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Systematic Review and Meta-Analysis of Urine Neutrophil Gelatinase–Associated Lipocalin for Acute Kidney Injury in Cirrhosis

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INTRODUCTION

Acute kidney injury (AKI) is a common complication in hospitalized patients with cirrhosis and is associated with significant mortality.[1-3] The most common causes of AKI in these patients are prerenal azotemia, acute tubular necrosis (ATN), and hepatorenal syndrome (HRS), and accurate determination of the etiology of AKI is paramount as treatments differ considerably.[2-4] In patients with cirrhosis, prerenal azotemia commonly results from excessive diuresis, gastrointestinal bleeding, and diarrhea and is reversible with volume expansion and discontinuation of diuretics. HRS is managed with vasoconstrictor therapy and volume expansion and often necessitates liver transplantation, whereas patients with ATN could have worsening of their renal dysfunction with vasoconstrictor therapy. Treatment of ATN is primarily supportive via hemodialysis until spontaneous reversal of renal dysfunction occurs, or a patient can undergo combined liver kidney transplantation.[5]

Differentiating HRS from ATN is challenging because there are no available objective tests to distinguish between the 2, leaving clinicians to make the diagnosis on clinical grounds. Moreover, standard diagnostic tests for AKI, such as urine microscopy and fractional excretion of sodium, are often inaccurate in advanced liver disease.[6,7] Because these methods may be inaccurate, they can lead to delays in diagnosis and administration of harmful therapies. As a result, international guidelines have called for developing novel biomarkers for the differentiation of structural (ATN) and functional (HRS and prerenal azotemia) causes of AKI.[4] Among these candidate biomarkers, urine neutrophil gelatinase–associated lipocalin (NGAL) has emerged as the most promising and well studied biomarker.

In 2016, our group published a systematic review and meta-analysis demonstrating the potential utility of urine NGAL as a biomarker for differentiating ATN from other causes of kidney impairment.[8] At that time, 5 studies were included that evaluated urine NGAL to diagnose ATN. However, several new studies have been conducted since its publication, providing a wealth of additional data. As such, we performed an updated systematic review and meta-analysis to evaluate the totality of data, incorporating recent studies to define the role of NGAL as a biomarker and establish an optimal cutoff value for its clinical use, particularly in the context of the US Food and Drug Administration's recent approval of terlipressin in September 2022 and NGAL testing in December 2023. The complete methodology and statistical analysis can be found in the Supplementary Methods.[S1,S13-S16]

RESULTS

The study selection process is shown in Supplementary Figure S1. Our database search identified 538 citations, from which 108 were selected for full-text evaluation. From these, we identified 11 articles eligible to be included in the meta-analysis.

Table 1. Summary of studies that assessed the accuracy of urine NGAL for diagnosing acute tubular necrosis in patients with cirrhosis

Study (yr)	Country	Enrollment period	Age (yr)	Male (%)	MELD score	No. of patients with kidney impairment	No. of patients with ATN	Biomarker assay	Optimal cutoff (ng/ml)	Optimal cutoff (μg/g creatinine)
Allegretti *et al.*,[S10] 2021	United States	2013–2019	58	69	23	161	49	TIA (BioPorto)	NR	244
Ariza *et al.*,[S5] 2015	Spain	2011–2014	58	78	23	39	12	Bead-based immunoassay (Bio-Rad)	236[a]	294
Belcher *et al.*,[S3] 2014	United States	2009–2011	55	69	26	110	39	ELISA (Bio Porto)	365	158[a]
Fagundes *et al.*,[S2] 2012	Spain	2009–2011	60	63	18	84	11	ELISA (BioPorto)	180[a]	194
Gambino *et al.*,[S11] 2023	Italy	2015–2020	62	77	25	162	27	CLIA (Abbott)	220	223[a]
George *et al.*,[S12] 2023	India	2020–2021	49	86	29	86	14	ELISA (Elabscience)	179[a]	215
Hamdy *et al.*,[S7] 2018	Egypt	2015–2016	54	59	20	70	14	ELISA (BioVendor)	NR	143
Huelin *et al.*,[S8] 2019	Spain	2013–2016	62	72	22	320	39	TIA (BioPorto)	NR	220
Qasem *et al.*,[S4] 2014	Egypt	2012	53	64	19	68	22	ELISA (BioVendor)	NR	286
Treeprasertsuk *et al.*,[S6] 2015	Thailand	2011–2013	57	62	15	35	9	CLIA (Abbott)	163[a]	NR
Udgirkar *et al.*,[S9] 2020	India	2016–2017	47	67	20	84	10	CLIA (Abbott)	650	NR

ATN, acute tubular necrosis; CLIA, chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; MELD, Model for End-Stage Liver Disease; NR, not reported; TIA, turbidimetric immunoassay.
[a]Data provided by corresponding author.

The characteristics of the 11 studies included in the meta-analysis are reported in Table 1. These studies encompassed 1219 hospitalized patients with AKI and cirrhosis enrolled from large tertiary care centers. The mean age ranged from 47 to 62 years, and the proportion of male patients ranged from 59% to 86%. The mean Model for End-Stage Liver Disease score ranged from 15 to 29. Studies were conducted in North America, Europe, Asia, and the Middle East. Urine NGAL measurements were obtained using a variety of commercially available assays (Abbott, BioPorto, Bio-Rad, BioVendor, Elabscience).

The pooled sensitivity for diagnosis of ATN for urine NGAL was 81% (95% CI, 73%–87%), and the pooled specificity was 82% (95% CI, 76%–87%). The pooled area under the receiver operating characteristic curve was 0.88 (95% CI, 0.83–0.92) (Figure 1). There was minimal heterogeneity between studies ($I^2 = 14\%$). There was no significant correlation between the prevalence of ATN and area under the curve, with a correlation coefficient (r) of −0.41 and a 95% CI of −0.81 to 0.25 ($P = 0.21$).

Each study identified optimal cutoffs for urine NGAL for the diagnosis of ATN (Table 1). Seven studies provided optimal cutoffs using raw biomarker values (ng/ml), and 9 studies reported optimal cutoffs using biomarker values normalized to urine creatinine (μg/g creatinine). The studies reported median optimal cutoff values of 220 ng/ml (interquartile range, 180–301) and 220 μg/g creatinine (interquartile range, 194–244), respectively, for the diagnosis of ATN.

DISCUSSION

Our updated systematic review and meta-analysis assesses the evidence supporting urine NGAL as a

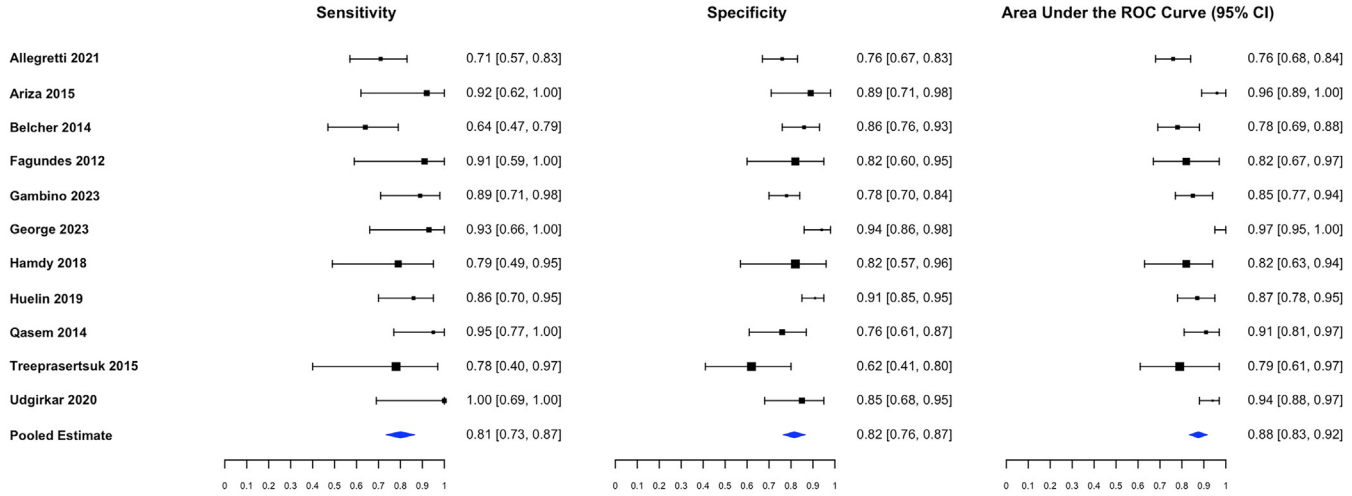

Figure 1. Urine neutrophil gelatinase–associated lipocalin for diagnosis of acute tubular necrosis. CI, confidence interval; ROC, receiver operating characteristic.

biomarker of ATN in patients with AKI and cirrhosis. This meta-analysis includes a further 6 studies published since 2016, more than doubling the size of our study cohort. The results demonstrate that urine NGAL has good diagnostic accuracy in differentiating patients with ATN and other types of kidney impairment, with a pooled sensitivity of 81%, specificity of 82%, and area under the curve of 0.88. Our meta-analysis shows studies reported a median optimal cutoff of 220 μg/g creatinine (interquartile range, 194–244), suggesting that values higher than this are helpful for discrimination of patients with ATN versus HRS.

In Europe and parts of Asia, NGAL is approved for clinical use, allowing physicians to immediately leverage this biomarker for enhanced diagnostic precision and patient management in cirrhosis. In the United States, BioPorto recently received US Food and Drug Administration approval for NGAL in December 2023 for use in pediatric patients.[9] Although this represents a significant milestone, it is important to note that approval does not yet extend to adults. Nevertheless, NGAL testing could be considered off-label for the management of patients with AKI and cirrhosis in the United States. Our findings underscore the need to seek approval for NGAL testing in a broader patient population to fully leverage its diagnostic potential.

Our meta-analysis has some limitations that should be acknowledged. First, it is crucial to recognize the inherent limitations in applying a universal NGAL cutoff for distinguishing ATN and HRS. Because study characteristics (e.g., age, gender) and prognostic factors (e.g., underlying chronic kidney disease, acute-on-chronic liver failure, infection, bleeding) were not consistently controlled across studies, there is the need for cautious interpretation of these cutoff values. Second, the definitions for HRS have undergone changes over the study period. In our meta-analysis, we relied on the HRS definitions utilized by the authors of the included studies. This variation in definitions is a limitation that warrants consideration when interpreting our findings, and future studies should evaluate this cutoff using the most current definition of HRS. Third, consistent with standard clinical practice, the diagnosis of ATN and HRS was made on clinical grounds, and kidney biopsies were not performed in any study to make a definitive histopathologic diagnosis. Finally, biomarker assays used differed across studies, and some studies reported optimal cutoffs using raw biomarker values, whereas other studies reported optimal cutoffs using biomarker values normalized to urine creatinine.

In conclusion, our meta-analysis demonstrates the utility of urine NGAL for distinguishing ATN in patients with AKI and cirrhosis at a cutoff of 220 μg/g creatinine. The recent US Food and Drug Administration approval of NGAL testing further underscores its relevance in the clinical landscape. As NGAL becomes part of the diagnostic toolkit in the United States, these finding indicate that incorporating urine NGAL into clinical decision making has the potential to guide treatment more accurately. Future studies should aim to explore the real-world impacts of NGAL testing and establish more definitive guidelines on the use of NGAL levels, ensuring its optimal utilization in various clinical contexts.

APPENDIX

List of TRIBE-AKI Consortium

Paolo Angeli, Justin Belcher, Carmine Gambino, Mohamed Salaheldin, Sombat Treepraertsuk.

DISCLOSURE

CRP is a member of the advisory board and owns equity in RenalytixAI. He also serves as a consultant for Genfit. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

JP and CRP designed the study. JP and NCL collected the data. YX and YD performed the statistical analysis. All authors interpreted the data and critically revised the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplemental References.

Figure S1. Flow diagram of study selection.

PRISMA Checklist.

REFERENCES

1. Fagundes C, Barreto R, Guevara M, et al. A modified acute kidney injury classification for diagnosis and risk stratification of impairment of kidney function in cirrhosis. *J Hepatol*. 2013;59:474–481. https://doi.org/10.1016/j.jhep.2013.04.036
2. Piano S, Rosi S, Maresio G, et al. Evaluation of the Acute Kidney Injury Network criteria in hospitalized patients with cirrhosis and ascites. *J Hepatol*. 2013;59:482–489. https://doi.org/10.1016/j.jhep.2013.03.039
3. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. *Hepatology*. 2008;48:2064–2077. https://doi.org/10.1002/hep.22605
4. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut*. 2015;64:531–537. https://doi.org/10.1136/gutjnl-2014-308874
5. Simonetto DA, Gines P, Kamath PS. Hepatorenal syndrome: pathophysiology, diagnosis, and management. *BMJ*. 2020;370:m2687. https://doi.org/10.1136/bmj.m2687
6. Diamond JR, Yoburn DC. Nonoliguric acute renal failure associated with a low fractional excretion of sodium. *Ann Intern Med*. 1982;96:597–600. https://doi.org/10.7326/0003-4819-96-5-597
7. Bagshaw SM, Langenberg C, Bellomo R. Urinary biochemistry and microscopy in septic acute renal failure: a systematic review. *Am J Kidney Dis*. 2006;48:695–705. https://doi.org/10.1053/j.ajkd.2006.07.017
8. Puthumana J, Ariza X, Belcher JM, Graupera I, Gines P, Parikh CR. Urine interleukin 18 and lipocalin 2 are biomarkers of acute tubular necrosis in patients with cirrhosis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2017;15:1003–1013e1003. https://doi.org/10.1016/j.cgh.2016.11.035
9. GlobeNewswire. BioPorto receives FDA 510(k) clearance for NGAL test in the United States first test to aid in assessing AKI risk for patients aged 3 months through 21 years. Accessed December 8, 2023. https://www.globenewswire.com/news-release/2023/12/07/2792907/0/en/BioPorto-Receives-FDA-510-k-Clearance-for-NGAL-Test-in-the-United-States-First-Test-to-Aid-in-Assessing-AKI-Risk-for-Patients-Aged-3-Months-Through-21-Years.html