Organ Procurement Organization Survey of Practices and Beliefs Regarding Prerecovery Percutaneous Liver Biopsy in Donation After Neurologic Determination of Death

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Background. Prerecovery liver biopsy (PLB) allows histological evaluation of the organ before procurement. The opinions and what factors might influence PLB use within Organ Procurement Organizations (OPOs) are unknown. **Methods.** A survey instrument was distributed by the Association of OPOs to the clinical directors of all 58 OPOs. Descriptive statistics were calculated. Results were also stratified based on OPO characteristics. **Results.** Forty-nine (84.5%) of 58 OPOs responded to the survey; 40 (81.6%) of 49 currently perform PLB. This did not vary based on land mass, population, livers discarded, transplanted, donor age, or recipient MELD scores. Donor age, obesity, alcohol abuse, hepatitis serology, liver only donor, imaging results, and transplant center request were the most common indications for PLB in over 80% of OPOs. The median rate of performance is 5% to 10% of donors. Most use interventional radiologists to perform and the donor hospital pathologist/s to interpret PLB. Most OPOs believe PLBs are safe, reliable, useful, and performed often enough. Most say they did not believe they are easy to obtain. Beliefs were mixed regarding accuracy. The topics likely to influence PLB use were utility and accuracy of PLB, and availability of staff to perform PLB. OPOs that perform PLB more often were more likely to have favorable opinions of safety and pathologist availability, and more influenced by safety, reliability, availability, and a national consensus on the use of PLB. **Conclusions.** Considerable variability exists in the use of PLB. Additional information on the utility, accuracy, and safety of PLB are needed to optimize its use.

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Due to increases in donor age and the prevalence of obesity, diabetes, and donors after cardiac determination of death within the deceased donor population, liver non-utilization rate has increased from 15% in 2003 to 21% in 2010.¹ Many livers are considered unsuitable for transplantation on clinical grounds alone before organ recovery; a decision carrying the risk of refusal of transplantable livers. Nearly half of the decisions to discard livers after recovery commences are based on intraoperative biopsy findings.² The most common histological risk factor for primary

nonfunction of the graft is steatosis.^{3–5} Other pathologies, such as fibrosis, cirrhosis, and necrosis, also are important.^{6,7} Prerecovery liver biopsy (PLB) offers a potential solution. Small studies have shown that PLB decreases futile liver recovery⁸ and reduces costs in donors after neurologic determination of death (DND).⁹ Despite its potential, several issues related to PLB in DND need further study. One such issue is lack of information on current nationwide practice patterns of use of PLB since practice patterns vary among Organ Procurement Organizations (OPOs) regarding

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donor management.¹⁰⁻¹⁴ Furthermore, the opinions of the OPO decision makers regarding PLB are vital to understanding of the barriers to wider adoption of PLB. We therefore conducted a survey of all 58 OPOs in the United States about their current practices, opinions, and beliefs that may influence the use of PLB in DND. It is anticipated that the results will generate discussion, particularly between transplant surgeons and the OPOs, identify potential obstacles to a wider use of PLB, and promote further research on this topic.

MATERIALS AND METHODS

Survey Development

The survey instrument was designed to address 3 domains: current practices, current opinions, and information that would influence future utilization of PLB. Two authors (J.B.O. and A.F.M.) created the instrument after consultations with coordinators and clinical managers at the New Jersey Sharing Network, the author's local OPO. Opinions and influential information were measured on a 5-point Likert-type scale. Another author (J.N.) provided input regarding content and face-validity. The Executive Board of the Association of Organ Procurement Organizations (AOPO) provided additional input. The final survey instrument (**Appendix 1, SDC**, <http://links.lww.com/TP/B389>) was approved by AOPO and Rutgers-Institutional Review Board. A waiver of written consent was granted. In the absence of standardized guidelines for reporting of survey research¹⁵ we adapted a checklist recommended by Draugalis et al in preparation of this manuscript¹⁶ (**Appendix 2, SDC**, <http://links.lww.com/TP/B389>).

Data Collection

The survey was disseminated electronically by the AOPO via SurveyMonkey (<http://www.surveymonkey.com>, Palo Alto, CA) to the Executive/Procurement Directors at each of the 58 OPOs. Respondents provided contact information for follow-up by the AOPO. All responses were de-identified before the study team received them. After the initial distribution, 3 follow-ups, approximately 2 to 4 weeks apart, were sent to nonrespondents. The identity of the OPOs that did not fill out the survey by the end of 2 weeks after the final email was revealed to 1 of 2 authors (JN and MP) and were contacted by telephone. The survey was closed 1 month after the completion of the phone calls. In the instance of multiple responses from the same OPO, the first complete response was used. Data were exported directly from SurveyMonkey to an electronic spreadsheet.

OPO demographics data were extracted from the Scientific Registry of Transplant Recipients (<http://www.srtr.org/opo/Default.aspx>) as of October 2015 by the study authors (JO and BK) and was classified into quartiles. To maintain anonymity, AOPO linked the demographic data quartiles to the appropriate survey responses. Demographic variables (and quartiles) include OPO population, land size in square miles, number of livers recovered but not transplanted (<5, 5-7, 8-15, and >15), number of livers transplanted (<60, 60-97, 98-137, and >137), percentage of donors aged 50 to 64 years (<22%, 22-27%, and 27-29%, >29%) and aged 65 years or older (<4%, 4-6%, 6-9%, and >9%), and percentage of recipients with a MELD of 21 to 30 (<15%,

15-22%, 22-28%, and >28%) and 31 to 40 (<16%, 16-22%, 22-32%, and >32%).

Statistical Analysis

All statistics were performed in SAS v9.3 64bit for Windows (SAS Institute, Carey, NC). Descriptive statistics were calculated using PROC SURVEYFREQ to correct for the finite population of 58 OPOs. Internal consistency was tested with Cronbach α . The relationship between organizational opinions and influential information was assessed using Pearson correlation of the sum of each scale. The 95% confidence intervals are reported in parentheses after point estimates. Bivariate analyses were performed using Fisher exact tests. For post hoc analysis comparing the rates of biopsy performance and the OPO attitudes and beliefs, the OPOs were divided into "low" (none, less than 5, and 5-10%) and "high" (11-20%, 21-30%, and greater than 30%) PLB use.

RESULTS

Forty-nine OPOs responded, yielding a response rate of 84.5%. Four OPOs responded twice. Of those, 3 first and a second complete responses were included.

Current Practices of PLB in OPOs in U.S

Frequency of PLB: 81.6% (77.2-86.1%) of responding OPOs perform PLB, whereas 8.2% (5.0-11.3%) performed them in the past, and 10.2% (6.7-13.7%) never performed PLB. Comparisons of the OPO demographics and whether the OPO currently performs PLB yielded no significant associations (**Table S1, SDC**, <http://links.lww.com/TP/B389>). The most common rate of PLB performance was 5% to 10% of donors (28.6% [23.4-33.7%]) and the maximum rate was 21% to 30%. Responses regarding use of intraoperative biopsy in donors that had PLB fell into 2 modes. Nearly one third (37.5% [31.3-43.7%]) of the OPOs performed them in only 1% to 10% of donors, whereas nearly half (47.5% [41.1-53.9%]) repeated the biopsies in over 50% of donors.

Reasons for Not Performing PLB

Nine respondents currently do not perform PLB. Three quarters reported the biopsies were difficult to perform, half reported loss of a donor due to complications of PLB and did not find PLB useful, and all preferred an intraoperative evaluation. Only 1 OPO reported PLB to be too expensive.

Indications for PLB

Transplant center request, obesity, positive hepatitis serology, imaging findings, liver only donor, alcohol abuse and donor age were indications in greater than 80% of OPOs (Figure 1). Diabetes, distance to donor hospital, and intravenous drug abuse were indications in fewer OPOs. A few (n = 3) OPOs reported that biopsies could be performed at the discretion of the medical director. Only 40% (33.7-46.3%) of OPOs have a written policy regarding whom to biopsy.

Performance, Interpretation, and Sharing of PLB Findings

In most OPOs, interventional radiologists perform PLB (86.1% [81.4-90.8%]). Most use the donor hospital pathology to process and interpret PLB (94.7% [91.8-97.7%]), with a third also report using a centralized hospital (37.1% [30.5-43.8%]). The results are communicated with oral

FIGURE 1. Nationwide organ procurement organization survey regarding PLB. Shown are percent of responses for each potential reason for performing PLB. Error bars represent the higher bounds of 95% confidence limits.

(94.9% [92.0-97.7%]) and written reports (97.4% [95.4-99.5%]). Few provide digitized images via Donor.net (12.9% [8.0-17.8%]), or via separate access (3.3% [0.6-6.0%]). More than 90% use a structured form to report all the following: Macrosteatosis, Microsteatosis, Inflammation, Fibrosis, and Necrosis. Several have a section for additional comments.

Current Opinions of OPO Leaders

Based on the opinions of individuals answering the survey, there is a consensus within the OPO regarding utilization of PLB in 79.6% (75.0-84.2%). No such consensus exists in 8.2% (5.0-11.3%), and respondents were unsure in 12.2% (8.5-16.0%). There was a preponderance of agreement (>50%) for opinions (Figure 2) that PLB were safe, reliable, useful, done frequently enough, and that surgeons care about the PLB findings. There was minimal agreement (<20%) that PLBs are easy to obtain. The opinions on the accuracy of the pathologists' interpretation of the results were mixed, with 35.6% agreeing, 44.4% neutral, and 20.0% disagreeing. Similarly, the opinion on whether PLB results in cost savings for the OPO was mixed; although 46.9% agreed, 32.7% were neutral, and 20.4% disagreed. There was strong internal consistency (Cronbach α , 0.757). OPOs with high volume of transplants thought it was hard to obtain PLB (64.0% vs 34.8%, $P = 0.04$); OPOs with high discard rates and high MELD scores believed that PLB would result in cost saving (59.3% vs 31.8%, $P = 0.05$ and 65.4% vs 26.1% $P < 0.01$).

FIGURE 2. Nation-wide organ procurement organization survey regarding PLB. Shown are percent of responses (on a Likert-type scale) regarding various opinions about PLB.

Information With Potential to Influence PLB Use

The items most commonly (>70%) found to be likely to influence opinions (Figure 3) were knowing that the results are accurate and reliable, staff to perform and interpret PLB were readily available, reduced futile liver recovery, increase liver utilization, could save resources, and a national consensus develops regarding indications. Items less likely to influence opinion were information regarding safety, could save money, or shorten case management time. There was strong internal consistency (Cronbach $\alpha = 0.939$). In addition, there was a significant positive correlation between higher-level responses of current opinions and willingness to have additional information influence opinions ($r = 0.42$, $P = 0.01$).

Attitudes and Beliefs in Relation to the Rate of Biopsy Performance

OPOs that perform biopsies at a higher frequency (Table S2, SDC, <http://links.lww.com/TP/B389>) are more likely to believe they are safe ($P = 0.01$) and pathologists are available to interpret ($P = 0.04$). The high frequency group was also more likely to be influenced to change their practice based on safety ($P = 0.02$), information regarding reliability ($P = 0.01$), 24/7 availability of biopsy performance, ($P = 0.03$), ability to shorten organ recovery time ($P = 0.04$), or a national consensus on the utilization of PLB ($P = 0.03$).

FIGURE 3. Nationwide organ procurement organization survey regarding PLB. Shown are percent of responses (on a Likert-type scale) regarding various factors that are likely to influence future utilization of PLB in their organization.

DISCUSSION

That a large percent of OPOs perform PLB despite the scarcity of published data is surprising and highlights the need for additional studies to address issues related to PLB. We found that the indications for PLB are fairly consistent among OPO's, and encompass pathologies that are likely to result in discarding livers, namely steatosis,³⁻⁵ and fibrosis.⁷ Also, they are consistent with the Paris conference recommendations for liver biopsy in extended criteria donors, the closest to practice guidelines available in the literature.¹⁷ Although there is a broad consensus among OPOs regarding indications for PLB, there is considerable variability in its performance. These variations in PLB use cannot be linked to specific demographics of the OPO because no consistent patterns were demonstrated in our study. However, our survey did not explore additional granularity among those indications. For example, it is very likely that in obese donors and "elderly" donors, various OPOs might use different thresholds for performing a PLB. Preliminary data from a multi-OPO study in progress support this notion.¹⁸ Even among OPO's that currently perform PLB, it is performed at rates that are substantially lower than the reported 23-28% biopsy rate during liver recovery.^{4,19} Thus, if PLB is considered useful in donor evaluation before commencement of liver recovery, there would be a considerable scope for its increased use.

Before increased use of PLB can be advocated, 2 of its important premises—availability of biopsy information would increase utilization of livers and decrease futile liver recovery—require proof. That the most influential item to increase PLB use would be evidence showing PLB increases utilization is consistent with the first premise. However, data do not exist in the literature to address this issue. Before this premise can be tested, secure and systematized access to digital images of the PLB and the pathologist report to all liver programs early during liver sharing will be important. Because only a few OPOs currently offer online access to digital PLB images, additional efforts are needed to make this practice uniform. A system similar to Europe's National Organ Retrieval Imaging System, which has had promising results,²⁰ incorporated into UNOS, may allow expansion of this. The second most influential item in changing practice would be information that PLB decreases futile liver recovery. Although 2 small studies show that PLB does decrease futile liver recovery,^{8,9} additional studies are needed.

A third premise is the notion that PLB would be as accurate and reliable as an intraoperative biopsy, the current criterion standard in histological evaluation of a donor liver. Concerns regarding this are represented by the responses of half of the OPOs that do not perform PLBs. Further underscoring the problem is that repeat biopsies are common. It is unclear whether the opinion about the low rate of agreement regarding the accuracy of interpretation of PLB reflects the adequacy of the sample or the expertise of the pathologists. It is noteworthy that in the majority of instances, both PLB and intraoperative liver biopsies are interpreted by donor hospital pathologists with no specialized expertise in hepatopathology. In a recent study, substantial agreement existed between the donor hospital and liver transplant pathologists in interpretation of both steatosis and fibrosis.⁸ This is consistent with the results of analysis of inter-observer variability in histopathology of liver biopsies.²¹ Finally, several studies have also demonstrated that

percutaneous liver biopsy provides a reliable representation of the underlying liver parenchyma.²²⁻²⁴ Therefore, although there is already some evidence demonstrating accuracy, further studies are likely to influence decisions.

The biggest concern expressed is the logistics of obtaining PLB. Because most OPOs use the services of interventional radiologists, it would be important to consider them as "stakeholders" in attempts to increase the use of PLB. Often, OPO's use the expertise of "in house" interventional cardiologists to perform cardiac catheterization in select heart donors. Similarly, seeking interventional radiologists' services early during an individual donor evaluation, and their inclusion in organized outreach at each potential donor hospital within the OPO are very likely to facilitate PLB performance. An alternative would be to train OPO staff to perform the PLB. This could occur in the setting of the donor hospital or within a centralized OPO managed donor center. Although not included in our survey questionnaire, a contributory logistical issue might be a concern that PLB delays liver allocation and organ recovery. Data from a small study showed that donor management time was 6 hours longer compared with those without a PLB.⁸ However, an increase in donor management time has no negative impact on number of organs recovered.²⁵ Nevertheless, delays engendered need to be examined from the context of hemodynamic stability of individual donors, OPO staff time, and costs at donor hospital.

Because intraoperative liver biopsies are very safe, PLBs also must be safe to supplant them. Although the reported rate of complications after percutaneous liver biopsy varies between 0% and 9%,^{8,26-28} information regarding the risks in DND is sparse. In a previous study, PLB was not associated with increased complications.⁸ However, additional studies to examine safety of PLB are needed.

Of concern is the association between the current rate of PLB and opinions regarding potential change in use. It is not surprising that the OPOs that currently perform PLB more frequently are more likely to believe that PLB are safe and that pathologists are available to interpret. Interestingly, the same group was significantly more likely to be willing to further change practices if biopsies were shown to be safe, reliable, readily available, shorten the recovery time, or if a national consensus came out regarding the utility of PLB. This suggests that if data support future expansion of PLB use, considerable dialogue and effort may be required to change the practice at the OPOs that currently do not perform PLB or perform them at a very low rate.

Our study has several strengths and limitations. It is the first to address practices related to PLB use in DND. It characterizes several issues from the OPOs perspective and raises questions that need further studies. The limitations are: (1) the study does not address other stakeholders including the liver transplant surgeons²⁹; (2) the 15% nonresponse rate, low by survey study standards but more than recent OPO survey studies¹⁰⁻¹⁴; (3) potential for bias exists from misinterpretation of the questions and recall.

In summary, most OPOs in the United States perform PLB, but the practices and opinions vary, particularly based on the rate of performance of PLB. Prerecovery liver biopsies are considered safe, reliable and useful but difficult to obtain. Disagreement exists regarding the accuracy of their interpretation and whether they save costs. Additional studies that

test the accuracy of PLB and whether PLB increases liver utilization and decreases futile recovery are needed. Addressing those issues and availability of staff to perform PLB are keys to its increased use in the future. Even with resolution of these issues, significant effort may be required to reach the OPOs that currently do not perform them or rarely perform them.

REFERENCES

- Orman ES, Barritt AS 4th, Wheeler SB, et al. Declining liver utilization for transplantation in the United States and the impact of donation after cardiac death. *Liver Transpl*. 2013;19:59–68.
- Kim WR, Stock PG, Smith JM, et al. OPTN/SRTR 2011 annual data report: liver. *Am J Transplant*. 2013;13(Suppl 1):73–102.
- Koneru B, Dikdan G. Hepatic steatosis and liver transplantation current clinical and experimental perspectives. *Transplantation*. 2002;73:325–330.
- Nocito A, El-Badry AM, Clavien PA. When is steatosis too much for transplantation? *J Hepatol*. 2006;45:494–499.
- Zamboni F, Franchello A, David E, et al. Effect of macrovesicular steatosis and other donor and recipient characteristics on the outcome of liver transplantation. *Clin Transplant*. 2001;15:53–57.
- Escartin A, Castro E, Dopazo C, et al. Analysis of discarded livers for transplantation. *Transplant Proc*. 2005;37:3859–3860.
- Ballarin R, Cucchetti A, Spaggiari M, et al. Long-term follow-up and outcome of liver transplantation from anti-hepatitis C virus-positive donors: a European multicentric case–control study. *Transplantation*. 2011;91:1265–1272.
- Oliver JB, Peters S, Bongu A, et al. Prerecovery liver biopsy in the brain-dead donor: a case-control study of logistics, safety, precision, and utility. *Liver Transpl*. 2014;20:237–244.
- Ganz S, Abdullah K, Gedaly R, et al. Use of percutaneous liver biopsies in marginal liver donors. *Transplant Proc*. 2001;33:1509–1511.
- Domen RE, Nelson KA. Results of a survey of infectious disease testing practices by organ procurement organizations in the United States. *Transplantation*. 1997;63:1790–1794.
- Kucirka LM, Alexander C, Namuyinga R, et al. Viral nucleic acid testing (NAT) and OPO-level disposition of high-risk donor organs. *Am J Transplant*. 2009;9:620–628.
- Singh P, Farber JL, Doria C, et al. Peritransplant kidney biopsies: comparison of pathologic interpretations and practice patterns of organ procurement organizations. *Clin Transplant*. 2012;26:E191–E199.
- Theodoropoulos N, Jaramillo A, Ladner DP, et al. Deceased organ donor screening for HIV, hepatitis B, and hepatitis C viruses: a survey of organ procurement organization practices. *Am J Transplant*. 2013;13:2186–2190.
- Chon WJ, Josephson MA, Gordon EJ, et al. When the living and the deceased cannot agree on organ donation: a survey of US organ procurement organizations (OPOs). *Am J Transplant*. 2014;14:172–177.
- Bennett C, Khangura S, Brehaut JC, et al. Reporting guidelines for survey research: an analysis of published guidance and reporting practices. *PLoS Med*. 2010;8:e1001069.
- Draugalis JR, Coons SJ, Plaza CM. Best practices for survey research reports: a synopsis for authors and reviewers. *Am J Pharm Educ*. 2008;72:11.
- Durand F, Renz JF, Alkofer B, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. *Liver Transpl*. 2008;14:1694–1707.
- Oliver J, Machineni P, Bongu A, et al. Multi-OPO case control study of safety and liver utilization with pre-recovery liver biopsy. *Am J Transplant*. 2014;14(S3):183.
- Spitzer AL, Lao OB, Dick AA, et al. The biopsied donor liver: incorporating macrosteatosis into high-risk donor assessment. *Liver Transpl*. 2010;16:874–884.
- Reddy MS, Bhati C, Neil D, et al. National Organ Retrieval Imaging System: results of the pilot study. *Transpl Int*. 2008;21:1036–1044.
- Winkfield B, Aubé C, Burtin P, et al. Inter-observer and intra-observer variability in hepatology. *Eur J Gastroenterol Hepatol*. 2003;15:959–966.
- Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. *Arch Intern Med*. 1979;139:667–669.
- Markin RS, Wisecarver JL, Radio SJ, et al. Frozen section evaluation of donor livers before transplantation. *Transplantation*. 1993;56:1403–1409.
- Frankel WL, Tranovich JG, Salter L, et al. The optimal number of donor biopsy sites to evaluate liver histology for transplantation. *Liver Transpl*. 2002;8:1044–1050.
- Inaba K, Branco BC, Lam L, et al. Organ donation and time to procurement: late is not too late. *J Trauma*. 2010;68:1362–1366.
- Perrault J, McGill DB, Ott BJ, et al. Liver biopsy: complications in 1000 inpatients and outpatients. *Gastroenterology*. 1978;74:103–106.
- Maharaj B, Bhoora IG. Complications associated with percutaneous needle biopsy of the liver when one, two or three specimens are taken. *Postgrad Med J*. 1992;68:964–967.
- Myers RP, Fong A, Shaheen AA. Utilization rates, complications and costs of percutaneous liver biopsy: a population-based study including 4275 biopsies. *Liver Int*. 2008;28:705–712.
- Imber CJ, St Peter SD, Lopez I, et al. Current practice regarding the use of fatty livers: a trans-Atlantic survey. *Liver Transpl*. 2002;8:545–549.