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

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 57% 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.

<table>
<thead>
<tr>
<th>Author, Year, Study Design, n</th>
<th>Type of Surgery</th>
<th>Measure of Frailty/ Sarcopenia</th>
<th>% Subjects Frail or Sarcopenic</th>
<th>Results- Resource Utilization (Frail/Sarcopenic vs. Non)</th>
<th>Results- Morbidity (Frail/Sarcopenic vs. Non)</th>
<th>Results- Mortality (Frail/Sarcopenic vs. Non)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harimoto [39], retrospective, N=186</td>
<td>Hepatic Resection</td>
<td>CT x-section of total skeletal muscle area at L3 region normalized for height</td>
<td>Cutoffs (cm²/m²): Men: 43.75, Women: 41.1</td>
<td>40.3%</td>
<td>Not assessed</td>
<td>No significant difference in Clavien-Dindo grade 3 post-op complications</td>
</tr>
<tr>
<td>Louwers [25], retrospective, N=10,300</td>
<td>Hepatic Resection (open)- malignant and benign indications</td>
<td>Modified Canadian Study of Health and Aging Frailty Index using variables from NSQIP database (mFI)²⁴, broken into quintiles (analyzed trends, HRs based on lowest vs. highest)</td>
<td>2.6%</td>
<td>Extended LOS (&gt;75th percentile for NSQIP surgery type) with increased mFI score p&lt;0.001; 43.0% rate in frail vs. 27.6% in non-frail group</td>
<td>Positive correlation between rate of Clavien grade 4 complications &amp; mFI (p=0.001); 16.8% in highest mFI group vs. 5.0% in lowest- Multivariate OR= 40.0 (p=0.001)</td>
<td>Significant positive trend in mortality with increasing mFI score (p&lt;0.001); 9.1% mortality rate in most vs. 1.5% in non-frail- Multivariate OR 26.4 (p&lt;0.001)</td>
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<tr>
<td>Peng [24], retrospective, N=557</td>
<td>Hepatic Resection or Resection + RFA for Colorectal Liver Mets</td>
<td>Peri-operative CT x-section of total psoas muscle area at L3</td>
<td>Cutoffs (cm²/m²): M&amp;F: 50</td>
<td>15.8%</td>
<td>Prolonged ICU stay (&gt;2 days) 15% vs. 4% (p=0.004); Overall longer hospital stay 6.6 vs. 5.4 days (p=0.03)</td>
<td>Increase in major complications (Clavien grade≥3) 22% vs. 8% (p=0.008), OR=3.12 (p&lt;0.002) on multivariate analysis</td>
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<tr>
<td>vanVledder, 2012 [30], prospective, N=196</td>
<td>Hepatic Resection for Colorectal Liver Mets</td>
<td>CT x-section of skeletal muscle area at L3 region normalized for height. Cutoffs (cm²/m²): M: 43.75, F: 41.1</td>
<td>19.4%</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>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&lt;0.001) overall survival; HR = 2.53 (p&lt;0.001) on multivariate analysis</td>
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<tr>
<td>Voron [31], retrospective, N=109</td>
<td>Hepatic Resection for HCC</td>
<td>CT x-section of total muscle area at L3 when both pedicles visible normalized for height Cutoffs (cm²/m²): M: 52.4, F: 38.9</td>
<td>54%</td>
<td>Not assessed</td>
<td>Similar rates of severe (Clavien grade≥3) complications: 20.3% vs. 16% (p=0.56)</td>
<td>No difference in 60 day mortality; Increased overall mortality- HR= 3.19 (p=0.013)</td>
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<tr>
<td>Valero [22], retrospective, N=96</td>
<td>Hepatic Resection or Transplant for HCC or ICC</td>
<td>CT x-section of total psoas muscle volume (TPV) at L3 Cutoffs (cm³/m³): M: 34.14, F: 22.93</td>
<td>48.9% (comparable rates resection vs. transplant)</td>
<td>No difference in LOS: 12.1 vs. 9.7 days (p=0.50)</td>
<td>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%</td>
<td>Nodifference in survival: 5 yr overall survival 41.8% vs. 52.5%- multivariate HR overall survival=1.34 (p=0.43)</td>
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<tr>
<td>DiMartini [23], retrospective, N=338</td>
<td>Liver Transplant- Donor type not specified</td>
<td>CT x-section of skeletal muscle area at L3-4region Cutoffs (cm²/m²): M: 52.4, F: 38.5</td>
<td>68% (M: 76%, F: 51%)</td>
<td>M: 12%, 9%; F: 4%, 3% longer ICU &amp; hospital LOS per 10% decrease in muscle mass (p&lt;0.001 for all) M: 18%increased likelihood of institutionalization at discharge per 10% decrease in muscle mass (p&lt;0.05) F: No difference</td>
<td>M: 13%, F: 7% increase in time intubated per 10% decrease in muscle mass (p&lt;0.001)</td>
<td>M: 5% decreased overall survival with each 1 unit reduction in muscle area; HR= 0.95 (p=0.01) F: No difference</td>
</tr>
<tr>
<td>Englesbe [28], retrospective, N= 163</td>
<td>Liver Transplant- Deceased Donor</td>
<td>Total psoas muscle area at L4 in mm², in quartiles</td>
<td>Broken into quartiles by TPA</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>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 1000mm² decrease in TPA HR=3.7 (p&lt;0.0001)</td>
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<tr>
<td>Kaido [44], retrospective, N=124</td>
<td>Liver Transplant- Living Donor</td>
<td>Bioelectrical impedance analysis. Cutoff: &lt;90% standard skeletal muscle mass</td>
<td>37.9%</td>
<td>Not assessed</td>
<td>Not assessed</td>
<td>Diminished 1 year survival: 59% vs. 87% (p=0.001)</td>
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Cholangiocarcinoma; L3/4- 3rd/4th
Abbreviations: Randeep Kashyap, et al., Clinics in Surgery - Transplant Surgery

Frailty in the liver transplant population, a growing number of older to be frail and at increased risk of waitlist mortality independent of another transplant center determined 17% of their studied evaluations heightened mortality on multivariate analysis (HR 2.18 p= 0.006); undergoing LT evaluation, 40% were sarcopenic, correlating with those with end stage liver disease. In a single center study of those to the rigors of the disease, frailty and sarcopenia are common in transplantation (LT), the debilitating condition may also be the chronic disease. As seen in patients with cirrhosis awaiting liver transplantation (LT), the debilitating condition may also be the consequence of

Sarcopenia and malnutrition are prevalent in older adults and are also undergoing transplant procedures. Between 2002 and 2015 the share of transplanted patients over the age of 64 more than doubled from 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, effects of frailty are more prevalent in this burgeoning population, effects of frailty are more prevalent in this burgeoning population, effects of frailty are more prevalent in this burgeoning population, effects of frailty are more prevalent in this burgeoning population.
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 (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-Dindo 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 1000mm² decrease in lean...
psosas 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**


Randeep Kashyap, et al., Clinics in Surgery - Transplant Surgery


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


