The Role of Body Composition in Predicting Outcomes in the Elderly Following Acute Abdominal Surgery

by

Mahmoud Alghamdi

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Department of Surgery
University of Alberta

ABSTRACT

Background:

The elderly are the fastest growing population in North America which has resulted in rising number of older patients undergoing emergency surgery. Often with aging, there is a decrease in skeletal muscle mass and an increase in intra-abdominal fat. Sarcopenia, severe muscle depletion, as identified by computed tomography (CT) has been found to be a strong predictor of poor outcomes following surgery. There is much less knowledge on the role of visceral and subcutaneous fat. Therefore, the aim of this study was to examine the association of body composition identified by CT scan with in-hospital mortality and postoperative complications after acute abdominal surgery in elderly.

Methods:

A retrospective cohort of elderly patients (≥ 65 years) underwent acute abdominal surgery between 2008 and 2010 at the University of Alberta Hospital was analysed by abdominal CT scan at lumbar vertebra 3. CT scan was used to measure muscularity, visceral fat, and subcutaneous fat surface areas adjusted to the height (cm^2/m^2), and, their radiodensities measured in Hounsfield Units (HU). Logistic regression was used to assess the relationship between body composition and in-hospital mortality and postoperative complications. Age, sex, and American Society of Anesthesiologists (ASA) classification were incorporated in all models as covariates. The receiver area under curve (AUC) was used to test the predictive ability of the models.

Results:

A two-hundred fifteen patients were identified with a mean age of 77.3 ± 7.3. Multivariate analysis identified Skeletal Muscle Index (SMI) (adjusted odds ratio (aOR): 0.922, 95% CI: 0.863-0.985, p-value= 0.016) as a strong predictor of in-hospital mortality. Subcutaneous fat area

radiodensity (SFA HU) (aOR: 1.028, 95% CI: 0.999-1.058, p-value= 0.055) showed a trend for association with in-hospital mortality. The best model including age, sex, ASA, SMI, and SFA HU had an AUC= 0.867. SMI (aOR: 0.977, 95% CI: 0.935-1.021, p-value= 0.307) and SFA (aOR: 1.013, 95% CI: 0.990-1.036, p-value= 0.272) were not significantly associated with major postoperative complications development (AUC= 0.755). Female sex (aOR: 0.455, 95% CI: 0.221-0.936, p-value= 0.032) and ASA score (aOR: 3.271, 95% CI: 2.026-5.279, p-value <0.001) were significantly associated with the risk of developing major complications.

Conclusion:

Sarcopenia was an independent predictor of in-hospital mortality. All body composition measurements were not associated with postoperative complications. Body composition measurements by CT scan can be used as a risk assessment tool, moreover, they represent a modifiable risk factor that can be targeted to improve the outcome perioperatively.

Keywords:

Acute abdominal surgery; Body composition; Computed tomography; Elderly; In-hospital mortality; Postoperative complications; Radiodensity; Sarcopenia; Skeletal muscle; Subcutaneous fat; Visceral fat

PREFACE

This thesis is an original work by Mahmoud Alghamdi. This study was approved by the Health Research Ethics Board at the University of Alberta (Pro00019426). May 9, 2017.

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LIST OF ABBREVIATIONS

ACE: Angiotensin-Converting Enzyme

adjusted Odds Ratio: aOR

ADP: Air Displacement Plethysmography

ASA: American Society of Anesthesiologists

ASM: Appendicular Skeletal Mass

AUROC: Area Under Receiver Operator Curve

BIA: Bioelectrical Impedance Analysis

BMI: Body Mass Index

CCI: Charlson Comorbidity Index

CDC: Clavien-Dindo Classification

CI: Confidence Interval

CIHI: Canadian Institute for Health Information

CT: Computed tomography

DXA: Dual X-ray Absorptiometry

ESPEN: European Society for Clinical Nutrition and Metabolism

EWGSOP: European Working Group on Sarcopenia in Older People

HR: Hazard Ratio

HU: Hounsfield Units

ICU: Intensive Care Unit

IGF-I: Insulin-like Growth Factor-1

IL-6: Interleukin-6

IQR: Interquartile Ranges

LOS: Length of Stay

MRI: Magnetic Resonant Imaging

OR: Odds Ratio

POPF: Post-Operative Pancreatic Fistula

SD: Standard Deviations

SFA (HU): Subcutaneous Fat Area Radiodensity

SFA: Subcutaneous Fat Area

SFI: Subcutaneous Fat Index

SMA (HU): Skeletal Muscle Radiodensity

SMA: Skeletal Muscle Area

SMI: Skeletal Muscle Index

tAFA: total Abdominal Fat Area

tAFI: total Abdominal Fat Index

TNF- α: Tumour Necrosis Factor- Alpha

VFA (HU): Visceral Fat Radiodensity

VFA: Visceral Fat Area

VFI: Visceral Fat Index

WC: Waist Circumference

WHR: Waist to Hip Ratio

I. CHAPTER ONE: INTRODUCTION

Aging is a heterogeneous process across population due to the diversity of our genetics and lifestyle.[1] Commonly, aging is measured by chronological age. The chronological age of 65 years or older has been accepted globally as the definition of elderly.[2] With increases in life expectancy, the number of people aged ≥ 65 years has increased more than 3 times the number recorded in 1963.[3] As of 2013, there were 5.4 million (15.3% of Canadians) that fit into this age group. By 2063, the number of seniors is estimated to reach 15.1 million, accounting for 28% of Canada's population.[3] As a result of an increase in life expectancy and increasing numbers of seniors, all fields of medicine are moving toward a better understanding of older adult's physiology and how that can impact their health.

I.1 Elderly and Healthcare Cost

Health care costs are highest for seniors according to the Canadian Institute for Health Information (CIHI).[4] Fifteen percent of the Canadian population is ≥ 65 years old, however, more than 45% of all public-sector health care dollars are consumed by seniors. The CIHI documented health care costs from 1975 to 2015 for Canadians 65 and older.[4] In 2013, the cost was $11,598 per person with an incremental age-related increase. Values for the 65-69 years were $6,298 compared to $20,917 for those 80 years and older. In 2012 the total spending by nursing homes was $9.8 billion.[4] This high cost of care for older adults can be explained by the increasing life expectancy, as well as the higher prevalence of co-morbidities; these factors necessitate more hospitalization. The causes of increased cost are due to several adverse outcomes following admission including surgical complications, hospital-acquired infection,

delirium, disability, poly-pharmacy, increased the length of stay, readmission, and transition to long-term healthcare facility.[5] Hospitalization often plays a critical role in elderly life. Seniors have higher rates of adverse health events during admission compared to younger adults. These include the loss of independent living capability. During hospitalization over one-third of older adults acquire a new disability in at least one activity of daily living.[6,7] Half of these subjects never recover their lost function.[5-7] The decrement in functional capacity is common in older people who are admitted to a hospital; this is often a consequence of hospitalization than the presenting illness.[8,9] The decline in functional ability in older patients experienced in hospitals can be directly related to the period of time spent in bed. Based on an observational study, 83% of older patients were in bedrest at least 24 hours during hospitalization.[10] Muscle strength declined at a rate of up to 5% per week (equivalent to 20% per month) in hospitalized older adults.[11] The elderly have a lower threshold for developing disabilities as they often enter a hospital with lower baseline muscle strength and mass.[12]

I.2 Elderly and Surgery

As the estimated proportion of Canadian people aged ≥ 65 years is expected to reach 28% by 2063[3], the number of individuals aged ≥ 65 years requiring acute abdominal surgery is expected to rise. The elderly present with unique health-care challenges compared to younger patients; they have special physiologic, pharmacologic, psychologic, and social attributes.[13-16] Consequently, the healthcare system needs to adopt new evidence-based and multidisciplinary approach in order to meet these challenges associated with the rapid increase of the aging population.

Aging itself remains an important risk factor for postoperative morbidity and mortality.[17] Mortality in emergency surgery reached 15-30%, doubled if associated with complications, and even higher in patients over 75 years.[18] Elderly patients undergoing acute abdominal surgery have higher rates of postoperative complications, loss of independence, mortality, and healthcare resources use.[19] Moreover, frailty, an age-associated increase in vulnerability and decline in body ability to manage acute stressors,[20] has been associated with higher mortality and morbidity after emergency abdominal surgery[19,21] and other surgical procedures.[22]

I.3 Risk Identification

The concept of preoperative identification of high-risk patients using specific patient-related factors gained a massive interest in the clinical practice.[23] Preoperative risk identification using patient-related biomarkers and parameters helps in decision making, and proper use of hospital resources, and facilitates the development of a tailored and individualized health care for the geriatric population.

There are two types of risk factors. The non-modifiable risk factors are characteristics in the individual that cannot be changed or adjusted, hence they are out of our control and little or nothing can be done to control them; such factors include age, sex, race, family history, genetic makeup. On the other hand, modifiable risk factors are attributes, characteristics, exposures or lifestyle patterns that can be adjusted or changed to prevent the development of the disease. These modifiable risk factors include; obesity, excessive salt intake, inactivity or lack of exercise, high fat diet, tobacco use, alcohol consumption.[24]

Body composition needs to be taken into consideration as a modifiable risk factor. The purpose of focusing on body composition in elderly as a risk assessment tool is to facilitate a more accurate prediction of adverse outcomes and to avoid deterioration for those patients with chronic diseases. Better prediction of those at risk of significant health problems will improve patient-selection for invasive surgical procedures versus conservative treatment. Improvements in predicting health outcomes will be able to reduce age-associated deterioration in senior's health and facilitate the development of a tailored and individualized health care.

I.4 Body Composition

I.4.1 Definition

Body composition is defined as the percentage of fat and fat-free mass in a human body. Fat-free mass includes muscles, bones, organs, and water. Body fat is distributed in two main compartments, abdominal and subcutaneous fat.[25] Abdominal fat is also referred to as visceral, intra-abdominal, or central fat.

I.4.2 Body Composition Changes in Elderly

Age-associated changes in body composition have a significant impact on health and physical function.[26] These changes may occur without a noticeable change in the Body Mass Index (BMI).[27] With aging, the total body fat increases and becomes redistributed more in the abdominal region, while the fat-free mass, such as skeletal muscle, bone mineral density, organ mass, body water, tend to decrease.[26,28] These changes grow out of a positive energy imbalance between the intake and expenditure due to an increasingly sedentary lifestyle in elderly

population.[29] Additionally, some changes could depend on age-related endocrine and metabolic alterations.[30,31]

In elderly, increased total body fat and abdominal fat distribution have been shown to be associated with cardiovascular diseases and non-insulin-dependent diabetes.[32] Bone mineral loss secondary to vitamin D deficiency is a major risk factor for bone fractures, which are a significant cause of morbidity, institutionalization in nursing homes, and mortality among the elderly.[33] Sarcopenia, an age-related loss of skeletal muscle mass and strength [34], has been associated with physical functional decline[35], disability, institutionalizations, and mortality.[36] In addition, the new concept of sarcopenic obesity, which is a combination of obesity and sarcopenia, is recognized as a public health risk in elderly.[37] It has been associated with cardiovascular morbidity and mortality.[38-42]

I.4.3 Sarcopenia

Lean mass peaks in the third decade of life, followed by a steady decline with advancing age.[43,44] The loss of muscle mass with aging is increasingly recognized as having association with weakness, disability, frailty, and death.[45] In 1989, Rosenberg described the loss of muscle mass with aging by giving it a name, *sarcopenia*. *Sarco*, from the Greek, denotes flesh (muscle), and *penia* means a loss; thus, "sarcopenia" translates as muscle loss.[46] It is different from muscle wasting and weight loss (*cachexia*) caused by inflammatory diseases, starvation, or cancer.[47] Primary sarcopenia is used to define age-associated muscle loss, whereas secondary sarcopenia describes muscle loss that is due to physical inactivity, chronic diseases, or cancers.[48]

I.4.3.1 Definitions of Sarcopenia

In 1998, Baumgartner et al.[49] proposed a method for diagnosing sarcopenia. Sarcopenia was measured by taking the muscle mass adjusted to a person's height. Appendicular skeletal mass (ASM) was measured in all four limbs with dual x-ray absorptiometry (DXA). Subjects with ASM/ht^2 (kg/m^2) of two standard deviations (SDs) below the mean for sex specific healthy younger adults were more likely to have sarcopenia. Janssen et al.[50] measured skeletal muscle mass using bioelectrical impedance analysis (BIA) and defined sarcopenia class I as a skeletal muscle index (skeletal muscle mass/whole body mass × 100) within 1 to 2 SD below the mean for young adult values, and sarcopenia class II in those with more that SD. Nevertheless, these definitions have many drawbacks including the use of indirect methods to assess body muscularity and failure to incorporate measures of muscle strength and physical performance.

The European Working Group on Sarcopenia in Older People (EWGSOP)[34] has proposed the diagnostic criteria for sarcopenia which is loss of muscle mass combined with a documented muscle weakness or poor physical performance. Considering the progressive nature of sarcopenia, three stages of sarcopenia have been described: pre-sarcopenia, sarcopenia and severe sarcopenia. Pre-sarcopenia is defined as loss of skeletal muscle mass alone; sarcopenia involves loss of muscle mass associated with either muscle weakness (e.g., handgrip) or poor physical performance (e.g., walking speed); and severe sarcopenia involves all three criteria (i.e. low muscle mass, muscle weakness, and poor physical performance). The European Society for Clinical Nutrition and Metabolism Special Interest Groups[51] defined sarcopenia as low skeletal muscle mass and low muscle strength which is assessed by walking speed. The International Working Group on Sarcopenia[52] defined sarcopenia as low skeletal muscle mass and low muscle

function which assessed by walking speed and "that sarcopenia is associated with muscle mass loss alone or in conjunction with increased fat mass"

Muscle strength is evaluated using handgrip strength which is an easy, reliable, valid, inexpensive method of screening to identify risk of disability in older adults.[53] Based on EWGSOP definition, cut-offs for handgrip strength value are < 20 kg for women and < 30 kg for men. [34] Knee flexion/ extension test is another method to test muscle strength, however, its use is limited as it requires specific machines.[37]

Muscle performance is assessed by using the Short Physical Performance Battery which involves balance tests, a timed 4-meter walk, and timed chair rise which can be easily performed in research and clinical setting. These tests are reproducible to activities of daily living. Gait speed can be used as a single test to provide a predictive value for disability in elderly.[54] A gait speed of < 0.8 m/sec has been associated with adverse outcomes.[55] Another test that can be used as a single test is Timed Up and Go test. A Timed Up and Go test is defined as the time in second required to stand from a chair and walk 10 feet, returning to the chair, and ends after person sits. The results were classified as fast ≤ 10 seconds, intermediate = 11-14 seconds, and slow ≥ 15 seconds. Patients with a slower Timed Up and go have been found to have higher rate of postoperative complications and 1-year mortality.[56]

I.4.3.2 Mechanism of Sarcopenia

The atrophic phenomenon responsible for muscle loss seems to be the main determinant of this age-related decline in muscle function. A study on *vastus lateralis* muscles has shown that older

people had a total muscle cross-sectional area that was about 40% smaller than young adults.[57] Depending on the expression of myosin heavy chain isoforms, there are two types of myofibers which are present in varying ratios for every muscle.[58] Type 1 myofibers are slow twitch; these are primarily, used for sustained, low-level activity and generate less force than type 2 fibers. Type 2 myofibers are fast twitch used for brief duration intense 'burst work' activity relying on anaerobic pathways for energy production.[58-60] With aging, type 2 fast twitch fibers are more affected than type 1.[61] Denervation of motor units which is then reinnervated with slow motor units plays a key role in declining muscle function. [62] Satellite cells are key cells in the repair and growth of muscle fibres after exercise or injury.[63] These cells have been found to be much lower in older people which contribute to the development of sarcopenia.[64] Another evident change in aging muscles is fatty infiltration or "myosteatosis". A higher intramuscular adipose tissue is a significant reason why muscle quality does not improve in some elder people even after training.[65,66] Age-related mitochondrial defects have been implicated in the pathogenesis of sarcopenia.[67,68]

Aging is associated with decline in many hormones, including testosterone, estrogen, growth hormone, and insulin-like growth factor-1 (IGF-1).[69] These hormones have anabolic effect on skeletal muscles. Age-related increases in insulin resistance is associated with fatty infiltration of skeletal muscles and loss of muscle function.[70] Tumour necrosis factor (TNF- α) and interleukin-6 (IL-6) have been found to have a catabolic effect in skeletal muscle. Age-related increases in the expression of these inflammatory markers is thought to contribute to the sarcopenic.[71,72]

I.4.3.3 Techniques and Tools Measuring Muscle Mass

Sarcopenia is detected using specific imaging technologies including ultrasound, DXA, CT scan, MRI. These methods differ remarkably in terms of reliability, exposure to radiation, duration to deliver the examination and analyze the results, the availability of the equipment, costs and applications. These tools used will be discussed in the body composition measurement tools section.

I.4.3.4 Treatment

Sarcopenia is an independent risk factor that is associated with important negative health outcomes and disabilities, therefore considered a public health problem. The prevalence of sarcopenia ranges from 8.4% to 27.6% depending on the method of diagnosis.[73] In 2000, the estimated cost of sarcopenia in the United States was $18.5 billion; this value represents 1.5% of total healthcare expenditures for that year.[74] Giving the high prevalence and healthcare cost burden, it is important that clinicians can easily employ strategies for prevention based on early identification of sarcopenia.

I.4.3.4.1 Exercise and Physical Activity

The American College of Sports Medicine and American Heart Association have recommended that at least 150 minutes per week physical activity for older adults. [75,76] The Department of Health and Human Services has published the Physical Activity Guidelines which have recommended that if older adults cannot do 150 minutes a week of moderate-intensity aerobic activity due to chronic conditions, they should be as physically active as their physical abilities and health conditions permit.[77] In addition, moderate to vigorous intensity resistance exercise at

least 2 days per week. This includes progressive weight training program or weight bearing calisthenics, stair climbing, and other strengthening activities that use the major muscle groups.[75] Resistance training has shown beneficial changes in muscle strength, muscle fiber size, muscle architecture, and stair walking power in elderly postoperative patients.[78]

I.4.3.4.2 Nutritional Supplements

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommended daily protein requirements in the elderly based on their nutritional status and comorbidities. Healthy older people require at least 1.0-1.2 g protein/kg body weight per day. Malnourished older people or those at risk of malnutrition because of acute or chronic illness, the diet should provide 1.2-1.5 g protein/kg body weight per day, with even higher intake for individuals with severe illness or injury. In addition, ESPEN recommended daily physical activity or exercise (resistance training, aerobic exercise).[79]

I.4.3.4.3 Pharmacotherapy

I.4.3.4.3.1 ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors have been used as a treatment in primary and secondary prevention of cardiovascular disease. ACE inhibitors may improve muscle function through increasing IGF-I levels and improving skeletal muscle blood flow by Increasing angiogenesis. [80,81] ACE inhibitors have anti-inflammatory effects by reducing the expression of pro-inflammatory cytokine.[82] A randomized controlled trail has found that the ACE inhibitor improved exercise capacity in functionally impaired elderly people and helped maintaining

health-related quality of life. This improvement was equivalent to that reported after 6-month exercise training.[83]

Long-term use of ACE inhibitors minimizes muscle strength loss and maintain walking speed in older hypertensive people.[84] A cross-sectional study has found that ACE inhibitors users have larger lower extremity muscle mass compared with users of other antihypertensive agents.[85] Therefore, elderly may benefit from ACE inhibitors effect on skeletal muscle as this medication is commonly prescribed in older adults due to their underlying cardiovascular problems.

I.4.3.4.3.2 Vitamin D

Vitamin D seems to play an important role in bone and muscle functions and might be a therapy for sarcopenia in older adults.[86] lower levels of vitamin D increase the risk of sarcopenia in older men and women.[87] Binding of vitamin D to the vitamin D receptor in skeletal muscle enhances muscle protein synthesis and calcium uptake across the cell membrane.[88] Older age was significantly associated with decreased vitamin D receptor expression. [89] Additionally, low vitamin D levels result in type 2 muscle fibers atrophy.[87] Low levels of vitamin D were associated with proximal muscle weakness, difficultly rising from a chair, difficulties in ascending stairs, and axial balance problems in older adults.[90] Several studies demonstrate vitamin D supplementation in adults with vitamin D deficiency may increase proximal muscle strength.[91]

I.4.3.4.3.3 Creatine

Creatine is a natural ingredient of food and it is highly present in meat products. Creatine increases the ability to perform high-intensity exercise as well as enhance muscle protein synthesis, muscle mass, and strength.[92] Creatine supplementation has been shown to decrease muscle fatigue in elderly, but it has no effect on muscle strength.[93] Another study examined the effect of twelve weeks of low-dose creatine supplementation combined with resistance training and found that it increases muscle mass.[94] However, creatine supplementation should be used with caution as it may increase the risk of interstitial nephritis.[95,96]

I.4.3.4.3.4 Hormonal Therapy

I.4.3.4.3.4.1 Testosterone

Testosterone increases muscle mass and muscle protein synthesis. [97] Leg muscle strength and the fractional synthetic rate of muscle protein have been shown to be increased after administration of testosterone in elderly.[98] Other studies have found that it increases lean body mass and hand grip strength with no effect on leg strength.[99] Another study has found that testosterone supplementation did not affect functional status or cognition but increased lean body mass.[100] However, testosterone has several side effects that limit its use as a treatment for sarcopenia including sleep apnea[101] , prostate cancer[102] , fluid retention, gynecomastia, and polycythemia.[103]

I.4.3.4.3.4.2 Estrogen

Muscle performance has been shown to decrease as estrogen secretion decrease in the postmenopausal period.[104] In a cross-sectional study of 840 well-functioning community-dwelling women, there was a minor effect of estrogen replacement therapy on muscle

composition and strength.[105] However, estrogen has been considered a strong risk factor for breast cancer, therefore, it is not recommended for sarcopenia treatment.[106]

I.4.3.4.3.4.3 Growth Hormones

Decreased levels of growth hormone and insulin like growth factor-1 (IGF-1) in older adults has been reported.[107] Growth hormone releasing hormone has been found to attenuate some of the effects of aging on skeletal muscle function as it increases muscle strength.[108] In a study of elderly with low levels of IGF-1, a 6-month growth hormone regimen has been found to increase lean tissue mass and decreased fat mass without improvement in functional ability, however, side effects occurred frequently.[109] Many growth hormone replacement therapy trials in elderly have reported a high incidence of side effects, including increased fluid retention, gynecomastia, orthostatic hypotension, and carpel tunnel syndrome.[109,110] This limiting its use as a treatment for sarcopenia.

I.4.4 Obesity

Fatty tissue is a loose connective tissue made of adipocytes. Fatty tissues have four functions in human body: 1) act as a cushion to protect the internal organs, 2) insulate our body and help sustain a normal body temperature, 3) energy storage, 4) endocrinological signaling.[111] Fatty tissue releases different proinflammatory cytokines and hormones, such as interleukin 6 (IL-6), tumour necrosis factor (TNF- α).[112-115] Fatty tissues distribution is influenced by many factors including sex, age, ethnicity, genetics, diet, physical activity, medications, and hormones level. The amount of fatty tissue is higher in overweight individuals, women, and elderly.[116-122]

Fatty tissue is distributed into two main compartments: subcutaneous fatty tissue (i.e. inside the skin) and visceral fatty tissue (i.e. around the abdominal organs). Visceral obesity is also referred to as abdominal, intra-abdominal, or central obesity. The age-related shift in fatty tissue is more important than the total body fat.[25] It has been linked to many diseases including cardiovascular risks[123] , metabolic syndrome[124] , and insulin resistance.[125] Furthermore, visceral obesity has been linked to cancers such as colon[126] , breast[127] , and prostate[128] . It has been associated with poor hospitalization outcomes[129] and helps to predict chemotherapy treatment outcomes[130] in cancer patients as well.

The amount of visceral fat increases with age in normal weight and overweight individuals. The visceral/subcutaneous fat ratio in 130 subjects were evaluated by CT scan at the abdominal level (i.e. upper renal pole). The ratio was found to increase in subjects over the age of 60 years old. There was a significant direct correlation between age and visceral/subcutaneous fat ratios in females ($r = 0.65$; $p < 0.00l$) and in males ($r = 0.61$; $p < 0.001$). [131] A cross-sectional study of body fat distribution using CT scan at L4 found that visceral fatty tissue increases with advanced age, even without significant changes in the total BMI. This study also found higher concentration of triacylglycerols and cholesterol and impairment of glucose tolerance in older subjects compared with younger subjects.[132] In men and women, visceral fat was found to increase with age, while subcutaneous fat increases with the degree of obesity.[133] Men have been found to have a significantly higher percentage of visceral fat than women.[134]

Several reasons for the central shift of body fat have been reported including hormonal and fatty-acid utilization changes, physical inactivity.[135,136] A study has reported that the link between

increased visceral fat and insulin resistance is the elevated level of free fatty acids that impair peripheral glucose utilization.[137] Sedentary lifestyle in elderly has been shown to increase visceral fatty tissue which can cause insulin resistance.[138,139] There are several drugs commonly used in the elderly which are known to cause weight gain including steroids, antipsychotics, antidepressants, antileptics, and anti-hyperglycemic agents.[140]

I.4.4.1 Techniques and Tools Measuring Obesity

Numerous techniques and tools have been developed to assess body fat. BMI is the most common used technique to assess obesity. A BMI $\geq$ 25 kg/m^2 is defined as overweight, while an obese individual defined as BMI $\geq$ 30 kg/m^2.[141] However, it cannot differentiate between lean and fat body mass, and it does not appreciate the difference between visceral and subcutaneous fat compartments. Other measures used in clinical practice are waist circumference (WC), waist to hip ratio (WHR), and sagittal abdominal diameter.[111] WC reflects visceral and subcutaneous fat, while hip circumference represents subcutaneous fat only.[142] Although these tools are clinically useful, it lacks the precision that CT scan and MRI can provide. There are other tools that are used to measure adiposity will be discussed in the body composition measurement tool section.

I.4.4.2 Treatment

Several studies have found that obesity in elderly is associated with increased difficulties in performing daily physical activities. A study of elderly aged 68 to 82 years, using objective measures of physical capacity, has shown that obesity contributed to lower physical capacity in performing 'Timed Up and Go', sit-to-stand test, walking speed, and one leg stand.[143] In a study

of women aged ≥ 75 years, using self-reported questionnaire for difficulties performing physical functions, obesity was associated with difficulty in performing simple tasks such as walking, climbing stairs, going down stairs, rising from a chair or bed and these difficulties were further increased if the individual was sarcopenic.[144] In a recent prospective study in gastric cancer patients, sarcopenic obese patients have been found to have higher risk of severe post-operative complications than sarcopenic patients (OR = 6.575 vs 2.571, p = 0.032, respectively).[145] Therefore, obesity should be prevented not only at younger age, but also for older individuals, to improve health outcomes and quality of life in later years.

I.4.4.2.1 Lifestyle Intervention

Weight loss in elderly improves quality of life, physical function, and obesity related physical complications.[146] The American College of Sports Medicine and American Heart Association have recommended that at least 150 minutes per week physical activity for older adults. [75,76] The Department of Health and Human Services has published the Physical Activity Guidelines which have recommended that if older adults cannot do 150 minutes a week of moderate-intensity aerobic activity due to chronic conditions, they should be as physically active as their physical abilities and health conditions permit.[77]

I.4.4.2.2 Pharmacotherapy

Orlistat is an anti-obesity medication that inhibits the action of lipase, an enzyme the break down triglyceride into free fatty acids to be absorbed in the small intestine. Thus, the primary effect of orlistat is to prevent the absorption of dietary fat and instead excreted in the feces.[147] Orlistat prevents the absorption of approximately 32% of the ingested fat.[148] Studies have reported that

patients experienced ≥ 5% loss of their initial weight after 1-year treatment period.[149,150] Orlistat can be used for long-term with minimal side effects such as steatorrhea. There are other anti-obesity drugs that act on the central nervous system to suppress appetite and reduce food intake such as sibutramine, fluoxetine, sertraline, topiramate, fenproporex, mazindol and amfepramone, however, should be used with caution as they are associated with serious side effects (e.g. increased heart rate and blood pressure).[151]

I.4.4.2.3 Surgery

The effectiveness and safety of bariatric surgery in elderly remains controversial. There are many points should be considered when performing bariatric surgery in elderly including fitness for surgery, comorbidities, and the commitment of the patient for long-term follow up. This requires a wise clinical decision by the surgeons, patients, and their families to weigh the benefits and risks of the operation. In a study evaluated the safety and efficacy of bariatric surgery in elderly, it has found that older patients had more perioperative complications and lost less weight than younger patients.[152] However, a recent systematic review has recommended that elderly should not refuse operation because of their age, and, should be carefully counseled about the possibility of increased risks and having less satisfactory outcomes.[153]

I.4.5 Sarcopenic Obesity

In elderly, visceral fat has an important role in the increase of pro-inflammatory cytokines. Visceral fatty tissue has been found to secrete IL-6 and TNF-α.[154] Both pro-inflammatory cytokines have a catabolic effect on muscles, indicating a link between age-associated shifting of fatty tissue and sarcopenia.[154,155] In a longitudinal study, visceral obesity was independently associated with the future loss of skeletal muscle mass after adjusting for confounding factors.[156]

A vicious circle may exist between obesity and sarcopenia since they have a reciprocal cause and effect on each other, leading to a worsening of the condition.[157] Sarcopenia reduces physical activity, which leads to decreased energy expenditure and increases the risk of obesity.[158] In contrast, an increase in visceral fat increases the inflammatory cytokines, which contributes to the development of sarcopenia.[159] A recent call for action aimed at increasing awareness on sarcopenic obesity among researchers and clinicians to reach an evidence-based consensus on definition, diagnostic criteria, diagnostic tools, and an optimal treatment. This will potentially help to reduce the burden of morbidity and mortality in the increasing elderly population across all medical specialties.[160] (Figure 3) illustrates the common underlying mechanism of sarcopenia and obesity and their common adverse health consequences.

I.4.6 Body Composition Measurement Tools

Several methods have been developed to assess body composition. There are indirect measures of body composition, which provide less accurate measurements, such as anthropometric techniques, BMI, bioelectrical impedance analysis, dual-energy X-ray absorptiometry (DXA), air displacement plethysmography (ADP) and ultrasound. The gold standard techniques to measure

body composition are CT scan and Magnetic Resonant Imaging (MRI), which can provide accurate and quantitative information of body composition.[111] Although MRI scan provides better assessment and with no risk of radiation, it is expensive and less available than CT scan. Table 15. summarizes the methods of body composition measurements.

I.4.6.1 Anthropometric Techniques

BMI is the most common used technique to assess obesity. A BMI ≥ 25 kg/m^2 is defined as overweight, while an obese individual defined as BMI ≥ 30 kg/m^2. For Asian populations, BMI ≥ 23 kg/m^2 is define as overweight, while an obese individual defined as BMI ≥ 30 kg/m^2. This due to the fact that Asian populations have different associations between BMI, percentage of body fat, and health risks than do European populations.[141] However, BMI cannot differentiate between lean and fat body mass, and it does not appreciate the difference between visceral and subcutaneous fat compartments. Other measures used in clinical practice are waist circumference (WC), waist to hip ratio (WHR), and sagittal abdominal diameter.[111] Although these techniques are the simplest, the most rapid, cheap, and most accessible, they do not provide a precise and quantitative assessment of body composition. Furthermore, they lack the ability to distinguish between different fatty tissue compartments.

I.4.6.2 Bioelectrical Impedance Analysis (BIA)

BIA is a cheap, safe, and accessible body composition measurement tool with no risk of radiation exposure. The mechanism of BIA for measuring body composition is based on the fact that tissues rich in water and electrolytes are less resistant to the passage of an electrical current than lipid-rich adipose tissue. Therefore, an individual with less fatty tissue would have

minimum impedance, and impedance would increase to a maximum when all lean tissue was replaced by lipid-filled adipose tissue. Then, impedance values are converted into values specific for total body water or extracellular fluid and then, into fat-free mass by means of equations that are population specific. Once fat-free mass is known, total body fat is calculated as the difference between body weight and fat-free mass.[161]

A study has shown that visceral fatty tissue obtained using abdominal BIA were highly correlated with visceral fatty tissue measured using abdominal CT ($r = 0.88$, $p < 0.0001$).[162] However, lean tissue measurements are influenced by conditions associated with fluid retention (e.g. chronic obstructive pulmonary disease, heart failure, ascites) which is often a problem in clinical populations.[163] As a result, this would make measurements by BIA not accurate.[111]

I.4.6.3 Dual energy X-ray Absorptiometry (DXA)

DXA provides rapid and low-cost assessment of body composition and has little radiation exposure. DXA considered a precise assessment tool compared to anthropometric techniques. The principle of using DXA is based on measuring the attenuation of two energies emitted from DXA distinguish fat, lean, and bone. However, it cannot differentiate between different fatty tissue deposit.[111] Furthermore, fatty tissue is less dense and bone tissue is the densest, pixels containing both can be identified as a lean tissue and affect the estimation of fatty tissue.[111,164]

I.4.6.4 Air Displacement Plethysmography (ADP)

ADP is another rapid, non-invasive tool used to measure body composition. The principle of using this tool is based on the relationship between pressure and volume to calculate the body volume of a subject seated inside a fiberglass chamber. Derivation of body volume, together with measurement of body mass, allows calculation of body density and subsequent estimation of percent fat and fat-free mass.[165] However, this tool has many limitations that underestimate the measurements including proper control of temperature and moisture, and, requires the patient to perform a complex breathing maneuver.[111]

I.4.6.5 Ultrasound

Ultrasound is a cheap, non-invasive technique to measure muscle mass, visceral and subcutaneous fatty tissue. Ultrasound can provide quantitative measurements of muscle mass by measuring muscle thickness, and, qualitative measurements of muscle such as the presence of fatty infiltration and fibrous tissue.[166] Visceral fat is measured as the space in centimeter between the internal (deep) fascia of the rectus abdominis muscle and the anterior wall of the aorta, determined during expiration. Subcutaneous fat is the space between the skin and the external (superficial) fascia of the rectus abdominis muscle.[167] However, ultrasound scanning has poor reproducibility and accuracy.[167] Additionally, ultrasound measurements are examiner-dependent and subjective. For example, ultrasound transducer orientation relative to the body surface[168] , or the inward compressive pressure applied by the operator on the tissue, can create errors that affect test's reproducibility.[169]

I.4.6.6 Computed Tomography (CT)

Currently, CT scan is considered the tool of choice for the quantitative assessment of soft tissues. The principle of using CT as body composition measurements tool is based on the use of X-ray beam, produced from a rotating source that passes through the patient. A series of detectors are used to monitor the X-ray exit transmission intensity. The latter results in the visual production of cross-sectional slices about 10 mm thick. The exit transmission is then used to calculate the average attenuation coefficient along the length of the X-ray beam.[161] Hounsfield units (HU) are used to report attenuation coefficients. Specific ranges of Hounsfield units (HU) are used to differentiate between different tissues. Water has a radiodensity of 0 HU, while air is -1000 HU, and bone is +1000 HU.[170] The radiodensity range of skeletal muscle is - 29 to + 150 HU[171] , visceral fat -150 to - 50 HU[172], and subcutaneous and intramuscular fat -190 to -30 HU [171]. The Hounsfield unit measure has been found to be reproducible within 1% and corresponds with approximately 1 Hounsfield unit change per 1% increase in lipid concentration.[173,174] The reported error for CT in the assessment of skeletal muscle compared to cadaveric studies was 1.3%.[175]

Images produced by CT scan can be presented as a single-slice or multi-slice. Several advantages of using single-slice has been reported. Firstly, cross-sectional image body composition analysis is the only technique that can reliably measure muscle and fat distribution in the trunk and can differentiate between the intra-abdominal organs, fatty tissue and muscle. Secondly, single-slice abdominal image can provide highly repeatable measures of adiposity and muscularity. Visceral fatty tissue is sensitive to slice selection and appears to be most robust at the L4–5 level. Skeletal muscle is ideally measured approximately 5–10 cm above L4–5 and the L3 vertebra is a

commonly used landmark. Finally, a cross-sectional area can be used as a derived measure of total body composition to compare mean values among larger populations.[176] Body composition measured by CT scan using cross-sectional area in a single slice at lumbar vertebra L3 has been found to be correlated with the whole-body volume.[177] Additionally, it is used to diagnose many medical and surgical diseases, therefore, it can be used without radiation re-exposure for research purpose.

Many potential practical limitations should be considered when using a single-slice abdominal image including errors in patient positioning (e.g. redundant skin folds), technical errors, presence of artifact that distort the image (e.g. metals or patient movement), slice selection and image interpretation (e.g. identification of specific muscles, peritoneum which may be incorrectly marked, and intestinal contents which may be incorrectly identified as anatomical fatty tissue[178]).[176]

I.4.6.7 Magnetic Resonance Imaging (MRI)

MRI is another gold standard tool to assess body composition as it can differentiate between muscle and fatty tissue. MRI measurements accuracy is obtained by using multi-slice techniques. MRI measurements of abdominal adipose tissue mass was shown to have an error less than 3% when compared to data obtained by direct weighing of adipose tissue after dissection from human cadavers.[179] MRI is associated with an error in quantifying quadriceps muscle that ranges between 1% and 4%.[180] MRI has a higher reproducibility because of the constant values that identify muscles and fatty tissue.[161] Finally, in contrast to CT and DXA, MRI does not expose

the patient to ionizing radiation, but, its high cost and complexity, and availability issues limit its use in research.[181]

I.4.7 Body Composition and Surgery

Body composition measures have demonstrated a significant association with surgical outcomes. Sarcopenia has been correlated with perioperative outcomes.[182] Sarcopenic obesity, which is defined as a combination of sarcopenia and obesity, has predicted short and long-term outcomes after gastrointestinal cancer surgery.[183] Previous studies, notably Cakir and colleagues[184] evaluated the relationship of visceral obesity to clinical outcomes after colorectal surgery. They concluded that visceral obesity identified by CT was associated with a longer hospital stay, higher morbidity and longer operative time after elective colon surgery. A study has shown that visceral obesity and reduced skeletal muscle mass resulted in poorer short-term recovery, oncological outcomes, and survival in a colorectal cancer population.[129] A systematic review and meta-analysis reviewed studies assessing the association of body composition with clinical outcomes in renal cell cancer and has found that skeletal muscle index and radiodensity are strongly associated with overall mortality.[185] Another study examined patients underwent laparoscopic colorectal surgery has demonstrated that visceral obesity is associated with increased surgical difficulty and post-operative morbidity.[186]

Several studies have examined the role of body composition measurements by CT scan in predicting perioperative outcomes.[187-189] Stidham et al.[187] , studied the relationship of body fat composition with postoperative infectious complications after bowel resection in Crohn's disease. To control for variations in body size, fat measurements have been obtained in two

different spinal levels T10 (i.e. the most cephalad level of the abdominal field) and L5(i.e. the most caudal). Subcutaneous fat to visceral fat ratio at T10 was divided by the subcutaneous/ visceral fat ratio at L5. Subcutaneous/ visceral fat ratio (OR: 2.01; 95% CI, 1.20 –3.19; P: 0.006) was identified as predictor of infectious complication. Roberts et al.[188] , examined the predictive ability of visceral fat at the umbilical level for postoperative pancreatic fistula (POPF) after pancreatoduodenectomy. Total abdominal fat area (AUROC: 0.692, p: 0.004), visceral fat area (AUROC: 0.678, p: 0.007), and superficial fat area (AUROC: 0.659, p: 0.017) were significantly associated with the development of POPF. Ninomiya et al.[189] , retrospectively examined sarcopenia and visceral obesity effect on perioperative outcomes in patients who underwent curative surgery for pancreatic ductal adenocarcinoma. CT scan images were obtained at L3. Sarcopenia were defined using Prado et al.[190] definition which is a sex-specific cut-off value of muscle surfaces area at L3 normalized to the height (52.4 cm^2/m^2 for men and 38.5 cm^2/m^2 for women) in adults with respiratory or gastrointestinal cancer populations. Visceral obesity were defined using values that are associated with metabolic abnormalities in Japan as VFA > 103 cm^2 for men and VFA > 69 cm^2 for women.[191] Patients with high visceral obesity had longer operation time (p: 0.006), higher amount of blood loss (p: 0.006), and higher number of postoperative complications (≥ Clavien-Dindo II) (p: <0.001) compared to low visceral obesity group. There was no significant difference between sarcopenic and none-sarcopenic patients in the length of operation time, blood loss, and postoperative complication.

In a pooled analysis of 2100 patients underwent elective surgery for colorectal cancer, body composition evaluated in relation to length of hospital stay (LOS) and postoperative outcomes.[192] The risk of readmission was associated with visceral obesity alone (OR, 2.66; 95% CI 1.18-6.00;

P = 0.018), visceral obesity combined with myosteatosis (OR, 2.72; 95% CI 1.36-5.46; P = 0.005), or visceral obesity combined with myosteatosis and sarcopenia (OR, 2.98; 95% CI 1.06-5.46; P = 0.038). A prospective study of patients with head of pancreas cancer reported that Low muscle radiation attenuation was associated with shorter survival in comparison with moderate and high muscle radiation attenuation [median survival 10.8 (95% CI: 8.8–12.8) vs. 17.4 (95% CI: 14.7–20.1), and 18.5 (95% CI: 9.2–27.8) months, respectively; P < 0.008]. [193] Additionally, high visceral adipose tissue was associated with an increased surgical site infection rate, OR: 2.4 (95% CI: 1.1–5.3; P = 0.027). A retrospective study of patients underwent liver transplantation showed that low SMI (hazard ratio [HR], 2.367, P = 0.002), high intramuscular adipose tissue content (HR, 2.096, P = 0.004), and high visceral to subcutaneous adipose tissue area ratio (HR, 2.213, P = 0.003) were identified as independent risk factors for death after living donor liver transplantation.[194]

There are three studies which have assessed the role of skeletal muscles and fatty tissues in perioperative outcomes in elderly. Underwood et al. [195] have found that subcutaneous fat measured at the L2/L3 disc space and adjusted to the patient height was associated with worse survival within the first year in liver transplantation geriatric patients. Fuminori[196] has noted that visceral fat was correlated with poor surgical outcomes after elective colorectal surgery in elderly patients. Du et al.[197] have found a strong association of sarcopenia with in-hospital mortality, higher complication rates, and institutionalization after acute abdominal surgery in elderly people older than 80 years.

I.5 Hypothesis

To our knowledge, we are the first to assess the association of body composition measurements (i.e. quantity and radiodensity of skeletal muscle, visceral fat, and subcutaneous fat) with postoperative outcomes after acute abdominal surgery in elderly. Therefore, the following research question, hypothesis, and objective were produced:

Research question: Can CT- identified body composition measurements predict in-hospital mortality and postoperative complications after acute abdominal surgery in the elderly?

Research hypothesis: We hypothesized that the quantity of skeletal muscles, visceral fat, subcutaneous fat, and their radiodensities are associated with in-hospital mortality and postoperative complications after acute abdominal surgery in the elderly.

Objective: To examine the relationship of body composition measurements identified by abdominal CT scan with in-hospital mortality and postoperative complications in the older adults underwent acute abdominal surgery.

II. CHAPTER TWO: METHODS

This study was approved by the Health Research Ethics Board at the University of Alberta (Pro00019426).

II.1 Patients Selection Criteria

A retrospective review was performed to identify patients ≥ 65 years who underwent an acute abdominal surgery at the University of Alberta between 2008 and 2010. Only patients who were ≥ 65 years old, underwent an acute abdominal surgery, and had abdominal CT scan performed within 30 days of the surgery were included. Patients underwent elective abdominal surgery, non-abdominal emergent surgery, incomplete clinical data, did not perform abdominal CT scan/ poor quality images, or aged < 65 were excluded.

II.2 Clinical Data

Chart review of patients' clinical data was performed and included: sex, age, weight, height, date of admission/discharge, diagnosis, date of operation, type of procedure, comorbidities, discharge disposition, postoperative complications, medications, and ASA scores. Postoperative complications were graded using the Clavien-Dindo Classification (CDC) of surgical complications.[198] Complications graded ≤ Grade II (requiring ± pharmacological treatment) were defined as minor complications, whereas complications graded Grade III- V (requiring surgical/ endoscopic/ radiological intervention, organ dysfunction, or death) were defined as major complications. The Charlson Comorbidity Index (CCI), a valid mortality prognostic tool, was used as an indicator of comorbidity burden.[199]

II.3 Body Composition Analysis

Two trained independent researchers analyzed CT scan images in anonymized format and were blinded to patients' outcomes. SliceOmatic software V4.3 (TomoVision, Montreal, Quebec, Canada) was used to analyze CT scan images and quantify different tissue types using predetermined Hounsfield Unit (HU) thresholds. Tissues HU range for skeletal muscle was - 29 to + 150 HU[171] , visceral fat -150 to - 50 HU[172], and subcutaneous and intramuscular fat -190 to - 30 HU[171]. Cross-sectional area at the level of L3 was quantified for skeletal muscle area [SMA (cm^2)], visceral fat area [VFA (cm^2)], subcutaneous fat area [SFA(cm^2)], and total abdominal fat area [tAFA (cm^2)], which is the sum of VFA and SFA. To provide better estimate of all body composition tissues, all measurements were adjusted for patient's height in square meters and presented as skeletal muscle index [SMI(cm^2/m^2)], visceral fat index [VFI (cm^2/m^2)], subcutaneous fat index [SFI (cm^2/m^2)], and total abdominal fat index [tAFI (cm^2/m^2)].[177] SMA HU, VFA HU, SFA HU were measured. Abdominal muscles included in the analysis were the internal and external obliques*, transversus abdominus, rectus abdominus*, *psoas major* and minor, *quadratus lumborum*, and *erector spinae* muscles. Intramuscular adipose tissue or "myosteatosis" was defined as the average HU of skeletal muscle at L3.

II.4 Body Composition Definitions

Visceral obesity was defined as VFA > 130 cm^2 for men and women. This cut-off value has been found to be associated with increased risk of diabetes and higher risk of cardiovascular disease in young adults. [200] Sarcopenia was defined according to Martin's definition, BMI specific cut-points, as at L3 underweight or normal weight SMI < 43 cm^2/m^2 for males; SMI <

41 cm^2/m^2 for females. Overweight or obese SMI < 53 cm^2/m^2 for males; SMI < 41 cm^2/m^2 for females. Those thresholds have been inferred from adult patients with diagnosis of gastrointestinal or respiratory tract cancer. [201] Sarcopenic obesity was defined as Martin's definition for sarcopenia and BMI ≥ 30.

II.5 Outcomes

The primary outcome was the association of in-hospital mortality with body composition measurements. The secondary outcomes were the association of postoperative complications (major vs minor and no complications), ICU admission, and LOS with body composition measurements by CT scan.

II.6 Study Size

Yang et al. [197] have found in-hospital mortality of 23% after acute abdominal surgery in elderly sarcopenic patients. In addition, Rangel et al., reported 30-day mortality of 23% and 1-year mortality of 32% in older sarcopenic patients who underwent emergency abdominal surgery.[202] Therefore, we anticipated that in-hospital mortality of 23% for the primary outcome with a margin of error of 10 and using a 0.05 level of significance and CI of 95%. Accordingly, a minimum number of 69 patients were required.

II.7 Missing Data

In the event of missing values, data were estimated using imputation method. There were four cases with missing height, three cases with hemi-scan (i.e. half cross-section), and one case with missing ASA score. For the height, the mean height of the cohort of the same sex was used to

estimate cases with missing height. Regarding the three cases with hemi-scan, measurements were multiplied by 2. For ASA score, the mean ASA score of the cohort was used to estimate the missing ASA score.

II.8 Statistical Analysis

Statistical analysis was performed using IBM SPSS version 19 (2010; SPSS Institute, Chicago, IL). Data were analyzed via the use of descriptive statistics to characterize demographics and other clinical variables. Categorical variables were compared by the χ^2 test or Fisher exact test (< 5 observations). For continuous variables, normally distributed variables were reported as means with standard deviations (SD) and compared by the Student *t* test. Non-normally distributed continuous data were reported as medians with interquartile ranges (IQR) and compared by Wilcoxon rank sum test. In-hospital mortality was defined as the dichotomous outcome. A multivariable logistic regression analysis was performed. Variables that may confound the effect of body composition on in-hospital mortality were controlled for. Given the common numerical values between fatty tissues measurements and radiodensities (i.e. VFA HU and SFA HU, and, VFI and SFI), it was important to test for collinearity to avoid overfitting the model. Collinearity was tested between SMI and SFA HU and showed minimal correlation between them (i.e. not collinear). This means they are expressing different information statistically and not overfitting the model. The prespecified prognostic variables included age, sex, ASA score, SFA radiodensity, and SMI. Model performance was assessed using the c-statistic (plotted as area under receiver operator curve [AUROC]) and the Hosmer-Lemeshow test for goodness of fit. Multivariate associations are reported as odds ratios (OR) with 95% confidence interval.

III. CHAPTER THREE: RESULTS

III.1 Population Clinical Characteristics

Between January 2008 and December 2010, 242 patients aged ≥ 65 years underwent emergency surgery at the University of Alberta. A total of 215 patients were included as they met the inclusion criteria. Selection of study patients flow diagram illustrated in (Figure 1) The baseline clinical characteristics and perioperative outcomes of the study population are summarized in (Table 1). The number of men was 109 with a mean age of 77 ± 7. There was no significant difference in BMI between men and women (27 ± 6, 26 ± 6, respectively). The mean ASA score was 3 ± 1 with no significant difference between men and women. The mean CCI was 5 ± 2 with no significant difference between men and women.

The median LOS in the hospital was 13 days (8-24) with a significant difference between men and women (16 (8-30), 12 (7-18), p value: 0.01, respectively). The most frequent diagnosis in descending order was large bowel diseases (21.9%), small bowel diseases (20%), colorectal neoplasm (17.2%), Other (acute pancreatitis, stomach neoplasm, etc.) (10.2%), appendicitis (9.3%), abdominal wall hernia (8.8%), gallbladder & biliary tree disease (6.5%), and peptic ulcer disease (6%). The most common operation was large bowel surgery (27.9%) followed by laparotomy (27.4%), and the least common was lysis of adhesion (1.4%). Thirty-one percent (31.2%) of patients transferred to intensive care unit (ICU) after surgery.

The majority of patients have gone to the operation room from the ward (60.3%), emergency department (22.9%), ICU (13.1%), observation unit (2.3%), and transferred from another

hospital (1.4%). Most of the patients transferred to the ward after the operation (68.4%), ICU (31.2%), while one patient (0.5%) died in the operation room. The majority of patients discharged home without services 30.7% while 19.5% required services. The percentage of patients transferred to another hospital 26.5%, required assisted care 4.2%, rehabilitation 2.8%, whereas in-hospital mortality was 16.3%.

Figure 1: Selection of study patients.

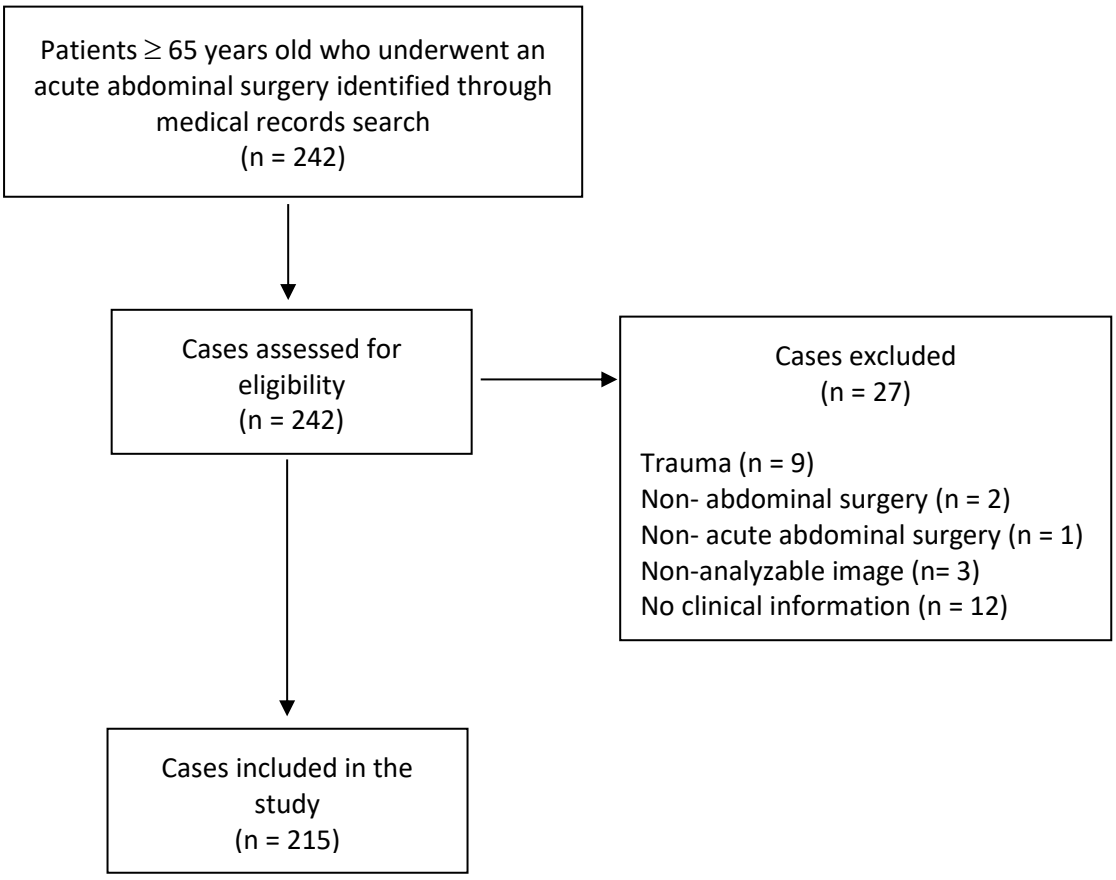

Table 1: Population general characteristics.

	All patients *n= 215* *Mean (SD)*	*Women* *n= 106* *Mean (SD)*	*Men* *n= 109* *Mean (SD)*	*p- value*
Age	77.3 (7.3)	77.9 (7.4)	76.7 (7.2)	0.228
BMI	26.3 (5.8)	25.9 (5.6)	26.8 (6)	0.242
ASA	3.2 (0.8)	3.2 (0.8)	3.1 (0.7)	0.458
CCI	5.4 (2.2)	5.4 (2.3)	5.3 (2.1)	0.663
*LOS***	13 (8-24)	12 (7-18)	16 (8-30)	0.010*
Diagnosis				0.093
Appendicitis	20 (9.3%)	8	12	
Gallbladder & biliary tree disease	14 (6.5%)	5	9	
Small bowel disease	43 (20%)	27	16	
Large bowel disease	47 (21.9%)	27	20	
Colorectal neoplasm	37 (17.2%)	14	23	
Abdominal wall hernia	19 (8.8%)	12	7	
Peptic ulcer disease	13 (6%)	6	7	
*Other****	22 (10.2%)	7	15	
Type of surgery				0.839
Abdominal wall repair	7 (3.3%)	3	4	
Appendectomy	15 (7%)	6	9	
Cholecystectomy	15 (7%)	5	10	
Laparotomy	59 (27.4%)	30	29	

Small bowel	29 (13.5%)	17	12	
Large bowel	60 (27.9%)	31	29	
Lysis of adhesion	3 (1.4%)	2	1	
Control of hemorrhage and suture of ulcer	8 (3.7%)	3	5	
*Other****	19 (8.8%)	9	10	
Preoperative Location				0.332
Floor bed	129 (60.3%)	62	67	
Emergency department	49 (22.9%)	29	20	
Intensive care unit	28 (13.1%)	10	18	
Transferred from another hospital	3 (1.4%)	1	2	
Observation unit	5 (2.3%)	3	2	
Postoperative Disposition				0.512
Floor bed	147 (68.4%)	74 (69.8%)	73 (67%)	
Intensive care unit	67 (31.2%)	31 (29.2%)	36 (33%)	
Died	1 (0.5%)	1 (0.9%)	0	
Discharge Disposition				0.941
Home without services	66 (30.7%)	32	34	
Home with services	42 (19.5%)	23	19	
Rehabilitation	6 (2.8%)	3	3	
Assisted care	9 (4.2%)	4	5	
Transferred to another hospital	57 (26.5%)	29	28	
Died	35 (16.3%)	15	20	

Abbreviations: Body Mass Index, ASA: American Society of Anesthesiologists, CCI: Charlson Comorbidity Index, LOS: Length of Stay

* p-value < 0.05

** Medians with interquartile ranges (IQR) and compared by Wilcoxon rank sum test.

*** Bleeding, neoplasm oropharyngeal ca, other neoplasm, stomach neoplasm, soft tissue infection or abscess, cellulitis/abscess, acute pancreatitis, abdominal pain/colic, shock, rectal or anal abscess, wound dehiscence, benign neoplasm - skin, soft tissue neoplasm, malignant neoplasms - Hodgkin's, abdominal/pelvic mass

**** General surgery procedure, abdominal wall debridement, drainage intra-abdominal abscess, gastrostomy tube placement, and examination under anesthesia.

Table 2: Population' co-morbidities.

Co-morbidities	*All patients* *n= 215* *n (%)*	*Women* *n= 106* *n*	*Men* *n= 109* *n*	*p- value*
Cancer	62 (28.8%)	30	32	0.881
Diabetes mellitus	57 (26.5%)	27	30	0.759
Chronic pulmonary disease	51 (23.7%)	23	28	0.524
Chronic kidney disease	33 (15.3%)	15	18	0.707
Congestive heart failure	26 (12.1%)	14	12	0.622
Myocardial infarction	24 (11.2%)	7	17	0.050
Cerebrovascular disease	19 (8.8%)	12	7	0.236
Peptic ulcer disease	15 (7%)	5	10	0.285
Peripheral vascular disease	10 (4.7%)	4	6	0.748
Dementia	9 (4.2%)	3	6	0.499
Mild liver disease	9 (4.2%)	5	4	0.746
Connective tissue disease	8 (3.7%)	6	2	0.167
Metastatic solid tumor	4 (1.9%)	4	0	0.570
Hemiplegia	1 (0.5%)	1	0	0.493
Diabetes with organ damage	1 (0.5%)	0	1	1.000
Leukemia	1 (0.5%)	1	0	0.493
Lymphoma	1 (0.5%)	1	0	0.493
Mod-Severe liver disease	1 (0.5%)	0	1	1.000
AIDS	0	0	0	

Table 3: Population' postoperative complications.

Post-op complications	*All patients n= 215 n (%)*	*Women n= 106 n*	*Men n= 109 n*	*p- value*
CDC Grade 1				
Delirium	16 (7.4%)	5	11	0.193
Decubitus Ulcer	1 (0.5%)	1	0	0.493
Surgical site infection	9 (4.2%)	0	9	0.003
Other	5 (2.3%)	1	4	0.369
CDC Grade 2				
Cardia Arrhythmia	14 (6.5%)	4	10	0.166
Aspiration Pneumonia	15 (7%)	4	11	0.106
Urinary tract infection	9 (4.2%)	6	3	0.328
Acute kidney injury	9 (4.2%)	3	6	0.499
Deep venous thrombosis / Pulmonary embolism	4 (1.9%)	1	3	0.622
Myocardial infarction	15 (7%)	6	9	0.594
Peptic ulcer disease	2 (0.9%)	0	2	0.498
Other	10 (4.7%)	4	6	0.748
CDC Grade 3a				
Surgical site infection	8 (3.7%)	3	5	0.722
Intraabdominal Abscess	13 (6%)	3	10	0.083
Other	1 (0.5%)	1	0	0.493
CDC Grade 3b				
Anastomotic Leak/fistula	9 (4.2%)	2	7	0.171
Abdominal Compartment Syndrome	1 (0.5%)	1	0	0.493
Bleeding	8 (3.7%)	4	4	1.000
Surgical site infection	2 (0.9%)	1	1	1.000
Wound Disruption	8 (3.7%)	1	7	0.065
Other	4 (1.9%)	0	4	0.122
CDC Grade 4 a + b				
Cardiac Arrest	10 (4.7%)	3	7	0.333
Systemic Sepsis	23 (10.7%)	9	14	0.379
Respiratory Failure	19 (8.8%)	8	11	0.633
Shock	5 (2.3%)	3	2	0.680
CDC Grade 5				
Death	35(16.3%)	15(14.2%)	20(18.3%)	0.462

III.2 Body Composition Measurements

Patients' CT scan body composition measurements are described in (Table 4). The SMA HU was significantly higher in men compared to women (22.2 (9.9) HU, 18.7 (9.8) HU, p-value= 0.010, respectively). There was no significant difference in VFA HU between men and women. The SFA HU was significantly higher in men compared to women (-85.2(13.9) HU, -91(14.2) HU, p-value= 0.002, respectively). SMI was significantly higher in men compared to women (42.2(8.8), 35.2(5.9), p-value= <0.001, respectively). VFI was significantly higher in men than in women (66.2(42.4) cm^2/m^2, 44(30.3) cm^2/m^2, p-value= <0.001, respectively). However, SFI was significantly higher in women than in men (87.2(47.4) cm^2/m^2, 57.4(35.8) cm^2/m^2, p-value= <0.001, respectively). There was no significant difference in the tAFI between men and women (131.2(73.1) cm^2/m^2, 123.5(69.9) cm^2/m^2, p-value= 0.434, respectively). VFA/SFA was significantly higher in men compared to women (1(0.7-1.57), 0.5(0.31-0.68), p-value= <0.001, respectively). VFA/SMA was significantly higher in men than in women (1.6(1), 1.3(0.9), p-value= 0.028, respectively).

Table 4: Body composition profile by sex.

	All patients	*Women*	*Men*	
	N= 215	*N=106*	*N=109*	*p-value*
	Mean (SD)	*Mean (SD)*	*Mean (SD)*	
Radiodensity				
SMA (HU)	20.5 (10.0)	18.7 (9.8)	22.2 (9.9)	0.010
VFA (HU)	-85.1 (10.5)	-84 (10.3)	-86.3 (10.7)	0.114
SFA (HU)	-88.1 (14.3)	-91 (14.2)	-85.2 (13.9)	0.002
Indexed surface area				
SMI (cm²/m²)	38.8 (8.3)	35.2 (5.9)	42.2 (8.8)	< 0.001
VFI (cm²/m²)	55.3 (38.5)	44 (30.3)	66.2 (42.4)	< 0.001
SFI (cm²/m²)	72.1 (44.4)	87.2 (47.4)	57.4 (35.8)	< 0.001
tAFI (cm²/m²)	127 (71)	131.2 (73.1)	123.5 (69.9)	0.434
Ratios				
VFA/SFA[*]	0.68 (0.39-1.06)	0.5 (0.31-0.68)	1 (0.7-1.57)	< 0.001
VFA/SMA	1.44 (0.99)	1.3 (0.9)	1.6 (1)	0.028

Abbreviations: SMI, Skeletal Muscle Index; SFI, Subcutaneous Fat Index; VFI, Visceral Fat Index; tAFI, total Abdominal Fat Index; SMA, Skeletal muscle area; VFA, Visceral fat area; SFA, Subcutaneous fat area.

*Medians with interquartile ranges (IQR) and compared by Wilcoxon rank sum test.

III.2.1 Sarcopenia

Patients' clinical characteristics by sarcopenia are described in (Table 5). The number of sarcopenic patients was 175 (81.4%) and non-sarcopenic 40 (18.6%). The mean age of sarcopenic patients was significantly higher compared to non-sarcopenic patients (77.9(7.4) years, 74.4(6.4) years, p-value= 0.006, respectively). There were no significant differences between sarcopenic and non-sarcopenic men and women (p-value= 0.222). The mean BMI for sarcopenic patients was less than non-sarcopenic patients, but, it was not significant (25.8(4.7), 28.5(8.9), p-value= 0.071, respectively). There was no significant difference in ASA score between sarcopenic patients 3.2(0.8) and non-sarcopenic patients 3.2(0.8) (p-value= 0.946). There was a significant difference in CCI between sarcopenic patients and non-sarcopenic patients (5.6(2.2), 4.3(1.9), p-value= <0.001, respectively).

Table 5: Patients' clinical characteristics by sarcopenia.

	Sarcopenia		*P-value*
	Yes (n= 175) Mean (SD)	*No (n= 40) Mean (SD)*	
Age	77.9(7.4)	74.4(6.4)	0.006
Sex			0.222
Female	90 (51.4%)	16 (40%)	
Male	85 (48.6%)	24 (60%)	
BMI	25.8(4.7)	28.5(8.9)	0.071
ASA	3.2(0.8)	3.2(0.8)	0.946
CCI	5.6(2.2)	4.3(1.9)	< 0.001

III.2.2 Visceral Obesity

Patients' clinical characteristics by visceral obesity are described in (Table 6). The number of viscerally obese patients was 115 (53.5%) and non-viscerally obese was 100 (46.5%). The mean age of viscerally obese patients was significantly lower compared to none viscerally obese patients (76(7), 78.7(7.4), p-value= 0.007, respectively). There were significant differences between viscerally obese and none viscerally obese men and women (p-value <0.001). The mean BMI for viscerally obese patients was significantly higher than none viscerally obese patients (29.1(5.9), 23.1(3.7), p-value <0.001, respectively). There was no significant difference in ASA score between viscerally obese patients 3.2(0.8) and none viscerally obese patients 3.1(0.8) (p-value= 0.315). There was no significant difference in CCI between viscerally obese patients and none viscerally obese patients (5.3(2.2), 5.5(2.1), p-value= 0.568, respectively).

Table 6: Patients' clinical characteristics by visceral obesity.

	Visceral obesity		*P-value*
	Yes (n= 115) Mean (SD)	*No (n= 100) Mean (SD)*	
Age	76(7)	78.7(7.4)	0.007
Sex			< 0.001
Female	40 (34.8%)	66 (66%)	
Male	75 (65.2%)	34 (34 %)	
BMI	29.1(5.9)	23.1(3.7)	< 0.001
ASA	3.2(0.8)	3.1(0.8)	0.315
CCI	5.3(2.2)	5.5(2.1)	0.568

III.2.3 Sarcopenic Obesity

Patients' clinical characteristics by sarcopenic obesity are described in (Table 7). The number of sarcopenic obese patients was 30 (14%) and non-sarcopenic obese was 185 (86%). The mean age of sarcopenic obese patients was significantly lower compared to non-sarcopenic obese patients (74(6.4), 77.8(7.3), p-value= 0.008, respectively). There were no significant differences between men and women (p-value= 0.845). The mean BMI for sarcopenic obese patients was significantly higher than non-sarcopenic obese patients (33.2(2.5), 25.2(5.4), p-value= <0.001, respectively). There was a significant difference in ASA score between sarcopenic obese patients and non-sarcopenic obese patients (3.4(0.7), 3.1(0.8), p-value= 0.044, respectively). There was no significant difference in CCI between sarcopenic obese patients and non-sarcopenic obese patients (5.5(2.5), 5.3(2.2), p-value= 0.771, respectively).

Table 7: Patients' clinical characteristics by sarcopenic obesity.

	Sarcopenic obesity		*P-value*
	Yes (n= 30) Mean (SD)	*No (n= 185) Mean (SD)*	
Age	74(6.4)	77.8(7.3)	0.008
Sex			0.845
Female	14 (46.7%)	92 (49.7%)	
Male	16 (53.3%)	93 (50.3%)	
BMI	33.2(2.5)	25.2(5.4)	< 0.001
ASA	3.4(0.7)	3.1(0.8)	0.044
CCI	5.5(2.5)	5.3(2.2)	0.771

Table 8: Pearson correlation between BMI and body composition measurements.

	BMI	*SMA (HU)*	*VFA (HU)*	*SFA (HU)*	*SMI (cm²/m²)*	*VFI (cm²/m²)*	*SFI (cm²/m²)*	*tAFI (cm²/m²)*
BMI	1	-.334**	-.579**	-.445**	.302**	.708**	.742**	.843**
SMA (HU)	-.334**	1	.268**	.069	.360**	-.367**	-.460**	-.484**
VFA (HU)	-.579**	.268**	1	.698**	-.145*	-.779**	-.548**	-.761**
SFA (HU)	-.445**	.069	.698**	1	-.092	-.414**	-.608**	-.601**
SMI (cm²/m²)	.302**	.360**	-.145*	-.092	1	.284**	-.065	.112
VFI (cm²/m²)	.708**	-.367**	-.779**	-.414**	.284**	1	.481**	.838**
SFI (cm²/m²)	.742**	-.460**	-.548**	-.608**	-.065	.481**	1	.881**
tAFI (cm²/m²)	.843**	-.484**	-.761**	-.601**	.112	.838**	.881**	1

* p-value < 0.05

** p-value < 0.001

Table 9: Clavien-Dindo Classification of surgical complications.

	All patients (n= 215)	*Women (n= 106)*	*Men (n= 109)*	*p- value*
Total complications	98 (45.6%)	39 (36.8%)	59 (54.1%)	0.014
Minor complications				0.167
Grade 1	10 (4.7%)	2 (1.9%)	8 (7.3%)	
Grade 2	21 (9.8%)	10 (9.4%)	11(10.1%)	
Major complications				
Grade 3a	5 (2.3%)	2 (1.9%)	3 (2.8%)	
Grade 3b	10 (4.7%)	3 (2.8%)	7 (6.4%)	
Grade 4a+b	17 (7.9%)	7 (6.6%)	10 (9.2%)	
Grade 5	35 (16.3%)	15 (14.2%)	20 (18.3%)	

Table 10: Body composition profile and the main outcomes following acute abdominal surgery.

	Sarcopenia		*P-value*	*Visceral obesity*		*P-value*	*Sarcopenic obesity*		*P-value*
	Yes n= 175	No n= 40		Yes n= 115	No n= 100		Yes n= 30	No n= 185	
Complications *Yes*	80 (45.7%)	18 (45%)	1.000	61(53%)	37 (37%)	**0.020**	17 (56.7%)	81 (43.8%)	0.236
Minor complications *CDC<=2*	25 (31.3%)	6 (33.3%)	1.000	17 (27.9%)	14 (37.8%)	0.372	4 (23.5%)	27 (33.3%)	0.570
Major complication *CDC >=3*	55 (68.8%)	12 (66.7%)		44 (72.1%)	23 (62.2%)		13 (76.5%)	54 (66.7%)	
ICU admission	55 (31.4%)	12 (30%)	0.874	41 (35.7%)	26 (26%)	0.189	16 (53.3%)	51 (27.6%)	**0.018**
*LOS**	14 (8-24)	10 (6.25-29)	0.245	15 (8-30)	13 (8-21)	0.211	15.5 (10.5-36.25)	13 (7-23)	0.105
In-hospital death	31 (17.7%)	4 (10%)	0.342	20 (17.4%)	15 (15%)	0.713	7 (23.3%)	28 (15.1%)	0.286

* Medians with interquartile ranges (IQR) and compared by Wilcoxon rank sum test

Table 11: Univariate analysis of body composition features with in-hospital mortality.

Variables	*Univariate analysis*	
	Odds ratio (95% CI)	*p-value*
Radiodensity		
SMA (HU)	0.939 (0.902 - 0.978)	**0.002**
VFA (HU)	0.998 (0.964 - 1.033)	0.893
SFA (HU)	1.039 (1.015 - 1.064)	**0.001**
Surface area index		
SMI (cm^2/m^2)	0.941 (0.895 - 0.990)	**0.018**
VFI (cm^2/m^2)	1.004 (0.995 - 1.013)	0.398
SFI (cm^2/m^2)	0.996 (0.988 - 1.005)	0.437

III.3 Association of Body Composition with In-hospital Mortality

III.3.1 Univariate analysis

The overall in-hospital mortality was 16.3% (35 patients). There was no significant difference in in-hospital mortality between sarcopenic patients (17.7%) and non-sarcopenic patients (10%), p-value= 0.342. There was no significant difference in in-hospital mortality between visceral obese patients (17.4%) and non-visceral obese patients (15%), p-value= 0.713. There was no significant difference in in-hospital mortality between sarcopenic obese patients (23.3%) and non- sarcopenic obese patients (15.1%), p-value= 0.286.

Table 12: Association of body composition with in-hospital mortality.

	Univariate analysis OR (95% CI)	*p-value*	*Model-1 (n=215) OR (95% CI)*	*p-value*	*Model-2 (n=215) OR (95% CI)*	*p-value*	*Model-3 (n=215) OR (95% CI)*	*p-value*	*Model-4 (n=215) OR (95% CI)*	*p-value*
Age	1.044 (0.993-1.099)	0.091	1.031 (0.972-1.094)	0.315	1.040 (0.980-1.103)	0.195	___	___	1.019 (0.959-1.084)	0.539
Sex (Female)	0.734 (0.353- 1.523)	0.406	0.305 (0.121-0.771)	0.012	0.542 (0.225-1.302)	0.171	___	___	0.356 (0.137-0.928)	0.035
ASA	5.822 (2.891-11.722)	<0.001	7.501 (3.412-16.488)	<0.001	7.021 (3.231-15.255)	<0.001	___	___	7.341 (3.322-16.218)	<0.001
SMI (cm2/m2)	0.941 (0.895-0.990)	0.018	0.915 (0.857-0.977)	0.007	___	___	0.944 (0.896-0.995)	0.031	0.922 (0.863-0.985)	0.016
SFA (HU)	1.039 (1.015-1.064)	0.001	___	___	1.033 (1.005-1.062)	0.022	1.037 (1.013-1.062)	0.003	1.028 (0.999-1.058)	0.055
c-statistic	___	___	0.856	___	0.844	___	0.712	___	0. 867	___

III.3.2 Multivariate analysis

Three models were generated to assess the predictive ability of SMI and SFA HU. Model-1 examined the sole effect of SMI, model-2 examined the sole effect of SFA HU, model-3 examined SMI and SFA HU without covariates, while model-4 tested the dual effect of SMI and SFA HU. Age, sex, and ASA classification were incorporated in all models as covariates. A multivariate analysis for in-hospital mortality is described in (Table 12).

In model-1, the effect of SMI alone was examined and showed increased SMI (i.e. increasing muscularity) was associated with significantly decreased mortality (aOR: 0.915, 95% CI: 0.857-0.977, p-value= 0.007) after adjusting for age (not significant), female sex (significant), and ASA classification (significant). Thus, for each 1 cm^2/m^2 increases in skeletal muscle the risk of death decreases by 8.5%. The ASA classification, which is a surrogate of comorbidities and highly associated with mortality, was found to increase the risk of death as for each 1 unit increase in ASA score the risk of death increases 7 times (aOR: 7.501, 95% CI: 3.412-16.488, p-value= <0.001).

In model-2, SFA HU was tested and found that it was significantly associated with in-hospital mortality (aOR: 1.033, 95% CI: 1.008-1.065, p-value= 0.022) after adjusting for age (not significant), female sex (not significant), and ASA classification (significant). Hence, SFA radiodensity was found to increases the risk of death by 3.3% for each 1 HU increment.

In model-3, SMI and SFA HU tested without adjusting for age, sex, and ASA score. SMI (aOR: 0.944, 95% CI: 0.896-0.995, p-value= 0.031) and SFA HU (aOR: 1.037, 95% CI1.013-1.062, p-value= 0.003) were significantly associated with in-hospital mortality. The Model c-statistic (0.712).

In model-4, SMI and SFA HU were tested and found that SMI (aOR: 0.922, 95% CI: 0.863-0.985, p-value= 0.016) was significantly associated with in-hospital mortality after adjusting for age (not significant), sex (significant), and ASA classification (significant). On the other hand, SFA HU (aOR: 1.028, 95% CI: 0.999-1.058, p-value= 0.055) was not significantly associated with in-hospital mortality after adjusting for age (not significant), sex (significant), and ASA classification (significant). Therefore, for each 1 cm^2/m^2 increases in skeletal muscle the risk of in-hospital mortality decreases by 7.8%.

The performance of all models was good with c-statistic > 0.8. However, the performance of the model improved after adding both SMI and SFA HU in model-4 (c-statistic: 0.867). Therefore, the incorporated influence of low muscle mass and high subcutaneous fat radiodensity provides the highest predictive ability for in-hospital mortality in the cohort.

III.4 Association of Body Composition with Postoperative Complications

III.4.1 Univariate analysis

Body composition profile and the main outcomes following acute abdominal surgery are described in (Table 10). The percentage of postoperative complications was 45.6% with significant difference between women and men (39(36.8%), 59(54.1%), p-value =0.014, respectively). The percentage of patients experienced Grade 1 complications was (4.7%), Grade 2 (9.8%), Grade 3a (2.3%), Grade 3b (4.7%), Grade 4a+b (7.9%), and Grade 5(16.3%).

There was no significant difference in the percentage of patients experienced complications between sarcopenic patients (45.7%) and non-sarcopenic patients (45%), p-value= 1.
There was a significant difference in the percentage of patients experienced complications between visceral obese patients (53%) and non-visceral obese patients (37%), p-value= 0.020.
There was no significant difference in the percentage of patients experienced complications between sarcopenic obese patients (56.7%) and non- sarcopenic obese patients (43.8%), p-value= 0.236.

There was no significant difference in the percentage of patients developed minor complications between sarcopenic patients (31.3%) and non-sarcopenic patients (33.3%), p-value= 1.
There was no significant difference in the percentage of patients developed minor complications between visceral obese patients (27.9%) and non-visceral obese patients (37.8%), p-value= 0.372. There was no significant difference in the percentage of patients developed minor complications between sarcopenic obese patients (23.5%) and non- sarcopenic obese patients (33.3%), p-value= 0.570.

There was no significant difference in the percentage of patients developed major complications between sarcopenic patients (68.8%) and non-sarcopenic patients (66.7%), p-value= 1.
There was no significant difference in the percentage of patients developed major complications between visceral obese patients (62.2%) and non-visceral obese patients (62.2%), p-value= 0.372. There was no significant difference in the percentage of patients developed major complications between sarcopenic obese patients (76.5%) and non- sarcopenic obese patients (66.7%), p-value= 0.570.

There was no significant difference in the patients admitted to ICU postoperatively between sarcopenic patients (31.4%) and non-sarcopenic patients (30%), p-value= 0.874.
There was no significant difference in the patients admitted to ICU postoperatively between visceral obese patients (35.7%) and non-visceral obese patients (26%), p-value= 0.189. There was a significant difference in the patients admitted to ICU postoperatively between sarcopenic obese patients (53.3%) and non- sarcopenic obese patients (27.6%), p-value= 0.018.

There was no significant difference in the patients' length of stay between sarcopenic patients 14(8-24) and non-sarcopenic patients 10(6.25-29), p-value= 0.245. There was no significant difference in the patients' length of stay between visceral obese patients 15(8-30) and non-visceral obese patients 13(8-21), p-value= 0.211. There was no significant difference in the patients' length of stay between sarcopenic obese patients 15.5(10.5-36.25) and non- sarcopenic obese patients 13(7-23), p-value= 0.105.

Table 13: Univariate analysis of body composition measurements with postoperative major compared to minor and no complications.

Variable	*Univariate analysis*	
	Odds ratio (95% CI)	*p-value*
Radiodensity		
SMA (HU)	0.959 (0.930 - 0.989)	**0.008**
VFA (HU)	0.968 (0.940 - 0.996)	**0.027**
SFA (HU)	1.020 (1.000 - 1.041)	0.050
Surface area index		
SMI (cm²/m²)	0.996 (0.961 - 1.031)	0.803
VFI (cm²/m²)	1.013 (1.005 - 1.021)	**0.001**
SFI (cm²/m²)	1.002 (0.995 - 1.008)	0.630

III.4.2 Multivariate analysis

Three models were generated to assess the predictive ability of SMI and SFA HU. Model-1 examined the sole effect of SMI, model-2 examined the sole effect of SFA HU, model-3 examined SMI and SFA HU without covariates, while model-4 tested the dual effect of SMI and SFA HU. Age, sex, and ASA classification were incorporated in all models as covariates. A multivariate analysis for in-hospital mortality is described in (Table 14).

Table 14: The effect of body composition on postoperative major compared to minor and no complications.

	Univariate analysis OR (95% CI)	*p-value*	*Model-1 (n=215) OR (95% CI)*	*p-value*	*Model-2 (n=215) OR (95% CI)*	*p-value*	*Model-3 (n=215) OR (95% CI)*	*p-value*	*Model-4 (n=215) OR (95% CI)*	*p-value*
Age	0.988 (0.950-1.028)	0.560	0.974 (0.931-1.018)	0.242	0.973 (0.930-1.018)	0.239	___	___	0.968 (0.924-1.014)	0.165
Sex (Female)	0.590 (0.328-1.059)	0.077	0.412 (0.205-0.827)	0.013	0.529 (0.273-1.023)	0.059	___	___	0.455 (0.221-0.936)	0.032
ASA	3.089 (1.948-4.898)	<0.001	3.344 (2.073-5.392)	<0.001	3.269 (2.027-5.272)	<0.001	___	___	3.271 (2.026-5.279)	<0.001
SMI (cm2/m2)	0.996 (0.961-1.031)	0.803	0.974 (0.932-1.017)	0.233	___	___	0.999 (0.964-1.035)	0.951	0.977 (0.935-1.021)	0.307
SFA (HU)	1.020 (1.000-1.041)	0.050	___	___	1.015 (0.992-1.037)	0.206	1.020 (1.000-1.041)	0.052	1.013 (0.990-1.036)	0.272
c-statistic	___	___	0.750	___	0.757	___	0.590	___	0. 755	___

In model-1, the effect of SMI alone was examined and showed SMI was not significantly associated with postoperative complications development (aOR: 0.974, 95% CI: 0.932-1.017, p-value= 0.233) after adjusting for age (not significant), female sex (significant), and ASA classification (significant). The ASA classification was found to increase the risk of developing major complications as for each 1 unit increase in ASA score the risk of developing major complications increases 3 times (aOR: 3.344, 95% CI: 2.073-5.392, p-value= <0.001). Female sex decreases the risk of developing major complications 60% (aOR: 0.412, 95% CI: 0.205-0.827, p-value= 0.013).

In model-2, SFA HU was tested and found that it was not significantly associated with postoperative complications development (aOR: 1.015, 95% CI: 0.992-1.037, p-value= 0.206) after adjusting for age (not significant), female sex (not significant), and ASA classification (significant).

In model-3, SMI and SFA HU tested without adjusting for age, sex, and ASA score. SMI (aOR: 0.999, 95% CI: 0.964-1.035, p-value= 0.951) and SFA HU (aOR: 1.020, 95% CI 1.000-1.041, p-value= 0.052) were not significantly associated with postoperative complications. The Model c-statistic (0.590).

In model-4, SMI and SFA HU were tested and found that SMI (aOR: 0.977, 95% CI: 0.935-1.021, p-value= 0.307) and SFA (aOR: 1.013, 95% CI: 0.990-1.036, p-value= 0.272) were not significantly associated with postoperative complications development after adjusting for age (not significant), sex (significant), and ASA classification (significant).

Female sex (aOR: 0.455, 95% CI: 0.221-0.936, p-value= 0.032) and ASA score (aOR: 3.271, 95% CI: 2.026-5.279, p-value <0.001) were significantly associated with the risk of developing major complications.

The performance of all models was fair with c-statistic > 0.7. However, the performance of model-2 (c-statistic: 0.757) was higher compared to model-1 and 4. Therefore, neither SMI nor SFA HU was associated with risk of developing major complications postoperatively.

IV. CHAPTER FOUR: DISCUSSION

Given the projected increase in elderly population, it is important to increase surgeons' awareness of risk factors that may affect surgical outcomes. To date, the influence of body composition measured by CT scan on outcomes after acute abdominal surgery in elderly has not been described clearly. The present results suggest that low SMI (i.e. sarcopenia) identified by abdominal CT scan was predictive of in-hospital mortality. The quantity and radiodensity of skeletal muscles, visceral and subcutaneous fat were not predictive of postoperative complications.

Sarcopenia and Mortality

In this study, the presence of sarcopenia in elderly population was a predictor of in-hospital mortality after adjusting for age, sex, ASA score, and SFA radiodensity. Similarly, a study in older adult patients underwent acute abdominal surgery has found that sarcopenia was an independent predictor of in-hospital mortality (RR, 2.61; 95% CI, 1.57–3.65; $p < 0.01$; AUC, 0.87; 95% CI, 0.82–0.92).[202] However, CT scan identified average bilateral *psoas* muscle cross-sectional area at L3 normalized for height was used instead of all abdominal wall muscles. Another study in oncologic colorectal surgery in elderly patients reported that sarcopenia independently predicted postoperative mortality (OR, 43.30; 95% CI, 2.74–685.2; $P = 0.007$) adjusted for age, sex and previous abdominal surgery.[203] However, Prado et al.[190] definition of sarcopenia was used.

SFA Quality and Mortality

Our findings have shown that SFA HU (i.e. subcutaneous fat radiodensity) association with in-hospital mortality has p-value close to significance. This could be explained by the small sample size which mask the statistical significance of SFA HU. A study examined the associations between adipose tissue radiodensity and 4 to 13- year mortality showed that higher visceral fat radiodensity in women (HR: 2.00, 95 % CI: 1.40–2.86, $p = 0.01$) and higher subcutaneous fat radiodensity (HR: 1.76, 95 % CI: 1.35–2.28, $p < 0.001$) were associated with mortality. In men, higher visceral fat radiodensity (HR:1.51, 95 % CI: 1.11–2.06, $p = 0.03$) and higher subcutaneous fat radiodensity (HR: 1.56, 95 % CI: 1.22–2.00, $p < 0.001$) were associated with mortality. All models were adjusted for age, race, study site, education, BMI, fat area, and sagittal diameter. [204] Another study assessed the association of abdominal fat quality and the risk of cardiometabolic disease reported that lower CT radiodensity of visceral and subcutaneous fat were correlated with adverse cardiometabolic risk independent of fat quantity.[205]

Body Composition and Postoperative Complications

Additionally, this study showed that all body composition measurements were not significantly associated with postoperative complications. Similarly, a study conducted in gastric cancer surgical patients reported that sarcopenia, visceral and subcutaneous fat quantities were not associated with in-hospital mortality, severe complications or 6-month mortality.[206] In contrast, a retrospective study in gastric cancer patients underwent laparoscopic total gastrectomy found that only sarcopenic obesity was associated with an increased incidence of surgical site infection (OR 4.59, 95 % CI: 1.18-17.78, $P = 0.028$).[207] However, this study examined body composition measurements as binary variable not continuous.

ASA, Mortality, and Complications

In our population, ASA score increases the risk of death six times for each 1 class increment in ASA score. This is because the all-inclusive definition of ASA score as it describes patient's comorbidities, physical fitness, and the severity of the presenting illness as a composite. Although ASA score is a subjective tool, it is a cheap, quick, and easy to apply clinically to identify people at risk. However, it stratifies patients based on inevitable factors (e.g. comorbidities and acute presenting illness) compared to body composition. Therefore, it lacks the dual benefit attained by body composition identified by CT scan which is the objectivity and capability for intervention as a modifiable risk factor.

Body Composition

Interestingly, higher fat quantity was associated with less radiodensity (e.g. higher subcutaneous fat quantity associated with less subcutaneous fat radiodensity) is consistent with the previous finding that fat quantity is inversely correlated with radiodensity.[208] In our population, there was a decrease in lean muscle mass and an increase in fatty tissue mass as BMI was directly related to SMI, visceral, and subcutaneous fat. Additionally, the mean BMI of sarcopenic patients was within the overweight range (i.e. sarcopenia was not associated with weight loss). Both findings were in line with age-associated body composition changes fact.[25] However, a recent study in patients with colorectal cancer found that sarcopenia was significantly associated with low BMI (21.0 ± 3.2, p-value < 0.001)[209] , and another study in acute abdominal surgery in elderly has shown similar results (BMI: 22 (20–27), p-value <0.001).[202] Acute abdominal surgery includes many gastrointestinal diseases ranging from acute appendicitis to gastrointestinal cancer which is

associated with weight loss. Thus, the number of cancer cases included may affect the mean BMI as it was obvious in the former colorectal cancer study. In addition, the latter study was in Asian population where the average BMI of Asian populations is lower than that of non-Asian populations.[141]

Different cut-off values for body composition were used to compare our cohort with other populations. Firstly, our cohort were described based on Martin's et al[201] definition for sarcopenia and were not statistically associated with adverse outcomes (Table 8). This is due to the fact that Martin et al, cut-off values were obtained from adult with respiratory or gastrointestinal cancer population. Secondly, viscerally obese patients were most likely to develop minor and major complications according to the predefined cut-off value (i.e. VFA > 130 cm^2). [200] However, this cut-off value was not sex-specific, and was inferred based on the risk of developing diabetes and cardiovascular disease. Finally, the rate of ICU admission was significantly higher in sarcopenic obese patients. Sarcopenic obesity was shown to be an independent predictor of survival in patients with solid tumors of the lung and gastrointestinal tract (HR 4.2, 95% CI: 2.4–7.2, p<0·0001).[190] In the ICU setting, body composition assessment may help identify high- risk patients where nutrition intervention can change clinical outcomes.[210]

Body Composition and ICU Admission

Sarcopenic obese patients significantly required ICU care postoperatively compared to sarcopenic and viscerally obese patients. A recent study in surgical ICU patients who underwent acute abdominal surgery has showed that sarcopenic obesity ICU lengths of stay (6 (3–14) days, $P < 0.001$) differed significantly among the patients without sarcopenia or obesity (3 (2–5) days), viscerally obese (5 (2−10) days) sarcopenic (5 (3−10) days).[211] However, this study used a definition for sarcopenic obesity that is suitable for the Asian population. Sarcopenic obesity defined as skeletal muscle index thresholds at L3 of 40.8 cm2/m2 for male and 34.9 cm2/m2 for female[212] , and visceral obesity > 100 cm^2 in both sexes.[213]

Body Composition and LOS

The LOS did not differ statistically between sarcopenic and non-sarcopenic, viscerally obese and non-viscerally obese, or sarcopenic obese and non-sarcopenic obese patients. Similarly, a study in surgical ICU patients who underwent acute abdominal surgery has shown that hospital LOS did not differ statistically between patients without sarcopenia or obesity (17 (11–29) days), viscerally obese (23 (16–43) days), sarcopenic 19 (12−30) days), or sarcopenic obese (20 (11–29) days), (p-value=0.139).[211]

Research Implications

CT scan is the gold standard diagnostic tool in acute abdomen cases as it is used throughout patient care, therefore, images can be used for research purpose with no risk for further radiation exposure. Additionally, in prospective studies and clinical trials, single-slice CT scan could be a convenient assessment tool as it offers less scanning time, cost, ionizing radiation exposure[214,215]

, and, has been validated to represent the total body skeletal muscles and fatty tissues at specific vertebral level.[177,216] This could encourage researchers to study the correlation of skeletal muscles and body fat amounts with serum inflammatory biomarkers and hormones, and, its role in the pathogenesis of several diseases.

Clinical Implications

Identifying patients with body composition changes using CT can stimulate clinicians and researchers to develop new intervention pathways or treatment protocols to reverse these changes and minimizing the incidence of complications. A variety of therapies can be used to optimize elderly patients' physical activity and nutritional status with the help of primary care providers or preoperatively in case of elective surgery. As result, this may help to minimize age-associated body composition changes and its negative health consequences. For example, resistance training remains the most effective intervention for sarcopenia as it preserves muscle mass, strength, and function.[217,218] Diet restriction and physical activity are the cornerstone of obesity management.[219]

Study Strength

This study has several strengths. By using a well-defined population, all cohort members were representative of elderly population underwent acute abdominal surgery. In addition, a specific protocol was used to ascertain assessors blindness during data transformation and images analysis. Hence, selection bias would have been minimized. Clinically relevant covariates that could have an impact on our predictors and outcomes have been controlled for in statistical analysis.

Limitations

This study has some limitations to be considered. Due to the observational nature of the study, we were able to examine only the association between body composition and in-hospital mortality. Hence, this study cannot examine causation relationship. The data were collected initially as a part of healthcare routine documentation and was not for research purposes. Accordingly, not all risk factors were identified and subsequently recorded. For example, many different healthcare professionals would have been involved in patient care, so the measurement of outcome(s), such as postoperative complications, throughout the database would probably be less accurate and consistent than that achieved with a prospective cohort study design. Another example is the ethnicity which was not controlled for in the analysis as the distribution of fatty tissues and skeletal muscles are highly affected by ethnicity.[122] Additionally, the physical activity and nutritional status of the cohort were unknown.

Recommendations & Future Direction

We recommend conducting a large sample-size prospective studies to minimize selection bias and having a better estimation of population at risk. Additionally, accounting for all covariates that could affect body composition to achieve standardized measurements based on age, sex, race, diet, and physical activity status. Body composition has been shown to be affected by sex[220-222] ; therefore, we recommend conducting stratified analysis by sex to test the effect of sex –specific body composition on surgical outcomes in this population. Furthermore, it is important to identify standardized cut-off values associated with outcomes in elderly undergoing acute abdominal surgery by conducting sensitivity and specificity analysis. Additionally, we recommend building an equation to describe the linear relationships between body composition

quantities (i.e. surface area) and qualities (i.e. radiodensity) by running a linear regression model to provide deep understanding of body composition parameters.

V. CHAPTER FIVE: CONCLUSION

In conclusion, age-associated changes in body composition is a risk factor for in-hospital mortality in elderly who underwent acute abdominal surgery. Low SMI (i.e. sarcopenia) identified by abdominal CT scan is predictive of in-hospital mortality. SMI and SFA HU measurements were not predictive of postoperative complications. Using CT scan can assist in surgical diagnosis and provide a quantitative assessment of body composition for risk stratification. This may provide surgeons with the opportunity to discuss the possible risk with patients and their families and choosing the optimal intervention pathway. With the addition of body composition measurements to our initial model, the predictive ability to identify patients with high-risk for in-hospital mortality was increased. Furthermore, using body composition as a modifiable risk factor can help minimizing the risk of mortality by using specific diet and lifestyle modification for a better health in elderly. Finally, our model suggests an objective tool for risk assessment in a high-risk population that may provide an additional insight to help surgeons make better predictions for outcomes.

LIST OF TABLES

Table 15: Methods of evaluation of body composition**.**

Method of evaluation	Availability	Specificity	Accuracy	Reproducibility	Quantitative assessment	Exposure to radiation	Other comments
Anthropometric: BMI, WC and sagittal abdominal diameter	Most accessible	Low	Low	Highly variable	Does not provide	No	Simplest and most rapid method
BIA	Easily accessible	Low	Medium	Coefficient of variability: 4–9.8% [50, 51]	Indirect assessment by measuring a voltage of current between the umbilicus and the back	No	Takes up to a few minutes. Does not require specific skills to operate equipment. Has maximum weight limit. Requires predictive equations
ADP	Less accessible	Medium	High	Coefficient of variability: adults, 1.7–4.5% [52]; children, 25% (boys), 44% (girls) [53]	Indirect assessment by monitoring changes in pressure within a closed chamber	No	Rapid and non-invasive May be feasible for morbidly obese patients Need to control temperature and moisture Requires patient to perform a complex breathing manoeuvre Volume of the body fat is often underestimated
Ultrasound	Easily accessible	Medium	High	Coefficient of variability: varies from <2% to 4.5–7.9% [54, 55]	Indirect assessment by measuring a distance between internal face of the recto-abdominal muscle and anterior wall of the aorta	No	Operator skills and training required Reliability and accuracy depend on operator
DXA	Less accessible	Low	High	Coefficient of variability: varies from <1% to 4% [50, 56, 57]	Indirect assessment by measuring a total body and trunk fat masses	The effective dose per scan: 0.003–0.06 mSv	Upper weight limit restricted by the size of the scanning area. Special software required
CT	Less accessible	Very high	Very high	Coefficient of variability: 1.2–4.3% [55, 58, 59]	Provides	The effective dose per scan: 6.0–10.0 mSv for abdominal multislice CT with routine protocol (2.5 mm slice collimation), but may be reduced with improved protocols	Can use single slices to predict whole body compartments Upper weight limit Specific software required for analysis
MRI	Much less available than other methods	Very high	Very high	Coefficient of variability: 2.1–6.5% [50, 57, 60, 61]	Provides	No	Duration of the scan is approximately 14–18 s Single-slice protocol is as accurate as multislice

ADP, air displacement plethysmography; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual energy X-ray absorptiometry; WC, waist circumference.

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Table 16: The Clavien-Dindo Classification.

TABLE 1. Classification of Surgical Complications

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
	Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

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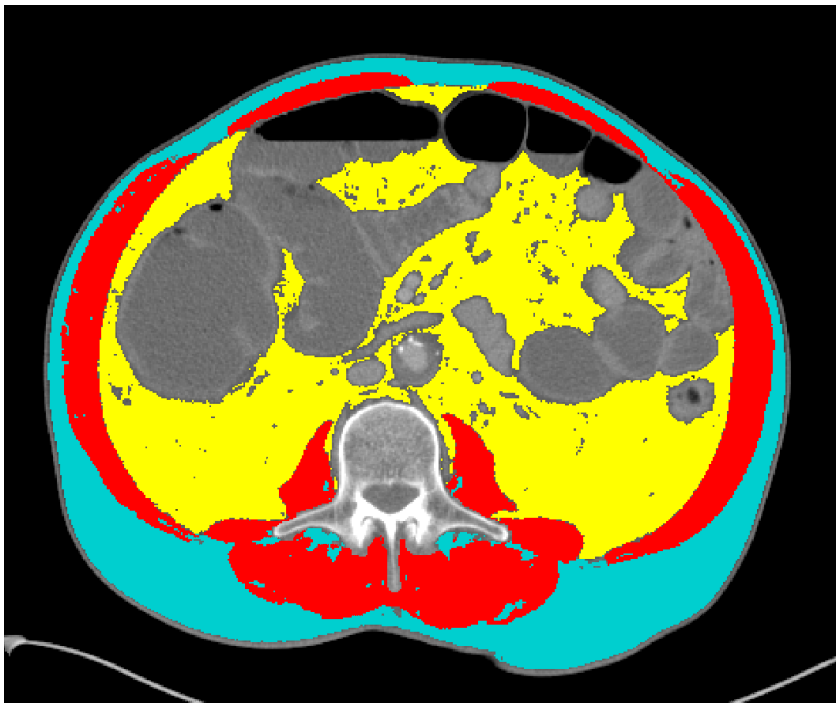
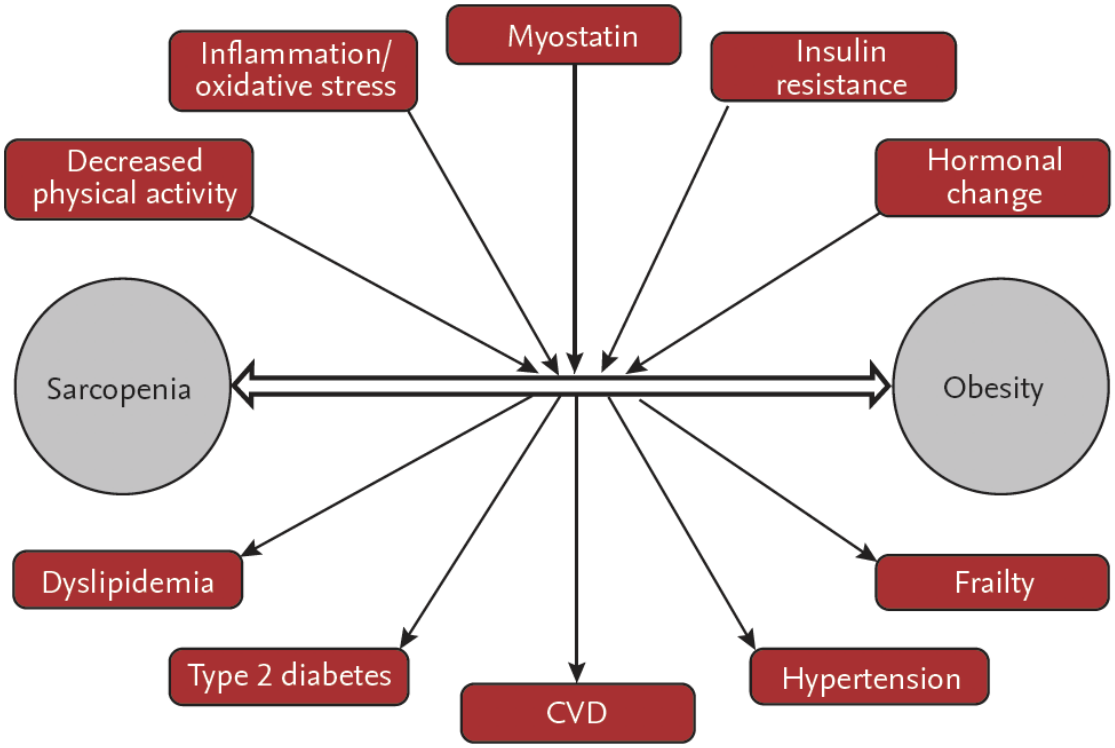
APPENDICES

Figure 2: A Single-slice cross-sectional CT scan image of the abdomen at L3 lumbar vertebra (right), and a radio-density table (left).



Tissue	Radio-density
Bone	+1000 (HU)
Skeletal muscle	- 29 to +150 (HU)
Visceral fat	- 150 to - 50 (HU)
Subcutaneous fat	- 190 to - 30 (HU)
Air	- 1000 (HU)

Figure 3: The vicious cycle of sarcopenia and obesity.



Choi KM. Sarcopenia and sarcopenic obesity. Korean J Intern Med 2016 - 11;31(6):1054-1060.

Figure 4: Charlson Comorbidity Index (CCI).

Predicts 10-year survival in patients with multiple comorbidities.

FORMULA

Addition of the selected points:

1 point	Myocardial infarction
	Congestive heart failure
	Peripheral vascular disease
	Cerebrovascular disease
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Ulcer disease
	Mild liver disease
	Diabetes
2 points	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end organ damage
	Any tumor
	Leukemia
	Lymphoma
3 points	Moderate or severe liver disease
6 points	Metastatic solid tumor
	AIDS*

Plus 1 point for every decade age 50 years and over, maximum 4 points.

Note: liver disease, diabetes, and cancer inputs are mutually exclusive (e.g. do not give points for both "mild liver disease" and "moderate or severe liver disease").

*This data is from the original Charlson study in 1987, before the widespread availability of effective antiretroviral therapy. We are not aware of any re-evaluations of the CCI using more recent data.

https://www.mdcalc.com/charlson-comorbidity-index-cci#evidence

Figure 5: Sample-size estimation.

Sample Size for Frequency in a Population

Population size(for finite population correction factor or fpc)(*N*):	1000000
Hypothesized % frequency of outcome factor in the population (*p*):	23%+/-10
Confidence limits as % of 100(absolute +/- %)(*d*):	10%
Design effect (for cluster surveys-*DEFF*):	1

Sample Size(*n*) for Various Confidence Levels

ConfidenceLevel(%)	Sample Size
95%	69
80%	30
90%	48
97%	84
99%	118
99.9%	192
99.99%	269

Equation

Sample size $n = [DEFF*Np(1-p)]/ [(d^2/Z^2_{1-\alpha/2}*(N-1)+p*(1-p)]$

Results from OpenEpi, Version 3, open source calculator--SSPropor
Print from the browser with ctrl-P
or select text to copy and paste to other programs.

http://www.openepi.com/SampleSize/SSCohort.htm