ADQI 29 Figures: Acute Kidney Injury in Patients with Cirrhosis: Acute Disease Quality Initiative (ADQI) and International Club of Ascites (ICA) Joint Multidisciplinary Consensus Meeting

Fig. 1. Definitions of AKI, AKD and CKD

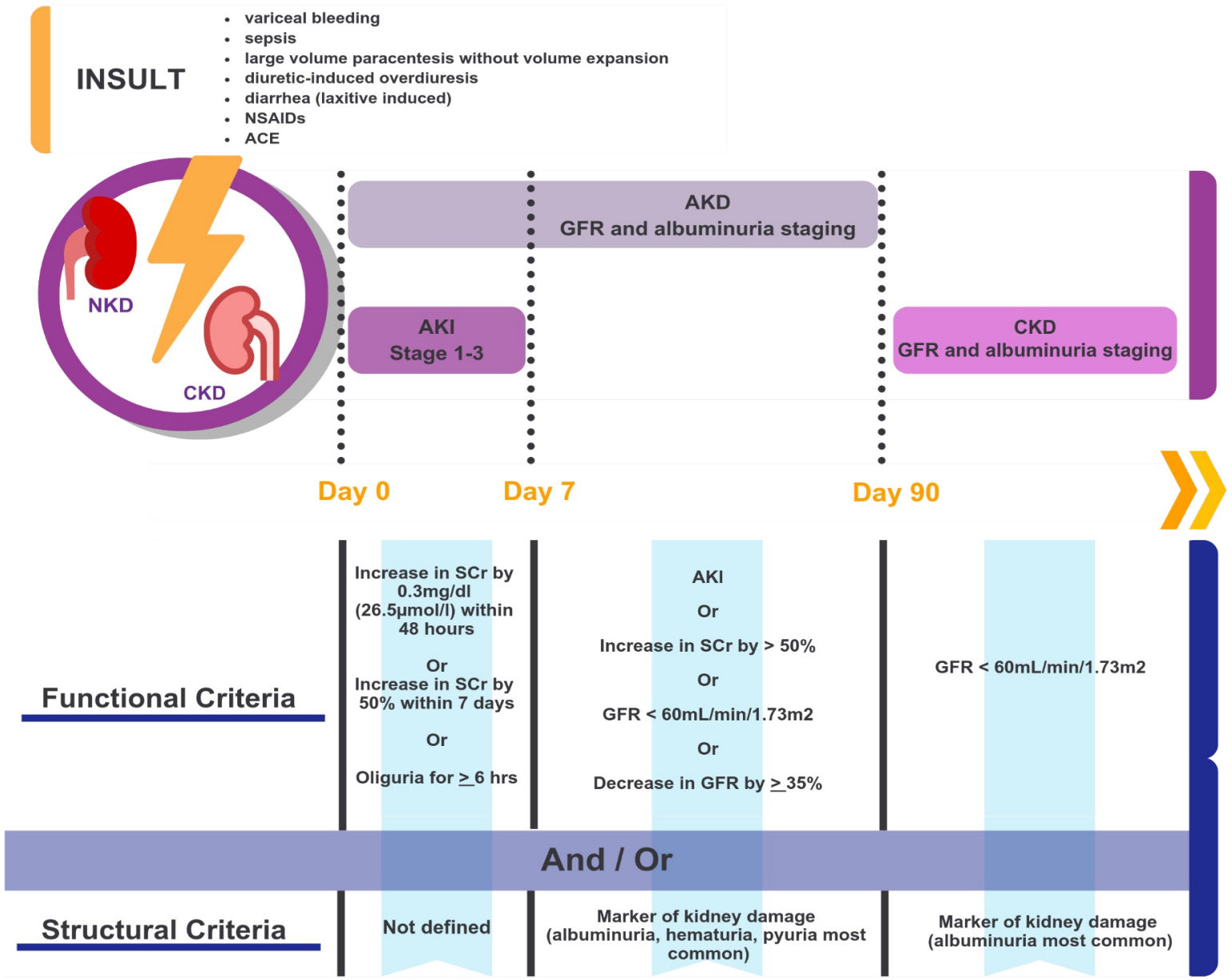

Figure 2. General prognosis of patients developing AKI and AKD in cirrhosis.

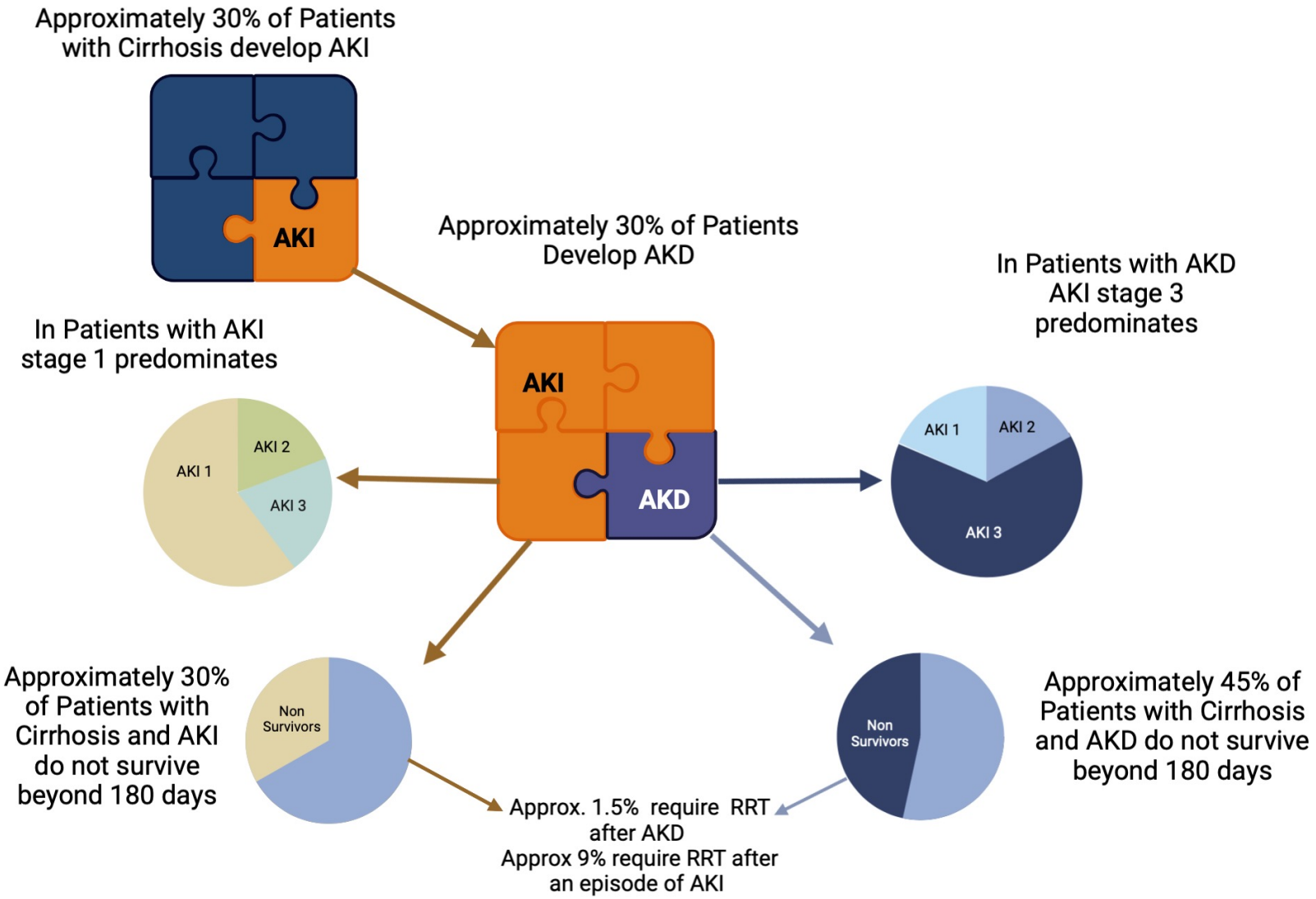

Fig. 3. Clinical course and outcomes of acute kidney injury (AKI) in patients with cirrhosis. AKI, AKD and CKD form a continuum whereby initial kidney injury can lead to recovery (adaptive repair), persistent renal injury, and/or eventually CKD (maladaptive repair). Multiple episodes of AKI may occur over the course of an illness within one individual. After AKI resolves, patients may still have abnormalities in kidney function and/or structure that fulfill the criteria for AKD. AKI is a subset of AKD, therefore, all patients with AKI are considered to have AKD. The absence of criteria for AKI, AKD or CKD represents no kidney disease (NKD). Liver or liver-kidney transplantation in select patients may occur at any time. Patients who meet HRS criteria are considered to have HRS-AKI, HRS-AKD or HRS-CKD based on timing and duration of kidney dysfunction. Patients with HRS-AKD meeting AKI criteria are classified as HRS-AKI. Patients with HRS for less than 90 days would be considered to have HRS-AKD, and HRS-CKD after 90 days. In contrast, a patient with pre-existing CKD (e.g., diabetic nephropathy) who develops HRS-AKI, would be considered to have HRS-AKI on CKD.

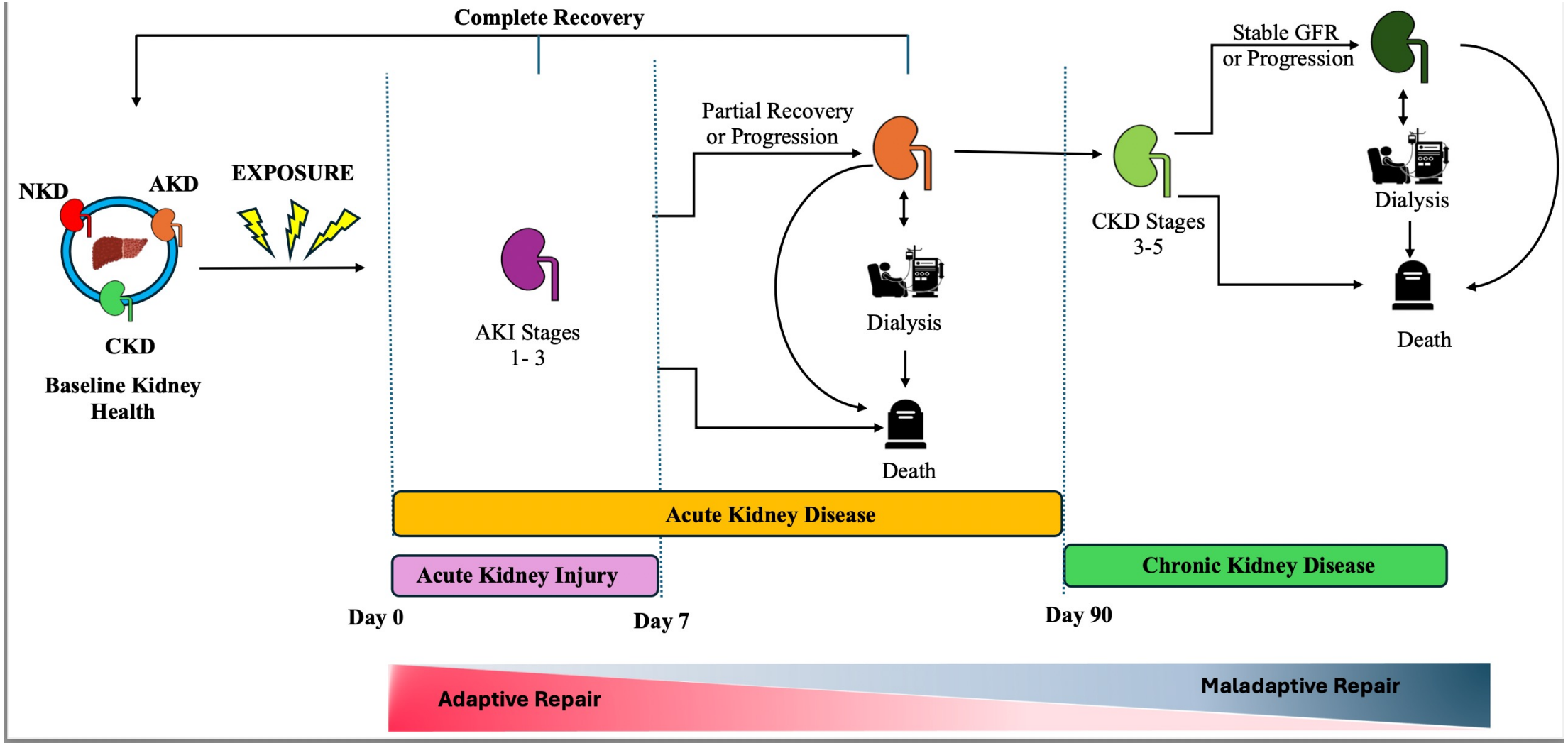

Fig. 4. Contemporary Concepts in the Pathophysiology of AKI in Cirrhosis. Multiple simultaneous mechanisms can contribute to acute kidney injury in cirrhosis. AKI in cirrhosis requires the presence of portal hypertension which leads to gut bacterial translocation resulting in systemic inflammation, splanchnic arterial vasodilation, hyperactivation of endogenous vasoconstrictor systems, and cardiac dysfunction. Additional processes, such as bile acid induced tubular injury, might also contribute to AKI in cirrhosis. Ultimately a reduction of effect circulating volume results in reduction of renal blood flow. Under normal conditions, renal autoregulation allows kidney perfusion (applicable to GFR/renal blood flow) to be maintained unchanged within a MAP range between approximately 65 – 150 mmHg. However, in HRS-AKI, the horizontal plateau phase of the curve is shortened or lost, and the range of autoregulation is approximately 90 to 120 mmHg. Further worsening liver disease results in sustained increases of systemic arterial vasodilation and maximal activation of compensatory neurohumoral systems. Collectively, these cause refractory ascites and severe renal vasoconstriction leading to renal hypoperfusion which is the hallmark of HRS physiology. Background susceptibility to renal injury varies across individuals, according to non-modifiable (e.g., comorbidity burden) and modifiable factors (e.g., sepsis) and includes liver-related (e.g., severity of liver disease, decompensating events), kidney-related (e.g., CKD, eGFR), cardiovascular (e.g., cirrhotic cardiomyopathy), comorbidities (e.g., hypertension, diabetes), and external factors (e.g., nephrotoxic drugs, sepsis, excessive diuretics or laxatives).

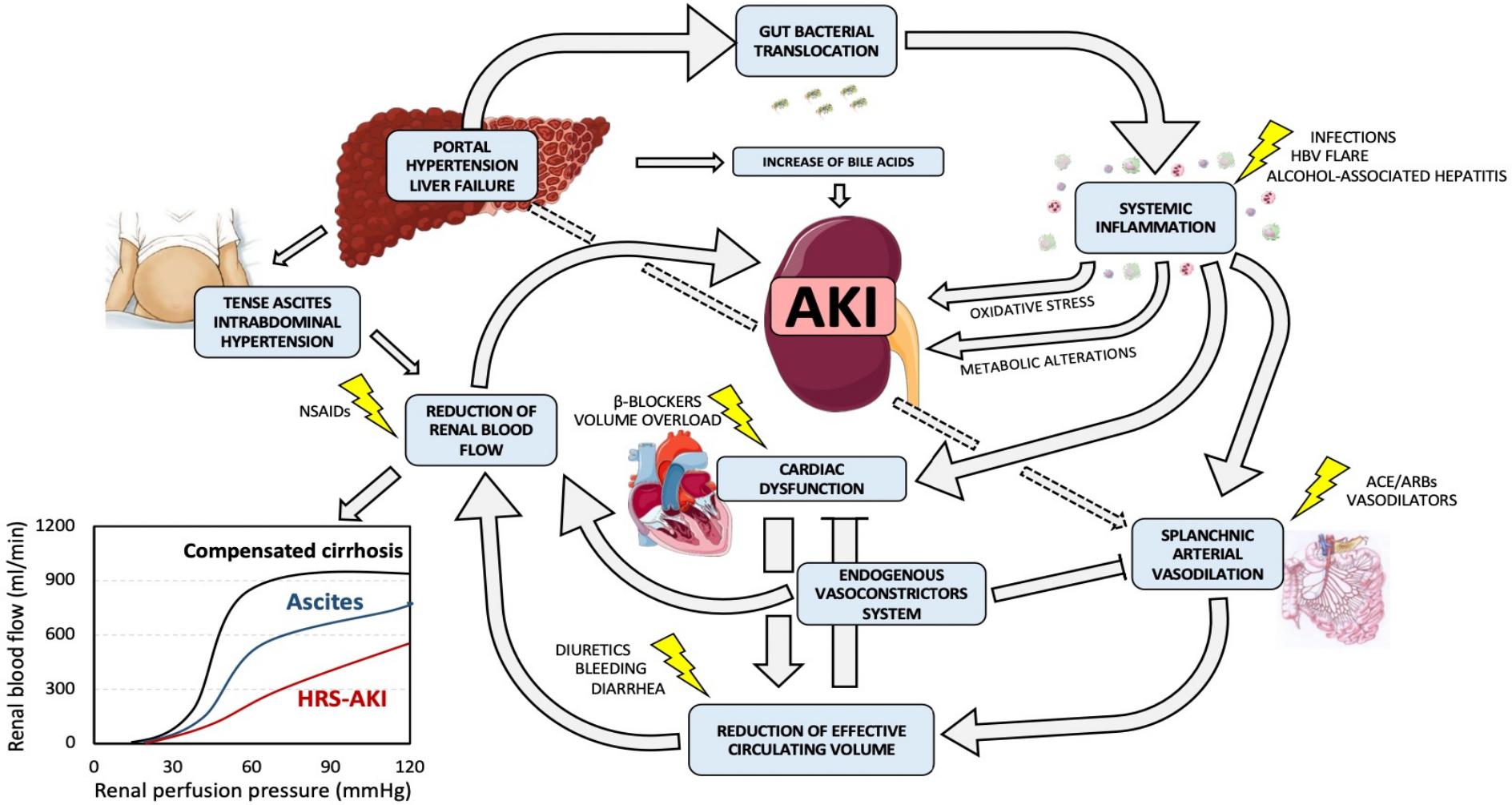

Fig 5. Relative Contribution of Mechanisms of AKI in Different Stages of Cirrhosis.

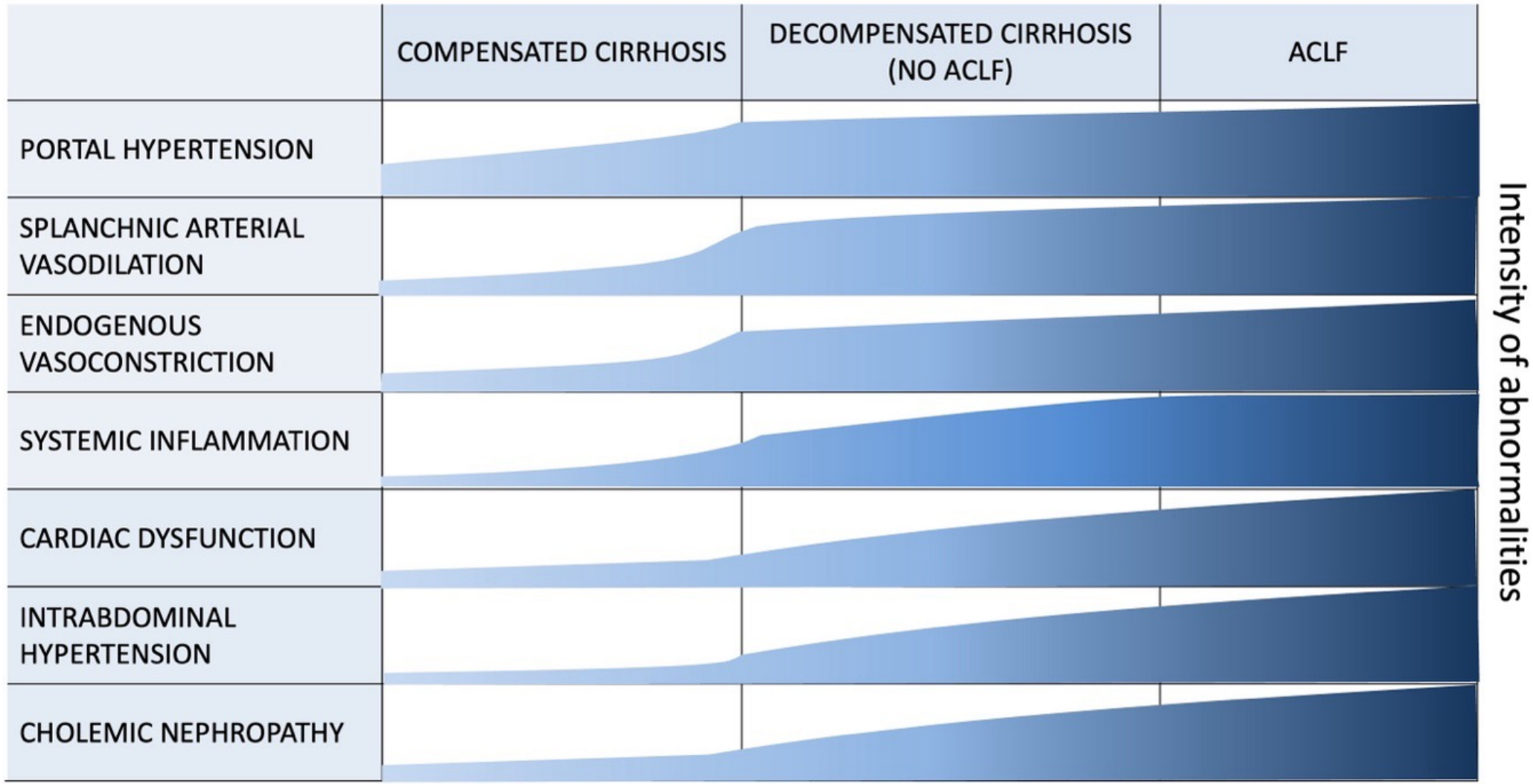

Fig. 6. Contemporary concepts in the pathophysiology of AKI. Multiple simultaneous mechanisms can contribute to the development of different phenotypes of AKI in patients with cirrhosis. Background susceptibility to renal injury varies across individuals, according to non-modifiable (e.g., comorbidity burden) and modifiable factors (e.g., sepsis) and includes liver-related (e.g., severity of liver disease, decompensating events), kidney-related (e.g., CKD, eGFR), cardiovascular (e.g., cirrhotic cardiomyopathy), comorbidities (e.g., hypertension, diabetes), and external factors (e.g., nephrotoxic drugs, sepsis, excessive diuretics or laxatives). The clinical condition of the liver, kidney, and heart, in addition to concomitant precipitating events and exposures (yellow arrows) may lead to a variety of clinical AKI phenotypes. The different phenotypes of AKI include presence of functional changes (ie. increase serum creatinine and / or cystatin C, and decrease urine output), structural damage (ie. albuminuria, urinary casts, urinary biomarkers) or both. The arrow shows progression (red), regression or recovery (green) between the different phenotypes.

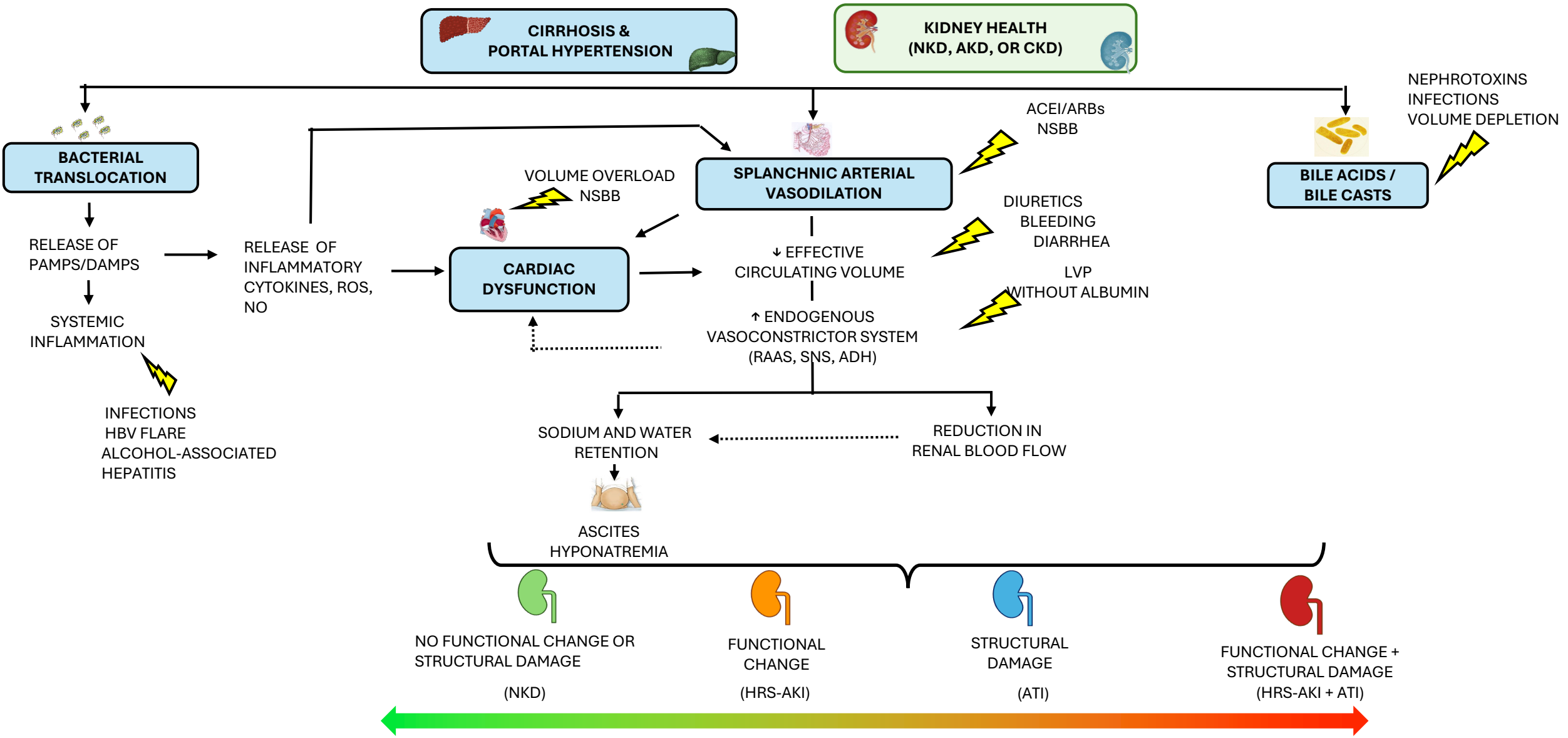

Fig 7. Kidney-liver health (KLH) assessment. KLH assessment is a 'living' process that should be repeated if the patient's condition changes and following planned or unplanned exposure, both during hospitalization and post-AKI care in the outpatient setting.

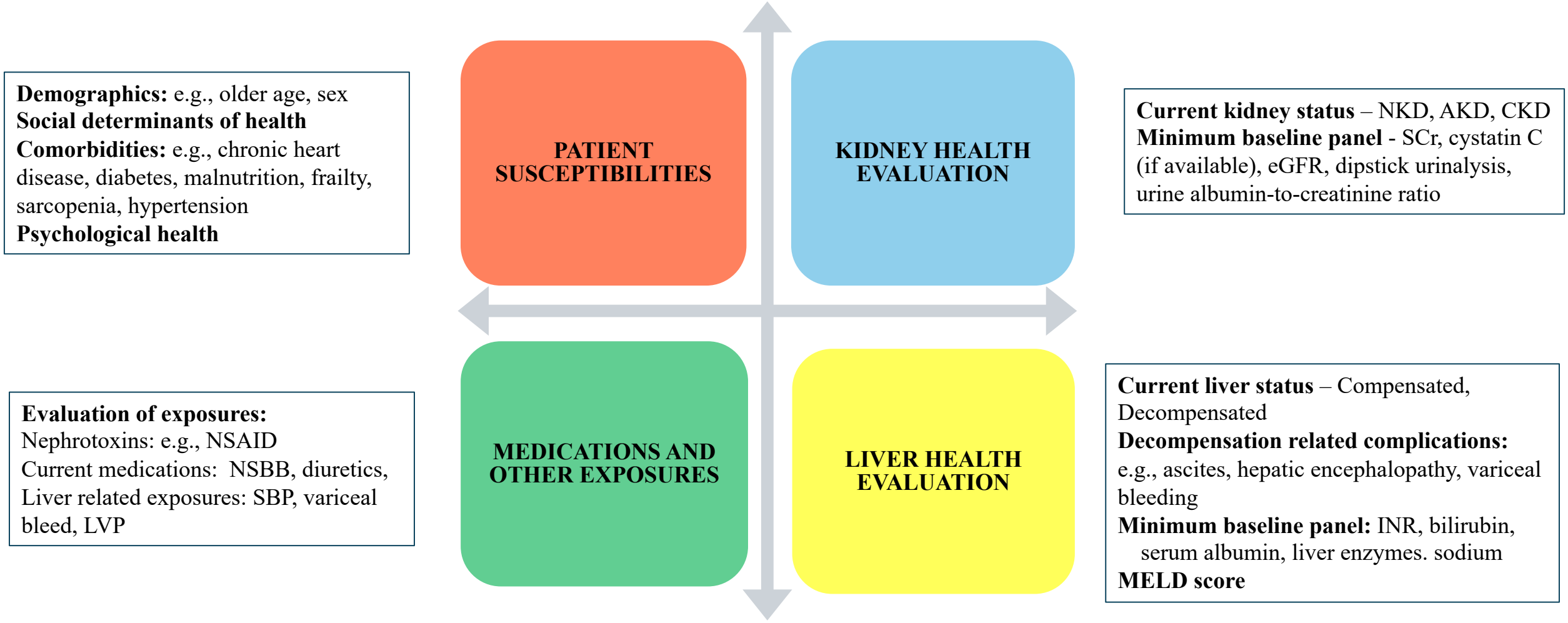

Fig. 8. The figure shows the potential trajectories of cirrhosis patients experiencing planned and unplanned exposures to events and insults that may cause acute kidney injury.

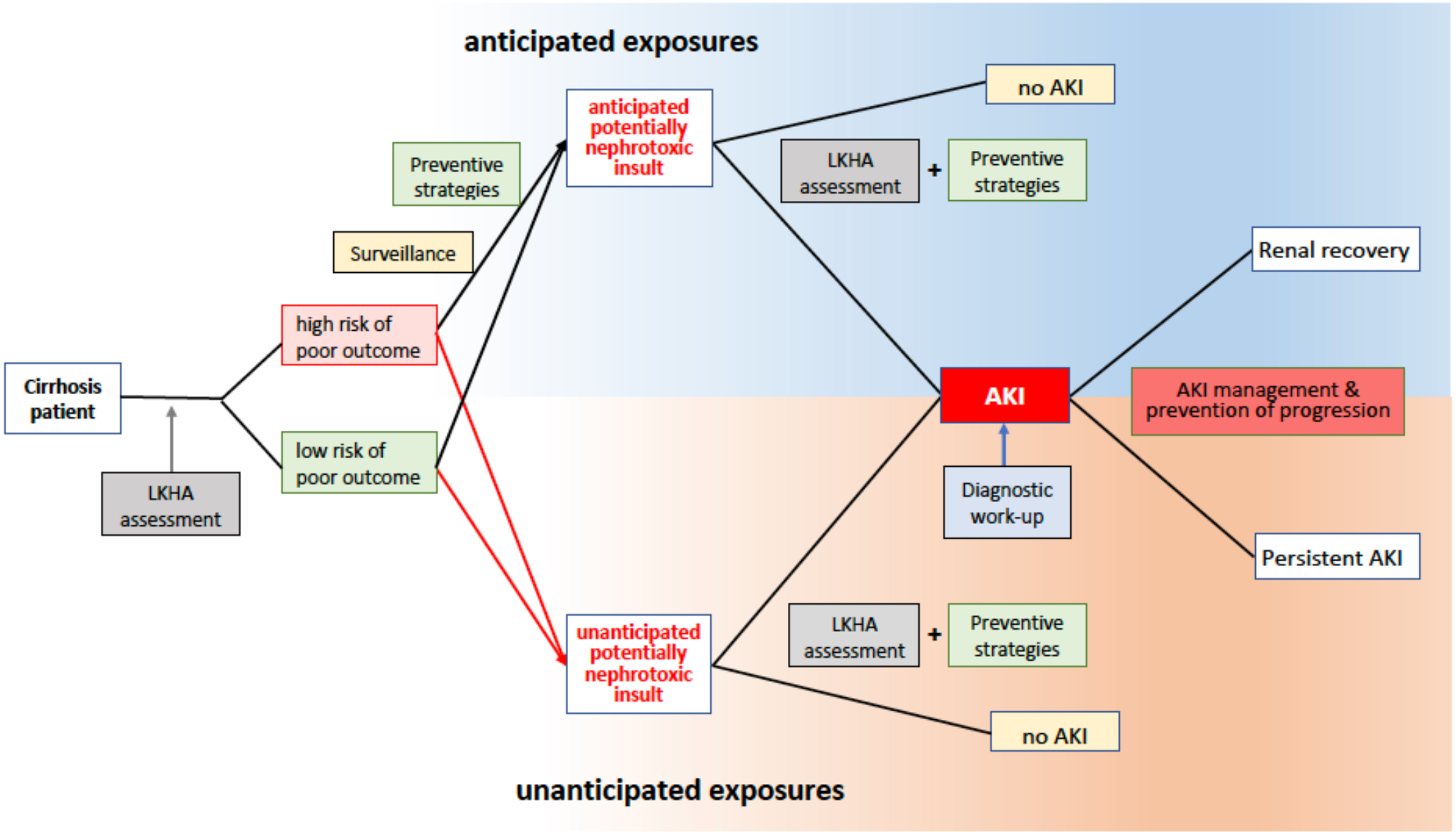

Fig. 9. Conceptual framework: Application of liver & kidney biomarkers

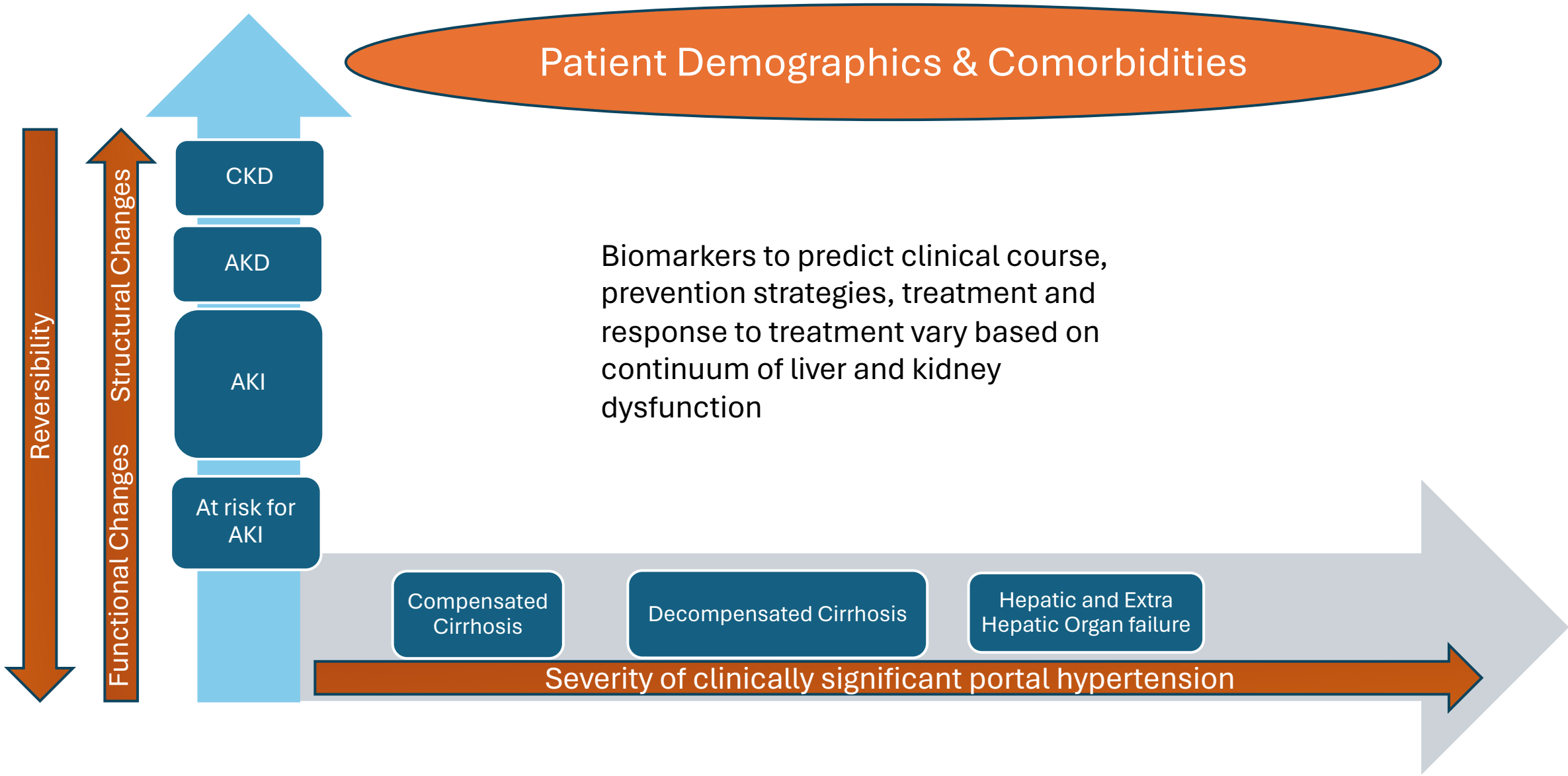

Fig 10: This figure shows components of the Liver Kidney Health Assessment. Abbreviations: ACLF, acute on chronic liver failure; AKI, acute kidney injury; CKD, chronic kidney disease; DM, diabetes mellitus; HTN, hypertension; SBP, spontaneous bacterial peritonitis

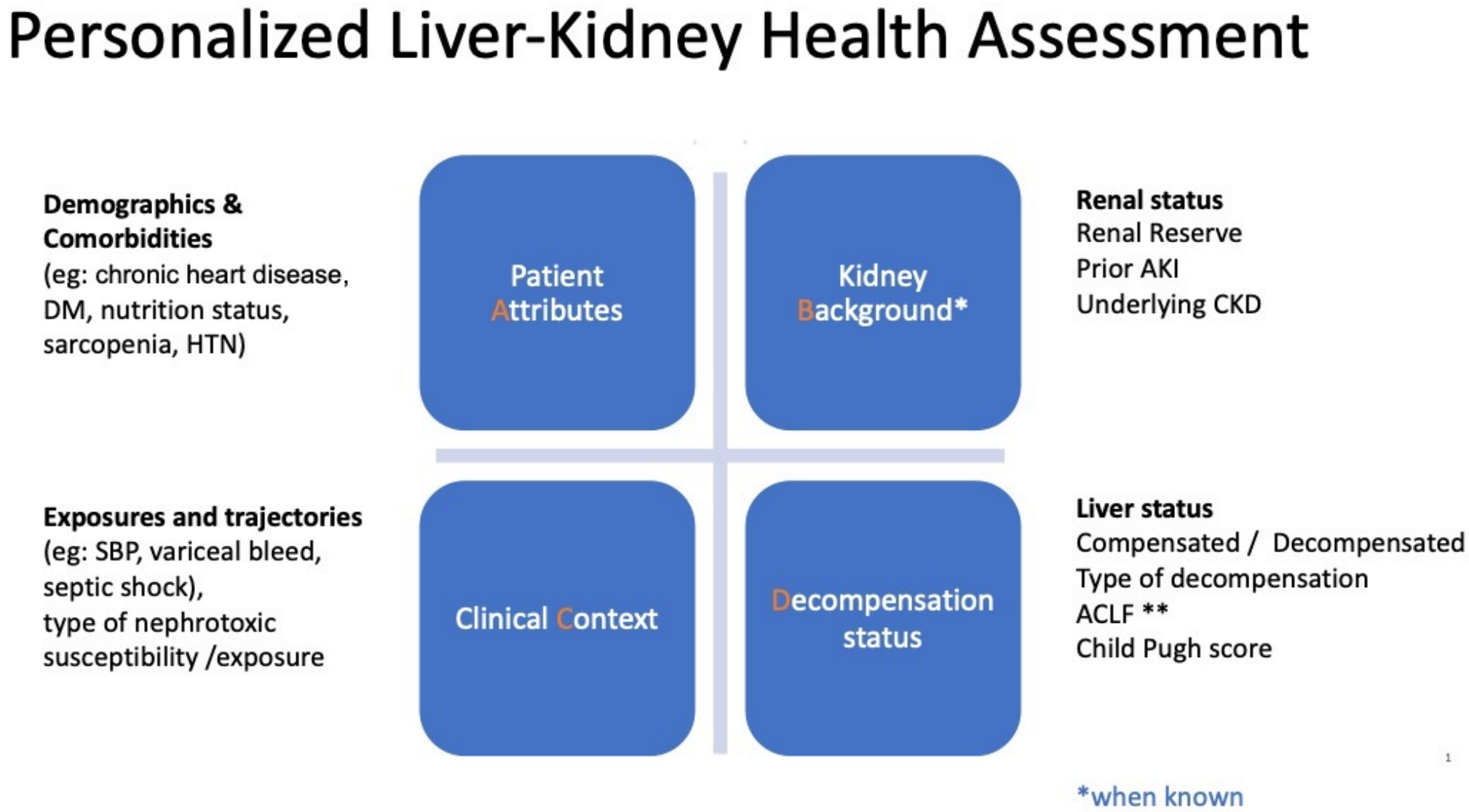

Fig. 11. Proposed framework for evaluating acute kidney injury (AKI) phenotypes based on combination of functional and damage markers. At any given point in time, patients would fall into one of the 4 quadrants, based on the results of the representative functional and damage marker tests and could be assessed over time to see their transitions across the categories. The ability to detect a state of damage alone (right upper quadrant) allows an expanded criteria for diagnosis of AKI that may represent a "subclinical " state in which loss of function might develop several days after detection of kidney damage or not at all. Markers of kidney damage may include albuminuria/proteinuria, hematuria, urinary casts, and biomarkers. Bottom left quadrant indicates an acute change in kidney filtration but without detectable kidney damage such as seen in patients with volume depletion. Patient who meets criteria for hepatorenal syndrome (HRS) may be either without evidence of damage (left lower quadrant) or have co-existing damage (right lower quadrant). Sequential assessments could provide information on which of the factors is prevalent for ongoing injury or resolution and offer opportunities for targeted intervention. It is expected that the process is dynamic, and patients may move from one phenotype to another during the course of their illness. Modified, with permission, from Acute Disease Quality Initiative 10, www.ADQI.org.

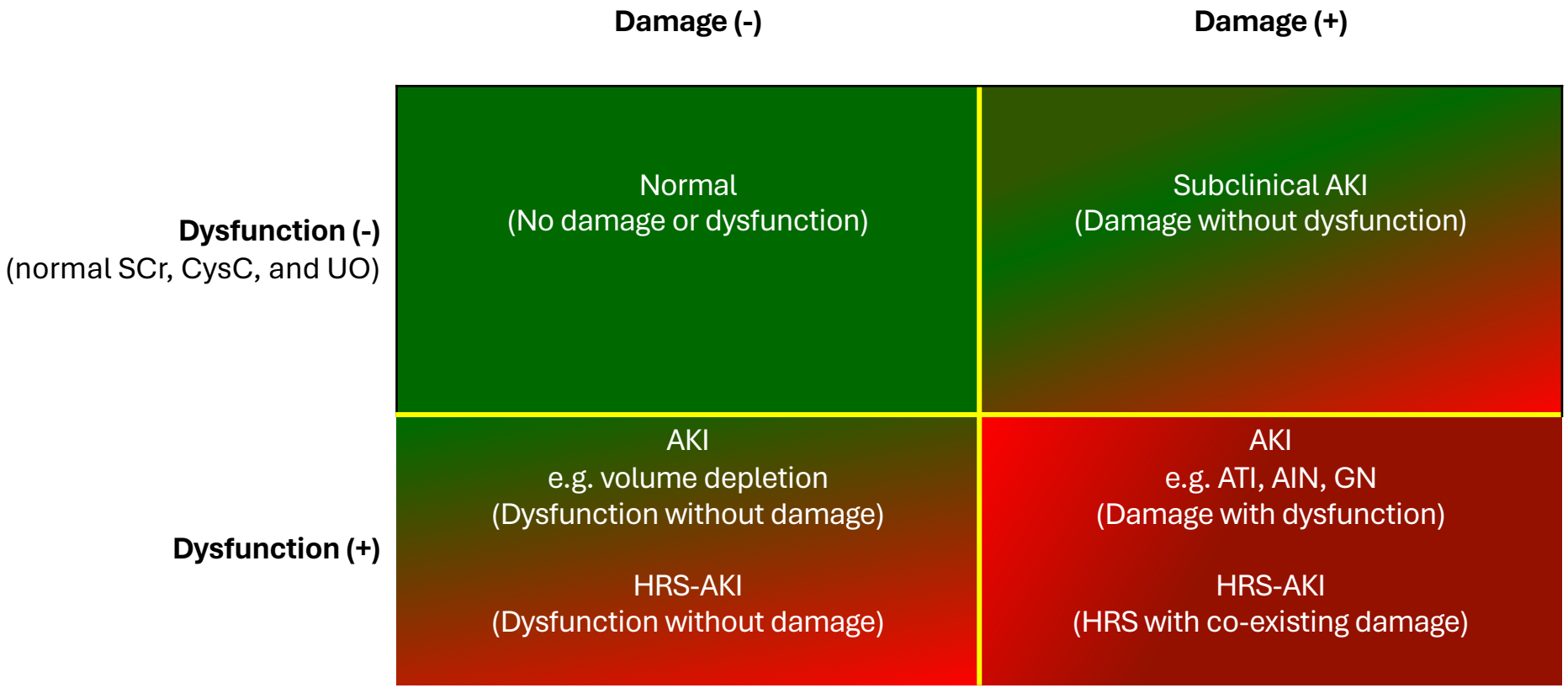

Fig. 12. Differential effects of various HRS-AKI treatments on vascular beds, cardiac function, renal perfusion as well as pulmonary effects. Terlipressin (T) increases renal perfusion pressure but also decreases cardiac output. By increasing cardiac preload (through shunting of splanchnic blood to central blood), increasing cardiac afterload (due to increase in systemic vascular resistance), and effecting pulmonary vasculature[228-231] (pulmonary artery dilation, pulmonary vein constriction, as well as possibly an increase in pulmonary capillary permeability), when combined with large doses of albumin, may be associated with an increased incidence of pulmonary edema. Norepinephrine (N) has a positive inotropic effect and causes systemic vasoconstriction, which then also increases renal perfusion pressure. In contrast to terlipressin, norepinephrine constricts pulmonary arteries without any effect on pulmonary vein. Midodrine (M) causes weak systemic vasoconstriction and Octreotide (O) causes temporary splanchnic vasoconstriction, effects that lead to an only modest increase in renal perfusion.

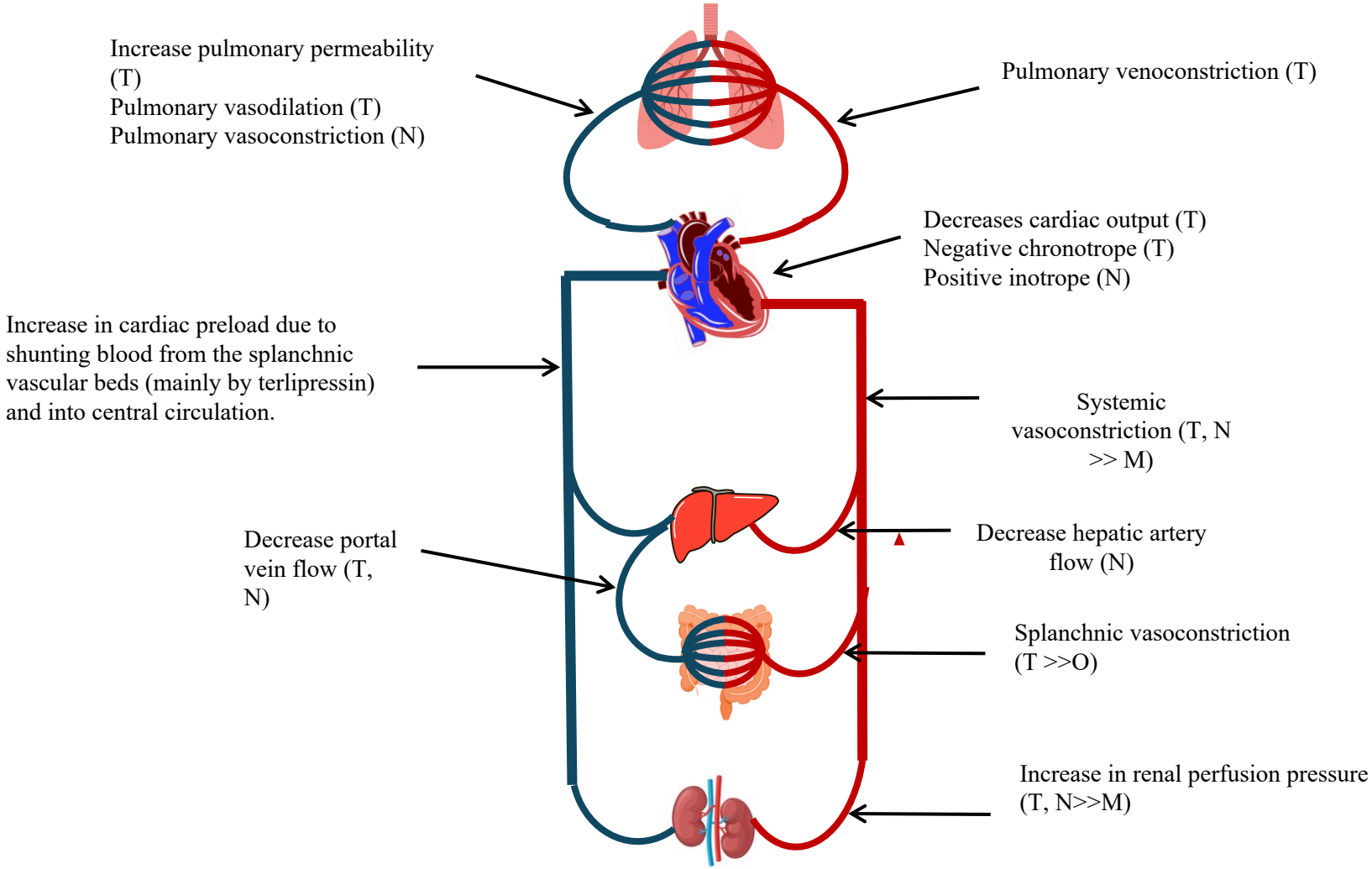

Fig 13. Overview of a patient-centered approach of post-AKI follow-up care in cirrhotic patients

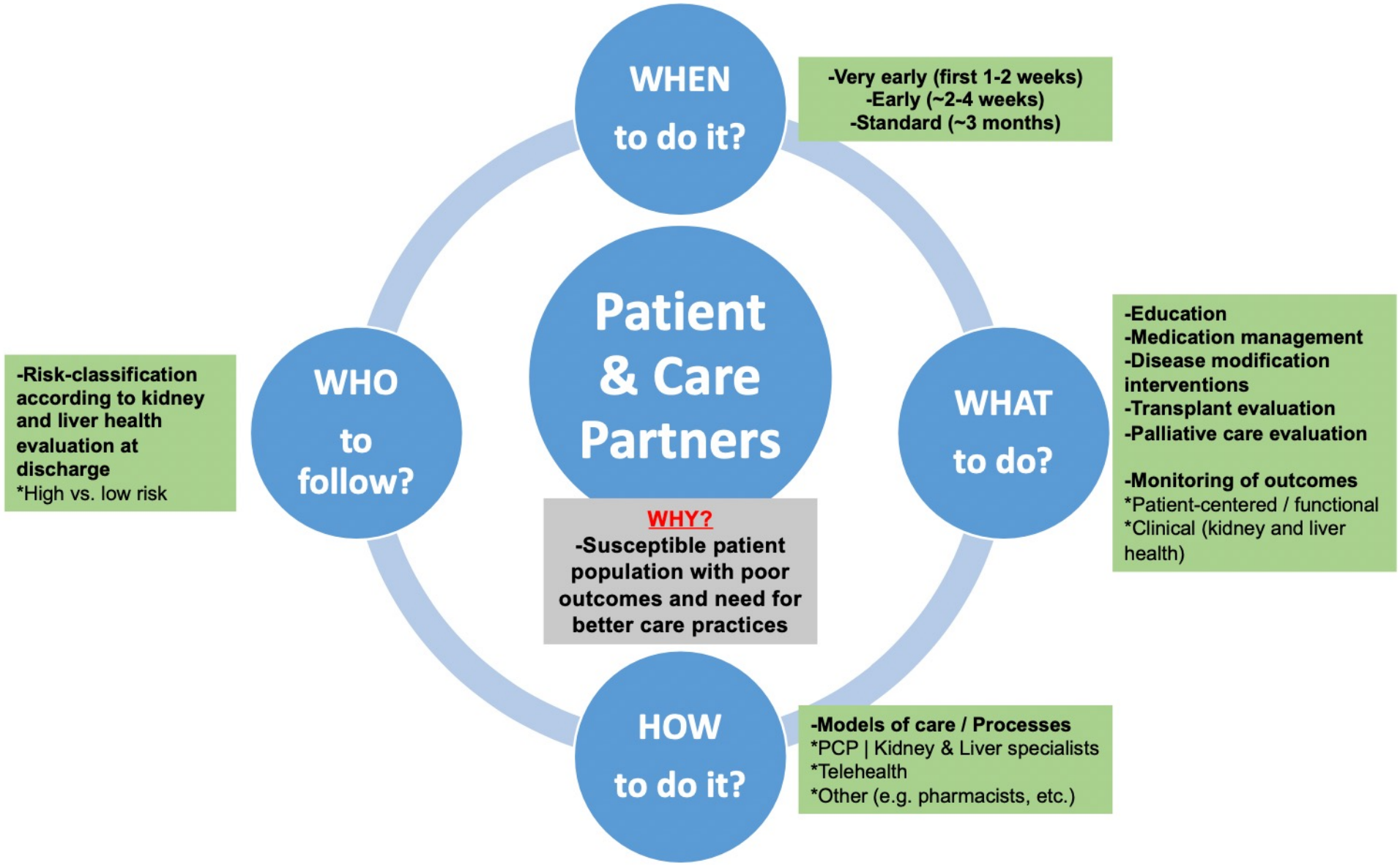

Fig. 14. Post-AKI Follow-up Kidney-Liver Health Assessment

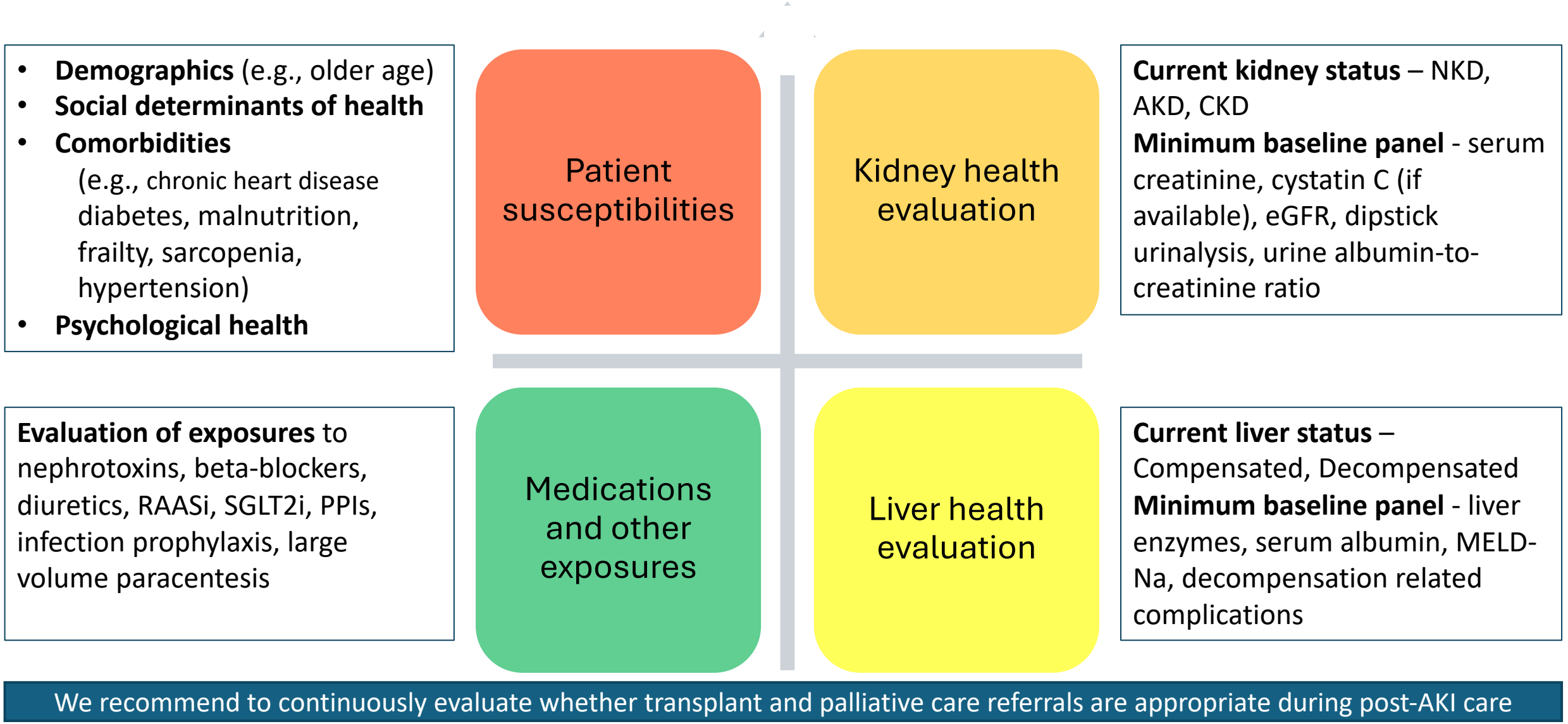

Fig. 15. Recommended structure of post-discharge follow-up according to the evaluation of the kidney axis (severity, duration, and recovery of AKI) and the liver axis (compensated vs. decompensated cirrhosis) performed at time of hospital discharge. Limited data are available to inform the timing and nature of monitoring for patients with cirrhosis who experience AKI or AKD in the hospital. The post-discharge follow-up will depend on the state of kidney and liver health at the time of discharge. We suggest that these patients should have their kidney function checked at a minimum, within 1 month of hospital discharge to confirm the extent of recovery or progression of kidney disease. Patients with persistent kidney dysfunction at 90 days should be formally assessed for the development or progression of CKD. Patients with less severe AKI or AKD can be monitored in primary care or by the base specialist with the degree of nephrology involvement in follow-up monitoring increasing with the duration and severity of AKI or AKD during hospitalization. Adapted, with permission, from Acute Disease Quality Initiative 24, www.ADQI.org.

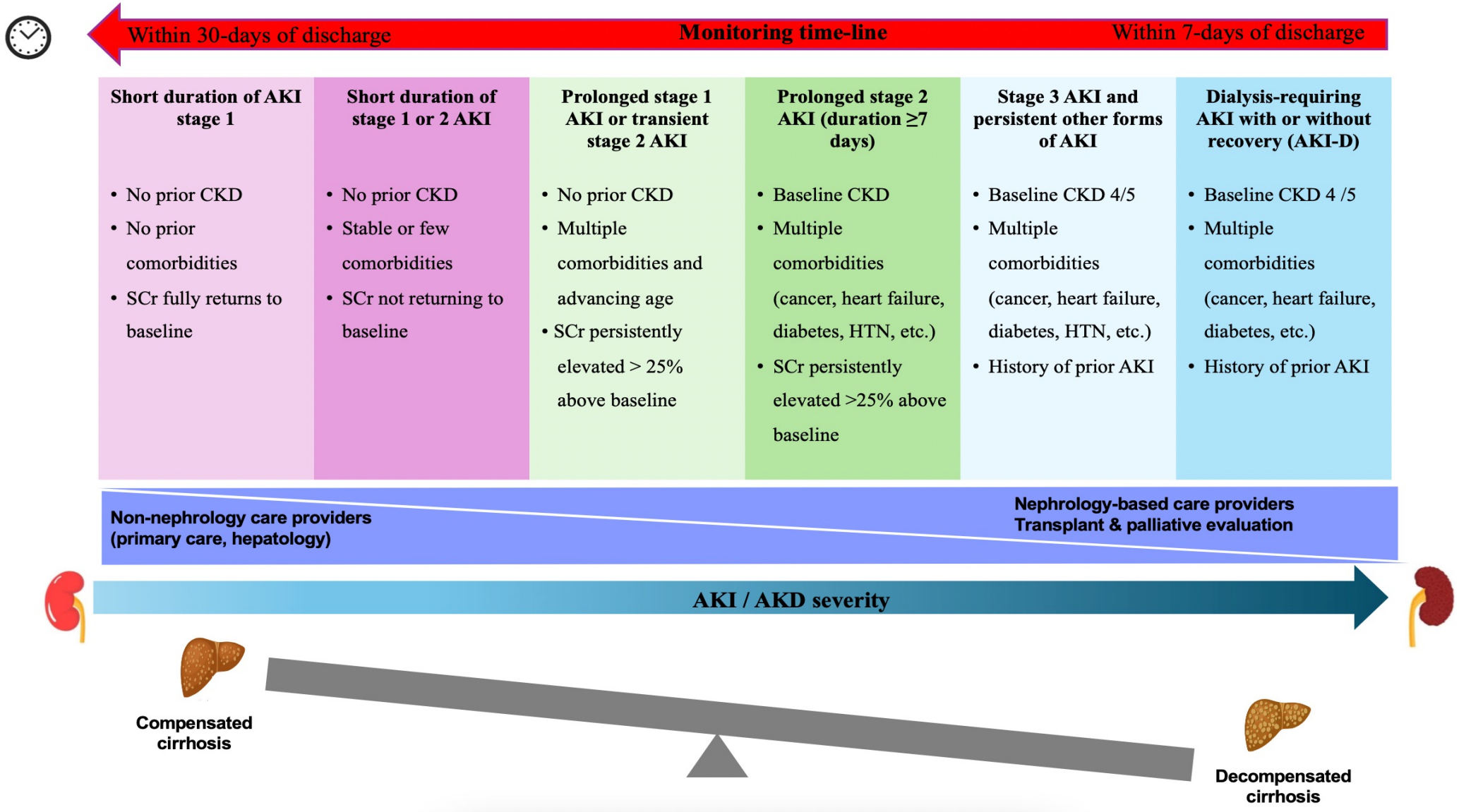

Fig. 16 Post-AKI Follow-up Kidney-Liver Health Management

Patient & Caregiver Education

AKI – risk factors and prevention of recurrence
Current status of kidney health
Diet and fluid intake
Home monitoring of blood pressure, glycemia and weight
Sick day advice to hold specific medications (e.g. diuretics, RAASi, SGLT2i, etc.)
Urgent and ED care alarm signs

Medication Management

Management of comorbid conditions including hypertension and diabetes
Management of volume status with diuretics
Other: antibiotic prophylaxis, beta blockers, vaccinations, avoidance of nephrotoxins and herbal remedies

Disease Modification

Liver: Treatment of liver disease etiology (e.g. AUD treatment, antiviral therapy for HBV/HCV, AIH therapy), or portal hypertension (NSBB, TIPS in select patients)

Kidney: RAASi, SGLT2i

Transplant

The necessity and timing of liver, kidney, or combined transplantation should be continuously assessed and discussed with the patient and caregiver

Palliative Care

Palliative care involves the optimization of symptoms, patient and caregiver well-being as well as frequent goals of care discussions