensity (SMD, quantified in Hounsfield units, HU), can be measured using computerized tomography (CT) images. Both these muscle abnormalities have been associated with the presence of specific co-morbid conditions as well as cancer prognosis, and thus are potential mechanisms explaining why certain co-morbid conditions are associated with worse cancer prognosis.[4–6] Low SMI, also termed sarcopenia, is highly prevalent and has been shown as a strong prognostic factor in CRC patients and in many other types of cancer.[7] Additionally, a recent meta-analysis of 7843 patients with solid tumours found a 44% higher risk of death for patients with low SMI vs. those with normal amount of muscle mass.[8] Furthermore, low SMI predicts clinical endpoints, such as a higher risk of surgical complications after resection, longer hospitalization, and/or higher risk of chemotherapy toxicity in various cancers.[7,9,10]

Skeletal muscle radiodensity reflects fat infiltration into muscle.[11] To date, the largest study investigating SMD included 1473 patients with lung or gastrointestinal tract cancer, showing this abnormality as an independent predictor of shorter survival.[12] Additional studies have reported that low SMD was associated with complications and short-term mortality after surgery in CRC and in other types of cancer.[13,14]

As CT-measured muscle abnormalities and co-morbidities both strongly predict cancer prognosis, there is good reason to believe they are interrelated. CRC patients with any pre-existing co-morbidity might be at higher risk for muscle abnormalities, the dual burden of which might negatively impact prognosis. Nevertheless, little is known on whether patients with co-morbidities are at higher risk of having muscle abnormalities compared with those without co-morbidities and on how different co-morbidities contribute to the presence of muscle abnormalities in CRC. Therefore, our goal was to investigate the prevalence of pre-existing co-morbidities by muscle abnormalities and evaluate which pre-existing co-morbidities predicted muscle abnormalities among newly diagnosed CRC patients.

Methods

Study cohort

The present cross-sectional study identified patients diagnosed with Stages I–III invasive CRC at Kaiser Permanente Northern California (KPNC, n = 3262) from 2006–11 as described elsewhere.[15] For this analysis, we restricted the cohort to patients who were members of KPNC for at least 1 year prior to CRC diagnosis (n = 3051). This study was approved by the KPNC and University of Alberta Institutional Review Boards.

Co-morbidities

Pre-existing co-morbidities were recorded using an adapted version of Charlson co-morbidities derived from International Classification of Disease-9 diagnostic codes.[16] Relevant International Classification of Disease-9 codes for all co-morbidities were obtained from all inpatient and outpatient encounters in the year prior to CRC diagnosis. To be confirmed as having a co-morbid condition, we required two diagnostic codes of the same condition for each patient at least 30 days apart in the 1-year period prior to CRC diagnosis We examined each component of the Charlson co-morbidities separately as a binary variable (presence or absence), including myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), cerebrovascular disease, dementia, chronic obstructive pulmonary disease (COPD), rheumatic disease (RD), peptic ulcer disease, mild liver disease, diabetes without chronic complication, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, any malignancy, metastatic solid tumour, and acquired immune deficiency syndrome and human immunodeficiency virus infection. Cancer-related categories (i.e. any malignancy and metastatic solid tumour) were excluded, and co-morbidities with less than three cases (i.e. dementia, n = 1; hemiplegia/paraplegia, n = 3; moderate or severe liver disease, n = 2; and acquired immune deficiency syndrome and human immunodeficiency virus infection, n = 3) were omitted for statistical reasons, leaving 11 co-morbidities included in the final analysis.

Body composition measurement

Abdominal CT images within 4 months of CRC diagnosis and before any chemotherapy or radiation treatment were obtained from the patients' electronic medical record. A single image at the third lumbar vertebra (L3) was selected for muscle mass and adipose tissue quantification, as skeletal muscle and adipose tissue cross-sectional areas at this landmark strongly correlate with tissue volumes at the whole body level.[17,18] According to the standard HU range for muscle (-29 to 150), visceral adipose tissue (-150 to -50), intermuscular adipose tissue (-190 to -30) and subcutaneous adipose tissue (-190 to -30),[18–20] cross-sectional areas of muscle and adipose tissue at L3 were analyzed by a single, trained researcher (J.X.) using SliceOmatic Software version 5.0 (TomoVision, Montreal, Quebec, Canada). Total adiposity was calculated as the sum of visceral adipose tissue, intermuscular adipose tissue, and subcutaneous adipose tissue.

Intra-observer coefficient variations of muscle mass, radiodensity, and total adiposity measurements at least 1 month apart were 0.7%, 1.2%, and 0.3%, respectively. Muscle mass was calculated as SMI from total muscle cross-sectional area divided by height square (cm^2/m^2).[18,21] SMD was generated by the software as the mean radiation attenuation value of the whole muscle group at L3. The optimal stratification method was used to determine the cohort specific threshold values of SMI and SMD as described elsewhere for this cohort.[15] This method identifies cut points that best separate patients' risk with respect to time to death based on the maximum absolute value of the log-rank statistic test[22]. For normal/overweight patients [body mass index (BMI) < 30 kg/m^2], the threshold values of SMI were 52.3 cm^2/m^2 for men and 38.6 cm^2/m^2 for women, while for obese patients (BMI ≥ 30 kg/m^2), these were 54.3 cm^2/m^2 for men and <46.6 cm^2/m^2 for women[15]. Similarly, threshold values of SMD were 35.5 HU for men and 32.5 for women[23]. Patients presenting below these threshold values were classified as having either low SMI or low SMD. Four muscle phenotypes were further defined according to the presence or absence of low SMI and low SMD: normal SMI, normal SMD; normal SMI, low SMD; low SMI, normal SMD; low SMI, low SMD.

Covariate assessment

Data sources of patients' electronic medical record and the Cancer Registry were reviewed for information on disease stage, tumour characteristics and demographics, including age, height, weight, weight change history prior to CRC diagnosis, sex, race/ethnicity, and smoking history. Height and weight measured at the clinical visit closest to the diagnostic CT scan were used to calculate BMI at CRC diagnosis. Weight change history was computed by subtracting the diagnostic weight from the weight taken 18 months prior to diagnosis. Cancer stage was defined according to the American Joint Committee on Cancer.[24]

Statistical analysis

Differences in patient characteristics by presence or absence of muscle abnormalities were analyzed using independent *t*-tests or Pearson's χ^2 tests, where appropriate. Prevalence of co-morbidities was compared by muscle abnormalities (categorical variables) using Pearson's χ^2 tests. Logistic regression models were used to evaluate associations between co-morbid condition(s) and dichotomous muscle abnormality outcomes. Multiple comparison tests were performed using Bonferroni correction method for each logistic regression model to account for the likelihood that findings could be due to chance. Multinominal logistic regression models were

conducted to further explore the associations between co-morbidities and four muscle phenotypes (i.e. phenotype analysis). In this analysis, the muscle phenotype was computed as the outcome variable, with normal SMI/normal SMD group as the reference. Covariates included age, sex, BMI at CRC diagnosis, weight change history, cancer stage, cancer site, ethnicity/race, and smoking history. In a sensitivity analysis, we compared models with and without adjustment for weight change history, as well as with adjustment of total adiposity instead of BMI. All statistical analyses were performed using STATA (version 14.2; StataCorp LP). Statistical significance was established with two-sided tests with α of 0.05.

Results

Low skeletal muscle index

Demographic and clinical parameters are shown in Table 1. Low SMI was highly prevalent at 43.1%. Among males, the prevalence of low SMI was 46.0%, and among females, the prevalence was 40.2% ($P = 0.001$). SMI was higher in males compared with females (Figure 1A). Total adiposity was lower for patients with low SMI compared with those with normal SMI in both sex. Patients with low SMI were approximately 6 years older, and their mean muscle attenuation was five HU lower compared with their counterparts (36.1 HU vs. 40.9 HU, $P < 0.001$). Differences by race/ethnicity and BMI distribution were also observed. Caucasians and Asian/Pacific Islanders were more likely to have low SMI than were African Americans or Hispanics. Patients with low SMI had lower BMI, which was consistent with the higher percentage of underweight/normal weight patients in the low SMI group. The correlation coefficient between SMI and BMI was 0.50. Patients with Stage II or colon cancer were more likely to present with low SMI than those with other stages or those with rectal cancer. Patients who were former or current smokers were more likely to have low SMI compared with those who never smoked.

Low skeletal muscle radiodensity

Approximately one-third (30.2%) of the patients had low SMD with a prevalence of 28.8% and 31.6% in males and females, respectively. Women had a slightly lower SMD than that of their male counterparts (Figure 1B). Mean SMI was lower while total adiposity was higher in the low SMD group than in the normal SMD group for both males and females. Compared with patients with normal SMD, those with low SMD were on average 9 years older, had a higher BMI and consequently, a greater prevalence of obesity. Mean muscle attenuation was moderately correlated with BMI ($r = 0.35$). More Caucasians and Hispanics were in the low SMD group.

Table 1 Characteristics of colorectal cancer patients with respect to the presence and absence of low SMI and low SMD

|	Overall ($n = 3051$)	Normal SMI ($n = 1736$)	Low SMI ($n = 1315$)	P-value	Normal SMD ($n = 2130$)	Low SMD ($n = 921$)	P-value
	Mean (standard deviation) or %						
Demographics							
Age, years	63.2 (11.2)	60.4 (11.1)	66.8 (10.1)	<0.001	60.5 (11.1)	69.4 (8.5)	<0.001
Males	50.1	47.5	53.5	0.001	51.1	47.8	0.09
Females	49.9	52.5	46.5		48.9	52.2	
Race/ethnicity, %							
Caucasian	65.9	62.2	70.7	<0.001	60.9	77.3	<0.001
African American	7.3	9.2	4.7		8.6	4.1	
Hispanic	10.7	12.9	7.8		10.2	11.9	
Asian/PI	15.6	15.0	16.4		19.8	6.1	
Others	0.6	0.8	0.3		0.6	0.5	
Body weight and composition							
BMI, kg/m^2	28.1 (6.0)	29.9 (6.2)	25.0 (4.3)	<0.001	27.1 (5.4)	30.6 (6.8)	<0.001
BMI, %							
Underweight,<18.5 kg/m^2	1.7	0.4	3.9	<0.001	1.9	1.2	<0.001
Normal, 18.5 to 25 kg/m^2	31.3	19.8	51.2		36.4	19.7	
Overweight, 25 to 30 kg/m^2	35.6	37.3	32.7		37.5	31.2	
Obese Class I, 30 to 35 kg/m^2	19.7	25.5	9.8		17.4	25.2	
Obese Class II/III, ≥35 kg/m^2	11.6	17.0	2.4		6.8	22.8	
Weight change prior to diagnosis							
Stable, <5% change	37.0	37.9	35.5	0.07	35.9	39.7	<0.001
≥5% loss	17.7	16.3	20.0		17.0	19.2	
≥5% gain	4.5	4.6	4.2		3.9	5.8	
SMI, cm^2/m^2, men	54.1 (9.3)	60.7 (6.5)	46.3 (4.9)	<0.001	55.4 (8.9)	50.9 (9.4)	<0.001
SMI, cm^2/m^2, women	43.0 (7.4)	46.8 (6.4)	37.3 (4.5)	<0.001	43.4 (7.2)	42.1 (7.6)	<0.001
SMM, cm^2, men	168.5 (30.7)	187.4 (25.2)	146.3 (19.7)	<0.001	171.1 (30.2)	162.0 (30.9)	<0.001
SMM, cm^2, women	112.4 (20.3)	121.3 (18.6)	99.1 (14.7)	<0.001	113.1 (19.9)	110.9 (20.9)	<0.001
Mean MA, HU, men	40.4 (9.6)	42.7 (8.8)	37.6 (9.7)	<0.001	45.0 (6.4)	28.9 (5.4)	<0.001
Mean MA, HU, women	37.2 (10.0)	39.1 (9.3)	34.4 (10.3)	<0.001	42.4 (6.8)	25.9 (5.3)	<0.001
TAT, cm^2, men	403.1 (195.4)	438.2 (198.2)	361.9 (183.7)	<0.001	355.3 (167.4)	521.4 (209.1)	<0.001
TAT, cm^2, women	361.6 (193.8)	369.6 (191.9)	349.7 (196.1)	0.05	313.6 (171.5)	465.7 (198.5)	<0.001
Tumour factors							
Stage							
Stage I	29.8	31.7	27.3	0.001	30.4	28.5	0.23
Stage II	31.7	29.2	35.1		30.8	33.9	
Stage III	38.5	39.2	37.6		38.8	37.7	
Type							
Colon	71.9	69.4	75.1	0.001	68.4	80.0	<0.001
Rectal	28.1	30.6	24.9		31.6	20.0	
Health characteristics							
Smoking history, %							
Never smoker	46.1	48.5	43.0	0.008	50.9	35.2	<0.001
Former smoker	41.9	39.8	44.7		37.7	51.8	
Current smoker	11.9	11.7	12.3		11.5	13.0	
Charlson index							
0	58.3	59.2	57.1	0.49	65.6	41.5	<0.001
1 or 2	31.1	30.5	31.9		27.9	38.6	
≥3	10.6	10.3	11.0		6.5	20.0	

*For BMI and weight change variables, low SMI was defined by optimal stratification with sex-specific cutpoints: men 52.3 cm^2/m^2, women 38.6 cm^2/m^2. Sample sizes were $n = 1931$ and $n = 1120$ for normal SMI and low SMI groups. BMI, body mass index; SMI, skeletal muscle index; SMD, skeletal muscle radiodensity; SMM, skeletal muscle mass; MA, muscle attenuation; TAT, total adipose tissue; PI, Pacific Islander. Percentage data were presented by columns.

Patients with stable weight or who had any weight fluctuation (gaining or losing ≥5% body weight) prior to CRC diagnosis were more likely to have low SMD. There were no differences in cancer stage between SMD groups. The findings for other clinical parameters by SMD, including cancer type and smoking history, were similar to those reported earlier by SMI groups (Table 1).

Co-morbidities and muscle abnormalities

No difference in Charlson index score was observed between SMI groups (Table 1). When analyzing the prevalence of co-morbidities by SMI group, those with low SMI were more likely to have PVD (4.9% versus 2.1%, p< 0.001) and cerebro-vascular disease (3.0% versus 1.9%, p=0.041) compared to

Figure 1 Boxplot showing the distribution of skeletal muscle index (SMI) (A) and skeletal muscle radiodensity (SMD) (B) stratified by sex. Cutpoints for low SMI (body mass index and sex specific) and low SMD (sex specific) are defined using optimal stratification method.
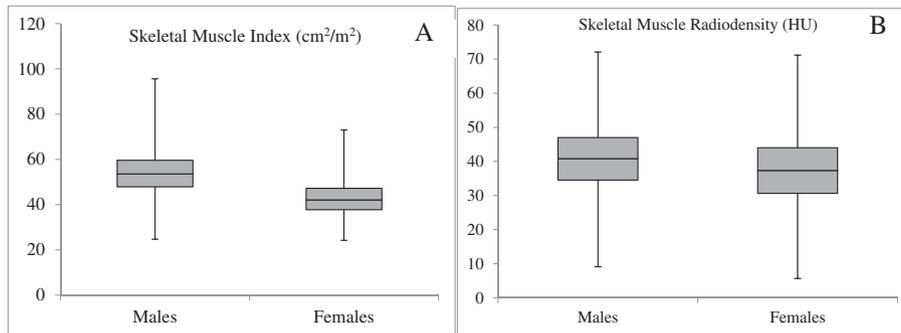
those with normal SMI, but not other co-morbidities. In contrast, patients with low SMD were more likely to have a Charlson co-morbidity index score equal or greater than one compared with those with normal SMD (Table 1), and those with low SMD had a higher prevalence of 9 of 11 co-morbidities (Figure 2).

Mean values of SMI and SMD were computed and compared for those with and without co-morbidities. Patients with PVD had lower SMI than those without PVD. In contrast, those who had diabetes had higher SMI compared with those without diabetes ($P = 0.048$ for complicated diabetes and $P < 0.001$ for non-complicated diabetes). We noted similar results stratified by sex. PVD was associated with lower SMI only in males, while diabetes with or without complications were related to higher SMI only in females (data not shown). SMD was much more consistently associated with co-morbidities with or without stratification by sex. Mean SMD was lower in patients with MI, CHF, PVD, cerebrovascular disease, COPD, RD, diabetes with/without complications, or renal disease than in patients without these conditions (data not shown).

Univariate and multivariate regression models

In logistic regression analysis, patients who had diabetes with complication were less likely to have low SMI in multivariate analysis (OR = 0.64, 95% CI 0.47–0.88). No other co-morbidities or Charlson index were associated with low SMI after controlling for confounding factors (Table 2).

In similar regression models, cardiovascular conditions, diabetes, and renal disease were associated with low SMD (Table 3). After adjusting for confounding factors, patients with MI or PVD were more likely to have low SMD. Patients who had pre-existing CHF were at particularly high risk of low SMD (OR = 3.27, 95% CI 1.97–5.41). Similarly, diabetes with or without complications both showed an association with low SMD; patients with pre-existing diabetes were more likely to have low SMD at CRC diagnosis. Likewise, patients with renal disease were more likely to have low SMD. A higher Charlson index score was associated with greater risks of having low SMD compared with patients without any co-morbid condition.

Figure 2 Prevalence of pre-existing co-morbidities with respect to skeletal muscle radiodensity (SMD). Low SMD is defined using optimal stratification. COPD, chronic obstructive pulmonary disease. *$P < 0.001$, **$P < 0.05$.
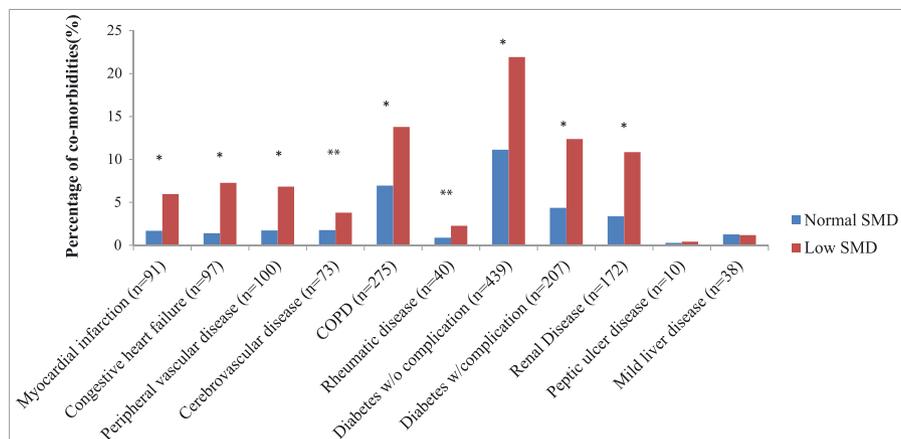
Table 2 Univariate and multivariate logistic regression analyses[a] of pre-existing co-morbidities predicting low SMI[b] at diagnosis among non-metastatic colorectal cancer patients at Kaiser Permanente Northern California (*n* = 3051)

Pre-existing co-morbidities (*n* = 11)	Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Myocardial infarction (*n* = 91)	1.36 (0.90,2.07)	0.147	1.03 (0.66,1.61)	0.899
Congestive heart failure (*n* = 97)	1.30 (0.87,1.95)	0.198	1.02 (0.66,1.59)	0.929
Peripheral vascular disease (*n* = 100)	2.42 (1.60,3.66)	<0.001	1.48 (0.94,2.34)	0.089
Cerebrovascular disease (*n* = 73)	1.62 (1.02,2.58)	0.043	1.02 (0.62,1.69)	0.939
Chronic obstructive pulmonary disease (*n* = 275)	1.04 (0.81,1.34)	0.752	0.82 (0.62,1.08)	0.163
Rheumatic disease (*n* = 40)	1.08 (0.58,2.02)	0.807	0.86 (0.44,1.72)	0.677
Peptic ulcer disease (*n* = 10)	1.98 (0.56,7.05)	0.289	2.27 (0.52,9.87)	0.275
Mild liver disease (*n* = 38)	0.96 (0.50,1.83)	0.901	0.75 (0.36,1.55)	0.435
Diabetes w/o complications (*n* = 439)	0.87 (0.70,1.06)	0.169	0.85 (0.68,1.07)	0.177
Diabetes w/complications (*n* = 207)	0.77 (0.57,1.03)	0.076	0.64 (0.47,0.88)	0.007
Renal disease (*n* = 172)	1.16 (0.85,1.58)	0.353	0.90 (0.64,1.27)	0.549
Charlson index[c]				
1 or 2	1.08 (0.92,1.27)	0.330	0.91 (0.76,1.09)	0.303
3	1.12 (0.88,1.42)	0.371	0.81 (0.61,1.06)	0.124

[a]Multivariable logistic regression model adjusted for age, sex, body mass index at diagnosis, weight change prior to diagnosis, stage, cancer site, race/ethnicity, and smoking history.
[b]Low skeletal muscle index (SMI) is defined using optimal stratification method. For BMI < 30 kg/m^2, the cutpoints were <52.3 and <38.6 cm^2/m^2 for men and women, respectively; for BMI ≥ 30 kg/m^2, the cutpoints were <54.3 and <46.6 cm^2/m^2 for men and women, respectively.
[c]With Charlson index score of 0 as the reference group.

In a sensitivity analysis for these regression models, results remained similar with or without adjustment for weight change history prior to diagnosis. We also adjusted by level of total adiposity (vs. BMI) with similar findings for SMD models. However, in addition to the six co-morbidities that predicted low SMD, in this sensitivity analysis, patients with COPD were more likely to have low SMD (OR = 1.37, 95% CI 1.03–1.82). As for low SMI, after adjustment for total adiposity, diabetes with complications lost association with low SMI.

In multiple comparison tests, a Bonferroni critical *P*-value of 0.0045 was calculated using 0.05 divided by 11 (the number of investigated co-morbidities). According to the Bonferroni critical *P*-value, no co-morbidities were associated with low SMI, while CHF, PVD, diabetes without complications, and renal disease remained independent predictors of low SMD.

We further examined co-morbidities predicting concurrent muscle abnormalities using patients with both normal SMI and normal SMD as the reference group. In multinomial logistic regression models, patients who had CHF or renal diseases were more likely to present with low SMD, regardless of concurrent low SMI, while patients with PVD were more likely to have both low SMI and low SMD. Patients who had diabetes were more likely to present with normal SMI and low SMD (Table S1).

Table 3 Univariate and multivariate logistic regression analyses[a] of pre-existing co-morbidities predicting low SMD[b] at diagnosis among non-metastatic colorectal cancer patients at Kaiser Permanente Northern California (*n* = 3051)

Pre-existing co-morbidities (*n* = 11)	Odds ratio (95% CI)	*P*-value	Adjusted odds ratio (95% CI)	*P*-value
Myocardial infarction (*n* = 91)	3.69 (2.41,5.67)	<0.001	1.77 (1.08,2.88)	0.023
Congestive heart failure (*n* = 97)	5.49 (3.54,8.51)	<0.001	3.27 (1.97,5.41)	<0.001
Peripheral vascular disease (*n* = 100)	4.15 (2.75,6.28)	<0.001	2.15 (1.33,3.47)	0.002
Cerebrovascular disease (*n* = 73)	2.17 (1.36,3.47)	0.001	1.32 (0.76,2.30)	0.328
Chronic obstructive pulmonary disease (*n* = 275)	2.14 (1.67,2.75)	<0.001	1.23 (0.91,1.66)	0.187
Rheumatic disease (*n* = 40)	2.59 (1.39,4.85)	0.003	1.74 (0.85,3.57)	0.131
Peptic ulcer disease (*n* = 10)	1.54 (0.43,5.48)	0.502	0.91 (0.22,3.74)	0.898
Mild liver disease (*n* = 38)	0.94 (0.47,1.91)	0.867	1.01 (0.44,2.33)	0.980
Diabetes w/o complications (*n* = 439)	2.24 (1.83,2.76)	<0.001	1.46 (1.13,1.89)	0.003
Diabetes w/complications (*n* = 207)	3.09 (2.33,4.12)	<0.001	1.61 (1.13,2.29)	0.008
Renal disease (*n* = 172)	3.48 (2.54,4.76)	<0.001	2.21 (1.50,3.25)	<0.001
Charlson index[c]				
1 or 2	2.19 (1.84,2.60)	<0.001	1.37 (1.11,1.68)	0.003
>=3	4.84 (3.78,6.20)	<0.001	2.34 (1.74,3.17)	<0.001

[a]Multivariable logistic regression model adjusted for age, sex, body mass index at diagnosis, weight change prior to diagnosis, stage, cancer site, ethnicity/race, and smoking history.
[b]Low skeletal muscle radiodensity (SMD) is defined using optimal stratification method. The cutpoints were <35.5 HU for men and <32.5 for women.
[c]With Charlson index score of 0 as the reference group.

Discussion

This is the first study to investigate the prevalence of co-morbidities and evaluate their associations with two CT-assessed muscle abnormalities (low SMI and low SMD) in a large sample of newly diagnosed CRC patients. Two important clinical findings emerged. First, 9 out of 11 co-morbidities were more prevalent in patients with low SMD, whereas only one co-morbidity had higher prevalence in patients with low SMI, compared with those with normal SMD or SMI. Second, most co-morbidities were associated with low SMD, with only one being associated with low SMI, independent of age, sex, BMI at diagnosis, ethnicity/race, cancer stage, cancer site, pre-diagnostic weight change, and smoking history. Previous studies in patients with CRC evaluated co-morbidities with only one type of muscle abnormality without adjusting for confounding factors[4,25]; our study, for the first time, demonstrated different associations of co-morbidities with each muscle abnormality using robust model adjustment.

We found males presented higher SMI and higher SMD compared with females. This finding is consistent with previously reported data from a large cohort (n = 1473) of patients with lung or gastrointestinal cancer[12]. In subgroup analysis, the effects of MI, PVD, and renal diseases on low SMD were only observed in men, while the effect of diabetes with complications was only evident in women (data not shown). RD and COPD additionally predicted higher risk of low SMD in men (data not shown). Despite these sex differences, none of the co-morbidities predicted low SMI in men, and only diabetes was associated with low SMI in women. The latter might be attributed to better health and medical care for these patients or well-controlled blood glucose level (e.g. use of insulin or metformin) potentially decreasing the risk of muscle loss[26]. Additionally, 76.6% female diabetic patients were overweight or obese, and the prevalence of low SMI is known to decrease with increasing BMI for most patients[9]. The higher observed prevalence of low SMI and low SMD in patients with colon and Stage II cancer is likely confounded by age. The prevalence of patients with ≥65 years was higher among those with colon cancer (54.1% vs. 36.7% rectal cancer, $P < 0.001$) and among those with Stage II cancer (53.9% vs. 47.1% other stages, $P < 0.001$).

Few studies have examined the relationship between presence of co-morbidities and muscle abnormalities in the context of cancer. Using a cohort of 234 patients with CRC, Lieffers et al. found a higher prevalence of cardiac arrhythmias, COPD, diabetes, and other disorders among individuals with lower SMI.[4] Although age, BMI, and SMI of their cohort were comparable to ours, we found PVD as the only condition more prevalent in patients with lower SMI. In Lieffers et al., the prevalence of low SMI was 38.9% (vs. 43.1% in the present study) while the majority of patients with low SMI had Stage IV CRC (37.4%). It is likely that the dual burden of tumour progression and co-morbidities may increase the risk for low SMI. In a cohort of colon cancer patients, Sabel et al. reported lower mean SMD values in patients with cardiac disease, pulmonary disease, diabetes, or prior non-CRC, compared with those of patients without the corresponding disease[25]. No other studies have investigated the association between co-morbidities and low SMD in CRC.

Evidence outside the oncology setting shows that low SMI is present in multiple disease states, including diabetes, COPD, arthritis, PVD, CHF, advanced renal disease, and cirrhosis.[27–33] Reduced SMD has been reported in elderly individuals and individuals with diverse types of diseases, such as diabetes, obesity, and cirrhosis.[34–36]

The pathogenesis of low SMI and low SMD in chronic diseases is not completely understood. Low SMI is likely a result of a complex network involving chronic inflammation, elevated protein catabolism, and disturbed hormonal balance.[37] These processes result in chronic imbalance in muscle protein turnover favouring protein breakdown and a shift in fibre distribution from Type II to Type I fibre, ultimately leading to morphological muscle depletion.[38,39] Among these mechanisms, inflammation-mediated muscle proteolysis through ubiquitin-proteasome pathway has been commonly recognized in cancer, CHF, COPD, diabetes, and chronic renal diseases.[40] As such, Anker et al. proposed the use of the term 'muscle wasting' to represent the common physiological process related to low muscularity across a spectrum of disorders, including cancer, CHF, CKD, COPD, neuromuscular disease, and chronic infection.[41] Comprehensive and detailed reviews regarding the mechanism of low SMI in cancer can be found elsewhere.[37,42]

Our previous findings from this cohort[43] and other studies have shown that both low SMI and low SMD to be independently associated with systematic inflammatory response in CRC.[44,45] Inflammatory networks have also been suggested to play a pathophysiological role in the development of co-morbidities, including cardiovascular diseases, renal disease, and diabetes.[46–48] Although inflammation might be a common pathway through which co-morbidities impact both SMI and SMD, we found a clear association of low SMD with six co-morbidities (i.e. MI, CHF, PVD, diabetes with or without complications, and renal disease), but the same was not true in regard to low SMI. Of note, most of the co-morbidities we identified predicting low SMD were cardiovascular and metabolic disorders, suggesting metabolic inefficiency at either local or systemic levels, such as myocardial energy deficiency and insulin resistance, could contribute to the decline in SMD. Physiological mechanisms of fat infiltration has only been investigated in diabetes and obesity, including alterations of mitochondrial structure and function, impaired fatty acid metabolism and a defect in the ability of adipose tissue to store excess fatty acids, and consequently an overflow of

adipose tissue into muscle.[39] Disuse of muscle might also impair the capacity of muscle cells to oxidize lipids, resulting in an accumulation of lipids within muscles.[49] Additionally, adipose tissue has been characterized as an active endocrine organ and up-regulates the activity of macrophage and T-cell expression, thus the secretion of pro-inflammatory cytokines, potentially creating a locally chronic low inflammatory status within muscle.[50,51] Collectively, these alterations related to fat infiltrated into muscle cells may explain the different findings of low SMI or low SMD in association with co-morbidities in this study. We also speculate that different findings between muscle abnormalities are possibly due to a higher rate of SMD decrease than that of SMI loss under certain chronic disorders, which makes SMD more likely to decline at the time point of CRC diagnosis. Although we cannot determine the exact time point of low SMD occurrence and the cause–effect associations of metabolic dysregulation, local/systematic inflammation, and low SMD, it is reasonable to assume that their impacts are bidirectional.

Our findings also suggest that fat infiltration into muscle might be a shared mechanism among these co-morbidities leading to low SMD, as discussed previously. The phenotype analysis in this study illustrates that patients with pre-existing co-morbidities are likely to have low SMD with or without compromised SMI. Rarely considered and even more occult than low SMI, low SMD may be a pathway through which co-morbidities influence cancer survival. Future examinations are warranted to evaluate whether patients with the concurrence of low SMD and pre-existing co-morbidities identified in this study were at higher risk for poorer prognosis. Of note, our findings of the associations between co-morbidities and low SMD were independent of BMI or total adiposity at diagnosis. Although obesity was not included as a co-morbidity in the Charlson's co-morbidity index, obesity itself (BMI $\geq$ 30 kg/m^2), as well as total adiposity (in quintiles, with the lowest quintile as the reference) were independent predictors of low SMD. Patients who were obese had four-fold higher risk of having low SMD (data not shown). A decrease in SMD in association with obesity (defined using either BMI or total adiposity) has been illustrated in patients with or without cancer.[35,52] Importantly, low SMD is potentially modifiable through resistance training or n-3 fatty acid supplementation.[53] Therefore, patients with co-morbidities may warrant evaluation for muscle abnormalities, as this may be a particularly vulnerable group of early-stage patients with a high mortality risk. Stratification of patients with co-morbidities and muscle abnormalities into different risk groups and individualized treatment strategies at early stages of cancer could represent a significant progress into the personalized medicine era.

Several limitations to our study should be acknowledged including our convenient sample and cross-sectional approach where causality cannot be inferred. Furthermore, we do not know whether co-morbidities lead to low SMI and low SMD or vice versa because the timing of the onset of muscle abnormalities could not be determined. Finally, while we were able to control for key confounders including smoking status, information on physical activity and dietary intake was not available in this study. Nonetheless, our study had several strengths. It is the first large CRC cohort examining the association of co-morbidities and muscle abnormalities. Additionally, we applied a state-of-the-art, highly precise, and clinically relevant tool, CT imaging, to assess muscle abnormalities.[54] The findings of muscle abnormalities, particularly low SMD, observed with certain co-morbidities among non-metastatic CRC patients have important clinical implications, as low SMD may be a parameter for screening at risk patients. This study also opens a new avenue of investigating the underlying pathological and physiological mechanism of low SMD, which may be shared across multiple chronic conditions.

Conclusion

In summary, our findings indicate an association of multiple co-morbidities, that is MI, CHF, PVD, diabetes, and renal disease, with low SMD rather than with low SMI in patients with non-metastatic CRC, suggesting fat infiltration into muscle is a shared mechanism across these diseases. Our results also highlight the clinical relevance of incorporating CT-assessed muscle abnormalities, particularly SMD, into future screening in order to guide patient risk stratification and individualized interventions.

Future mechanistic studies should seek to clarify whether the pathways that augment the breakdown of muscle mass and that promote fat infiltration into muscle overlap or are distinct from each other, and to what extent these pathways vary among different diseases. Clinical trials are also needed to demonstrate the feasibility and efficacy of modifying muscle abnormalities in cancer patients.

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comply with the ethical guidelines for authorship and publishing of the Journal of Cachexia, Sarcopenia, and Muscle.[55]

Online supplementary material

Additional Supporting Information may be found online in the supporting information tab for this article.

Supplementary Table 1. Adjusted multinomial logistic regression analyses[1] of pre-existing comorbidities predicting muscle phenotypes at diagnosis among non-metastatic colorectal cancer patients at Kaiser Permanente Northern California (n=3,051)

Conflicts of interest

The authors declare no potential conflicts of interest.

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