LETTER TO THE EDITORS

Role of symmetric dimethylarginine in predicting future renal impairment in liver transplant recipients

Manhal Izzy[1,2], Mounika Angirekula[2], Andrew Bentall[3], Matthew Plevak[4], Ross Dierkhising[4], Lilach O. Lerman[3], Hui Tang[3], LaTonya Hickson[3] & Kymberly D. Watt[2]

1 Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA
2 Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
3 Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
4 Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
E-mail: manhal.izzy@vumc.org

Dear Editors

Chronic kidney disease (CKD) is common among liver transplant recipients (LTR) and is associated with worse graft and patient survival. Multiple factors are associated with development of renal dysfunction in LTRs including use of calcineurin inhibitors, diabetes mellitus (DM), and hypertension [1]. The underlying pathophysiology for the development of CKD involves changes in renal endothelium [2]. Symmetric dimethylarginine (SDMA) is believed to be related to endothelial dysfunction [3], and it is eliminated mainly by the kidney [4]. SDMA was shown to predict worsening renal function in kidney transplant recipients [5]. However, it is unknown if SDMA demonstrates the same advantage in LTR.

We studied SDMA levels in the early post-transplant period relative to later decline in kidney function. The study was a pilot retrospective analysis of records of LTRs who underwent liver transplant between 2/2012 and 2/2015 at Mayo Clinic-Rochester and had stored serum specimens from prior a research study. The original cohort included patients between 18 and 70 years old who, during liver transplant evaluation, were enrolled in a prospective long-term follow-up study. The specimens had been collected 3 weeks post-transplant. Recipients of simultaneous kidney–liver transplant were excluded. The SDMA testing was performed using enzyme-linked immunosorbent assay kits provided by ALPCO®. Demographic, clinical, and biochemical data were collected. The primary endpoint was poor renal outcomes defined by decline of eGFR to < 30 ml/min per 1.73 m^2. Statistical analysis was performed using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA).

There were forty-nine LTRs in this study with mean age 55.4 (±11.8) years of whom 18 were females. Median pretransplant eGFR was 78.3 (IQR 58.5, 123.1) ml/min/1.73 m^2. Median eGFR at 3 weeks post-transplant was 73.6 (IQR 60.9–91.1) ml/min/1.73 m^2. 17 patients had DM. The median follow-up time of the whole cohort was 4.2 years during which twenty-five patients reached the endpoint. Median SDMA level was 1.1 (IQR 0.7, 1.6) μmol/l at 3 weeks. On univariate analysis, for every 1.0 μmol/l increase in SDMA level at 3 weeks post-transplant there was increased risk of future poor renal outcomes (HR 1.99, 95% CI 1.03–3.84, $P = 0.04$). Upon analyzing the cohort based on SDMA quartiles, higher quartiles associated with higher risk of poor renal outcomes (Fig. 1). After controlling for DM, on bivariate analysis, 3 weeks post-transplant SDMA showed a trend toward significance (HR 1.92, CI 95% 0.97–3.82, $P = 0.06$) in relation to future poor renal outcomes. Upon adjusting for baseline eGFR, neither SDMA nor baseline eGFR showed statistically significant association with eventual poor renal outcomes.

This pilot study sheds light on the potential utility of SDMA in LTRs and suggests that higher levels of SDMA in the early post-transplant setting, reflective of increased endothelial dysfunction and decreased renal clearance, may relate to future poor renal outcomes. While the high rate of poor renal outcomes suggests selection bias as specimens were obtained from prior study repository, this would not affect the study concept regarding predicting renal outcomes. These preliminary observations identify a potential for future investigation of this novel biomarker to aid in early prediction of poor renal outcomes after liver transplant.

doi:10.1111/tri.13771

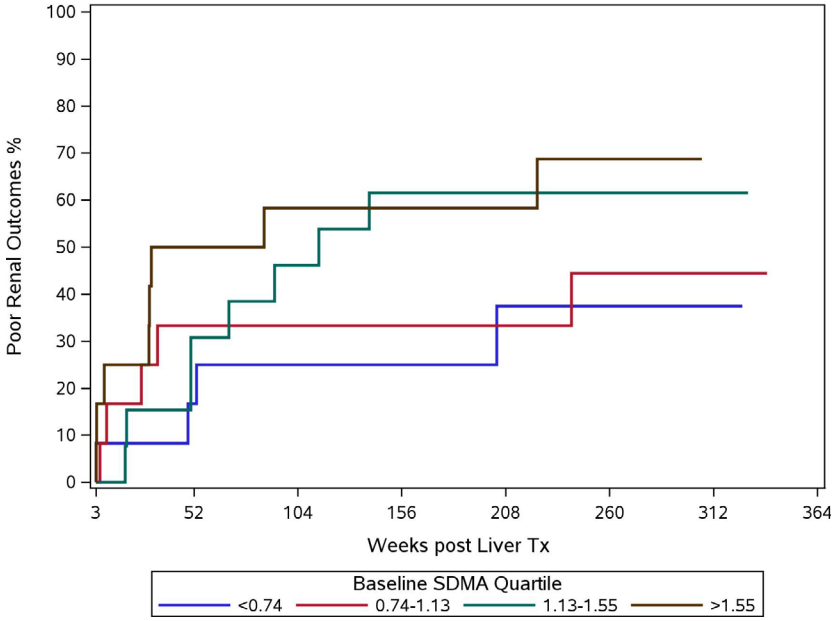

Figure 1 Differences in poor renal outcomes based on SDMA quartiles in liver transplant recipients. SDMA, symmetric dimethylarginine

Funding

The testing kits for symmetric dimethylarginine were provided by the manufacturer (ALPCO®).

Conflict of interest

The authors have declared no conflicts of interest.

REFERENCES

1. Allen AM, Kim WR, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation – a time-dependent analysis using measured glomerular filtration rate. *J Hepatol* 2014; **61**: 286.
2. Seliger SL, Salimi S, Pierre V, Giffuni J, Katzel L, Parsa A. Microvascular endothelial dysfunction is associated with albuminuria and CKD in older adults. *BMC Nephrol* 2016; **17**: 82.
3. Jud P, Hafner F, Verheyen N, *et al.* Homoarginine/ADMA ratio and homoarginine/SDMA ratio as indepen dent predictors of cardiovascular mortality and cardiovascular events in lower extremity arterial disease. *Sci Rep* 2018; **8**: 14197.
4. Rysz J, Gluba-Brzozka A, Franczyk B, Jablonowski Z, Cialkowska-Rysz A. Novel biomarkers in the diagnosis of chronic kidney disease and the prediction of its outcome. *Int J Mol Sci* 2017; **18**.
5. Pihlstrom H, Mjoen G, Dahle DO, *et al.* Symmetric dimethylarginine as predictor of graft loss and all-cause mortality in renal transplant recipients. *Transplantation* 2014; **98**: 1219.