Liver Transplantation for Hepatic Adenoma: A UNOS Database Analysis and Systematic Review of the Literature

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Background. Liver transplantation (LT) has been employed for hepatic adenoma (HA) on a case-oriented basis. We aimed to describe the characteristics, waitlist, and post-LT outcomes of patients requiring LT for HA. **Methods.** All patients listed or transplanted for HA in the United States were identified in the United Network for Organ Sharing (UNOS) database (1987–2020). A systematic literature review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement. **Results.** A total of 199 HA patients were listed for LT in UNOS and the crude waitlist mortality was 9.0%. A total of 142 HA patients underwent LT; 118 of these were among those listed with an indication of HA who underwent LT, and 24 were diagnosed incidentally. Most did not experience hepatocellular carcinoma transformation (89.4%). Over a median follow-up of 62.9 mo, death was reported in 18.3%. The 1-, 3-, and 5-y patient survival rates were 94.2%, 89.7%, and 86.3% in the UNOS cohort. The systematic review yielded 61 articles reporting on 99 nonoverlapping patients undergoing LT for HA and 2 articles reporting on multicenter studies. The most common LT indications were suspected malignancy (39.7%), unresectable HA (31.7%), and increasing size (27.0%), whereas 53.1% had glycogen storage disease. Over a median follow-up of 36.5 mo, death was reported in 6.0% (n=5/84). The 1-, 3-, and 5-y patient survival rates were all 95.0% in the systematic review. **Conclusions.** LT for HA can lead to excellent long-term outcomes in well-selected patients. Prospective granular data are needed to develop more optimal selection criteria and further improve outcomes.

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Hepatic adenoma (HA) is a benign liver tumor that most commonly occurs in women of reproductive age, classically receiving oral contraceptives.[1] Development of HA has also been associated with underlying diseases of the liver,

including glycogen storage disease (GSD) and absence of the portal vein (Abernethy malformation).[2,3] In 1985, Flejou et al[4] described liver adenomatosis, a variant of HA, referring to patients with >10 HAs in an otherwise normal liver

parenchyma. The clinical presentation of HA is variable, with the most noticeable features being abdominal pain and bloating, hepatomegaly, or rupture with intraperitoneal bleeding, whereas some patients may be asymptomatic and have an incidental diagnosis of HA.[5-7] The management of HA is also variable and relies mostly on symptom severity, the risk of hemorrhage or rupture, and the risk of malignant transformation.[7-9] Treatment options range from regular follow-up accompanied with imaging and withdrawal of hormone-containing pills to liver resection or liver transplantation (LT).[5,7-10]

Despite the broadening of indications of LT for liver neoplasms, particularly of malignant nature,[11-13] LT has been only rarely used for the management of HA. The current United Network for Organ Sharing (UNOS) guidance for granting exception points for HA includes having HA with risk of malignant transformation, not amenable to resection, and either or both (1) biopsy-proven malignancy or (2) presence of GSD. The available evidence is limited mostly to case reports or small case series. The only large report is a multicenter study from Europe reporting on <50 cases of LT for liver adenomatosis that span between 1986 and 2013.[14] On account of the importance and rarity of employing LT for HA and the inability to draw solid conclusions based on the currently available level of evidence, revisiting this topic is of paramount importance. Therefore, we aimed to describe the demographics, clinical characteristics, indications, and outcomes of LT for HA through a retrospective analysis of a US transplant registry and a systematic review of the global literature.

MATERIALS AND METHODS

UNOS Analysis

Data Source, Patient Identification, Data Encoding

The UNOS database administers the Organ Procurement and Transplantation Network under contract with the US Department of Health and Human Services. This database contains data on all transplant candidates undergoing listing for solid organ transplantation in the United States since October 1987. All data were deidentified, and thus no Institutional Review Board approval was required.

Patient pretransplant, transplant, and follow-up data were obtained from the UNOS Standard Transplant Analysis and Research data file (released on September 4, 2020). In this retrospective cohort study, we included patients of all ages listed for LT or undergoing LT for HA between October 1987 and September 2020 in the United States. To avoid the introduction of bias by intrapatient correlation, when patients had multiple listings, only the most recent listing of each patient was used. Patients were identified using the primary and secondary listing diagnosis codes and transplant diagnosis codes from UNOS for HA (code 4450). In addition, to identify potentially missed patients with HA, we searched in the free-text field of the diagnosis codes using the word fragment "aden." Recipients were considered to have a nonincidental HA, if HA was a listing diagnosis, whereas they were considered to have an incidental HA if they were listed for another indication, but HA was identified only among transplant recipient diagnosis variables. Recipients were considered to have a listing hepatocellular carcinoma (HCC) codiagnosis if HCC was a listing diagnosis, whereas they were considered to have an incidental HCC if it was identified only among transplant recipient diagnosis variables (codes 4400 or 4401). Recipients were also considered to have a codiagnosis of GSD

if they had any GSD diagnosis code (code 4303 or 4304) or if GSD was present in any free-text field.

Statistical Analysis

Continuous variables were presented using medians and interquartile ranges (IQRs), whereas categorical variables were presented using frequencies and percentages. Univariable linear regression was used to assess the number of patients listed for LT over the study period.

For the waitlist outcomes analysis, there are 2 competing risks/outcomes: (1) waitlist mortality, defined as death/delisting due to being too sick, which was the main risk/outcome of interest, and (2) other reason for waitlist removal (including LT), which was the competing risk/outcome. Patients who were still on the waitlist by the date of the last follow-up were censored. Survival was measured from the date of listing for LT until the date of removal from the waitlist for any reason or until the date of the last follow-up. The effect of patient characteristics on waitlist mortality was explored using Fine-Gray[15] competing risks regression modeling for competing risks analysis. In contrast to the cause-specific hazards estimates provided by the Cox regression models, the Fine-Gray[15] competing risks regression models provide the subdistribution hazard ratios and 95% confidence intervals (95% CIs) of each competing outcome.

Post-LT patient and graft survival were defined as the duration from the date of LT until the date of last patient contact or patient death/graft loss, respectively. The Kaplan-Meier method was used to determine the 1-, 3-, and 5-y patient and graft survival rates. Cox regression models were also fitted to estimate the hazard ratio and 95% CI and to determine the effect of patient characteristics on patient mortality and graft loss. Cohort development and statistical analyses were performed using Stata IC 16.0 (StataCorp LLC, College Station, TX). All tests were 2-sided and $P < 0.05$ was considered statistically significant.

Systematic Review

Study Design, Search Strategy, Study Eligibility, and Selection

A systematic review of the literature was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement.[16] No Institutional Review Board approval or patient written consent was necessary, since the systematic review used only published data. Articles published in English reporting on demographic, clinical characteristics, and outcomes of patients undergoing LT for HA were searched through the MEDLINE (via PubMed), Embase, Scopus, and Cochrane Library databases (last search date: March 2, 2021) using the following algorithm: (transpl*) AND (hepatic adenoma OR liver adenoma OR hepatic adenomatosis OR liver adenomatosis). Two researchers (I.A.Z., P.T.T.) performed the title/abstract and full-text screening stages of the literature search independently. The citations of the systematically reviewed studies were hand-searched for potentially eligible, missed studies using the snowball methodology.[17] No sample size restriction or other search filters were applied. Any conflicts were resolved through quality control discussions. The Covidence reference and article manager software was used for all stages of the database search and study selection.[18]

Data Extraction and Tabulation

A standardized, prepiloted form was used for data tabulation and extraction from the included studies for evidence

synthesis. Two reviewers (P.T.T., N.S.) extracted the data independently and any discrepancies were identified and resolved through quality control discussions with another author (I.A.Z.). The following data were extracted for each eligible study: first author, year of publication, transplant center and country, number of patients, age at diagnosis and at LT, sex, time of HA diagnosis (pre-LT or incidentally on explant pathology), clinical presentation and laboratory results, HA characteristics (number, size, liver location), indication for LT, underlying liver disease, immunohistochemistry findings, previous interventions, graft type and multiorgan transplant type, post-LT complications, and survival data (patient status, follow-up time, cause of death).

Data on characteristics and outcomes of interest were tabulated and analyzed cumulatively, whereas all relative rates were estimated based on the availability of data for each variable of interest. In case of overlapping study populations, only the larger study was included. When analyses on additional outcomes were presented in several eligible articles, data were extracted from all as their population was not summed in the overall subject numbers, but rather represented additional analyses on the same cohorts. Univariable linear regression was used to assess the number of patients undergoing LT for HA outside the United States (since the data in the United States were assessed using the UNOS database) over the study publication date.

RESULTS

UNOS Analysis
Waitlist Cohort

A total of 199 patients were listed for LT with an indication of HA between January 1994 and August 2020. No patient listed for HA was identified between 1987 and 1994. The number of patients listed for HA increased over the study period ($P = 0.003$). Data on number of HAs and HA size were not available. The overall crude waitlist mortality was 9.0% (n = 18 of 199), with the cause of death being available for 7 patients and that included cardiac arrest (n = 3), hemorrhage (n = 2), multiple organ failure (n = 1), infection/sepsis (n = 1); 118 patients underwent LT (Figure 1). The median age at listing was 36 y, 81.9% were female, the median waitlist time was 8.7 mo, and previous ablative therapy was

administered in 4.7% (n = 6 of 128). Detailed characteristics for the patients with HA listed for LT in the UNOS database are presented in Table 1.

Univariable Fine-Gray[15] competing risks regression modeling showed that increasing age, laboratory model for end-stage liver disease (MELD)/pediatric end-stage liver disease (PELD) score, international normalized ratio, serum creatinine, decreasing albumin, ascites, and being on life support were associated with an increased risk of waitlist mortality (**Table S1, SDC**, http://links.lww.com/TXD/A391).

Transplant Cohort

A total of 142 patients with HA underwent LT; 118 of these were among those mentioned previously who were listed for LT with an indication of HA and ended up undergoing LT, and 24 were diagnosed incidentally. The median age at LT was 34.5 y with 32 (22.5%) patients being children (<18 y), the majority (79.6%) were female, and 9 patients had a codiagnosis of GSD (6.3%). Data on number of HAs and HA size were not available. The median laboratory MELD/PELD score was 8 and 61.3% received exception points. Most patients received a deceased donor whole graft (90.1%), and 4 patients underwent simultaneous liver-kidney transplant (2.8%), whereas 1 patient underwent simultaneous liver-pancreas-small bowel transplant (0.7%). The majority did not experience HCC transformation (89.4%), whereas 7 (4.9%) had a listing codiagnosis of HCC, and 8 (5.6%) had an incidental HCC noted on explant. Detailed characteristics for the patients with HA undergoing LT in the UNOS database are presented in Table 2.

Over a median follow-up of 62.9 (IQR, 13.6–124.1) mo, death was reported in 18.3% (n = 26 of 142) and the cause of death was liver malignancy (n = 3), secondary extrahepatic cancer unrelated to the liver (n = 6), infection (n = 7; 6 had sepsis, 1 had multifocal pneumonia), pulmonary edema/respiratory failure (n = 3; 2 also had pneumonia), operative mortality/cardiac arrest (n = 2), primary graft failure with concomitant renal failure (n = 1), renal failure (n = 1), congestive heart failure (n = 1), hemorrhagic shock (n = 1), and unknown (n = 1). The 1-, 3-, and 5-y patient survival rates were 94.2% (95% CI, 88.7%-97.0%), 89.7% (95% CI, 82.8%-93.9%), and 86.3% (95% CI, 78.5%-91.5%) (Figure 2A). The 1-, 3-, and 5-y graft survival rates were
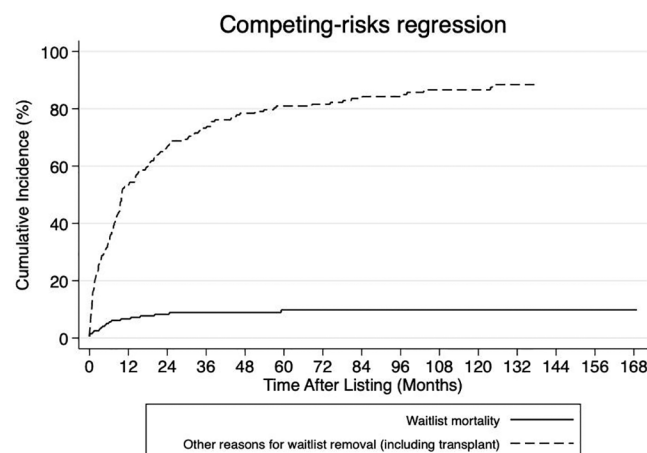

FIGURE 1. Cumulative incidence competing risk curves of waitlist removal due to death or being too sick and due to other reasons in patients listed for liver transplant for hepatic adenoma from the United Network for Organ Sharing database.

Characteristics of waitlisted patients in the UNOS database

Characteristic at listing[a]	Total (n = 199)
Age, y	36.0 (22.0–46.0)
Waitlist time, mo	8.7 (2.0–23.8)
Sex	
Female	163 (81.9%)
Male	36 (18.1%)
Race	
White	126 (63.3%)
Black	37 (18.6%)
Hispanic	20 (10.1%)
Asian	11 (5.5%)
American Indian/Alaska Native	2 (1.0%)
Multiracial	3 (1.5%)
Blood type	
A	67 (33.7%)
AB	6 (3.0%)
B	26 (13.1%)
O	100 (50.3%)
Height, cm (n = 193)	162.6 (155.0–170.2)
Weight, kg (n = 198)	71.6 (58.1–87.0)
BMI, kg/m^2 (n = 193)	26.4 (21.9–31.7)
Laboratory PELD/MELD score (n = 155)	7.0 (6.0–9.0)
Albumin, g/dL (n = 164)	4.0 (3.5–4.4)
Bilirubin, mg/dL (n = 164)	0.6 (0.4–1.2)
INR (n = 164)	1.0 (1.0–1.2)
Serum creatinine, mg/dL (n = 163)	0.6 (0.5–0.8)
Serum sodium, mEq/L (n = 144)	139.0 (137.5–141.0)
Ascites (n = 160)	15 (9.4%)
Encephalopathy (n = 159)	13 (8.2%)
PVT (n = 173)	14 (8.1%)
Dialysis within prior wk (n = 161)	3 (1.9%)
On life support	4 (2.0%)
Exception points given	91 (45.7%)
Previous ablative therapy (n = 128)	6 (4.7%)
Outcome	
Died	12 (6.0%)
Delisted for being too sick	6 (3.0%)
Condition improved	23 (11.6%)
Transplanted	118 (59.3%)
Refused transplant	2 (1.0%)
Still waiting	16 (8.0%)
Other	17 (8.5%)
Unable to contact	5 (2.5%)

[a]The data are available for the whole cohort of 199 patients unless otherwise specified. Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages.
BMI, body mass index; INR, international normalized ratio; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease; PVT, portal vein thrombosis; UNOS, United Network for Organ Sharing.

89.3% (95% CI, 82.8%-93.4%), 84.1% (95% CI, 76.6%-89.4%), and 80.0% (95% CI, 71.7%-86.1%) (Figure 2B). Univariable Cox regression modeling showed that increasing age and laboratory MELD/PELD score, male sex, decreasing albumin and serum sodium, ascites, encephalopathy, and being on life support were associated with an increased risk of post-LT patient mortality (Table S2, **SDC**, http://links.lww.com/TXD/A391). However, only increasing laboratory MELD/PELD score, decreasing albumin and serum sodium, and being on life support were associated with an increased risk of post-LT graft loss in univariable Cox regression (Table S2, **SDC**, http://links.lww.com/TXD/A391).

Characteristics of transplanted patients in the UNOS database

Characteristic at transplant[a]	Total (n = 142)
Time of HA diagnosis	
Pre-LT/listing	118 (83.1%)
Incidental (explant pathology)	24 (16.9%)
Age, y	34.5 (19.0–47.0)
Sex	
Female	113 (79.6%)
Male	29 (20.4%)
Race	
White	96 (67.6%)
Black	23 (16.2%)
Hispanic	15 (10.6%)
Asian	4 (2.8%)
American Indian/Alaska Native	2 (1.4%)
Multiracial	2 (1.4%)
Blood type	
A	50 (35.2%)
AB	6 (4.2%)
B	18 (12.7%)
O	68 (47.9%)
Height, cm	162.6 (154.9–170.0)
Weight, kg	68.1 (55.1–84.5)
BMI, kg/m^2	24.9 (21.0–30.8)
Laboratory PELD/MELD score (n = 110)	8.0 (6.0–13.0)
Albumin, g/dL (n = 140)	3.9 (3.2–4.4)
Bilirubin, mg/dL (n = 141)	0.7 (0.4–1.8)
INR (n = 116)	1.1 (1.0–1.3)
Serum creatinine, mg/dL	0.7 (0.5–0.9)
Serum sodium, mEq/L (n = 103)	139.0 (137.0–141.0)
Ascites (n = 107)	19 (17.8%)
Encephalopathy (n = 107)	15 (14.0%)
PVT (n = 121)	18 (14.9%)
Dialysis within prior wk (n = 131)	5 (3.8%)
On life support (n = 141)	8 (5.7%)
Exception points given	87 (61.3%)
Previous ablative therapy (n = 92)	3 (3.3%)
Malignant transformation/HCC	
No	127 (89.4%)
Pre-LT/listing HCC	7 (4.9%)
Incidental HCC	8 (5.6%)
Graft type	
Deceased donor whole graft	128 (90.1%)
Deceased donor partial/split graft	5 (3.5%)
Living donor graft	9 (6.3%)

[a]The data are available for the whole cohort of 142 patients unless otherwise specified. Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages.
BMI, body mass index; HA, hepatic adenoma; HCC, hepatocellular carcinoma; INR, international normalized ratio; LT, liver transplantation; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease; PVT, portal vein thrombosis; UNOS, United Network for Organ Sharing.

Systematic Review
Study Characteristics

Our initial database search yielded 748 unique records, 91 of which were retrieved for full-text assessment, 53 of which fulfilled the inclusion criteria and were ultimately included. Another 21 records were retrieved for full-text assessment, 13 of which were ultimately included. Overall, 66 reports were included[2,10,14,19-81]; since 4 of them reported on overlapping patients,[39,50,61,72] only the largest series of 4 was included,[39] whereas data were extracted from all as their population
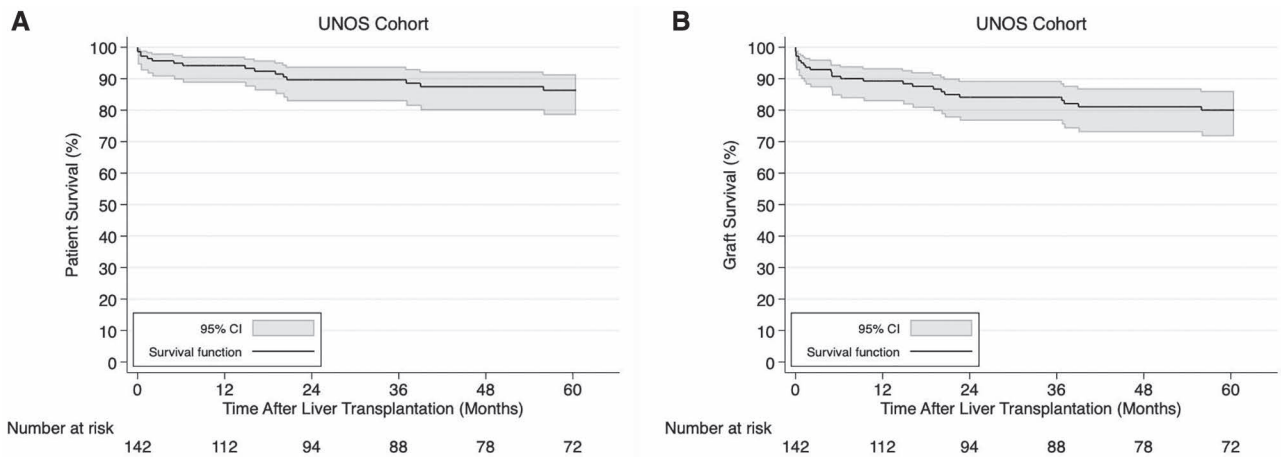
FIGURE 2. Kaplan-Meier patient (A) and graft (B) survival curves in hepatic adenoma liver transplant recipients from the United Network for Organ Sharing (UNOS) database. CI, confidence interval.

represented additional analyses on the same patients, yielding a total of 63 included studies (Figure 3). Two of the 63 studies were multicenter[14,79] and reported on 5 patients[79] and 49 patients[14] (that may be overlapping to a certain extent), respectively, whereas the rest 61 studies reported on 99 non-overlapping (unique) patients who underwent LT for HA (Table 3). Sixty-seven patients underwent LT for HA outside the United States, and the number of patients did not appear to change over the publication date ($P = 0.62$).

Patient Characteristics

As not all reports contained all variables of interest, relative rates were estimated based on the availability of data. The median age at diagnosis and at LT in the nonoverlapping systematically reviewed patients was 19.5 and 25.0, respectively, with 24 of 86 (27.9%) patients being children at the time of LT. Most patients were female (60.7%), and most had multiple HAs (75.3%), whereas 93.5% were diagnosed before LT and only 6.5% were incidental. The most common indications for LT were suspected malignancy (39.7%), unresectable HA (31.7%), and increasing HA size (27.0%). Biopsy-confirmed HCC transformation pre-LT was an indication in 9.5% (n = 6), whereas more than half of the patients (53.1%) had GSD. The graft type for LT was reported in only 27 of the 99 cases (27.3%). Thirteen were performed using whole deceased donor graft, 1 using reduced-size deceased donor graft, 1 using split deceased donor graft, and 12 using living donor graft. Multiorgan transplant was performed in 10.7% (n = 9 of 84; 8 were simultaneous liver-kidney transplants and 1 was simultaneous liver-small bowel transplant). Malignant transformation was reported in 18 (23.1%) with 6 (7.7%) being biopsy-confirmed HCC transformation pre-LT and 12 (15.4%) incidental HCC on explant pathology. Detailed characteristics for the systematically reviewed patients with HA undergoing LT are presented in Table 4.

Clinical Presentation

Patients with HA presented with abdominal pain, hepatomegaly, pruritus, subclinical hemorrhage, hepatic encephalopathy, whereas few of the patients were asymptomatic. Five of the 99 patients (5.1%) presented initially with HA intraperitoneal rupture; 2 of them underwent upfront LT during the same admission, 1 was managed conservatively and underwent interval LT, 1 was managed with left lobectomy

but 5 y after presentation the patient underwent LT for suspected malignant transformation, and 1 patient underwent left lateral segmentectomy followed by a second liver resection for HA recurrence and finally underwent interval LT due to recurrence of numerous HAs. Another 2 patients presented with intratumoral rupture and underwent interval LT due to increased risk of hemorrhage and worsening symptoms.

Immunohistochemistry

Immunohistochemistry post-LT was reported in only 21 of the 99 patients (21.2%) and had positive findings in 18 of them. One patient had HA positive to both hepatocyte nuclear factor-1 alpha and beta-catenin (b-CAT), 3 patients had HA positive to both inflammatory hepatocellular adenoma (IHCA) immunohistochemistry and b-CAT, 3 patients had HA positive to only IHCA, and 11 patients had HA positive to only b-CAT. Pretransplant histology was not reported.

Previous Interventions

Thirty-three patients had a previous intervention (39.3%, n = 33 of 84). Twenty-seven of them underwent a previous liver resection (32.1%; 3 patients underwent previous liver resection twice), 4 patients underwent portocaval shunt (4.8%; 1 of them had undergone a previous liver resection), 3 patients underwent previous embolization (3.6%; 2 of them had undergone a previous liver resection), 1 mesocaval anastomosis (1.2%), and 1 patient underwent diagnostic laparotomy (1.2%).

Outcomes

Retransplantation was required in 2.3% (n = 2 of 87). Post-LT complications were reported in 25.0% (n = 21 of 84). These included acute rejection (13.1%, n = 11 of 84), renal failure (4.8%, n = 4 of 84; 2 patients also experienced acute rejection, whereas 1 patient also experienced arthritis secondary to tacrolimus, left upper extremity deep vein thrombosis, incisional hernia, diabetes mellitus, and osteopenia), cytomegalovirus infection (n = 3; 1 of them also experienced acute rejection), tremor secondary to tacrolimus (n = 1), ischemic stroke (n = 1), hepatitis C virus infection (n = 1), portal vein thrombosis (n = 2; 1 of them also experienced bile leak and subphrenic hematoma), and hepatic vein thrombosis (n = 1).

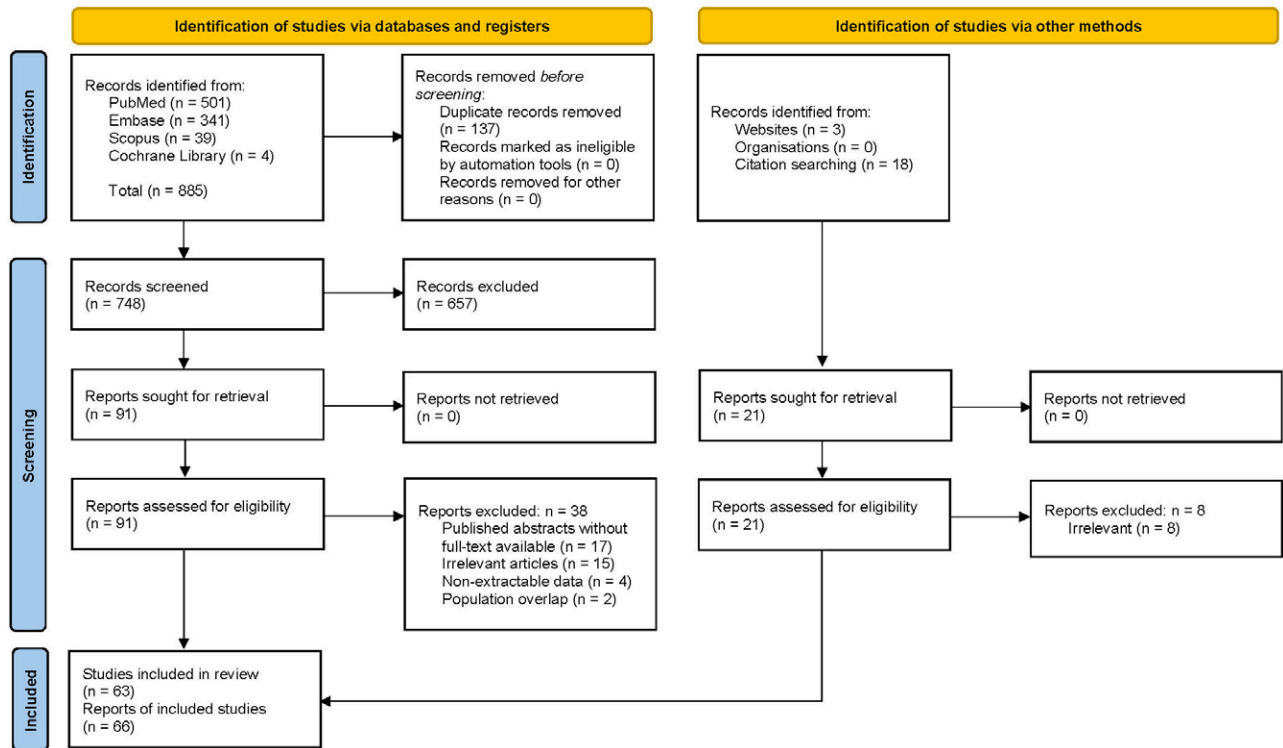Over a median follow-up of 36.5 (IQR, 19.0–72.0) mo, death was reported in 6.0% (n = 5 of 84) and the cause of

FIGURE 3. Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram of the search strategy and study selection.

TABLE 3.

Characteristics of studies included in the systematic review

Author, year	Center, city	Country	Number of patients
Registry studies			
Current UNOS analysis	Multicenter	United States	142
Baiges, 2020[79]	Multicenter	International	5
Chiche, 2016[14]	Multicenter	European	49
Unique patients			
Intaraprasong et al, 2021[57]	Ramathibodi Hospital Mahidol University, Bangkok	Thailand	1
Singh et al, 2020[30]	The Ohio State University Wexner Medical Center, Columbus	United States	1
Barbier et al, 2019[36]	University of Tours, Tours	France	1
Salhanick et al, 2019[31]	University of Texas Southwestern Medical Center, Dallas	United States	1
Timothy et al, 2019[24]	Mayo Clinic, Rochester	United States	1
Vali et al, 2019[75]	Tartu University Hospital, Tartu	Estonia	1
Mohkam et al, 2017[42]	Croix-Rousse University Hospital, Lyon	France	1
Leone et al, 2016[34]	Tampa General Hospital, Tampa	United States	1
Samuk et al, 2016[32]	University of Miami Miller School of Medicine, Miami	United States	1
Sorkin et al, 2016[69]	King's College Hospital, London	United Kingdom	1
Szili et al, 2016[74]	Semmelweis University, Budapest	Hungary	1
Brasoveanu et al, 2015[45]	Fundeni Clinical Institute, Bucharest	Romania	1
Nacif et al, 2015[47]	University of São Paulo School of Medicine, São Paulo	Brazil	1
Oterdoom et al, 2015[76]	Erasmus Medical Center, Rotterdam	Netherlands	1
Sanada et al, 2015[70]	Jichi Medical University, Shimotsuke	Japan	5
Solbach et al, 2015[71]	Medizinische Hochschule, Hannover	Germany	1
Fernández-Vega et al, 2014[55]	Hospital Universitario Central de Asturias, Oviedo	Spain	1
Gordon-Burroughs et al, 2014[27]	Houston Methodist Hospital, Houston	United States	1
Burgis et al, 2013[19]	Lucile Packard Children's Hospital, Palo Alto	United States	1
Carvalho et al, 2013[49]	Coimbra University Hospital, Coimbra	Portugal	1
Colle et al, 2013[53]	Ghent University Hospital, Ghent	Belgium	1

Continued next page

TABLE 3. (Continued)

Characteristics of studies included in the systematic review

Author, year	Center, city	Country	Number of patients
Maya Aparicio et al, 2013[56]	Virgen del Rocio University Hospitals, Seville	Spain	1
Vennarecci et al, 2013[64]	San Camillo Hospital, Rome	Italy	1
Sakellariou et al, 2012[2]	King's College Hospital, London	United Kingdom	7
Manzia et al, 2011[68]	Tor Vergata University, Rome	Italy	1
Marega et al, 2011[63]	Universitaria S. Maria della Misericordia, Udine	Italy	1
Franchi-Abella et al, 2010[44]	Hopital Bicetre, Le Kremlin Bicetre	France	1
Raphe et al, 2010[48]	Hospital de Base, São José do Rio Preto	Brazil	1
Wellen et al, 2010[22]	Washington University School of Medicine, St. Louis	United States	1
Bioulac-Sage et al, 2009[43]	Centre Hospitalier Universitaire (CHU) Bordeaux, Bordeaux	France	3
Di Sandro et al, 2009[62]	Niguarda Ca' Granda Hospital, Milan	Italy	1
Dokmak et al, 2009[10]	University of Paris 7 and Beaujon Hospital, Clichy	France	1
Ji et al, 2009[60]	Zhejiang University School of Medicine, Hangzhou	China	1
Reddy et al, 2009[21]	Duke University Medical Center, Durham	United States	5
Santambrogio et al, 2009[65]	University of Milan, Milan	Italy	1
Sibulesky et al, 2009[29]	Mayo Clinic, Jacksonville	United States	1
Di Rocco et al, 2008[67]	Gaslini Institut, Genoa	Italy	2
Carreiro et al, 2007[46]	Clementino Fraga Filho University Hospital, Rio de Janeiro	Brazil	1
Davis and Weinstein, 2007[26]	University of Florida College of Medicine, Gainesville	United States	1
Iyer et al, 2007[58]	Chang Gung Memorial Hospital-Kaohsiung Medical Center, Niao-Sung	Taiwan	3
Morotti et al, 2007[28]	Mount Sinai School of Medicine, New York City	United States	1
Fujita et al, 2006[25]	University of Florida College of Medicine, Gainesville	United States	1
Panaro et al, 2004[66]	St. Martino Hospital University of Genoa, Genoa	Italy	1
Wojcicki et al, 2004[77]	University Hospital Groningen, Groningen	Netherlands	1
Lerut et al, 2003[54]	Universite´ catholique de Louvain, Brussels	Belgium	3
Liu et al, 2003[59]	Kaohsiung Medical Center, Kaohsiung	Taiwan	2
Chiche et al, 2000[41]	University Hospital of Caen, Caen	France	2
Koestinger et al, 2000[78]	Lausanne University School of Medicine, Lausanne	Switzerland	1
Weimann et al, 2000[73]	Medizinische Hochschule Hannover, Hannover	Germany	4
Faivre et al, 1999[38]	Hopital Bicetre, Le Kremlin Bicetre	France	3
Matern et al, 1999[80]	Duke University Medical Center, Durham	United States	2
Reid and Hebert, 1996[52]	Hospital for Sick Children, Toronto	Canada	2
Mueller et al, 1995[20]	California Pacific Medical Center, San Francisco	United States	2
Tepetes et al, 1995[39]	University of Pittsburgh Medical Center, Pittsburgh	United States	6
Marino et al, 1992[50]			
Malatack et al, 1983[61]			
Selby et al, 1993[72]			
Alshak et al, 1994[81]	Cedars-Sinai Medical Center, Los Angeles	United States	1
Bernard et al, 1994[37]	University of Bordeaux, Bordeaux	France	1
Janes et al, 1993[23]	Mayo Clinic, Rochester	United States	1
Kirschner et al, 1991[33]	University of Chicago Hospitals, Chicago,	United States	1
Leese et al, 1988[40]	Hopital Paul Brousse, Villejuif	France	2
Poe and Snover, 1988[35]	University of Minnesota Medical School, Minneapolis	United States	2
Coire et al, 1987[51]	Henderson General Hospital and McMaster University, Toronto	Canada	1
Total			99

UNOS, United Network for Organ Sharing.

death was necrotizing pancreatitis (n = 1), postoperative complications (n = 1), multiorgan failure (n = 1), septic organ failure (n = 1), and recurrent HCC (n = 1). Complete survival data (patient status and follow-up) were available for 62 patients. The 1-, 3-, and 5-y patient survival rates after LT were all 95.0% (95% CI, 85.2%-98.4%) (Figure 4).

DISCUSSION

HA constitutes an entity with heterogeneous clinical presentation that requires a case-oriented management approach.[9] LT has been proposed as a treatment option in certain patients with HA, yet the indications and outcomes have been unclear.

In the present study, we are the first to use the UNOS data to examine the characteristics and waitlist outcomes of patients with HA listed for LT and showed that <1 out of 10 patients with HA experience waitlist mortality, and the main causes include cardiac arrest and hemorrhage with excellent post-LT outcomes. Interestingly, majority of patients do not fit the UNOS Regional Board Guidelines of awarding exception points for HA because 62.5% of listed patients received MELD exception points, but only 6.3% had diagnosis of GSD and 4.9% had listing codiagnosis of HCC. Furthermore, only 5.6% had additional incidental explant finding of HCC.

We also compiled all the previously published data through a systematic literature review to examine the characteristics
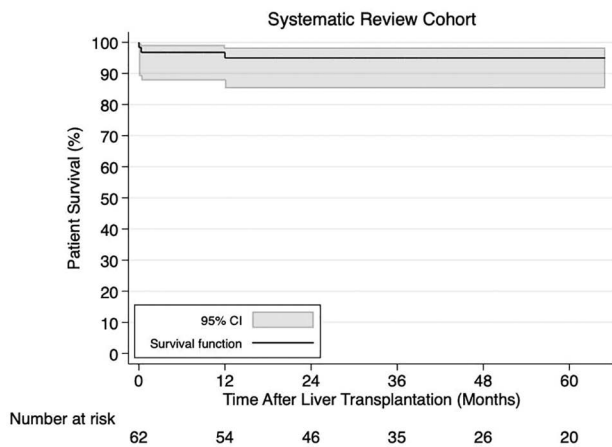
FIGURE 4. Kaplan-Meier patient survival curve in hepatic adenoma liver transplant recipients from the systematically reviewed articles. CI, confidence interval.

and outcomes of patients with HA undergoing LT. Our findings suggest that the typical LT recipient is a White woman of reproductive age with multiple HAs diagnosed pre-LT (nonincidental) and a low laboratory MELD score. The most common reasons for LT appear to be the inability to surgically resect the HA, suspicion for malignancy, increase in size and risk of rupture, underlying liver disease, or recurrence after liver resection.

The only other large study in the literature is a 2016 European report by Chiche et al[14] on LT for 49 patients with liver adenomatosis. About one-third of that cohort had underlying GSD, which is lower than the respective proportion of our systematic review, whereas a similar proportion of patients had underlying vascular abnormality (14%–15%). Although confirmed pre-LT HCC was reported in a smaller proportion of patients in our UNOS analysis and systematic review (5%–8%), a similar proportion of patients had suspected malignancy in both our systematic review and in the European multicenter study.[14] A similar proportion of patients underwent prior embolization in our systematic review and in the European report (both 4%), whereas a slightly higher proportion of patients underwent prior liver resection in the European report (43%) compared with our systematic review (32%). These differences might reflect a difference in practices among healthcare systems but may also be subject to reporting bias or heterogeneity. Although a similar post-LT mortality was described in the European report (16.3%) and in our UNOS analysis (18.3%), the respective proportion was lower in the systematic review (6%), which can be attributed to either publication bias (cases with dismal outcomes are less likely to be published) or the shorter follow-up period in the systematic review given the fact that the most common causes of death in this population are recurrence of liver malignancy or unrelated extrahepatic post-LT malignancy. Additionally, in an international observational study, Baiges et al[79] described 5 patients with Abernethy malformation undergoing LT for HA and reported only 1 death, which was due to septic complications.

The current study represents the largest cohort of LT recipients for HA, as well as the first systematic review of the literature to synthesize the currently available data on the demographic, clinicopathological characteristics, and outcomes in these patients. Although there is the possibility of patient overlap between the systematic review and the UNOS cohort, the value of the systematic review lies in its role to supplement the UNOS analysis and provide further insight and

TABLE 4.

Characteristics of patients included in the systematic review

Characteristic	Total (n = 99)
Age at diagnosis (n = 52)	19.5 (14.8–31.0)
Age at LT (n = 86)	25.0 (17.0–31.0)
Sex (n = 84)	
Female	51 (60.7%)
Male	33 (39.3%)
Number of HAs (n = 77)	
1	14 (18.2%)
2	5 (6.5%)
Multiple (>2)	58 (75.3%)
Size of largest HA (n = 43)	5.0 (2.0-10.0)
Location of HA (n = 40)	
Left lobe	4 (10.0%)
Right lobe	9 (22.5%)
Both lobes	27 (67.5%)
Time of diagnosis (n = 92)	
Pre-LT	86 (93.5%)
Incidental (explant pathology)	6 (6.5%)
Indication (n = 63)[a]	
Suspected malignancy	25 (39.7%)
Unresectable HA	20 (31.7%)
Increasing HA size	17 (27.0%)
Clinical deterioration[b]	14 (22.2%)
Recurrent HA after resection	10 (15.9%)
Biopsy-confirmed HCC transformation pre-LT	6 (9.5%)
Risk of rupture	5 (7.9%)
Encephalopathy	3 (4.8%)
Rupture	2 (3.2%)
Lipoprotein lipase deficiency	1 (1.6%)
Underlying liver disease (n = 98)	
No	27 (27.6%)
Glycogen storage disease	52 (53.1%)
Abernethy malformation/absence of portal vein	14 (14.3%)
Steatosis	4 (4.1%)
Idiopathic portal hypertension with portal vein patency	1 (1.0%)
Malignant transformation/HCC (n = 78)	
No	60 (76.9%)
Biopsy-confirmed HCC transformation pre-LT	6 (7.7%)
Incidental HCC (explant pathology)	12 (15.4%)

Continuous variables are presented as medians and interquartile ranges. Categorical variables are presented as frequencies and percentages.
[a]The numbers do not add up to 63 because many patients had >1 indication for LT.
[b]Refers to worsening abdominal pain, end-stage liver disease–related symptoms, metabolic derangement, or hormonal disturbances.
HA, hepatic adenoma; HCC, hepatocellular carcinoma; LT, liver transplantation.

granularity into important parameters of interest that are currently not captured in US transplant registries. Although nearly 5% of patients in the UNOS cohort had a listing codiagnosis of HCC, more granular data on the specific indications for LT for HA are not available in the registry. However, according to the systematic review, the most common specific indications for LT for HA were suspected malignancy (39.7%), unresectable HA (31.7%), and increasing HA size (27.0%) with about 9.5% of patients having been diagnosed with HCC pre-LT. Given the limitation of underreporting liver codiagnoses in US transplant registries, the systematic review data showed that more than half of the patients had GSD and nearly 15% had Abernethy malformation or absence of the portal vein.

Given the favorable outcomes of LT for HA and the limited use of grafts from living donors not only in our analysis of the UNOS data and our systematic review, but also in the European experience,[14] we believe that earlier LT evaluation of patients at high risk of requiring LT for HA—including patients with HA and suspected malignancy, patients with HA of increasing size or multiple and unresectable HAs, or even patients with GSD under surveillance who are at risk for developing HA—will allow for more time to identify a potential living donor and take advantage of this important yet underutilized source of grafts in the future. Moreover, advancements in the risk assessment for malignant transformation of HA could contribute to an efficient selection system of patients in need of LT and to an improved system for allocation of deceased donor grafts in this patient population. HA is a heterogeneous disease comprising of different molecular subtypes, such as the hepatocyte nuclear factor-1 alpha (30%–35%), b-CAT (10%–15%), IHCA (40%–50%), and unclassified (<10%) subtypes.[82,83] In addition to biopsy, MRI-based approaches of HA subtyping have been described and, although the accuracy for b-CAT—which is associated with an increased risk of malignant transformation—may be limited, further refinement and validation of these methods can individualize the surveillance and management of HA in the future, as well as provide further insight about the role of LT in our armamentarium against HA.[83,84]

Our study has some limitations. These include the potential miscoding of retrospective US transplant registry data (HA or HCC may be underreported or misclassified as another pretransplant diagnosis in some patients with HA or HCC) and paucity of data on clinically important parameters relevant to the disease process, such as pre-LT management and more specific listing indication data for HA. Regarding the systematic review, all included articles were retrospective case reports or series, and thus impart a degree of inherent selection bias and heterogeneity. It is likely that some patients in the systematic review cohort may also be represented in the UNOS cohort. In addition, the published articles did not report on the same variables that are available in UNOS, and therefore some data are presented only in the UNOS cohort and some only in the systematic review cohort. Moreover, not all studies reported on all variables of interest, and therefore, all analyses were performed according to the availability of data. For instance, laboratory values were only available for ≈10%–20% of the patients at the time of diagnosis, at the time of LT, and post-LT, and thus no meaningful analyses could be pursued. Clinical manifestations were also significantly underreported in the literature (<25% of the patients), and because we could not accurately quantify the respective relative rates, these findings were presented qualitatively. Finally, the number of LTs for HA performed outside the United States did not change over publication date according to our systematic review, but this is subject to publication bias and may not necessarily reflect what happens in the real world.

In conclusion, LT constitutes a feasible option for patients with HAs at high risk of malignant transformation, proven malignancy, and underlying diagnosis of GSD with very low waitlist mortality and excellent post-LT outcomes. The rarity of this condition precludes any definitive conclusions from available data that may change current allocation guidelines. Development of a multicenter registry collecting prospective granular data is warranted to develop more optimal patient selection criteria and further improve outcomes in this complex patient population.

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