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Impact of Skeletal Muscle Loss and Functional Deconditioning on Outcomes in Hepatic Resection and Liver Transplantation: A Review

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Abstract

A growing number of older and sicker patients are being offered surgical intervention for their ailments. The effects of frailty and sarcopenia, syndromes characterized by loss of muscle mass and functional reserve are more prevalent in this population, and operative outcomes are just beginning to be elucidated. Here, we provide a review of published reports on mortality, morbidity and resource utilization in liver transplant and hepatectomy on frail and/or sarcopenic adults. Fourteen studies were selected for review; 82% of analyses reporting described greater resource utilization (e.g. length of stay, readmissions) in the frail cohort, 80% demonstrated increased rates of morbidity. The majority of included studies (69%) reported higher mortality in the debilitated groups undergoing liver transplant or hepatectomy with hazard of death ranging from 1.05-26.4. Though the preponderance of studies pointed to worse outcomes for frail or sarcopenic patients; lack of uniformity on the operational definition of these concepts makes generalization and clinical application difficult. A validated, practicable measure can help surgical teams identify candidates at greater risk of poor outcomes and implement interventions to reduce such hazards.

Keywords: Frail; Sarcopenia; Liver transplantation; Liver surgery; Outcomes

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Introduction

Healthcare providers are amidst a dynamic shift in the demographics of their surgical candidate population. The benefits of intervention, innovations in anesthesia and surgical technique as well as improvements in medical care have offered older and sicker patients an operative option for their ailments. Based on 2010 data, adults over 65 in the United States underwent 37% of all inpatient procedures- a rate much higher than their 13% share of the population [1,2]. This proportion is only certain to escalate. By 2030, 72 million Americans (1 in 5) will be an older adult [3]. Likewise, the global population of older persons is increasing at 2.6% per year, a rate more than twice that of the population as a whole [4].

Despite progress, research continues to show that older individuals suffer worse outcomes in terms of 30-day post-operative mortality and greater perioperative complications than their younger counterparts [5-9]. Arguments for distinctions between numerical and physiological age, however, are becoming more prevalent. Proponents argue that chronological age has incorrectly been used as a surrogate for that which has greater influence on outcomes: physiological deconditioning [10,11]. Debility has been operationalized in surgical research in two broad categories: frailty and sarcopenia.

Frailty, generally described as the loss of reserve capacity across organ systems and high susceptibility to stressors, has been a growing concept in the literature over the past two decades. Though not fully understood, its pathophysiology is marked by chronic inflammation, compromised immunity, neuroendocrine and metabolic dysregulations, with contributing psychosocial factors [12]. The frailty syndrome has been correlated with higher mortality, falls, and hospitalizations [10]. Sarcopenia, first described as the loss of skeletal muscle mass, has evolved to incorporate cellular processes and outcomes such as decreased muscle strength, diminished mobility and function; it has also been associated with heightened risk of adverse events [13]. Though not inclusive of the psychosocial component of the frailty syndrome, phenotypically the two are similar and arguments to utilize sarcopenia in research and clinically are proliferating in the literature [14,15].

Two leading models to measure frailty are deficit accumulation and the frailty phenotype. Deficit accumulation, popularized by Mitnitski et al. [16] outlines the consequences of frailty in

Table 1: Characteristics and results of included studies.

Author, Year, Study Design, n	Type of Surgery	Measure of Frailty/ Sarcopenia	% Subjects Frail or Sarcopenic	Results- Resource Utilization (Frail/Sarcopenic vs. Non)	Results- Morbidity (Frail/Sarcopenic vs. Non)	Results- Mortality (Frail/Sarcopenic vs. Non)
Harimoto [39], retrospective, N=186	Hepatic Resection	CT x-section of total skeletal muscle area at L3 region normalized for height Cutoffs (cm^2/m^2): Men: 43.75, Women: 41.1	40.3%	Not assessed	No significant difference in Clavien-Dondo grade 3 post-op complications	Decreased 5 yr overall: 71% vs 83.7% (p=0.001) survival; Diminished survival with low muscle mass: HR= 0.90 (p=0.002) on multivariate analysis
Louwers [25], retrospective, N=10,300	Hepatic Resection (open)- malignant and benign indications	Modified Canadian Study of Health and Aging Frailty Index using variables from NSQIP database (mFI)[43], broken intoquintiles (analyzed trends, HRs based on lowest vs. highest)	2.6%	Extended LOS (>75th percentile for NSQIP surgery type) with increased mFI score p<0.001; 43.0% rate in frailest vs. 27.6% in non-frail group	Positive correlation between rate of Clavien grade 4 complications & mFI (p<0.001); 15.8% in highest mFI group vs. 5.0% in lowest- Multivariate OR= 40.0 (p<0.001)	Significant positive trend in mortality with increasing mFI score (p<0.001);9.1%mortality rate in most vs. 1.5% in non-frail- Multivariate OR 26.4 (p<0.001)
Peng [24], retrospective, N=557	Hepatic Resection or Resection + RFA for Colorectal Liver Mets	Peri-operative CT x-section of total psoas muscle area at L3 Cutoffs (cm^2/m^2): M&F: 50	15.8%	Prolonged ICU stay (>2 days) 15% vs. 4% (p= 0.004); Overall longer hospital stay 6.6 vs. 5.4 days (p= 0.03)	Increase in major complications (Clavien grade≥3) 22% vs. 8% (p=0.008), OR=3.12 (p=0.02) on multivariate analysis	No difference in 5-yr survival: 23% vs. 27% (p=ns)
vanVledder, 2012[30], prospective, N=196	Hepatic Resection for Colorectal Liver Mets	CT x-section of skeletal muscle area at L3 region normalized for height. Cutoffs (cm^2/m^2): M: 43.75, F: 41.1	19.4%	Not assessed	Not assessed	Overall reduced median survival: 23.8 vs. 59.8 mo (p=0.001). Lower 1 yr: 84% vs. 96.2%, 3 yr: 34% vs. 64.6%, and 5 yr: 28.5% vs. 49.9% (p<0.001) overall survival; HR = 2.53 (p<0.001) on multivariate analysis
Voron [31], retrospective, N=109	Hepatic Resection for HCC	CT x-section of total muscle area at L3 when both pedicles visible normalized for height Cutoffs (cm^2/m^2): M: 52.4,F: 38.9	54%	Not assessed	Similar rates of severe (Clavien grade ≥ 3) complications: 20.3% vs. 16% (p=0.56)	No difference in 60 day mortality; Increased overall mortality- HR= 3.19 (p=0.013)
Valero [22], retrospective, N=96	Hepatic Resection or Transplant for HCC or ICC	CT x-section of total psoas muscle volume (TPV) at L3 Cutoffs (cm^3/m): M: 34.14, F: 22.93	48.9% (comparable rates resection vs. transplant)	No difference in LOS: 12.1 vs. 9.7 days (p=0.50)	Higher rates of overall complications: 40.4% vs. 18.4%- multivariate OR= 3.06 (p=0.03); Greater incidence of Clavien grade 3: 23.4% vs 0%	Nodifferencein survival: 5 yr overall survival 41.8% vs. 52.5%- multivariate HR overall survival=1.34 (p=0.43)
DiMartini [23], retrospective, N=338	Liver Transplant- Donor type not specified	CT x-section of skeletal muscle area at L3-4region Cutoffs (cm^2/m^2): M: 52.4, F: 38.5	68% (M: 76%, F: 51%)	M: 12%, 9%; F: 4%, 3% longer ICU & hospital LOS per 10% decrease in muscle mass (p<0.001 for all) M: 18%increased likelihood of institutionalization at discharge per 10% decrease in muscle mass (p<0.05) F: No difference	M: 13%, F: 7% increase in time intubated per 10% decrease in muscle mass (p<0.001)	M: 5% decreased overall survival with each 1 unit reduction in muscle area; HR= 0.95 (p=0.01) F: No difference
Englesbe [28], retrospective, N= 163	Liver Transplant- Deceased Donor	Total psoas muscle area at L4 in mm2, in quartiles	Broken into quartiles by TPA	Not assessed	Not assessed	Lower 1 and 3 year survival in lowest TPA quartile vs. highest: 49.7% vs. 87.0%, 26.4% vs. 77.2%; Correlated with higher mortality: per $1000mm^2$ decrease in TPA HR=3.7 (p<0.0001)
Kaido [44], retrospective, N=124	Liver Transplant- Living Donor	Bioelectrical impedance analysis; Cutoff: <90% standard skeletal muscle mass	37.9%	Not assessed	Not assessed	Diminished 1 year survival: 59% vs. 87% (p< 0.001)

Krell [45], retrospective, N=207	Liver Transplant-Deceased Donor	Total psoas muscle area at L4 in mm^2, in tertiles	Broken into tertiles by TPA	Not assessed	Lower TPA associated with increased odds of infection: OR 4.6 (p< 0.01)- lowest tertile vs. highest tertile	Infection confers lower 1 yr survival 76% vs. 92%; OR= 2.4 (p=0.003)
Lee [29], retrospective, N=325	Liver Transplant-Donor type not specified	CT of dorsal muscle group area (DMGA) at T12	Broken into tertiles by DMGA	Not assessed	Greater incidence of complications: 90.3% vs. 69.8%- lowest tertile vs. highest tertile- 1.4 fold higher adjusted complication rate	Higher rates of adjusted 1 and 5 year mortality: 24.9% vs. 7.6%; 62.3% vs. 10% in lowest vs. highest muscle area tertile- post-transplant mortality OR=1.62 per SD decrease in muscle area (p<0.001)
Masuda [46], retrospective, N=204	Liver Transplant-Living Donor	CT x-section of psoas muscle area at L3. Sarcopenia Cutoffs ($cm^{2)}$: M: 800, F: 380	47.1%	Not assessed	Higher rates of sepsis: 17.7% vs. 7.4% (p=0.03), held on multivariate analysis (p=0.009)	Lower 3 and 5 yr survival 74.5% vs. 88.9% (p=0.02); 69.7% vs. 85.4% (p=0.02); Increased risk of death HR=2.06 (p=0.047) on multivariate
Montano-Loza [26], retrospective, N=248	Liver Transplant-Donor type not specified	Mean muscle attenuation at L3 in Hounsfield units (HU). Sarcopenia cutoffs: BMI<25: <41 HU, BMI≥25: <33 HU	45%	Longer overall and intensive care unit length of stay: 40 vs. 25 (p=0.005); 12 vs. 6 days (p=0.001).	Greater frequency of bacterial infections in first 90 days post-transplant: 26% vs. 15% (p=0.04). No difference in overall infection rate: 29% vs 20% (p=0.1).	Statistically insignificant difference in median, 1 yr and 5 yr survival: 117 vs. 146mo median survival (p=0.4); 89% vs. 91% 1-year and 74% vs. 76% 5-year survival; Unadjusted overall HR= 1.23 (p=0.4)
Sonnenday (abstract) [27], prospective, N=73	Liver Transplant-Deceased Donor	Frailty instrument- walking speed, grip strength, unintentional weight loss, self-reported exhaustion and weekly physical activity	Not reported	Higher rates of discharge to skilled nursing facility: 20% vs. 9.3%; Higher 90 day readmission rates 67% vs. 43%	Greater rates of biliary complications 33% vs. 20%; renal failure 29% vs. 14%; and reoperation 8% in non-frail vs 100% in the most frail	Equivalent 1 yr post-transplant survival

Abbreviations: ADL: Activities of Daily Living; DMGA: Dorsal Muscle Group Area; F: Female; HCC: Hepatocellular Carcinoma; HU: Hounsfield Units; ICC: Intrahepatic Cholangiocarcinoma; L3/4- 3rd/4th: Lumbar Vertebrae; LOS: Length of Stay; M: Male; Mets: Metastasis; mFI: Modified Frailty Index; T12- 12th Thoracic Vertebrae; TPA: Total Psoas Area; TPV: Total Psoas Volume

terms of illness and impairments in physical function, lifestyle, and cognition. Fried's frailty phenotype standardizes the definition via biometric and self-reported variables including weight loss, grip strength, and activity level [10]. Akin to frailty, there is no agreed upon operational definition of sarcopenia; but most research protocols utilize quantitative methods such as muscle area on MR or CT, DXA, or bioelectrical impedance. Surgeons typically have the additional resource of abdominal imaging for pre-operative planning which can be used to incorporate assessment of muscle mass into routine evaluation. A recent review of biomarkers by the International Working Group on Sarcopenia, though, recommends adopting a comprehensive operational definition of the concept-gauging physical functioning of muscle above simply measuring mass [17].

Though more frequent in older adults, deconditioning is not synonymous with aging, it may also be a consequence of chronic disease. As seen in patients with cirrhosis awaiting liver transplantation (LT), the debilitating condition may also be the reason for operative intervention. Resulting from altered protein metabolism, poor nutritional intake due to factors including ascites and encephalopathy, as well as sedentary lifestyle partly attributed to the rigors of the disease, frailty and sarcopenia are common in those with end stage liver disease. In a single center study of those undergoing LT evaluation, 40% were sarcopenic, correlating with heightened mortality on multivariate analysis (HR 2.18 p= 0.006); another transplant center determined 17% of their studied evaluations to be frail and at increased risk of waitlist mortality independent of their model for end-stage liver disease (MELD) score (HR 1.45, p= 0.03) [18,19]. While disease burden is a significant contributor to frailty in the liver transplant population, a growing number of older

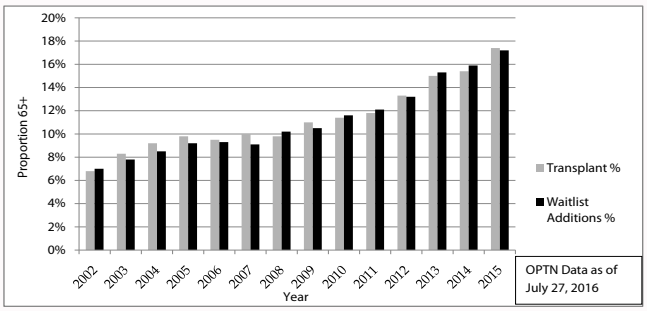

Figure 1: Proportion of Liver Transplants and Waitlisted Patients in the US Aged 65+.

adults are also undergoing transplant procedures. Between 2002 and 2015 the share of transplanted patients over the age of 64 more than doubled from to 6.8 to 17.4% (Figure 1).

Challenged with organ demand far outstripping supply and implementation of MELD system in 2002, LT patients tend to become more deconditioned while waiting for a viable organ to be offered. Transplant programs must balance equity with selecting the patients who are going to achieve the best outcomes with this precious resource.

Transplant is not the only surgical field which has seen growth, and whose trend is poised to continue in the near future. Attributed to the aging population, Etzioni et al. [20] project a twenty-year growth rate of 31% in general surgery (including abdominal and GI procedures) by 2020. Hepatobiliary specialties are expected to increase procedure volume by 25% between 2006 and 2020 [21]. The effects of frailty are more prevalent in this burgeoning population,

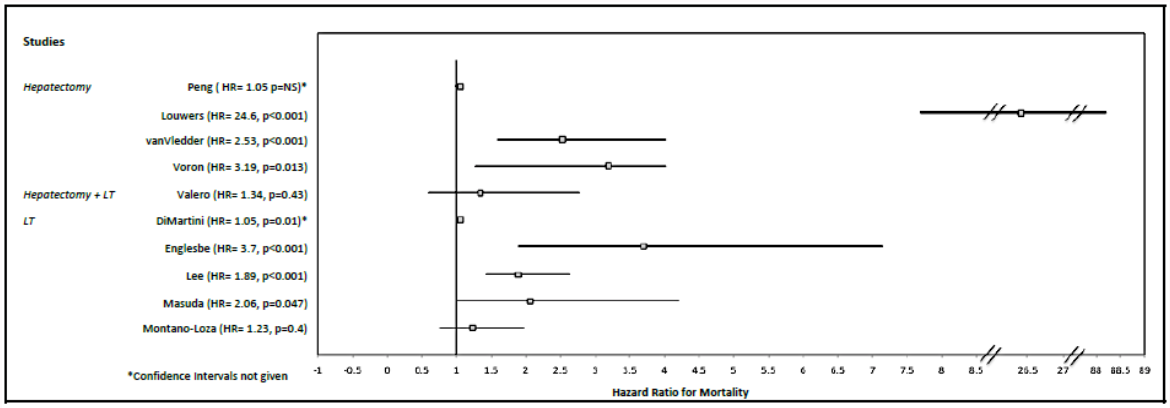

Figure 2: Hazard of Mortality in Included Studies.

and operative results are just beginning to be elucidated. Here, we provide a review of current research on the outcomes of hepatectomy and liver transplantation in frail and/or sarcopenic adults.

To qualify for inclusion, studies must have reported on post-surgical mortality in patients undergoing liver resection or transplantation (from deceased or living donors). Major complications and health care resource utilization are reported as secondary outcomes. Prospective and retrospective cohort studies and case-control analyses were eligible for inclusion. Studies measuring sarcopenia or frailty, though acknowledged as separate, yet intrinsically related clinical entities were included. Articles not published in English, and studies that did not report on the primary outcome measure (mortality) were excluded from review.

Findings

Characteristics and results of included studies are summarized on Table 1.

Fourteen studies were included. Rates of frailty or sarcopenia ranged from 2.6% to as high as 68% of included subjects. The selected papers consisted of eight studies on outcomes in liver transplantation (two of which were living donor), five in the resection population, and one paper that included both patients undergoing hepatectomy and those receiving a liver transplant for HCC.

Resource Utilization

All studies reporting on health care delivery metrics, save one, found at least one measure (overall or ICU length of stay (LOS), readmission, cost, etc.) of heavier utilization in the frailty/sarcopenia group. Length of stay was reported in five studies and ranged from non-significant [22] to 1.2-15 days, or 22-133% longer in the frail/sarcopenic contingent [6,23-26]. Average ICU LOS was increased by a range of 1-6 days [24,26] The only study to report on readmissions described 90-day post-transplant rates 24% above non-frail [27]. Institutionalization at discharge or inpatient rehab was assessed in two protocols and elevated in the frailty/sarcopenic arm in both by 11.7-18% [23,27].

Morbidity

The majority of studies (9 of 11 reporting) showed a greater incidence of morbidity in frail or sarcopenic subjects; all liver transplant articles described more complications in the debilitated cohort. Complications Clavien-Dondo grade ≥3 were analyzed in five studies and significantly elevated in three, with the odds of major complications 3.1-40.6 times greater than the non-frail comparator group [22,24,25]. Common morbidities included infection, respiratory failure, biliary complications, renal failure, and universal reoperation in the frailest LT patients in one study [27].

Mortality

Of the ten studies that provided hazard ratios, 70% found significantly greater likelihood of mortality with frailty/sarcopenia ranging from HR of 1.05 to 26.4 (Figure 2). Survival was assessed at different time points across studies. Peri-operative and one year survival rates were inconsistent between the six published reports with this outcome. Three of studies showed significantly higher 1 year mortality in those considered frail or sarcopenic (2 LT, 1 hepatectomy) [28-30]; whereas three others (2 LT, 1 hepatectomy) reported no short-term survival difference between groups [18,27,31]. Long-term survival ≥3 years were significantly diminished in frail/sarcopenic individuals in the majority of studies reporting this outcome (5/8). Of the four studies exclusively examining the liver transplant population, three reported greater hazard of death in sarcopenic patients.

Discussion

The past few years have seen frailty emerging from the world of geriatrics into the medical arena at large. As demonstrated by this review, there has been a recent burgeoning of studies in the surgical literature- all included papers have been published after 2010 and the majority in the past three years. This is likely a reflection both of the population surgeons are serving and the increasing recognition of frailty as a risk factor in outcomes. Other pressures are also impacting surgical practice. In an environment of ever-increasing scrutiny on outcomes and costs, it is essential to balance what is right for our patients with optimization of resources, be that cost and in the case of transplant- precious donated organs. Though not uniformly, the majority of studies on hepatectomy and liver transplant surgeries reported worse outcomes in morbidity and mortality, as well as greater health care utilization in frail patients.

Unsurprisingly, all studies that demonstrated greater health care utilization described statistically higher complication rates in the frail/sarcopenic group. A wealth of studies has demonstrated that post-operative complications and infections contribute to greater LOS, higher readmissions and costs and lower per patient contribution margins. [32-34] A recent in depth analysis specifically in the sarcopenic population, by Sheetz et al. [35] quantified the financial impact of surgery in this population: per 1000mm^2 decrease in lean

psoas area, there was a $6,989.17 increase in payer cost ($p < 0.001$). This figure increased dramatically- to $26,988.41 if complications arose. Robinson et al. [36] also performed a cost analysis in their study of veterans undergoing colorectal surgery and observed average 6-month post-operative health care costs to be $77,249 higher in the frail group. Though complications were not reported, greater discharge institutionalization and readmission rates were seen in the frail group.

Little consensus was reached across studies in regards to short-term mortality. This finding is especially interesting in the studies of liver transplant patients, where complication rates were clearly higher in frail/sarcopenic patients. This may be a result of these patients being followed closely to assess for and promptly manage any complications that arise. Long-term mortality in frail individuals was diminished in more than two-thirds of studies reporting on this outcome. This is likely not an effect of the intervention, but health status, including underlying operative indication. However, some recent studies have demonstrated halting and even reversal of sarcopenia post-transplant [26,37].

In 2002, MELD score was implemented across the United States to prioritize listing based on severity of liver disease. The utilization of MELD score has led to the reduction in a number of deaths of patients on the waiting list [38]. One of the major limitations of the MELD score, however, is its inability to evaluate and recognize the nutritional and functional status of patients with cirrhosis. Though both frailty/sarcopenia and MELD are predictors of pre-transplant mortality, MELD has not been shown to be associated with sarcopenia and only weakly linked with frailty [18,19,27,39,40]. It therefore should not be utilized as a surrogate for a validated measure of physical deconditioning in LT patients. Future studies should explore whether the addition of a debility measure to MELD score to prioritize listing would improve waitlist mortality or post-transplant outcomes.

In a recent systematic review, de Vries, et al. [41] identified 20 unique frailty instruments. Of course, proper identification of frail and sarcopenic patients is hampered by a paucity of consensus among disparate definitions, instruments and cutoffs. Eight different measures (2 frailty, 6 sarcopenia) were used in the studies included in our review; even in those using the same imaging analysis techniques, only two pairs used the same cut-off to delineate sarcopenia [23,30,31,39].

Because of the wide range of available assessments and lack of uniformity in the studied population, it is difficult for the authors to recommend a tool to measure debility in the liver resection and transplant population. What is clear is that the measure should be validated with additional studies, based upon assessments that are readily available or easily administered in the clinical setting and incorporate both physical and psychosocial components of well-being. Along with non-standardized definitions, the indications for included surgeries and variety of reported endpoints makes generalizations difficult, an acknowledged limitation of this review.

Conclusion

Based upon a review of the current literature, physical deconditioning and skeletal muscle loss appear to confer higher rates of morbidity and mortality and greater resource utilization in patients undergoing liver transplant or resection. Additional prospective investigations of surgical outcomes using a standard operational definition of frailty or sarcopenia are warranted. A validated, practicable measure can help surgical teams identify candidates at greater risk of poor outcomes and implement pre-habilitative interventions such as nutritional support, physical therapy/exercise [42], and pharmacotherapy to reduce such hazards.

References

1. Centers for Disease Control and Prevention NCfHS. National Hospital Discharge Survey, 2010. In: Survey CNNHD. Hyattsville, editor. 2012.
2. Werner CA. The Older Population: 2010. 2010 Census Briefs. In: Bureau USDoCEaSAUSC, ed. Washington DC. 2011.
3. Prevention CfDCa. The State of Agining and Health in America 2013. Atlanta, GA: US Department of Health and Human Services. 2013.
4. United Nations. Department of Economic and Social Affairs. Population Division. World population ageing. 2007. New York: United Nations, Dept. of Economic and Social Affairs, Population Division. 2007.
5. Al-Refaie WB, Parsons HM, Henderson WG, Jensen EH, Tuttle TM, Vickers SM, et al. Major cancer surgery in the elderly: results from the American College of Surgeons National Surgical Quality Improvement Program. Ann Surg. 2010; 251: 311-318.
6. Duron JJ, Duron E, Dugue T, Pujol J, Muscari F, Collet D, et al. Risk factors for mortality in major digestive surgery in the elderly: a multicenter prospective study. Ann Surg. 2011; 254: 375-382.
7. Gajdos C, Kile D, Hawn MT, Finlayson E, Henderson WG, Robinson TN. Advancing age and 30-day adverse outcomes after nonemergent general surgeries. J Am Geriatr Soc. 2013; 61: 1608-1614.
8. Hamel MB, Henderson WG, Khuri SF, Daley J. Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. J Am Geriatr Soc. 2005; 53: 424-429.
9. Kurian AA, Wang L, Grunkemeier G, Bhayani NH, Swanstrom LL. Defining "the elderly" undergoing major gastrointestinal resections: receiver operating characteristic analysis of a large ACS-NSQIP cohort. Annals of surgery. 2013; 258: 483-489.
10. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001; 56: M146-156.
11. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 2011; 183: E487-494.
12. Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, et al. Aging, frailty and age-related diseases. Biogerontology. 2010; 11: 547-563.
13. Lang T, Streeper T, Cawthon P, Baldwin K, Taaffe DR, Harris TB. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int. 2010; 21: 543-559.
14. Cruz-Jentoft AJ, Michel JP. Sarcopenia: A useful paradigm for physical frailty. Eur Geriatr Med. 2013; 4: 102-105.
15. Rizzoli R, Reginster JY, Arnal JF, Bautmans I, Beaudart C, Bischoff-Ferrari H, et al. Quality of life in sarcopenia and frailty. Calcif Tissue Int. 2013; 93: 101-120.
16. Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. Scientific World Journal. 2001; 1: 323-336.
17. Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA, et al. Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. J Cachexia Sarcopenia Muscle. 2012; 3: 181-190.
18. Montano-Loza AJ, Meza-Junco J, Prado CM, Lieffers JR, Baracos VE, Bain VG, et al. Muscle wasting is associated with mortality in patients with cirrhosis. Clin Gastroenterol Hepatol. 2012; 10: 166-173, 173 e1.
19. Lai JC, Feng S, Terrault NA, Lizaola B, Hayssen H, Covinsky K. Frailty

predicts waitlist mortality in liver transplant candidates. Am J Transplant. 2014; 14: 1870-1879.

20. Etzioni DA, Liu JH, Maggard MA, Ko CY. The aging population and its impact on the surgery workforce. Ann Surg. 2003; 238: 170-177.

21. Scarborough JE, Pietrobon R, Bennett KM, Clary BM, Kuo PC, Tyler DS, et al. Workforce projections for hepato-pancreato-biliary surgery. J Am Coll Surg. 2008; 206: 678-684.

22. Valero V 3rd, Amini N, Spolverato G, Weiss MJ, Hirose K, Dagher NN, et al. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. J Gastrointest Surg. 2015; 19: 272-281.

23. DiMartini A, Cruz RJ Jr, Dew MA, Myaskovsky L, Goodpaster B, Fox K, et al. Muscle mass predicts outcomes following liver transplantation. Liver Transpl. 2013; 19: 1172-1180.

24. Peng PD, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, et al. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. HPB(Oxford). 2011; 13: 439-446.

25. Louwers L, Schnickel G, Rubinfeld I. Use of a simplified frailty index to predict Clavien 4 complications and mortality after hepatectomy: analysis of the National Surgical Quality Improvement Project database. Am J Surg. 2016; 211: 1071-1076.

26. Montano-Loza AJ, Meza-Junco J, Baracos VE, Prado CM, Ma M, Meeberg G. et al. Severe muscle depletion predicts postoperative length of stay but is not associated with survival after liver transplantation. Liver transplant. 2014; 20: 640-648.

27. Sonnenday CJ, Englesbe MJ. Frailty Score Predicts Outcomes Among Liver Transplant Candidates and Recipients. The Liver Meeting. 2013; Washington, D.C.

28. Englesbe MJ, Patel SP, He K, Lynch RJ, Schaubel DE, Harbaugh C, et al. Sarcopenia and mortality after liver transplantation. J Am Coll Surg. 2010; 211: 271-278.

29. Lee CS, Cron DC, Terjimanian MN, Canvasser LD, Mazurek AA, Vonfoerster E, et al. Dorsal muscle group area and surgical outcomes in liver transplantation. Clin Transplant. 2014; 28: 1092-1098.

30. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg. 2012; 99: 550-557.

31. Voron T, Tselikas L, Pietrasz D, Pigneur F, Laurent A, Compagnon P, et al. Sarcopenia Impacts on Short- and Long-term Results of Hepatectomy for Hepatocellular Carcinoma. Ann Surg. 2015; 261: 1173-1183.

32. Eappen S, Lane BH, Rosenberg B, Lipsitz SA, Sadoff D, Matheson D, et al. Relationship Between Occurrence of Surgical Complications and Hospital Finances. Jama-J Am Med Assoc. 2013; 309: 1599-1606.

33. Lawson EH, Hall BL, Louie R, Ettner SL, Zingmond DS, Han L, et al. Association between Occurrence of a Postoperative Complication and Readmission Implications for Quality Improvement and Cost Savings. Ann Surgery. 2013; 258: 10-18.

34. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, et al. Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system. JAMA internal medicine. 2013; 173: 2039-2046.

35. Sheetz KH, Waits SA, Terjimanian MN, Sullivan J, Campbell DA, Wang SC, et al. Cost of major surgery in the sarcopenic patient. J Am Coll Surg. 2013; 217: 813-818.

36. Robinson TN, Wu DS, Stiegmann GV, Moss M. Frailty predicts increased hospital and six-month healthcare cost following colorectal surgery in older adults. Am J Surg. 2011; 202: 511-514.

37. Bergerson JT, Lee JG, Furlan A, Sourianarayanane A, Fetzer DT, Tevar AD, et al. Liver transplantation arrests and reverses muscle wasting. Clin Transplant. 2015; 29: 216-221.

38. Kamath PS, Kim WR; Advanced Liver Disease Study G. The model for end-stage liver disease (MELD). Hepatology. 2007; 45: 797-805.

39. Harimoto N, Shirabe K, Yamashita YI, Ikegami T, Yoshizumi T, Soejima Y, et al. Sarcopenia as a predictor of prognosis in patients following hepatectomy for hepatocellular carcinoma. Br J Surg. 2013; 100: 1523-1530.

40. Meza-Junco J, Montano-Loza AJ, Baracos VE, Prado CM, Bain VG, Beaumont C, et al. Sarcopenia as a prognostic index of nutritional status in concurrent cirrhosis and hepatocellular carcinoma. J Clinical Gastroenterol. 2013; 47: 861-870.

41. de Vries NM, Staal JB, van Ravensberg CD, Hobbelen JS, Olde Rikkert MG, Nijhuis-van der Sanden MW. Outcome instruments to measure frailty: a systematic review. Ageing Res Rev. 2011; 10: 104-114.

42. Mathur S, Janaudis-Ferreira T, Wickerson L, Singer LG, Patcai J, Rozenberg D, et al. Meeting report: consensus recommendations for a research agenda in exercise in solid organ transplantation. Am J Transplant. 2014; 14: 2235-2245.

43. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013; 183: 104-110.

44. Kaido T, Ogawa K, Fujimoto Y, Ogura Y, Hata K, Ito T, et al. Impact of sarcopenia on survival in patients undergoing living donor liver transplantation. Am J Transplant. 2013; 13: 1549-1556.

45. Krell RW, Kaul DR, Martin AR, Englesbe MJ, Sonnenday CJ, Cai S, et al. Association between Sarcopenia and the Risk of Serious Infection Among Adults Undergoing Liver Transplantation. Liver Transplant. 2013; 19: 1396-1402.

46. Masuda T, Shirabe K, Ikegami T, Harimoto N, Yoshizumi T, Soejima Y, et al. Sarcopenia is a prognostic factor in living donor liver transplantation. Liver Transpl. 2014; 20: 401-407.