# Albuminuria Predicts Adverse Renal Outcomes and Death After Liver Transplant: A Retrospective Cohort Study

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## Background

- CKD is common in liver transplant (LT) recipients
- Almost 20% have eGFR <30 mL/min/1.73 m$^2$ at 5 years, and they are at increased risk of end stage renal disease (ESRD) and death[1]
- Albuminuria is a marker of CKD that predicts increased risk of ESRD and death in the general population, independent of the level of GFR[2]
- The prevalence of albuminuria in LT and its association with adverse long term outcomes after LT has not been studied
- Since 2011, the LT clinic at Vancouver General Hospital (VGH) has included assessment of albuminuria as part of routine care

## Objectives

- To determine the prevalence of albuminuria in LT recipients
- To determine the association between the baseline level of albuminuria and loss of kidney function and death after LT

## Methods

- Retrospective cohort study
- Study period: December 31, 2011 (date urine albumin measurement was incorporated into routine care) to December 31, 2017
- Inclusion criteria:
  - Patients who had LT at VGH between 1989-2011 and were being followed at the VGH LT Clinic
  - Age at LT ≥18 years old
  - Survived at least 3 months after LT
  - Urine albumin and serum creatinine measurement available at ≥3 months after LT
- Exclusion criteria:
  - ESRD (chronic dialysis, kidney transplant) before LT
  - AKI still on dialysis at 3 months following LT
  - ESRD developed after LT and before study start
  - No creatinine measurement available within 1 month of the first ACR measurement
- GFR estimated using CKD-EPI equation[3]; albuminuria measured using random urine albumin to creatinine ratio (ACR)
- **Primary outcome**: combined outcome of death, doubling of serum creatinine, or ESRD
- **Secondary outcome**: decline in eGFR ≥ 30% during follow-up
- GFR estimated using CKD-EPI equation; albuminuria measured using random urine albumin to creatinine ratio (ACR)
- Cox multivariable regression: Factors were included in the model based on clinical relevance (age, diabetes, time from LT) or if significant in univariate analysis with P <0.1

## Results

- There were 346 LT patients being followed as of Dec 31, 2011
- 294 (85%) were included in the analyses. The most common exclusion was due to missing baseline ACR (N = 36)
- At baseline, the median eGFR was 67 mL/min/1.73m$^2$, and N = 105 (36%) had abnormal ACR: 77 (26%) moderate (3 – 30 mg/mmol), 28 (10%) severe (>30 mg/mmol)
- N = 60 (20.4%) developed the primary outcome and N = 64 (21.8%) developed the secondary outcome during a median follow up time of 71 months

**Table 1: Baseline characteristics and univariate analyses.**

| Characteristic | Overall | Death, Doubling Serum Creatinine, ESRD | | P | Decline in eGFR by ≥30% | | P |
|---|---|---|---|---|---|---|---|
| | | Yes | No | | Yes | No | |
| N | 294 | **60 (20.4%)** | 234 (79.6%) | | **64 (21.8%)** | 230 (78.2%) | |
| Age at baseline (SD) | 57.2 (±11.1) | 60.1 (±11.1) | 56.4 (±10.9) | **0.01** | 57.7 (±10.6) | 57.0 (±11.2) | 0.5 |
| Male (n, %) | 173 (58.8%) | 37 (61.7%) | 136 (58.1%) | 0.6 | 38 (59.4%) | 135 (58.7%) | 0.9 |
| Race (n, %) | | | | | | | |
| Caucasian | 212 (72.1%) | 45 (75%) | 167 (71.3%) | 0.7 | 49 (76.6%) | 163 (70.9%) | 0.6 |
| Asian | 38 (12.9%) | 6 (10%) | 32 (13.7%) | | 6 (9.4%) | 32 (13.9%) | |
| Other | 44 (15%) | 9 (15%) | 35 (15%) | | 9 (14%) | 35 (15.2%) | |
| Primary cause of liver disease (n, %) | | | | | | | |
| Alcohol | 17 (5.8%) | 5 (8.3%) | 12 (5.1%) | 0.5 | 4 (6.3%) | 13 (5.7%) | 0.9 |
| Autoimmune | 30 (10.2%) | 2 (3.4%) | 28 (12%) | | 7 (10.9%) | 23 (10%) | |
| Hepatitis B | 28 (9.5%) | 5 (8.3%) | 23 (9.8%) | | 7 (10.9%) | 21 (9.1%) | |
| Hepatitis C | 114 (38.8%) | 26 (43.3%) | 88 (37.6%) | | 25 (39.1%) | 89 (38.7%) | |
| Primary biliary cirrhosis | 27 (9.2%) | 5 (8.3%) | 22 (9.4%) | | 4 (6.3%) | 23 (10%) | |
| Primary sclerosing cholangitis | 25 (8.5%) | 5 (8.3%) | 20 (8.6%) | | 7 (10.9%) | 18 (7.8%) | |
| Other | 53 (18%) | 12 (20%) | 41 (17.5%) | | 10 (15.6%) | 43 (18.7%) | |
| Number of LT (n, %) | | | | | | | |
| 1 | 271 (92.2%) | 55 (91.7%) | 216 (92.3%) | 0.5 | 60 (93.8%) | 211 (91.7%) | 0.6 |
| 2 | 17 (5.8%) | 2 (3.3%) | 15 (6.4%) | | 3 (4.7%) | 14 (6.1%) | |
| 3 | 2 (0.7%) | 0 (0%) | 2 (0.9%) | | 1 (1.5%) | 1 (0.4%) | |
| Unknown | 4 (1.3%) | 3 (5%) | 1 (0.4%) | | 0 (0%) | 4 (1.7%) | |
| Post-transplant CMV | 31 (10.5%) | 7 (11.7%) | 24 (10.3%) | 0.8 | 7 (10.9%) | 24 (10.4%) | 0.9 |
| Acute rejection | 135 (45.9%) | 27 (45%) | 108 (46.2%) | 0.9 | 23 (35.9%) | 112 (48.7%) | **0.07** |
| Comorbidities: | | | | | | | |
| Hypertension | 116 (39.5%) | 22 (36.7%) | 94 (40.2%) | 0.6 | 31 (48.4%) | 85 (37%) | 0.1 |
| Diabetes | 81 (27.6%) | 22 (36.7%) | 59 (25.2%) | 0.08 | 28 (43.8%) | 53 (23%) | **0.001** |
| Cardiovascular disease | 32 (10.9%) | 9 (15%) | 23 (9.8%) | 0.3 | 12 (18.8%) | 20 (8.7%) | **0.02** |
| Smoking | 72 (24.5%) | 19 (31.7%) | 53 (22.7%) | 0.1 | 18 (28.1%) | 54 (23.5%) | 0.4 |
| Medications: | | | | | | | |
| Statin | 28 (9.5%) | 7 (11.7%) | 21 (9%) | 0.5 | 10 (15.6%) | 18 (7.8%) | **0.06** |
| Calcineurin inhibitor (CNI) | 254 (86.4%) | 44 (73.3%) | 210 (89.7%) | **<0.001** | 54 (84.4%) | 200 (87%) | 0.6 |
| ACEi/ARB | 59 (20.1%) | 11 (18.3%) | 48 (20.5%) | 0.7 | 16 (25%) | 43 (18.7%) | 0.3 |
| Median time from LT to baseline (months) [IQR] | 66.5 [22.9 - 124.3] | 70.6 [39.9 – 132.8] | 64.5 [22.9 – 122.4] | 0.4 | 61.7 [21.2 – 144.8] | 70.4 [23.2 – 122.4] | 0.8 |
| Median ACR at baseline (mg/mmol) [IQR] | 1.6 [1 - 4.9] | 3.6 [1.1 – 32.4] | 1.4 [1.0 – 3.7] | **<0.001** | 4 [1.2 – 42] | 1.4 [1.0 – 3.4] | **<0.001** |
| Mean eGFR at baseline (SD) (mL/minute/1.73 m$^2$) | 67 (±20.9) | 61.1 (±20.9) | 68.5 (±20.7) | **0.03** | 66.8 (±24.6) | 67.1 (±19.8) | 1.0 |

## Conclusion

- A high degree of albuminuria (ACR >30 mg/mmol) is associated with increased risk of loss of renal function and death after LT
- Prospective studies are needed to confirm this association, and to determine if specific interventions directing at reducing albuminuria can improve long-term outcomes in LT

## References

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3. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J (2009). A new equation to estimate glomerular filtration rate. *Ann Intern Med.* 150(9):604-12.

## Results

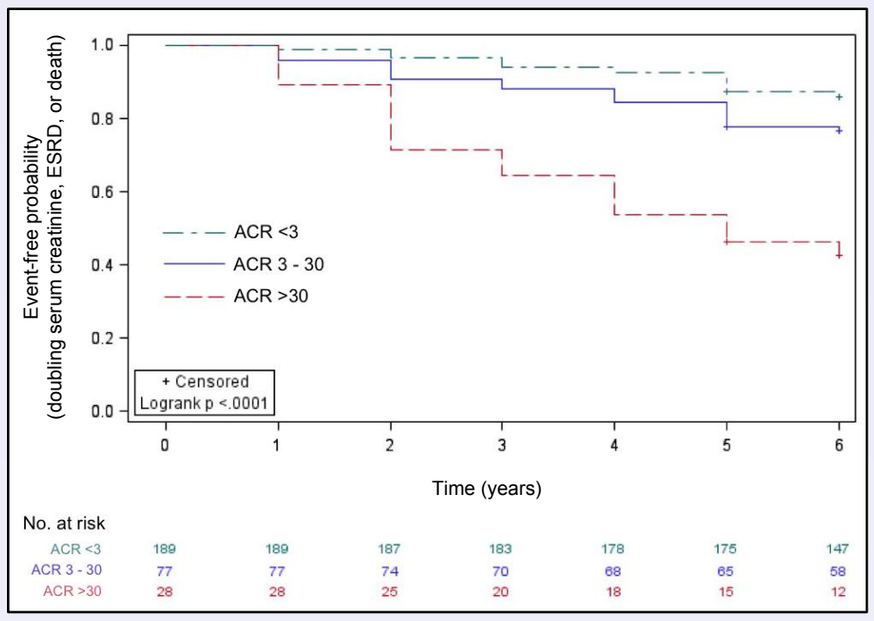


**Figure 1: Kaplan-Meier curves for the primary outcome of death, doubling of serum creatinine or ESRD.**
Abnormal ACR is associated with increased risk (P <0.0001).

**Table 2: Cox proportional hazard model for primary outcome of death, doubling of serum creatinine or ESRD.**

| Characteristic | Hazard Ratio | 95% CI | | P value |
|---|---|---|---|---|
| ACR < 3 | 1.00 | -- | -- | ref |
| ACR 3 - 30 | 1.41 | 0.76 | 2.62 | 0.28 |
| ACR > 30 | **4.27** | **2.17** | **8.39** | **<0.0001** |
| eGFR at Baseline | 0.99 | 0.98 | 1.01 | 0.24 |
| Age at Baseline | 1.02 | 0.99 | 1.05 | 0.08 |
| Diabetes | 1.49 | 0.85 | 2.60 | 0.16 |
| Liver Vintage* | 0.99 | 0.94 | 1.05 | 0.79 |
| CNI | **0.52** | **0.28** | **0.97** | **0.04** |

*Liver vintage defined as time from liver transplant to date of first ACR measurement.

Severe albuminuria (ACR > 30 mg/mmol) at baseline is independently associated with increased risk of doubling serum creatinine, ESRD, or death. CNI use was associated with a lower risk.

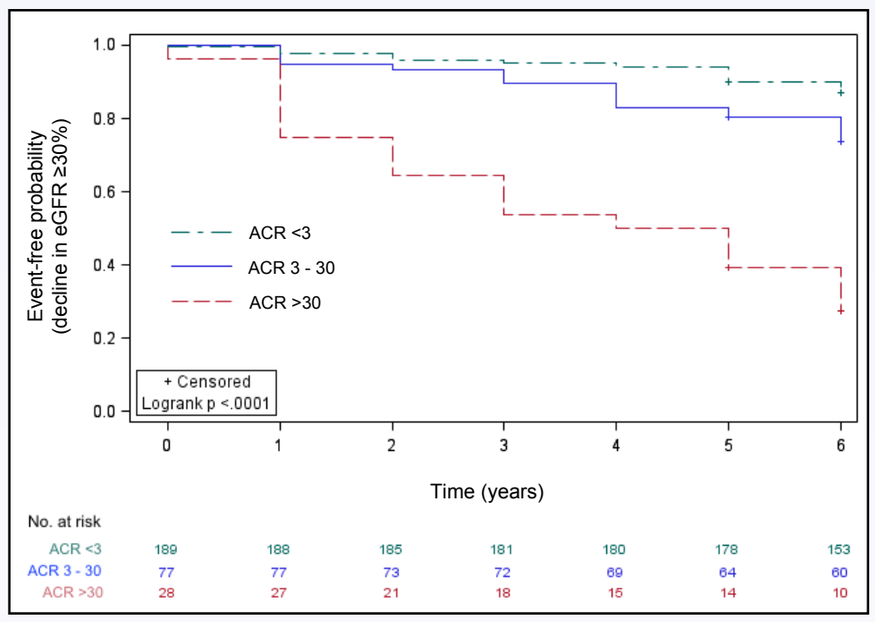


**Figure 2: Kaplan-Meier curves for the secondary outcome of decline in eGFR by ≥ 30%.**
Abnormal ACR is associated with increased risk (P <0.0001).

**Table 3: Cox proportional hazard model for secondary outcome of decline in eGFR by ≥ 30%.**

| | Hazard Ratio | 95% CI | | P value |
|---|---|---|---|---|
| ACR < 3 | 1.00 | -- | -- | ref |
| ACR 3 - 30 | **2.16** | **1.18** | **3.96** | **0.01** |
| ACR > 30 | **7.77** | **4.14** | **14.57** | **<0.0001** |
| eGFR at Baseline | 1.01 | 1.00 | 1.02 | 0.45 |
| Liver Vintage* | 0.98 | 0.94 | 1.03 | 0.53 |
| Diabetes | **1.80** | **1.08** | **3.02** | **0.02** |
| Cardiovascular disease | **2.11** | **1.10** | **4.05** | **0.02** |
| Acute Rejection | 0.71 | 0.41 | 1.21 | 0.20 |

Abnormal ACR shows a graded independent association with decline in eGFR ≥ 30% during follow up. Cardiovascular disease is also associated with a significantly higher risk. Although statin use was associated with the outcome in univariate analysis with P<0.1, it was not included in this analysis due to its strong correlation with a history of cardiovascular disease.