Title

Elevated Serum Renin Before Liver Transplantation Is Associated With Increased Intraoperative Vasopressor Requirements and Posttransplant Acute Kidney Injury.

Journal

Transplantation

ISSN

0041-1337

Authors

St Hilaire, Liam
Tran, Amy
Kothari, Rishi P
et al.

Publication Date

2026-08-17

DOI

10.1097/tp.0000000000005877

Title Page

Elevated serum renin before liver transplantation is associated with increased intraoperative vasopressor requirements and post-transplant acute kidney injury.

Liam St. Hilaire, MD[1]; Amy Tran, BS BA[1]; Rishi P. Kothari, MD[2]; Dieter Adelmann, MD PhD[1]; Judith Hellman, MD[1]; Michael P. Bokoch, MD PhD[1]

[1]Department of Anesthesiology and Perioperative Care, University of California, San Francisco, CA, USA; [2]Department of Anesthesiology & Perioperative Medicine, Thomas Jefferson University, Philadelphia, PA, USA

ORCIDs: Adelmann 0000-0001-7645-3530, Bokoch: 0000-0003-1387-9547, Hellman: 0000-0003-2278-6625, Kothari: 0000-0002-7148-970X, St. Hilaire: 0009-0001-4206-4374

Corresponding author: Michael.Bokoch@ucsf.edu

521 Parnassus Ave

Floor 04, Rm # 4231

San Francisco, CA, 94143-0648

Authorship Page

Author contributions

LSH – Participated in research design, performance of the research, data analysis and writing of the paper.

AT – Participated in the performance of the research.

RK – Participated in data analysis and the writing of the paper.

DA – Participated in data analysis and the writing of the paper.

JH – Participated in research design, writing of the paper, and data analysis.

MB – Participated in research design, performance of the research, data analysis, and writing of the paper.

Disclosures

The authors have no conflicts of interest directly related to the current work. MPB received research funding totaling $7,000 from La Jolla Pharmaceuticals/InnoViva Pharmaceuticals (the manufacturers of Angiotensin II) to offset costs related to a randomized clinical trial of Angiotensin II in liver transplantation (NCT04901169). This trial is thematically related to the current work on the renin-angiotensin system, but none of the La Jolla/InnoViva funding supported the current work. The company had no input

into the current research design or data interpretation, and they have not reviewed the manuscript.

Funding

LSH received research funding totaling $4,500 from UCSF School of Medicine to conduct this project. MPB received funding from an International Anesthesia Research Society Mentored Research Award, and additional support was from the UCSF Dept. of Anesthesia and Perioperative Care.

Abbreviations Page

AKI: Acute Kidney Injury

AngII: Angiotensin II

EAD: Early Allograft Dysfunction

eGFR: Estimated Glomerular Filtration Rate

KDIGO: Kidney Disease Improving Global Outcome

LT: Liver Transplantation

MELD-Na: Model for End-Stage Liver Disease sodium

NED: Norepinephrine Equivalent Dosage

RAAS: Renin-Angiotensin-Aldosterone System

Abstract

Background

Derangements of the renin–angiotensin–aldosterone system (RAAS) may contribute to circulatory dysfunction in cirrhosis. We hypothesized that renin is elevated in patients undergoing liver transplantation (LT) and is associated with vasopressor requirements and postoperative organ dysfunction.

Materials and Methods

We collected serum from 138 patients before LT and measured renin by enzyme-linked immunosorbent assays. Eligible patients were adults with cirrhosis undergoing LT from a deceased or living donor. Detailed clinical data was obtained from a perioperative data warehouse. The primary outcome was vasopressor dosage during the dissection phase of LT. The secondary outcomes were postoperative acute kidney injury (AKI) and early allograft dysfunction.

Results

Renin was elevated up to 100-fold above normal and strongly correlated with MELD-Na. A 10-fold increase in renin was associated with a 0.03 $mcg \cdot kg^{-1} \cdot min^{-1}$ (95% CI 0.01-0.05) higher vasopressor dose during dissection measured in norepinephrine equivalents. Renin was unassociated with early allograft dysfunction but strongly associated with AKI. A 10-fold increase in renin was associated with an odds ratio of 1.77 (95% CI 1.12-2.77) for AKI. The association with AKI persisted in a sensitivity analysis limited to 105 patients with preoperative estimated glomerular filtration rate ³ 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (OR 1.74, 95% CI 1.05-2.88).

Conclusion

RAAS perturbations may contribute to negative outcomes after LT. Elevated renin may help predict postoperative AKI even when kidney function is preserved before LT. Since renin is associated with increased vasopressor requirements, measuring renin may help identify patients for consideration of treatment with infusion of novel vasopressor angiotensin II during LT.

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) has evolved to maintain blood pressure and organ perfusion through systemic vasoconstriction and sodium retention[1,2]. In patients with cirrhosis, the RAAS plays a vital role in both the splanchnic and systemic circulations[3]. Liver fibrosis results in altered hepatic blood flow and increased portal venous pressure[4]. The resultant portal hypertension leads to splanchnic vasodilation and renal hypoperfusion that may strongly stimulate renin secretion from the juxtaglomerular apparatus[5]. Angiotensin II (AngII) deficiency is another potential factor that drives renin secretion by relieving negative feedback mechanisms[6–9]. Indeed, angiotensin peptide levels and angiotensin converting enzyme activity are known to be altered in patients with decompensated cirrhosis, particularly in those with low systemic vascular resistance and high cardiac output (a hyperdynamic circulatory state)[10]. However, the net effect of these RAAS perturbations on serum renin levels in patients presenting for liver transplantation (LT) and the impact of renin on postoperative outcomes remain unknown.

Because low systemic vascular resistance in patients undergoing LT may be partially attributable to AngII deficiency, we hypothesized that renin levels would identify patients who require higher vasopressor doses during LT. Exogenous AngII is now US Food and Drug Administration-approved for vasopressor infusion and is used to treat vasoplegia in the critical care and cardiac surgery settings[7,9,11]. So far, the use of AngII as a vasopressor in LT has been limited by a lack of evidence from prospective trials and an incomplete understanding of RAAS physiology in this setting[12–14].

Renin may help identify patients at increased risk of organ injury[15]. This hypothesis is true in other settings, such as critical illness, where renin predicts mortality and major adverse kidney events[9,16]. The kidneys and the new liver graft are key organs at risk of hypoperfusion during the perioperative period. Therefore, we further hypothesized that preoperative renin would be associated with posttransplant acute kidney injury (AKI) and early allograft dysfunction (EAD). To test these hypotheses, we measured serum renin in a cohort of patients presenting for LT. Our objective was to determine the association of preoperative renin levels with intraoperative vasopressor requirements and postoperative AKI and EAD following LT.

2. Materials and Methods

2.1. Study population

Eligible patients were aged 18 years or older and underwent LT at a single academic transplant center between July 2018 and August 2023. All patients were prospectively enrolled and provided written informed consent for the collection of biological specimens for research. The local Institutional Review Board approved all study procedures (IRB #17-22384, 20-30179, and 20-30948). We excluded patients who were intubated before LT, in acute liver failure, who lacked decision-making capacity without an available surrogate, or for whom the consent materials were not accessible in their preferred language. Consent documents were available in English, Spanish, and Chinese.

All patients received calcineurin inhibitors for immunosuppression after transplant. The calcineurin inhibitor was normally started on postoperative day 1 or 2, but could have been delayed until postoperative day 3 in patients with rising creatinine at the surgeon's discretion.

2.2. Biospecimen collection

Anesthesia and surgical care were performed according to local standards and protocols[17]. Blood was drawn from a radial artery catheter after induction of anesthesia and before the surgical incision with the patient in the supine position. Serum aliquots were prepared and stored as previously described[18]. Serum aliquots were thawed once, and the renin concentration was measured using an enzyme-linked immunosorbent

assay (DRG International, Springfield, NJ, EIA5125R). The upper limit of normal for this renin assay in healthy adults in the supine position is 54 pg mL^{-1} (the 97.5th percentile). If the first renin measurement was out of range for the assay, additional serum aliquots were thawed and diluted in assay buffer until they fell within the linear range.

2.3. Primary and secondary outcomes

The primary outcome was defined as the total vasopressor dose administered during the dissection phase (between the surgical incision and portal vein clamping). To account for multiple vasopressors used at our center (typically norepinephrine as the first line and vasopressin as the second-line infusion), vasopressor doses were totaled and converted to norepinephrine equivalent dosage (NED)[19]. The secondary outcomes were postoperative AKI of stage 1 or greater within 48 hours of the end of transplant and EAD. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine-based definition, as recommended for patients with cirrhosis[20]. AKI was staged according to the following KDIGO definitions: stage 1, peak creatinine ≥ 1.5× baseline or an absolute increase ≥ 0.3 mg dL^{-1}; stage 2, peak creatinine > 2× baseline; stage 3, peak creatinine ≥ 3× baseline, ≥ 4.0 mg dL^{-1}, or initiation of renal replacement therapy. The baseline creatinine was defined as the lowest value within 48 hours before transplant. Severe AKI was defined as KDIGO stage 2 or 3. EAD was determined by the Olthoff criteria[21].

2.4. Clinical variables and data extraction

Clinical data were extracted from the institutional Transplant Outcomes in Anesthesia Database, a data warehouse comprising perioperative information on both liver donors and recipients[22]. The clinical dataset includes perioperative variables such as demographics, diagnoses, laboratory values, fluids, transfusions, medications, and hemodynamics; surgical parameters such as warm and cold ischemia times; and key donor variables such as donor type (living, deceased, or donor after cardiac death). The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, based on the lowest creatinine value within 48 hours before surgery. Patients with calculated eGFR ≥ 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ were defined as having "preserved" renal function before transplant, while those with eGFR < 60 were defined as having "impaired" renal function.

2.5. Statistical analysis

Renin concentrations were $\log_{10}$-transformed before analysis. To describe clinical factors associated with serum renin, the cohort was divided into equal groups based on the median value ("low-renin" versus "high-renin"). Patient and surgical characteristics were summarized using the *table1_mc* package in Stata 18 (StataCorp LLC, College Station, TX), and standardized mean differences were calculated using the *stddiff* package. The associations of $\log_{10}$[renin] with the Model for End-Stage Liver Disease sodium score (MELD-Na) and vasopressor doses were analyzed by unadjusted linear regression. Mann-Whitney U tests were also used to compare renin levels between patients with and without AKI, and those with and without EAD. The associations between $\log_{10}$[renin] and secondary outcomes were analyzed using unadjusted logistic

regression. AKI analyses were repeated for the subsets of patients with preserved and impaired renal function before transplant. Patients who received preoperative renal replacement therapy or underwent joint liver and kidney transplantation were excluded from the AKI analyses. Statistical significance was defined as $\alpha = 0.05$. All analyses were conducted using Stata 18 or GraphPad Prism version 10.0.1 (GraphPad Software, Boston, MA).

3. Results

3.1. Patient characteristics

Serum renin was measured in 138 patients undergoing liver transplantation. The median age was 60 years (Q1-Q3, 53-67), and the median MELD-Na score was 18 (Q1-Q3, 12-28). The most common diagnoses were alcoholic cirrhosis, metabolic dysfunction-associated steatohepatitis, and hepatitis C. Additional patient characteristics are shown in Table 1. The majority (82%) of patients received a graft from a deceased donor, and 13% were admitted to the hospital before transplant (Table 2).

3.2. Distribution and characterization of serum renin levels

In the overall cohort, preoperative renin concentrations ranged from 3 to 8935 pg mL^{-1}, with a median of 138 pg mL^{-1} (Q1-Q3, 22-510 pg mL^{-1}, Figure 1). The high-renin group had a higher proportion of non-white race and Hispanic or Latino ethnicity (Table

1). The high-renin group was younger, had more alcoholic or metabolic dysfunction-associated steatohepatitis cirrhosis, and had less hepatocellular carcinoma. Patients in the high-renin group were also more likely to use spironolactone before transplant and have a history of ascites requiring large-volume paracentesis.

Notably, MELD-Na scores were substantially higher in the high-renin group. We explored this association using unadjusted linear regression of $\log_{10}$[renin] on MELD-Na. There was a strong positive association ($F(1,136) = 60.76$, $p < 0.001$) with an $R^2 = 0.31$ and a slope of 0.051 (95% CI 0.038-0.064), corresponding to a 12.5% increase (95% CI, 9.2-15.9%) in serum renin for a one-point increase in MELD-Na (Figure 2). Preoperative international normalized ratio and bilirubin were positively correlated with renin, while serum sodium levels were negatively correlated (Figure S1). Notably, preoperative serum creatinine was not associated with renin. Intraoperative and surgical factors were similar between groups, except for slightly higher blood product transfusions in the high-renin group (Table 2).

3.3. Primary outcome: vasopressor dose

The high-renin group received more vasopressors (median 0.05 mcg kg^{-1} min^{-1} NED, Q1-Q3 0.02-0.10) during the dissection phase of LT as compared with the low-renin group (0.03 mcg kg^{-1} min^{-1} NED, Q1-Q3 0.01-0.05, $p = 0.023$, Mann-Whitney U-test). In unadjusted linear regression, there was a positive correlation between $\log_{10}$[renin] and vasopressor dosage ($F(1,136) = 10.51$, $p = 0.002$), with an R^2 of 0.07

and a slope of 0.03 (95% CI 0.01 to 0.05, Figure 3). Thus, a 10-fold increase in renin corresponded to a 0.03 mcg kg^{-1} min^{-1} increase in NED.

3.4. Secondary outcomes

After excluding five patients who required preoperative renal replacement therapy, 85 of 133 (64%) patients developed postoperative AKI. Renin levels were higher in patients who developed postoperative AKI (median 244 pg mL^{-1}, Q1-Q3 26-720) compared with those who did not (54 pg mL-1, Q1-Q3 16-286, p = 0.014, Mann-Whitney U test, Figure 4A). The difference in renin levels was even more accentuated when comparing those who developed severe postoperative AKI (304 pg mL^{-1}, Q1-Q3 195-747) with those who had no AKI or AKI stage 1 (69 pg mL^{-1}, Q1-Q3 19-384, p = 0.003, Table S1). There was no association between renin and EAD (Table 3 and Table S1). In an unadjusted logistic regression including all 133 patients, regardless of preoperative eGFR, a 10-fold increase in serum renin was associated with postoperative AKI (OR 1.77; 95% CI 1.12-2.77; Table 3). A 10-fold increase in renin was associated with higher odds of severe AKI (OR 2.13; 95% CI 1.27–3.57).

3.5. Subgroup analysis of AKI in patients with preserved renal function before transplant

28 of 133 patients (21%) who were not on preoperative renal replacement therapy had impaired renal function before surgery. The baseline characteristics of these patients compared to those with preserved renal function are shown in Table S2.

In the 105 patients with preserved preoperative renal function, renin was significantly higher in those who developed postoperative AKI (median 278 pg mL^{-1}, Q1-Q3 24-772) compared with those who did not (median 52 pg mL^{-1}, Q1-Q3 14-325, p = 0.039, Mann-Whitney U test, Figure 4B). A similar trend was seen in the 28 patients with impaired preoperative renal function (postoperative AKI: median renin 190 pg mL^{-1}, Q1-Q3 83-415; no AKI: median renin 61 pg mL^{-1}, Q1-Q3 30-248), but the difference was not statistically significant (p = 0.23, Figure 4C). The sensitivity analysis of the 105 patients with preserved preoperative renal function using an unadjusted logistic regression model showed associations between renin and postoperative AKI (OR 1.74; 95% CI 1.05-2.88; Table 4) and between renin and severe AKI (OR 2.22; 95% CI 1.25-3.93).

4. Discussion

In a cohort of 138 patients with cirrhosis undergoing LT, serum renin at the start of surgery was markedly elevated in most patients. The renin levels we observed are considerably higher than those previously reported for other critically ill, non-transplant populations. For instance, in a mixed population of critically ill patients, the top tertile of renin levels ranged from 180 to 1032 pg per mL[16], whereas in our study, the top tertile ranged from 325 to 8935 pg mL^{-1}. Only six of our patients were in the ICU before surgery, demonstrating that renin is drastically elevated in many LT patients even when not critically ill.

We observed higher preoperative serum renin levels with increasing severity of liver disease as measured by the MELD-Na score. Bilirubin and international normalized ratio were positively correlated with renin. Serum sodium was negatively correlated with renin, likely because RAAS activation drives fluid retention and the release of antidiuretic hormone, which together lead to hyponatremia. Surprisingly, we found no association between preoperative serum creatinine and renin. The juxtaglomerular apparatus in the kidney secretes renin in response to renal hypoperfusion. Our observation that renin and creatinine are uncorrelated indicates that renin elevation may precede a clinically apparent decrease in eGFR or indicate situations in which compensatory mechanisms have effectively maintained renal filtration.

Because elevated renin can indicate low systemic vascular resistance[23], we hypothesized that preoperative renin levels would indicate a greater difficulty maintaining adequate mean arterial blood pressure during the LT. Therefore, renin

levels should correlate with the vasopressor dose administered. This question is of interest because renin may help identify patients at risk of profound vasodilation, some of whom may have a relative AngII deficiency and be candidates for AngII infusion during LT (see below)[12,13,24]. We limited our vasopressor analysis to the dissection phase, because hypotension during this phase is not confounded by vasodilation from liver graft reperfusion. We found a statistically significant association between preoperative renin levels and vasopressor dose during dissection. However, renin accounted for only a small portion of the variance in vasopressor dose. This is likely due to multiple additional factors contributing to hypotension during the dissection phase, such as blood loss, compression of hepatic vasculature, and anesthetics.

Preoperative renin was associated with both the incidence and severity of postoperative AKI in our cohort, but not early allograft dysfunction. A 10-fold increase in serum renin levels was associated with an odds ratio of 1.77 for AKI. The association remained significant in a sensitivity analysis excluding the 28 patients with significant renal impairment before transplant. These findings suggest that renin may help identify patients at risk of posttransplant AKI, even when renal function appears intact by eGFR. We propose renin as a candidate marker of circulatory impairment that increases the risk of postoperative AKI after LT, as observed after cardiac surgery[25]. It would be valuable to determine if renin predicts AKI in a larger, multicenter cohort of patients undergoing LT, especially given the importance of AKI to long-term patient outcomes such as progression to chronic kidney disease[26].

We demonstrate that preoperative serum renin is associated with higher intraoperative vasopressor requirements and posttransplant AKI. However, we do not

yet know whether intervening upon the RAAS pathway in LT patients can improve outcomes. Intriguing data exists from other clinical settings using AngII as a vasopressor, including cardiac surgery and kidney transplantation[27–29]. AngII was approved by the US Food and Drug Administration in 2017 as an intravenous vasopressor for patients with vasodilatory shock[11]. In a post hoc analysis of patients in the ATHOS-3 trial, patients with elevated renin who received AngII therapy had lower mortality than those receiving placebo[7]. Patients with high renin also had an elevated angiotensin I/AngII ratio, indicating a relative deficit in AngII[6]. We hypothesize that an AngII deficiency may also exist in our LT population and drive renin secretion by relieving negative feedback, but this has not yet been measured. Our group is currently conducting a randomized, double-blind, placebo-controlled pilot trial of AngII infusion in patients with MELD-Na ³ 25 to investigate the efficacy of this vasopressor in LT[14]. The findings of this trial may help elucidate whether AngII is a useful vasopressor in patients undergoing LT.

Point-of-care renin measurements are not currently available, which creates a barrier to integrating this marker into clinical decision-making. Our finding of a strong positive correlation between MELD-Na and renin is helpful for identifying patients with elevated renin before LT. While MELD-Na is a strong correlate of renin, it is not the only factor. Medications such as spironolactone, a mineralocorticoid antagonist that blocks aldosterone from binding to its receptor, will also increase renin through feedback mechanisms and should be considered.

This study has several limitations. First, the serum samples were collected at a single time point before the start of LT. We do not know the trajectory of serum renin in

our cohort, either before or after the start of surgery. Fluctuations may occur. Renin levels at unmeasured time points, or the change in renin in response to vasopressor therapy[7], may be more causally related to postoperative organ injury. A second limitation is the relatively small sample size of our single-center study. We deemed our cohort to be too small to adjust for known risk factors and assess whether preoperative renin is independently associated with posttransplant AKI, especially given the large number and variation of risk factors across published studies[22,30,31]. Preoperative comorbidities such as metabolic-dysfunction associated steatotic liver disease or diabetes mellitus, donor characteristics such as donor risk index and use of normothermic machine perfusion, and intraoperative characteristics such as transfusions or vena cava technique are a few of the variables that should be analyzed in larger future studies of renin and posttransplant AKI. Finally, we were unable to determine the exact etiology of preoperative renal dysfunction in our patients, which is known to be multifactorial.

In conclusion, our findings suggest that renin may be an important marker of cardiovascular impairment and indicate an elevated risk of AKI after LT, even in patients with preserved renal function before surgery. The robust association of renin with post-transplant AKI and the potential to intervene with AngII as a vasopressor infusion suggest that a deeper characterization of the RAAS during LT is a promising area for future study and may help improve patient outcomes.

Acknowledgements

The authors would like to thank Nicholas Fong for additional project detailing and data consultation.

5. References

1. Oyama T, Taniguchi K, Jin T, Satone T, Kudo T. Effect of anaesthesia and surgery on plasma aldosterone concentration and renin activity in man. *Br J Anaesth*. 1979;51(8):747-752. doi:10.1093/bja/51.8.747

2. Forrester SJ, Booz GW, Sigmund CD, et al. Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. *Physiol Rev*. 2018;98(3):1627-1738. doi:10.1152/physrev.00038.2017

3. Paternostro R, Reiberger T, Mandorfer M, et al. Plasma renin concentration represents an independent risk factor for mortality and is associated with liver dysfunction in patients with cirrhosis. *J Gastroenterol Hepatol*. 2017;32(1):184-190. doi:10.1111/jgh.13439

4. Shim KY, Eom YW, Kim MY, Kang SH, Baik SK. Role of the renin-angiotensin system in hepatic fibrosis and portal hypertension. *Korean J Intern Med*. 2018;33(3):453-461. doi:10.3904/kjim.2017.317

5. Lubel JS, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol*. 2008;23(9):1327-1338. doi:10.1111/j.1440-1746.2008.05461.x

6. Bellomo R, Wunderink RG, Szerlip H, et al. Angiotensin I and angiotensin II concentrations and their ratio in catecholamine-resistant vasodilatory shock. *Crit Care*. 2020;24(1):1-8. doi:10.1186/s13054-020-2733-x

7. Bellomo R, Forni LG, Busse LW, et al. Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock. A Clinical Trial. *Am J Respir Crit Care Med*. 2020;202(9):1253-1261. doi:10.1164/rccm.201911-2172OC

8. Legrand M, Bokoch MP. The Yin and Yang of the Renin-Angiotensin-Aldosterone System in Acute Kidney Injury. *Am J Respir Crit Care Med*. 2021;203(9):1053-1055. doi:10.1164/rccm.202012-4419ED

9. Kotani Y, Chappell M, Landoni G, Zarbock A, Bellomo R, Khanna AK. Renin in critically ill patients. *Ann Intensive Care*. 2024;14(1):79. doi:10.1186/s13613-024-01304-3

10. Casey S, Schierwagen R, Mak K, et al. Activation of the Alternate Renin-Angiotensin System Correlates with the Clinical Status in Human Cirrhosis and Corrects Post Liver Transplantation. *J Clin Med*. 2019;8(4):419-13. doi:10.3390/jcm8040419

11. Khanna A, English SW, Wang XS, et al. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017;377(5):419-430. doi:10.1056/NEJMoa1704154

12. Coleman PJ, Nissen AP, Kim DE, et al. Angiotensin II in Decompensated Cirrhosis Complicated by Septic Shock. *Semin Cardiothorac Vasc Anesth*. 2019;5:108925321987787-7. doi:10.1177/1089253219877876

13. Running K, Weinberg D, Trudo W, Sullivan CL, Patel GP. Intraoperative Use of Angiotensin II for Severe Vasodilatory Shock During Liver Transplantation: A Case Report. *Pr*. 2021;15(2):e01402. doi:10.1213/XAA.0000000000001402

14. Bokoch MP, Tran AT, Brinson EL, et al. Angiotensin II in liver transplantation (AngLT-1): protocol of a randomised, double-blind, placebo-controlled trial. *BMJ Open*. 2023;13(11):e078713. doi:10.1136/bmjopen-2023-078713

15. Sansoè G, Aragno M, Wong F. Pathways of hepatic and renal damage through non-classical activation of the renin-angiotensin system in chronic liver disease. *Liver Int*. 2020;40(1):18-31. doi:10.1111/liv.14272

16. Flannery AH, Ortiz-Soriano V, Li X, et al. Serum renin and major adverse kidney events in critically ill patients: a multicenter prospective study. *Crit Care*. 2021;25(1):294. doi:10.1186/s13054-021-03725-z

17. Adelmann D, Kronish K, Ramsay MA. Anesthesia for Liver Transplantation. *Anesthesiol Clin*. 2017;35(3):491-508. doi:10.1016/j.anclin.2017.04.006

18. Bokoch MP, Xu F, Govindaraju K, et al. Serum from patients with cirrhosis undergoing liver transplantation induces permeability in human pulmonary microvascular endothelial cells ex vivo. *Front Med*. 2024;11:1412891. doi:10.3389/fmed.2024.1412891

19. Kotani Y, Di Gioia A, Landoni G, Belletti A, Khanna AK. An updated “norepinephrine equivalent” score in intensive care as a marker of shock severity. *Crit Care*. 2023;27(1):29. doi:10.1186/s13054-023-04322-y

20. Nadim MK, Kellum JA, Forni L, et al. Acute kidney injury in patients with cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) joint multidisciplinary consensus meeting. *J Hepatol*. 2024;81(1):163-183. doi:10.1016/j.jhep.2024.03.031

21. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010;16(8):943-949. doi:10.1002/lt.22091

22. Hannon V, Kothari RP, Zhang L, et al. The Association Between Vena Cava Implantation Technique and Acute Kidney Injury After Liver Transplantation. *Transplantation*. 2020;104(11):e308-e316. doi:10.1097/TP.0000000000003331

23. Coulson TG, Miles LF, Zarbock A, et al. Renin-angiotensin-aldosterone system dynamics after targeted blood pressure control using angiotensin II or

norepinephrine in cardiac surgery: mechanistic randomised controlled trial. *Br J Anaesth*. 2023;131(4):664-672. doi:10.1016/j.bja.2023.06.056

24. Benken ST, Thomas R, Fraidenburg DR, Benken JJ. Angiotensin II as a Vasopressor for Perioperative Hypotension in Solid Organ Transplant. *Biomedicines*. 2024;12(8):1817. doi:10.3390/biomedicines12081817

25. Küllmar M, Saadat-Gilani K, Weiss R, et al. Kinetic Changes of Plasma Renin Concentrations Predict Acute Kidney Injury in Cardiac Surgery Patients. *Am J Respir Crit Care Med*. 2021;203(9):1119-1126. doi:10.1164/rccm.202005-2050OC

26. Mendez NV, Chan D, Thompson T, et al. Contribution of Acute Kidney Injury After Liver Transplant in Development of Chronic Kidney Disease: A Single-Center Retrospective Cohort Study. *Anesth Analg*. Published online January 26, 2026. doi:10.1213/ANE.0000000000007911

27. Sadjadi M, Von Groote T, Weiss R, et al. A Pilot Study of Renin-Guided Angiotensin-II Infusion to Reduce Kidney Stress After Cardiac Surgery. *Anesth Analg*. 2024;139(1):165-173. doi:10.1213/ANE.0000000000006839

28. Coulson TG, Miles LF, Serpa Neto A, et al. A double-blind randomised feasibility trial of angiotensin-2 in cardiac surgery. *Anaesthesia*. 2022;77(9):999-1009. doi:10.1111/anae.15802

29. Beltran LP, Benken J, Jou J, et al. Efficacy and Safety of Perioperative Angiotensin II Versus Phenylephrine as a First-Line Continuous Infusion Vasopressor in Kidney Transplant Recipients. *Clin Transplant*. 2024;38(8):e15432. doi:10.1111/ctr.15432

30. Hilmi IA, Damian D, Al-Khafaji A, et al. Acute kidney injury following orthotopic liver transplantation: incidence, risk factors, and effects on patient and graft outcomes. *Br J Anaesth*. 2015;114(6):919-926. doi:10.1093/bja/aeu556

31. Zhou J, Zhang X, Lyu L, Ma X, Miao G, Chu H. Modifiable risk factors of acute kidney injury after liver transplantation: a systematic review and meta-analysis. *BMC Nephrol*. 2021;22(1):149. doi:10.1186/s12882-021-02360-8

Figure Legends

Figure 1. Distribution of serum renin in 138 patients at the start of liver transplantation. Dark bars indicate median (138 pg mL^{-1}) and Q1-Q3 (22-510 pg mL^{-1}).

Figure 2. Linear regression of MELD-Na and log_{10}[renin]. Solid line indicates the best-fit regression line (F (1,136) = 60.76, $p < 0.001$), with an $R^2 = 0.31$ and a slope of 0.051 (95% CI 0.038-0.064). Dashed lines indicate 95% CI.

Figure 3. Linear regression of log_{10}[renin] and Norepinephrine Equivalent Dosage (NED) during the dissection phase of LT. Solid line indicates the best-fit regression line (F (1,136) = 10.51, $p = 0.002$), with an R^2 of 0.07 and a slope of 0.03 (95% CI 0.01-0.05). Dashed lines indicate 95% CI.

Figure 4. Association of preoperative serum renin with postoperative acute kidney injury (AKI). Box-and-whiskers plots are calculated according to the Tukey method. (A) All patients in the cohort, excluding five who received preoperative renal replacement therapy. (B) Patients with preserved preoperative renal function, defined as preoperative eGFR ≥ 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. (C) Patients with impaired preoperative renal function, defined as eGFR < 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. * $p < 0.05$, Mann-Whitney U test.

Table 1: Recipient and Donor Characteristics. Low and high renin indicate patients above and below the median value.

Variable	Total	Low [Renin]	High [Renin]	|SMD|
	n=138	n=69	n=69	
Preoperative [Renin] (pg mL^{-1}), Q1-Q3	138.1 (21.7-510.1)	21.7 (11.6-52.5)	510.1 (298.6-1278.5)	
Sex (Male) - n (%)	93 (67.4)	45 (65.2)	48 (69.6)	0.09
Race – n (%)				
White	78 (56.5)	42 (60.9)	36 (52.2)	**0.67**
Asian	16 (11.6)	11 (15.9)	5 (7.2)	
Black or African American	2 (1.4)	1 (1.4)	1 (1.4)	
Native American or Alaska Native	3 (2.29)	1 (1.4)	2 (2.9)	
Native Hawaiian or Pacific Islander	4 (2.9)	4 (5.8)	0	
Other	34 (24.6)	10 (14.5)	24 (34.8)	
Unknown / not stated	1 (0.7)	0	1 (1.4)	
Ethnic Group – n (%)				
Hispanic or Latino	44 (31.9)	15 (21.7)	29 (42.0)	0.45
Not Hispanic or Latino	91 (66.7)	53 (76.8)	39 (56.5)	
Declined	2 (1.4)	1 (1.4)	1 (1.4)	
Recipient Age (y) – Median, (Q1-Q3)	60 (53-67)	63 (56-69)	57 (50-63)	0.42
BMI (kg m^{-2}) – Median, (Q1-Q3)	29.1 (24.9-32.7)	28.2 (25.4-31.6)	30.5 (24.5-34.7)	0.31
Past Medical History				
Hypertension – n (%)	68 (49.3)	37 (53.6)	31 (44.9)	0.17
Diabetes Miletus – n (%)	52 (37.7)	27 (39.1)	25 (36.2)	0.06
Chronic Kidney Disease – n (%)	9 (6.5)	7 (10.1)	2 (2.9)	0.30

Etiology of Liver Disease – n (%)				
Hepatitis C	28 (20.3)	21 (30.4)	7 (10.1)	
Hepatitis B	14 (10.1)	8 (11.6)	6 (8.7)	
Alcoholic	35 (25.4)	10 (14.5)	25 (36.2)	
MASH	32 (23.2)	15 (21.5)	17 (24.6)	**0.68**
Cryptogenic	7 (5.1)	3 (4.3)	4 (5.8)	
Other	12 (8.7)	6 (8.7)	6 (8.7)	
Primary sclerosing cholangitis	10 (7.2)	6 (8.7)	4(5.8)	
Large Ascites – n (%)	76 (55)	27 (39)	49 (71)	**0.68**
Hepatocellular Carcinoma – n (%)	71 (51.4)	51 (73.9)	20 (29.0)	**1.01**
Preoperative Spironolactone Use – n (%)	56 (40.6)	12 (17.4)	44 (63.8)	**1.07**
MELD-Na – Median, (Q1-Q3)	18 (12-28)	13 (10-18)	25 (18-31)	**1.20**
Preoperative Labs – Median (Q1-Q3)				
Creatinine (mg dL^{-1})	0.88 (0.74-1.16)	0.84 (0.71-1.12)	0.92 (0.77-1.16)	0.01
eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$)	92.3 (67.7 – 100.8)	94.4 (67.9 – 101.0)	92.3 (67.7 - 100.8)	0.15
International Normalized Ratio	1.5 (1.2-2.1)	1.3 (1.1-1.6)	1.8 (1.4-2.6)	**0.96**
Sodium ($mEqL^{-1}$)	137 (133-139)	138 (137-140)	133 (131-137)	**1.20**
Total Bilirubin ($mgdL^{-1}$)	2.5 (1.2-7.2)	1.7 (0.9-2.7)	4.9 (2.0-12.5)	**0.53**
Albumin (gdL^{-1})	3.0 (2.6-3.4)	3.1 (2.6-3.5)	2.9 (2.5-3.4)	0.32
Fibrinogen ($mgdL^{-1}$)	249 (160-329)	280 (199-357)	204 (141-286)	**0.64**
Platelets (x10^9/L)	72 (50-114)	76 (52-140)	68 (49-106)	0.40
Hemoglobin (gdL^{-1})	10.1 (8.7-12.6)	11.4 (9.2-13.0)	9.4 (8.3-11.1)	**0.66**
Hematocrit (%)	30.9 (25.8-37.3)	34.7 (29.2-38.6)	28.0 (23.9-33.8)	**0.79**
Inpatient Before Surgery – n (%)	18 (13.0)	6 (8.7)	12 (17.4)	0.26

ICU Prior to Surgery – n (%)	6(4.3)	0	6(8.7)	0.44
Preoperative RRT – n (%)	5(3.6)	2 (2.9%)	3 (4.3)	0.08

ICU, Intensive Care Unit, eGFR, estimated Glomerular Filtration Rate, MASH, Metabolic dysfunction-associated steatohepatitis, MELD-Na, Model for End-Stage Liver Disease sodium, RRT, Renal Replacement Therapy, SMD, Standardized Mean Difference.

Table 2: Surgical characteristics. Low and high renin indicate patients above and below the median value.

Variable		Total	Low [Renin]	High [Renin]	|SMD|
		n=138	n=69	n=69	
Donor Type - n (%)	DBD	107 (77.5)	51 (73.9)	56 (81.2)	0.19
	DCD	6 (4.3)	4 (5.8)	2 (2.9)	
	LD	25 (18.1)	14 (20.3)	11 (15.9)	
Operative Time (min) – Median, (Q1-Q3)		418 (356-487)	420 (345-473)	413 (368-494)	0.19
Fluids and Blood Products – Median, (Q1-Q3)					
Crystalloids (mL)		1500 (1000-2500)	2000 (1000-2500)	1500 (1000-2000)	0.22
Albumin 5% (mL)		1000 (0-2000)	1500 (750-2000)	1000 (0-1500)	0.4
Red blood cells (units)		4 (0-6)	2 (0-5)	5 (2-7)	**0.69**
Fresh frozen plasma (units)		8 (4-13)	5 (2-10)	10 (6-16)	**0.67**
Platelet concentrates (units)		2 (0-3)	1 (0-2)	2 (1-4)	**0.58**
Cellsaver blood returned (mL)		600 (250-1300)	485 (225-1000)	700 (450-1400)	0.42
Urine (mL) – Median, (Q1-Q3)		775 (450-1475)	750 (500-1400)	900 (400-1500)	0.12
Estimated blood loss (mL)		2500 (1400-5000)	1900 (1000-4500)	3200 (2000-6000)	**0.60**

DBD, donor after brain death, DCD, donor after circulatory death, LD, Living Donor, SMD, Standardized Mean Difference.

Table 3: Unadjusted logistic regressions of postoperative secondary outcomes using $\log_{10}$[renin] as the predictor. Five patients receiving preoperative renal replacement therapy were excluded from the AKI analyses.

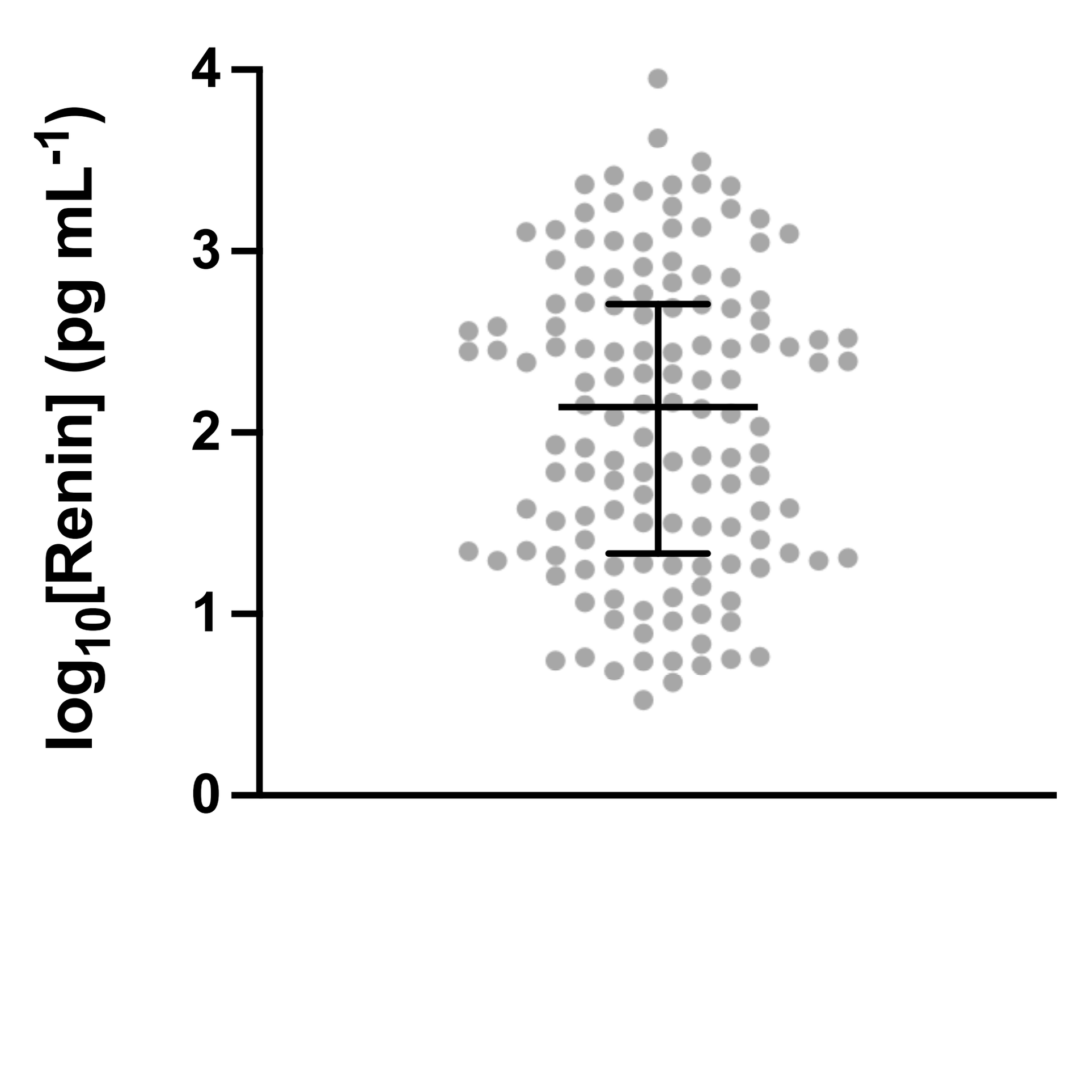
Outcome	N	Odds Ratio	95% CI	P
AKI (stage ≥ 1)	133	1.77	1.12-2.77	0.014
Severe AKI (stage 2 or 3)	133	2.13	1.27-3.57	0.004
Early Allograft Dysfunction	138	0.95	0.62-1.46	0.82

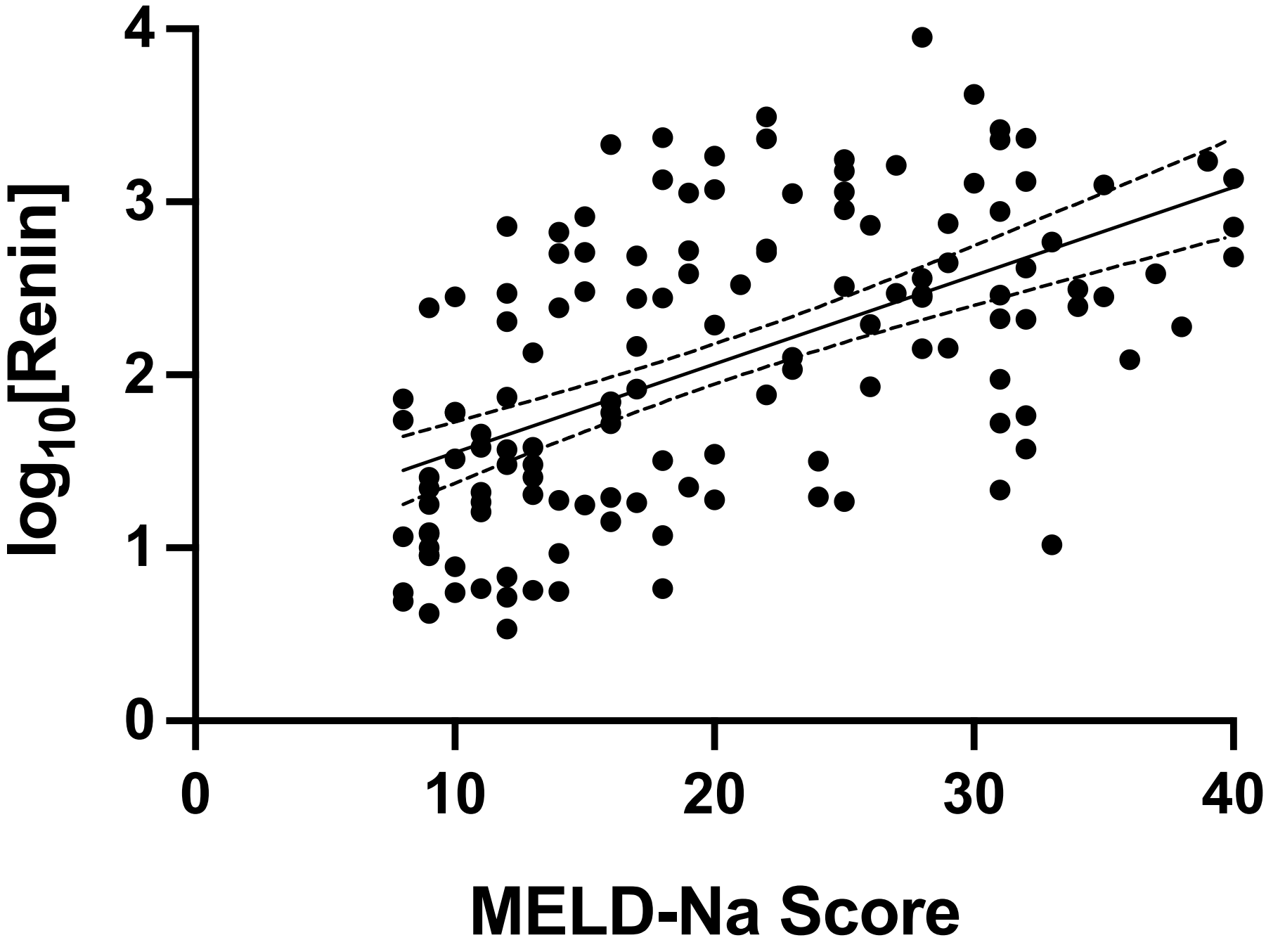
AKI, acute kidney injury.

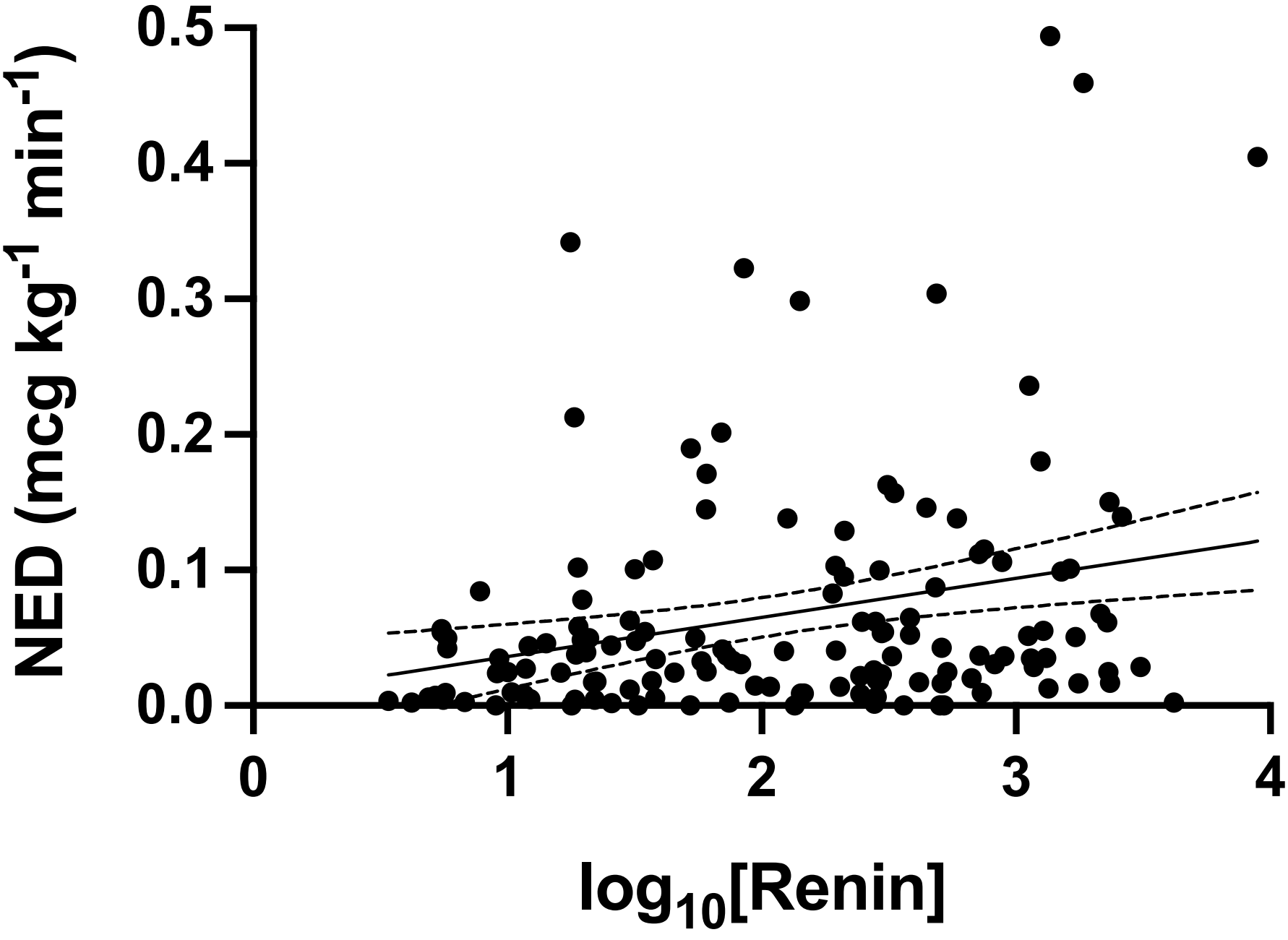
Table 4: Unadjusted logistic regressions of AKI outcomes in 105 individuals with preserved preoperative renal function using $\log_{10}$[renin] as the predictor.

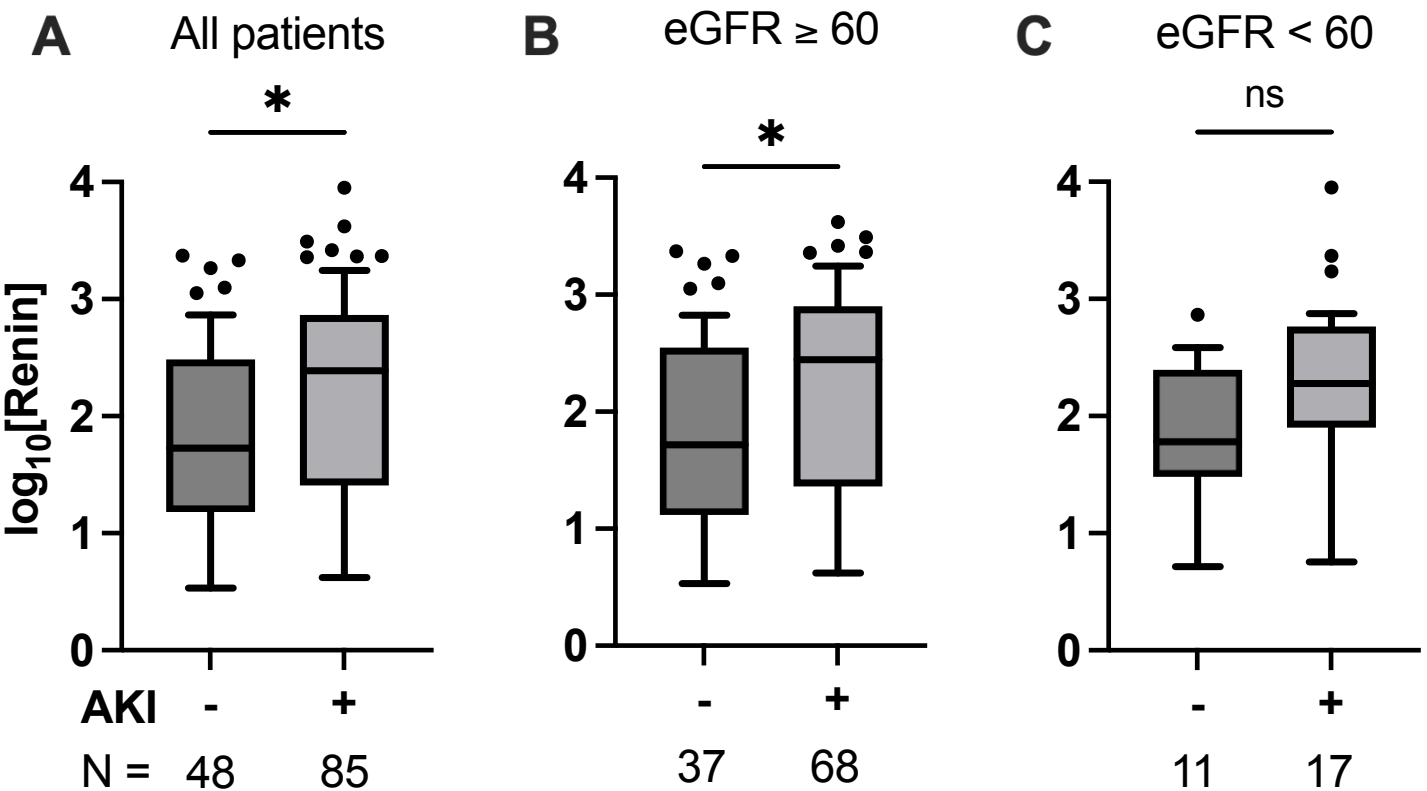
Outcome	Odds Ratio	95% CI	P
AKI (stage ≥ 1)	1.74	1.05-2.88	0.032
Severe AKI (stage 2 or 3)	2.22	1.25-3.93	0.006

AKI, Acute Kidney Injury.


log10[Renin] (pg mL-1)
4
3
2
1
0


4
3
2
1
0
log10[Renin]
0
10
20
30
40
MELD-Na Score


NED (mcg kg-1 min-1)
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
log10[Renin]


A
All patients
*
B
eGFR ≥ 60
*
C
eGFR < 60
ns
log10[Renin]
4
3
2
1
0
AKI
-
+
N =
48
85
37
68
11
17

Supplementary Tables

Table S1

		Outcome = No	Outcome = Yes	P-Value
AKI, stage 1+	n (%)	48 (36%)	85 (64%)	**0.014**
	[Renin], median (Q1-Q3)	54 (16 - 286)	244 (26-720)	
Severe AKI, stage 2 or 3	n (%)	99 (74%)	34 (26%)	**0.003**
	[Renin], median (Q1-Q3)	69 (19-384)	304 (195-747)	
EAD	n (%)	89 (64%)	49 (36%)	0.85
	[Renin] Median (Q1-Q3)	122 (26-501)	190 (18-720)	

Table S1: Secondary Outcomes. For AKI and Severe AKI, N=133 as five patients were excluded from the analysis as they were on preoperative renal replacement therapy. For EAD, N=138. AKI, acute kidney injury; EAD, Early Allograft Dysfunction. P-values indicate results of Mann-Whitney U-tests.

Table S2

Variable	Total	Preserved Preoperative Renal Function	Impaired Preoperative Renal Function	|SMD|
	N= 133	N = 105 (78.9)	N = 28 (21.1)	
Sex (Male) – n (%)	90 (67.7)	73 (69.5)	17 (60.7)	0.18
Race – n (%)				
White	73 (54.9)	57 (54.3)	16 (57.1)	0.34
Asian	16 (12.0)	13 (12.4)	3 (10.7)	
Black or African American	2 (1)	1 (1.0)	1 (3.6)	
Native American or Alaska Native	3 (2.3)	3 (2.9)	0	
Native Hawaiian or Pacific Islander	4 (3.0)	3 (2.9)	1 (3.6)	
Other	34 (25.6)	27 (25.7)	7 (25.0)	
Unknown/Declined	1 (0.8%)	1 (1.0)	0	
Ethnic Group – n (%)				
Hispanic or Latino	42 (31.6)	35 (33.3)	7 (25.0)	0.28
Not Hispanic or Latino	89 (66.9)	68 (64.8)	21 (75.0)	
Declined	2 (1.5)	2 (1.9)	0	
Recipient Age (years) – Median, (Q1-Q3)	60 (53-67)	60 (52-67)	60 (54-67)	0.24
BMI (kg m^{-2}) – Median, (Q1-Q3)	29.0 (24.9-32.3)	29.6 (24.8-32.3)	27.5 (25.4-32.5)	0.05

Hypertension – n (%)	66 (49.6)	51 (48.6)	15 (53.6)	0.10
Diabetes Miletus – n (%)	52 (39.1)	41 (39.0)	11 (39.3)	0.004
Etiology of Liver Disease – n (%)				
Hepatitis C	27 (20.3)	23 (21.9)	4 (14.3)	0.47
Hepatitis B	14 (10.5)	12 (11.4)	2 (7.1)	
Alcoholic	31 (23.3)	24 (22.9)	7 (25.0)	
MASH	32 (24.1)	25 (23.8)	7 (25.0)	
Cryptogenic	7 (5.3)	5 (4.8)	2 (7.1)	
Other	12 (9.0)	7 (6.7)	5 (17.9)	
Primary sclerosing cholangitis	10 (7.5)	9 (8.6)	1 (3.6)	
Hepatocellular Carcinoma – n (%)	69 (51.9)	61 (58.1)	8 (28.6)	**0.62**
Preoperative Spironolactone Use – n (%)	55 (41.4)	43 (41.0)	12 (42.9)	0.04
MELD-Na – Median, (Q1-Q3)	18 (12-27)	16 (12-24)	28 (18-32)	**0.95**
Preoperative Labs – Median, (Q1 – Q3)				
INR	1.5 (1.2-2.1)	1.4 (1.2-1.9)	1.7 (1.5-2.5)	0.37
Sodium (mEq L^{-1})	137 (133-139)	137 (133-139)	136 (134-138)	0.05
Total Bilirubin (mg dL^{-1})	2.5 (1.2-6.9)	2.0 (1.2-5.0)	5.0 (1.2-13.6)	**0.56**

Albumin (g dL^{-1})	2.9 (2.6-3.4)	3.0 (2.5-3.4)	2.9 (2.6-3.5)	0.13
Fibrinogen (mg dL^{-1})	252 (168-332)	259 (170-334)	214 (155-309)	0.33
Platelets (x10^9 L^{-1})	74 (51-121)	75 (54-123)	71 (46-105)	0.002
Hemoglobin (g dL^{-1})	10.1 (8.9-12.6)	11.1 (9.0-13.0)	9.2 (8.1-10.1)	**0.86**
Hematocrit (%)	31.0 (26.4-37.4)	32.8 (28.6-38.1)	27.2 (23.9-31.0)	**0.83**
ICU Prior to Surgery – n (%)	3 (2.3)	1 (1.0)	2 (7.1)	0.31

Table S2. Baseline characteristics categorized by preoperative estimated Glomerular Filtration Rate. Preserved Preoperative Renal Function defined as estimated Glomerular Filtration Rate ≥ 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. Impaired Preoperative Renal Function defined as estimated Glomerular Filtration Rate < 60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$. MASH, Metabolic dysfunction-associated steatohepatitis SMD, Standardized Mean Difference.

Supplementary Figure

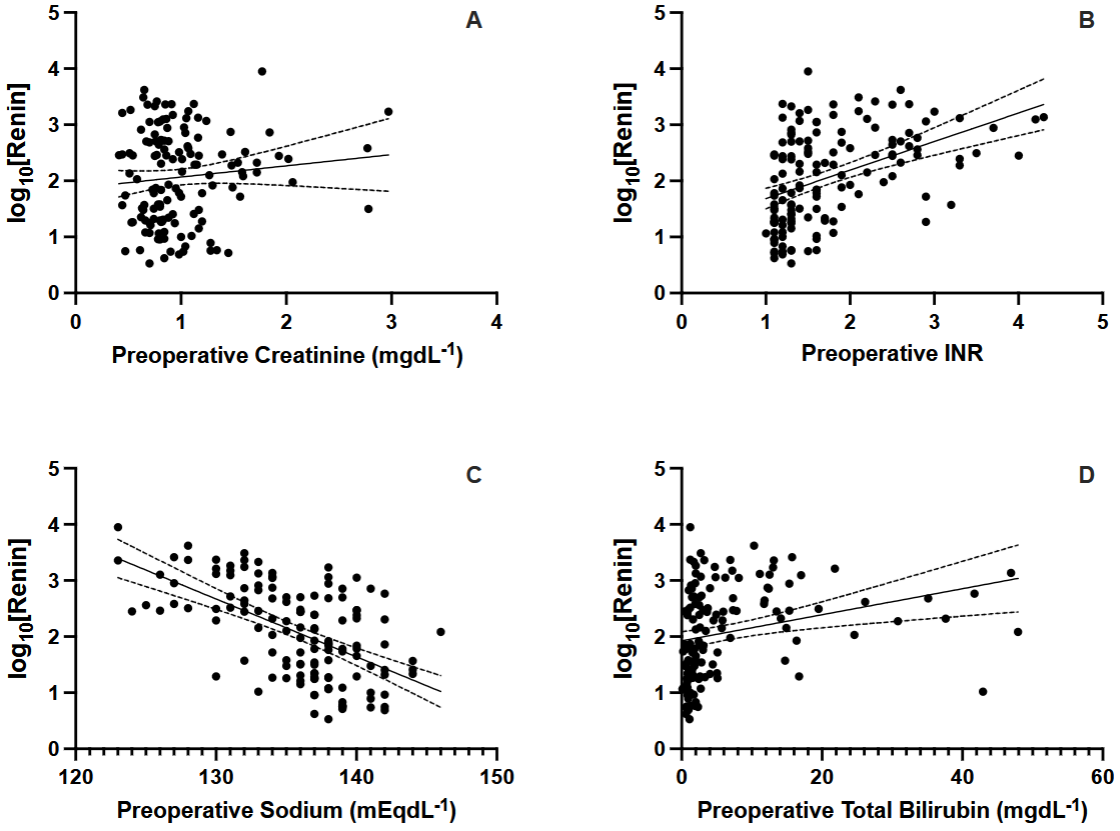


Figure S1. Unadjusted linear regression of MELD-Na components and Serum log_{10}[renin]. Solid lines represent fit. Dotted lines represent 95% CI. A. R^2 = 0.1153, p<0.2187. B. R^2 = 0.2010, p<0.001. C. R^2 = .3238, p<0.001. D. R^2 = .07288, p<0.001.