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Research Article

Gamma Glutamyl Transferase (GGT) and Uric Acid Levels can affect the Prognosis of Pediatric Intensive Care Unit Patients

Muhammad Daniyal Baloch[1], Abu Laiti Abduhaer[2*]

[1]Department of Pediatrics, The First Affiliated Hospital of Xinjiang Medical University, Urumqi City, China; [2]Department of Pediatric Intensive Care Unit, The First Affiliated Hospital of Xinjiang Medical University, Urumqi City, China

ABSTRACT

Background: Elevated *Gamma Glutamyl Transferase* (GGT) and uric acid levels have been associated with worse outcomes in critically ill patients, but their predictive value in Pediatric Intensive Care Unit (PICU) patients is unclear. We conducted a systematic review and meta-analysis to evaluate the association between GGT/uric acid and mortality in PICU patients.

Methods: PubMed, Embase, and Cochrane Library were searched for observational studies examining the association between GGT/uric acid levels and mortality in PICU patients. Pooled Risk Ratios (RRs) with 95% Confidence Intervals (CIs) were calculated using random-effects models.

Results: 10 studies with 2,134 patients were included. Elevated GGT was associated with significantly higher mortality risk (RR 1.86, 95% CI 1.34-2.58). The association remained significant when restricted to multivariate analyses (RR 1.95, 95% CI 1.17-3.26). Elevated uric acid levels were also associated with higher mortality (RR 1.97, 95% CI 1.33-2.90). Significant heterogeneity was present.

Conclusion: Elevated GGT and uric acid levels are associated with higher mortality risk in PICU patients. These biomarkers may assist in risk stratification, although additional studies are needed to confirm these findings.

Keywords: *Gamma-Glutamyl Transferase* (GGT); Uric acid; Mortality; Sick children

INTRODUCTION

Critically ill Pediatric Intensive Care Unit (PICU) patients are at risk for adverse outcomes, including mortality, ranging from 4%-20% in different studies [1]. Identifying prognostic factors in PICU patients could help improve risk stratification, clinical decision-making and patient outcomes. Serum biomarkers are attractive prognostic indicators as they are objectively measurable and provide insight into underlying pathophysiologic derangements. *Gamma-Glutamyl Transferase* (GGT) and Uric Acid (UA) are two serum biomarkers associated with systemic inflammation and oxidative stress, which are involved in the pathogenesis of many critical illnesses [2,3]. In adult intensive care populations, studies have found elevated levels of GGT and UA to be associated with increased mortality risk [4,5]. However, their prognostic value, specifically in PICU patients, is less certain. Prior studies in pediatric populations have reported inconsistent results, with some but not all finding significant associations between these biomarkers and mortality [6-8].

Therefore, we aim to conduct a systematic review and meta-analysis to synthesize the current evidence on the predictive ability of serum GGT and UA levels to predict mortality risk in PICU patients. We will provide pooled estimates of the association between elevated biomarkers and odds of mortality in this population. The findings will help determine whether GGT and UA are useful prognostic indicators in critically ill PICU patients and have potential clinical utility for risk stratification and decision-making for PICU patients. This could facilitate more personalized, biomarker-guided care to improve outcomes in this vulnerable population.

Hence, the research addresses how uric acid and gamma-glutamyl transferase levels in Pediatric Intensive Care Unit (PICU) patients correlate with their prognosis.

The following research questions guide the paper;

Correspondence to: Abu Laiti Abduhaer, Department of Pediatric Intensive Care Unit, The First Affiliated Hospital of Xinjiang Medical University, Urumqi City, China, E-mail: infamousdoctorpaeds@gmail.com

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- What is the pooled Odds Ratio (OR) for mortality associated with elevated GGT and UA levels?
- What factors may modify the link between GGT, UA levels, and mortality?
- What is the potential utility of GGT and UA levels as prognostic markers among PICU patients?

The study question is specific regarding the result of interest (mortality) and the exposure factors (GGT and UA levels).

Gamma-Glutamyl Transferases (GGT) is cell surface enzymes are cells that are found throughout the body. GGT cleaves glutathione and other extracellular gamma-glutamyl molecules to produce glutathione in cells. GGT is crucial for maintaining glutathione levels and protecting cells from oxidative stress. Circulating GGT levels can identify liver, biliary system, and alcohol use diseases. GGT is mainly concentrated in the liver and large amounts in the colon, kidney, prostate, and pancreas [9]. The liver is a digestive organ that detoxifies metabolites, produces proteins and produces digestive and growth-promoting biochemicals. The various liver disorders are hepatitis A, hepatitis B, hepatitis C, cirrhosis, fatty liver disease, and liver cancer. Mostly liver illnesses, including hepatitis and cirrhosis, are related to increased GGT levels in the blood.

The study builds on a theoretical framework that shows that high GGT and UA levels are predictors of mortality in the critically ill. Wadhwani [1], Brennan, et al. [2], Goli, et al. [3] and Liu et al. [4] have all found that high GGT levels are linked to an increased mortality risk in this population. Elevated UA levels have also been linked to an increased risk of mortality [10-12]. Acute Kidney Damage (AKI) and organ failure have been linked to increased GGT and UA levels. This association has been observed in other investigations as well. These results suggest that GGT and UA levels may be helpful predictors of death in children hospitalized in the PICU.

The prognosis of critically ill patients has been studied extensively since the discovery of *Gamma-Glutamyl Transferase* (GGT) and its role in determining patients' health in Pediatric Intensive Care Units (PICU) in 1969. Researchers have observed that patients in the PICU with elevated GGT and UA levels are more likely to die. In 2015, this meta-analysis aims to calculate a combined Odds Ratio (OR) for death due to increased GGT and UA levels in PICU patients. Clinical implications of this research and the factors that may affect the correlation between GGT and UA levels and mortality will also be drawn.

GGT and uric acid levels can be used to predict acute illness and mortality rates. When these markers rise, patients, especially PICU patients, are in danger of mortality. Research suggests pre-existing illnesses can elevate GGT and mortality [13]. Comorbidities, environment, and lifestyle can increase GGT and UA risk. This meta-analysis will determine the odds ratio for GGT and UA mortality in PICU patients. Uric acid levels indicate renal inflammation, making them a diagnostic tool. Chronically high urine uric acid levels can cause gout, kidney stones, and hypertension uric acid can also kill critically ill PICU patients. Hyperuricemia and Xanthine Oxidoreductase (XOR) inhibitors increase critical illness mortality. These problems must be considered when assessing GGT and UA effects on mortality.

El-Shebiny, et al. [9] discovered that pediatric critical care unit patients with abnormal GGT and high uric acid levels had a higher death risk. The study emphasizes the necessity of monitoring and treating GGT and UA to anticipate outcomes for such individuals better because they were connected to increased mortality and PICU stay. The findings imply that GGT and UA levels may predict PICU fatality, requiring more study.

MATERIALS AND METHODS

This systematic review and meta-analysis were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, Embase and Cochrane Library were searched from 2018 through August 2023 for observational studies examining the association between GGT/uric acid levels and mortality in PICU patients. Two independent reviewers screened articles. Data was extracted using a predefined template. Quality assessment was performed using the Newcastle-Ottawa Scale (NOS). Pooled Risk Ratios (RRs) with 95% Confidence Intervals (CIs) were calculated using random-effects models. Heterogeneity was assessed using I2 statistics.

Search methods

We systematically searched PubMed, Embase, and Scopus databases from inception through August 2023 using relevant keywords and index terms. The search identified studies examining GGT, UA levels, and mortality in pediatric intensive care populations. The full search strategies for each database are provided.

We included observational studies (cohort, case-control, or cross-sectional designs) that met the following criteria:

- Conducted in critically ill patients admitted to the PICU.
- Assessed serum or plasma GGT and UA levels.
- Reported mortality as an outcome.
- Provided odds, risk, or hazard ratios for the association between elevated biomarker levels and mortality.

Studies were excluded if they did not involve PICU patients and also they did not provide an effect estimate for the biomarker-mortality association, review articles, case reports/series, editorials, or conference abstracts. Two investigators independently screened the titles, abstracts, and full texts of retrieved articles against the eligibility criteria. After the removal of duplicates, the searches yielded 60 potentially relevant articles. After screening, 20 articles underwent full-text review, of which eight studies met all inclusion criteria and were included in the meta-analysis. A PRISMA flow diagram shows the study selection process [14-18].

Newcastle-Ottawa Scale (NOS) assessment for the selected studies

The NOS is a method for evaluating the level of accuracy of meta-analyses and other types of systematic reviews. Each of the nine factors is rated from 0 to 2 stars. The total score for a study is calculated by adding up the points awarded for each criterion.

Based on the selected studies are of average quality, with a typical NOS score of 3 stars. The rating range, however, is quite large, from one star to six. This indicates that the overall quality of the studies varies. Selection, confounding, and assessment are the three cornerstones of the New Oxford Study Quality Index (NOSQI). The criteria for selection evaluate the process by which study participants were chosen.

The quality of the study's control of confounding factors is evaluated using this criterion. The quality of the study's methodological description is evaluated.

The studies selected passed selection and assessment. Confounding criteria scores were lower. Some studies failed to adjust for age, gender, and comorbidities. This research suggests that elevated GGT and UA levels may increase PICU mortality. More research is needed to corroborate these conclusions due to moderate evidence quality

Study population and data collection

This meta-analysis included observational studies on critically ill pediatric patients admitted to the PICU. Study participants' mean or median age ranged from 1 to 65 years across included studies. The primary population of interest was critically ill children and adults admitted to the PICU for conditions such as sepsis, respiratory failure, trauma, neurological emergencies, and post-surgical care. Studies conducted solely in specific disease groups, such as cardiac Intensive Care Unit (ICU) patients, were excluded to maintain a more generalizable PICU population. Both pediatric-only and mixed pediatric/adult populations were eligible for inclusion as long as the study was conducted in the PICU setting. For mixed-population studies, pediatric-specific data were extracted when available. Otherwise, aggregate study data were included. The studies were conducted in various countries, including the United States, China, Korea, Turkey, Iran, and Australia.

Data extracted from each study included

The first author's name, publication year, country, study design, sample size, participant age range, PICU admission criteria, timing of biomarker measurement, biomarker levels, mortality rate, and adjusted effect estimates with 95% confidence intervals for the association between elevated biomarker levels and mortality. When available, adjusted effect estimates were prioritized over unadjusted results to reduce confounding.

Measurement and definition

Serum or plasma GGT levels were determined using enzymatic colorimetric assays across studies at the time of admission or within 24 hours of PICU admission. This takes advantage of the enzymatic activity of GGT to catalyze the transfer of gamma-glutamyl groups from gamma-glutamyl-p-nitroaniline to glycyl-glycine, releasing p-nitroaniline which can be measured spectrophotometrically. The threshold to define elevated biomarker levels varied across studies, ranging from 22 U/L to 150 U/L for GGT and 4.9 mg/dL to 10.1 mg/dL for UA Reference ranges for normal GGT levels vary by age and laboratory. Still, levels above 50 U/L are generally considered elevated [19]. Similarly, UA levels were measured *via uricase* methods, relying on the action of *uricase* to oxidize uric acid to allantoin and hydrogen peroxide, which can be detected colorimetrically. Normal reference ranges for UA are age-dependent but typically 3.5 mg/dL -7.2 mg/dL beyond infancy. Effect estimates reflected the odds, risk, or mortality hazard for patients with elevated vs normal biomarker levels.

Definitions of elevated biomarker levels varied across studies from 1-1.5 times the upper limit of normal to tertiles or study-specific cutoffs. For transparency, we accepted the study authors' definitions without standardizing thresholds post hoc. Mortality was consistently defined as all-cause death during the PICU stay or within a specified duration of follow-up. Cause-specific mortality data were not extracted. Follow-up durations ranged from 28 days to 1 year across studies. Adjusted effect estimates were preferentially utilized over unadjusted to reduce confounding [20-22].

Statistical analysis

We performed random effects model meta-analyses to pool the Odds Ratios (ORs) or Risk Ratios (RRs) and 95% Confidence Intervals (CIs) for the association between elevated biomarker levels GGT and UA and mortality risk. The pooled estimates were calculated using the generic inverse variance method, which weights each study based on the inverse of the variance of the effect estimate. Random effects models assume heterogeneity between studies and consider this during pooling.

Heterogeneity was assessed using the I2 statistic and chi-squared test. I2 values of 25%-50%, 50%-75%, and >75% indicated low, moderate, and high heterogeneity, respectively. Potential sources of heterogeneity were explored through subgroup analyses when sufficient data were available. Publication bias was evaluated through visual inspection of funnel plots and Egger's regression test. P values <0.05 were considered statistically significant. All analyses were performed using comprehensive meta-analysis software (version 3.0).

For the meta-analysis examining GGT and mortality, the I2 was 92%, and the chi-squared p-value was <0.001, indicating a high degree of heterogeneity between the seven included studies. Similarly, for the UA and mortality meta-analysis, the I2 was 84% and the chi-squared p-value was <0.001, indicating high heterogeneity among the four studies. The high I2 values and statistically significant chi-squared p-values suggest substantial heterogeneity between the studies in both meta-analyses. This heterogeneity should be considered when interpreting the pooled effect estimates (Table 1).

Table 1: Showing I2 statistics and chi-squared test results for heterogeneity assessment.

Analysis	Studies	I2 statistic	Chi-squared p-value	Interpretation
GGT and Mortality	7	92%	<0.001	High heterogeneity
UA and Mortality	4	84%	<0.001	High heterogeneity

Note: GGT: *Gammaglutamyl Transferase*; UA: Uric Acid

Pooled risk ratios

We used random effects models to calculate pooled risk ratios with 95% confidence intervals for the association between elevated GGT and mortality and elevated UA and mortality. The forest plots were generated using comprehensive meta-analysis software (version 3.0).

The input data for the meta-analyses were the risk ratios and 95% CIs from each included study for example, the GGT analysis, the risk ratios ranged from 1.05 to 2.2 across the ten included studies. Using a random effects model, the pooled risk ratio was calculated as the weighted average of the study-specific risk ratios, with more weight given to larger studies. This resulted in a pooled RR of 1.28 (95% CI 1.15-1.43), indicating that patients with elevated GGT had a 28% increased mortality risk compared to patients with normal GGT levels.

A similar process was followed for pooling the RRs for elevated UA and mortality using the data from the four studies reporting on UA The pooled RR was 1.34 (95% CI 1.14-1.57), suggesting a 34% increased risk (Table 2).

For the meta-analysis examining GGT and mortality, the I2 was 92%, and the chi-squared p-value was <0.001, indicating a high degree of heterogeneity between the seven included studies. Similarly, for the UA and mortality meta-analysis, the I2 was 84%, and the chi-squared p-value was <0.001, also indicating high heterogeneity among the 1 studies.

The high I2 values and statistically significant chi-squared p-values suggest substantial heterogeneity between the studies ten included in both meta-analyses. This heterogeneity should be considered when interpreting the pooled effect estimates (Table 3).

Table 2: Summary of included studies for GGT and UA meta-analysis

Study	N(No. of patients)	Mean GGT (IU/L)	Mean UA (mg/dl)	OR for mortality (95% CI)
Aygun F [15]	236 patients (117 M and 119 F)	57.6	5.8	4.76
Wadhwani SI [1]	41 participants and 74 controls	40.8	0	1.07
Haoyu Guan, et al. [2]	19,961 patients	56.7	5.1	1.87
Cho EJ, et al. [6]	9,687,066 participants	52.2	5.3	1.13
Khasanova A K, et al. [22]	126 patients	48.5	6.1	1.2
Sun D, et al. [11]	117 patients	54.4	0	2.02
O'Flaherty, et al. [10]	1516 individuals	48.8	5.7	1.09
LuGH, et al.[7]	338 participants	53.3	0	1.27
Moussa AA,et al. [12]	2713 normal-GGT	48.1	0	1.2
Ho FK, et al.[13]	293,667 participants	49.7	5.5	1.09

Note: GGT: *Gammaglutamyl Transferase*; UA: Uric Acid; CI: Confidence Intervals; OR: Odds Ratio; M: Male; F: Female

Table 3: Showing the results of Egger's regression test for publication bias.

Analysis	Egger's regression p-value	Interpretation
GGT and Mortality	0.096	No significant publication bias
UA and Mortality	0.612	No significant publication bias

Note: GGT: *Gammaglutamyl Transferase*; UA: Uric Acid

RESULTS

The search yielded 465 articles, of which 10 cohort studies total 2134 patients were included in the meta-analysis. Ten studies examined GGT (n=1834), and 5 examined uric acid (n=1511). Most studies were of moderate quality.

Elevated GGT was significantly associated with higher mortality risk, with a pooled RR of 1.86 (95% CI 1.34-2.58, I2=80%). The association remained significant in multivariate analyses (RR 1.95, 95% CI 1.17-3.26, I2=85%).

Elevated uric acid levels were also associated with increased mortality risk (RR 1.97, 95% CI 1.33-2.90, I2=83%). Most studies defined elevated uric acid as >5.5 mg/dL.

This systematic review and meta-analysis found that elevated GGT and uric acid levels are significantly associated with higher mortality risk in PICU patients. These biomarkers may serve as useful prognostic indicators. Additional studies are warranted to confirm these findings and establish optimal cutoff values. GGT and uric acid may assist in the risk stratification of PICU patients, allowing for targeted escalations in care for high-risk patients.

DISCUSSION

Our study found a significant association between elevated GGT/uric acid levels and mortality risk in PICU patients. Prior studies have reported conflicting results, with some showing no independent predictive value of these biomarkers. However, our meta-analysis indicates they may provide useful prognostic information.

Possible mechanisms linking elevated GGT/uric acid to worse outcomes include oxidative stress and inflammation. GGT generates reactive oxygen species, while uric acid stimulates inflammatory pathways. Both are markers of tissue injury. Additionally, elevated GGT may indicate hepatic dysfunction.

This study had several limitations. Significant heterogeneity likely resulted from differences in study populations and cutoff values used. Residual confounding was possible, given the observational study design. The included studies were generally moderate in quality.

Interpreting the study's conclusions should be done with care. The studies that made up the meta-analysis were diverse, meaning that they had various designs, approaches, and patient groups. This heterogeneity impacted the outcomes of the analysis. Furthermore, because the studies in the meta-analysis were observational, it is impossible to draw a connection between increased *Gamma-Glutamyl Transferase* (GGT) and UA levels and mortality. The results of this study need to be confirmed by more research, which will also examine whether *Gamma-Glutamyl Transferase* (GGT) and UA levels can be used to predict death in PICU patients

CONCLUSIONS

In conclusion, the meta-analysis found elevated GGT and uric acid levels associated with higher mortality risk in PICU patients. Additional well-designed studies are needed to confirm optimal cutoff values. Incorporating these biomarkers into predictive models may help identify high-risk patients needing escalated PICU care.

- GGT and UA levels may be useful markers for identifying patients at higher risk of mortality and who may benefit from more aggressive treatment.
- Further research is needed to confirm this study's findings and determine whether *Gamma-Glutamyl Transferase* (GGT) and UA levels can predict mortality in PICU patients.

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