Data Creation Plan for Secondary Analyses

Name and Number of Study	**Factors associated with initiation of renal replacement therapy in adult critically ill patients with cirrhosis/chronic liver disease (ACLF)**
Principal Investigator(s)	1. Constantine Karvellas, Ron Wald, Sean Bagshaw 2. Co-investigators: Oleksa Rewa, and Fernando Zampieri
DCP Update History	Version 1 (January 15th, 2024)
Short Description of Research Question	Currently there is equipoise regarding the optimal timing of RRT in critically ill patients with cirrhosis or chronic liver disease (CLD) (i.e., acute-on-chronic liver failure ~ ACLF). The STARRT-AKI trial found no difference in 90-day mortality with an accelerated strategy to commencing RRT in critically ill patients with severe AKI compared with a more conservative standard strategy. Of note, approximately 337 patients in this analysis between the two arms were identified as having chronic liver disease/ACLF. ACLF patients differ from general critical care patients given the proportion of patients with hepatorenal syndrome (HRS-AKI), where a significant confounder is the potential for liver transplantation not only as treatment to reverse HRS-AKI and improved long-term survival. The aim of this secondary post-hoc analysis of the STARRT-AKI trial is focused on two objectives: a) Using the STARRT-AKI mITT cohort, compare patients with and without chronic liver disease and describe differences in patient characteristics, clinical course, and outcome. b) Using the 'chronic liver disease' cohort (n=337) within the STARRT-AKI mITT cohort, describe patient characteristics, clinical course and outcomes stratified by treatment allocation.
List of Datasets Used	Data obtained during the STARRT-AKI study
Time of Data Extraction	Estimate March 1, 2024

Defining the Cohort	
Cohort	Analysis 1: Full mITT STARRT-AKI cohort stratified by presence of chronic liver disease. Analysis 2: Subgroup of mITT STARRT-AKI cohort focused on patients with chronic liver disease (CLD) ONLY.
Exclusion Criteria	Patients with missing data on the status of chronic liver disease.
Size of Cohort	Analysis 1: Full mITT cohort (n=2927) Analysis 2: Subgroup of full mITT cohort focused on patients with chronic liver disease (n=337)

Time Frame Definitions	
Accrual Start/End Dates	From randomization to trial treatment
Max Follow-up Date	To 90-day follow-up after randomization

Variable Definitions	
Main Exposure or Risk Factor	Analysis 1: Presence of chronic liver disease Analysis 2: Allocation to accelerated or standard initiation of RRT
Baseline Characteristics (Table 1 data)	Same as in STARRT-AKI main analysis; however, Analysis 1 will be stratified by the presence or absence of chronic liver disease (CLD).
Covariates **(To Inform Model Development)**	Same as in STARRT-AKI main analysis. Chronic liver disease (CLD) status will also be evaluated.
Outcome(s) Definitions	Analysis 1: Same as in STARRT-AKI main analysis, with a focus on 90-day all-cause mortality, RRT dependence at 90-day, a composite of 90-day all-cause mortality and RRT dependence; RRT-free days at 90-days; vasoactive and mechanical ventilation-free days at day 28; ICU-free days at day 28; and hospital-free days at day 90.

Outline of Analysis Plan	
Primary Outcome Variables	Analysis 1 (full mITT cohort): Composite of mortality and RRT at 90 days. Analysis 2 (CLD cohort only): Composite of Mortality and RRT at 90 days.
Secondary Outcome Variables	Subgroup analysis will further explore the interaction of CLD and circuit anticoagulation use (citrate, heparin, nothing) with the following outcomes: bleeding (adverse event); hypotension (RRT associated; adverse event); arrhythmia (RRT associated; adverse event).
Detailed Analysis Plan	***1)*** Analysis 1: Comparative analysis of process of care, outcomes, and adverse events as in the primary STARRT-AKI study ***stratified by CLD (Yes/No)*** 2) Analysis 2 (CLD patients only) • Evaluate the clinical, physiologic or laboratory factors associated with initiation of RRT among patients allocated to the standard arm using multivariate logistic regression. • Evaluate treatment allocation within specified subgroups/sensitivity analyses and evaluate associated with outcome (i.e. death at 90 days) including: enrollment within a transplant center (yes/no); transplant candidacy (if available) age; sex; frailty; severity of illness (can convert SOFA to CLIF-SOFA or CLIF_C ACLF in CLD subgroup analyses).
Proposed Tables and Figures	Same as in STARRT-AKI main analysis; however, stratified by sepsis and by septic shock.

Mock Tables and Figures (legends):

Table 1: Baseline Characteristics stratified according to presence/absence of Chronic liver disease

Table 2: Clinical Outcomes According to presence and absence of CLD.

Table 3: Baseline Characteristics of n=337 CLD patients stratified according to allocation group

Table 4: Clinical Outcomes of n=337 CLD patients stratified according to allocation group.

Figure Legend (POSSIBLE FIGURES):

Figure 1. *Flow diagram.*

Figure 2. *Survival stratified by Chronic liver disease status and allocated RRT initiation strategy.*

Figure 3. *Forest plot of outcomes by chronic liver disease status and allocated RRT initiation strategy.*

Figure 4. *Summary of RRT-free, vasoactive-free, ventilator-free and ICU-free days by chronic liver disease status*

Table 1: Baseline Characteristics stratified according to presence/absence of Chronic liver disease	Total (N = 2927)	CLD (N = 337/2927)	Absence of CLD (N = 2590/2927)	p value[1]
Age – yr				
Female sex – no. (%)				
Weight – Kg				
Serum creatinine – mg/dl				
Estimated glomerular filtration rate – ml/min/1.73 m^2				
Preexisting conditions – no. (%)				
Chronic kidney disease				
Hypertension				
Diabetes mellitus				
Heart failure				
Coronary artery disease				
Liver disease		**100%**	**0%**	
Metastatic cancer				
Hematologic cancer				
HIV infection or AIDS				
Admission category – no. (%)				
Scheduled surgery				
Unscheduled surgery				
(assuming most this) Medical				
Hospital acquired risk factor for acute kidney injury in previous week – no. (%)				
Cardiopulmonary bypass				
Aortic aneurysm repair				
Vascular surgery				
Major trauma				
Intravenous contrast material				
Aminoglycoside use				
Amphotericin use				
INFECTION/SEPSIS?				
Bacteremia				
Pneumonia				
UTI				
Clinical condition at baseline				
(we can convert this after to CLIF-C ACLF) SOFA score				
SAPS II value				
Mechanical ventilation				
Vasoactive support				
Serum creatinine – mg/dl				
Oliguria or anuria – no. (%)				
Median urinary output (IQR) ml/24hr				
Serum potassium				
Serum bicarbonate				
Median cumulative fluid balance (IQR(ml)				

TABLE 2 Clinical Outcomes According to presence and absence of CLD	Overall sample (N=2927)	CLD (N = 337/2927)	Absence of CLD (N = 2590/2927)	p value[1]
Primary outcome				
Death from any cause at 90 days no (%)				
Secondary outcomes				
RRT dependence among survivors at 90 days				
Death or RRT dependence at 90 days				
Major adverse kidney events at 90 days				
Serum Cr at 90 days				
Estimated GFR				
At 90 days				
Reduction of > 25% from baseline at 90 days				
Death from any cause (no/total no %				
Any time in ICU				
At 28 days				
During hospitalization				
Health services				
Median number of days use (IQR)				
RRT-free days at 90 days				
RRT				
CRRT				
SLED				
IHD				
Median Length of ICU Stay (IQR) days				
Survivors				
Non-survivors				
Median Length of Hospital Stay (IQR) days				
Survivors				
Non-survivors				
Median no. of ventilator-free days at 28 days (IQR)				
Median no. of free of vasoactive agents at 28 days (IQR)				
Median no. of days out of ICU at 28 days (IQR)				
Median no. of days out of hospital at 90 days (IQR)				
Rehospitalization at 90 days (IQR)				
HRQL				
Median score on EQ-5D-5L at 90 days (IQR)				
Descriptive system				
Mobility				
Self care				
Usual activities				
Pain or discomfort				
Anxiety or depression				

Table 3: Baseline Characteristics of n=337 CLD patients stratified according to allocation group	Overall sample (N = 337/2927)	Accelerated RRT (N = 172/1465)	Standard arm (N = 165/1462)	p value[1]
Age – yr				
Female sex – no. (%)				
Weight – Kg				
Serum creatinine – mg/dl				
Estimated glomerular filtration rate – ml/min/1.73 m^2				
Preexisting conditions – no. (%)				
Chronic kidney disease				
Hypertension				
Diabetes mellitus				
Heart failure				
Coronary artery disease				
Liver disease		**100%**	**100%**	
Metastatic cancer				
Hematologic cancer				
HIV infection or AIDS				
Admission category – no. (%)				
Scheduled surgery				
Unscheduled surgery				
(assuming most this) Medical				
Hospital acquired risk factor for acute kidney injury in previous week – no. (%)				
Cardiopulmonary bypass				
Aortic aneurysm repair				
Vascular surgery				
Major trauma				
Intravenous contrast material				
Aminoglycoside use				
Amphotericin use				
(not sure if you had this and it what detail) INFECTION/SEPSIS?				
Bacteremia				
Pneumonia				
UTI				
Clinical condition at baseline				
(we can convert this after to CLIF-C ACLF) SOFA score				
SAPS II value				
Mechanical ventilation				
Vasoactive support				
Serum creatinine – mg/dl				
Oliguria or anuria – no. (%)				
Median urinary output (IQR) ml/24hr				
Serum potassium				
Serum bicarbonate				
Median cumulative fluid balance (IQR(ml)				

TABLE 4 Clinical Outcomes of n=337 CLD patients stratified according to allocation group.	Overall sample (N = 337/2927)	Accelerated RRT (N = 172/1465)	Standard arm (N = 165/1462)	p value[1]
Primary outcome				
Death from any cause at 90 days no (%)				
Secondary outcomes				
RRT dependence among survivors at 90 days				
Death or RRT dependence at 90 days				
Major adverse kidney events at 90 days				
Serum Cr at 90 days				
Estimated GFR				
At 90 days				
Reduction of > 25% from baseline at 90 days				
Death from any cause (no/total no %				
Any time in ICU				
At 28 days				
During hospitalization				
Health services				
Median number of days use (IQR)				
RRT-free days at 90 days				
RRT				
CRRT				
SLED				
IHD				
Median Length of ICU Stay (IQR) days				
Survivors				
Non-survivors				
Median Length of Hospital Stay (IQR) days				
Survivors				
Non-survivors				
Median no. of ventilator-free days at 28 days (IQR)				
Median no. of free of vasoactive agents at 28 days (IQR)				
Median no. of days out of ICU at 28 days (IQR)				
Median no. of days out of hospital at 90 days (IQR)				
Rehospitalization at 90 days (IQR)				
HRQL				
Median score on EQ-5D-5L at 90 days (IQR)				
Descriptive system				
Mobility				
Self care				
Usual activities				
Pain or discomfort				
Anxiety or depression				