

Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery

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Author contributions: Wagner D, DeMarco MM, Amini N and Pawlik TM study concept and design; Wagner D, DeMarco MM, Amini N, Buttner S, Gani F and Pawlik TM acquired analysis or interpretation of data; all authors contributed to the manuscript.

Conflict-of-interest statement: No potential conflicts of interest relevant to this article were reported.

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Received: June 24, 2015

Peer-review started: June 24, 2015

First decision: September 17, 2015

Revised: September 19, 2015

Accepted: October 20, 2015

Article in press: October 27, 2015

Published online: January 27, 2016

Abstract

According to the United States census bureau 20%

of Americans will be older than 65 years in 2030 and half of them will need an operation - equating to about 36 million older surgical patients. Older adults are prone to complications during gastrointestinal cancer treatment and therefore may need to undergo special pretreatment assessments that incorporate frailty and sarcopenia assessments. A focused, structured literature review on PubMed and Google Scholar was performed to identify primary research articles, review articles, as well as practice guidelines on frailty and sarcopenia among patients undergoing gastrointestinal surgery. The initial search identified 450 articles; after eliminating duplicates, reports that did not include surgical patients, case series, as well as case reports, 42 publications on the impact of frailty and/or sarcopenia on outcome of patients undergoing gastrointestinal surgery were included. Frailty is defined as a clinically recognizable state of increased vulnerability to physiologic stressors resulting from aging. Frailty is associated with a decline in physiologic reserve and function across multiple physiologic systems. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Unlike cachexia, which is typically associated with weight loss due to chemotherapy or a general malignancy-related cachexia syndrome, sarcopenia relates to muscle mass rather than simply weight. As such, while weight reflects nutritional status, sarcopenia - the loss of muscle mass - is a more accurate and quantitative global marker of frailty. While chronologic age is an important element in assessing a patient's peri-operative risk, physiologic age is a more important determinant of outcomes. Geriatric assessment tools are important components of the pre-operative work-up and can help identify patients who suffer from frailty. Such data are important, as frailty and sarcopenia have repeatedly been demonstrated among the strongest predictors of both short- and long-term outcome following complicated surgical procedures such as esophageal, gastric, colorectal, and hepato-pancreatico-biliary resections.

Key words: Sarcopenia; Outcomes; Frailty; Morbidity;

Mortality

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Core tip: It is estimated that by the year 2030, 36 million Americans > 65 years will require surgery. Frailty as defined by a clinically recognizable state of increased vulnerability due to physiologic stressors resulting from aging has been associated with a decreased physiologic reserve and function across multiple physiological systems. Recently, a loss of muscle mass or sarcopenia has been proposed as an accurate and quantitative global marker of frailty. The current review demonstrates that frailty as defined by sarcopenia can be accurately used as a preoperative predictor of poor short- and long-term postoperative outcomes following complex gastrointestinal surgery.

Wagner D, DeMarco M, Amini N, Buttner S, Segev D, Gani F, Pawlik TM. Role of frailty and sarcopenia in predicting outcomes among patients undergoing gastrointestinal surgery. *World J Gastrointest Surg* 2016; 8(1): 27-40 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v8/i1/27.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v8.i1.27>

INTRODUCTION

The life expectancy of the average person doubled over the course of the last century. In addition, between 1982 and 2003 the American population aged over 65 years doubled and the population older than 85 years quadrupled^[1]. According to the United States census bureau 20% of Americans will be older than 65 years in 2030 and half of them will need an operation - equating to about 36 million older surgical patients^[2]. The process of aging is associated with an increasing prevalence of frailty, comorbidities, a decline of functional reserve and a progressive restriction in personal and social resources. All of these factors can contribute to less favorable postoperative outcomes among older patients^[3]. Older patients are at increased risk for complications which include delirium, urinary incontinence, pressure ulcers, depression, infection, functional decline and adverse drug affects^[4-8]. Despite the fact that surgery is the most effective cancer therapy, complication rates, mortality, length of hospital stay and intensive care unit admissions increase with patient age, which can offset oncologic advantages^[9-13].

Many cancer treatment guidelines have been formulated based on clinical data that may have under-represented older and more frail patients; therefore, more attention is needed to guide the management of this vulnerable population^[14,15]. Several studies have noted potential differences in gastrointestinal surgical care between older and younger patients^[16,17]. For example, commonly used predictor scores for postoperative complications like the American Society of Anesthesiology

score have substantial limitations in older patients, as most are based on a single organ system, are subjective and none measures the patients' physiologic reserve^[18]. In fact, a recent review by McCleary *et al*^[16] stressed that older adults are prone to complications during gastrointestinal cancer treatment and therefore need to undergo special pretreatment assessments incorporating frailty and sarcopenia assessments.

More recently, sarcopenia and frailty have increasingly been recognized as important factors that can be markers of decreased physiologic reserve. Several studies have highlighted the importance of frailty and sarcopenia to predict perioperative outcomes among patients undergoing surgery for gastrointestinal cancer^[19-22]. Recent guidelines from the American College of Surgeons have highlighted the importance of assessing both frailty and sarcopenia prior to oncologic surgery in the elderly^[23]. As such, there is increasing interest in screening patients for frailty and sarcopenia to better predict patients at highest risk of complications after surgery^[24]. Given this, we sought to review the available literature on the association of frailty and sarcopenia with patient outcome, as well as the risk of perioperative morbidity and mortality after gastrointestinal surgeries.

SYSTEMATIC LITERATURE REVIEW

A focused, structured literature review was performed using PubMed and Google Scholar to identify primary research articles, review articles, as well as practice guidelines on frailty and sarcopenia among patients undergoing gastrointestinal surgery. Articles published between January 2000 to March 2015 were identified using the search terms "sarcopenia and gastrointestinal surgery", "frailty and gastrointestinal surgery", "sarcopenia and outcome and surgery", as well as "frailty and outcome and surgery". In addition, references of relevant articles were also reviewed to identify potentially eligible studies. As per the methodology specified under the PRISMA guidelines, only studies published in English were included, while conference abstracts that did not proceed to publication in peer-reviewed journals were excluded^[25]. The initial search identified 343 articles; 53 duplicates were eliminated and 290 abstracts were reviewed for further assessment. Among these 25 editorials, 97 studies that did not include gastrointestinal patients, 99 articles that did not use standard frailty or sarcopenia assessments, 19 case series, as well as 5 case reports and 3 consensus statements were eliminated (Figure 1). In total 42 publications assessing the impact of frailty and/or sarcopenia on postoperative outcomes among patients undergoing gastrointestinal surgery were identified that met inclusion criteria. Among all studies that were included, 10 studies were performed prospectively (2 gastroesophageal surgery, 6 colorectal surgery, and 2 hepato-pancreaticobiliary surgery, Tables 1-3)^[26-33]. Sixteen studies were conducted retrospectively on an unmatched cohort (2 gastroesophageal, 4 colorectal, and 10 hepato-

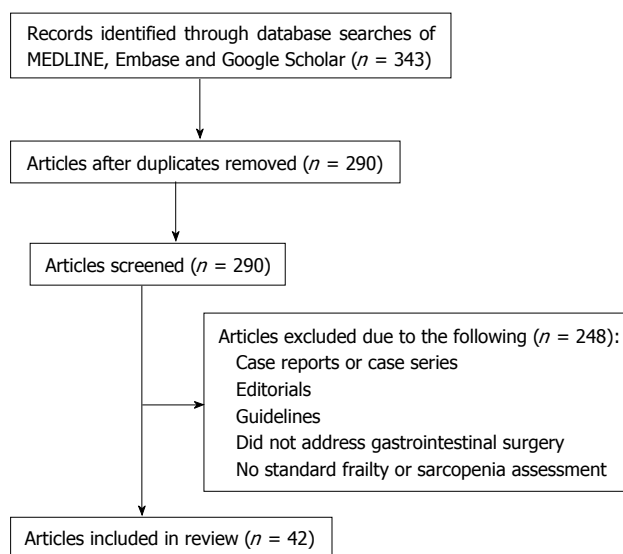


Figure 1 Flow chart depicting the review process for the inclusion of publications.

pancreatico-biliary), 2 studies retrospectively analyzed prospectively collected data while two articles analyzed data from multiple centers in the United States^[34-50]. Additionally, 15 narrative reviews were included in the study. The quality of each study was assessed using the Newcastle-Ottawa Scale based on case selection, comparability, and outcome reporting (Tables 1-3); the median quality score of the studies was 6.5 (range 4-9).

Data pertaining to patient demographics (age and sex), assessment used, type of surgery and the number of patients were collected for each article and are displayed in Table 4. Additionally, data relating to short-term clinical outcomes such as 30-d morbidity and mortality, as well as long-term outcomes including median, 5-year overall and 1-year overall survival were recorded from each study. Sarcopenia and frailty, as well as other end points used for analyses were not homogeneously defined throughout the studies. The different approaches to define sarcopenia and frailty along with relevant clinical and outcome parameters used along with the quality scale of the included studies (Tables 1-3). While a direct comparison between the studies was therefore not possible due to their heterogeneity, data were amassed from these studies to inform a comprehensive review.

FRAILTY AND SARCOPENIA IN OLDER ADULTS UNDERGOING SURGERY: GENERAL CONSIDERATIONS

Frailty is associated with a decline in physiologic reserve and function across multiple physiologic systems^[51]. In the absence of a gold standard, frailty has been operationally defined by Fried *et al.*^[20] as meeting 3 out of 5 phenotypic criteria indicating compromised energetics: Low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss.

While frailty has not been widely evaluated in surgical patients, Makary *et al.*^[22] did report on the surgical outcomes of a large cohort of older patients in which frailty was assessed using a frailty scale based on the Fried frailty phenotype (Table 4). The authors reported that preoperative frailty was associated with an increased risk of postoperative complications. Specifically, patients with moderate or severe frailty had roughly twice (moderate: OR = 2.06, 95%CI: 1.18-3.6; severe: OR = 2.54, 95%CI: 1.12-5.77) the odds of complications compared with non-frail patients. The authors also reported that frailty independently predicted length of stay with moderate or severe frailty having a 44%-53% and 65%-89%, respectively, longer hospital stays than non-frail patients. Of note, the power of frailty to predict worse outcomes was much higher than traditional peri-operative assessments alone (Figure 2). These data emphasize how frailty adds valuable information to standard preoperative risk assessments, yet highlight how defining frailty in the peri-operative period can be challenging.

A full combined geriatric assessment (CGA) can take several hours and includes assessments such as activities of daily living, geriatric depression scores, and timed "up and go" tests^[52]. Specifically, the risk of mortality among patients with frailty ranged from 1.1%-11.7%, with frail patients up to 12 times more likely to die compared with non-frail patients in a recent review on the use of CGA in gastrointestinal surgery^[52]. Due to its time consuming nature, the National Cancer Institute and the National Institute of Aging recommends this scoring system only for patients with special needs who are deemed at high risk^[7]. In addition to CGA, other parameters have been used to assess frailty and sarcopenia in older patients undergoing gastrointestinal surgery. For example, in a large cohort study of 76106 patients from the NSQIP database, Amrock *et al.*^[53] reported that preoperative impaired cognition, low albumin level, previous falls, low hematocrit levels and a high prevalence of comorbidities were associated with an increased 6 mo mortality and post discharge institutionalization among older patients undergoing major abdominal operations. While the authors concluded that preoperative data could help define frailty and predict the geriatric-specific surgical risk, the study failed to provide a clear definition for frailty in gastrointestinal surgical patients. Other studies have suggested that the Charlson index, timed "up and go" tests, Katz score or the Mini cog score, as well as serum albumin levels below 3.4 g/dL and the Braden score all may be associated with postoperative outcomes^[28,54,55]. Each of these parameters have not been shown, however, to improve the risk prediction compared with the Fried Frailty Phenotype when used alone.

Sarcopenia has been proposed as another means to assess frailty. In fact, when Fried *et al.*^[20] first described the frailty phenotype and its association with mortality and morbidity, the potential link between frailty and sarcopenia was noted. Specifically, patients deemed

Table 1 Compiles all studies evaluated in patients undergoing esophageal or gastric resection

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up (mo)	30-d morbidity (%)	30-d mortality (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/OS (OR)
Hodari <i>et al</i> ^[54]	United States	5	R	2095	NR	NR	Esophagectomy	Modified Canadian age index	17.8	NR	NR	NR	96	NR	Postoperative complications	OR = 31.84, P = 0.015
Sheetz <i>et al</i> ^[55]	United States	7	R	230	62	88	Transhiatal esophagectomy	Lean psoas area (L4 level)	57.8	12.8	NR	NR	11	0	Overall survival	OR = 0.456; 95%CI: 0.197-1.054; P = 0.067
Yip <i>et al</i> ^[26]	United Kingdom	5	P	36	63	86	Neoadjuvant chemotherapy and esophagectomy	Body composition	26	30	26	0	NR	NR	No multivariate outcome analysis	NR - significant increase in complications and decrease in survival
Awad <i>et al</i> ^[27]	United Kingdom	7	P	47	63		Esophagectomy gastrectomy	Body composition	NR	24	NR	2.2	23.9	19	No multivariate outcome analysis	NR - significant increase in complications with frailty
Tegels <i>et al</i> ^[60]	The Netherlands	5	R/P	70	59		Gastrectomy	Groningen frailty index	28	6	NR	9.1	NR	NR	30-d mortality	3.96 (95%CI: 1.12-14.09, P = 0.03)

¹ According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

to be frail who had a concomitant decrease in muscle mass were more likely to suffer from disabilities and a worsening in their mobility vs non-frail patients. Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Unlike cachexia, which is typically associated with weight loss due to chemotherapy or a general malignancy-related cachexia syndrome, sarcopenia relates to muscle mass rather than simply weight. As such, while weight reflects nutritional status, sarcopenia - the loss of muscle mass - is a more accurate and quantitative global marker of frailty^[56]. Usually characterized as low muscle mass and low muscle function (strength/performance), sarcopenia is typically defined using an axial cross-sectional image of the psoas muscle at the level of L3^[57,58]. Using this technique, sarcopenia is defined as the total psoas area (TPA), with sarcopenic patients having a smaller TPA^[58]. More recent studies have suggested that assessment of the entire volume of the psoas muscle (TPV) may be a better means to define sarcopenia rather than a single axial image (Figure 3)^[47,59]. In addition, other investigators have suggested the use of dual X-ray absorptiometry as an alternative means to screen for sarcopenia. This tool has not been widely adopted, however, as routine computed tomography is more commonly utilized in patients prior to surgery.

Both the European and the American Society of Ageing have recommended that sarcopenia be recognized as a geriatric syndrome^[57]. In addition, several studies have noted an association between sarcopenia and increased risk of adverse outcomes following surgery^[15,59]. For example, Brant *et al*^[58] reported that patients with sarcopenia were particularly vulnerable in the setting of significant physiologic stressors like major surgery. The importance of sarcopenia in the prediction of outcome after gastrointestinal surgery has been particularly highlighted in several studies^[43,47,59]. The hope is that identification of patients with frailty or sarcopenia who are at high risk of perioperative morbidity can guide patient-physician discussions prior to surgery, as well as identify appropriate patients for "pre-habilitation"^[60].

GASTRO-ESOPHAGEAL MALIGNANCIES

Gastric and esophageal cancer represent a worldwide major health problem. While the incidence in Western countries is relatively low with 18170 and 22220 new esophageal

Table 2 Compiles the characteristics of all studies evaluated in patients undergoing colorectal resections

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up 30-d morbidity (no)	30-d morbidity (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/outcome (OR)
Rønning <i>et al</i> ^[67]	New Zealand	6	P	84	82	41	Colorectal surgery	Combined geriatric assessment	NR	22	NR	NR	NR	No outcome analysis	NR - significant postoperative decrease of ADL
Obeid <i>et al</i> ^[36]	United States	5	R	58448	NR	48	Colectomy (33% malignant causes)	Canadian frailty index	26	NR	15.9	NR	NR	30 d mortality and morbidity	OR = 14.4; 95%CI: 18.76-31.2
Neuman <i>et al</i> ^[67]	United States	6	R	12979	84	39	Colectomy for colorectal cancer	Johns Hopkins adjusted case mix system	NR	16	NR	85.7	NR	1 yr survival	OR = 8.4; 95%CI: 6.4-11.1, P = 0.001
Robinson <i>et al</i> ^[68]	United States	4	P	60	75	97	Colectomy for colorectal cancer	Individual frailty score	10	6	10	NR	NR	Hospital and health care costs	NR - significant association to costs and length of stay
Tran Ba Loc <i>et al</i> ^[20]	France	7	P	1186	76	NR	Major colorectal surgery	Elderly POSSUM score	41	3	NR	NR	NR	30 d mortality	AUC 0.86 (0.81-0.92)
Tan <i>et al</i> ^[31]	China	6	P	83	82	NR	Colorectal resections	Fried frailty criteria	22	NR	29	NR	NR	30 d morbidity	OR = 4.08; 95%CI: 1.43-11.64, P = 0.006
Sabel <i>et al</i> ^[38]	United States	5	R	302	68	52	Colorectal resection	Psoas area;	58	34	NR	NR	NR	No outcome analysis	NR
Lieffers <i>et al</i> ^[39]	Canada	5	R	234	63	135	Colorectal resection	Skeletal muscle index	6	NR	NR	NR	NR	Postoperative complications	OR = 4.6; 95%CI: 1.513-9, P = 0.007
Reisinger <i>et al</i> ^[50]	The Netherlands	5	P/R	340	69	50	Colorectal resection	L3 muscle index	21	24	NR	NR	NR	Postoperative complications	OR = 43.3; 95%CI: 2.74-685.2, P = 0.007
Huang <i>et al</i> ^[30]	China	6	P	142	62	62	Colorectal resection	L3 muscle index and gait speed and grip strength	28	NR	NR	NR	NR	Postoperative complications	OR = 4.524, 95%CI: 1.584-12.921, P = 0.007

¹According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

United States in 2014, gastro-esophageal cancer is a leading indication for cancer resection in the Eastern hemisphere^[61,62].

Frailty and gastro-esophageal malignancies

Because the incidence of esophageal and gastric cancer increases with age, there has been a particular interest in the management of these diseases in older patients. In

Table 3 Compiles the characteristics of all trials which evaluated frailty in patients undergoing hepato-pancreaticobiliary resections

Ref.	Country	Quality score ¹	Study design	Sample size	Age (yr)	Male sex (%)	Surgery type	Parameter used to define frailty	Postoperative complication rate	Follow-up (mo)	30-d morbidity (%)	30-d mortality (%)	1-yr OS (%)	5-yr OS (%)	Outcome parameter	Frailty/outcome (OR)
Harimoto <i>et al</i> ^[40]	Japanese	6	R	186	67	40	Partial hepatectomy HCC	L3 muscle area	NR	60	NR	NR	NR	71	5 yr survival	OR = 0.9; 95%CI: 0.84-0.93, P = 0.002
van Vledder <i>et al</i> ^[41]	The Netherlands	5	R	196	65	61	Liver resection for CRLM	Skeletal muscle mass	NR	29	NR	NR	94	43	Overall survival	OR = 14.4; 95%CI: 18.76-31.2
Valero <i>et al</i> ^[42]	United States	7	R	96	62	61	Liver resection liver transplantation	Total psoas area and total psoas volume	29	26	NR	NR	82	47	Complication rate	OR = 3.06; 95%CI: 1.07-8.52, P = 0.003
Englesbe <i>et al</i> ^[43]	United States	5	R	163	53	NR	Liver transplantation	Total psoas area and psoas density	NR	36	NR	NR	NR	NR	Overall survival rate	OR = 0.27; 95%CI: 0.11-0.33, P = 0.001
Waits <i>et al</i> ^[44]	United States	8	R	348	51	62	Liver transplantation	Total psoas area and psoas density and age - summarized in new parameter "monomorphometric age"	NR	60	NR	NR	85	59	1 and 5 yr survival	OR = 1.04; 95%CI: 1.03-1.06, P = 0.001
Masuda <i>et al</i> ^[45]	Japanese	5	R	2014	48	50	Living donor liver transplantation	Total psoas area	18	60	NR	NR	75	89	1 and 5 yr survival	OR = 2.06; 95%CI: 1.1-4.2, P = 0.05
Kaido <i>et al</i> ^[46]	Japanese	6	P	124	54	NR	Living donor liver transplantation	Skeletal muscle mass and bioimpedance analysis	NR	60	NR	NR	80	73	1 and 5 yr survival	OR = 4.85; 95%CI: 2.092-11.79, P = 0.001
Peng <i>et al</i> ^[46]	United States	6	R	259	68	60	Liver resection for CRLM	Total psoas area	10	60	NR	NR	65	26	Postoperative complications	OR = 3.1; 95%CI: 1.14-8.29, P = 0.02
Amini <i>et al</i> ^[47]	United States	7	R	763	67	57	Pancreatic resection	Total psoas area and total psoas volume	48	24	0.5	48	76	24	Postoperative complications	OR = 1.79; 95%CI: 1.15-2.56, P = 0.002
Dale <i>et al</i> ^[48]	United States	9	P	76	67	55	Pancreaticoduodenectomy	Fried's criteria, Short Battery, Vulnerable Elderly Survey	80	1	4	21	NR	NR	Postoperative complications	OR = 4.06, P = 0.01
Joglekar <i>et al</i> ^[49]	United States	6	R	118	65	75	Pancreatic resection	Total psoas index and psoas density	78	3	NR	23	NR	NR	Postoperative complications	OR = 2.78; 95%CI: 2.28-22, P = 0.02
Peng <i>et al</i> ^[45]	United States	6	R	557	66	53	Pancreatic resection	Total psoas area	47	36	NR	NR	62	3 a OS: 36	3 yr OS	OR = 1.68; 95%CI: 1.32-2.11; P = 0.001

¹According to the Newcastle-Ottawa Scale ranging from 1 to 9 stars. Age and OS are presented as median values unless indicated otherwise. NR: Not reported; OS: Overall survival; OR: Odds ratio; P: Prospective trial; P/R: Retrospective analysis on prospectively collected data; R: Retrospective trial.

fact, in 2014 Balducci *et al*^[63] published guidelines on the treatment of older patients with gastro-esophageal malignancies. The authors noted that for individuals whose life expectancy without cancer exceed that with cancer, the estimated risk of chemotherapy complications may reveal those patients in need of additional care and those patients in whom the risk of treatment may exceed the potential benefits. Importantly, the authors noted that the individual's general life expectancy should be defined using the CGA and an assessment of patient frailty.

Table 4 Makary *et al*^[22] did report on the surgical outcomes of a large cohort of older patients in which frailty was assessed using a frailty scale based on the fried frailty phenotype

Characteristic	
Weakness	Weakness should be assessed by grip strength and measured directly with a hand held JAMAR dynamometer (Sammons, Preston Rolyan). Three serial tests of maximum grip strength with the dominant hand will be performed and a mean of the three values will be calculated and adjusted by body mass index and gender. Actual weakness will be defined in the lowest 20 th percentile of a community dwelling adults of 65 yr and older
Shrinking	Shrinking should be defined through a self-report as unintentional weight loss above 10 pounds during the last year
Exhaustion	Exhaustion should be measured by responses following 2 statements from the modified 10 items Center for Epidemiological Studies - Depression scale: "I felt that everything I did was an effort and I could not get going" and "How often in the last week did you feel way?" and will be given the opportunity to reply with 0 = rarely or none of the time (< 1 d); 1 = some or a little time (1-2 d); 2 = a moderate amount of time (3-4 d); and 3 = most of the time. Patients answering either with 2 or 3 will be classified as exhausted
Low activity	Physical activities should be assessed using the Minnesota Leisure Time Activities Questionnaire which includes frequency and duration. The focus should be placed on activities in the past 2 wk prior to operation. Weekly tasks will be converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure in the lowest 20 th percentile for their gender will be classified as having low activity
Slow walking speed	Walking speed should be measured combining 3 trials of walking 15 feet at a normal pace for the patient. Patients with a walking speed in the lowest 20 th percentile, adjusted for gender and height, will be scored as having a slow walking speed

Sarcopenia and gastro-esophageal malignancies

Specific publications on the impact of frailty and sarcopenia on postoperative outcomes following gastro-esophageal surgery are rather scarce (Table 1)^[34,35,63]. In a small study, Pultrum *et al*^[64] reported that esophagectomy was justified in older patients as advanced age alone had only a minor impact on a patients' postoperative course. The authors noted, however, that frailty was much more strongly associated with both short- and long-term outcomes among patients undergoing esophageal surgery. In a separate study, Hodari *et al*^[34] examined a much larger cohort of 2095 patients undergoing esophagectomy and reported that higher frailty scores were associated with increased postoperative morbidity and mortality. In this study, the frailty score was divided into 5 different categories and the incidence of peri-operative mortality incrementally increased with the frailty score, with mortality only 1.8% among patients with a frailty score 0 vs 23.1% among those patients with a frailty score 5 ($P = 0.001$). While the authors assessed several other parameters associated with postoperative outcomes, only age and

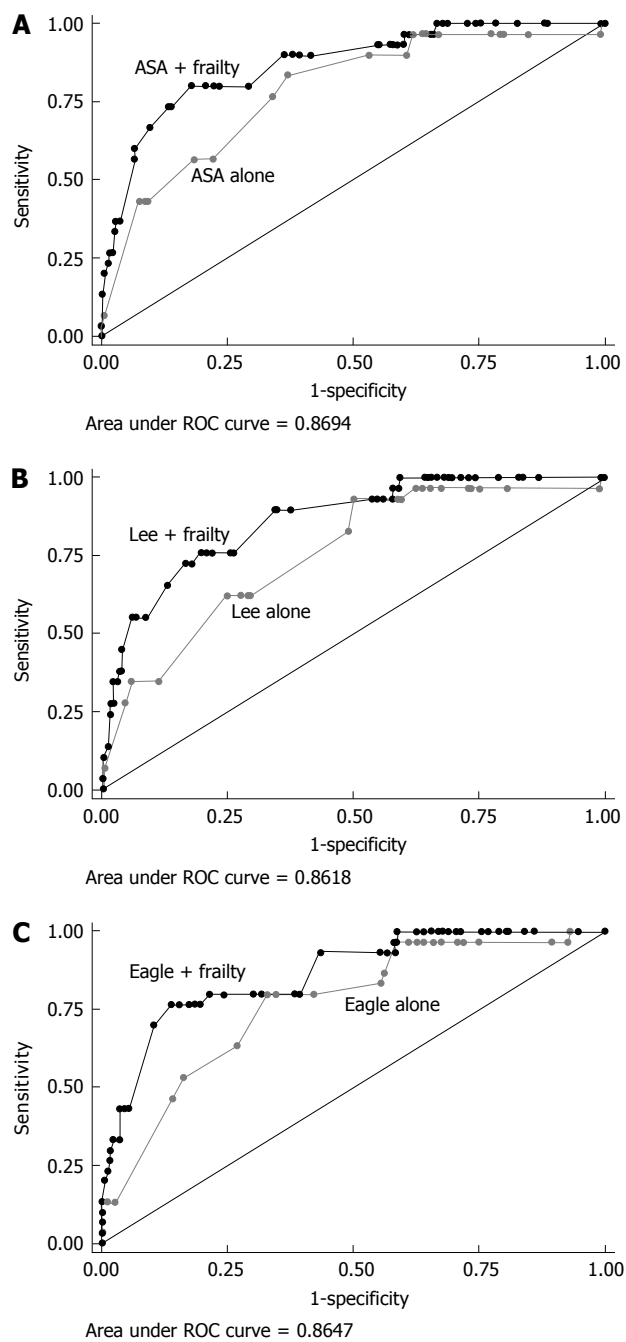


Figure 2 Power of frailty to predict worse outcomes was much higher than traditional peri-operative assessments. A: American Society of Anesthesiologists (ASA); B: Lee; C: Eagle risk indices. Each panel shows the area under the receiver operator characteristics (ROC) curve to demonstrate the ability of the specific risk index to predict surgical complications and discharge to an assisted or skilled nursing facility. Frailty was added to the risk index scoring to demonstrate the combined ability of these indices to predict discharge disposition. Used with permission Makary *et al*^[22], 2010.

frailty were significantly associated with risk of peri-operative morbidity and mortality. Examining a separate cohort of patients undergoing esophageal cancer, Sheetz *et al*^[35] confirmed a strong association between frailty, sarcopenia and peri-operative risk of morbidity among patients undergoing esophagectomy. Using preoperative computed tomography scans in 230 subjects who had undergone transhiatal esophagectomy for malignancy,

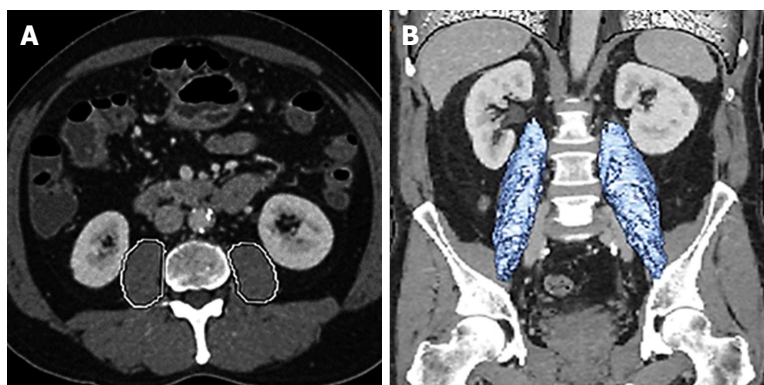


Figure 3 Define sarcopenia rather than a single axial image. A: Total psoas area is measured by circling both psoas muscles at the level of the patients computed tomography where both iliac crests are visible; B: Total psoas volume is measured at the full length of the psoas muscles and normalized for the patients body surface area. Used with permission Amini *et al*^[47], 2015.

the authors assessed lean psoas area (LPA) and correlated it with overall and disease-free survival^[35]. Analyses demonstrated that increasing LPA correlated with both overall and disease-free survival and the authors concluded that core muscle size appeared to be an independent predictor of outcome^[35].

To date, the role of sarcopenia to predict perioperative outcomes among patients undergoing esophagectomy has been evaluated in only a handful of studies^[26,27]. Yip *et al*^[26] studied 35 patients who received neoadjuvant chemotherapy followed by surgical resection for esophageal cancer. The authors noted that changes in computed tomography body composition were associated with outcomes. Specifically, fat mass, subcutaneous fat to muscle ratio and visceral to subcutaneous adipose tissue ratio were each associated with circumferential resection margin. While sarcopenia was more prevalent after neoadjuvant chemotherapy, changes in body composition were not associated with perioperative complication or survival. In a separate study, Awad *et al*^[27] similarly noted marked changes in body composition following neoadjuvant chemotherapy for esophageal cancer. In this study, the authors reported on 47 patients treated with neoadjuvant chemotherapy for esophageal cancer. The proportion of patients with sarcopenia increased from 57% pre-therapy to 79% post-neoadjuvant therapy. Similar to the study by Yip *et al*^[26], no association was demonstrated between sarcopenia and hospital stay, morbidity or mortality. Given the very small number of patients included in the studies by Yip *et al*^[26] ($n = 35$) and Awad *et al*^[27] ($n = 47$), the lack of association between sarcopenia and peri-operative outcomes may have been due to low sample size and a type II statistical error. Future larger studies are necessary to better delineate the impact of sarcopenia on peri-operative and long-term outcomes among patients with esophageal cancer undergoing surgical resection.

Similar to esophageal cancer, gastric cancer patients are at high risk for malnutrition and therefore older patients with gastric cancer may be at a particularly high risk of frailty. In fact, the prevalence of frailty and

sarcopenia among patients with gastric cancer has been reported to be as high as 30% and 38%, respectively^[49,65]. Despite the high incidence, data on the association of frailty, sarcopenia and outcomes of patients after gastric resection are limited. In a review on the topic of gastric cancer surgery, Tegels *et al*^[49] described a strong association between frailty, sarcopenia and increased postoperative mortality after gastric resections. Specifically, the authors highlighted the need for better preoperative risk assessment using comorbidity index, assessment of nutritional status, and frailty assessment. In particular, Tegels *et al*^[65] noted that assessment tools such as the Groningen Frailty Indicator (GFI), Edmonton frail scale, or the Hopkins frailty scale should be used to help identify patients for preoperative optimization using pre-habilitation. In a separate prospective study of 180 patients with gastric cancer, the same authors examined the association of frailty with morbidity and mortality after gastric cancer surgery. In this study, patients scheduled for gastric cancer surgery were preoperatively assessed with the GFI and the Short Nutritional Assessment Questionnaire (SNAQ). Of note, patients with a $GFI \geq 3$ had a mortality of 23.3% vs 5.2% in the lower GFI group. Similarly, those patients who scored poorly on the SNAQ had a higher mortality (13.3%) vs those deemed to have better nutritional status (3.2%). The authors concluded that frailty and nutritional status were important factors in preoperative decision making among elderly patients being considered for gastric resection. While the impact of frailty and malnutrition on perioperative outcomes has been examined, no study on the role sarcopenia to predict morbidity and mortality of patients undergoing gastric surgery has been reported to date.

COLORECTAL CANCER

In 2014, 132700 patients were diagnosed with colorectal cancer in the United States. More than half of patients with colorectal cancer are older than 65 years and approximately 70% are diagnosed at early stages, when surgical resection is feasible^[66].

Frailty and colorectal cancer

Among older patients undergoing surgery for colorectal cancer, frailty and sarcopenia have been investigated as predictors of outcome in a small number (Table 2). In particular, pre-operative frailty has been associated with a decline in the patients' activities of daily living and the instrumental activities of daily living after colon resection^[67]. Other studies have noted that frailty can significantly impact peri-operative outcomes. For example, Obeid *et al*^[36] reported on a large group of patients ($n = 58448$) with colorectal cancer derived from the NSQIP database. The authors noted that the proportion of patients who experienced a severe Clavien class IV-V complication following colorectal surgery increased from 5.8% to 56.3% when comparing non-frail vs frail patients ($P = 0.0001$). Frailty was also independently associated with a longer intensive care unit stay and increased peri-operative mortality. In a different study, Neuman *et al*^[37] reported on 12979 patients from the SEER-Medicare database above the age of 80 who underwent a colorectal resection. Older age, male gender, frailty, and dementia were all associated with decreased survival at 1 year. Although only 4.4% of patients were considered frail, this factor had the strongest association with mortality with an odds ratio of 8.4. While the authors concluded that frailty was an important predictor of outcome, the study was limited due to the nature of the administrative data used in the analyses. In a different study that utilized institutional data, Robinson *et al*^[68] reported on 201 subjects, many of whom underwent an elective colorectal surgery. Pre-operative frailty was associated with increased post-operative complications after colorectal surgery (frail 58% vs non-frail 21%); frail patients also had longer hospital stays and higher 30-d readmission rates. Furthermore, frailty has noted to be a good predictor of complications (AUC 0.702). Other authors have noted that an elderly modified Physiological and Operative Severity Score for the enumeration of Mortality and morbidity (E-POSSUM) is also a good tool for predicting mortality after major colorectal surgery in the elderly (AUC 0.86)^[29,31].

Sarcopenia and colorectal cancer

Similar to frailty, the effect of sarcopenia on post-surgical outcomes of patients with colorectal cancer has only been evaluated in a limited fashion. Robinson *et al*^[68] prospectively examined 302 patients who underwent resection of colorectal cancer and noted that psoas density was a better predictor of postoperative complications compared with age, body mass index or preoperative patient comorbidities. The authors reviewed patient computed tomography scans to measure psoas area, density, subcutaneous fat, visceral fat and total body fat. Among the parameters studied, psoas density was found to be the best predictor of surgical complications among patients undergoing colectomy for colon cancer. In a separate prospective study by Lieffers *et al*^[39] that included 234 older patients who underwent

colon resection, sarcopenia was strongly associated with delayed recovery, postoperative infections (23.7% sarcopenic patients vs 12.5% non sarcopenic patients, $P = 0.025$), as well as an increased risk of discharge to a nursing facility (14.3% sarcopenic patients vs 5.6% non sarcopenic patients, $P = 0.024$)^[39]. Similarly, Reisinger *et al*^[50] reported a series of 331 older patients who underwent colorectal cancer surgery and demonstrated that a combination of age related parameters such as frailty, sarcopenia and malnutrition were strongly associated with adverse outcomes. Sarcopenia alone was predictive of 30 d in hospital mortality (8.8% sarcopenic vs 0.7% nonsarcopenic patients, $P = 0.001$). Most recently, Huang *et al*^[30] defined sarcopenia through a combination of monomorphometric measurements and physical performance and used it to define low postoperative outcomes. By this, the authors showed, that including the muscles' functional aspect (handgrip strength and 6-m usual gait speed) to the definition of sarcopenia results in a better prediction for postoperative complications as compared to measurement alone.

HEPATO-PANCREATO-BILIARY MALIGNANCIES

Surgery is commonly used to treat patients with a wide variety of hepato-pancreato-biliary (HPB) diseases. Many of these disease including liver, biliary, and pancreatic malignancies are more common in an aged population. In addition, HPB procedures tend to be complex operations that can be associated with substantial possible morbidity. As such, accurate preoperative assessment of aged patients being considered for HPB surgery is of particular importance.

In 1997, in one of the earlier studies to examine the impact of age on HPB surgery, Fong *et al*^[69] reported on the outcome of 133 patients over the age of 65 years who underwent a hepatic resection. In this study, Fong *et al*^[69] noted that age was an independent risk factor for increased risk of morbidity. Perhaps more importantly, however, the authors noted that major hepatic resection could be performed safely and with good functional outcomes among well-selected aged patients. Over the last several decades, multiple other investigators have similarly reported good outcomes in well-selected older patients undergoing hepatic resection^[70,71]. For example, Reddy *et al*^[71] reported on 856 patients who underwent a major hepatectomy (resection of 3 or more segments) and noted that increasing age was independently associated with postoperative mortality. In fact, each 1-year and 10-year increase in age resulted in an odds ratio of mortality after major hepatic resection of 1.036 and 1.426, respectively. In a separate study of 7764 patients who had colorectal liver metastasis, Adam *et al*^[72] noted that age was associated with outcome, but major resection could be performed in elderly patients with acceptable morbidity. The authors found higher

mortality and morbidity rates in older than in younger patients [3.8% and 32.3% in older, 1.6% and 28.7% in younger patients (both $P < 0.001$)] but did not further investigate frailty or sarcopenia in this cohort. Sixty-day postoperative mortality and morbidity were 3.8% and 32.3%, respectively, compared with 1.6% and 28.7% in younger patients. Of note, 5-year survival was relatively comparable even among very aged patients (70–75 years: 57.8% vs 75–80 years: 55.3% vs > 80 years: 54.1%), suggesting that surgery may have potential benefit even in very well selected aged patients.

Frailty and hepato pancreatico biliary malignancies

While age has been the topic of several investigations, the specific impact of frailty itself has been less well studied. Giovannini *et al.*^[73] suggested that a decrease in serum albumin may be a marker of frailty due to an altered albumin synthesis and the patient's inability to compensate for albumin loss. Unlike frailty, while still limited, several papers have investigated the impact of sarcopenia on outcomes after liver surgery^[40,43,74,75]. Several studies have noted an association between sarcopenia and both short- and long-term outcomes among patients undergoing hepatic surgery^[40,41,43,74,75]. For example, Durand *et al.*^[74] studied whether muscle atrophy was of prognostic value among patients with cirrhosis undergoing surgery. The authors demonstrated that transversal psoas muscle thickness was significantly associated with mortality, independent of Model for End Stage Liver Disease (MELD) score. In a different study, Valero *et al.*^[42] examined whether sarcopenia impacted the risk of post-operative complications following resection or transplantation in patients with primary liver tumors. Among 96 patients, the presence of sarcopenia was an independent predictive factor of post-operative complications, but was not associated with long-term survival. In a study that examined only liver transplant recipients, Englesbe *et al.*^[43] noted that psoas area correlated poorly with MELD score and serum albumin. Central sarcopenia strongly correlated with mortality after liver transplantation, as 1-year survival was 49.7% among transplant recipients with the smallest psoas area vs 87.0% among transplant recipients with the largest psoas area. Kaido *et al.*^[32] reported a similar effect on a cohort of 124 living donor liver transplant patients in 2013. In this study the overall survival rate in patients with low skeletal muscle mass was significantly lower than in patients with normal/high skeletal muscle mass ($P < 0.001$). Other studies have similarly noted that morphometric age correlated with morbidity and mortality after liver transplantation with better discrimination than chronological age^[44,76]. Sarcopenia has similarly been demonstrated to be an important prognostic factor for patients undergoing liver resection for colorectal liver metastasis. Peng *et al.*^[46] reported that sarcopenia was strongly associated with an increased risk of major complications, extended intensive care unit stay, and a longer overall hospital.

Sarcopenia and hepato pancreatico biliary malignancies

Similar to liver resection, frailty and sarcopenia have not been widely assessed in patients after pancreatic operations. Several studies have reported that age is a risk factor for increased morbidity and mortality^[77-79]. For example, in one large study that investigated over three-thousand patients who underwent pancreatic resection in the state of Texas, Riall *et al.*^[77] reported that increased age was an independent risk factor for mortality after pancreatic resection. In fact, in-hospital mortality increased with each increasing age group from 2.4% among patients < 60 years to 11.4% among patients > 80 years. Likewise, postoperative length of stay increased with each increasing age group, going from 11 to 15 d. Of particular interest was the authors' finding that the increase in mortality among older patients was most pronounced among those patients treated at a low vs high volume hospital. While these data and others suggest therefore that age may be associated with outcomes, multiple other studies have noted that pancreatic surgery can be performed safely in well selected older patients^[78-80]. Dale *et al.*^[33] prospectively evaluated the additional value of geriatric assessment in a cohort of older patients undergoing a pancreaticoduodenectomy for pancreatic tumors. Among 76 older patients, significant unrecognized vulnerability was identified using the geriatric assessment. In turn, Fried's exhaustion, a vulnerable elders survey score > 3, as well as a short physical performance battery score < 10 all correlated with an increased risk of severe complication after pancreaticoduodenectomy. As such, the authors concluded that geriatric assessment may help identify older patients at high risk for complication from pancreatic surgery.

Several series have similarly suggested that sarcopenia may be an important predictor of post-operative morbidity and mortality following pancreatic surgery^[45-48]. For example, Joglekar *et al.*^[48] reported a relation between sarcopenia defined by the psoas muscle density and worse outcome after pancreatic resection. In a separate study, Peng *et al.*^[45] examined 557 patients undergoing resection of pancreatic adenocarcinoma and reported on the impact of sarcopenia on outcomes following surgery. Sarcopenia was associated with an increased three year mortality (HR = 1.63, $P < 0.001$) (Figure 4A). Of note, even after controlling for tumor-specific factors such as poor tumor differentiation, margin status, and lymph node metastasis, sarcopenia defined by TPA remained independently associated with risk of long-term death. More recently, rather than assessing sarcopenia using only two-dimensional imaging, the same group reported on the effect of three-dimensional psoas volume (TPV) on outcomes following pancreatic resection^[47]. In this study, Amini *et al.*^[47] noted that more patients were identified as sarcopenic by TPA than TPV. Perhaps more importantly, while TPA-sarcopenia was not associated with a higher risk of postoperative complications (OR = 1.06), TPV-sarcopenia was as strong predictor of post-operative morbidity (OR = 1.79). On multivariate analysis, TPV

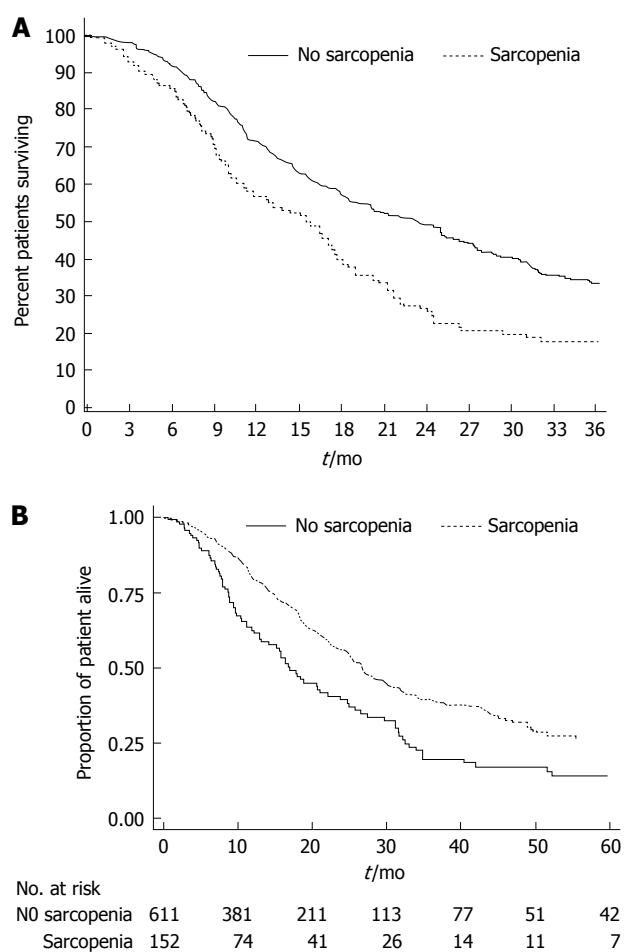


Figure 4 Sarcopenia was associated with an increased three year mortality. A: The presence of sarcopenia was also associated with the risk of death (no sarcopenia, 18.0 mo; 40.0% vs sarcopenia, 13.7 mo; 23.0% vs median, 3-yr survival, respectively; $P = 0.01$) in patients undergoing pancreatic surgery. Used with permission Peng *et al*^[45], 2012; B: The overall survival according to total psoas volume stratified by sarcopenia patients vs no sarcopenia patients quartiles in patients undergoing pancreatic surgeries. Used with permission Amini *et al*^[47], 2015.

- sarcopenia remained an independent risk factor of postoperative complications (OR = 1.69), as well as long-term survival (OR = 1.46) (both $P < 0.05$) (Figure 4B).

CONCLUSION

As the population ages, an increasing number of older patients will require complex gastrointestinal surgical procedures. While chronologic age is an important element in assessing a patient's peri-operative risk, physiologic age is a more important determinant of outcomes. Geriatric assessment tools are important components of the pre-operative work-up and can help identify patients who suffer from frailty. Such data are important, as frailty has repeatedly been demonstrated to be one of the strongest predictors of both short- and long-term outcome following complicated surgical procedures such as esophageal, gastric, colorectal, and HPB resections. Frailty can sometimes, however, be difficult to assess in an accurate and timely manner.

As such, there has been an increasing interest in determining a patient's "morphometric age". Sarcopenia, or wasting of lean muscle mass, has been noted to be an emerging important metric of frailty that is associated with peri-operative outcomes. As demonstrated by the data herein reviewed, screening of patients being considered for gastrointestinal surgery should include an assessment of frailty and sarcopenia to target high risk patients for pre-habilitation. Future studies will need to continue to define the optimal combination of factors (e.g., clinical, performance, and morphometric) to predict optimally a patient's peri-operative risk.

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