Association Between Elevated Alkaline Phosphatase and Healthcare Utilization and Costs Among Individuals With Primary Biliary Cholangitis in the United States

EE492

EPIC Study

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Key Takeaways

- Treatment of primary biliary cholangitis aims to improve biochemical markers of disease progression, including alkaline phosphatase (ALP)
- In this study, higher ALP was independently associated with substantially elevated 1-year healthcare resource utilization and costs
- Individuals with the highest ALP levels had the lowest rates of PBC-specific prescriptions, suggesting a gap in care for those with the greatest unmet need

Plain Language Summary

- In this study of patients with primary biliary cholangitis, higher levels of ALP were linked to more healthcare visits and higher costs
- These results suggest that a goal in primary biliary cholangitis management of reaching normal ALP levels can also reduce healthcare use and costs

References

1. Gershwin ME, Selmi C, Worman HJ, et al. Risk factors and comorbidities in primary biliary cirrhosis: a controlled interview-based study of 1032 patients. Hepatology. Nov 2005;42(5):1194-202.
2. Shamseddine N, Bozas A, Yang H, et al. Real-World Clinical and Economic Burden of Primary Biliary Cholangitis in the United States. presented at: ISPOR; May 5, 2024; Atlanta, GA, USA. https://www.ispor.org/docs/default-source/intl2024/us-boi-econ-treatment-posterispor-2024139379-pdf.pdf?sfvrsn=c7f5e977_0
3. Sayiner M, Golabi P, Stepanova M, et al. Primary Biliary Cholangitis in Medicare Population: The Impact on Mortality and Resource Use. Hepatology. Jan 2019;69(1):237-244.

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Introduction

- Primary biliary cholangitis (PBC) is a chronic inflammatory liver disease marked by bile duct inflammation and destruction, leading to cholestasis and long-term liver complications including ascites, variceal hemorrhage, hepatic encephalopathy, hepatocellular carcinoma, and liver failure
- Previous economic studies have reported significant clinical and economic burden[1,2], and high and rising costs to payers associated with PBC[3]
- ALP (alkaline phosphatase) is an important biomarker in the management of the disease, however, evidence on the relationship between ALP and healthcare resource utilization (HCRU) and costs remains limited
- This study evaluates the association between ALP with HCRU and costs using a large national sample of individuals with PBC in routine clinical practice settings in the U.S.

Methods

- A retrospective, longitudinal cohort study of individuals diagnosed with PBC in the U.S. was conducted using the Komodo Healthcare Map database, linking claims and Quest Diagnostics laboratory data from September 1, 2017 to September 30, 2023
- Inclusion Criteria:
  - Individuals with ≥2 ALP tests at least 30 days apart. The Index date was defined as the date of the second ALP test
  - ≥1 PBC diagnosis during the 12-month pre-index or 12-month post index period
  - ≥12 months of continuous health plan coverage pre- and post-index
  - ≥Age 18 on each patient's index date
- 4 mutually exclusive cohorts were created based on ALP levels:

  Reference Group: Normal (ALP ≤1 x upper limit of normal (ULN))

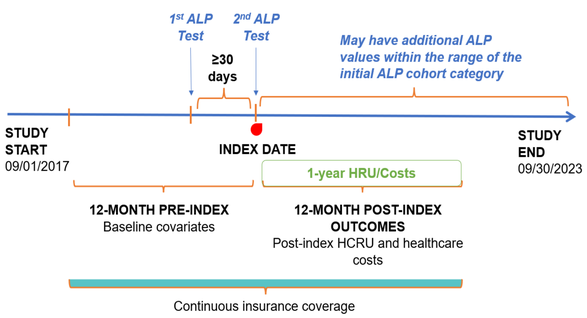
  Cases: Mildly Elevated (ALP>1 x ULN but ≤1.67 x ULN)

  Elevated (ALP>1.67 x ULN but ≤3 x ULN)

  Highly Elevated (ALP>3 x ULN)

  Individuals with ALP values that fell into more than one category during the study period were excluded from these analyses
- The ULN thresholds utilized in this analysis were defined by Quest Diagnostics (Quest Diagnostics ULN Reference Ranges)
- The percentage of patients with inpatient, outpatient, emergency room, and pharmacy care and total mean all-cause healthcare costs over a 1-year post-index period, were compared between cases and the reference group
- Negative binomials models estimated the rate ratios for each type of HCRU among cases versus the reference group
- Linear regression models estimated the incremental effect of each ALP level on total 1-year all-cause costs
  - All regression estimates were adjusted for sex, age at index, race, ethnicity, type of insurance at index, geographic location, baseline Charlson Comorbidity Index (CCI), cirrhosis, pruritus, other PBC-related comorbidities, total bilirubin and any PBC-related treatment evaluated during the 12-month baseline

Figure 1. Study Design



Results

- Among 10,933 individuals with PBC who met this study inclusion criteria, the median age was 66 years, most were female (86%) and with a Charlson comorbidity index ≥2 (60%). Only 51% received PBC-specific prescriptions during the 1-year baseline, with the highly elevated ALP group having the lowest rate
- Higher ALP levels were associated with increased presence of cirrhosis and pruritus

Table 1. Baseline Characteristics of Patients with PBC by ALP Group

	Normal ALP*	Mildly Elevated ALP*	p-value‡	Elevated ALP*	p-value‡	Highly Elevated ALP*	p-value‡
	N=9,544	N=904		N=297		N=248	
Female	8,230 (86.2%)	777 (86.0%)	.814	252 (84.9%)	. 496	189 (76.2%)	<.001
Age, median [Q1-Q3]	66 [58-74]	65 [56-72]		61 [51-71]		53 [44-65]	
CCI, mean (SD)	2.8 (2.5)	2.9 (2.7)	.908	2.7 (2.5)	.199	3.3 (3)	.065
PBC-related Comorbidities, n (%)							
Alcohol use disorder	238 (2.5%)	25 (2.8%)	0.618	8 (2.7%)	0.828	12 (4.8%)	0.021
Autoimmune hepatitis	990 (10.4%)	72 (8.0%)	0.022	24 (8.1%)	0.201	34 (13.7%)	0.090
Autoimmune thyroid disease	257 (2.7%)	12 (1.3%)	0.013	1 (0.3%)	0.012	2 (0.8%)	0.068
Cirrhosis	2,784 (29.2%)	339 (37.5%)	<.001	114 (38.4%)	<.001	89 (35.9%)	0.022
Hypercholesterolemia	1,398 (14.7%)	109 (12.1%)	0.034	26 (8.8%)	0.004	27 (10.9%)	0.097
MetALD	1,497 (15.7%)	133 (14.7%)	0.441	32 (10.8%)	0.021	25 (10.1%)	0.016
MASH	536 (5.6%)	45 (5.0%)	0.424	7 (2.4%)	0.015	17 (6.9%)	0.404
Metabolic syndrome	5,946 (62.3%)	518 (57.3%)	0.003	175 (58.9%)	0.237	150 (60.5%)	0.506
Osteoporosis	1526 (16.0%)	116 (12.8%)	0.013	34 (11.5%)	0.035	24 (9.7%)	0.006
Raynaud syndrome	294 (3.1%)	12 (1.3%)	0.003	5 (1.7%)	0.167	3 (1.2%)	0.090
Rheumatoid arthritis	800 (8.4%)	38 (4.2%)	<.001	20 (6.7%)	0.312	16 (6.5%)	0.277
Sjogren's syndrome	539 (5.7%)	29 (3.2%)	0.002	16 (5.4%)	0.848	2 (0.8%)	0.001
System lupus erythematosus	386 (4.0%)	22 (2.4%)	0.017	9 (3.0%)	0.381	11 (4.4%)	0.758
Urinary tract infection	1,330 (13.9%)	106 (11.7%)	0.065	42 (14.1%)	0.920	30 (12.1%)	0.408
Pruritus diagnosis or treatment	1,057 (11.1%)	103 (11.4%)	0.770	73 (24.6%)	<.001	84 (33.9%)	<.001
PBC treatment‡ (n, %)	4,761 (49.9%)	545 (60.3%)	<.001	155 (52.2%)	0.434	103 (41.5%)	0.009
ALP at Index (U/L),Mean (SD)	88.9 (26.1)	190 (26.4)	<.001	319.1 (57.2)	<.001	786.1 (366.5)	<.001
Total Bilirubin (at index or nearest test within 6 months prior) (mg/dL)							
Mean (SD)	0.7 (0.5)	0.9 (1.1)	<.001	1.2 (2)	<.001	2.6 (3.5)	<.001

*Normal ALP = ALP ≤1 x ULN; Mildly Elevated ALP = ALP >1 x ULN to ≤1.67 x ULN; Elevated ALP = ALP >1.67 x ULN to ≤3 x ULN; Highly Elevated = ALP >3 x ULN; ‡p values are based on Wilcoxon rank-sum tests for continuous and chi-square tests of independence for categorical variables compared to the Normal ALP cohort; ‡PBC treatments include at least one ursodeoxycholic acid (UDCA) or obeticholic acid (OCA) prescription in the 12-month baseline period; ALP, alkaline phosphatase; MetALD, metabolic dysfunction-associated alcohol-related liver disease; MASH, metabolic dysfunction-associated steatohepatitis; PBC, primary biliary cholangitis; Q1, first quartile; Q3, third quartile; SD, standard deviation

- Mildly elevated, elevated and highly elevated ALP groups were significantly associated with increased inpatient visits, while elevated and highly elevated ALP groups were significantly associated with more emergency room visits. No difference in outpatient and prescription utilization was observed

Figure 2. Unadjusted 1-year All-cause HCRU by ALP

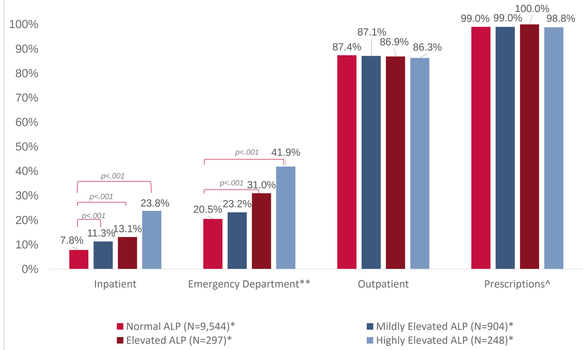


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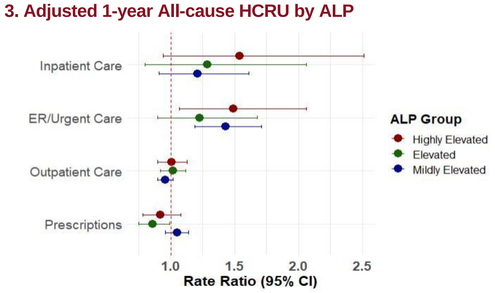
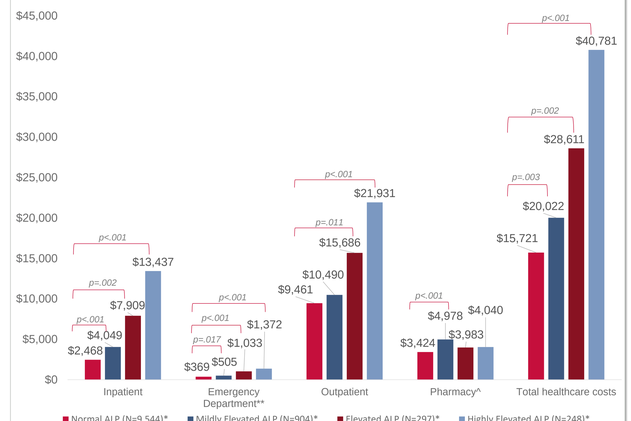
Figure 3. Adjusted 1-year All-cause HCRU by ALP



Adjusting for sex, age at index, race/ethnicity, type of insurance, geographical region, baseline CCI score, baseline PBC-related comorbidities (alcohol use disorder, autoimmune hepatitis, autoimmune thyroid disease, cirrhosis, hypercholesterolemia, MetALD, MASH, MetS, Raynaud syndrome, rheumatoid arthritis, systemic lupus erythematosus, urinary tract infection), pruritus, total bilirubin level

- Mean 1-year healthcare costs for the entire sample was $18,747 (SD=$48,621). The mean 1-year unadjusted healthcare costs were significantly higher for the mildly elevated, elevated and highly elevated ALP groups compared to the normal ALP group

Figure 4. Unadjusted Mean 1-year Healthcare Costs by ALP



'Normal ALP = ALP ≤1 x ULN; Mildly Elevated ALP = ALP >1 x ULN to ≤1.67 x ULN; Elevated ALP = ALP >1.67 x ULN to ≤3 x ULN; Highly Elevated = ALP >3 x ULN

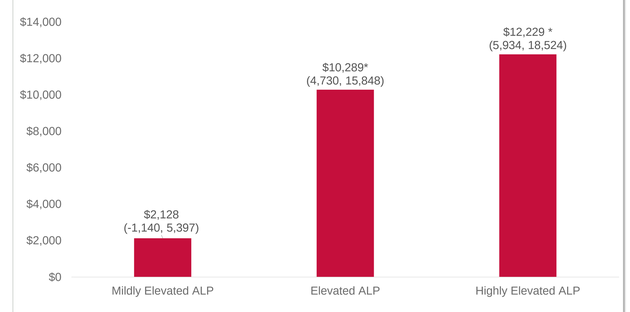
"Emergency room costs include urgent care visits

^Pharmacy costs include any prescribed medications

ALP, alkaline phosphatase

- Compared to the normal ALP group, regression-adjusted 1-year healthcare costs were significantly higher among those with elevated ALP and highly elevated ALP groups

Figure 5. Adjusted Incremental 1-year All-Cause Healthcare Costs and 95% Confidence Intervals Associated with ALP ±



^All estimates are contrasted to Normal ALP group

*p<.001

±Model adjusted for sex, age at index, race/ethnicity, type of insurance, geographical region, baseline CCI score, baseline PBC-related comorbidities (alcohol use disorder, autoimmune hepatitis, autoimmune thyroid disease, cirrhosis, hypercholesterolemia, MetALD, MASH, MetS, Raynaud syndrome, rheumatoid arthritis, systemic lupus erythematosus, urinary tract infection), pruritus, total bilirubin level

ALP, alkaline phosphatase

Limitations

- Patients may have been misclassified as having PBC when diagnosis is established using ICD-10 codes
- The second ALP test was used as the index date to verify ALP stabilization. However, this may have introduced bias due to the non-uniform administration of tests in clinical practice and the normal fluctuations in ALP levels
- Patients were followed for 12 months post-index therefore, the longer-term impact on HCRU and costs were not assessed