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ORIGINAL PAPER

Low muscle mass, obesity, and cause-specific mortality in cancer patients: a nationwide cohort study

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Abstract

Purpose Low muscle mass (LMM) is a risk factor for adverse health outcomes, but its prognostic relevance in cancer remains insufficiently studied. We investigated the independent and combined effects of LMM and obesity on mortality in cancer patients.

Methods This cohort study included 635,867 cancer patients. LMM was defined as the lowest quartile on the appendicular skeletal muscle mass index (ASMI). Obesity was defined as body mass index ≥25 kg/m^2 and abdominal obesity as waist circumference ≥90 cm (males) and ≥85 cm (females). Patients were classified into four groups based on muscle mass and obesity status. Cox proportional hazards models calculated adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for mortality.

Results Compared with individuals in the highest ASMI quartile, LMM had significantly higher risks of all-cause (aHR 1.25, 95% CI 1.23–1.27), cancer-specific (aHR 1.21, 95% CI 1.19–1.23), cardiovascular (aHR 1.49, 95% CI 1.36–1.64), and respiratory mortality (aHR 2.26, 95% CI 1.99–2.56). While obesity was associated with lower mortality risks than non-obese status, the LMM with obesity group exhibited the highest risk for all-cause (aHR 1.22; 95% CI, 1.16–1.28) and cancer-specific mortality (aHR 1.22; 95% CI, 1.16–1.29).

Conclusions LMM was independently associated with increased mortality in cancer patients, regardless of obesity status. The adverse effect was amplified in those with both LMM and obesity, but obesity alone showed a modest inverse association. These findings highlight the clinical relevance of evaluating muscle mass and body composition in cancer.

Keywords Sarcopenia · Sarcopenic obesity · Low muscle mass · Cancer patients · Mortality

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Introduction

With advances in early detection and treatment, the number of cancer survivors has steadily increased, making long-term survivorship outcomes a public health concern [1]. Although cancer-specific mortality remains a leading cause of death, non-cancer causes—particularly cardiovascular and respiratory diseases—have emerged as major contributors to late mortality [2, 3]. Identifying host-related factors that influence these outcomes is essential for improving post-treatment care.

Body composition is a critical determinant of cancer prognosis [4]. Obesity, typically assessed using the body mass index (BMI), has been associated with adverse outcomes [5], including increased recurrence, reduced overall survival, and higher cancer-specific mortality. More recently, sarcopenia—the progressive loss of muscle mass and function—has gained recognition as an independent risk factor for poor prognosis [6]. Low muscle mass (LMM) is prevalent at diagnosis and often persists after treatment [7]. Sarcopenia is associated with increased all-cause and cancer-specific mortality, decreased disease-free survival duration, higher treatment-related toxicity, and elevated recurrence risk [6].

The coexistence of sarcopenia and obesity, termed *sarcopenic obesity*, represents a distinct clinical phenotype with potentially synergistic adverse impacts [8]. However, standardized diagnostic criteria remain under development, and the clinical implications for cancer survivors are not fully understood. Previous studies on survival outcomes have yielded inconsistent findings, with debates over whether obesity exacerbates the adverse impacts of LMM or provides a protective 'obesity paradox' effect [9]. However, much of the existing evidence has been derived from Western populations [10], and the association between body composition and cancer outcomes remains less well characterized in Asian populations [11], where body composition and obesity criteria differ [12, 13].

Although sarcopenia is increasingly studied in relation to cancer prognosis, its role in long-term non-cancer mortality remains unclear [14–16]. In particular, evidence is limited regarding cardiovascular- and respiratory-related mortality, both of which account for substantial proportions of late deaths.

Therefore, the present study aimed to investigate the associations between LMM, with and without obesity, and the risks of all-cause, cancer-specific, cardiovascular, and respiratory mortality in a large, population-based cohort of patients with cancer.

Methods

Data source and study setting

This study used data from the Cancer Public Library Database (CPLD), part of the Korean Clinical Data Utilization for Research Excellence (K-CURE) initiative [17]. The CPLD provides annually updated, linked records encompassing cancer diagnoses, mortality, demographics, and healthcare utilization. It integrates the Korea National Cancer Incidence Database from the Korean Central Cancer Registry (KCCR) [18], mortality records from Statistics Korea, and health screening data [19] and insurance claims data from the National Health Insurance Service (NHIS) [20]. Further details on the database structure and the NHIS framework are provided in the eMethods.

Study population

This study included patients aged ≥40 years who were diagnosed with cancer and registered in the KCCR between January 1, 2013, and December 31, 2018. Among 1,223,539 patients newly diagnosed during that period, 635,867 also underwent a general health screening within the two years before their cancer diagnosis date. The age cutoff of 40 years was selected considering the age distribution of cancer incidence and mortality and the availability and structure of national health screening data during the study period.

Cancer diagnoses were identified using the ICD-10 codes. A total of 23 primary cancer sites were included in the analysis, with detailed ICD-10 code classifications provided in eMethods.

Assessment of LMM and obesity

LMM was assessed using the appendicular skeletal muscle mass index (ASMI), calculated as appendicular skeletal mass (ASM, in kilograms) divided by height in meters squared. ASM was estimated using a validated prediction formula developed for the Korean population [21]: ASM = –7.816 + (0.002 × age) + (0.090 × height in cm) + (0.207 × weight in kg) – (0.037 × waist circumference in cm). This model demonstrated good predictive performance in the validation dataset ($R^2 = 0.71$; standard error = 1.2 kg). Individuals were categorized into sex-specific ASMI quartiles; those in the lowest quartile (Q1) were defined as having LMM, while those in the remaining quartiles (Q2–Q4) were classified as normal muscle mass (NMM). LMM was defined based on anthropometrically estimated ASMI and is hereafter referred to as estimated LMM [11]. Cancer patients were classified according to ASMI quantiles relative to this

age-standardized reference population, with the lowest quartile (Q1) classified as LMM and Q2–Q4 as NMM, and their associations with mortality were reassessed using the same multivariable-adjusted models.

BMI was computed as weight (kg) divided by height squared (m^2). Obesity was defined according to the Asia–Pacific World Health Organization guidelines, which recommend a BMI cutoff of ≥25 kg/m^2 [22].

Mortality and follow-up

The primary outcomes of this study were all-cause, cancer-specific (C00–C97), cardiovascular (I00–I99), and respiratory (J00–J99) mortality. Information on cause of death was obtained from Statistics Korea, which compiles official mortality data that have been verified and certified by medical professionals and institutions. Participants were followed from the index date (date of initial cancer diagnosis) until death, emigration, or the end of the observation period (December 31, 2020), whichever occurred first.

Covariates

To address potential confounding in the relationships among LMM, obesity, and mortality outcomes, covariates were selected based on associations reported in the literature. Variables such as age, comorbid conditions, physical activity, and nutritional status have been shown to independently influence both ASMI and survival [23].

Sociodemographic factors, lifestyle habits, and clinical cancer characteristics—including SEER stage and initial treatment—were obtained from the NHIS records and KCCR database. Comorbidities, including hypertension, diabetes, dyslipidemia, and chronic kidney disease, were defined using a combination of ICD-10 codes, prescription records, and laboratory findings; further details are provided in the eMethods.

Statistical analysis

Baseline characteristics were summarized using means and standard deviations for continuous variables and counts with percentages for categorical variables. The study cohort was initially categorized into quartiles according to the ASMI distribution (Q1 representing the lowest and Q4 the highest), with Q4 serving as the reference group in outcome analyses. Mortality outcomes were assessed across ASMI quartiles [24]. Comparisons between these two groups were performed using the chi-square test for categorical variables and Student's t-test for continuous variables.

The incidence rates of the outcomes were calculated per 1,000 person-years. To assess the combined effects of muscle mass and obesity, participants were classified into four body composition phenotypes: (1) NMM without obesity (reference), (2) LMM without obesity, (3) NMM with obesity, and (4) LMM with obesity. The associations between those phenotypes and the study outcomes were analyzed using Cox proportional hazards models with stepwise adjustments.

Model 1 included no covariates (unadjusted).

Model 2 adjusted for sex and age at diagnosis.

Model 3 further adjusted for income level, smoking, alcohol use, physical activity, comorbidities, and SEER stage.

Model 4 further adjusted for cancer treatment within four months of diagnosis and cancer types.

In addition, as a sensitivity analysis, LMM was defined using age-standardized ASMI thresholds derived from the general Korean population rather than cohort-specific quartiles. Cancer patients were classified according to ASMI quantiles relative to this age-standardized reference population, with the lowest quartile (Q1) classified as LMM and Q2–Q4 as NMM, and their associations with mortality were reassessed using the same multivariable-adjusted models.

As a sensitivity analysis to address potential reverse causation, we repeated the analyses after applying a 1-year lag, excluding deaths occurring within the first year after cancer diagnosis [25]. For cause-specific mortality outcomes, we additionally performed Fine–Gray competing-risk regression analyses, treating deaths from causes other than the outcome of interest as competing events. Subdistribution hazard ratios (sHRs) and 95% confidence intervals (CIs) were estimated.

Subgroup analyses were performed according to age strata and SEER stage at diagnosis. For these analyses, the ASMI quartile thresholds derived from the entire cancer cohort were applied consistently across all cancer subgroups. Additionally, to assess the interaction between LMM and obesity, we evaluated both multiplicative and additive interactions. Multiplicative interaction was assessed by including a product term between LMM and obesity in the fully adjusted Cox proportional hazards model. Additive interaction was evaluated using the relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (S), with 95% CIs. A positive additive interaction was considered present when the 95% CI of RERI and AP excluded 0 or that of S excluded 1.[26] All analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC), and statistical significance was defined as a two-sided P-value < 0.05.

Results

Baseline characteristics by ASMI quartile and obesity status

The baseline characteristics of the study population according to muscle mass and obesity status are presented in Table 1. Among the 635,867 participants, 158,900 were classified as LMM, and 476,967 had NMM. Regarding lifestyle factors, the LMM group had a higher proportion of current smokers (17.94% in NMM vs. 22.61% in LMM) and was less likely to engage in regular physical activity (22.24 vs. 18.93%) compared to the NMM group ($P < 0.001$ for all). Hypertension (48.37% in NMM vs. 39.28% in LMM), DM (20.27 vs. 16.73%), and dyslipidemia (35.18 vs. 25.64%) were more prevalent in the NMM group, and CKD was slightly more common in the LMM group (8.28 vs. 8.86%) ($P < 0.0001$ for all).

Obese individuals (36.48%) exhibited higher ASM (21.78 ± 4.54 kg vs. 18.52 ± 3.58 kg) and ASMI (7.92 ± 1.22 kg/m^2 vs. 6.79 ± 0.96 kg/m^2). The obese group was characterized by a higher prevalence of former smokers and abdominal obesity, alongside a greater burden of metabolic comorbidities (Table 1).

Mortality by ASMI quartile and obesity status

Over a mean follow-up of 3.74±2.12 years, 177,861 deaths occurred, 161,793 from cancer, 4,067 from cardiovascular causes, and 2,961 from respiratory causes (Table 2). After full adjustment (Model 4), LMM (lowest quartile of ASMI) had significantly higher risks of all-cause mortality (aHR 1.25, 95% CI 1.23–1.27), cancer mortality (aHR 1.21, 95% CI 1.19–1.23), cardiovascular mortality (aHR 1.49, 95% CI 1.36–1.64), and respiratory mortality (aHR 2.26, 95% CI 1.99–2.56) than those in the highest ASMI quartile.

On the other hand, patients with obesity showed significantly lower risks of all-cause (aHR 0.89, 95% CI 0.89–0.90), cancer-specific (aHR 0.91, 95% CI 0.90–0.92), cardiovascular (aHR 0.82, 95% CI 0.77–0.88), and respiratory mortality (aHR 0.64, 95% CI 0.59–0.70) than those without obesity.

When stratified by both muscle mass and obesity status using the NMM without obesity group as the reference, patients with LMM without obesity showed increased risks of all-cause (aHR 1.19, 95% CI 1.17–1.20), cancer-specific (aHR 1.16, 95% CI 1.14–1.17), cardiovascular (aHR 1.39, 95% CI 1.28–1.50), and respiratory mortality (aHR 1.68, 95% CI 1.54–1.83). Similarly, those with LMM with obesity also showed elevated risks of all-cause mortality (aHR 1.22, 95% CI 1.16–1.28) and cancer mortality (aHR 1.22, 95% CI 1.16–1.29).

Risk patterns varied across the four groups relative to the NMM without obesity reference. For all-cause and cancer-specific mortality, the greatest risk was observed in the LMM with obesity group (all-cause: aHR 1.22, 95% CI 1.16–1.28; cancer-specific: aHR 1.22, 95% CI 1.16–1.29), followed by the LMM without obesity (all-cause: aHR 1.19, 95% CI 1.17–1.20; cancer-specific: aHR 1.16, 95% CI 1.14–1.17). Conversely, the highest risks for cardiovascular (aHR 1.39, 95% CI 1.28–1.50) and respiratory mortality (aHR 1.68, 95% CI 1.54–1.83) were found in individuals with LMM without obesity. While those with both LMM and obesity showed a trend toward increased cardiovascular and respiratory mortality, these associations were not statistically significant.

Sensitivity analyses

In the sensitivity analysis using ASMI thresholds derived from the general Korean population, the associations were consistent with those of the primary analysis (eTable 1). Compared with Q2–Q4, LMM (Q1) was associated with higher all-cause (HR, 1.22; 95% CI, 1.21–1.23), cancer-specific (HR, 1.19; 95% CI, 1.17–1.20), cardiovascular (HR, 1.46; 95% CI, 1.37–1.56), and respiratory mortality (HR, 1.98; 95% CI, 1.83–2.14). Similar patterns were observed in the combined analyses of LMM with obesity.

In the 1-year lag sensitivity analysis excluding deaths occurring within the first year after cancer diagnosis, the associations were generally consistent with those observed in the primary analysis (Table 2).

In the competing-risk analyses using Fine–Gray regression, the associations of LMM and obesity with cancer-specific, cardiovascular, and respiratory mortality were generally consistent with those observed in the conventional Cox proportional hazards models (eTable 2).

Interaction between LMM and obesity

No significant multiplicative interaction between LMM and obesity was observed for all-cause (P for interaction=0.256) or cancer-specific mortality (*P* for interaction=0.182). In contrast, significant positive additive interactions were observed for both outcomes. For all-cause mortality, the RERI was 0.08 (95% CI, 0.01–0.14), AP was 0.06 (95% CI, 0.01–0.11), and S was 1.536 (95% CI, 1.14–2.08). For cancer-specific mortality, the corresponding estimates were 0.102 (95% CI, 0.04–0.17), 0.083 (95% CI, 0.03–0.13), and 1.84 (95% CI, 1.33–2.53), respectively, indicating a super-additive joint association of LMM and obesity with all-cause and cancer-specific mortality. No significant additive or multiplicative interactions

Table 1 Baseline characteristics of the study population

	Total	Low muscle mass (ASMI quartiles)			Obesity (BMI<25lg/m2)		
		No (Q2–Q4)	Yes (Q1)	*P*-value	No	Yes	*P*-value
Study population, *N* (%)	635,867	476,967 (75.00)	158,900 (25.00)		403,931(47.90)	231,936 (36.48)	
Appendicular skeletal muscle mass index					155,414(38.48)	3,486 (1.50)	<.0001
Obesity	231,936 (36.48)	228,450 (47.90)	3,486 (2.19)	<.0001			
Abdominal obesity	236,958 (37.27)	220,858 (46.30)	16,100 (10.13)	<.0001	67,837 (16.79)	169,121 (72.92)	<.0001
ASM, kg	19.70±4.25	20.52±4.33	17.23±2.78	<.0001	18.52±3.58	21.75±4.54	<.0001
ASMI, kg/m^2	7.21±1.19	7.50±1.18	6.33±0.69	<.0001	6.79±0.96	7.92±1.22	<.0001
Height, cm				<.0001			<.0001
< 159	249,436 (39.23)	189,419 (39.71)	60,017 (37.77)		157,865 (39.08)	91,571 (39.48)	
160–169	261,653 (41.15)	192,049 (40.26)	69,604 (43.80)		172,696 (42.75)	88,957 (38.35)	
170–179	115,112 (18.10)	86,300 (18.09)	28,812 (18.13)		68,357 (16.92)	46,755 (20.16)	
≥ 180	9,666 (1.52)	9,199 (1.93)	467 (0.29)		5,013 (1.24)	4,653 (2.01)	
Weight, kg				<.0001			<.0001
< 50	56,006 (8.81)		56,006 (35.25)		55,678 (13.78)	328 (0.14)	
50–59	197,006 (30.98)	114,764 (24.06)	82,242 (51.76)		178,668 (44.23)	18,338 (7.91)	
60–69	213,987 (33.65)	193,335 (40.53)	20,652 (13.00)		135,742 (33.61)	78,245 (33.74)	
70–79	120,786 (19.00)	120,786 (25.32)			32,726 (8.10)	88,060 (37.97)	
80–89	37,315 (5.87)	37,315 (7.82)			1,112 (0.28)	36,203 (15.61)	
≥ 90	10,767 (1.69)	10,767 (2.26)			5(0)	10,762 (4.64)	
Waist circumference, cm				<.0001			<.0001
< 70	50,778 (7.99)	21,815 (4.57)	28,963 (18.23)		50,463 (12.49)	315(0.14)	
70–79	183,705 (28.89)	113,180 (23.73)	70,525 (44.38)		167,634 (41.50)	16,071 (6.93)	
80–89	262,156 (41.23)	211,090 (44.26)	51,066 (32.14)		162,320 (40.19)	99,836 (43.04)	
≥ 90	139,228 (21.9)	130,882 (27.44)	8,346 (5.25)		23,514 (5.82)	115,714 (49.89)	
Age at diagnosis, years	61.55±12.57	60.77±12.09	63.89±13.64	<.0001	61.55±12.92	61.54±11.93	0.7996
Sex, Male	341,254 (53.67)	255,949 (53.66)	85,305 (53.68)	0.8739	211,992 (52.48)	129,262 (55.73)	<.0001
Income status, Low 20%	110,197 (17.33)	81,697 (17.13)	28,500 (17.94)	<.0001	70,420 (17.43)	39,777 (17.15)	0.004
Residential area, Urban	283,039(44.51)	214,901(45.06)	68,138(42.88)	<.0001	181,356(44.9)	101,683(43.84)	<.0001
Smoking				<.0001			<.0001
Never smoker	386,242 (60.74)	291,478 (61.11)	94,764 (59.64)		246,745 (61.09)	139,497 (60.14)	
Former smoker	128,151 (20.15)	99,943 (20.95)	28,208 (17.75)		75,720 (18.75)	52,431 (22.61)	
Current smoker	121,474 (19.10)	85,546 (17.94)	35,928 (22.61)		81,466 (20.17)	40,008 (17.25)	
Alcohol consumption				<.0001			<.0001
None	386,344 (60.76)	286,276 (60.02)	100,068 (62.98)		247,266 (61.21)	139,078 (59.96)	
Mild	203,084 (31.94)	155,742 (32.65)	47,342 (29.79)		128,588 (31.83)	74,496 (32.12)	
Heavy	46,439 (7.30)	34,949 (7.33)	11,490 (7.23)		28,077 (6.95)	18,362 (7.92)	
Regular physical activity	136,133 (21.41)	106,060 (22.24)	30,073 (18.93)	<.0001	86,447 (21.40)	49,686 (21.42)	0.8452
Comorbidity							
Hypertension	293,145 (46.10)	230,728 (48.37)	62,417 (39.28)	<.0001	157,912 (39.09)	135,233 (58.31)	<.0001
Diabetes	123,282 (19.39)	96,705 (20.27)	26,577 (16.73)	<.0001	65,989 (16.34)	57,293 (24.70)	<.0001
Dyslipidemia	208,530 (32.79)	167,785 (35.18)	40,745 (25.64)	<.0001	113,764 (28.16)	94,766 (40.86)	<.0001
Chronic kidney disease	53,573 (8.43)	39,489 (8.28)	14,084 (8.86)	<.0001	31,488 (7.80)	22,085 (9.52)	<.0001
SEER grade				<.0001			<.0001
Localized	305,194 (48.00)	232,707 (48.79)	72,487 (45.62)		192,661 (47.70)	112,533 (48.52)	
Regional	187,533 (29.49)	142,249 (29.82)	45,284 (28.50)		117,830 (29.17)	69,703 (30.05)	
Distant	98,231 (15.45)	70,226 (14.72)	28,005 (17.62)		64,215 (15.90)	34,016 (14.67)	
Cancer treatment							
Surgery	431,929(67.93)	333,665(69.96)	98,264(61.84)	<.0001	270,085(66.86)	161,844(69.78)	<.0001
Chemotherapy	183,953(28.93)	139,504(29.25)	44,449(27.97)	<.0001	117,279(29.03)	66,674(28.75)	0.0149
Radiation therapy	74,579(11.73)	56,095(11.76)	18,484(11.63)	0.1686	47,946(11.87)	26,633(11.48)	<.0001

Low muscle mass was defined as Q1 of sex-specific quartiles of calculated appendicular skeletal muscle mass index

ASM Appendicular skeletal muscle mass, *ASMI* Appendicular skeletal muscle mass index, *SEER* Surveillance, epidemiology, and end Results

Table 1 (continued)

Data were presented as mean ± standard deviation or number (%)

P-values were calculated using ANOVA for continuous variables and chi-square test for categorical variables

were observed for cardiovascular or respiratory mortality (**eTable 3**).

Stratified analyses

A stage-dependent pattern was evident across all mortality outcomes, where the impact of LMM on all-cause mortality was most significant in patients with early-stage cancers. Likewise, the protective effect of obesity (inverse association with mortality) was most prominent in early stages and diminished with advancing stage. For both LMM with and without obesity, the increased mortality risk was most apparent in localized cancers, particularly for respiratory-related mortality (eTable 4).

Age-stratified analyses showed that the association between LMM and mortality remained consistent across all age groups. For all-cause and cancer-specific mortality, the impact of LMM was more pronounced in older adults (≥ 60 years) than in younger individuals. In contrast, the excess risk for cardiovascular mortality was significantly higher in those aged <60 years (aHR 2.10 for <60 years vs. 1.41 for ≥60 years). The association between LMM and respiratory mortality was similar in the two age groups (eTable 2). Additionally, sex-stratified analyses revealed no significant differences in the magnitude of these associations (eTable 5).

Exploratory analyses stratified by cancer site showed similar patterns across cancers, with increased mortality linked to LMM and decreased risk associated with obesity, although the magnitude of the association varied by cancer type (eTable 6 and Forest plot).

A few exceptions to this overall pattern were noted, though LMM without obesity was consistently associated with increased mortality across most cancer types. For instance, that association was particularly strong in stomach cancer (HR 1.27, 95% CI 1.23–1.32) and laryngeal cancer (HR 1.32, 95% CI 1.12–1.56), whereas the combined effect of LMM and obesity showed relatively higher associations with mortality in liver cancer (HR 1.33, 95% CI 1.14–1.56) and thyroid cancer (HR 1.92, 95% CI 1.20–3.06). Ultimately, these site-specific variations did not indicate a clear or consistent pattern across cancer types.

Discussion

In this large nationwide cohort study of 635,867 patients with cancer, LMM was consistently associated with increased risk of all-cause, cancer-specific, cardiovascular, and respiratory mortality, even after accounting for obesity status. This link was more pronounced in early-stage cancer. In contrast, obesity was associated with a protective effect across all outcomes.

Our findings align with previous research showing that LMM is a significant predictor of poor outcomes in cancer survivors [6, 27, 28]. For example, a large meta-analysis demonstrated that LMM prior to treatment was significantly associated with poorer overall survival (HR 1.44, 95% CI 1.32–1.56), cancer-specific survival (HR 1.93, 95% CI 1.38–2.70), and disease-free survival (HR 1.16, 95% CI 1.00–1.30) durations.[6].

LMM is associated with pathophysiological mechanisms that contribute to poor clinical outcomes. First, LMM leads to reduced secretion of myokines, which impairs innate and adaptive immunity and promotes a state of chronic systemic inflammation [29]. Second, because muscle is the primary site of insulin-dependent glucose uptake, LMM induces insulin resistance [30], creating a hyperglycemic environment that can support tumor growth and progression [31]. Third, LMM is linked to mitochondrial dysfunction, contributing to fatigue, muscle wasting, and heightened treatment toxicity [32]. Fourth, poor protein status due to malnutrition and reduced anabolic signaling in muscle leads to hypoalbuminemia and impaired protein synthesis [33], which are associated with increased postoperative complications and short-term mortality [34]. Finally, the pharmacokinetics of anticancer drugs are altered in patients with LMM such that drug dosing based on body surface area can increase the risk of toxicity [35].

In our analysis, LMM was also significantly associated with increased cardiovascular and respiratory mortality. These findings align with prior research showing cardiovascular disease as a significant cause of mortality among cancer survivors [36], influenced by pre-existing comorbidities [37] and the cardiotoxic effects of cancer therapies [38, 39]. In addition, reduced muscle mass, particularly of respiratory muscles such as the diaphragm, can impair ventilation and coughing capacity, increasing the risk of pneumonia and other respiratory infections [40, 41]. Diaphragm muscle atrophy leads to reduced tidal volume and a diminished ability to respond to respiratory challenges [42]. Furthermore, dysphagia caused by atrophy of the swallowing muscles can further increase aspiration risk [43]. These conditions suggest that LMM could have lower physiological resilience than those with NMM and are more susceptible to adverse outcomes following cardiovascular or respiratory events.

Table 2 Hazard ratios for mortality according to appendicular skeletal muscle mass index (ASMI) quartiles and obesity status

Outcome			Subjects (N)	Event *n* (%)	IR per 1,000 Person–years	Model 1 (crude) HR (95% CI)	Model 2 aHR (95% CI)	Model 3 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI) (1-year lag)
All–cause mortality	ASMI quartile	Q1 (lowest)	158,900	57,817(36.4)	105.60	1.83(1.80,1.85)	1.37(1.35,1.39)	1.30(1.28,1.31)	1.25(1.23,1.27)	1.26(1.24, 1.29)
		Q2	159,193	45,997(28.9)	77.26	1.36(1.34,1.38)	1.07(1.06,1.09)	1.06(1.05,1.08)	1.07(1.06,1.09)	1.06(1.04, 1.08)
		Q3	158,822	38,912(24.5)	63.40	1.12(1.11,1.14)	1.02(1.01,1.04)	1.06(1.01,1.04)	1.02(1.00,1.03)	0.99(0.97, 1.01)
		Q4 (highest)	158,952	35,135(22.1)	56.35	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
	Obesity	No	403,931	118,719(29.4)	79.22	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		Yes	231,936	59,142(25.5)	67.09	0.85(0.84,0.86)	0.86(0.85,0.87)	0.89(0.88,0.90)	0.89(0.89,0.90)	0.89(0.88, 0.90)
	Combined group	NMM without obesity	248,517	62,525(25.2)	65.02	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		LMM without obesity	155,414	56,194(36.2)	104.64	1.57(1.55,1.58)	1.29(1.27,1.30)	1.23(1.21,1.24)	1.19(1.17,1.20)	1.22(1.20, 1.24)
		NMM with obesity	228,450	57,519(25.2)	66.04	1.01(1.00,1.02)	0.95(0.94,0.96)	0.96(0.95,0.97)	0.96(0.94,0.97)	0.97(0.95, 0.98)
		LMM with obesity	3,486	1,623(46.6)	155.20	2.24(2.13,2.35)	1.40(1.33,1.47)	1.32(1.26,1.40)	1.22(1.16,1.28)	1.22(1.04, 1.42)
Cancer mortality	ASMI quartile	Q1 (lowest)	158,900	51,641(32.5)	94.32	1.75(1.73,1.78)	1.34(1.32,1.36)	1.25(1.23,1.27)	1.21(1.19,1.23)	1.19(1.17, 1.22)
		Q2	159,193	41,744(26.2)	70.12	1.33(1.31,1.35)	1.07(1.05,1.08)	1.05(1.03,1.06)	1.06(1.04,1.07)	1.04(1.02, 1.06)
		Q3	158,822	35,824(22.6)	58.37	1.12(1.10,1.13)	1.02(1.01,1.04)	1.02(1.00,1.03)	1.01(0.99,1.03)	0.99(0.97, 1.01)
		Q4 (highest)	158,952	32,584(20.5)	52.26	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
	Obesity	No	403,931	107,484(26.6)	71.72	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		Yes	231,936	54,309(23.4)	61.61	0.86(0.85,0.87)	0.87(0.86,0.88)	0.90(0.89,0.91)	0.91(0.90,0.92)	0.92(0.91, 0.93)
	Combined group	NMM without obesity	248,517	57,314(23.1)	59.60	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		LMM without obesity	155,414	50,170(32.3)	93.42	1.52(1.50,1.54)	1.26(1.25,1.28)	1.20(1.19,1.21)	1.16(1.14,1.17)	1.17(1.15, 1.19)
		NMM with obesity	228,450	52,838(23.1)	60.66	1.01(1.00,1.02)	0.96(0.94,0.97)	0.97(0.96,0.98)	0.96(0.95,0.98)	0.98(0.96, 1.00)
		LMM with obesity	3,486	1,471(42.2)	140.66	2.20(2.09,2.32)	1.41(1.34,1.48)	1.34(1.27,1.41)	1.22(1.16,1.29)	1.18(0.99, 1.41)

Table 2 (continued)

Outcome			Subjects (N)	Event *n* (%)	IR per 1,000 Person–years	Model 1 (crude) HR (95% CI)	Model 2 aHR (95% CI)	Model 3 aHR (95% CI)	Model 4 aHR (95% CI)	Model 4 aHR (95% CI) (1-year lag)
Cardiovascular mortality	ASMI quartile	Q1 (lowest)	158,900	1,477(0.9)	2.70	2.39(2.18,2.61)	1.33(1.21,1.46)	1.53(1.39,1.68)	1.49(1.36,1.64)	1.44(1.29, 1.60)
		Q2	159,193	1,077(0.7)	1.81	1.60(1.46,1.76)	1.02(0.92,1.12)	1.12(1.01,1.23)	1.11(1.01,1.22)	1.12(1.01, 1.26)
		Q3	158,822	809(0.5)	1.32	1.17(1.06,1.29)	0.94(0.85,1.04)	1.02(0.92,1.13)	1.02(0.92,1.13)	0.94(0.84, 1.06)
		Q4 (highest)	158,952	704(0.4)	1.13	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
	Obesity	No	403,931	2,724(0.7)	1.82	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		Yes	231,936	1,343(0.6)	1.52	0.84(0.79,0.90)	0.90(0.84,0.96)	0.81(0.76,0.87)	0.82(0.77,0.88)	0.82(0.76, 0.88)
	Combined group	NMM without obesity	248,517	1,295(0.5)	1.35	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		LMM without obesity	155,414	1,429(0.9)	2.66	1.98(1.83,2.13)	1.37(1.27,1.48)	1.41(1.31,1.52)	1.39(1.28,1.50)	1.37(1.25, 1.50)
		NMM with obesity	228,450	1,295(0.5)	1.49	1.11(1.02,1.19)	1.04(0.96,1.12)	0.94(0.87,1.02)	0.94(0.87,1.02)	0.95(0.87, 1.04)
		LMM with obesity	3,486	48(1.4)	4.59	3.41(2.55,4.55)	1.33(1.00,1.79)	1.19(0.89,1.59)	1.14(0.85,1.53)	0.70(0.31, 1.57)
Respiratory mortality	ASMI quartile	Q1 (lowest)	158,900	1,361(0.9)	2.49	4.85(4.29,5.47)	2.30(2.03,2.61)	2.34(2.07,2.66)	2.26(1.99,2.56)	2.37(2.06, 2.72)
		Q2	159,193	780(0.5)	1.31	2.55(2.24,2.90)	1.37(1.20,1.57)	1.40(1.23,1.60)	1.38(1.21,1.58)	1.41(1.21, 1.64)
		Q3	158,822	499(0.3)	0.81	1.58(1.37,1.82)	1.16(1.01,1.33)	1.19(1.03,1.37)	1.18(1.02,1.36)	1.11(0.95, 1.30)
		Q4 (highest)	158,952	321(0.2)	0.51	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
	Obesity	No	403,931	2,239(0.6)	1.49	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		Yes	231,936	722(0.3)	0.82	0.55(0.51,0.60)	0.63(0.58,0.69)	0.63(0.58,0.68)	0.64(0.59,0.70)	0.61(0.56, 0.68)
	Combined group	NMM without obesity	248,517	906(0.4)	0.94	1(Ref.)	1(Ref.)	1(Ref.)	1(Ref.)	1 (ref.)
		LMM without obesity	155,414	1,333(0.9)	2.48	2.65(2.43,2.88)	1.74(1.60,1.89)	1.72(1.58,1.87)	1.68(1.54,1.83)	1.79(1.62, 1.98)
		NMM with obesity	228,450	694(0.3)	0.80	0.85(0.77,0.94)	0.83(0.75,0.91)	0.80(0.73,0.89)	0.81(0.74,0.90)	0.83(0.74, 0.94)
		LMM with obesity	3,486	28(0.8)	2.68	2.88(1.98,4.19)	1.53(1.05,2.25)	1.45(0.99,2.12)	1.41(0.97,2.07)	1.80(0.96, 3.38)

ASMI Appendicular skeletal muscle mass index, *IR* incidence rate, *HR* hazard ratio, *CI* confidence interval, *NMM* normal muscle mass, *LMM* low muscle mass

Data were presented as number (%)

Model 2: Adjusted for sex and age at diagnosis

Model 3: Adjusted for variables used in Model 2, and additionally with SEER grade, income, smoking, alcohol consumption, physical activity, hypertension, diabetes, dyslipidemia, chronic kidney disease

Model 4: Adjusted for variables used in Model 3, and additionally with cancer treatment and cancer type

In our study, obesity was associated with decreased risk of all-cause, cancer-specific, cardiovascular, and respiratory mortality. Although the link between obesity and mortality is well-documented, a meta-analysis of cancer survivors reported that obese individuals (BMI ≥30 kg/m^2) had a significantly higher risk of overall mortality (HR 1.14, 95% CI 1.09–1.19) and cancer-specific mortality (HR 1.17, 95% CI 1.12–1.23) [5]. However, a more recent systematic review and meta-analysis of 73 studies (using various obesity criteria) found no significant association between obesity and overall survival duration (HR 0.96, 95% CI 0.81–1.13) [44]. Some studies have reported a phenomenon known as the "obesity paradox," where overweight or obese individuals exhibit better survival outcomes than in patients with lower BMI, particularly in cancers such as lung, kidney, liver, and melanoma [5, 44, 45]. This paradox might reflect limitations of BMI, which fails to distinguish between fat and lean mass or account for fat distribution [45]. Proposed mechanisms include the protective metabolic reserve provided by preserved adipose and muscle tissue and enhanced responses to immunotherapy due to improved systemic resilience [45, 46]. Although BMI can reflect overall body size, it does not distinguish between fat and muscle mass and can mask underlying muscle depletion [45]. Our findings help clarify this paradox by showing that obesity with NMM was associated with a decreased risk, whereas it markedly worsened outcomes when combined with LMM. However, this apparent protective effect must be interpreted with caution, as it may be confounded by reverse causation, preclinical cancer-related weight loss, residual confounding by disease severity [47], or health screening selection bias [48].

Recent research highlights LMM as an independent prognostic factor in cancer patients [49]. Our findings further clarify LMM as a key determinant of poor prognosis, and its impact appears to be more influential than obesity status. The mortality risks associated with LMM play a dominant role in predicting mortality. This finding is supported by multiple studies, including those on patients with locally advanced rectal [28] and esophageal cancer [27], in whom sarcopenia was consistently linked to poorer long-term outcomes. A recent meta-analysis of solid tumor patients [50] confirmed this link, showing that a low ASMI is associated with poor overall, cancer-specific, and disease-free survival times.

Although sarcopenic obesity is also recognized as a predictor of poor outcomes [51–53], most studies indicate no significant prognostic difference between patients with sarcopenia alone and those with sarcopenic obesity [50, 51]. This strongly suggests that the quantity of muscle mass itself is a more critical factor than obesity. Our findings show that sarcopenic obesity was associated with the highest increase in HRs for both overall and cancer mortality. This suggests the combined effect of LMM and obesity may have a particularly detrimental impact on patient survival.

Notably, although no significant multiplicative interaction was observed between LMM and obesity, significant positive additive interactions were identified for all-cause and cancer-specific mortality, suggesting a super-additive joint association. These findings indicate that the excess mortality associated with the coexistence of LMM and obesity may exceed the sum of their individual associations, highlighting the potential importance of considering both muscle mass and obesity simultaneously when assessing mortality risk in patients with cancer.

Given the strong association between LMM and mortality, early detection of LMM and targeted interventions should be a clinical priority for cancer patients. Current evidence supports personalized nutritional strategies combined with structured exercise programs to help maintain or enhance muscle mass [54].

Several interventions have been proposed to mitigate LMM, particularly resistance exercise and protein supplementation [55]. For example, randomized controlled trials in breast cancer survivors have shown that 12-week supervised resistance training programs performed two to three times per week significantly improved lean body mass and reduced fatigue [56]. Dietary interventions have also been associated with improvements in body composition and quality of life [57]. Based on that evidence, the American Cancer Society recommends at least 150 min of moderate aerobic activity per week, combined with resistance training twice weekly, for cancer survivors [55]. These strategies could help preserve or restore muscle mass, potentially lengthening lifespans.

This study has limitations. ASMI was estimated rather than directly measured, but the prediction model used has been validated in a large Korean population as showing high correlation, minimal bias, and acceptable predictive accuracy [21]. Although direct imaging techniques offer greater precision, they are impractical for large-scale epidemiologic research. The equation used in this study has been applied in multiple studies involving cancer survivors [58].

Importantly, LMM in this study should not be considered synonymous with either sarcopenia or cancer-related cachexia. LMM may result from heterogeneous processes, including aging, physical inactivity, inadequate nutrition, and cancer-related wasting. Because information on muscle strength, physical performance, longitudinal changes in body composition, and the underlying cause of muscle loss was unavailable, we could not distinguish among these potential contributors to LMM. Therefore, the observed association between LMM and mortality should be interpreted as reflecting low estimated muscle mass rather than a specific effect of sarcopenia or cachexia.

Furthermore, the ASMI prediction equation includes anthropometric measures also used to define obesity. This overlap may have influenced the combined LMM and obesity analyses. Additionally, although participation in the Korean National Health Screening Program is relatively high [20], restricting the study population to individuals with available health screening data may have introduced selection bias, as screening participants may be systematically healthier than non-participants [48]. This selection may limit the generalizability of our findings to all patients with cancer. Furthermore, because our study was conducted within a single Korean cohort, these factors together may limit the generalizability of our findings to the broader cancer population.

However, our study also has notable strengths. The large-scale cohort design and use of nationwide cancer registry data provided a robust dataset, allowing comprehensive analysis of the association between body composition and mortality. Moreover, this nationwide cohort provides population-specific evidence from an Asian population, in which body composition and obesity criteria differ from those applied in Western populations. Furthermore, our detailed stratified analysis by cancer stage and type and the inclusion of various potential confounding factors enhance the reliability and clinical relevance of our findings.

This large nationwide cohort demonstrates that LMM is significantly and independently associated with increased risk of all-cause, cancer-specific, cardiovascular, and respiratory mortality among patients with cancer, regardless of obesity status. These findings highlight the importance of muscle mass as a prognostic factor and suggest that early identification and management of LMM could help improve outcomes.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests The authors declare that they have no competing interests.

Ethical approval This study received approval by the Institutional Review Board of Soongsil University (IRB File No. SSU-202007-HR-236-02). The requirement for informed consent was waived because we used de-identified data under confidentiality guidelines.

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