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Impact of Terlipressin-Albumin Therapy on Serum Metabolomics in Emergency Department Patients with Hepatorenal Syndrome: A Pilot Observational Study

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Abstract

Study objective:

Hepatorenal syndrome (HRS) carries high short-term mortality, and emergency physicians often initiate terlipressin-albumin therapy with limited tools to judge early response.

Methods

This was a single-center prospective observational study conducted in the ED of a tertiary-care academic center from July 2023 to July 2024. Adults with liver disease who met HRS criteria, were admitted through the ED, and were started on terlipressin-albumin at the recommendation of the gastromedicine service, were eligible. Patients with chronic kidney disease were excluded. Serum was collected before treatment and at 24 and 72 hours for routine laboratory testing and proton nuclear magnetic resonance-based metabolomics. Analyses were complete-case and exploratory, and no adjustment was made for multiple comparisons.

Results

Forty patients were enrolled. Mean age was 51.1 years, 92.5% were men, 60.0% had alcohol-related liver disease, and 85.0% had a MELD-Na score of 25 or greater. In-hospital mortality was 50.0%. Thirty-seven serum metabolites were identified. Among patients with paired samples, creatinine decreased from 2.55 ± 1.14 to 1.91 ± 1.76 mg/dL and sodium increased from 130.52 ± 7.23 to 135.15 ± 6.01 mEq/L over the first 24 hours. These changes were accompanied by declines in metabolites linked to energy stress and osmotic balance, including 3-hydroxybutyrate, succinate, creatinine, glutamate, urea, dimethylsulfone, trimethylamine N-oxide, and myo-inositol.

Conclusion

In ED patients with HRS treated with terlipressin and albumin, serial serum metabolomics revealed early shifts in metabolites related to energy and osmotic homeostasis that paralleled conventional laboratory changes. These pilot findings support the feasibility of metabolomic profiling in the ED and identify candidate metabolites that merit evaluation in larger multicenter studies.

Introduction

Hepatorenal syndrome (HRS) is one of the most catastrophic complications encountered in patients with advanced cirrhosis. Kidney function can deteriorate quickly, hemodynamics may become unstable, and decisions about vasopressors, albumin, organ support, and disposition often need to be made within hours of arrival in the emergency department (ED).1–3 In this setting, distinguishing HRS from sepsis-

associated acute kidney injury, hypovolemia, or acute tubular injury is often difficult, yet treatment decisions cannot wait. 4–8

The circulatory physiology underlying HRS is well described. Splanchnic vasodilation, effective arterial underfilling, compensatory neurohormonal activation, renal vasoconstriction, and systemic inflammation together produce a state in which kidney dysfunction reflects severe circulatory derangement rather than primary structural renal disease.4–8 Terlipressin plus albumin is the main pharmacologic strategy used to counter this process, but clinicians still rely largely on routine laboratory tests and bedside trends to judge whether treatment is working.9–12 Those signals may be clinically useful, but they provide only a narrow view of a much broader biologic response.

Metabolomics offers a complementary way to examine that response. By profiling metabolites involved in energy production, nitrogen handling, osmotic regulation, and inflammatory stress, metabolomics can provide a systems-level picture of what is happening during acute illness.13,14 Proton nuclear magnetic resonance spectroscopy is especially attractive in this context because it permits reproducible, quantitative measurement of a broad panel of metabolites from small serum samples and is well suited to serial sampling in routine care.15–18 Prior work in cirrhosis and hepatorenal dysfunction suggests that metabolomic signatures may reflect disease severity and adverse outcomes, but the ED phase of HRS and the early biologic response to terlipressin-albumin therapy have not been well characterized.13,19,20

Among candidate metabolites, mannose has been linked to outcomes in other forms of critical illness, while 3-hydroxybutyrate, succinate, and myo-inositol are biologically connected to energy stress, inflammatory signaling, and renal-osmotic dysfunction.21–24 These observations make them plausible candidates for study in HRS, where clinicians need better markers of early response and risk. The present pilot study was designed to describe the baseline serum metabolomic profile of ED patients with HRS, explore early metabolite changes during terlipressin-albumin therapy, and identify metabolites that may generate signals for short-term in-hospital outcomes.

Methods

Study design and setting

This was a single-center prospective observational pilot study conducted in the Department of Emergency Medicine, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, in collaboration with the Centre of BioMedical Research, between July 2023 and July 2024.

Participants and case definition

Adults aged 18 years or older with liver disease who met clinical criteria for HRS, were admitted through the ED, and were started on terlipressin-albumin at the recommendation of the gastromedicine service

were eligible. Patients with known chronic kidney disease and those unwilling to participate were excluded. HRS classification reflected real-time specialty assessment during emergency care rather than adjudication through a study-specific committee, so some overlap with other acute kidney injury phenotypes cannot be excluded.1–3,6

Clinical management context

Clinical care followed routine institutional pathways and bedside decisions by the treating emergency and specialty teams. Terlipressin plus albumin was initiated on clinical advice from the gastromedicine service. Other co-interventions, including antimicrobial therapy, fluid resuscitation, vasopressor support, mechanical ventilation, and renal replacement therapy, were not protocolized within the study.

Clinical data and sample collection

At admission, age, sex, etiology of liver disease, presence of ascites, hepatic encephalopathy, serum bilirubin, INR, creatinine, sodium, and albumin were recorded. MELD-Na was calculated using established methods.20 Two blood samples were drawn before the start of terlipressin-albumin therapy on day 1, with repeat paired sampling at 24 hours and 72 hours after treatment initiation. One sample at each time-point was used for routine laboratory testing, and the other was stored at -80°C for metabolomic analysis.

Metabolomic analysis

Stored serum samples were analyzed en-bloc by proton NMR spectroscopy on an 800 MHz platform. Metabolite identification was performed using CHENOMX software and was further supported by two-dimensional NMR methods, including HSQC, TOCSY, and J-resolved spectroscopy, with spiking experiments for selected assignments.15–18

Outcomes

Patients were followed until discharge, death, or leaving against medical advice. For exploratory outcome analysis, the primary comparison was in-hospital death versus discharge, excluding patients who left against medical advice.

Statistical analysis

Categorical variables were summarized as counts and percentages. Continuous variables were summarized as mean ± SD or median with interquartile range, as appropriate. Complete-case analysis was used for each comparison, and the number of available observations varied across time points because of death, discharge, leaving against medical advice, financial constraints, and sample

contamination. No multiplicity correction was applied because the study was designed as a pilot, hypothesis-generating investigation.

Ethical approval

Approval of the study was obtained from the Institutional Ethics Committee of SGPGIMS, Lucknow (IEC code: 2022-189-MD-129), before patient recruitment. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Consent to participate

Written informed consent was obtained from all participants or, when required in the emergency setting, from the first available legally acceptable family representative before enrollment and sample collection.

Results

Cohort characteristics

Forty patients were enrolled. Mean age was 51.1 ± 11.9 years, 37 of 40 patients were men, and alcohol-related liver disease was the most common etiology, present in 24 patients. Ascites was present in 34 patients, hepatic encephalopathy in 26, and mean MELD-Na was 31.38 ± 8.17. Most patients, 34 of 40, had a MELD-Na score of 25 or greater. [Table 1]

Overall, 20 patients died during the index hospitalization, 15 were discharged alive, and 5 left against medical advice. This was therefore a severely ill ED cohort with advanced liver disease and high early mortality. [Fig. 1]

Early metabolomic response during therapy

Thirty-seven metabolites were identified in baseline serum samples. At first follow-up, routine laboratory data were available in 31 patients and paired metabolite data in 27. Over the first 24 hours, serum creatinine decreased from 2.55 ± 1.14 to 1.91 ± 1.76 mg/dL, sodium increased from 130.52 ± 7.23 to 135.15 ± 6.01 mEq/L, and INR decreased from 2.56 ± 1.32 to 2.09 ± 0.65. In parallel, several metabolites linked to energy stress and osmotic imbalance declined, including 3-hydroxybutyrate, succinate, creatinine, glutamate, urea, dimethylsulfone, trimethylamine N-oxide, and myo-inositol. [Fig. 2]

At second follow-up, routine laboratory data were available in 21 patients and paired metabolite data in 17. Routine laboratory variables did not show statistically significant change from baseline to 72 hours, but alanine, creatine, creatinine, glutamate, proline, urea, dimethylamine, and myo-inositol showed directional declines.

Exploratory outcome analysis

In the exploratory analysis excluding patients who left against medical advice, mean MELD-Na was higher in non-survivors than in survivors, 34.15 ± 6.63 versus 29.60 ± 7.73, although this difference did

not reach statistical significance. Among baseline metabolites, mannose was lower in non-survivors than survivors, with medians of 17.0 (15.0-27.3) and 30.6 (19.6-50.1) μmol/mL, respectively. [Table 2] [Fig. 3]

Among all measured metabolites, mannose was the clearest outcome-associated signal in this pilot cohort. Even so, this finding should be viewed as hypothesis-generating only.

Discussion

This pilot study provides an early look at what is happening beneath the surface when ED patients with HRS receive terlipressin and albumin. While clinicians track creatinine, sodium, and bedside hemodynamics, the serum metabolome appears to move away from a pattern associated with energy depletion and osmotic stress over the first 24 to 72 hours. Although the study does not establish causality, the observed changes support the idea that standard therapy in HRS is accompanied by broader biologic shifts than routine laboratory testing alone can capture.9-12

The observed declines in 3-hydroxybutyrate, succinate, and myo-inositol are biologically plausible. These metabolites have been linked to metabolic stress, inflammatory signaling, and renal-osmotic dysfunction in other settings, and their movement in this cohort fits with the clinical picture of partial stabilization during therapy.22-24 The value of these findings is not that they immediately change practice, but that they suggest a measurable biologic signature of response that may be relevant in future studies.

The results are also clinically relevant because conventional baseline variables did not clearly separate survivors from non-survivors in this cohort, despite severe illness and a high mortality rate. Serial metabolomic profiling may eventually offer insight into dimensions of stress and treatment response that are not fully represented by MELD-Na, serum creatinine, or sodium trends.

Among the metabolites examined, mannose stood out as the only baseline metabolite that differed clearly between survivors and non-survivors. Patients who ultimately died tended to have lower mannose concentrations at presentation. This finding is noteworthy because mannose has been associated with outcome discrimination in other critical illness settings.21 In the present study, however, mannose should be considered a candidate biomarker rather than a validated one.

Several limitations deserve emphasis. This was a single-center study of a small number of patients, so precision and generalizability are limited. Treatment decisions, including initiation of terlipressin-albumin and use of other co-interventions, were made by treating clinicians rather than by protocol. Some of the sickest patients died before later samples could be obtained, which means that later metabolomic patterns likely overrepresent survivors. Multiple metabolite comparisons were performed without multiplicity correction, so false-positive findings are possible. Finally, HRS classification reflected clinical judgment during emergency care rather than formal adjudication, and misclassification of acute kidney injury phenotype cannot be excluded.1-3,6

Conclusion

In ED patients with HRS treated with terlipressin and albumin, serial serum metabolomics revealed early and biologically plausible shifts in metabolites related to energy and osmotic homeostasis. These findings support the feasibility of metabolomic profiling in emergency HRS care and identify candidate metabolites for future validation. At present, however, they should be viewed as exploratory and hypothesis-generating rather than practice-changing.

Declarations

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Tables

Tables are available in the Supplementary Files section.

Figures

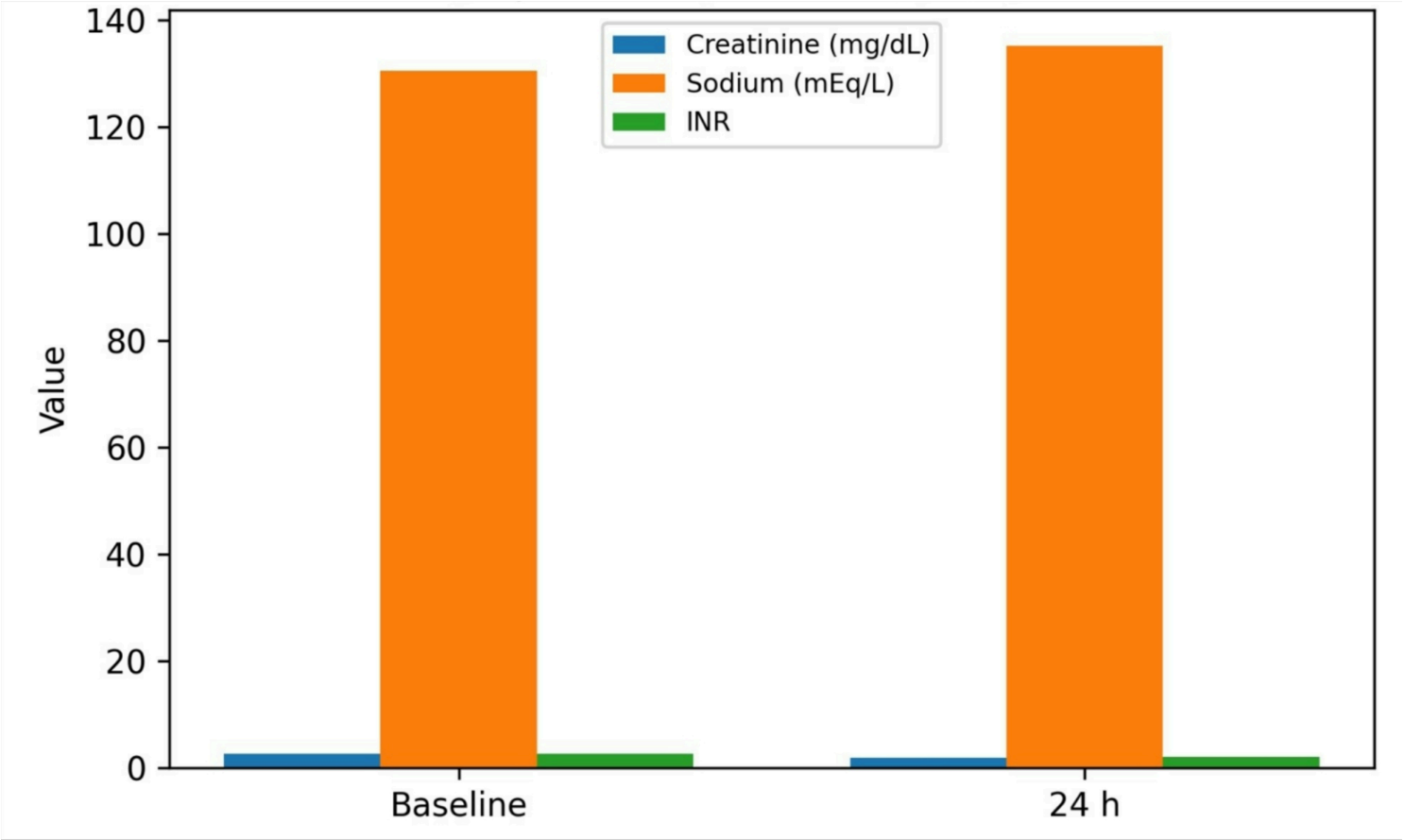


Figure 1

Early Laboratory Response

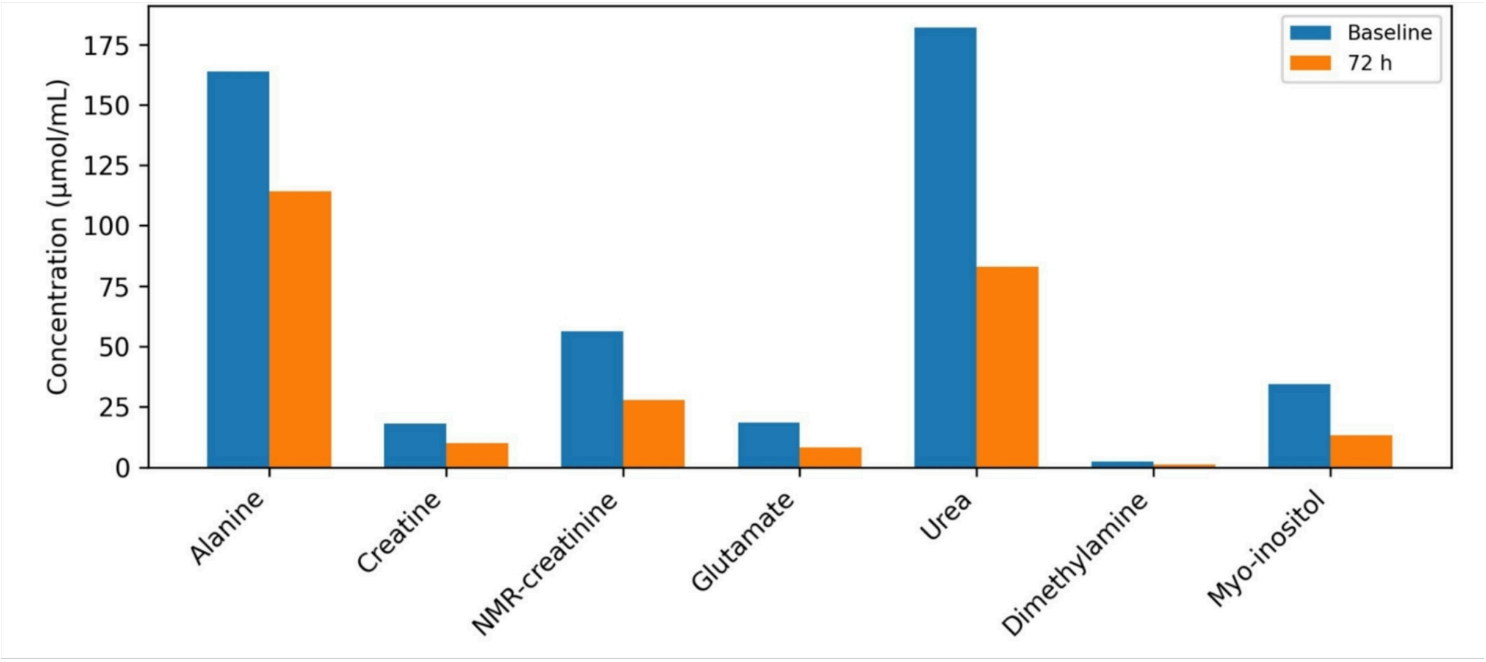


Figure 2

Early metabolomic response

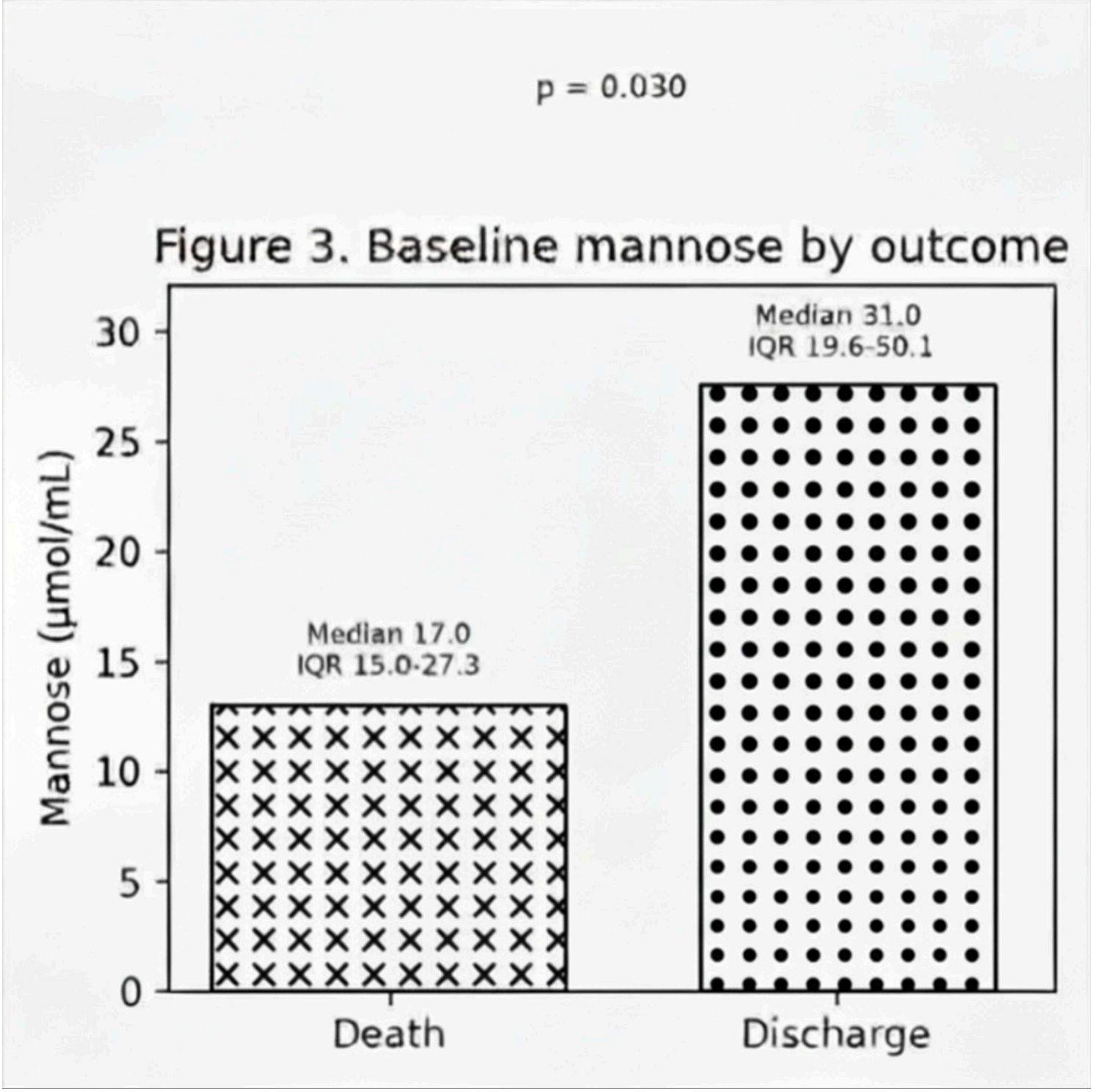


Figure 3

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