LETTER TO THE EDITORS

Hypomagnesemia and risk of post-transplant lymphoproliferative disorder in liver transplant recipients

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Dear Editors,

Liver recipients have substantial risk of post-transplant lymphoproliferative disorder (PTLD) [1]. Most PTLDs result from uncontrolled replication of Epstein–Barr virus (EBV) due to immunosuppressive therapy [1].

A role of magnesium in modulating immune response and in lymphomagenesis is increasingly being recognized [2]. Decreased intracellular magnesium causes impaired T-cell and B-cell function, decreased expression of natural killer-activating receptor (*NKG2D*) in natural killer and T-cells leading to a blunted anti-EBV response, and increased risk of EBV-positive lymphomas [2,3]. Hypomagnesemia was associated with EBV viral load and Burkitt lymphoma in Ugandan women, and associations of EBV with other lymphomas are also documented [4].

People with cirrhosis or end-stage liver disease commonly have decreased serum magnesium levels [5], and persisting hypomagnesemia after liver transplantation may increase PTLD risk. We evaluated the association between post-transplant hypomagnesemia and risk of PTLD in a cohort of 3,507 adult liver recipients at Baylor University Medical Center (Dallas, Texas) during 1985–2015.

Patient follow-up began at transplantation and ended at the first of graft failure, retransplantation, death, or loss to follow-up. Serum magnesium levels were measured during routine follow-up visits. Follow-up time was divided into intervals by these visits. Hypomagnesemia was defined as serum magnesium $\leq$ 1.7 mg/dl at the beginning of each interval, if available. In the absence of magnesium measurement, measurements from previous intervals were carried forward. Magnesium measurements were missing for 50.4% of follow-up time and were carried over from the previous interval. Because calcineurin inhibitors (CNIs) can cause hypomagnesemia, we ascertained receipt of CNIs at each visit.

PTLD (any type, including monomorphic or polymorphic) was ascertained from patient reports at follow-up visits and review of electronic medical records. We used Cox regression to evaluate associations of hypomagnesemia (treated as a time-dependent variable) with PTLD.

Median age at transplantation was 51 years (interquartile range, 45–58 years). Most recipients were men (60.2%) and non-Hispanic white (75.0%), and common indications for transplant included hepatitis virus infection (23.9%) or malignancy (22.6%). During follow-up, 81 PTLD cases were reported (incidence 3.25 cases per 1000 person-years) (Table 1). Hypomagnesemia was not associated with risk of PTLD (adjusted hazard ratio [aHR]=1.02; 95% confidence intervals [CI] =0.52–1.98) (Table 1). Adjustment for CNI use as a time-dependent variable did not materially change the aHRs (aHR = 1.01; 95%CI = 0.52–1.97). There was no significant association between hypomagnesemia and PTLD when the time since transplantation was either $\leq$ 5 years (aHR = 0.82; 95%CI = 0.32–2.10) or> 5 years (aHR = 1.29; 95%CI = 0.50–3.35). In a sensitivity analysis, we retained only the person-time where intervals between magnesium measurements were $\leq$ 365 days, but the association with hypomagnesemia remained null (aHR = 1.03; 95%CI = 0.47–2.25).

Our study did not find a significant association between hypomagnesemia and risk of PTLD. However, we did not have data on intracellular magnesium which is relevant for T-cell function. Also, magnesium was not

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Table 1. Incidence of PTLD in liver transplant recipients

	Outcomes, N	Person-years	Incidence rate, per 1,000 person-years	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Total	81	24,873.80	3.25	–	–
Magnesium level (mg/dl)					
Low (≤1.7)	15	5,000.40	2.99	1.04 (0.54–2.03)	1.02 (0.52–1.98)
Normal/high (>1.7)	21	7,338.33	2.86	Reference	Reference
Missing	45	12,535.07	3.59	1.28 (0.76–2.16)	0.78 (0.40–1.53)

CI, confidence intervals; HR, hazard ratio; IQR, interquartile range; PTLD, post-transplant lymphoproliferative disorder.
*Hazard ratios were adjusted for age at transplantation, sex, race/ethnicity, and calendar year of transplantation.

measured uniformly during follow-up and we did not have data on duration of hypomagnesemia. Possible use of magnesium supplements in the post-transplant period may have also affected our results. Future studies with more complete magnesium assessment may overcome these limitations.

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Conflict of interest

The authors have no conflict of interest to disclose.

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