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The inter- and intra-rater reliability and feasibility of dietetic assessment of sarcopenia and frailty in potential liver transplant recipients: a mixed methods study.

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Abstract:

Sarcopenia and frailty are associated with poorer outcomes in potential liver transplant (LT) recipients. We examined the reliability and feasibility of dietitians assessing sarcopenia and frailty. Seventy-five adults referred for LT underwent assessments of muscle mass (abdominal CTs); physical function (handgrip strength; HGS, short physical performance battery; SPPB); and frailty, (Liver Frailty Index; LFI). Inter- and intra-rater reliability and agreement were assessed in subsets of patients using intraclass correlation coefficients (ICCs) and Bland-Altman plots. CTs were analysed by a dietitian and two independent experts, two dietitians assessed function and frailty. Feasibility assessed system, patient and profession factors (staff survey). Inter- and intra-rater reliability for CT defined low muscle were excellent (ICCs >0.97). Reliability between dietitians was excellent for HGS (0.968, 95% CI, 0.928-0.986), SPPB (0.932, 95% CI, 0.798–0.973) and LFI (0.938, 95% CI 0.861–0.973). Bland-Altman analysis indicated excellent agreement for HGS. All transplant clinicians valued sarcopenia and frailty in LT assessments and considered the dietitian appropriate to perform them. Seven saw no barriers to implementation into practice, while five queried test standardisation, learning from repeat testing, and resource cost. Dietetic assessments of sarcopenia and frailty are reliable, feasible and valued measures in the assessment of potential LT recipients.

Keywords: Advanced liver disease, liver transplant, nutrition, physical function, sarcopenia, frailty

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Introduction

Advanced liver disease is frequently complicated by sarcopenia and frailty[1]. Traditional definitions of sarcopenia refer to significant depletion of muscle mass, present in up to 60% of patients with advanced liver disease[2], combined with functional impairment such as low muscle strength and/or poor physical performance[3]. In liver transplant (LT), the clinical interpretation of sarcopenia generally refers to loss of muscle mass alone[4,5]. Cross-sectional abdominal computed tomography (CT) images are considered the gold standard to identify reduced muscle mass in patients with advanced liver disease[4,6].

Frailty refers to a biological syndrome, whereby a reduction in multiple systems that occurs with aging or chronic disease leads to weakness, instabilities and limitations[7]. Patients with advanced liver disease have many of the features of frailty seen in the elderly with sarcopenia, with malnutrition a prominent feature alongside physical vulnerability, poor cardiorespiratory fitness, impaired balance and gait all leading to reduced activity, loss of confidence, and falls[8,9]. The recently described Liver Frailty Index (LFI) includes assessments of physical function including components of the short physical performance battery (SPPB; chair stands and balance) and strength (hand grip strength; HGS) to stratify patients into frail, pre-frail and robust groups[10]. The LFI has been shown to significantly improve mortality risk prediction compared to a clinician's subjective assessment[11]. Sarcopenia and frailty in advanced liver disease have been linked to poorer prognosis and adverse outcomes independent of Model for End stage Liver Disease (MELD)[12] and radiological assessment of muscle mass has been recommended in recent guidelines as part of the nutrition assessment prior to LT[4,6].

Despite these recommendations and evidence, sarcopenia and frailty have not traditionally been measured as part of nutrition assessments. In a real-world clinical environment, there may be a rotation of multiple dietitians performing nutrition assessments in potential transplant candidates. Therefore, as a component of implementation, the inter- and intra-rater reliability and agreement of dietetic assessment of sarcopenia and frailty needs to be established. Consideration of what is an acceptable degree of variation between clinician measurements in real world practice is key to the utility of the measures. The minimal clinically important difference (MCID) is the smallest change identified as either beneficial or harmful that may result in a change of management[13].

It is known that effective implementation of evidence based guidelines into clinical care requires engagement from key stakeholders to ensure support for change and sustainability[14]. Therefore, an evaluation of barriers to knowledge use and feasibility measures such as accessibility, acceptability, time and cost are needed.

The aims of this study were to 1) assess the inter and intra-rater reliability and agreement of dietitian estimation of muscle mass from CTs compared to radiology experts, 2) assess the inter-rater reliability and agreement of different dietitians completing physical function and frailty assessments and 3) determine the feasibility and clinical utility of introducing sarcopenia and frailty assessments as a component of the dietitian assessment of potential LT recipients.

Materials and Methods

Study population

Data were collected from adult (>18yrs) patients undergoing assessment for LT by the Queensland Liver Transplant Service in Brisbane Australia, between May 2018 and January 2019. The data captured patients seen for an initial consultation with the transplant hepatologist and dietitian in the outpatient clinic. The time frame coincided with when the assessments (HGS, SPPB and LFI) were implemented into dietetic assessments following the new guideline recommendations[4,6]. Participants were excluded if they were considered inappropriate by the treating clinician due to having overt hepatic encephalopathy. The study was approved by the Metro South Human Research Ethics Committee (HREC/2018/QMS/46728).

Demographic and clinical data

Electronic medical records were accessed to obtain pre-existing data reported in the hepatologist and dietitian initial assessment. Clinical data included age, sex, etiology of liver disease, MELD score and presence of ascites (yes/no) or oedema (yes/no). Anthropometric assessments included weight and height (using digital scales and a stadiometer), the presence of malnutrition (subjective global assessment)[15], and body mass index (BMI). If ascites was present, dry weight was taken from last weight post-paracentesis or by subtracting 5%, 10%, 15% of total body weight for mild, moderate and severe ascites, respectively. An additional 5% was subtracted for bilateral pedal oedema[16].

CT analysis of muscle mass and sarcopenia diagnosis

The cross-sectional area of muscle was measured on a CT at the superior-inferior midpoint of the third lumber vertebra (L3). Imaging at the L3 region is the most widely reported level to identify skeletal muscle loss[17] and used in the advanced liver disease population[5,16,18]. The image slice was exported from proprietary software Impax 6 (Agfa-Gevaert N.V, Mortsel, Belgium) by the dietitian to the software ImageJ (National Institutes of Health, Bethesda, Maryland). The estimation of skeletal muscle mass followed the protocol described by Gomez-Perez et al[19]. Hounsfield Units of -29 to +150 were applied for skeletal muscle attenuation. Skeletal muscle index (SMI) was determined by normalising skeletal muscle area (SMA) for height in meters squared (cm^2/m^2). Using the SMI, sarcopenia was defined following cut-points specific to advanced liver disease (SMI <50 cm^2/m^2 for men and <39 cm^2/m^2 for women)[20]. Sarcopenia was classified according to the European Working Group of Sarcopenia in Older People (EWSOP), whereby there was a presence of low muscle mass via CT in combination with either low muscle strength via HGS and/or low functional performance on the SPPB[3].

Physical Function and Frailty Assessment

The functional assessments included HGS[21,22] and the SPPB[23]. A Jamar digital dynamometer was used to measure HGS, the average of three readings from the dominant hand was recorded and poor HGS defined as <27kg for males and <16kg for females[3]. The SPPB consists of measures of gait speed (time to walk 4 metres), chair stands (time to complete 5 chair stands) and three timed balance positions[24], providing a total SPPB score range from 0 to 12. A score of 9 or less was classified as a deficit in physical function[25]. The LFI was used to identify frailty, and was calculated from HGS, three balance positions and chair-stand tests utilising an online calculator, providing a continuous variable between 1-7, and classification of frail, pre-frail, or robust[10].

Inter- and intra-rater reliability and agreement of dietetic assessments

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For reliability and agreement in SMI and the diagnosis of CT-defined low muscle mass, inter-rater reliability was determined between three independent clinicians (dietitian, radiologist and radiation therapist) in a random subset of participants (n=21) with existing abdominal CTs performed as part of pre-transplant evaluation. To determine intra-rater reliability, the dietitian reviewed 21 CT scans twice within an interval of at least one week between readings. Raters were blinded to the other's results, as well as patient sex and body weight.

For function and frailty assessments, a subset of patients (n=25) were invited to voluntarily repeat the assessments by two different dietitians on the same day. The first dietitian was trained by an exercise physiologist and this dietitian trained the second dietitian using a developed protocol and standardised data collection form. Test order was randomised (using a randomisation tool[26] and each rater was blinded to the other's results. Each patient completed HGS, SPPB and LFI with each dietitian with a 45-minute rest period in between.

Determining clinically meaningful agreement

To further interpret the levels of agreement between clinicians, and what is meaningful in clinical practice, results were compared with MCID, determined a priori using both anchor-based and distribution-based methods[27]. Existing anchor-based MCIDs reported in the literature were utilised for LFI[28] and HGS[29]. The established MCID for the LFI is ≤0.20 and HGS is <6kg. While an MCID of 1-point change for the SPPB has been proposed for research trials[30,31], there is minimal literature for comparison at an individual level. Therefore, the results are reported as ≤1point as this is the smallest amount of change available. Due to minimal literature, distribution methods, which are based on statistical characteristics of our own data, were used to evaluate whether a MCID could be determined for CT measures, by calculating ½ Standard Deviation (SD)[32]. We also reviewed similar

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studies that assessed inter-rater reliability of CT scans, and compared the ICCs to our results. Agreement between clinicians was considered acceptable if it fell under the MCID. Overall acceptability of the measure was considered if results were within the limits of agreement >80% of the time.

Feasibility and acceptability

The Knowledge to Action (KTA)[14] and the National Institute of Clinical Studies[33] frameworks were utilised to evaluate the implementation of evidence-based guidelines into standard clinical care. We assessed the feasibility of implementing change in practice, the acceptability of this change with the clinical staff and patients, barriers to implementation and whether assessments are valued. Barriers to evidence uptake were explored across system-, patient- and profession-related levels. System-related factors included the proportion of patients with CT available within six months of dietetic assessment (%); dietitian time taken to complete CT analysis of muscle area and completion rate of function and frailty assessments (SPPB, HGS and LFI); and reasons for not completing them. Patient-related factors included the patient's ability (yes/no) to perform the function and frailty assessments; and time taken (minutes), and reasons for non-participation. Patients reported their confidence in their ability to perform the assessments (self-scoring 1-10; 10 being very confident), as well as the acceptability of the tests (yes/no). Any adverse events were recorded. Profession-related factors included assessing frontline clinicians perceived acceptability and clinical utility of sarcopenia and frailty assessments in relation to LT evaluation. A 20-item survey included open-ended questions, yes/no responses and 5-point Likert scales, some questions allowed for multiple responses. The questions were developed in alignment with the Theoretical Domains Framework (TDF)[34] investigating professional behaviours; knowledge about the measures; perceived barriers and enablers and value of incorporating into practice. Clinicians involved in decision-making related to transplant suitability, plus nursing LT recipient coordinators were invited to participate in December 2018. Nursing coordinators received a shortened version as some questions regarding transplant suitability were not directly related to their care. The online survey was voluntary and anonymous. Accepting the invitation was deemed as consenting to participate.

Statistical analysis

Descriptive analyses were conducted on demographic, clinical variables and survey data. Values are either presented as % (n), mean ± SD (normally distributed data) or median [IQR]. To assess inter-rater reliability, the sample size required for 90% power is dependent on the degree of variation observed (as measured by intraclass correlation co-efficient; ICCs) and the number of raters[35]. For CT estimation of muscle mass involving three raters, an ICC of 0.6 (indicating poor agreement), requires a sample size of at least 10 participants for 90% power, or at least 20 participants for the functional assessments, which compared two raters. If good agreement is obtained (ICC 0.7 – 0.9), a minimum sample size of 4 – 8 participants are required for 90% power when comparing three raters, or 6-13 participants when comparing two raters[35].

Reliability for CT analysis and functional assessments were assessed using ICCs with 95% confidence intervals (CI) for continuous variables. ICC values were interpreted as: 0.5-0.75 fair reproducibility, 0.75-0.9 good reproducibility, and >0.9 excellent reproducibility[36]. Cohen's Kappa was calculated to assess agreement for two categorical variables, while Fleiss' Kappa was used for comparing >2 ratings. Kappa values were interpreted as: 0.0-0.2 poor agreement, 0.2-0.4 fair agreement, 0.4-0.6 moderate agreement, 0.6-0.8 substantial agreement, and 0.8-1 almost perfect agreement[37].

Bland-Altman Plots were performed to assess agreement between raters[38]. Limits of agreement were calculated as mean difference±1.96·SD. Systemic bias was determined if the line of equality (y=0) was outside the 95% confidence intervals. Linear regression analysis was performed to determine proportional bias, to see if the average of the measures (independent variable) were significantly related to the difference between the measures (dependent variable). Statistical analysis was conducted using SPSS 25 (IBM, New York, NY, USA).

Results

Seventy-five patients referred for LT were evaluated. Demographic and clinical data are in Table 1.

Inter- and intra-rater reliability and agreement

Inter- and intra-rater agreement and reliability and MCID results for CT assessed muscle mass, LFI, HGS and SPPB are shown in Table 2. Due to ICC data all >0.9, sample size of between 4-13 for two and three rater comparisons was deemed adequate across variables. Twenty-four patients were included in analysis of functional and frailty assessments as one outlier was removed due to clinical factors impacting ability to perform tests. There were no significant differences between mean measurements between raters for all assessments.

For CT estimation of SMI between the radiologist, radiation therapist and dietitian, reproducibility of the SMI measures across all three raters and between these raters was excellent ICC >0.9 (Table 2). BA analysis of the dietitian versus radiologist and the radiation therapist versus dietitian are seen in Figures 1a and b. The mean differences in SMI for the radiologist versus dietitian and radiation therapist versus dietitian were close to zero (0.35 and 0.29, respectively). No systemic or proportional bias was observed (r=0.192, p=0.040 between radiologist and dietitian; and r=0.126, p=0.59 between radiation therapist and dietitian).

As there are no anchor-based methods for MCID for CT assessed low muscle mass, when applying the distribution-based method of ½ SD for the MCID, this produced very narrow range (from 0.25 to 0.97, Table 2). Using this method, approximately half of the results fell under the acceptable MCID (52% for radiologist and dietitian; 48% for the radiation therapist and dietitian, and 48% for the intra-rater dietitian results). However, the mean SMI difference between raters was <1cm^2/m^2, and limits of agreement were <4cm^2/m^2 (Table 2).

When categorising low muscle mass to diagnose sarcopenia based on pre-determined cut-points, agreement between all three raters was also excellent with a κ coefficient 0.932 (0.762-1.00) and > 0.8 for all comparisons. Both the radiologist and dietitian categorised low muscle in 38% (n=8) of patients, κ coefficient 1.00 (1.00-1.00). This was the same for intra-rater agreement for the dietitian, κ coefficient 1.00 (1.00-1.00). The radiation therapist categorised 33% (n=7), with a κ coefficient 0.897 (0.640-1.000) compared with the dietitian.

Measurements between the two dietitians for the functional and frailty assessments (HGS, LFI and SPPB) demonstrated excellent reliability with ICCs (>0.9) (Table 2). BA analysis for LFI, SPPB and HGS are seen in Figures 2a, b and c respectively. Linear regression analysis demonstrated no proportional bias across all three measures, for LFI ($r=0.268$, $p=0.438$); for SPPB ($r=0.218$, $p=0.306$); and for HGS ($r=0.350$, $p=0.093$). No systemic bias was observed in the LFI or HGS. For the SPPB systemic bias was observed, whereby the 95% confidence intervals were outside the line of equality (y=0).

Moderate inter-rater agreement was observed for frailty status (robust, pre-frail or frail), κ coefficient 0.541 (95% CI, 0.229 - 0.853). When defining poor function with the SPPB (≤9/12), there was 100% agreement. Both dietitians found 21% (n=5) had poor function κ=1.00. When considering the MCIDs, for HGS, 100% of the measures fell under the MCID of <6kg. For the LFI 83% (n=20) fell below the MCID of ≤0.2. For the SPPB, 96% (n=23) of the scores were either within 1 point of difference or below.

Feasibility results

System-related factors: 78% (n=58) of patients had a CT available for muscle mass assessment. Reasons for CT being unavailable included; abdominal MRI performed as alternative to CT (n=7), CT performed > 6 months ago (n=4), five patients didn't progress further down the LT pathway and one patient was awaiting their CT when data collection stopped. The average time taken for a dietitian to complete CT analysis of muscle mass (calculated from a subset of n=35) was 9.1 ± 1.2 minutes.

Patient-related factors: 97% (n=72) of patients were able to complete the functional and frailty tests (SPPB, HGS and LFI) during the dietetic assessment. Non-completion reasons included time constraints for the participant (n=2), or clinician (n=1). The average time to complete the assessments was 7.0±1.6 minutes. All patients found the assessments acceptable and were able to complete these during their dietetic consultation. The patients mean confidence score (out of 10) for undertaking these assessments was 8.0 ±1.8. There were no adverse events associated with completing them.

Profession-related factors (staff survey): 80% (n=12) of invited clinicians completed the survey (Hepatologist n=6; Anaesthetist n=2; Nurse n=2; Transplant Surgeon n=2). More than half (n=10, 60%) of clinicians involved in waitlist decision making indicated they always considered sarcopenia and frailty in their assessment for LT suitability; followed by 40% considering sarcopenia and frailty sometimes. No respondents reported "never" to these questions. Table 3 provides clinician responses regarding the value and acceptability of the sarcopenia and frailty assessments.

When clinicians were asked how they assess for sarcopenia and frailty, 90**%** provided open-ended responses. Of these responses, more than half (60%) reported their assessment relied on the dietetics report of sarcopenia and frailty. Twenty percent reported they based assessment on their clinical or visual assessment and 20% reported using other tools including Activities of Daily Living[39]. When clinicians were asked how sarcopenia and frailty measures are used in decision making for transplant suitability, 33% (n=4) indicated they would use the information to determine how well the individual would tolerate and recover from surgery. Other responses stated the information is used to assist decision-making for borderline cases and inform recommendations for pre-transplant diet and physical activity.

Seven clinicians saw no barriers to implementation of sarcopenia and frailty assessments by the dietitian. Five clinicians identified potential barriers including concerns around the validity and standardisation of the measures; concerns regarding the impact of training related to repeated measurements on subsequent functional assessments; and the cost of including these measures in the dietetic assessment.

All clinicians felt a dietitian was an appropriate clinician to perform the physical function assessments within the current model of care. Although 50% of staff felt the clinic dietitian was an appropriate clinician to perform CT assessment of muscle mass, staff also deemed a radiologist affiliated with the transplant service (68%, n=8), or a radiographer (60%; n=7) was also appropriate.

Discussion

Quality care requires health professionals to respond to emerging evidence and implement change in their practice. New guidelines recommend dietetic assessment of sarcopenia and frailty and this study demonstrated this is a reliable, feasible and an acceptable component of the nutrition assessment of potential LT recipients and valued in clinical decision making. Dietitian's analysis of abdominal CT scans following a protocol-based approach, replicates similar low muscle mass diagnostic results to health professionals who regularly view CT scans. This presents an opportunity to extend scope of practice for dietitians or for muscle mass quantification to be added to radiological reports. Additionally, different dietitians can reliably perform physical function assessments in a clinical setting and the assessments are safe and acceptable for these patients. A formal diagnosis of sarcopenia and frailty provides an opportunity to refine risk assessment and enable opportunities to intervene with "prehabilitation" approaches[40-42]. Whilst CT defined sarcopenia in patients awaiting LT is most widely reported in the literature[5] recent data and practice guidelines are recognising the additional value of physical function and muscle strength as predictors of adverse outcomes compared to CT estimated muscle mass alone[3,25].

This study shows excellent inter- and intra-rater reliability for SMI (using ICCs), in the estimation of low muscle mass for sarcopenia diagnosis between dietetic professionals and radiology experts. Previous studies have identified that health professionals other than radiology specialists can show excellent inter-rater variation of muscle mass after appropriate protocol led training[43-45]. Agreement of CT analysis (via Bland Altman analysis) was good. While no MCID was available in the literature, and distribution methods showed extremely tight boundaries due to low variability, we based our reliability assessment from ICCs and comparative results to other studies. Our results were similar to published data where the authors deemed their inter-rater variability of CT estimated muscle mass not clinically significant[45-47]. To compare results to other studies, we performed ICCs for SMA alone (without correction for height) which also produced excellent repeatability for both dietitian and radiologist and radiation therapist (data not shown).

Despite excellent reliability and agreement, the dietetic time burden (approximately nine minutes per patient) and the staff preference for radiology expertise involvement may be a barrier to sustaining CT analysis of muscle mass into dietetic workloads. Alternative system disruptions, such as incorporating SMI estimation into the original radiography CT report for dietitians to then utilise to diagnose sarcopenia may be an acceptable solution to be tested.

The physical function tests (HGS, LFI and SPPB) are simple, inexpensive and validated tests[9,48] that provide objective data for the transplant decision making process[49-51]. This study confirms dietitians are well placed to implement these into a nutrition assessment in a real-world setting. While the LFI is the first tool to progress standardising frailty diagnosis in the LT population, this study adds further confirmation that different dietitians achieve similar reliability (using ICCs) of the LFI to that found in research settings[48] and can confidently interpret frailty changes over time on subsequent assessments.

The use of the SPPB in a clinical setting, outside of research studies, has not been widely published and therefore the clinically meaningful change in score for an individual and the relationship with outcomes in a transplant candidate remains unclear[31]. Systemic bias was observed with the SPPB, whereby one clinician consistently recorded a higher result, despite test order randomisation. It is possible the difference in staff training provider may influence test performance and indicates a potential need to standardise training of staff and refine protocols to minimise clinician variability.

The shift from "end of bed" assessments of sarcopenia and frailty to utilisation of quantifiable assessment tools requires a strategic implementation and evaluation to determine uptake, acceptability and feasibility in clinical practice. A key component of this feasibility study was the use of implementation frameworks to guide clinicians through implementing and sustaining practice change[14]. There is little point implementing guidelines if they are not used in clinical decision making, or in informing patient care priorities. This study has demonstrated that the frontline staff value and accept these assessments. There is complexity in implementing and sustaining practice change in time poor settings. Whilst this study assessed the role of dietetics, the results indicate that engaging the broader team to expand their roles, for example radiography reporting muscle mass as part of the standard CT analysis, may be important for distributing time burden across the service.

To ensure consistency and sustainability of implementing practice change, resource costs combined with protocol development and training should be considered. While most patients undergoing assessment for LT will have an abdominal CT performed as standard practice, some patients did not have CT available due to use of other forms of cross-sectional imaging. Tandon et al, (2016) has shown that both CT and MRI can be used interchangeably[47], therefore developing contingency protocols for estimation of muscle mass from MRI will capture those without CTs.

Strengths and limitations

Whilst the sample group in this study was representative of the local patient population, we can appreciate that the severity of liver disease may not be as representative of other international liver transplant centres. While in our study the average MELD was 15.5, and a third with ascites or oedema, it is important to consider those with more advanced disease and the impact that may have on the ability to complete the functional assessments. Ensuring the translation of evidence into practice can be challenging. The sustainability of practice change over time in accordance with implementation frameworks needs to be investigated.

Conclusion

Assessment of sarcopenia and frailty are feasible and acceptable components of the nutrition assessment of potential LT candidates and add value to the clinical decision making prior to transplant. We have demonstrated through use of the KTA framework, implementation of evidence into clinical practice is achievable. With appropriate training, dietetic professionals can reliably estimate muscle mass from CTs and perform physical function assessments that add further value to the diagnosis of sarcopenia in this vulnerable population.

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