Association between Admission Serum Albumin and 12-weeks Mortality in AIDS/HIV Late Diagnosis Patients in Hospital: A Retrospective Cohort Study

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Research Article

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Abstract

Background:

Many patients with human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) are still undiagnosed or diagnosed late, which leads to serious consequences and burdens. Low serum albumin levels are significantly correlated with disease prognosis. This study investigated the association between serum albumin concentration and 12-week mortality of HIV/AIDS with late diagnosis in mainland China.

Methods:

In this single-center retrospective cohort study, 1,079 inpatients with late HIV/AIDS diagnosis between January 2018 and December 2021 were included. The strata of serum albumin levels were categorized into tertiles. Disease progression was estimated using the 12-week mortality. Cox proportional hazards regression models were used to evaluate the serum albumin concentration with disease progression. The Kaplan–Meier method was used to analyze the effect of different serum albumin levels on mortality.

Results:

During the 12-week follow-up, 77 patients (7.1%) died. Serum albumin concentration was significantly correlated with late HIV/AIDS diagnosis progression. In Cox proportional hazards regression models, the mortality risk decreased by 8% with the increase in every 1g/L serum albumin after adjustment (hazard ratio [HR] = 0.92, 95% confidence interval [CI]: 0.88–0.97). Compared with that of the low serum albumin group (< 28 g/L), the middle group (28–33 g/L) mortality risk decreased by 70% (HR = 0.30, 95% CI: 0.16–0.60), and that of the high group (≥ 34 g/L) decreased by 45% (HR = 0.55, 95% CI: 0.27–1.15) after adjustment.

Conclusions: Hospitalized patients with late HIV/AIDS diagnosis and low serum albumin concentrations in mainland China had a relatively high short-term mortality rate. Further research is needed to characterize the role of serum albumin in the timely prevention of 12-week mortality in patients with a late diagnosis.

Background

Although early combination antiretroviral therapy (cART) has significant clinical benefits for people living with human immunodeficiency virus (HIV), even with a CD4 count > 500 cells/µL [1], several cases are undiagnosed or diagnosed late [2]. Late diagnosis is defined as confirmation of HIV infection with CD4 count < 350 cells/µL or progression to AIDS within 90 days of diagnosis [3, 4]. According to real data from the Joint United Nations Program on HIV/AIDS (UNAIDS) from 85 countries, 29% of newly diagnosed HIV infections are associated with CD4 cell counts < 200 cells/µL [5]. The median threshold duration from HIV infection to a CD4 cell count ≤ 350 cells/µL was 4–6 years [6]. During this period, failure to promptly diagnose and implement effective antiviral treatment will greatly increase the infection and death rates of AIDS-related diseases such as tuberculosis [7, 8]. Late diagnosis and treatment are the leading causes of death among people living with HIV in Europe [9].

Metabolic biomarkers such as alkaline phosphatase (AP) and plasma hemoglobin are closely related to mortality in people living with HIV [10]. Serum albumin level is a predictor of short- and long-term severe non-
AIDS events [11] and is associated with mortality after HIV/hepatitis C virus (HCV) co-infection [12]. Several studies have been conducted to determine the association between death risk and serum albumin levels. Serum albumin is an important blood index that acts as a carrier for various endogenous and exogenous compounds [13] and has antioxidant and anti-inflammatory properties [14]. Although it cannot be used as a single indicator to evaluate nutritional status, serum albumin is closely related to disease severity [15, 16], which is helpful for health care providers to better understand a patient’s condition and is important for maintaining clinical records of HIV/AIDS progression.

However, few studies have focused on the relationship between serum albumin levels and mortality in patients with late HIV/AIDS diagnosis. Therefore, this study will discuss the effect of serum albumin concentration upon admission on the 12-week mortality rate of this group of people.

**Methods**

**Study Design and Participants**

This single-center, retrospective cohort study was performed at a 617-bed capacity hospital, the largest designated HIV/AIDS care hospital in Southeast China, between January 2018 and December 2021. This study was approved by the ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University. Late diagnosis was defined as a CD4 count < 350 cells/µL or an AIDS-defining condition within 3 months of HIV diagnosis. All patients with late HIV/AIDS diagnosis were admitted, treated, and evaluated at the hospital. All discharged patients were followed up via telephone by the health manager. Patients younger than 18 years, with no serum albumin data, and who died from non-medical causes (suicide and trauma) were excluded. Additionally, patients who were lost to telephone follow-up at 12 weeks were excluded. Furthermore, 12-week mortality was defined as death from any cause within 12 weeks of hospitalization for HIV/AIDS. The strata of serum albumin levels of the final cohort of 1,079 patients were categorized into tertiles.

**Data Collection and Measurements**

Participants’ sociodemographic variables, clinical characteristics, and laboratory data were collected from electronic medical records. Blood test samples were collected within 24 h upon admission.

Mortality data were extracted from the medical records of the participants and the hospital telephone follow-up system. The telephone follow-up system in this hospital is used to maintain records of the deaths of patients who have been discharged; all death events and times were recorded in this system. All data were carefully checked after abstraction.

All study laboratories successfully completed a standardization and certification program. CD4 and CD8 counts were measured using a BD facscount system (Becton Biosciences). In addition, serum albumin, total bilirubin (TBIL), glutamic-pyruvic transaminase (ALT), and serum creatinine (Cr) concentrations were measured using a biochemical analyzer (AU5800, Beckman Coulter, Inc.), and hemoglobin, thrombocyte, and C-reactive protein (CRP) levels were analyzed using a hematology analyzer (Sysmex, Kobe, Japan) [17].

**Statistical Analysis**
Continuous variables were presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), and categorical variables were presented as numbers and percentages. For the baseline characteristics, the statistical differences among the tertiles of serum albumin concentration were tested using a one-way analysis of variance (ANOVA) for continuous variables and the chi-squared test for categorical variables. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for 12-week mortality associated with serum albumin using Cox proportional hazards models.

Variables considered confounders based on the existing literature and clinical judgments were included. We performed tests for linear trends by entering the median value of each category of serum albumin as a continuous variable. The associations between serum albumin levels and 12-week mortality were evaluated on a continuous scale with restricted cubic spline curves based on Cox proportional hazards models. Interaction and stratified analyses were conducted according to sex, age, thrombocyte count, hemoglobin, CD4, CD8, CRP, procalcitonin (PCT), Cr, ALT and TBIL levels. The cumulative rates of death were compared using Kaplan–Meier curves.

The percentage of missing data was low (PCT, 1.02%; Body Mass Index (BMI), 2.13%) and no imputation was performed. All analyses were performed using the statistical software packages R 3.3.2 (http://www.Rproject.org, The R Foundation) and Free Statistics software versions 1.7.

**Results**

**Baseline Characteristics of the Study Participants**

Of the 2,071 inpatients, 1,079 who fulfilled the inclusion criteria were identified (Figure 1). The baseline characteristics of the study participants according to albumin categories are summarized in Table 1. A total of 929 (86.1%) patients were male, and 150 (13.9%) were female. The median CD4 count was 74.3 cells/µL and 21.3% of patients had no ART before discharge. During the 12-week follow-up period, 77 patients (7.1%) died.

**Association between Serum Albumin and 12-week Mortality in Different Models**

Figure 2 presents a linear-shaped association between serum albumin level and 12-week mortality after adjusting for potential confounding factors using Cox proportional hazards models. The solid line indicates the estimated risk of death, and the dotted lines represent point-wise 95% CIs adjusted for age, sex, hemoglobin, thrombocyte, CD4, CD8, ALT, TBIL, Cr, CRP, PCT and BMI.

The overall survival was improved for late diagnosis in the high serum albumin concentration group, and the risk of mortality decreased by 8% with every 1g/L increase in serum albumin concentration after adjustment (HR = 0.92, 95% CI: 0.88–0.97) (Table 2). The study also showed that the non-adjusted HR for the middle serum albumin group relative to the low group was 0.31 (95% CI: 0.17–0.54; \( P < 0.001 \)). Furthermore, after adjustment, the results did not change substantially. In Model 1, adjusted for age, sex, hemoglobin, thrombocyte, CD4, and CD8, HR was 0.32 (95% CI: 0.18–0.57; \( P < 0.001 \)), and in Model 2, additionally adjusted for TBIL, ALT, Cr, CRP, PCT and BMI, HR was 0.30 (95% CI: 0.16–0.60; \( P = 0.001 \)).

**Subgroup Analysis of Serum Albumin and Mortality**
Figure 3 shows the association between the stratification and interaction analysis results for serum albumin concentration and mortality in all participants. The effect size of serum albumin on the 12-week mortality was stable. Stratified analysis showed a negative correlation between serum albumin level and 12-week mortality in patients with late HIV/AIDS diagnosis. These results were consistent with the Cox proportional hazards model analysis. Subgroup analysis didn’t show a significant interaction between serum albumin level and the primary outcome (all $P$ for interaction > 0.05).

**Kaplan–Meier Curve**

Kaplan-Meier curve of 12-week survival in patients with late diagnosis stratified by serum albumin: group 1 (< 28 g/L), group 2 (28–33 g/L), and group 3 (≥ 33 g/L) (Figure 4). The log-rank test showed that the overall survival was worse for patients with late HIV/AIDS diagnosis in the lowest serum albumin group than that in the high and moderate serum albumin concentration groups ($P < 0.0001$).

**Discussion**

Late diagnosis of HIV is still common in South China [18, 19], which affects patients receiving highly active ART and increasing mortality [20]. This cohort study provided evidence for a linear relationship between serum albumin and 12-week mortality in patients with late HIV/AIDS diagnosis, which was independent of age, sex, hemoglobin, thrombocyte count, CD4, CD8, TBIL, ALT, Cr, CRP, PCT and BMI. The risk of 12-week mortality decreased by 6% with every 1 g/L increase in the serum albumin concentration. Furthermore, stratified analysis reflected a persistent positive association between serum albumin concentration and 12-week mortality.

In recent decades, many studies have explored the association between serum albumin levels and mortality. Some studies have shown that serum albumin levels upon admission are inversely associated with short-term mortality in various diseases [20, 21]. It is not only used as a predictor of short-term mortality in patients with HIV/tuberculosis (TB) co-infection [22], but also as a predictor of in-hospital mortality in those with HIV [23]. However, it has been suggested that increasing serum albumin levels by infusion does not alter the survival rate [24]. In patients with sepsis, additional albumin infusion did not improve survival compared with that of crystalloid infusion alone [25].

AIDS-defining illnesses are the main cause of death in patients with late HIV diagnosis [26, 27]. Blood markers traditionally used to assess disease severity in patients with AIDS include CD4 and CD8 [28], inflammation markers, such as neutrophil-lymphocyte ratio [29], and CRP [30, 31]. The development of T-cell exhaustion in chronic HIV infection is due to high levels of HIV antigen, strong proinflammatory immune activation, and impaired T-cell homeostasis [28]. However, researchers have increasingly recognized that serum albumin is also an important indicator for evaluating the degree of inflammation and disease prognosis, and low baseline serum albumin levels and impaired immunity reliably predict mortality [32]. The main causes of hypoproteinemia due to chronic inflammatory states include albumin leakage during the inflammatory response [33] resulting from increased capillary permeability [34]. Meanwhile, the total albumin mass decreases with the short half-life of albumin [34]. HIV infection also reduces serum concentrations through different mechanisms, such as HIV-1 Tat-1 protein, which damages the barrier function of the endothelium.
[35]. On the contrary, some studies used cohort studies to find a moderate-weak negative correlation between serum albumin level and the inflammatory index CRP; however, serum albumin is more affected by serum sodium and hemoglobin [36]. This may be because different experts used different indicators to evaluate inflammation.

Our study had several strengths. Cases were collected continuously from January 2018 to December 2021 to avoid selection bias. To ensure an independent association of serum albumin and outcomes, the study was adjusted for several potential confounding factors, including age, sex, CD4, CD8, CRP, PCT, ALT, TBIL, Cr and BMI. In this study, we conducted a subgroup analysis using age, gender, hemoglobin, TBIL, ALT, PCT, CRP and Cr levels as stratification factors and tested the interaction. The effect size of serum on 12-week mortality in most subgroups was stable, and no interaction was found between stratified factors and 12-week mortality. The selection of mortality at 12 weeks after admission in this study could reduce missing samples and ensure outcomes to truly reflect the early mortality of patients with late HIV/AIDS diagnosis in the real world. We included all newly diagnosed patients and evaluated the mortality rate within 12 weeks after admission to reduce sample loss and calculation bias caused by admission criteria.

This study has some limitations. First, age, sex, CD4, CD8, CRP, PCT, ALT, TBIL, Cr and BMI were adjusted in this study, and we aimed to prevent the influence of other factors; however, some influences were not recorded or observed. Therefore, the effect of residual confounding factors could not be eliminated. Second, we could not conclusively determine the causal relationship between serum albumin concentration and 12-week mortality. Third, all participants were Chinese, and the findings of this study may not apply to other ethnicities.

**Conclusion**

Among a sample of Southeast Chinese patients with late HIV diagnosis, low serum albumin concentration was independently associated with an elevated risk of 12-week mortality. Serum albumin is a simple but effective nutrition and inflammation marker routinely detected in clinical settings and deserves more attention from medical staff. Further research is needed to characterize the role of serum albumin in the timely prevention of 12-week mortality in patients with a late diagnosis.

**Abbreviations**

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; HR: hazard ratio; CI: confidence interval; cART: combination antiretroviral therapy; AP: alkaline phosphatase; HCV: hepatitis C virus; TBIL: total bilirubin; ALT: glutamic-pyruvic transaminase; Cr: serum creatinine; CRP: C-reactive protein; SD: standard deviations; IQR: interquartile ranges; HRs: Hazard ratios; PCT: procalcitonin; BMI: Body Mass Index.

**Declarations**

**Ethics Statement**

The study protocol was approved by the medical ethics committee of Mengchao Hepatobiliary Hospital of Fujian Medical University (2022-017-01)
Author Contributions

RH and YS conducted data analysis and wrote the manuscript. LH and RH designed the study and reviewed the manuscript. YY and YS conducted data collection and interpretation. YY, HZ, and JH collected data. JW and LW reviewed the data. All authors read and approved the final manuscript.

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Conflict of interest statement

All authors have nothing to disclose

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Data Availability Statement

The raw data required to reproduce these findings cannot be shared at this time as the data from an ongoing study. If necessary, some or all the data used during the study are available from the corresponding author upon reasonable request.

References


Tables

Table 1 Baseline characteristics of the study participants
<table>
<thead>
<tr>
<th>Variables</th>
<th>Serum Albumin</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 1079)</td>
<td>≤28g/L (n = 304)</td>
<td>28-33g/L (n = 391)</td>
<td>≥34g/L (n = 384)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>0.768</td>
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<td></td>
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<tr>
<td>Male</td>
<td>929 (86.1)</td>
<td>262 (86.2)</td>
<td>340 (87)</td>
<td>327 (85.2)</td>
</tr>
<tr>
<td>Female</td>
<td>150 (13.9)</td>
<td>42 (13.8)</td>
<td>51 (13)</td>
<td>57 (14.8)</td>
</tr>
<tr>
<td>Age(years), Mean ± SD</td>
<td>47.0 ± 15.3</td>
<td>47.5 ± 15.0</td>
<td>48.9 ± 15.4</td>
<td>44.8 ± 15.3</td>
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<td>Diagnosis, n (%)</td>
<td>&lt; 0.001</td>
<td></td>
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<tr>
<td>HIV</td>
<td>57 (5.3)</td>
<td>5 (1.6)</td>
<td>11 (2.8)</td>
<td>41 (10.7)</td>
</tr>
<tr>
<td>AIDS</td>
<td>1022 (94.7)</td>
<td>299 (98.4)</td>
<td>380 (97.2)</td>
<td>343 (89.3)</td>
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<tr>
<td>CD4(cells/ul), Mean ± SD</td>
<td>74.3 ± 86.1</td>
<td>44.0 ± 64.6</td>
<td>62.6 ± 72.6</td>
<td>110.1 ± 100.3</td>
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<tr>
<td>CD8(cells/ul), Mean ± SD</td>
<td>538.0 ± 577.7</td>
<td>368.8 ± 356.2</td>
<td>487.8 ± 411.4</td>
<td>722.9 ± 779.1</td>
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<td>BMI, Mean ± SD</td>
<td>20.1 ± 3.0</td>
<td>19.5 ± 3.0</td>
<td>19.8 ± 2.9</td>
<td>20.8 ± 3.1</td>
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<td>ART before discharge, n (%)</td>
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<td>230 (21.3)</td>
<td>93 (30.6)</td>
<td>53 (13.6)</td>
<td>84 (21.9)</td>
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<td>Yes</td>
<td>849 (78.7)</td>
<td>211 (69.4)</td>
<td>338 (86.4)</td>
<td>300 (78.1)</td>
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<td>Albumin infusion, n (%)</td>
<td>&lt; 0.001</td>
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<td>No</td>
<td>428 (39.7)</td>
<td>25 (8.2)</td>
<td>171 (43.7)</td>
<td>232 (60.4)</td>
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<td>Yes</td>
<td>651 (60.3)</td>
<td>279 (91.8)</td>
<td>220 (56.3)</td>
<td>152 (39.6)</td>
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<td>12-week mortality, n (%)</td>
<td>&lt; 0.001</td>
<td></td>
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<td>1002 (92.9)</td>
<td>263 (86.5)</td>
<td>374 (95.7)</td>
<td>365 (95.1)</td>
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<td>77 (7.1)</td>
<td>41 (13.5)</td>
<td>17 (4.3)</td>
<td>19 (4.9)</td>
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Table 2 Association between serum albumin and 12-weeks mortality in Cox proportional hazards models
<table>
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<th>Variable</th>
<th>n total</th>
<th>n event_%</th>
<th>Uadjusted</th>
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<td>HR 95%CI P-value</td>
<td>HR 95%CI P-value</td>
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<td>Albumin</td>
<td>1079</td>
<td>77 (7.1)</td>
<td>0.92 (0.89~0.95) &lt;0.001</td>
<td>0.93 (0.89~0.96) &lt;0.001</td>
<td>0.92 (0.88~0.97) 0.001</td>
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<td>Subgroups</td>
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<td>28g/L</td>
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<td>1(Ref)</td>
<td>1(Ref)</td>
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<td>28-33g/L</td>
<td>391</td>
<td>17 (4.3)</td>
<td>0.31 (0.17~0.54) &lt;0.001</td>
<td>0.32 (0.18~0.57) &lt;0.001</td>
<td>0.30 (0.16~0.60) 0.001</td>
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<tr>
<td>≥34g/L</td>
<td>384</td>
<td>19 (4.9)</td>
<td>0.35 (0.2~0.6) &lt;0.001</td>
<td>0.45 (0.24~0.86) 0.015</td>
<td>0.55 (0.27~1.15) 0.112</td>
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<tr>
<td>Trend.test</td>
<td>1079</td>
<td>77 (7.1)</td>
<td>&lt;0.001</td>
<td>0.004</td>
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Note: TBIL, total bilirubin; ALT, glutaminc-pyruvic transaminase; Cr, serum creatinine; CRP, c reactive protein; PCT, procalcitonin, BIM, Body Mass Index.

Model 1: adjusted by gender, age, hemoglobin, thrombocyte, CD4, CD8

Model 2: adjusted by model 1 plus TBIL, ALT, Cr, CRP, PCT, BMI

Figures
Admitted to the AIDS center for the first time from 2018 to 2021 (n=2071)

Hospitalized AIDS patients with late diagnosis from 2018 to 2021 (n=1092)

Patients including in study (n=1079)

Excluded:
1. Undiagnosed AIDS/HIV (n=11)
2. AIDS/HIV was first identified more than 3 months (n=658)
3. Missing CD4 value (n=202)
4. CD4 ≥350 (n=108)

Excluded:
1. Missing Serum albumin value (n=3)
2. <18 years (n=9)
3. Suicide (n=1)

Figure 1

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Figure 2

Legend not included with this version
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Total</th>
<th>Event (%)</th>
<th>HR (95% CI)</th>
<th>P for interaction</th>
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<td><strong>Sex</strong></td>
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<td>Male</td>
<td>929</td>
<td>67 (7.2)</td>
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<td>150</td>
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<td><strong>Age (Years)</strong></td>
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<tr>
<td>&lt;50</td>
<td>572</td>
<td>38 (6.6)</td>
<td>0.91 (0.85-0.98)</td>
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<td>507</td>
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<td>0.91 (0.85-0.98)</td>
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<td><strong>Hemoglobin (g/L)</strong></td>
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<td>&lt;110</td>
<td>525</td>
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<td>≥110</td>
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<td>&lt;20</td>
<td>939</td>
<td>56 (6)</td>
<td>0.92 (0.86-0.98)</td>
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<td><strong>ALT (U/L)</strong></td>
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<td>&lt;40</td>
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<td>385</td>
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<td><strong>PCT (µg/L)</strong></td>
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<td>&lt;0.5</td>
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<td>&lt;8</td>
<td>312</td>
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<td>≥8</td>
<td>767</td>
<td>65 (8.5)</td>
<td>0.92 (0.87-0.97)</td>
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<td><strong>Cr (umol/L)</strong></td>
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<tr>
<td>&lt;100</td>
<td>998</td>
<td>62 (6.2)</td>
<td>0.91 (0.87-0.96)</td>
<td>0.714</td>
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<td>≥100</td>
<td>81</td>
<td>15 (18.5)</td>
<td>0.92 (0.81-1.05)</td>
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</tr>
</tbody>
</table>

**Figure 3**

Legend not included with this version
Figure 4

Legend not included with this version