Hepatic Cholate Clearance as Assessed by HepQuant-SHUNT Is Predictive of Clinical Outcomes in Individuals with Fontan Circulation

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Introduction

- Fontan-associated liver disease (FALD) is universal in individuals with Fontan circulation (FC).
- The dual cholate clearance test is a noninvasive, flow-dependent measure of liver function. With progressive liver disease, there is relative reduction of portal clearance compared to systemic clearance of cholate.
- Cholate clearance is predictive of clinical outcomes in non-Fontan liver disease.

Objectives

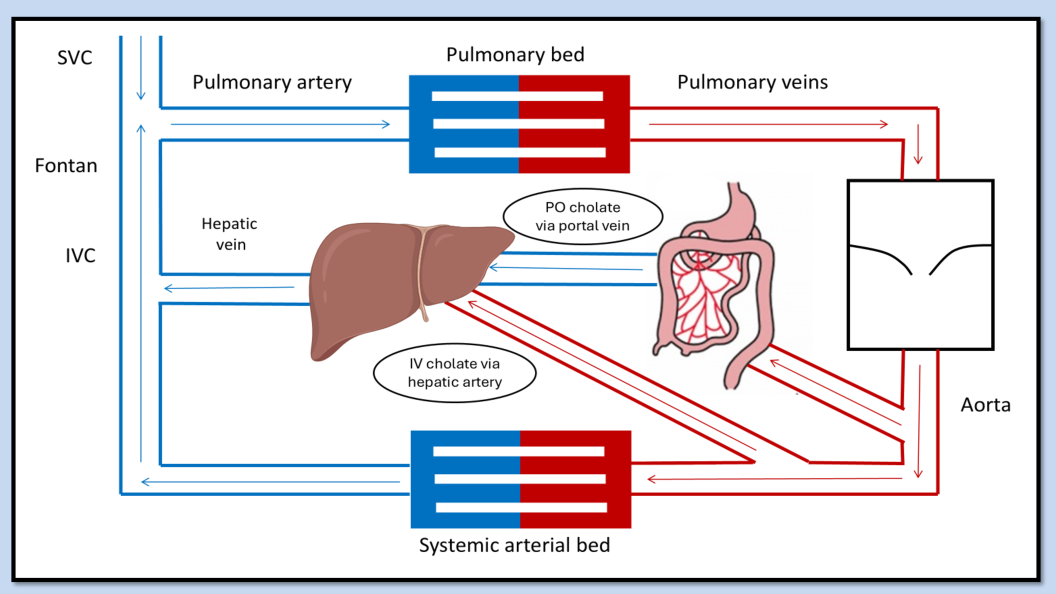
- To explore the association between cholate clearance and clinical outcomes in individuals with FC.

Methods

- Two-center cohort of 50 adults with FC from University of Pennsylvania (PENN) and Northwestern University (NU) who underwent HepQuant-SHUNT test between 2015-2022 and followed until 2025.
- Primary outcome was transplant-free survival. Secondary outcome was composite of death, transplant, new onset heart failure, ascites, protein losing enteropathy, or hepatocellular carcinoma.

Dual Cholate SHUNT test

- Participants were administered radiolabeled cholate intravenously (13C-cholate) and orally (d4-cholate). Blood was drawn at baseline and serially up to 90 minutes. Samples were analyzed by liquid chromatography-tandem mass spectrometry.



- Systemic and portal HFR were quantified from area under the concentration versus time curves. SHUNT% = systemic HFR/portal HFR with abnormal SHUNT% defined as >30%.

Statistical Methods

- Kaplan-Meier curves and log-rank test or Cox regression was performed to assess association between SHUNT% and primary outcome.
- Logistic regression was performed to assess association between SHUNT% and secondary outcome.

Results

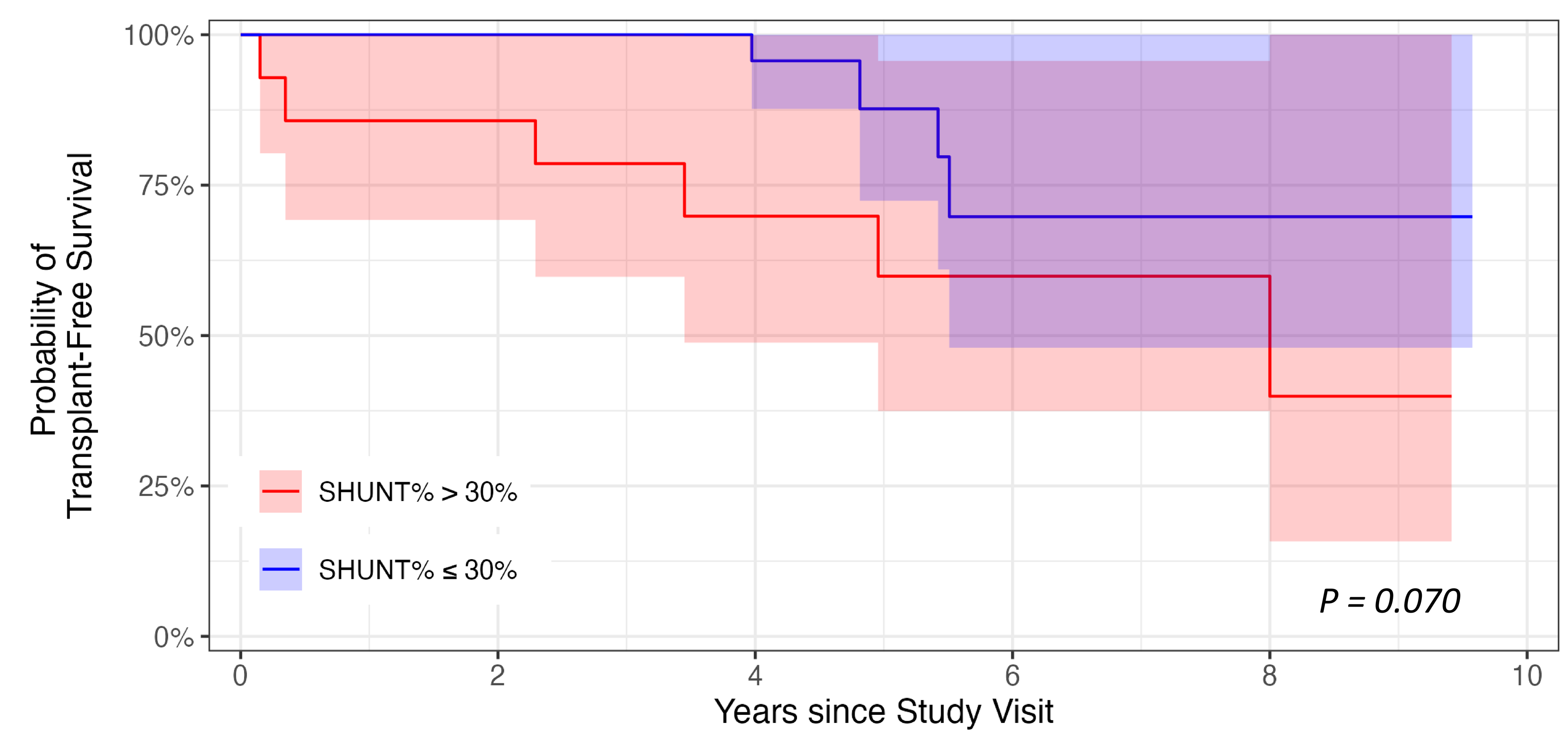
Table 1. Participant characteristics, cholate clearance, and outcomes.

	Penn N=35	NU N=15	p-value
Age (yr)	30 (25, 37)	36 (30, 41)	0.075
Female	19 (54)	7 (47)	0.621
White	32 (91)	11 (85)	0.602
Age at Fontan (mo)	31 (22, 57)	57 (38, 124)	**0.026**
Fontan type			**0.002**
TCPC	28 (80)	3 (23)	
RA-PA	5 (14)	7 (54)	
Other	2 (6)	3 (23)	
Laboratory			
Creatinine	0.8 (0.7, 1.0)	0.8 (0.7, 1.1)	0.615
AST	26 (21, 38)	25 (19, 28)	0.171
ALT	25 (21, 37)	25 (16, 28)	0.290
Total bilirubin	1.0 (0.6, 1.3)	1.1 (0.6, 1.5)	0.717
Alk phosphatase	76 (66, 97)	78 (68, 100)	>0.999
Albumin	4.7 (4.2, 4.8)	4.5 (4.3, 4.7)	0.248
Platelet (10^3/µL)	175 (144, 205)	112 (96, 141)	**<0.001**
Alpha fetoprotein	2.2 (1.8, 3.8)	4.4 (2.8, 5.4)	**0.017**
Cholate Clearance			
Portal HFR	15 (12, 17)	14 (13, 16)	0.874
Systemic HFR	3.6 (2.8, 4.0)	4.6 (3.6, 5.5)	**0.002**
SHUNT% (%)	24 (19, 29)	27 (25, 37)	**0.048**
Outcomes			
Death	2 (5.7)	4 (29)	**0.048**
Transplant	3 (8.6)	3 (23)	0.323
Composite outcome	6 (17)	8 (62)	**0.005**
Time to outcome or last follow-up (yr)	4.0 (3.4, 4.8)	7.1 (5.0, 8.9)	**0.006**

Values expressed as count (%) or median (IQR).
TCPC, total cavopulmonary anastomosis; RA-PA, right atrium to pulmonary artery; HFR, hepatic filtration rate (ml/min/kg).

- No significant differences in prevalence of baseline cardiac (e.g. heart failure, arrhythmia, pacemaker, cyanosis, etc.) or hepatic (e.g. ascites, varices) comorbidities were observed.
- Unadjusted 1-, 3-, and 5-year transplant-free survival was 96%, 94%, and 79%, respectively.

Figure 1. Transplant-free survival stratified by SHUNT%. There is a trend towards lower survival in those with elevated SHUNT% (>30%) over the entire study period (p=0.70). At 5 years, those with elevated SHUNT% had lower transplant-free survival (60% vs 88%; p = 0.016).



	0	2	4	6	8	10
SHUNT% > 30%						
At risk	14	12	8	3	3	0
Events	0	2	4	5	6	6
SHUNT% ≤ 30%						
At risk	34	32	20	4	3	0
Events	0	0	1	4	4	4

- For every 10% incremental increase in SHUNT%, hazard for death/transplant increased by 60% (95% CI 1.14 – 2.27; p=0.006) when adjusted for institution.
- The composite outcome was reached in 14/50 (29%), including death (n=4), combined heart-liver transplant (n=4), or both (n=2).
- Elevated SHUNT% was associated with 3.9-fold increase odds of composite outcome (95% CI 1.02 – 15.3; p=0.048).

Conclusions

- SHUNT%, a measure of porto-systemic spillover of cholate in the liver, is associated with transplant-free survival in individuals with FC.
- Elevated SHUNT% >30% has excellent discrimination in identifying those at risk for mid-term adverse clinical events.
- **If validated, this would be the first measure of liver function in FALD prognostic of survival in FC.**