The Optimal Number of Donor Biopsy Sites to Evaluate Liver Histology for Transplantation

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Macrovesicular steatosis (MaS), fibrosis, and inflammation have been associated with poor graft function after liver transplantation. We evaluated histological variation in livers to determine the optimal number of biopsies to estimate pathological characteristics in livers for transplantation. Specimens from autopsies performed during 3 months in 16- to 70-years-olds without known liver disease or drug and/or alcohol abuse were examined. Eight needle biopsies were performed, and hematoxylin and eosin–stained slides were evaluated. Percentages of MaS and microvesicular steatosis (MiS) were determined, and inflammation and fibrosis were scored as 0 to 4. MaS correlated positively with MiS, and inflammation correlated positively with fibrosis, whereas patient weight showed a significant correlation with liver weight and body mass index. No patient characteristic showed a significant correlation with histological findings. Subjects 55 years and older showed no increase in pathological findings compared with those younger than 55 years. When any site was compared with the average of the other sites, Spearman's ρ correlation ranged from 0.89 to 0.95 for MaS, 0.89 to 0.94 for MiS, 0.54 to 0.80 for inflammation, and 0.66 to 0.80 for fibrosis. Two biopsies explained 95% of variations for MaS and MiS and 85% for inflammation and fibrosis. There was no significant difference between findings in the right and left lobes of livers. These findings suggest that no single site best predicts pathological findings, and there is little variation among sites. In borderline cases of MaS, significant pathological characteristics may be found in additional biopsies. Therefore, we recommend two biopsy sites to evaluate donor livers with suspicious clinical histories. (*Liver Transpl 2002;8:1044-1050.*)

The number of liver transplantations continues to increase, and patients awaiting transplantation outnumber the supply of donor livers. Every potential donor organ needs consideration to meet this demand. However, immediate liver function is essential; therefore, careful organ selection is necessary. Certain clinical features in the donor, such as morbid obesity, history of drug or alcohol abuse, or prolonged hemodynamic instability, have been considered relative contraindications for transplantation. Frequently, clinical histories are incomplete or unknown, and additional evaluation is necessary for the determination of donor organ suitability.

When the donor history suggests possible underlying liver disease and/or the liver appears grossly abnormal, liver biopsy can help determine the suitability of the organ for transplantation.[1] This determination is based on severity of steatosis, fibrosis, and inflammation. The association between steatosis and poor graft function was suggested by Portman and Wight[2] in 1987. Others have classified the degree of steatosis into mild (<30%), moderate (30% to 60%), and severe (>60%). It has been reported that livers with moderate and severe steatosis show a significantly greater incidence of primary nonfunction (13%) compared with nonsteatotic livers (2.5%).[3,4] Steatosis is considered by some to be a relative risk factor for liver dysfunction when greater than 30% and an absolute risk factor when greater than 60%.[5] Steatosis can be divided into macrovesicular (MaS) and microvesicular steatosis (MiS). Whereas MaS has been associated with poor graft function posttransplantation, the role of MiS is more controversial,[6] but many believe it is not an important predictor of poor function.[3,7-9]

It has been assumed in the past that findings from one biopsy are representative of the liver as a whole.[10,11] To our knowledge, no studies have systematically evaluated variations in liver histological characteristics in a population simulating transplant donors. Autopsy livers were used, rather than true donor livers, because multiple biopsies were needed from each liver to evaluate variations in findings among different sites. We evaluated different liver biopsy sites and studied the optimal number of biopsies to estimate overall liver histological characteristics. Patient characteristics, including age, weight, height, body mass index (BMI), liver weight, and manner of death, were examined to determine whether these characteristics could help suggest the presence of liver pathological states in potential organ donors.

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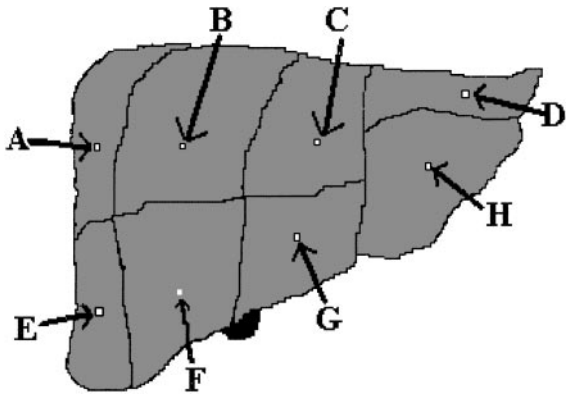

Figure 1. Map of location for the eight liver biopsy sites; A through H indicate standardized biopsy sites.

Materials and Methods

Forty-six autopsies performed from June to August 1998 were studied from the Franklin County Coroner's office. Subjects were included based on the following criteria, which are typically used to choose optimal organ donors: age 16 to 70 years, no known chronic liver disease, no known history of alcohol and/or drug abuse, and no prolonged hemodynamic instability. All patients were autopsied between 4 and 15 hours from the presumed time of death. Data collected included subject age, sex, weight, height, and manner of death. BMI was calculated by dividing body weight in kilograms by the square of the height in meters. Guidelines for human subjects for research were followed, the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and individual patients were not identified.

Livers were weighed and evaluated for gross disease. Livers with obvious cirrhosis were excluded because they would be in the typical clinical situation. Only one liver was excluded because of a nodular appearance by gross examination. Eight needle core biopsies were performed using a Tru-cut biopsy needle with a 14-G by 4.5-inch cannula (catalogue no. 2N2702X; Baxter, Obetz, OH). Biopsy specimens were obtained from the center of eight standardized segments of the livers (Fig. 1).

Core biopsy specimens were formalin fixed, processed, and stained with hematoxylin and eosin. Formalin-fixed tissue was used rather than frozen because the purpose of this study was to determine histological variability in the liver, and any artifact introduced by processing should not vary between biopsies fixed in the same manner. Two levels were examined for each biopsy. Two investigators (J.G.T. and W.L.F.) without knowledge of biopsy site examined the slides and evaluated them for amounts of MaS, MiS, inflammation, and fibrosis. MaS and MiS were determined as percentages based on the number of hepatocytes containing cytoplasmic fat inclusions. MaS is defined as the presence of one large vacuole of fat that displaces the nuclei to the cell periphery, whereas in MiS, the cytoplasm contains many small fatty inclusions and the nucleus remains in the center of the cells.[12] Fibrosis and inflammation were scored from 0 to 4, with 0 representing normal liver. As degree of interface hepatitis and lobular inflammation increased, inflammation score was progressively graded up to 4, representing severe inflammation. Fibrosis was scored as 1, portal only; 2, portal and periportal; 3, bridging; and 4, cirrhosis.

Correlations between variables were examined using Spearman's ρ. Wilcoxon's rank-sum test was used to compare medians of variables of interest. Regression analysis was used to examine the change in amount of total liver histological variability explained by increasing the number of biopsy sites.

A ratio estimate was derived for the probability of observing a certain level, d, of MaS at any of the remaining sites, given the level, c, at any particular site. The probability of interest thus is:

$$P(\text{MaS} \geq d \mid \text{MaS} = c) = \frac{P(\text{MaS} \geq d \text{ and MaS} = c)}{P(\text{MaS} = c)}$$

To estimate this probability, let Y_i be the proportion of sites for subject i at which the observed MaS is equal to c and the maximum MaS observed for that subject is d or greater. Similarly, let X_i be the proportion of sites for subject i at which the observed MaS is equal to c. Then the ratio of the average of these two values, $\bar{Y}/\bar{X}$, is an estimate of the probability of interest. The SE for this estimate was obtained using the delta method.

Results

Table 1 lists subject demographic information. Age ranged from 16 to 70 years, and there were 33 men and 13 women. Histological findings from livers for MaS, MiS, fibrosis, and inflammation are listed in Table 2. Significant pathological findings were discovered in 4 of 46 livers (9%); 2 livers had 30% or greater MaS, 1 liver had both bridging fibrosis and piecemeal necrosis, and 1 liver had bridging fibrosis.

Correlation of Patient Characteristics and Histological Findings

Patient characteristics and histological findings were compared, and correlation coefficients are listed in Table 3.

Table 1. Patient Demographics

	Mean	Median	SD	Range
Age (y)	40	38	13	16-70
Height (m)	1.7	1.8	0.1	1.5-1.9
Weight (kg)	80.6	84.3	17.5	48.6-122.2
BMI	26.6	25.7	5.2	18-39
Liver weight (g)	1,636	1,613	410.2	750-3,150

Table 2. Histological Findings in Livers

	Mean	Median	SD	Range
MaS (%)	5.8	2.4	9	0-50
MiS (%)	10.7	6.4	13.8	0-80
Fibrosis	0.5	0.3	0.7	0-3
Inflammation	0.3	0	0.4	0-2

Because multiple tests are performed in Table 3, a Bonferroni correction was applied, resulting in a significance level of 0.05/36 = 0.0014. At this level, only four correlations are statistically significant: fibrosis and inflammation ($\rho = 0.46$; $P = .001$), MaS and MiS ($\rho = 0.79$; $P = .0001$), and body weight with liver weight ($\rho = 0.52$; $P = .0002$) and BMI ($\rho = 0.76$; $P = .0001$). No patient characteristic showed a significant correlation with histological findings. Liver weight showed only marginal significance after a Bonferroni correction was applied with MaS ($\rho = 0.34$; $P = .02$), MiS ($\rho = 0.31$; $P = .04$), inflammation ($\rho = 0.38$; $P = .01$), and fibrosis ($\rho = 0.38$; $P = .008$).

Age did not correlate significantly with any of the histological findings evaluated. To further investigate the relationship between age and liver histological findings, subjects were divided into two groups; those younger than 55 years and those 55 years and older. Medians for MaS, MiS, fibrosis, and inflammation were compared between these groups using Wilcoxon's rank-sum test, and there was no significant difference between age groups.

The manner of death for each patient was categorized as accidental, suicide, homicide, natural, and unknown. There were 13 accidental deaths, 9 suicides, 14 homicides, and 10 natural deaths. Natural deaths included such acute events as anaphylactic shock and a ruptured berry aneurysm. None of the deaths was classified as unknown. There were no significant differences between histological findings or patient characteristics among different classifications of manner of death.

Table 4. Correlation of Histological Findings in Each Liver Biopsy Site With Average Findings in the Liver

Biopsy Site	MaS	MiS	Fibrosis	Inflammation
A	0.93 (.60)	0.92 (.59)	0.73 (.03)	0.67 (.52)
B	0.93 (1.00)	0.94 (.74)	0.70 (.02)	0.63 (.02)
C	0.93 (.41)	0.89 (.32)	0.78 (.20)	0.68 (.04)
D	0.89 (.36)	0.94 (.43)	0.66 (.75)	0.73 (.28)
E	0.95 (1.00)	0.89 (.63)	0.75 (.07)	0.62 (.11)
F	0.93 (.87)	0.92 (.92)	0.73 (.14)	0.54 (.24)
G	0.94 (.96)	0.93 (.64)	0.80 (.82)	0.65 (.02)
H	0.94 (.65)	0.90 (.81)	0.71 (.25)	0.80 (.35)

NOTE. Values listed as correlation coefficient (*P*).

Value of One Biopsy

Each biopsy was compared with the average of the remaining seven biopsy sites to ascertain how well a single biopsy represented pathological findings in the entire liver. In general, a single biopsy site had good correlation with overall findings in the liver. Spearman's correlation coefficients varied from 0.89 to 0.94 for MaS, 0.89 to 0.95 for MiS, 0.89 to 0.95 for fibrosis, and 0.54 to 0.80 for inflammation (Table 4). No single site or group of sites correlated more positively with average pathological findings for MaS, MiS, inflammation, or fibrosis in the livers than any other site or combination of sites. In addition to examining these correlations, Wilcoxon's rank-sum test was used to compare medians for each site with the average of the remaining seven sites (*P* for the test are listed in Table 4). Because

Table 3. Correlation Coefficients Between Patient Characteristics and Histological Variables

	Inflammation	Fibrosis	MiS	MaS	Liver Weight	BMI	Weight	Height	Age
Age	0.15 (.31)	0.23 (.13)	−0.02 (.88)	−0.03 (.83)	0.31 (.04)	0.00 (1.00)	−0.11 (.45)	−0.05 (.75)	1.00 (.0)
Height	0.21 (.17)	0.30 (.04)	0.25 (.9)	0.30 (.04)	0.34 (.02)	−0.17 (.25)	0.43 (.002)	1.00 (.0)	
Weight	0.06 (.71)	0.08 (.58)	0.21 (.17)	0.28 (.06)	0.52 (.0002)	0.76 (.0001)	1.00 (.0)		
BMI	−0.07 (.66)	−0.06 (.69)	0.05 (.75)	0.09 (.57)	0.37 (.01)	1.00 (.0)			
Liver Weight	0.38 (.01)	0.38 (.008)	0.31 (.04)	0.34 (.02)	1.00 (.0)				
MaS	0.14 (.36)	0.34 (.02)	0.79 (.0001)	1.00 (.0)					
MiS	0.11 (.47)	0.12 (.40)	1.00 (.0)						
Fibrosis	0.46 (.001)	1.00 (.0)							
Inflammation	1.00 (.0)								

NOTE. Values expressed as correlation coefficient (*P*).

Table 5. Comparison Among Biopsy Sites and/or Groups of Sites to Determine the Optimal Number of Sites to Estimate Overall Liver Histological Characteristics With Adjusted R^2 for MaS, MiS, Fibrosis, and Inflammation

No. of Variables in Model	No. of Possible Models	Adjusted R^2							
		MaS		MiS		Fibrosis		Inflammation	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	8	0.92	0.014	0.88	0.104	0.75	0.053	0.72	0.093
2	28	0.97	0.01	0.96	0.013	0.88	0.037	0.86	0.036
3	56	0.98	0.006	0.97	0.007	0.93	0.023	0.92	0.024
4	70	0.99	0.004	0.98	0.006	0.96	0.014	0.95	0.16
5	56	0.99	0.003	0.99	0.006	0.98	0.008	0.97	0.009
6	28	1	0.001	0.99	0.005	0.99	0.005	0.98	0.005
7	8	1	0.0003	1	0.004	0.99	0.001	0.99	0.002

NOTE. The number of variables in models equals the number of biopsy sites, and the number of possible models equals the number of combinations of biopsy sites that were possible.

this involves 32 separate tests, a Bonferroni-corrected significance level of $\alpha = 0.05/32 = 0.0015$ was used to assess significance. At this level, no significant differences were found for any of the sites.

Optimal Number of Biopsies

The optimal number of biopsy sites needed to estimate overall liver pathological findings was determined by comparing all possible combinations of single and all combinations of multiple biopsy sites. All possible adjusted R^2 values were generated by fitting regressions of all possible combinations of biopsy sites against the average of the others. Means and SDs of adjusted R^2 values for MaS, MiS, fibrosis, and inflammation are listed in Table 5. Mean adjusted R^2 values are shown in Figure 2.

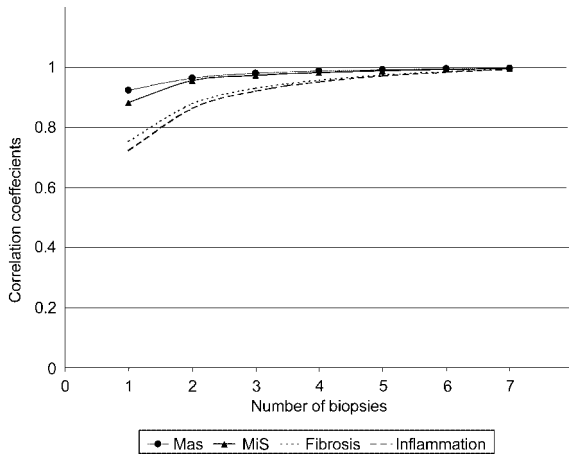

Figure 2. Mean adjusted R^2 values for all possible regression models of variables on the average measurement across all sites for MaS, MiS, fibrosis, and inflammation.

Estimated Probability of MaS

Table 6 lists estimated probabilities of observing various levels of MaS in any of the remaining seven biopsy sites given the level of MaS observed at a randomly selected site. MaS less than 20% generally is believed to not preclude the use of a donor liver. Therefore, we evaluated the possibility of finding more significant MaS in another biopsy site when one biopsy showed less than 20% MaS. Because MaS levels of 30% and 40% are believed, in some cases, to exclude a liver for transplantation, the possibility of finding these levels of MaS in another biopsy site was evaluated. For example, if a single biopsy site showed 16% to 20% MaS (Fig. 3), the estimated probability that any core from the remaining seven sites would show 20% MaS or greater would be 100%. The estimated probability that one of the remaining seven cores would show 30% MaS or greater is 31.6% ± 5.2%. The estimated probability that one of the remaining seven biopsy sites would show 40% MaS or greater (Fig. 4) is 5.3% ± 1.6%.

Liver Biopsy From the Right Versus Left Lobe

Representative values for the right and left lobes were obtained by averaging the four measurements obtained within each lobe for each subject. Medians of histological variables for the two sides then were compared using Wilcoxon's rank-sum test. There were no significant differences between the left and right lobes for any variable considered ($P = .69$ for MaS; $P = .53$ for MiS; $P = .28$ for fibrosis; $P = .57$ for inflammation). Correlations between average values for the left and right lobes also were computed, and measurements were found to correlate highly ($\rho = 0.9523$ for MaS; $\rho =$

Table 6. Estimated Probability of the Maximum Percentage of MaS in Any Other Biopsy Site When a Single Biopsy Is Randomly Selected

MaS in Single Biopsy (%)	Probability a Remaining Biopsy is ≥20% MaS (%)	Probability a Remaining Biopsy is ≥30% MaS (%)	Probability a Remaining Biopsy is ≥40% MaS (%)
0-5	0	0	0
6-10	16.7 ± 2.6	3.3 ± 1	0
11-15	91.7 ± 2.5	25.0 ± 6.2	0
16-20	100	31.6 ± 5.2	5.3 ± 1.6

0.9638 for MiS; $\rho = 0.9441$ for fibrosis; $\rho = 0.9078$ for inflammation).

Discussion

Histological findings, such as steatosis, fibrosis, and inflammation, have been associated with poor graft function after transplantation.[2-6,8,9] This study examines these features and evaluates histological variation within the liver using a population of subjects that simulated optimal cadaveric organ donors. Although frozen sections typically are used to evaluate these features before transplantation, formalin-fixed paraffin-embedded sections were used in our study because our purpose was to evaluate variation within the liver, not the correlation between frozen and permanent sections. We determined how many biopsies were necessary to represent overall pathological findings in the liver and whether the particular site of biopsy was important. Patient characteristics were compared with histological findings to determine whether any of these factors suggested liver pathological findings.

Several known patient factors, such as obesity, drug and/or alcohol use, and length of intensive care unit stay, have been associated with liver disease.[13] To determine which characteristics were related to liver pathological findings in our patient population, we examined the correlation of patient characteristics with histological findings. No patient characteristic showed a significant correlation with histological findings. Liver weight was the characteristic that showed a marginally significant positive correlation with all histological findings. Liver weight may be a useful screening tool to suggest potential liver pathological states. Additional studies are necessary to define what qualifies as a heavy liver.

Age, sex, BMI, and manner of death did not show a significant relationship with the histological variables examined. Interestingly, there was no significant difference in liver histological findings between patients younger than 55 years and those 55 years or older. This finding is similar to results of a study that evaluated 368 adult transplant donors. In this study, 300 donors were younger than 55 years and 68 donors were older than 55 years. No increase in dysfunction was found in livers of older donors compared with younger donors.[14] A

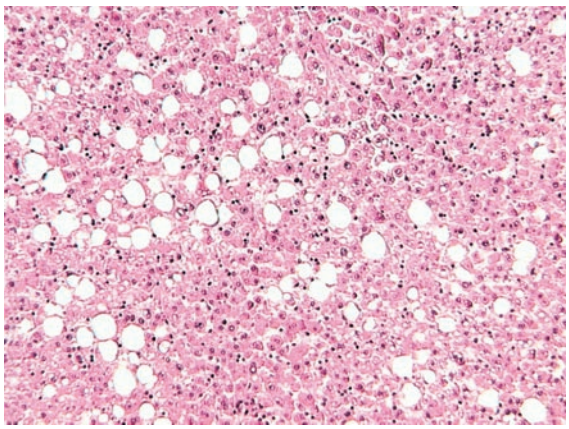

Figure 3. Liver biopsy specimen showing 16% to 20% MaS.

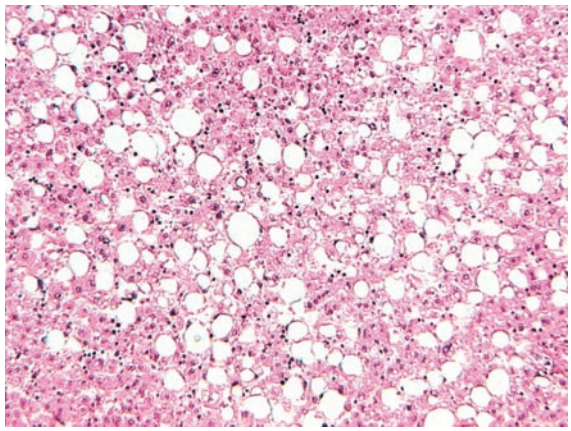

Figure 4. Another liver biopsy site from the same liver as in Figure 3 showing 50% to 55% MaS.

small series of four cases showed that octogenarian donor livers can be used safely when there are no other contraindications for donor use.[15] The inclusion of older donors is a significant way to expand the pool of potential organs for transplantation.

There is no standardized site for biopsy of a potential donor liver. We found that all eight biopsy sites examined had similar histological findings, and the range of variation for the eight biopsy sites was small. No single biopsy or group of biopsies was more representative of overall liver histological findings than any others. This is in agreement with other studies evaluating variation in liver histological characteristics. Using autopsy liver specimens from patients with many different diseases, two studies evaluated histological variation in the liver. Both studies concluded that pathological findings were uniform.[10,11] Another study examined histological variation in patients with hepatitis. Two biopsy cores from the right and left lobes of the liver were compared and showed no significant differences among pathological findings.[16] However, these studies did not address the difference between MaS and MiS, which is considered important for the evaluation of potential donor livers. Patient populations in these studies were different from the optimal donor pool of potential cadaveric organ donors that usually includes otherwise healthy acutely injured patients. Although our study shows that one biopsy is a reasonably good predictor of pathological state, there is some variation within the liver.

In the transplantation setting, it is important to use the least number of biopsies possible to detect the overall pathological variation within the liver to avoid excess risk to the organ. Therefore, we determined the least number of biopsies necessary to best evaluate overall liver histological characteristics. We found that it takes at least two biopsies to reach an adjusted R^2 of 0.95 for the histological parameters of MaS and MiS. Five biopsies would be necessary to reach an adjusted R^2 of 0.95 for fibrosis and inflammation. Two biopsies show an increase in the adjusted R^2 from one biopsy, but three or more biopsies show less of an increase with each additional biopsy for MaS, MiS, fibrosis, or inflammation.

MaS has been shown to be one of the most important predictors of graft function posttransplantation.[2-4,9] Therefore, we evaluated MaS in the eight biopsy sites in each liver and estimated the probability of various levels of MaS when the result of only one biopsy was known. If there is minimal steatosis on a single biopsy, there is little chance that a second biopsy will show severe steatosis in the remaining liver. In such a case, a single biopsy would be adequate to represent the liver. However, when a biopsy shows mild MaS (20%), there is a 32% chance of finding more significant MaS (≥30%) and a 5% chance of finding MaS (≥40%) that may be of a sufficient severity to preclude transplantation. In this case, a second biopsy might be helpful. When mild to moderate pathological characteristics are identified, we recommend two biopsies to help explain the variation in MaS.

Currently, when a liver pathological state is suspected in a donor and a discrete lesion is not identified, a random biopsy is obtained. Our data show that no single site predicted pathological findings better than any other site. Additionally, no significant difference was seen in histological findings between biopsies from the right compared with the left lobe of the liver. Our results are in agreement with a previous study comparing biopsies in the right and left lobes of the liver in hospitalized patients with known liver disease. It was concluded that the two lobes were equal in providing diagnostic information.[17] Our results suggest that no significantly different information is obtained by evaluating biopsies from the right and left sides of the liver.

There is current controversy regarding the importance of MiS in predicting posttransplantation liver function. Some researchers have suggested that donor livers with significant MiS should not preclude use for transplantation.[6,8] Others argue that MiS may be more predictive of posttransplantation primary nonfunction than MaS, particularly in cases of liver retransplantation.[7] Our finding that MiS correlated with MaS to such a high degree ($\rho = 0.79$; $P = .0001$) suggests that livers with significant MiS also may have MaS.

In summary, age and BMI did not predict abnormal liver pathological characteristics. MaS and MiS correlated positively with each other, suggesting that significant MiS may help predict MaS, even if MiS alone is not an important factor for liver dysfunction. One liver biopsy is a very good representation of histological characteristics in the liver, and site of the biopsy does not seem to affect findings. However, in some cases, important information can be obtained from a second biopsy. Because it may not be clinically practical to wait until results of one biopsy are obtained (in borderline cases) to return to the donor organ and perform a second biopsy, when possible, two biopsies may best predict overall liver histological characteristics to evaluate potential donor livers for transplantation.

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