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Clinical utility of postoperative phosphate recovery profiles to predict liver insufficiency after living donor hepatectomy☆

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ABSTRACT

Background: Living donor hepatectomy (LDH) is associated with significant postoperative hypophosphatemia.
Methods: From January 1997 through July 2017, we performed 176 LDH and compared donors who developed liver insufficiency (LI) to those that did not within 30 days of LDH. Using smoothing splines, we constructed a mixed-effects model and assessed receiver operating characteristic curves.
Results: Of the 176 donors, 161 were included in our study and 10 (6.2%) developed LI. The cohorts differed in minimum observed phosphate levels (1.77 mg/dL, LI cohort; 2.01 mg/dL No LI cohort) at a median nadir of 1.6 days (38 h) postoperatively ($p = 0.003$). In the ROC analysis, intraoperative time and postoperative phosphate levels best predicted LI (sensitivity, 90%; specificity, 55.6%).
Conclusion: Mean postoperative phosphate profiles differ significantly between those patients who develop LI and those who do not in the first 38 h after LDH.

Introduction

A liver transplant (LT) is an established treatment for patients with end-stage liver disease (ESLD). Improvements in surgical technique, coupled with a worsening organ shortage, have stimulated the enthusiasm for living donor liver transplants (LDLTs). In recent years, the number of LDLTs has dramatically increased around the world, with a unique geographic distribution. The largest growth rate in LDLTs has been in Asian countries, where deceased donor liver transplants (DDLTs) are not as common for a variety of cultural and religious reasons.[1–6] By contrast, in the U.S., the number of LDLTs peaked at 524 in 2001 to the current plateau of approximately 350 per year.[7] A major impediment to expansion of LDLTs in the U.S. has been the significant morbidity associated with the procedure for the donors.

In one of the most comprehensive and recent evaluations of Western LDLTs, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) consortium reported outcomes from 9 high-volume centers in the United States from 1998 through 2008.[8,9] According to the A2ALL findings, overall donor mortality postoperatively was 0.4%, with an overall complication rate of 40%. The most common complications were biliary leaks (9%), bacterial infections (12%), and incisional hernias (6%). Of note, the incidence of serious complications resulting in long-term disability was about 1.1%.

Living donor hepatectomy (LDH) is associated with significant postoperative hypophosphatemia (POH). Because liver tissue contains about 0.3% phosphate by weight,[10] it has been assumed that a

Abbreviations: A2ALL, Adult-to-Adult Living Donor Liver Transplantation Cohort Study; BMI, body mass index; CT, computed tomography; DDLT, deceased donor liver transplant; ESLD, end-stage liver disease; HTK, histidine-tryptophan-ketoglutarate; INR, international normalized ratio; IQR, interquartile range; LDH, living donor hepatectomy; LDLT, living donor liver transplant; LI, liver insufficiency; LLH, left-lobe hepatectomy; LLS, left lateral segmentectomy; LT, liver transplant; PDS, polydioxanone; PHI, postoperative hepatic insufficiency; POH, postoperative hypophosphatemia; POD, postoperative day; RLH, right-lobe hepatectomy; ROC, receiver operating characteristic.

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substantial amount of exogenous phosphate would be needed during hepatocyte regeneration and that POH would result from massive movement of phosphate into hepatocytes. Given that assumption, POH has been studied as a surrogate marker of anabolic liver regeneration. Early reports have shown an association between low phosphate levels and a significantly better prognosis,[11] while others have correlated POH with postoperative complications.[12,13]

In this single-center retrospective study of the records of 176 living donors over 20 years, we analyzed phosphate recovery profiles from LDH and estimated their clinical utility to predict liver insufficiency (LI).

Materials and methods

From January 1997 through July 2017, 176 adults underwent LDH at the University of Minnesota. To gather data on donor characteristics and postoperative complications, we used a clinical transplant database that is prospectively maintained for our program. The institutional review board at the University of Minnesota approved our study (No. 0301M39762). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

After discharge from our hospital, donors returned for follow-up appointments in our transplant clinic at 1 week, 3 months, 6 months, 1 year, and 2 years postdonation. For our study, we defined early postoperative complications as complications occurring within 30 days after donation. We defined LI as a serum bilirubin concentration >3 mg/dL and/or an international normalized ratio (INR) > 1.7, observed at least 5 days post-donation.[14]

Donor evaluation

Our donor evaluation process was previously detailed.[15] Briefly, during our 20-year study period, we considered healthy adult individuals (age, 18–59 years) as potential donors. Donor evaluation consisted of a complete medical and psychosocial history and physical examination. A physician not involved in the care of the recipient, i.e., someone who could be an unbiased advocate for the donor, carried out the donor evaluation. At multiple points during the evaluation, the risks and benefits of the procedure were explained. Donors were also assessed for altruism and possible coercion; they were counseled that they could withdraw at any time.

Anatomic assessment was done with computed tomography (CT) and magnetic resonance imaging. Graft volume was estimated predonation by CT scan volumetry measurements. Magnetic resonance imaging was used to evaluate biliary anatomy. Liver biopsies were performed in donors whose body mass index (BMI) was more than 30, or if imaging studies were suggestive of steatosis.

Surgical technique

Our surgical technique for LDH has previously been detailed.[16,17]

Right lobe hepatectomy

To open the abdomen for a right-lobe hepatectomy (RLH), a subcostal incision is made with a vertical midline extension. After a satisfactory on-table assessment of the donor liver, the right lobe (including the caudate lobe off the inferior vena cava) is mobilized and a standard cholecystectomy is performed. An intraoperative cholangiogram via the cystic duct is performed. To mark the site of the right duct, a radiopaque marker is used. To encircle the right hepatic vein, a Penrose drain (diameter, 0.5") is used as a sling, posterior to the liver. The right portal vein is encircled. To demarcate the right lobe and the left lobe, a soft vascular clamp is placed on the vascular structures of the right lobe. Using ultrasound, the middle hepatic vein is marked, then the parenchymal dissection is completed along the line of demarcation, staying to the right of the middle hepatic vein. For that dissection, an Erbe waterjet dissector (Erbe USA, Incorporated, Marietta, GA) is used.

After completing about 70% of the parenchymal transection, a repeat cholangiogram is obtained to mark the site of the right duct division and the right bile duct is divided with sharp scissors. To complete the parenchymal dissection, the sling superior to the right hepatic artery and the right portal vein is passed. After the lobes are completely separated, heparin (5000 IU) intravenously are administered. Then, the right hepatic artery and the right portal vein are ligated and divided. To divide the right hepatic vein, a vascular stapler (Ethicon US, LLC, Somerville, NJ) is used. Next, the right-lobe graft is flushed with cold histidine-tryptophan-ketoglutarate (HTK) solution, weighed, and given to the recipient team for the transplant. To inspect for leaks or strictures at the site of the bile duct closure, a completion cholangiogram is obtained.

Left lobe hepatectomy

To open the abdomen for a left-lobe hepatectomy (LLH), a midline incision is made. Otherwise, the procedure is very similar to a RLH. The left lobe is mobilized and the left hepatic artery and portal vein are encircled. The caudate lobe is taken with the graft, primarily because doing so makes it easier to place the sling during the parenchymal dissection.

Postoperative care and phosphate measurements

All donors were closely monitored during their postoperative recovery room; once stable, they were transferred to the transplant ward. Before transfer, all donors had an ultrasound Doppler evaluation of the remnant liver. Once bowel activity resumed, oral nutrition was encouraged.

Preoperatively, intraoperatively, and postoperatively, serum phosphate levels were monitored. Initially, standard protocol calls for postoperative phosphate level checks every 6 h, for at least the first 48 h; once the levels normalized, they are checked twice daily for the next 2 days and then once daily. According to their phosphate nadir, donors were divided into these 4 POH severity groups: normal (>2.5 mg/dL), mild (1.5–2.5 mg/dL), moderate (1.0–1.5 mg/dL), and severe (<1.0 mg/dL). The following sliding scale for phosphate repletion was applied to all donors: for a phosphate level <1.1 mg/dL, 25 mmol of elemental phosphate was adminisered; 1.1–1.9 mg/dL, 20 mmol; 2.0–2.3 mg/dL, 15 mmol; and 2.4–2.7 mg/dL, 10 mmol.

In addition, donors had the following laboratory tests daily: a comprehensive metabolic panel, a complete blood cell count, and a coagulation panel. For this study, data on the renal excretion of phosphate was not available.

Statistical analysis

Our primary outcome was the occurrence of LI within 30 postoperative days, defined as a serum bilirubin concentration >3 mg/dL and/or INR >1.7, observed at least 5 days post-donation.[16] Our secondary outcomes were liver-specific (i.e. bile leaks) and non-liver-specific (i.e. bleeding, urinary tract infection) morbidity, mortality, and readmission within 30 days postoperatively. To evaluate the postoperative phosphate recovery profiles of donors as a predictor of LI, we compared 2 cohorts: donors with LI (hereafter labeled "LI") vs. donors without LI within 30 days of surgery (hereafter labeled "No LI").

Results were summarized as the number (percent) for categorical data; as the mean (±standard deviation), for continuous

variables by LI status. To perform overall composite tests comparing the LI cohort to the no LI cohort, Fisher's exact test was used for categorical variables and analysis of variance (ANOVA) was used for continuous variables. Donor–specific profiles of phosphate concentrations over time were modeled as mixed effects using natural cubic splines, as well as partial linear models.[18–20] The mixed effects model yielded an estimate of mean phosphate concentration over time as a smooth curve for each donor, as well as an overall mean curve for each donor group by LI status. Features that distinguished the profiles of patients with LI were identified graphically, and combined with other baseline covariates to build decision rules to predict LI. Receiver operating characteristic (ROC) curves were used to assess the potential performance of these rules. All statistics and graphics were produced in the 'R' statistical software environment, version 3.2.3.[21] Variables were assumed to be significant with a corresponding adjusted $P < 0.05$.

Results

Donors

Overall, 176 adults underwent living donor hepatectomy at the University of Minnesota from January 1997 through December 2016 (Table 1). Of those 176 donors, 161 (91.5%) had at least 1 serum phosphate measurement within 10 postoperative days, and thus comprised the study group. Of those 161 donors, 10 (6.2%) had LI postoperatively. In addition, we had 3 postoperative bile leaks and 5 postoperative bleeds.

The median age at donation was 35.7 years for the No LI cohort ($n = 151$); 42.2 years for the LI cohort ($p = 0.05$). About half of the 161 donors were female, with an overwhelming Caucasian proportion.

Intraoperative time did not significantly differ between the 2 cohorts, but improved the prediction of LI when considered jointly with phosphate profile. Most of our donors did not require blood products during or after their LDH. The estimated blood loss in the LI cohort trended lower (398 ± 89 ml) than in the No LI cohort (470 ± 281 ml; $p = 0.06$). Neither remnant weight nor remnant liver volume different between the LI and No LI groups. The LI cohort had a longer hospital stay (mean, 11 days) than the No LI cohort (mean, 7.0 days; $p = 0.05$).

The phosphate nadir was reached in the No LI cohort sooner (median, 1.9 days) than in the LI cohort (median, 3.1 days) but this was not statistically-significant. The median time to diagnosis of LI was 5.6 days. Finally, liver-specific and non-liver-specific complications (or complications incurred more than 30 days after surgery) were not statistically-different among the groups.

Table 1
Demographic characteristics.

	No LI cohort	LI cohort	*p*
n (%)	151 (93.8)	10 (6.2)	
Age at donation, years	35.7 (10)	42.2 (9.0)	**0.05**
Gender, female	79 (52.3)	3 (30)	0.21
Race			1.00
Caucasian/White	142 (94)	10 (100)	
Other	9 (6)	0 (0)	
Donor type			0.51
LRD	95 (63)	5 (50)	
LURD	56 (37.1)	5 (50)	
Donor status			1.00
Alive	121 (80)	8 (80)	
Dead	1 (0.7)	0	
Lost to Follow-up for > 4Yr	20 (19)	2 (20)	
Intra-op time, hours	8 (1.6)	7.7 (1)	0.45
Intra-op transfusion			1.00
1–3 Units	3 (2)	0	
None	148 (98)	10 (100)	
Estimated blood loss, mL	470 (281)	398 (89)	0.06
Remnant weight (gm)	821 (241)	857 (174)	0.56
Remnant liver volume (%)	49 (10)	48 (5.2)	0.60
Length of stay, days	7.0 (3.1)	11 (5.7)	**0.05**
Time to min Phos within 30 days	1.9 (1)	3.1 (2.4)	0.15
Time to complication within 30 days		5.6 (0)	
Non-liver specific complications	48 (32)	5 (50)	0.30
Any complication >30 days	17 (11)	2 (20)	0.34

Phosphate measurements

The serum phosphate measurements recorded within the first 10 postoperative days are shown in Fig. 1. The frequency of measurements varied by donor (median, 7; interquartile range [IQR], 5 to 9). The 2 cohorts significantly differed in mean minimum observed phosphate levels (1.77 mg/dL for LI cohort, 2.01 mg/dL for No LI cohort) at a median of 1.6 days (38 h) postoperatively ($p = 0.003$), according to our linear model focused on the phosphate recovery phase (postoperative day [POD] 2 through 7).

Our predictive model for the first 30 postoperative days is shown in Fig. 2. According to the ROC curve analysis, we found that intraoperative time and postoperative phosphate levels through the first 38 h best predicted LI (sensitivity, 90%; specificity, 55.6%; positive predictive value, 11.8%; negative predictive value, 98.8%; area under the curve, 0.731), compared to measurement limited to the first 24 h (sensitivity, 60%; specificity, 75.5%; positive predictive value, 14%; negative predictive value, 96.6%; area under the curve, 0.674). In particular, the joint effect of (a) steeper phosphate declines in the 12- to 24-h interval, and (b) lower phosphate levels at 38 h, indicated greater risk of subsequent LI. However, when we assessed our estimates of phosphate levels only through the first 24 h postoperatively, predictions were in general less sensitive and more specific.

Discussion

LDLTs have not been widely adopted in the United States, in substantial part because of their significant morbidity, which affects around 40% of donors.[8,9] For LDLTs to experience an upsurge in enthusiasm, novel approaches for detecting and treating post-donation morbidity are needed. In this single-center study of phosphate recovery profiles over a 20-year period, our objective was to estimate their clinical utility to predict LI after LDH, early in the postoperative period (i.e. within 30 days). In an effort to identify predictors of LI, we applied mathematical models of POH patterns. Although POH has been previously studied as a surrogate marker of anabolic liver regeneration, the hypophosphatemic response of a wide array of donors to the surgical insult of LDH has yielded conflicting data.

Recently, in a 12-year study involving 719 donors, Squires et al. analyzed the effect of POH after major hepatectomy, focusing on these outcomes: postoperative hepatic insufficiency (PHI), which they defined by a peak serum bilirubin concentration >7 mg/dL; the occurrence of major complications; and the 30- and 90-day mortality rate. In their study, donors with a phosphate level >2.4 mg/dL on POD 2 had a significantly higher incidence of PHI, major complications, and mortality—an effect that was evident even on multivariate analysis. The 30- and 90-day mortality rate in those donors was more than twice the rate of donors with a phosphate level <2.4 mg/dL on POD 2. Similarly, donors whose phosphate level reached its nadir after POD 3 had a higher incidence of PHI, major complications, and mortality.[22]

In a similar study involving 402 patients who underwent liver resections (including nonanatomic resections), Hallet et al.

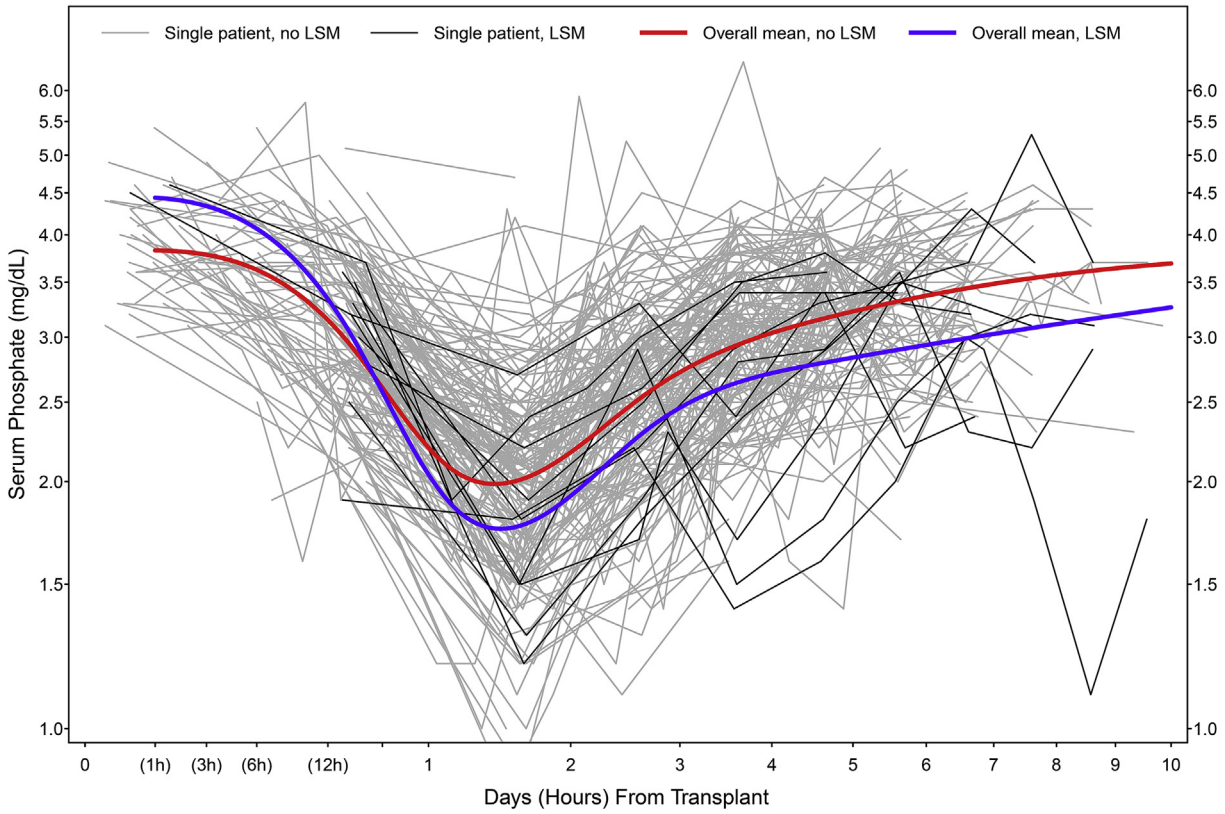

Fig. 1. Serum Phosphate Concentrations Following Live Donor Hepatectomy. Among 176 live donor hepatectomies performed from 1997 to 2017 with serum phosphate measurements recorded in the first 10 days after surgery, 10 (6.2%) patients were diagnosed with liver insufficiency (LI) within 30 days. Each sequence of phosphate concentrations is traced by a narrow line in the plot (gray = No LI, black = LI). A linear model focused on the phosphate recovery phase (2nd through 7th day) and showed a significant difference ($p = 0.003$) between fitted lines by LI status at the median time of minimum observed phosphate, 1.6 days (38h) after surgery. A mixed effects model with natural cubic (smoothing) splines was then used to estimate each patient–specific mean phosphate profile, as well as overall means by LI status, displayed as wider, smooth lines in the plot (red = No LI, blue = LI).

examined the relationship between POH and PHI, which they defined by a serum bilirubin concentration >50 μmol/L or an INR >1.7 within 72 h postoperatively. Hospital length of stay and 30-day postoperative major morbidity, mortality, and readmission were similar between patients with and without POH and those with both POH and PHI recovered more often.[23] Note, however, that only about half of the resections in the study by Hallet et al. were considered a major hepatectomy (defined as ≥3 segments).

Both the study by Squires et al. and the study by Hallet et al. deviate from ours, in that their patients had a diverse assortment of liver diseases and a considerable percentage of them underwent preoperative chemotherapy and other interventional procedures, such as embolization. In addition, the magnitude of parenchymal resection was highly variable in those 2 studies.[22,23]

In contrast, our study involved a much more homogenous group of patients, namely, healthy individuals who had undergone a rigorous medical evaluation before having a major hepatectomy of over 50% of their liver, for the purposes of donation. Therefore, we were able to more straightforwardly isolate the biochemical effect of POH on LI. The association between POH and postoperative complications in living liver donors has been explored previously, but the topic continues to stir boisterous debate. Currently, 6 studies in the literature have examined POH in living liver donors: 3 of them found an association between POH and postoperative complications, while the other 3 did not.

Among those 6 studies was one from Lahey Clinic, in which Pomposelli et al. correlated the severity of POH and postoperative complications in 30 right-lobe donors.[24] In a smaller study from Mayo Clinic, Burak et al. examined 9 right-lobe donors and suggested that complications might be related to POH.[25] Both of those studies were fraught with selection and small-sample bias. In the largest of those 6 studies, Yuan et al. described outcomes after 102 living donor hemihepatectomies.[26] They found that 98% of donors developed POH, with 19% classified as severe POH. The phosphate nadir (1.89 ± 0.72 mg/dL) was reached on POD 3; the degree of severity correlated with the incidence of postoperative liver dysfunction, which they defined by a serum bilirubin concentration >3 mg/dL and/or an INR >1.7[26].

The 3 studies that did not find an association between POH and postoperative complications in living liver donors were from 3 different countries: the United States, South Korea, and Turkey. Tan et al., from the University of Pittsburgh, found no increased morbidity in 95 living liver donors whose POH had been zealously corrected, but provided no details on the stoichiometric scale used.[27] Similarly, in a later study from South Korea, Lee et al. reported on 88 living liver donors who had undergone right hemihepatectomy.[28] All 88 donors developed POH, with a mean phosphate nadir of 1.4 ± 0.04 mg/dL. But no significant difference was observed in the incidence of postoperative complications. Furthermore, the postoperative phosphate level positively correlated with the remnant liver volume, but negatively correlated with a postoperative increase in the alkaline phosphatase level.[28] Finally, a smaller study from Turkey bolstered the notion that the remnant liver volume is inversely correlated with the degree of POH, but did not demonstrate any clinically significant increase in postoperative morbidity.[29]

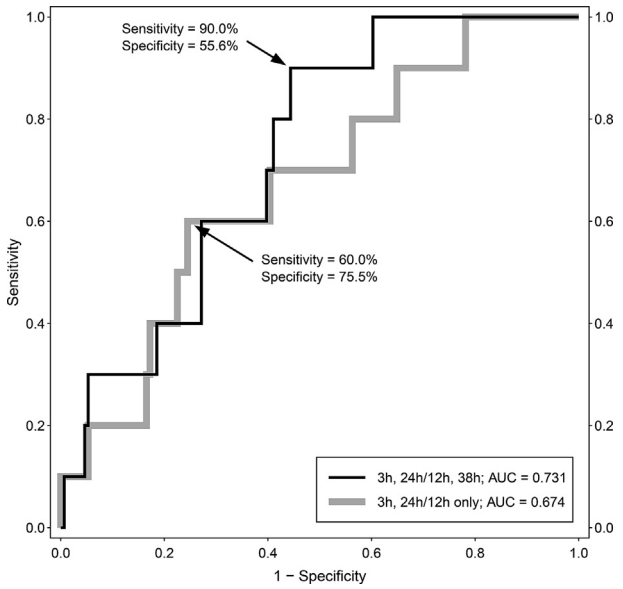

Fig. 2. Receiver Operating Characteristic Curves for Prediction of Liver Insufficiency. Features that distinguish group–wide profiles (LI vs No LI) were identified graphically and combined with OR time to predict risk of LI for each patient. These features included the forward ratio of phosphate concentrations at 24 and 12 h ('24h/12h') and estimated concentrations at critical time points 3h and 38h after surgery. Predictive values for the first decision rule (narrower black line) corresponding to the highlighted point where sensitivity = 90% and specificity = 55.6%, are as follows: positive predictive value (PPV) = 11.8%, negative predictive value (NPV) = 98.8%, areas under the curve = 0.731. The second set of decision rules (wider gray line) was based on phosphate estimates through the first 24h only. One element of this second set yielded sensitivity = 60% and specificity = 75.5%, with a PPV = 14%, NPV = 96.9% and an area under the curve = 0.674.

Clearly, a well-designed and well-powered study has long been overdue to furnish a definitive answer to this glaring clinical conundrum. We hope that our study—involving the largest contemporary single-center series of living liver donors, in an established program with standard phosphate repletion protocols—is a helpful step in the right direction. Using a mixed-effects model, with smoothing splines to represent donor-specific profiles of phosphate levels at various times post-donation, we found that donors who developed LI within 38 h postoperatively had a phenotypically distinct hypophosphatemic profile than donors who did not develop LI. These sensitivity and specificity estimates appear optimistic because we determined them using the same data that produced our prediction algorithm, and the incidence of LI in our study was low. Still, we believe that this analysis yields relevant information on the clinical utility of these phosphate profiles in a range of different donors, perhaps offering a useful supplement to standard statistical comparisons of means in clinical data.

In addition, donors who developed LI experienced a dampened recovery from the hypophosphatemic insult beyond POD 5, indicating that the effect is long-lasting and that such donors are somehow physiologically impaired in their phosphate repletion composition. This would suggest a hyperutilization of phosphate or a diminished effectiveness of phosphate absorption.

A number of limitations to our study must be pointed out. As a single-center study, it was limited to center-specific populations and treatment practices. Furthermore, even though our database is prospectively maintained, the retrospective nature of our study limited our ability to directly control for confounding variables that could have affected our primary outcome. Our study also experienced patient and data attrition. Given our long study period (20 years), era effect no doubt was a factor, because surgical practices and postoperative care continuously changed over short periods within that timeframe. For example, OR time was found to be generally lower from 2007 to 2012, and this factor was included in the predictive model. Other era effects could not be discerned in these data.

Conclusions

We found evidence of an association between the degree of POH and LI in living liver donors. We believe that phosphate profiles within 38 h postoperatively may play a central role in predicting LI. Our study represents the largest single-center living liver donor series in North America, in the modern era, in which the effects of POH on LI have been rigorously and systematically examined. Our results should help with early identification of donors who might be susceptible to LI for a more vigilant approach to their recovery.

Disclosure

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