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ORIGINAL ARTICLE

Laboratory Test Results After Living Liver Donation in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study

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Information on the long-term health of living liver donors is incomplete. Because changes in standard laboratory tests may reflect the underlying health of donors, results before and after donation were examined in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL). A2ALL followed 487 living liver donors who donated at 9 US transplant centers between 1998 and 2009. The aminotransferase [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] and alkaline phosphatase (AP) activities, bilirubin, international normalized ratio (INR), albumin, white blood cell count (WBC), hemoglobin (HGB), platelet count, ferritin, serum creatinine (SCR), and blood urea nitrogen (BUN) were measured at the evaluation and after donation (1 week, 1 month, 3 months, 1 year, and yearly thereafter). Repeated measures models were used to estimate median laboratory values at each time point and to test for differences between values at the evaluation (baseline) and postdonation time points. Platelet counts were significantly decreased at every time point in comparison with the baseline, and at 3 years, they were 19% lower. Approximately 10% of donors had a platelet count $< 150 \times 1000/mm^3$ 2 to 3 years post-donation. Donors with a platelet count $\leq 150 \times 1000/mm^3$ at 1 year had significantly lower mean platelet counts ($189 \pm 32 \times 1000/mm^3$) versus the remainder of the cohort ($267 \pm 56 \times 1000/mm^3$, $P < 0.0001$) at the evaluation. Statistically significant differences compared to the evaluation values were noted for AST, AP, INR, and albumin through the first year, although most measurements were in the normal range. The median values for WBC, HGB, ferritin,

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; GW/TLV, graft weight to total liver volume ratio; HGB, hemoglobin; INR, international normalized ratio; LLN, lower limit of normal; SCR, serum creatinine; ULN, upper limit of normal; WBC, white blood cell count.

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albumin, SCR, BUN, and INR were not substantially outside the normal range at any time point. In conclusion, after 3 months, most laboratory values return to normal among right hepatic lobe liver donors, with a slower return to baseline levels for AST, AP, INR, and albumin. Persistently decreased platelet counts warrant further investigation. ***Liver Transpl 17:409-417, 2011.*** © **2011 AASLD.**

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Donor safety is paramount to the success of living donor liver transplantation. Thus, it is imperative that transplant physicians have a complete understanding of potential complications in living donors so that the risk of the procedure can be accurately described to donor candidates and steps can be taken to mitigate that risk. Early in the experience of the procedure, reported complication rates[1,2] were relatively low (estimated to be 10%-20%), but reports may have underestimated complications as a result of incomplete data collection and underreporting. In addition, the full spectrum and prevalence of complications may have been underappreciated because of the relatively small numbers of patients studied and their short follow-up intervals. A subsequent and more comprehensive study reported a substantially higher overall complication rate of 38%; 2% and 0.8% of these complications were grades 3 and 4 (serious), respectively.[3]

Routine clinical laboratory tests are performed regularly after living donor hepatectomy to determine a patient's return to health and to detect postdonation complications. However, there is little information on either the patterns of laboratory test results or their abnormalities. One single-center study of a subset of the donors reported herein reported results of laboratory tests for up to 1 year after surgery.[4] Among 70 living liver donors in that study, 22 were evaluated 1 year post-donation. Only 1 donor had abnormal liver test results, but 5 (23%) had thrombocytopenia (platelet count $< 150 \times 1000/mm^3$). Because of this relative paucity of information, we undertook this study to describe the long-term changes in common laboratory tests for living liver donors enrolled in the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL). Because A2ALL enrolled donors before liver donation and attempted regular follow-up afterward, it has the ability to identify changes in laboratory results and their abnormalities. The major aims of this study were (1) to improve our understanding of potential long-term donor complications and (2) to provide donors with more information on laboratory abnormalities after liver transplantation.

PATIENTS AND METHODS

Protocol and Data Collection

This study included information on the 487 living donors enrolled in A2ALL for the 12-year period from 1998 through 2009 at 9 US transplant centers. Data were recorded by each of the participating transplant centers according to a common protocol. Through October 2004, all donor laboratory results were collected retrospectively from medical records. Laboratory results collected after October 2004 were a mixture of retrospective (in the case of patient consent after the initial donor evaluation) and prospective data collection. The prospective protocol specified the blood tests to be performed at the initial evaluation and at 1 week, 1 month, 3 months, 12 months, and yearly post-donation. Collected laboratory values included the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP), total bilirubin, international normalized ratio (INR), albumin, platelet count, white blood cell count (WBC), ferritin, hemoglobin (HGB), serum creatinine (SCR), and blood urea nitrogen (BUN).

The upper (ULN) and lower (LLN) limits of normal differed at the 9 A2ALL centers. The ranges and the values chosen for presenting the percents above or below normal were as follows: 41 to 75 (ULN) and 47 IU/L for ALT, 35 to 59 (ULN) and 47 IU/L for AST, 1.1 to 1.3 (ULN) and 1.3 mg/dL for total bilirubin, 96 to 150 (ULN) and 117 IU/L for AP, 140 to 172 (LLN) and $150 \times 1000/mm^3$ for the platelet count, 3.4 to 4.0 (LLN) and 3.4 g/dL for albumin, and 1.1 to 1.2 (ULN) and 1.1 for INR.

Protection of Human Subjects

This study was approved by the institutional review boards and privacy boards of each of the 9 participating

TABLE 1. Characteristics of 487 Liver Transplant Donors at the Time of Evaluation

Characteristic	n	Mean (Standard Deviation) or %	Range
Age (years)	487	37.6 (10.2)	20-65.3
Sex			
Male	235	48%	
Female	252	52%	
Ethnicity			
Hispanic	75	15%	
Non-Hispanic	412	85%	
Race			
White	431	88%	
African American	14	3%	
Asian	9	2%	
Other	33	7%	
Height (cm)*	479	171.7 (10)	134.6-195.6
Weight (kg)*	478	77.1 (14.5)	43.1-135
Body mass index (kg/m^2)*	475	26.3 (3.9)	13.8-42.5

*Data were missing for less than 2.5%.

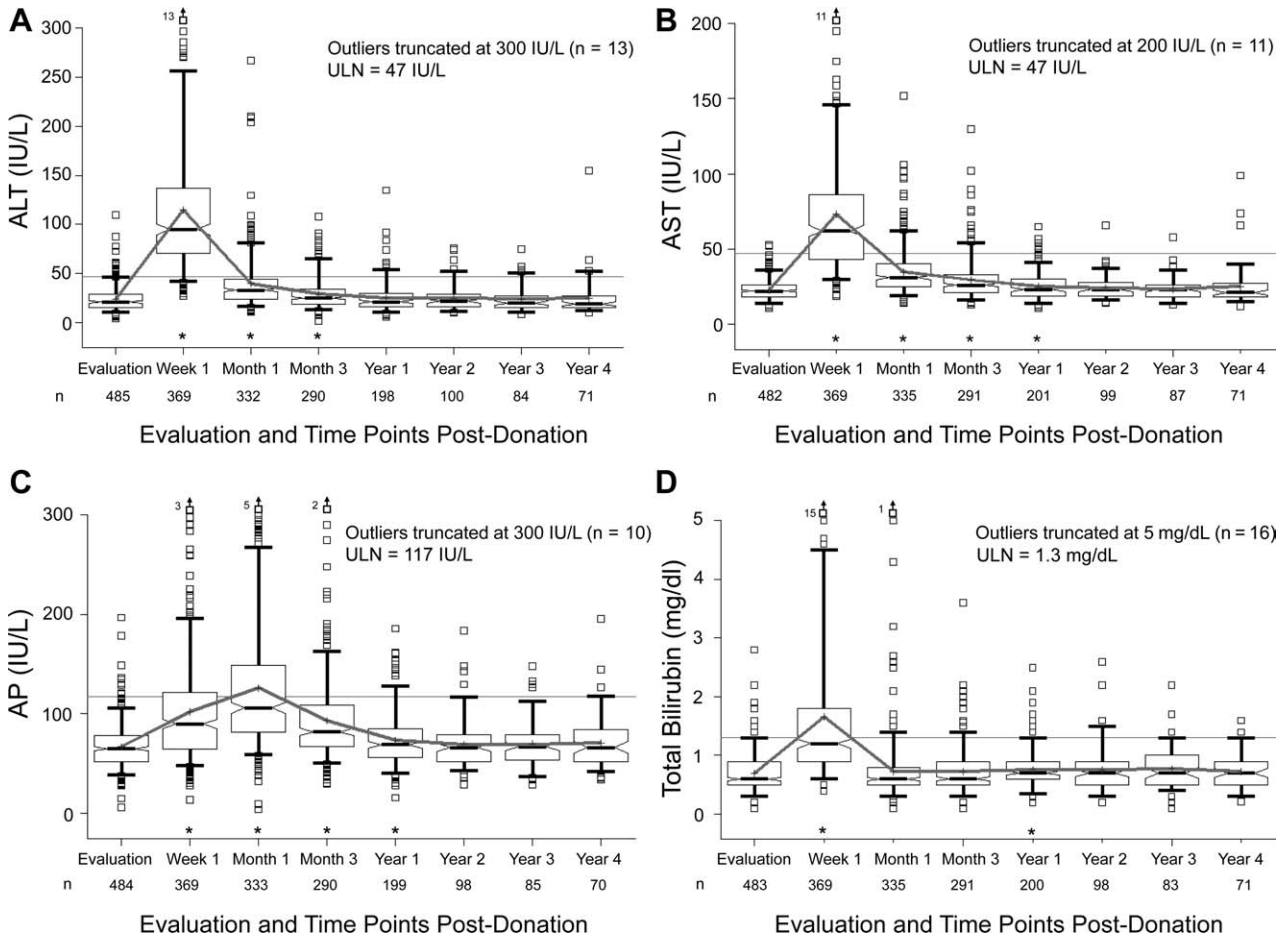

Figure 1. Laboratory tests at the evaluation and 7 time points post-donation: (A) ALT, (B) AST, (C) AP, and (D) total bilirubin. Asterisks just above the *x* axis indicate time points at which the median was significantly different from the evaluation value ($P < 0.05$). Boxes include the 25th to 75th percentiles, with indentations indicating medians and plus signs indicating mean values (connected by gray lines). Whiskers extend to the 5th and 95th percentiles.

transplant centers and the University of Michigan Data Coordinating Center. Researchers began to obtain the consent of past donors (for retrospective data) and donor candidates (for prospective data) in September 2004.

Statistical Analysis

The distributions of laboratory values over time are shown as box plots with whiskers extending to the 5th and 95th percentiles. Scatter plots of week 1, month 1, and year 1 values versus the baseline values are shown for selected laboratory tests. Pearson correlation coefficients were used to estimate the strength of the linear relationship between WBCs and platelet counts at several time points. Differences between the number of abnormal values at the baseline and at the first follow-up at least 1 year later among patients without missing values at both time points were examined with McNemar's test for paired data. Exact conditional logistic regression was used to estimate the odds ratios and 95% confidence intervals for abnormal laboratory results at follow-up versus the baseline. A repeated measures model using the SAS mixed procedure (SAS Institute, Inc., Cary, NC) was used to estimate median laboratory values over time and to test for significant changes in postdonation values from the baseline. This model used a Toeplitz covariance structure for repeated measurements of the same subject over time and remained valid in the presence of randomly missing laboratory values. For statistical testing, all laboratory values were log-transformed to remove skewness. All analyses were performed with SAS version 9.2 (SAS Institute).

RESULTS

Among the 487 living donors, the mean donor age was 37.6 years (range = 18-62 years), 88% were white (Table 1), and 62% were biologically related. Of the 487 donors, 486 had baseline, predonation laboratory results, and 466 (94%) had laboratory results from at least 1 postdonation time point (235 from 4 or more time points, 123 from 3, 76 from 2, and 32 from 1).

Figures 1A-D and 2A-C depict the distributions of laboratory values over time from donation through year 4. The greatest changes occurred in the immediate

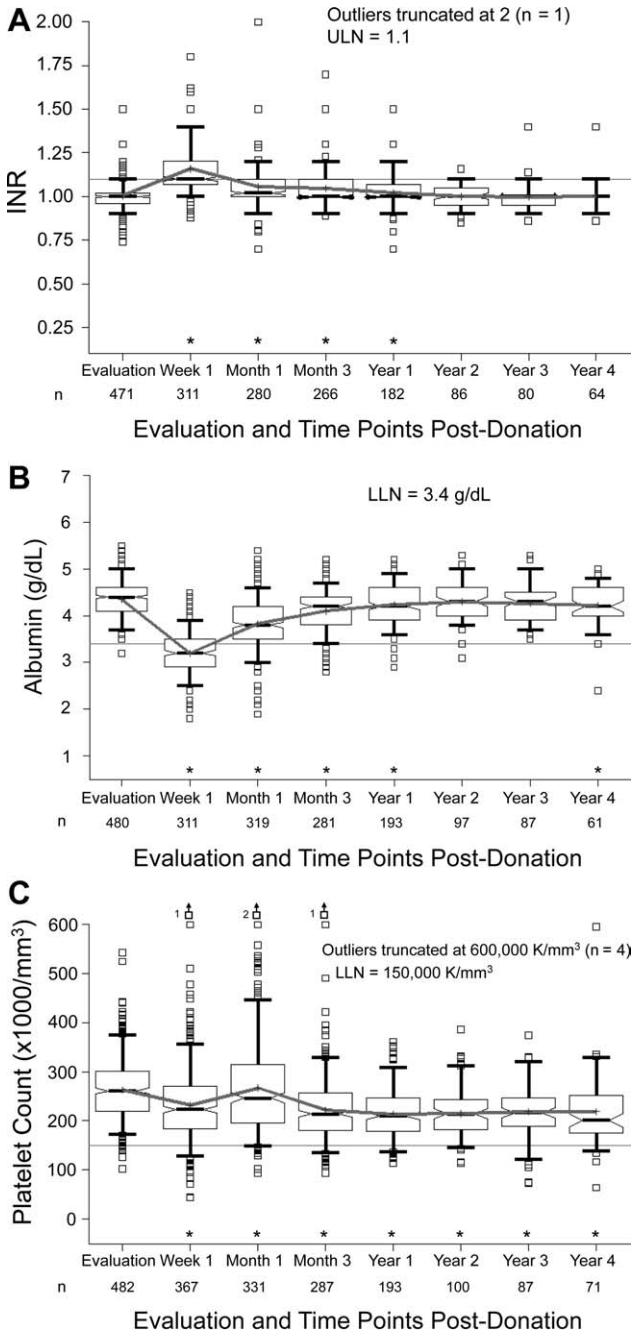

Figure 2. Laboratory tests at the evaluation and 7 time points post-donation: (A) INR, (B) albumin, and (C) platelet count. Asterisks just above the *x* axis indicate time points at which the median was significantly different from the evaluation value ($P < 0.05$). Boxes include the 25th to 75th percentiles, with indentations indicating medians and plus signs indicating mean values (connected by gray lines). Whiskers extend to the 5th and 95th percentiles.

postoperative period, as shown in the week 1 levels, and most values approached baseline levels by 3 months. However, statistically significant differences in median values versus baseline values were noted for up to 1 year for AST, AP, total bilirubin, INR, and albumin. Platelet counts were significantly lower than those before liver transplantation at each of the follow-up intervals (Fig. 2C). The average reduction in the platelet count from the baseline to year 4 was 16%.

Figures 3A-D and 4A-C show scatter plots of the laboratory values at year 1 plotted against baseline values for each patient. Points below the equivalence line indicate patients whose 1-year values were lower than the baseline, and points above the line indicate 1-year values that were higher than the baseline. For ALT and INR, the distribution is equally displaced around the equivalence line, and this suggests that there was no overall shift in values between the baseline and 1 year. Figure 5A,B shows the week 1 and month 1 INR values plotted against baseline values; INR increased substantially by week 1 but was nearly back to normal by month 1. The variances of the distributions of AST ($P < 0.0001$), AP ($P < 0.0001$), and bilirubin ($P = 0.09$) were larger at 1 year versus the baseline, mostly because of more outliers at 1 year. Albumin showed a modest shift downward but no difference in the variance between the baseline and 1-year values ($P = 0.39$). Figure 5C,D show the week 1 and month 1 albumin values plotted against the baseline values; albumin decreased substantially by week 1 and recovered only partially by month 1. The most striking changes occurred in the platelet count: there was an obvious downward shift in the platelet distribution post-donation and a significant decrease in variance ($P = 0.004$) at 1 year versus the baseline (Fig. 4C). In comparison with the baseline, 89.4% of the patients had lower platelet counts at 1 year. Donors with a platelet count $< 150 \times 1000/mm^3$ at 1 year had a significantly lower mean platelet count at the evaluation ($189 \pm 32 \times 1000/mm^3$) in comparison with the remainder of the cohort ($267 \pm 56 \times 1000/mm^3$, $P < 0.0001$).

To further investigate the relationships shown in Figs. 3 and 4, we compared abnormal laboratory values at the baseline and at the first follow-up visit that occurred 1 year or more post-donation (Table 2), and we tested the likelihood of previously normal values becoming abnormal versus the likelihood of previously abnormal values becoming normal. Significantly more abnormal values were found at 1 year or later for the platelet count, AST, and albumin, and nearly significant results were found for AP and total bilirubin ($P = 0.07$ and 0.08, respectively)

For all 7 laboratory measures, the covariates that were tested for their ability to predict the difference between the 1-year and baseline values included age, sex, weight at the baseline, weight changes between the baseline and 1 year, baseline values, and interactions between these variables and baseline values. Donors tended to gain weight after donation (mean = 1.0 kg, standard deviation = 5.7 kg, $P = 0.02$). A 10-year older age was associated with higher values at 1 year for ALT ($b = 1.9$ IU/L, $P = 0.011$), AST ($b = 1.7$ IU/L, $P = 0.001$), and AP ($b = 4.5$ IU/L, $P = 0.0003$) and with lower values for albumin ($b = -0.06$ g/dL, $P = 0.006$). Women had lower values at 1 year for bilirubin and albumin by averages of −0.13 mg/dL ($P = 0.0008$) and −0.11 g/dL ($P = 0.030$),

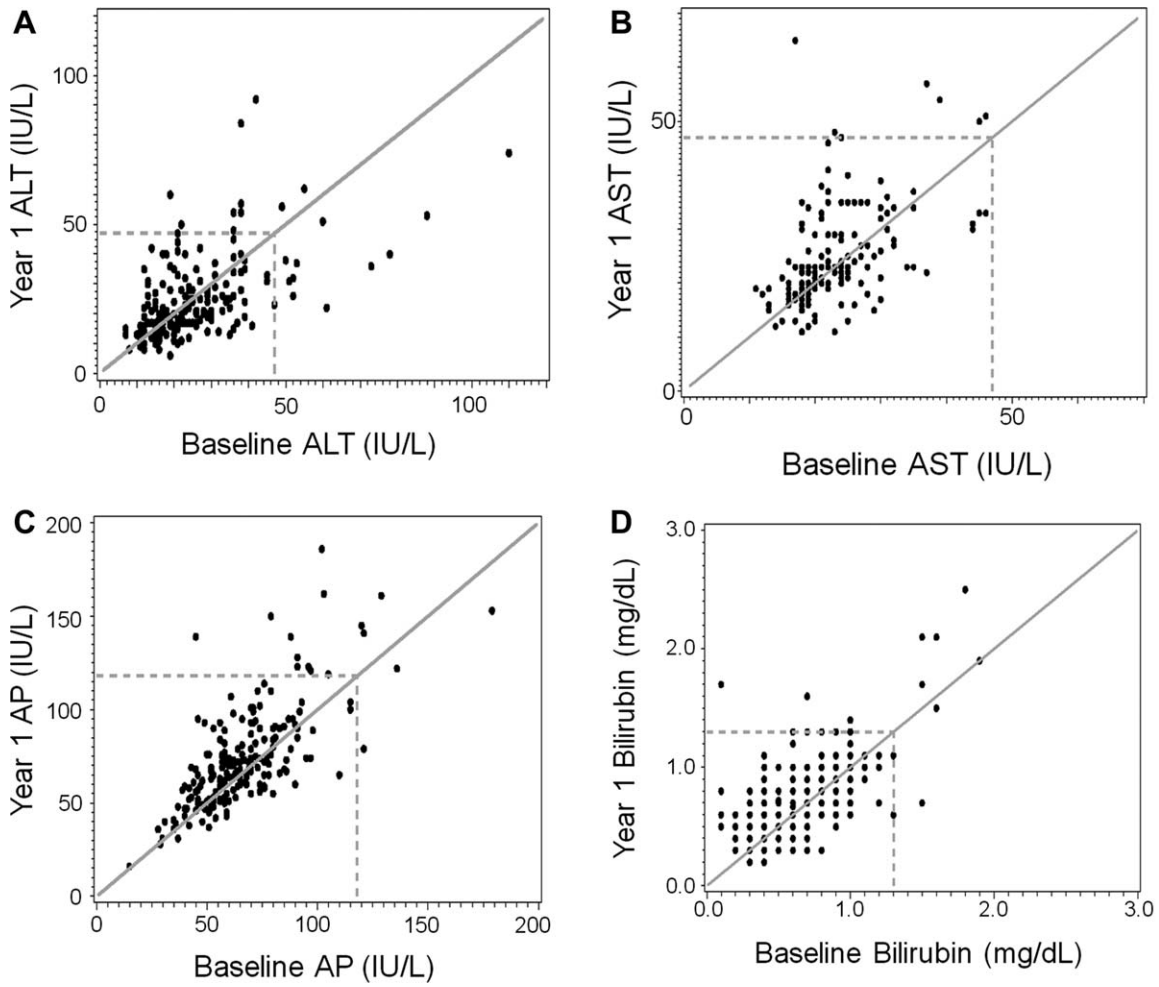

Figure 3. Laboratory values at year 1 versus the baseline: (A) ALT (ULN = 47 IU/L, n = 198), (B) AST (ULN = 47 IU/L, n = 200), (C) AP (ULN = 117 IU/L, n = 199), and (D) total bilirubin (ULN = 1.3 mg/dL, n = 200). The diagonal lines are lines of equality: points below the lines indicate larger values at the baseline, and points above the lines indicate larger values at year 1.

respectively. Baseline values were highly predictive of values at 1 year for all laboratory measures; this is obvious in Figs. 3 and 4 ($P < 0.05$ for all and $P < 0.0001$ for most). The weight change from the baseline was significantly predictive of AP ($b = 0.64$/kg, $P = 0.013$) and was close to significant for ALT ($b = 0.30$/kg, $P = 0.082$) and bilirubin ($b = 0.006$/kg, $P = 0.086$). No other factors were predictive of changes in platelets from the baseline to 1 year.

We further tested the correlation between platelet counts and WBCs, which would be expected if the drop in platelet counts were related to portal hypertension. We found significant correlations ($P < 0.0001$ for all) at all time points tested (through year 3), and most were substantially larger than the correlation seen at the baseline ($r = 0.23$): $r = 0.32$ at 1 week, $r = 0.40$ at 1 month, $r = 0.22$ at 3 months, $r = 0.35$ at 1 year, $r = 0.45$ at 2 years, and $r = 0.43$ at 3 years.

Because a higher graft weight to total liver volume ratio (GW/TLV) had been associated with both a larger spleen volume and lower platelet counts after donation,[5] we tested the correlation between GW/TLV and the platelet count at each postdonation time point divided by the baseline count. The early postdonation correlations were significant, but the correlations at 1 year and beyond were not (week 1, $r = -0.16$, $P = 0.011$; month 1, $r = -0.19$, $P = 0.004$; month 3, $r = -0.21$, $P = 0.003$; year 1, $r = -0.09$; $P = 0.29$; year 2, $r = -0.03$, $P = 0.83$; and year 3, $r = -0.08$, $P = 0.60$). We also tested GW/TLV in the previously reported year 1 platelet regression model, but it was not significant ($P = 0.853$). However, in similar models for months 1 and 3, GW/TLV was a significant predictor of a reduction in platelets. With an increase of 0.10 in GW/TLV, the platelet counts were lower on average by $12.6 \times 1000/mm^3$ at 1 month ($P = 0.013$) and by $7.0 \times 1000/mm^3$ at 3 months ($P = 0.013$). Left lobe donors (n = 24) had lower GW/TLV values ($P < 0.0001$) and higher platelet counts at 1 week ($P = 0.029$) than right lobe donors. Platelet counts were not significantly different at subsequent time points between left and right lobe donors.

Additional laboratory tests were analyzed (WBC, ferritin, HGB, SCR, and BUN), but they are not reported in detail because the findings are less likely to be clinically relevant. The median values of these tests

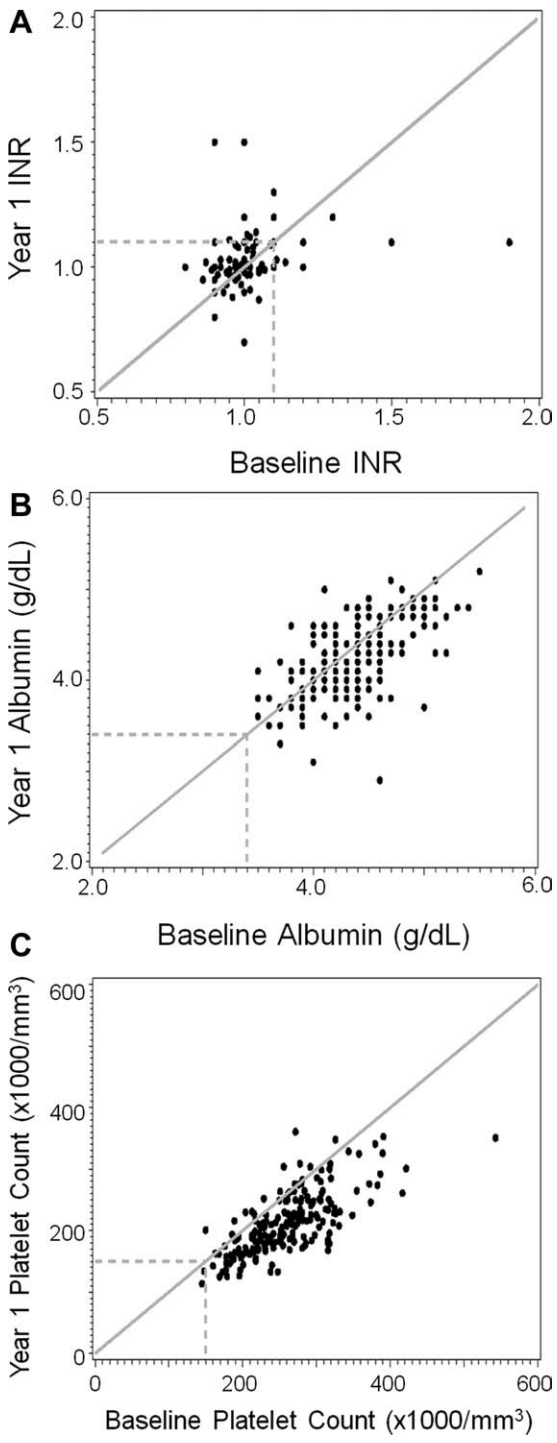

Figure 4. Laboratory values at year 1 versus the baseline: (A) INR (ULN = 1.1, n = 178), (B) albumin (LLN = 3.4 g/dL, n = 192), and (C) platelet count (LLN = 150 × 1000/mm^3, n = 192). The diagonal lines are lines of equality: points below the lines indicate larger values at the baseline, and points above the lines indicate larger values at year 1.

followed trends similar to those of the laboratory medians already discussed. Median SCR, BUN, and HGB values all dropped significantly from the baseline to week 1 and recovered gradually to baseline values by year 1 (SCR and BUN) or year 2 (HGB). WBC peaked significantly at week 1 and then returned to baseline values by month 1. Ferritin did not stabilize until year 2: it peaked at week 1, then descended below the baseline value through month 3, and slowly increased to approach the baseline value by year 2.

DISCUSSION

There are 2 important observations from our analyses. First, except for the platelet count, laboratory values approached baseline levels within 90 days after donation. Although statistically significant differences in median values versus evaluation values were noted for up to 1 year for AST, AP, total bilirubin, INR, and albumin, these differences at 1 year were very small numerically and were likely clinically irrelevant. This information should be reassuring to donors and donor candidates as well as their physicians. Second, we found a significant reduction in the platelet count. The etiology of the low platelet count is unclear, although there are several possibilities. First, some donors could have elevated portal pressure. This could be caused by inadequate regeneration of the hepatic remnant and a small remnant size, relative portal or hepatic venous insufficiency, or sinusoidal hyperperfusion, which could lead to increased portal pressure, splenomegaly, and a reduced platelet count. Second, thrombopoietin, the growth factor responsible for platelet production, is produced in the liver. A small study of 10 right hepatic lobe living donors found that thrombopoietin levels, peaking 7 days after surgery, doubled from 12 to 24 fm/mL.[6] The increase in thrombopoietin corresponded to a doubling of the platelet count. If postoperative hepatic regeneration is incomplete, a reduction in the hepatic mass could lead to reduced thrombopoietin levels and a reduction in the platelet count. Finally, portal vein thrombosis has been reported in less than 1% of living liver donors. Complete thrombosis or partial stenosis of the portal vein could result in splenomegaly and subsequent thrombocytopenia.[2,4,7,8]

Numerous studies have reported changes in laboratory tests immediately after hepatic lobe donation. As noted previously, all but one study[4] measured values in the immediate postoperative period (<30 days). Peak values of AST and ALT were noted on the day of surgery or on the day after surgery[9-15] and then returned to normal values (or approached normal values) between 5 days and 1 month. In comparison with AST and ALT, maximum postoperative bilirubin values generally occurred somewhat later: bilirubin peaked between 1 and 7 days and then returned to normal or nearly normal values between 7 and 30 days.[9-11,13,14,16,17] The INR or prothrombin time was evaluated in fewer studies; it reached a peak 1 to 2 days after surgery and returned to or approached baseline levels 7 to 14 days after surgery.[9-11,13-15,17] The platelet count dropped in up to one-half of patients and reached a nadir at approximately 3 days.[5,6,11,15] Its values returned to or approached normal levels by 30 days, but this was evaluated in

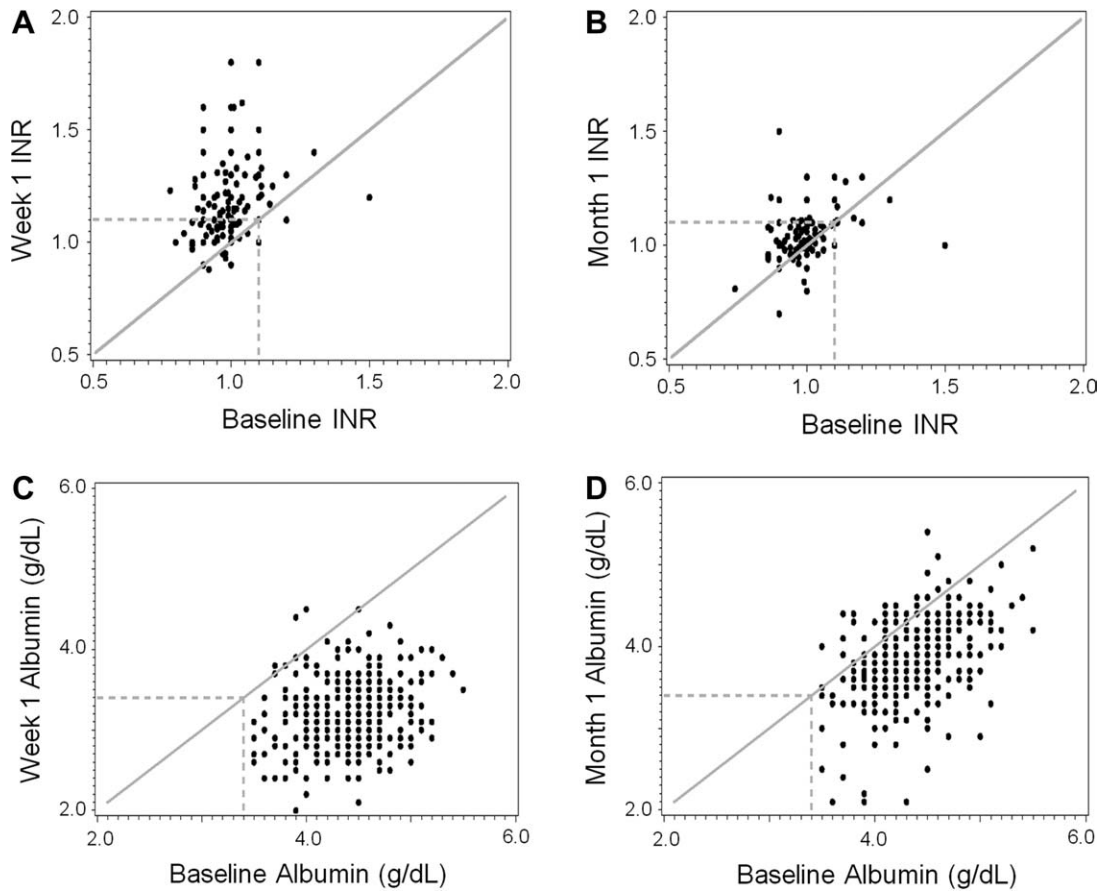

Figure 5. Laboratory values in (A,C) week 1 and (B,D) month 1 versus the baseline: (A) INR (ULN = 1.1, n = 305), (B) INR (ULN = 1.1, n = 277), (C) albumin (LLN = 3.4 g/dL, n = 310), and (D) albumin (LLN = 3.4 g/dL, n = 317). The diagonal lines are lines of equality: points below the lines indicate larger values at the baseline, and points above the lines indicate larger values at year 1.

TABLE 2. Abnormal Laboratory Values Among Donors With Values Both at the Baseline (Before Donation) and at the First Follow-Up at Least One Year Later

Laboratory Test	Donors (n)	Abnormal at Baseline [n (%)]	Abnormal at Year 1 or Later [n (%)]	Abnormal at Baseline, Normal at Year 1 or Later [n (%)]	Normal at Baseline, Abnormal at Year 1 or Later [n (%)]	McNemar's Test *P* Value*	Odds Ratio (95% Confidence Interval)†
ALT	333	18 (5%)	28 (8%)	12 (4%)	22 (7%)	0.09	1.8 (0.87, 4.06)
AST	332	0 (0%)	14 (4%)	0 (0%)	14 (4%)	0.0001	19.7 (3.32, ∞)‡
AP	332	11 (3%)	19 (6%)	6 (2%)	14 (4%)	0.07	2.3 (0.84, 7.41)
Total bilirubin	331	12 (4%)	18 (5%)	3 (1%)	9 (3%)	0.08	3.0 (0.75, 17.2)
INR	310	15 (5%)	18 (6%)	13 (4%)	16 (5%)	0.58	1.2 (0.56, 2.78)
Albumin	324	1 (<1%)	8 (2%)	1 (<1%)	8 (2%)	0.02	8.0 (1.07, 355)
Platelet count	327	5 (2%)	24 (7%)	2 (1%)	21 (6%)	<0.0001	10.5 (2.57, 92.4)

*A significant result indicated significantly more abnormal values at 1 year or later versus the baseline (the paired values for each person were considered).

†Odds ratios (comparing the odds of an abnormal value at the first follow-up 1 year after donation or later versus the baseline) and 95% confidence intervals were generated with exact conditional logistic regression models.

‡Because there were no abnormal AST values at the baseline, the upper limit of the confidence interval was infinite. The *P* value was calculated with exact conditional logistic regression instead of McNemar's test.

only 1 study. Spleen size was evaluated in a few studies and increased 34% to 52% from the baseline size by 7 days to 6 months.[6,18,19] Spleen measurements were not available for our analyses but are being undertaken.

Our analysis differed in several important respects from previously published reports. The number of donors evaluated in the aforementioned studies was relatively small; the mean and median numbers were 88 and 52, respectively. In addition, these studies evaluated changes in laboratory tests only in the immediate postoperative period and rarely after more than 14 days. None made statistical comparisons between baseline and follow-up values. As a result, the changes in laboratory tests over time were largely descriptive and not quantitative. However, these studies reported more values during the immediate postoperative period (usually on a daily basis) than our study. Therefore, our study likely did not capture the greatest changes, which typically occurred within 7 days of the operation. In this respect, the most striking difference between our study and other published reports concerns platelet counts. In earlier studies, the platelet count increased from the baseline in the first 1 to 3 postoperative days and decreased thereafter. Because our analysis did not report values before day 7, we may have missed an immediate but transient postoperative increase in the platelet count. Our study has follow-up data for a much longer period of time for a large number of donors at specified intervals long after 30 days post-donation.

Our analysis has several shortcomings. We do not have data for the immediate postoperative period (<7 days) when the greatest changes are noted in laboratory tests. In addition, not every donor had data for each of the follow-up intervals. This could lead to underreporting of abnormal tests of donors with complications or could lead to overestimates of abnormalities if those with normal values were less likely to be tested. Also, follow-up laboratory tests were performed at multiple clinical laboratories. The baseline and 1-week values were measured at the transplant center performing the donation. Thereafter, some tests were done outside the transplant center, and this added some variability because the normal value ranges for each test differed among the clinical laboratories. We also noted that a small percentage of donors underwent living liver donation with mild abnormalities in their baseline laboratory tests at the time of their operation (most commonly ALT, bilirubin, and INR). However, the number of patients with these abnormalities was insufficient to make any meaningful observations about outcomes.

In conclusion, we found that most blood tests (aside from the platelet count) returned to the normal range and approached baseline levels within 1 year of operation in living liver donors, although the probability of abnormal values remained elevated for AST, AP, INR, and albumin. The cause of low platelet counts in living liver donors warrants further evaluation. This information may be used by donors, donor candidates, and their physicians for the further understanding of outcomes following live liver donation.

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