Bone Mineral Density Predicts Posttransplant Survival Among Hepatocellular Carcinoma Liver Transplant Recipients

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Hepatocellular carcinoma (HCC) is a common indication for liver transplantation (LT). Recent data suggest that body composition features strongly affect post-LT mortality. We examined the impact of body composition on post-LT mortality in patients with HCC. Data on adult LT recipients who received Model for End-Stage Liver Disease exception for HCC between February 29, 2002, and December 31, 2013, and who had a computed tomography (CT) scan any time 6 months prior to LT were reviewed (n = 118). All available CT scan Digital Imaging and Communication in Medicine files were analyzed using a semiautomated high throughput methodology with algorithms programmed in MATLAB. Analytic morphomics measurements including dorsal muscle group (DMG) area, visceral and subcutaneous fat, and bone mineral density (BMD) were taken at the bottom of the eleventh thoracic vertebral level. Thirty-two (27%) patients died during the median follow-up of 4.4 years. The number of HCC lesions (hazard ratio [HR], 2.81; $P < 0.001$), BMD (HR = 0.90/Hounsfield units [HU]; $P = 0.03$), pre-LT locoregional therapy (HR = 0.14; $P < 0.001$), and donor age (HR = 1.05; $P < 0.001$) were the independent predictors of post-LT mortality. DMG area did not affect post-LT survival. In conclusion, in addition to number of HCC lesions and pre-LT locoregional therapy, low BMD, a surrogate for bone loss rather than DMG area, was independently associated with post-LT mortality in HCC patients. Bone loss may be an early marker of deconditioning that precedes sarcopenia and may affect transplant outcomes.

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Hepatocellular carcinoma (HCC) has become one of the leading indications for liver transplantation (LT) in the Model for End-Stage Liver Disease (MELD) era.[1,2] Candidates with decompensated cirrhosis and HCC who meet Milan criteria (1 lesion 2-5 cm or 3 lesions <3 cm in largest diameter) have been listed with exception MELD score since the adoption of MELD-based allocation.[3] Although MELD score is an excellent predictor of wait-list mortality, it does not perform well in predicting posttransplant survival.[4]

Emerging data suggest that frailty and sarcopenia affect survival after LT independent of recipient and donor factors. Using analytic morphomics, we and others have shown that body composition, especially the dorsal muscle group (DMG) area (psoas and paraspinal muscles), predicts postoperative complications[5-7] and survival after LT independent of MELD score.[6,8-12] Analytic morphomics is a novel approach that uses high throughput semiautomated image-processing techniques to assess body composition, such as body dimensions, visceral fat (VF), and muscle mass, and to link

Abbreviations: AFP, alpha-fetoprotein; BMD, bone mineral density; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; DMG, dorsal muscle group; GUI, graphical user interface; HCC, hepatocellular carcinoma; HR, hazard ratio; HU, Hounsfield units; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SF, subcutaneous fat; T11, eleventh thoracic vertebral level; VF, visceral fat.

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it to clinical outcomes.[13,14] In one of our initial studies, Englesbe et al.[8] showed that psoas muscle area was independently associated with posttransplant mortality. The psoas muscle area was correlated with the DMG area.[10] Patients with a larger DMG area had improved survival and fewer complications after transplantation.[10]

Sarcopenia and bone loss are prevalent in the candidates awaiting LT. This is more pronounced among the decompensated end-stage liver disease population with high MELD score awaiting LT because of debility and lower muscle mass. HCC candidates have lower calculated MELD score and well-preserved muscle mass compared to non-HCC candidates with high laboratory MELD score because of the exception MELD score policy for HCC.[1,15] Given that the HCC candidates have well-preserved muscle mass, we hypothesized that there might be other body composition components, such as bone mineral density (BMD), VF, and subcutaneous fat (SF), rather than DMG areas that affect posttransplant survival. Therefore, we examined the impact of body composition (DMG area, BMD, VF, and SF) in addition to traditional recipient and donor factors on posttransplant survival among HCC LT recipients.

Patients and Methods

Medical records of all adult patients (age $\geq$ 18 years) who received a deceased donor LT between February 28, 2002, and December 31, 2013, for HCC with exception MELD score and had a computed tomography (CT) scan of chest or abdomen/pelvis any time prior to 6 months before LT at the University of Michigan were reviewed. The study was a priori approved by the University of Michigan institutional review board. Candidates who were listed as status 1, received living donor LT, received repeat LT, received multiorgan transplant, were found to have incidental HCC on explants, or did not have the CT scan prior to 6 months before LT were excluded. Patients were followed until December 31, 2014.

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DEMOGRAPHIC AND CLINICAL DATA

Data collected included demographics (age, sex, race/ethnicity); date of listing; date of transplant; date of HCC recurrence; date of last follow-up and death; diagnosis; history of smoking, alcohol; pre-LT history of hypertension, diabetes; laboratory MELD score at the time of listing and transplant; alpha-fetoprotein (AFP) within 6 months of listing and LT; pre-LT radiology data including number of lesions, size of each lesion (cm), size of largest lesion (cm); portal venous thrombosis; meeting Milan criteria pre-LT; and history of locoregional therapy. We also collected data on donor factors, such as donor age, sex, and cold ischemia time, and on post-LT recipient factors, such as immunosuppression, history of rejection, date of recurrence of HCC, site of recurrence, status at the end of follow-up, and history of graft failure.

MORPHOMICS AND BODY COMPOSITION

All available CT scan Digital Imaging and Communication in Medicine files were analyzed using a semiautomated high throughput methodology with algorithms programmed in MATLAB (MathWorks Inc., Natick, MA) as described previously.[13,16-19] Our methodology allowed for accurate anatomic indexing of every individual based on the spine. All algorithms involved a combination of user-defined points, automated image processing, and user editing and verification. All measurements were taken at the bottom of the eleventh thoracic vertebral level (T11). This anatomic landmark was chosen because this was felt to have the highest likelihood of being available on all abdominal and chest CT scans. The data included the DMG area, BMD, VF, and SF. Furthermore, the age-related decline in trabecular bone strength at the thoracic vertebral level is similar to lumbar vertebra.[20] BMD was measured only on the trabecular bone with calculation of the average pixel density within a circle defined as the midvertebral core sample. A ratio of VF to SF was also calculated.

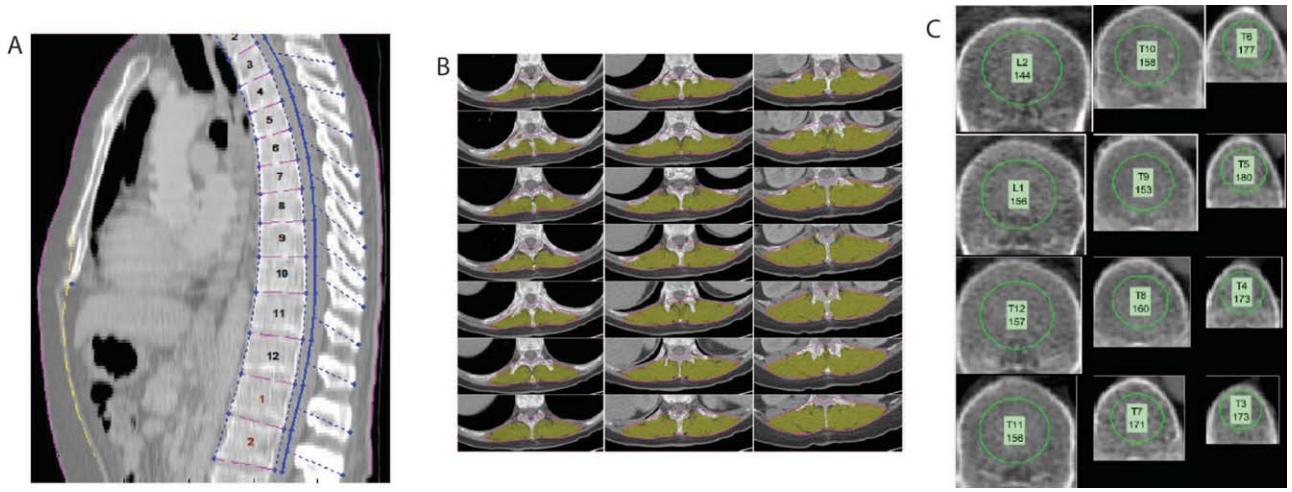

FIG. 1. Computer-generated GUI of the (A) anatomic indexing showing the spinal vertebral levels, which serves as an anatomical reference system for each patient. (B) Example of the DMG measured (shaded in yellow) defined automatically after delineation of paraspinous lateral seams at specified vertebra points that is processed in each patient. (C) Example of the trabecular bone density areas measured within the circle within the midvertebral core.

An illustration of the measurements taken from 1 patient is shown in Fig. 1.

STATISTICAL ANALYSIS

Continuous variables were expressed as median and interquartile range (IQR), and the categorical variables were expressed as counts and percentage. The primary outcome was posttransplant mortality. For reference purposes, the DMG area and BMD of HCC LT recipients were compared with age- and sex-matched non-HCC LT recipients who underwent transplantation during the study duration at our institution using the Mann-Whitney U test. Cox regression analysis was used to examine the predictors of posttransplant mortality. DMG area, VF area, SF area, and BMD were included as the variables of interest in addition to various donor and recipient factors including age at LT, sex, AFP, diabetes, etiology of liver disease, serum bilirubin, creatinine, and international normalized ratio (INR) at LT, pretransplant number of lesions, largest diameter, donor age, and cold ischemia time. Because explant information is not known prior to the time of LT, the number of lesions and the largest diameter on the explant were not included as predictive variables. Variables with a P value < 0.1 on univariate analysis were included to perform the multivariate analysis. Because we were interested in the effect of DMG area on posttransplant mortality, DMG area was forced in the multivariate model. All analyses were performed using SPSS 22.0 statistical package (IBM, Armonk, NY).

Results

PATIENT CHARACTERISTICS AT LT

There were a total of 199 patients transplanted for HCC during the study period; 118 HCC patients met the inclusion criteria (availability of CT scan any time prior to 6 months before LT). The baseline characteristics of the cohort (n = 118) at the time of LT are shown in Table 1. The median age was 56 years, 78% were males, 75% were Caucasians, and 64% had hepatitis C as the etiology of liver disease. The median donor age was 41 years old.

PRE-LT RADIOLOGICAL AND MORPHOMICS CHARACTERISTICS

Table 2 shows the pre-LT radiological and morphomics characteristics. The median number of HCC lesions was 1, and the median largest diameter was 2.5 cm. None of the patients had portal vein thrombosis. At presentation, 87% met Milan criteria, 59% received some type of locoregional therapy, and 12% were

TABLE 1. Recipient and Donor Characteristics at LT

Variables	Value (n = 118)
Age at LT, years, median (IQR)	56 (23-71)
Sex, males, %	78
Race, %	
Caucasian	75
African American	15
Other	10
Etiology, %	
Hepatitis C	64.4
Hepatitis B	4.2
Alcohol	15.3
Cryptogenic	9.3
Other	6.8
Laboratory MELD, median (IQR)	14 (8-18)
Log AFP, median (IQR)	1.44 (0.08-4.30)
Bilirubin, mg/dL, median (IQR)	2.5 (1.4-3.6)
INR, median (IQR)	1.2 (0.9-1.4)
Creatinine, mg/dL, median (IQR)	1.2 (0.9-1.4)
Donor age, years, median (IQR)	41 (24-53)

TABLE 2. Pre-LT Radiological Tumor Characteristics and Analytic Morphomics Characteristics

Variables	Value
Number of lesions, median (IQR)	1 (1-2)
Largest diameter, cm, median (IQR)	2.5 (1.9-3.2)
Locoregional therapy, %	59
Meeting Milan criteria, %	87
DMG area, mm^2, median (IQR)	3636.2 (2770-4903)
DMG volume, mm^3, median (IQR)	77,408.4 (49,415-92,153.8)
VF area, mm^2, median (IQR)	8014.5 (4203.8-13,153.5)
SF area, mm^2, median (IQR)	9731.6 (6057.8-15,398.8)
Ratio VF/SF, median (IQR)	0.9 (0.5-1.3)
BMD, HU, median (IQR)	184.9 (162-216.8)

downsized. All the patients were within Milan criteria at the time of LT based on the most recent imaging prior to LT.

The median DMG area was 3636.2 mm^2; median VF area was 8014.5 mm^2; median SF was 9731.6 mm^2; and the ratio of VF to SF was 0.87. Figure 2 shows the distribution of BMD in the cohort. The median BMD was 185 Hounsfield units (HU). The 25th and 75th percentile were 162 and 216 HU, respectively. Only 2.5% of the patients had BMD $\leq$ 100 Hounsfield units (HU), suggestive of osteoporosis.

The age- and sex-matched median BMD at T11 of HCC LT-recipients was similar to the age- and sex-matched BMD of non-HCC LT recipients transplanted during the study period (HCC males, 176.6 HU versus non-HCC males, 173.6 HU; HCC females, 209.8 HU versus non-HCC females, 182.9 HU) were similar. The median age-matched DMG area at T11 for female HCC LT recipients was also

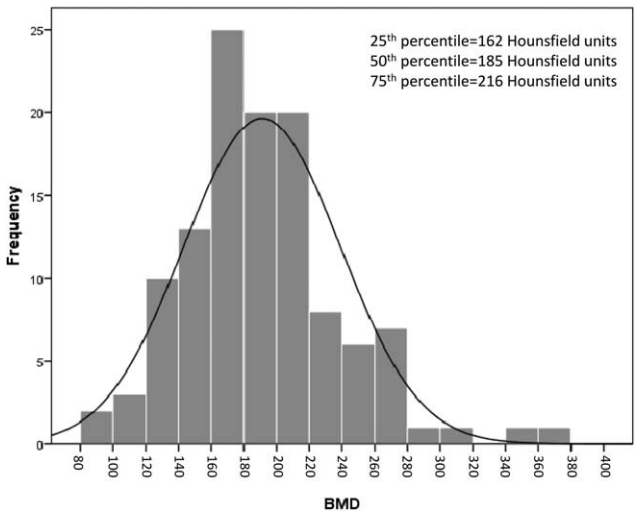

FIG. 2. Distribution of BMD before LT among HCC LT recipients.

similar for HCC (2826.6 mm^2) and female non-HCC LT recipients (3073.8 mm^2). However, the age-matched median DMG of male HCC LT recipients was significantly higher than the age-matched male non-HCC LT recipients who underwent transplantation during the same study period (HCC, 4033 mm^2 versus non-HCC, 3167 mm^2; $P < 0.001$).

POST-LT DEATHS

There were a total of 32 post-LT deaths after a median follow-up of 4.4 years. The unadjusted 1-year, 3-year, and 5-year survival was 87%, 77%, and 73%, respectively. The median time to death was 10.9 months from LT. The cause of death was primary nonfunction in 5; hepatitis C–related graft failure in 4; sepsis and multiorgan failure in 6; metastatic HCC in 11; and cause unknown in 6 patients. The median BMD in 32 patients who died was 186.5 HU (IQR, 156.0-210.6) and only 1 (3%) patient had BMD < 110 HU. Notably, fewer patients received locoregional therapy among those who died compared to those who survived after LT (39% versus 69%; $P = 0.006$).

INDEPENDENT PREDICTORS OF POST-LT DEATHS

Table 3 shows the independent predictors of post-LT mortality among HCC LT candidates in a model

TABLE 3. Independent Predictors of Post-LT Mortality Among HCC LT Recipients

Covariates*	HR (95% CI)	*P* Value
Dorsal muscle area	1.0 (1.00–1.00)	0.7
Number of lesions	2.81 (1.74–4.53)	<0.001
Locoregional therapy (versus not)	0.14 (0.06–0.36)	<0.001
BMD (per 10 HU)	0.90 (0.83–0.99)	0.03
Donor age, per year	1.05 (1.02–1.07)	<0.001

*Model was adjusted for age and sex.

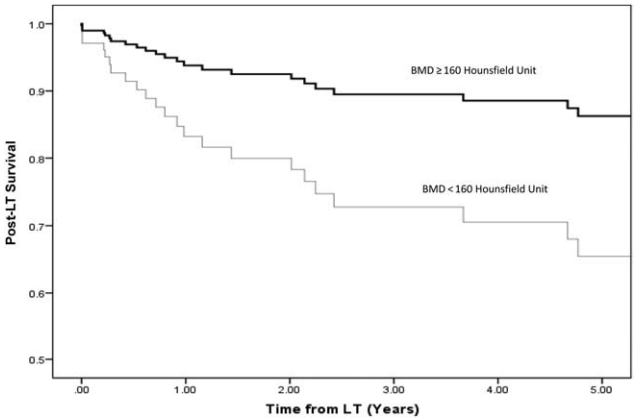

FIG. 3. Adjusted post-LT survival among HCC LT recipients stratified by BMD.

adjusted for age and sex. Meeting pre-LT Milan criteria was not a predictor of post-LT mortality, although the number of patients transplanted outside of Milan criteria in this cohort was small. Evidence of locoregional therapy before LT was associated with an 86% lower risk of post-LT death. Factors independently associated with high post-LT mortality included higher number of HCC lesions, low BMD, and older donor age (Table 3). Every 10 HU decrease in BMD was associated with a 10% increased risk of post-LT mortality. In the multivariate model, DMG area was not associated with post-LT mortality.

On the basis of the published literature, BMD < 160 HU is 90% sensitive for distinguishing osteoporosis.[21] Therefore, we dichotomized BMD as <160 HU and ≥160 HU. After adjusting for sex, DMG area, number of lesions, and donor age, BMD < 160 HU was associated with a 2.8-fold higher hazard of post-LT mortality than those with BMD ≥ 160 HU (HR = 2.87; $P = 0.018$; Fig. 3).

Discussion

This is the first study to identify the novel association between BMD and posttransplant survival among HCC LT recipients. Additionally, tumor burden and advanced donor age were also associated with poor post-LT survival. Pre-LT locoregional therapy of any kind was associated with lower risk of post-LT mortality. Our study did not find any association between DMG area and post-LT survival in HCC LT recipients.

BMD is the most important determinant of bone fragility. Dual energy X-ray absorptiometry (DEXA) is currently the standard for assessing BMD and has been correlated with fracture risk and treatment efficacy. The use of HU from the CT scans to assess regional BMD of the spine has recently been described, with several subsequent studies exploring its utility in assessing fracture risk and prognosticating fusion success.[21-23] There is growing evidence that quantitative CT is excellent for predicting vertebral fractures and serial measuring for bone loss, with better sensitivity compared to DEXA as the trabecular bone can be selectively measured and overlying densities (such as aortic calcifications) can be excluded from the study.[20,21,23] The added advantage is that BMD can be assessed accurately from the CT scans obtained for other indications without exposing patients to the additional risk for ionizing radiation.

We used the cutoff of BMD < 160 HU in order to further explore the association between BMD and post-LT mortality and found that the adjusted risk of death was close to 3-fold higher among those who have BMD ≥ 160 HU. Pickhardt et al.[21] demonstrated that the CT-attenuation threshold of 160 HU or less was 90% sensitive at the first lumbar vertebrae and a threshold of 110 HU was more than 90% specific for distinguishing osteoporosis from osteopenia and normal BMD. Positive predictive values for osteoporosis were 68% or greater at the first lumbar vertebrae CT-attenuation thresholds less than 200 HU; negative predictive values were 99% at thresholds greater than 200 HU. Only 2.5% had BMD < 110 HU suggestive of osteoporosis in our cohort, but 25% of the patients who died had BMD < 160 suggestive of osteopenia. These results suggest that early intervention such as rehabilitation and medical therapy to improve low BMD (osteopenia) and to prevent further bone loss prior to LT may improve post-LT outcomes.

This becomes all the more relevant in the context of the revised HCC allocation policy where HCC candidates would have to wait for 6 months to receive an exception MELD score of 28.

Sarcopenia and frailty are common among LT candidates and are associated with poor posttransplant survival after solid organ transplant.[5,8,10,24-26] Data suggest that the bone loss may begin before loss of muscle mass in patients with end-stage liver disease and may become apparent before the loss of muscle mass.[27] Our study appears to validate this observation. Decrease in bone strength, reflected by low BMD, may be the earliest hallmark of the "bone loss–sarcopenia–frailty" spectrum among HCC candidates who have relatively preserved muscle mass compared to non-HCC candidates listed for LT of comparable allocation MELD. The definition of sarcopenia varies from study to study.[5,8-11,13,28-30] Englesbe et al.[8,13] used total psoas area as a surrogate for sarcopenia in their pioneer study. Some recent studies have used DMG area to define sarcopenia because it includes the core muscles which can be measured at T11.[10] Our study used the DMG area as a surrogate of sarcopenia because psoas muscle is not generally present above L2 and thus would not be generally measureable in a thoracic CT. Moreover, there is an excellent correlation between total psoas muscle area and DMG area.[10]

A recent study of 94 patients who underwent either resection or LT for primary liver tumor found that sarcopenia (defined as total psoas volume) was associated with a 3-fold increased likelihood of postoperative complications.[11] Almost all Clavien grade $\geq$3 complications occurred in the sarcopenic group.[11] However, sarcopenia was not associated with longterm survival.[11] Similarly, our study did not find any relationship between sarcopenia (defined as DMG area) and posttransplant mortality among HCC LT recipients. It is plausible that although sarcopenia appears to be important for non-HCC patients with profound muscle mass loss, it does not really seem to impact post-LT survival in HCC patients due to MELD exception policies.

In our study, pre-LT tumor burden was independently associated with poor posttransplant survival. High tumor burden is one the most important causes of HCC recurrence and post-LT mortality among HCC LT recipients.[31] Our study also showed that pre-LT locoregional therapy improved patient survival after LT. This improved survival was likely related to pre-LT palliation of HCC tumors and change in programmatic practice of waiting for at least 3 months after locoregional therapy. The waiting time eliminates HCC candidates with aggressive tumor biology (shorter doubling time) because of progression of HCC. The combination of these 2 practices has also attenuated early HCC recurrence and improved posttransplant survival among HCC LT recipients. Donor age is a known predictor of graft failure and post-LT mortality.[32] Our study validated this finding in HCC LT recipients.

The limitations of our study include the inherent biases associated with retrospective study design. Although analytic morphomics is versatile, at the present time we can only perform image analysis on CT data files. We were unable to include those patients who had magnetic resonance imaging. This resulted in attenuation of sample size and loss of power. Despite these limitations, our hypothesis-generating study found a novel association between BMD and posttransplant survival among HCC LT recipients.

In conclusion, bone loss, high tumor burden, and advanced donor age are the important determinants of post-LT mortality among HCC LT recipients. Modification of BMD, through pre-LT rehabilitation programs and medical therapy (eg, calcium/vitamin D, bisphosphonate therapy) and utilization of pre-LT locoregional therapy may further improve post-LT survival among this subgroup of patients.

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