Intraindividual variability of sCr in healthy patients can be due to biological variability and technical variability of the assay used to measure sCr. In healthy individuals, the biological variability of sCr is about 4.5%.1,3 Biological variability may be higher in a kidney that has suffered prior injury, such as flares of LN. The analytic variability of the Jaffe method, a commonly used technique for measuring sCr, is 5.5%.4 Between biological and analytical variability, the smallest change between 2 sCr measurements in an individual that warrants clinical concern is 19%.6 Commonly used medications, such sulfamethoxazole/trimethoprim, angiotensin-converting enzyme inhibitors, and angiotensin blockers, can also cause fluctuations in sCr. We cannot exclude that a change in medications affected the measurements seen in our patients.

In summary, variability in sCr measurements is commonly observed in clinical practice and does not necessarily indicate a decline or improvement in kidney function. In a cohort of lupus patients who have had at least 1 episode of LN, a large proportion of patients who otherwise appear to have achieved a stable complete renal response based on proteinuria criteria have sCr fluctuations of 15% or more, suggesting that a 15% cutoff to define the success of a trial may be overly conservative. To define complete renal response, we recommend that a 25% cutoff for the upper limit of change in sCr might be more appropriate. Furthermore, a single measurement of sCr at the end of a trial cannot be put into an appropriate context, and sCr should be measured on at least 2 occasions.

DISCLOSURE

SA reports receiving personal fees from Aurinia Pharmaceuticals Inc. outside of the submitted work. CA reports receiving nonfinancial support from Bristol Myers Squibb and Glaxo-Smith Kline and a grant from Exagen, outside of the submitted work. NS is an employee and shareholder at Aurinia Pharmaceuticals Inc. BHR reports personal fees from Aurinia, Callidatis, Chemocentryx, Retrophin, Novartis, MorphoSys, EMD Serono, Bristol Myers Squibb, Janssen, AstraZeneca; and Omeros; nonfinancial support from Lupus Foundation of America; and grants from the National Institutes of Health, outside the submitted work. All the other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)
Supplementary Methods.
Supplementary References.

REFERENCES

1. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12:825–835.
2. Mackay M, Dall’Era M, Fishbein J, et al. Establishing surrogate kidney end points for lupus nephritis clinical trials: development and validation of a novel approach to predict future kidney outcomes. Arthritis Rheum. 2019;71:411–419.
3. Hilderink JM, van der Linden N, Kimenai DM, et al. Biological variation of creatinine, cystatin C, and eGFR over 24 hours. Clin Chem. 2018;64:851–860.
4. Ricos C, Alvarez V, Cava F, et al. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest. 1999;59:491–500.
5. Carobene A, Marino I, Coskun A, et al. The EuBIVAS Project: within- and between-subject biological variation data for serum creatinine using enzymatic and alkaline picrate methods and implications for monitoring. Clin Chem. 2017;63:1527–1536.
6. Delaney P, Cavalier E, Pottel H. Serum creatinine: not so simple! Nephron. 2017;136:302–308.

Acute Kidney Injury Following Paracentesis Among Inpatients With Cirrhosis

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Refractory ascites is a common cause of hospitalization in patients with cirrhosis and is associated with high morbidity and mortality. Therapeutic paracentesis is routinely used to manage refractory ascites. However, in patients hospitalized with decompensated liver disease, therapeutic paracentesis is often delayed, inadequately performed, or avoided altogether due to concern about precipitating acute kidney injury (AKI) from fluid shifts and altered hemodynamics. This practice could have negative effects on symptom burden and quality of life. Few studies have rigorously examined the incidence and risk factors for AKI following paracentesis among inpatients with cirrhosis. We evaluated the effect of paracentesis on kidney function in a large cohort of patients admitted at an academic liver transplant medical center.

RESULTS

The final cohort consisted of 258 paracenteses performed in 102 patients (Figure 1). Most of the paracenteses (67%) were <5L. The mean (±SD) age of the entire cohort was 58 years (±13 years), 67% were male, and 77% were Caucasian. The mean (±SD) baseline creatinine and Model for End Stage Liver Disease

![Figure 1. Patient flow diagram demonstrating the incidence of acute kidney injury (AKI) with paracentesis. Acute kidney injury occurred in 14 of 258 (5%) paracenteses. Among these, the serum creatinine (Cr) was already rising in 6 patients; the other 8 had “new” AKI, 4 of which had no alternative etiology other than paracentesis (1.6% overall incidence of paracentesis-related AKI).](image-url)
(MELD) score were 1.25 mg/dl (±0.69 mg/dl) and 21 points (±7 points), respectively. The most common etiology of cirrhosis was alcohol (43%), followed by hepatitis C virus (19%). Mean albumin replacement (25%) per paracentesis was 37 g (±30 g). Inpatient mortality was 9%, and 15% of patients received a liver transplant within 1 year of paracentesis. Additional baseline characteristics are shown in Table 1.

Acute kidney injury, defined as an increase in creatinine ≥0.3 mg/dl or ≥50% within 48 hours, was observed in 14 of 258 paracenteses (5%). An improvement in renal function, defined as a decrease in creatinine ≥0.3 mg/dl within 48 hours, was observed in 25 of 258 (10%) paracenteses. The patients who had AKI received 10.3 g/l (±SD, 7.3 g/l) of fluid removal, whereas the 10% of patients whose kidney function improved received 14.6 g/l (±SD, 14.5 g/l) of fluid removal (P = 0.23). The remaining 218 of 258 paracenteses (85%) had stable renal function (Figure 1). On chart review of the 14 paracenteses associated with AKI, we found that the creatinine was already rising in 6 of the events. Of the remaining 8 AKI events, 4 had an alternative explanation for the AKI (Figure 1). Thus, only 4 of 258 paracenteses (1.6%) were accompanied by new AKI without an alternative cause. All 4 of these paracenteses were <5 L and none had spontaneous bacterial peritonitis at the time of paracentesis. Two of these episodes were part of a deteriorating clinical course culminating in death/hospice, whereas in the other 2 cases the kidney function stabilized but did not recover to the previous baseline. One patient, who required dialysis, had progressive hepatorenal syndrome but stable creatinine in the days before the paracentesis was performed; the creatinine worsened after the paracentesis.

Overall, mean creatinine was similar pre- and post-paracentesis (1.32 mg/dl [±0.80 mg/dl] and 1.30 mg/dl [±0.84 mg/dl], respectively, P = 0.14). This finding was consistent regardless of whether albumin repletion guidelines were followed (6–8 g of albumin per liter of ascitic fluid removed for paracentesis ≥5 L). After adjusting for MELD score, albumin replacement, and baseline creatinine, there was a small but statistically significant decrease in creatinine in the ≥5-L group when compared to the <5-L group (0.1 mg/dl; 95% confidence interval, 0.02–0.16; P = .04). When the analysis was repeated at the patient level (with the first large-volume paracentesis of each patient, n = 102) rather than at the level of the paracentesis, the findings remained the same.

On average, systolic blood pressure decreased after paracentesis by 3 mm Hg (±14 mm Hg; P < 0.01), and diastolic blood pressure decreased by 2 mm Hg (±9 mm Hg; P < 0.01). Hypotension (defined as a drop in systolic blood pressure of 20–mm Hg or a 10–mm Hg drop in diastolic blood pressure within 6 hours) occurred after 61 of 258 paracenteses (24%). Hypotension was more common in the ≥5-L group (26 of 85; 31%) compared to the <5-L group (35 of 173; 20%), but was not associated with development of AKI (P = 0.40) or change in serum creatinine (P = 0.67).

**Table 1.** Baseline characteristics of inpatients undergoing a large-volume paracentesis.

| Baseline characteristics | All paracenteses | Paracentesis volume < 5 L | Paracentesis volume ≥ 5 L |
|--------------------------|------------------|--------------------------|--------------------------|
| Total paracenteses       | 258              | 173                      | 85                       |
| Individual patients      | 102              | 71 (70)                  | 31 (30)                  |
| Age, yr                  | 58 ± 13          | 59 ± 12                  | 55 ± 13                  |
| Male                     | 174 (67)         | 110 (64)                 | 64 (75)                  |
| White race               | 196 (77)         | 130 (75)                 | 68 (80)                  |
| Baseline creatinine, mg/dl | 1.25 ± 0.69     | 1.27 ± 0.74              | 1.24 ± 0.57              |
| MELD score               | 21 ± 7           | 21 ± 7                   | 22 ± 6                   |
| Cirrhosis etiology       |                  |                          |                          |
| Alcohol                  | 110 (43)         | 77 (44)                  | 33 (39)                  |
| HCV                      | 49 (19)          | 36 (21)                  | 13 (15)                  |
| Alcohol + HCV            | 49 (19)          | 26 (15)                  | 23 (27)                  |
| Diabetes mellitus        | 73 (29)          | 55 (32)                  | 18 (21)                  |
| Prior spontaneous bacterial peritonitis | 65 (25) | 39 (23) | 26 (31) |
| Prior hepatocellular carcinoma | 25 (10) | 14 (8) | 11 (13) |
| Albumin replacement, g    | 37 ± 30          | 32 ± 28                  | 50 ± 28                  |
| Albumin replacement, g/l  | 11 (14)          | 12 (17)                  | 9 (6)                    |
| No albumin               | 59 (23)          | 49 (28)                  | 10 (12)                  |
| <6 g/l                   | 24 (9)           | 7 (4)                    | 17 (46)                  |
| ≥6 g/l                   | 175 (68)         | 117 (88)                 | 58 (42)                  |
| Loop diuretic usea        | 124 (48)         | 83 (48)                  | 41 (48)                  |
| Spironolactone usea³      | 102 (40)         | 70 (40)                  | 32 (38)                  |

HCV, hepatitis C virus; MELD, Model for End Stage Liver Disease.

*Medication use was derived from manual review of electronic medical records 24 hours pre- or postparacentesis.

Data are mean ± SD, n, or n (%).

**DISCUSSION**

We report that the incidence of AKI following paracentesis among inpatients with cirrhosis is low (5%), and the incidence of paracentesis as a major contributory factor for AKI is even lower (1.6%). We also report improvement in kidney function in 10% of paracenteses, which could be attributed to decreased intra-abdominal pressure resulting in decreased renal vein pressures, thus improving venous outflow.² ⁵

Postparacentesis circulatory dysfunction is a well-described phenomenon.⁶ ⁸ However, its clinical significance, namely its impact on kidney function, has not been rigorously investigated. Small studies have suggested that decreasing intra-abdominal pressure in patients with intra-abdominal hypertension can lead to improvement of kidney function.⁶ ⁵ This suggests that the known decrease in effective circulating volume following a paracentesis may be counterbalanced
by improvement in intra-abdominal pressure. However, this may pertain only to patients with massive abdominal ascites, the presence or absence of which could not be confirmed in our study population. A prospective study in which paracentesis volume is dictated by real-time changes in intra-abdominal pressure would be required to confirm this hypothesis.

Clinicians may be hesitant to pursue a paracentesis in hospitalized cirrhotic patients, as these patients are considered more vulnerable to AKI because of ongoing comorbidities such as gastrointestinal bleeding, hepatic encephalopathy, or infection. There is also a concern that removing higher volumes of ascitic fluid may be associated with higher risk of AKI, which, albeit logical, lacks supportive evidence. Indeed, two-thirds of paracenteses in our study were <5 L, which supports the hypothesis that higher-volume paracentesis may be less commonly performed in the inpatient setting. However, the low AKI event rates in our study and, in particular, the complete absence of AKI events in the ≥5-L group, are reassuring and support the notion that paracentesis of any size, with guideline-driven albumin repletion, are well tolerated from a kidney standpoint. Clinicians should balance this low risk of AKI with the symptomatic benefit provided by therapeutic paracentesis.

Several strengths and limitations of this study should be noted. This is a retrospective analysis; thus, all findings should be viewed as associations, rather than causal relationships. One strength of this study is a relatively large and homogeneous patient population, which helps to address a specific clinical question around paracentesis in the inpatient setting. All patients were hospitalized, and had granular data around medication use, overall clinical course, hemodynamic parameters, and kidney function. Some physiologic information was not available, including renin and aldosterone levels, urine output, and bladder pressures (a surrogate for intra-abdominal pressure), which would have added to the rigor of hemodynamic analysis. We were able to evaluate each episode of AKI in detail, providing the clinical context that helped to eliminate paracentesis as the primary cause for the majority of AKI events. Our population also had a relatively high baseline creatinine (mean, 1.3 mg/dl) and MELD score (mean, 21), putting them at higher risk for AKI, thus enriching this population for adverse events. Although our low AKI rate was reassuring, the small number of events limited our ability to identify predictors of AKI. Our low AKI rate may also have been affected by clinicians limiting paracentesis volumes, with 67% of paracentesis being <5 L, or avoiding it altogether in the most unstable patients.

In summary, therapeutic paracentesis among inpatients with cirrhosis carries a low risk of AKI. Larger studies are required to further examine the safety of paracentesis in this population.

**DISCLOSURE**

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**SUPPLEMENTARY MATERIAL**

Supplementary File (PDF)

Short Methods.

**REFERENCES**

1. Planas R, Montoliu S, Ballesté B, et al. Natural history of patients hospitalized for management of cirrhotic ascites. *Clin Gastroenterol Hepatol*. 2006;4:1385–1394.
2. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. *Hepatology*. 2013;57:1651–1653.
3. Gines P, Schrier RW. Renal failure in cirrhosis. *N Engl J Med*. 2009;361:1279–1290.
4. Savino J, Cerabona T, Agarwal N, Byrne D. Manipulation of ascitic fluid pressure in cirrhotics to optimize hemodynamic and renal function. *Ann Surg*. 1988;208:504–511.
5. Cade R, Wagemaker H, Vogel S, et al. Hepatorenal syndrome. Studies of the effect of vascular volume and intraperitoneal pressure on renal and hepatic function. *Am J Med*. 1987;82:427–438.
6. Molina L, Coll S, Gana J, et al. Hemodynamic changes in patients developing effective hypovolemia after total paracentesis. *J Hepatol*. 1998;28:639–645.
7. Pinto PC, Amerian J, Reynolds TB. Large-volume paracentesis in nonedematous patients with tense ascites: its effect on intravascular volume. *Hepatology*. 1988;8:207–210.
8. Ruiz-Del-Arbol L, Monescillo A, Jimenez W, et al. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology*. 1997;113:579–586.