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Serum Bilirubin within Normal Range Is Associated with an Increasing Risk of Mortality in Patients with Primary Biliary Cholangitis Regardless of Ursodeoxycholic Acid Treatment

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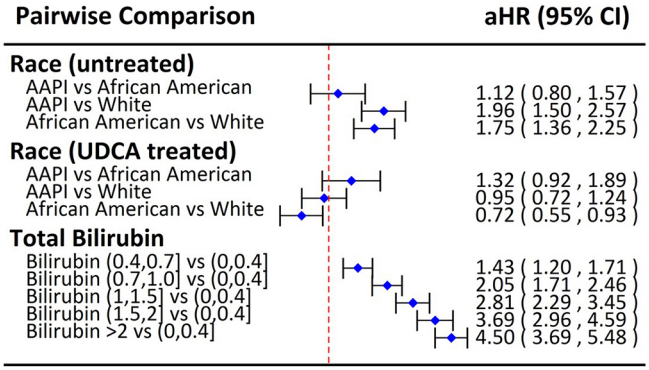
Abstract Text

Background: A rise in bilirubin indicates worsening liver function in patients with primary biliary cholangitis (PBC). Recent reports have suggested that total bilirubin above 0.7 mg/dL may be linked to increased risk for liver transplantation and mortality. The Fibrotic Liver Disease Consortium analyzed the impact of bilirubin as well as race, gender, and ursodeoxycholic acid (UDCA) treatment on risk of all-cause mortality in patients from 11 US health systems.

Methods: Data were collected from “index date” (the latest among PBC diagnosis date, UDCA initiation date, or 1/1/2006) through 12/31/2016. Bilirubin was categorized as >2, 2–>1.5, 1.5–>1.0, 1.0–>0.7, 0.7–>0.4, and ≤0.4 mg/dL. Inverse Probability of Treatment Weighting (IPTW) was used to adjust for UDCA selection bias. Cox regression (univariate, including variable-by-UDCA interactions, followed by multivariate) was used to estimate the impact of risk factors on mortality.

Results: Among 4243 patients (8% African American, 7% Asian American/ Pacific Islander (AAPI), 21% Hispanic), 25% died after index date through 2016. Variables retained in the final multivariate model included age at index, Hispanic ethnicity, baseline bilirubin, alkaline phosphatase, and interactions of UDCA with 4 variables (race, gender, AST/ALT>1.1, and albumin). Among UDCA-treated patients, African Americans had significantly lower mortality than Whites (adjusted Hazard Ratio [aHR]=0.72, 95%CI 0.55–0.93); among untreated patients, this relationship was reversed (aHR=1.96, 95%CI 1.50–2.57). Bilirubin level was strongly and positively associated with increasing mortality; compared to patients with low-normal bilirubin (≤0.4 mg/dL), those in the mid-normal (0.7–>0.4) or high-normal (1.0–>0.7) ranges had significantly higher mortality (Figure). Mortality was higher among men, Hispanics, and patients with hypoalbuminemia. After IPTW, UDCA treatment was associated with reduced mortality in all categories except in White women with AST/ALT>1.1 and hypoalbuminemia.

Conclusion: UDCA treatment was associated with reduced mortality across most patient groups. Regardless of UDCA treatment, high-normal bilirubin (1.0–>0.7 mg/dL) was associated with twice the risk of death compared to bilirubin ≤0.4 mg/dL. The divergent mortality rates observed between African Americans and Whites regarding UDCA treatment are novel and require further research. Our results suggest that, even within the normal range, higher serum bilirubin levels are associated with increased mortality among PBC patients.



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