Title: *Severe Acute Kidney Injury Following Liver Ablation – A Case Series*

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BACKGROUND: Cryoablation is a procedure that utilizes extreme cold to destroy tumor cells in the setting of both primary and metastatic liver tumors; however, it has been associated with a broad spectrum of complications, ranging from fever and tachycardia to multi-organ failure, coagulopathy, and acute kidney injury (AKI). In comparison, histotripsy is a novel focused ultrasound technique that mechanically disrupts tumor tissue while sparing surrounding structures, thus potentially reducing systemic toxicity.

METHODS AND CASE DESCRIPTIONS: We retrospectively reviewed three cases of severe, stage 3 AKI following liver tumor ablation: two after histotripsy and one after cryoablation. All patients were women, aged 58-68 years, with normal baseline eGFRcr who developed AKI within 24 hours of their procedures. Two required kidney replacement therapy (KRT). Kidney biopsies in all three patients demonstrated acute tubular injury with features of pigment nephropathy, inflammatory infiltrates, hypoperfusion-related changes, and oxalate crystals. Hemoglobin-positive, myoglobin-negative casts were observed in two of the cases (Figure 1). Laboratory findings included elevated creatine kinase, lactate dehydrogenase, and myoglobin levels. Additionally, in two patients, cystatin C-based estimates of eGFR were consistently higher than those derived from serum creatinine values. Treatment of all three cases involved corticosteroids, and complete recovery of kidney function occurred in all patients, including those requiring KRT.

CONCLUSION: Both cryoablation and histotripsy may precipitate severe AKI, potentially through shared mechanisms involving cytokine release, pigment-mediated tubular injury, and hemodynamic perturbations. The inflammatory features and response to corticosteroids in select cases support a contributory immune-mediated component. Our findings emphasize the importance of identifying biomarkers that could shed light on the pathophysiology of AKI following liver ablation and potentially explain the discordant serum creatinine/cystatin C measurements. Larger studies with detailed risk profiling and phenotyping are needed to clarify risk factors and clinical features of AKI following cryoablation and histotripsy.

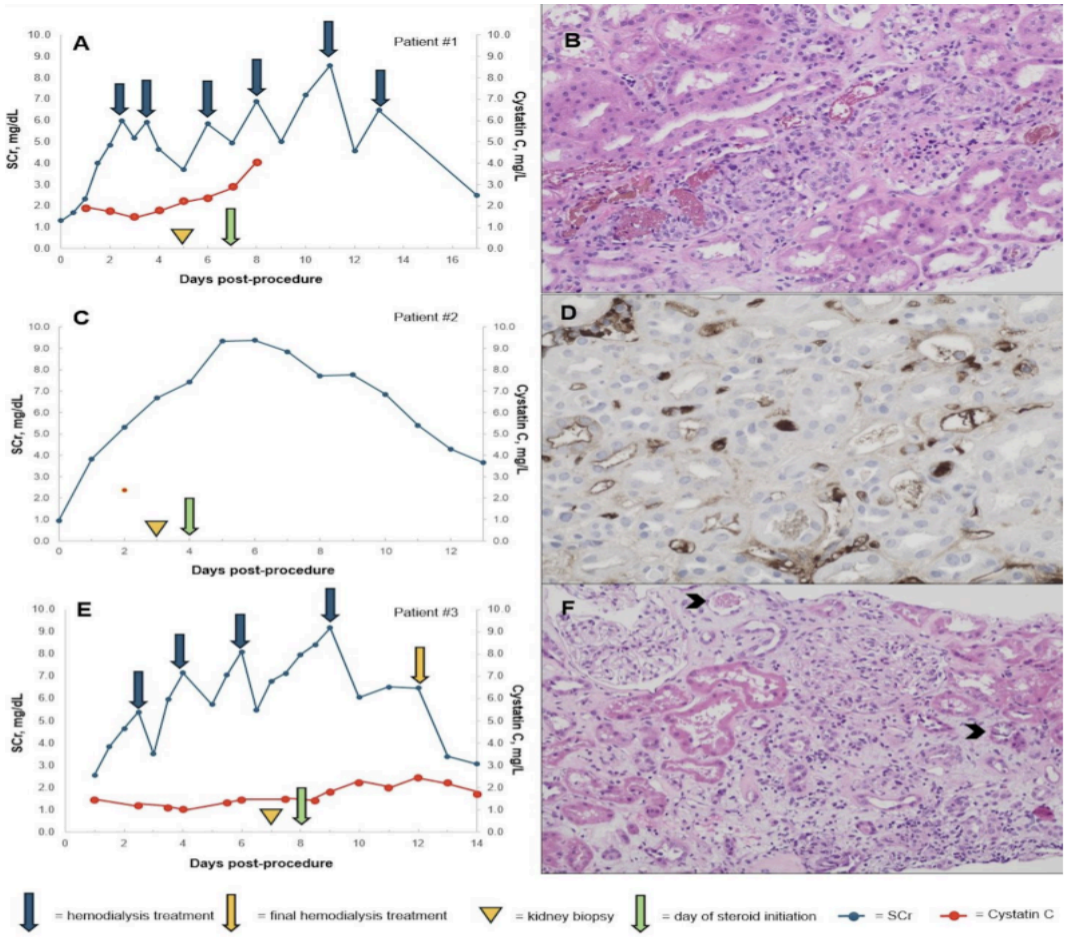

Figure 1. Panels A, C, and E show the rapid onset of AKI as evidenced by the steep rise in serum creatinine post-procedure, and Panels B, D, and F show a representative light microscopy image from each patients' kidney biopsy. The blue points represent serum creatinine in mg/dL (primary y axis) over days (x-axis), and the red points correspond to the cystatin C in mg/L (secondary y axis). The vertical blue arrows represent kidney replacement therapy (KRT) treatments, while the yellow arrow indicates the final KRT treatment. The yellow triangle represents the day of kidney biopsy, while the green diagonal arrow indicates the day of steroid initiation. A) Patient 1; initiated KRT day 2 post procedure, biopsy day 5, and started 60mg prednisone day 7 which was tapered over 25 days. Remained KRT dependent for 24 days post-procedure. (B) Hematoxylin and eosin (H&E) stain, 20x magnification showing numerous granular casts. (C) Patient 2; kidney biopsy day 3 post-procedure, had 3 days of IV methylprednisolone 80mg with no oral steroid taper when biopsy showed predominantly acute tubular necrosis (ATN). No KRT was required. (D) Hemoglobin stain, 40x magnification, showing positive staining within the granular cast material. (E) Patient 3; required KRT initiation day 2 post-procedure and had 5 hemodialysis treatments in the hospital. Biopsy on day 7 with IV methylprednisolone 100mg daily started on day 8 with a 4-week oral prednisone taper. Final hemodialysis treatment 12 days post-procedure (yellow arrow). (F) H&E stain, 20x magnification, showing a calcium oxalate crystal (arrowhead, center-right), a tubular granular cast (arrow, top left), and interstitial edema with a mixed infiltrate including lymphocytes, plasma cells, and few eosinophils.

Abbreviations: milligrams per deciliter (mg/dL), milligrams per liter (mg/dL), Serum creatinine (SCr).