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Longitudinal Relationship Between Elevated Liver Biochemical Tests and Negative Clinical Outcomes in Primary Biliary Cholangitis: A Population-Based Study

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ABSTRACT

Background: Elevated liver biochemistries are associated with increased risk of negative outcomes in patients with primary biliary cholangitis (PBC).

Aims: To evaluate whether longitudinal monitoring of liver biochemistries and fibrosis scores provides additional prognostic value and to assess the relationship between the degree of elevation of multiple biomarkers within different alkaline phosphatase (ALP) strata.

Methods: Adults with PBC were identified from Komodo's Healthcare Map. A Cox proportional hazards model examined time to first occurrence of hospitalisation due to hepatic decompensation, liver transplantation, or death as a function of the proportion of time during follow-up that liver biochemistries and fibrosis scores exceeded thresholds. Within ALP strata (ALP ≤ upper limit of normal [ULN]; ALP>ULN to ≤1.67×ULN; ALP >1.67×ULN), separate multivariate Cox hazard models assessed the association between time-varying covariates and the composite endpoint.

Results: Overall, 3974 patients were included; 88.2% were female, with a mean age of 59.4 years. The median follow-up was 2.5 years. Increasing magnitude and duration beyond established thresholds of ALP, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TB), AST/platelet ratio index (APRI) and fibrosis-4 (FIB-4) were associated with increased risk of negative outcomes. Elevated ALT, AST, TB, APRI and FIB-4 were associated with increased risk of negative outcomes across all ALP strata.

Conclusions: Prolonged elevation of multiple hepatic biomarkers and fibrosis scores is associated with a greater risk of negative clinical outcomes, underscoring the importance of ongoing monitoring beyond the guideline-recommended initial treatment response to guide timely treatment decisions and improve PBC management.

Darren Wheeler's affiliation was at the time of study.

1 | Introduction

Primary biliary cholangitis (PBC) is a rare progressive autoimmune liver disease characterised by chronic inflammation and progressive destruction of intrahepatic bile ducts [1, 2]. If left untreated, PBC may progress to cirrhosis, liver failure and/or death [3, 4]. PBC disproportionally affects women, with an estimated US female: male ratio of 4:1, and is typically diagnosed between age 40 and 60 years [2, 5]. The 2021 adjusted prevalence of PBC in the US was reported to be 40.9 per 100,000 adult population [6], slightly higher than the 39.2 per 100,000 reported by the Fibrotic Liver Disease Consortium in 2014 [7].

Ursodeoxycholic acid (UDCA) is the first-line pharmacotherapy for PBC and has been shown to slow disease progression, improve liver function, and enhance survival [8–10]; however, approximately 40% of patients with PBC may have an inadequate response to treatment with UDCA, and 3% to 5% are intolerant to it [11]. The biochemical response to UDCA is a robust predictor of long-term outcomes used to identify patients who may benefit from second-line therapy [11]. Obeticholic acid (OCA), the only farnesoid X receptor agonist approved for the second-line treatment of PBC, has been commercially available under accelerated approval since 2016 for patients who either have an inadequate response to UDCA or are unable to tolerate it [8–10]. In 2024, two peroxisome proliferator-activated receptor agonists, elafibranor and seladelpar, became available under accelerated approval as additional second-line treatment options [12–15].

Current guidelines recommend evaluating the biochemical response (e.g., changes in serum alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin [TB] levels) to UDCA after 1 year of treatment using established criteria and risk scores (e.g., GLOBE [16], Paris I [17] and II [18], Barcelona [19], Toronto [20], and Rotterdam [21] criteria). In patients with more advanced fibrosis, compensated liver disease, and no signs of portal hypertension, assessments may be performed after 6 months of UDCA treatment (e.g., Chronic Liver Disease Foundation criteria) [22]. Most criteria use a reduction of ALP levels to 1.4 to 3 × upper limit of normal (ULN) as the primary marker of response [8–10].

While ALP is a valuable and informative indicator of treatment response, it alone may not fully capture the risk for negative clinical outcomes, as other hepatic biomarkers are also associated with the risk of hepatic decompensation, liver transplantation, and/or death [23]. For example, recent data showed higher rates of liver transplantation or death even when ALP and TB levels were maintained below current guideline-recommended thresholds [1]. The same study found that patients with ALP ≤ 1 × ULN had better survival rates than those with ALP above ULN but < 1.67 × ULN [1]. Emerging evidence suggests that other biochemical parameters in addition to ALP and TB (e.g., ALT) may be associated with the risk for liver transplantation or death in patients with PBC [23, 24].

Although fibrosis progression is a hallmark of PBC, established criteria for determining UDCA treatment response do not consider fibrosis scores [25, 26]. While some nascent studies have begun to explore the predictive ability of fibrosis scores in PBC [27, 28], a comprehensive analysis of various hepatic biomarkers and fibrosis scores may provide additional prognostic value in fully characterising the risk of negative clinical outcomes in patients with PBC [26].

This study investigated whether repeated measurements of biochemical markers offer additional value, particularly in assessing whether the inclusion of ALT and AST, as well as serum-based fibrosis scores, such as the AST/platelet ratio index (APRI) and fibrosis-4 (FIB-4) alongside ALP and TB, provide further insight into the risk profile of patients with PBC. These assessments were conducted within different ALP strata to further understand their relevance across varying levels of ALP.

2 | Methods

2.1 | Data Source

This retrospective cohort study was conducted using Komodo's Healthcare Map, which is derived primarily from claims data. The database included de-identified longitudinal administrative medical and pharmacy claims data merged with national laboratory data linked via Datavant tokenisation methodology [29].

2.2 | Study Inclusion/Exclusion Criteria

Patients diagnosed with PBC (at least one hospitalisation claim or at least two outpatient claims on separate days; International Classification of Disease (ICD)-9 code 571.6 or ICD-10 code K74.3) between July 1, 2014, and February 28, 2022, were included in this study. The date of the first PBC diagnosis claim was defined as the index date. Patients were required to be ≥ 18 years of age at the index date, with ≥ 6 months' continuous enrolment in a health plan with medical and pharmacy coverage before index, including the index date (baseline period). Patients were also required to have ALP, AST, ALT and TB laboratory data during the 6-month baseline period and at least one of these liver biomarker values during the follow-up period (post-index).

In order to avoid confounding, patients with any of the following conditions were excluded from the study: concomitant liver diseases (e.g., hepatitis C or hepatitis B infection, primary sclerosing cholangitis, alcohol-associated liver disease, Gilbert syndrome, hepatocellular carcinoma), HIV infection, Paget disease, hepatic decompensation, abnormally high ALP (> 2000 U/L), ALT (> 1000 U/L), AST (> 1000 U/L), or abnormally low platelet count (< 100,000/mL). Additionally, patients with a record of any decompensating events (variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome or hepatic hydrothorax), those who had undergone gastric bypass procedures excluding gastric lap band and those who had an ileal resection during baseline were also excluded. Patients with a history or evidence of liver transplantation during the pre-index period and those with a record of second-line OCA or fibrates on or before the index date were also excluded.

2.3 | Time-Dependent Exposure Variable

As the hepatic biomarkers may vary over time in the available follow-up period, this analysis examined the proportion of time that biomarkers and fibrosis scores exceeded normal limits or specific thresholds as a time-dependent covariate. The analysis used fixed thresholds for hepatic biomarkers based on standard UDCA treatment response criteria (i.e., Paris I, Paris II and Rotterdam) [17, 18, 21] and those described by Ritter et al. [30] (ALP ULN, 120 U/L; ALT ULN, 40 U/L; AST ULN, 35 U/L for males, 30 U/L for females; TB ULN, 1 mg/dL). The thresholds for APRI (ULN, 0.5) and FIB-4 were chosen based on increased risk of adverse outcomes observed by Chou et al. and Sterling et al., respectively [31, 32].

2.4 | Outcome Variables

The composite endpoint was defined as the first occurrence of hospitalisation for a decompensating event (variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal syndrome, hepatopulmonary syndrome, hepatic hydrothorax or hepatic failure), liver transplantation or death (all-cause). Patients were censored at the initiation of second-line treatment, end of enrolment or end of follow-up, whichever occurred first.

2.5 | Statistical Analyses

Baseline patient characteristics were summarised using descriptive statistics. A Cox proportional hazard risk model was used to examine the time to the first occurrence of hospitalisation due to hepatic decompensation, liver transplantation, or death. The fixed effects of age, sex, metabolic dysfunction-associated steatohepatitis (MASH), cirrhosis, portal hypertension and autoimmune hepatitis, among other baseline patient characteristics, were accounted for, and the time-varying covariates included ALT, AST, FIB-4 and APRI expressed categorically. This analysis accounts for the effect of both the magnitude and duration of elevated biomarker levels on negative clinical outcomes. Exposure for each hepatic biomarker and fibrosis score was quantified as the cumulative proportion of time beyond its clinical threshold [30]. Hazard ratios were calculated over a 5-year follow-up period. Two sensitivity analyses were conducted: (i) one included only individuals with a PBC diagnosis based on ICD-10 codes and (ii) another excluded patients with MASH and/or cirrhosis at index.

As levels of TB $>0.6\times$ULN are associated with increased risk of liver transplantation and death in patients with PBC [1], we performed a multivariate Cox proportional hazards model of the cumulative proportion of follow-up time that ALP and TB were beyond thresholds for ALP $\geq$ ULN and TB $>0.6\times$ULN.

Within the specified ALP stratum (ALP $\leq$ ULN; ALP>ULN to $\leq 1.67\times$ULN; ALP $>1.67\times$ULN), a multivariate Cox proportional hazards model assessed the association between a time-varying covariate and the composite endpoint. A separate model was run for each biomarker and fibrosis score within each ALP stratum.

2.6 | Ethics Statement

This study utilised retrospective de-identified data and was considered to be of minimal or no risk to subjects.

3 | Results

3.1 | Patient Characteristics

Of the 113,446 adult patients with PBC in the Komodo Health Database, 3974 met all eligibility criteria for this study and were included in subsequent analyses (Figure 1). Baseline patient characteristics were consistent with the known epidemiology of PBC (Table 1) [30, 33, 34]. Overall, eligible patients were predominantly female (88.2%) and White (49.4%). One-fifth of patients identified as Hispanic or Latino ethnicity (24.3%). The mean (standard deviation) age of eligible patients was 59.4 (12.6) years.

At baseline, slightly less than half of the patients had commercial insurance (43.0%), while 24.2% had Medicare and 13.4% had Medicaid coverage. Approximately half of all patients (49.9%) were being treated with UDCA, 8.5% had cirrhosis, 6.9% had MASH and 5.5% had portal hypertension at baseline (Table 1). The overall median follow-up time was 2.5 years (interquartile range [IQR], 1.3–4.2), during which 75.0% of patients received UDCA (Table S1). During the follow-up period, most patients were censored due to end of enrolment (43.1%) or end of study (45.3%).

Patients were stratified into three ALP strata: ALP $\leq$ ULN ($n=1443$), ALP>ULN to $\leq 1.67\times$ULN ($n=1279$), and ALP $>1.67\times$ULN ($n=1252$). The median (IQR) follow-up time was 2.8 (1.5–4.7), 2.4 (1.3–4.1) and 2.3 (1.1–3.8) years for the ALP $\leq$ ULN, ALP>ULN to $\leq 1.67\times$ULN and ALP $>1.67\times$ULN groups, respectively. Hepatic decompensation occurred in 3.4% of patients overall, and a greater proportion of patients with ALP $>1.67\times$ULN experienced hepatic decompensation during the follow-up period than those with ALP $\leq 1.67\times$ULN (4.9% vs. 2.7%). Laboratory values out of the normal range are presented in Table S2.

3.2 | Risk of Negative Clinical Outcomes

Increasing magnitude and duration beyond established thresholds of PBC disease progression biomarkers (ALP, ALT, AST and TB) and fibrosis scores (APRI and FIB-4) were associated with increased risk of negative outcomes (Figure 2 and Table S3). Regardless of ALP strata, and even when ALP was within ULN, PBC disease progression biomarkers and fibrosis scores were associated with an increased risk of negative outcomes (Figure 3 and Table S4). Patients with FIB-4 ≥ 3.25 and/or APRI >0.5 had a consistently higher risk for negative outcomes than those with FIB-4 <1.3 and/or APRI ≤ 0.5. Despite low ALP levels (ALP $\leq 1.67\times$ULN), patients with ALT $\geq 2\times$ULN or AST $\geq 1.5\times$ULN had an increased risk for negative outcomes than patients with ALT or AST<ULN. Higher TB levels ($>1.0\times$ULN) were also associated with an increased risk of negative outcomes regardless of ALP levels.

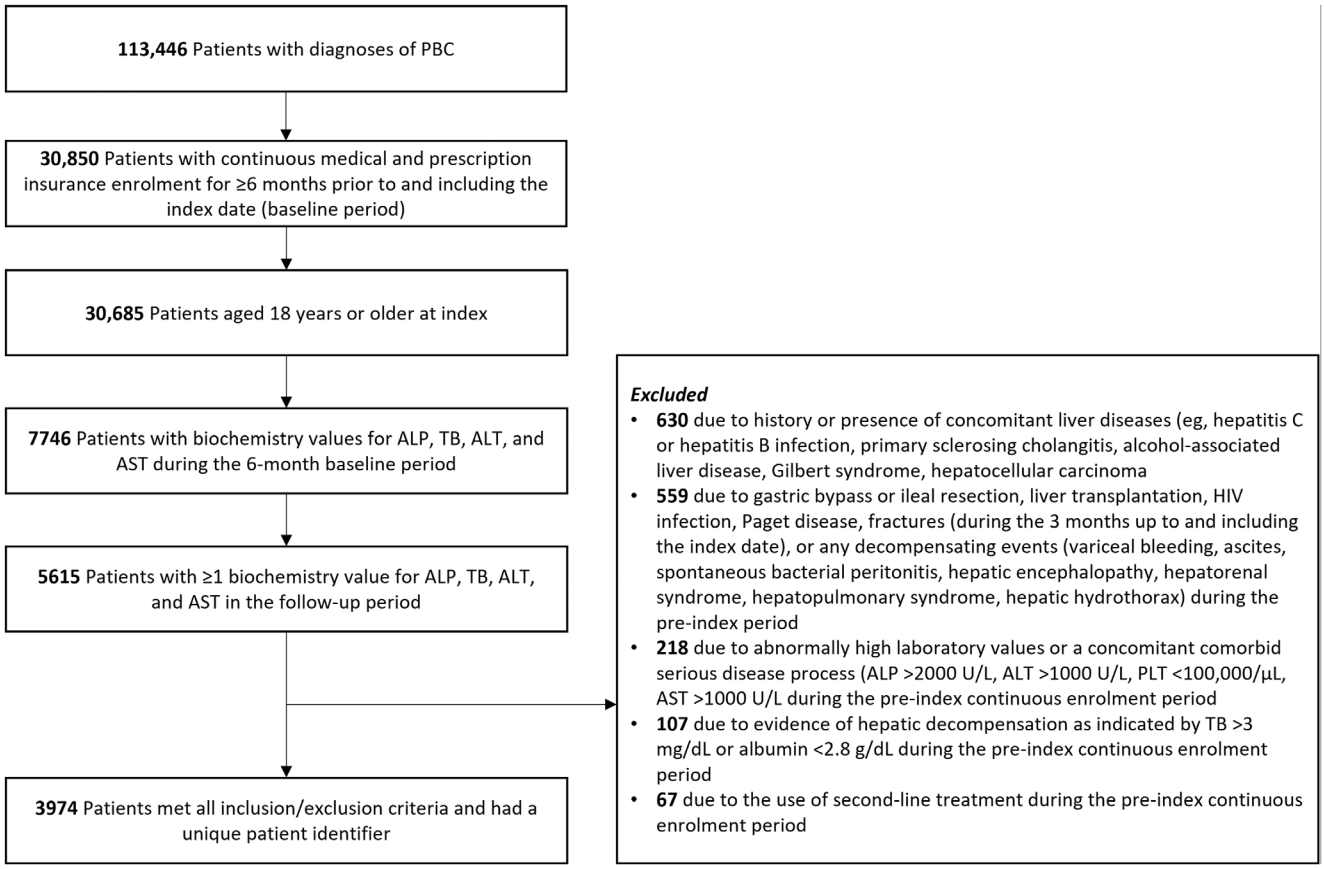

FIGURE 1 | Flow diagram of patient selection criteria. ALP, alanine phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; PLT, platelet; TB, total bilirubin.

There was a nearly six-fold increase in the risk of a negative outcome in patients with elevations of TB ≥ 0.6 × ULN and ALP ≥ ULN (Figure 4) for 100% of follow-up time relative to patients who never exceeded these thresholds during follow-up. A patient with an elevation of ALP ≥ ULN for 3 years had a 71.0% increased risk of negative outcomes. When combined with a TB ≥ 0.6 × ULN for the same period, the risk of these outcomes was 2.89-fold greater than the risk in a patient who never exceeded these biomarker thresholds. In general, the combined risk associated with both biomarkers being above their thresholds becomes exponentially greater than the sum of the individual risks over time.

3.3 | Sensitivity Analyses

In the sensitivity analyses of only patients with ICD-10 diagnosis codes for PBC or excluding patients with baseline MASH and/or cirrhosis, the estimated hazard ratios (HRs) of a negative clinical outcome associated with hepatic biomarkers and fibrosis scores beyond established thresholds were statistically significant and similar in magnitude and direction across the various evaluated clinical thresholds (Table S3). In the sensitivity analysis of patients without baseline MASH and/or cirrhosis, only FIB-4 ≥ 1.3 was not statistically significant (Table S3).

4 | Discussion

In our analyses of the prognostic value of each of the evaluated hepatic biomarkers and fibrosis scores among our study population, irrespective of ALP strata, elevated liver biochemical tests and fibrosis scores were associated with an increased risk of hospitalisation for hepatic decompensation, liver transplantation or death, even when ALP was below ULN. Importantly, even in patients with low ALP levels, elevated ALT or AST increased the risk of negative outcomes. Increasing magnitude and time spent beyond ULN for ALP, AST, ALT, TB (0.6 × ULN), APRI and FIB-4 were associated with significantly greater risks of negative outcomes.

These findings suggest that using a more comprehensive set of commonly evaluated hepatic biomarkers and fibrosis scores may provide additional prognostic value in differentiating patients with PBC who are at a higher risk for negative clinical outcomes. This approach aligns with the more recently developed criteria for assessing UDCA treatment response, stratifying risk for negative clinical outcomes and guiding management of patients with PBC [16, 35]. For example, the GLOBE scoring system incorporates age at initiation of UDCA therapy with TB level, ALP level, albumin level and platelet count measured at 12 months after initiation of UDCA treatment [16], and the UK-PBC scoring system integrates baseline

TABLE 1 | Baseline patient characteristics.

Characteristic	Overall ($N = 3974$)	ALP ≤ ULN ($n = 1443$)	ULN<ALP ≤1.67×ULN ($n = 1279$)	ALP >1.67×ULN ($n = 1252$)
Age, years				
Mean (SD)	59.4 (12.6)	59.7 (13.3)	59.9 (11.9)	58.5 (12.4)
Median (IQR)	60.0 (51.0–68.0)	61.0 (51.0–69.0)	60.0 (53.0–68.0)	59.0 (51.0–67.0)
Female, *n* (%)	3505 (88.2)	1244 (86.2)	1159 (90.6)	1102 (88.0)
Race/ethnicity, *n* (%)				
White	1964 (49.4)	792 (54.9)	617 (48.2)	555 (44.3)
Hispanic or Latino	795 (20.0)	248 (17.2)	263 (20.6)	284 (22.7)
Black or African American	218 (5.5)	63 (4.4)	74 (5.8)	81 (6.5)
Asian or Pacific Islander	150 (3.8)	68 (4.7)	43 (3.4)	39 (3.1)
Other	138 (3.5)	49 (3.4)	37 (2.9)	52 (4.2)
Unknown	709 (17.8)	223 (15.5)	245 (19.2)	241 (19.2)
Insurance, *n* (%)				
Commercial	1708 (43.0)	580 (40.2)	573 (44.8)	555 (44.3)
Medicare	962 (24.2)	386 (26.7)	307 (24.0)	269 (21.5)
Medicaid	532 (13.4)	180 (12.5)	164 (12.8)	188 (15.0)
Other	772 (19.4)	297 (20.6)	235 (18.4)	240 (19.2)
Patients with liver comorbidities, *n* (%)				
Autoimmune hepatitis	427 (10.7)	155 (10.7)	123 (9.6)	149 (11.9)
Cirrhosis	336 (8.5)	114 (7.9)	98 (7.7)	124 (9.9)
MASH	275 (6.9)	117 (8.1)	87 (6.8)	71 (5.7)
Portal hypertension	219 (5.5)	70 (4.9)	65 (5.1)	84 (6.7)
UDCA use, *n* (%)	1985 (49.9)	665 (46.1)	698 (54.6)	622 (49.7)

Abbreviations: ALP, alkaline phosphatase; IQR, interquartile range; MASH, metabolic dysfunction-associated steatohepatitis; SD, standard deviation; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

albumin level and platelet count with TB, ALP and AST (or ALT) measured at 12 months after initiation of UDCA treatment [35].

Furthermore, our findings indicate that routine monitoring of hepatic biomarkers and fibrosis scores in patients with PBC may allow for timely intervention with second-line therapy to better mitigate the risk of negative clinical outcomes. We found that patients with TB ≥ 0.6 × ULN and ALP ≥ ULN for the entire follow-up period had a nearly six-fold increased risk of a negative outcome compared with patients whose TB or ALP never exceeded these thresholds. This is consistent with previous studies showing that various thresholds of elevated TB or ALP levels are strongly associated with an increased risk of liver transplantation or death [36] and that patients with TB ≤ 0.6 × ULN or normal ALP levels have a lower risk for these events [1]. Furthermore, the combination of ALP and TB levels has been shown to enhance prognostic prediction [36].

The findings of our current study, along with those of Ritter et al. [30], underscore the importance of incorporating all available hepatic biomarkers and fibrosis scores beyond ALP as a continuous function into the assessment of clinical outcomes. This approach would provide a more comprehensive view of PBC management and treatment response, aiding in more informed treatment decisions. A systematic review of 13 studies published between 2013 and 2019 in patients with metabolic dysfunction-associated steatotic liver disease found that the noninvasive fibrosis scores, APRI and FIB-4, are comparable to liver biopsy for predicting liver-related morbidity and mortality [37], highlighting the importance and need for similar research in patients with PBC. Although the American Association for the Study of Liver Diseases [8] and European Association for the Study of the Liver [10] guidelines recommend assessing biochemical response to UDCA treatment after 1 year using established criteria, both guidelines note that these prognostic tools do not account for markers of disease stage. More frequent early monitoring (< 1 year), monitoring beyond 1 year, and the

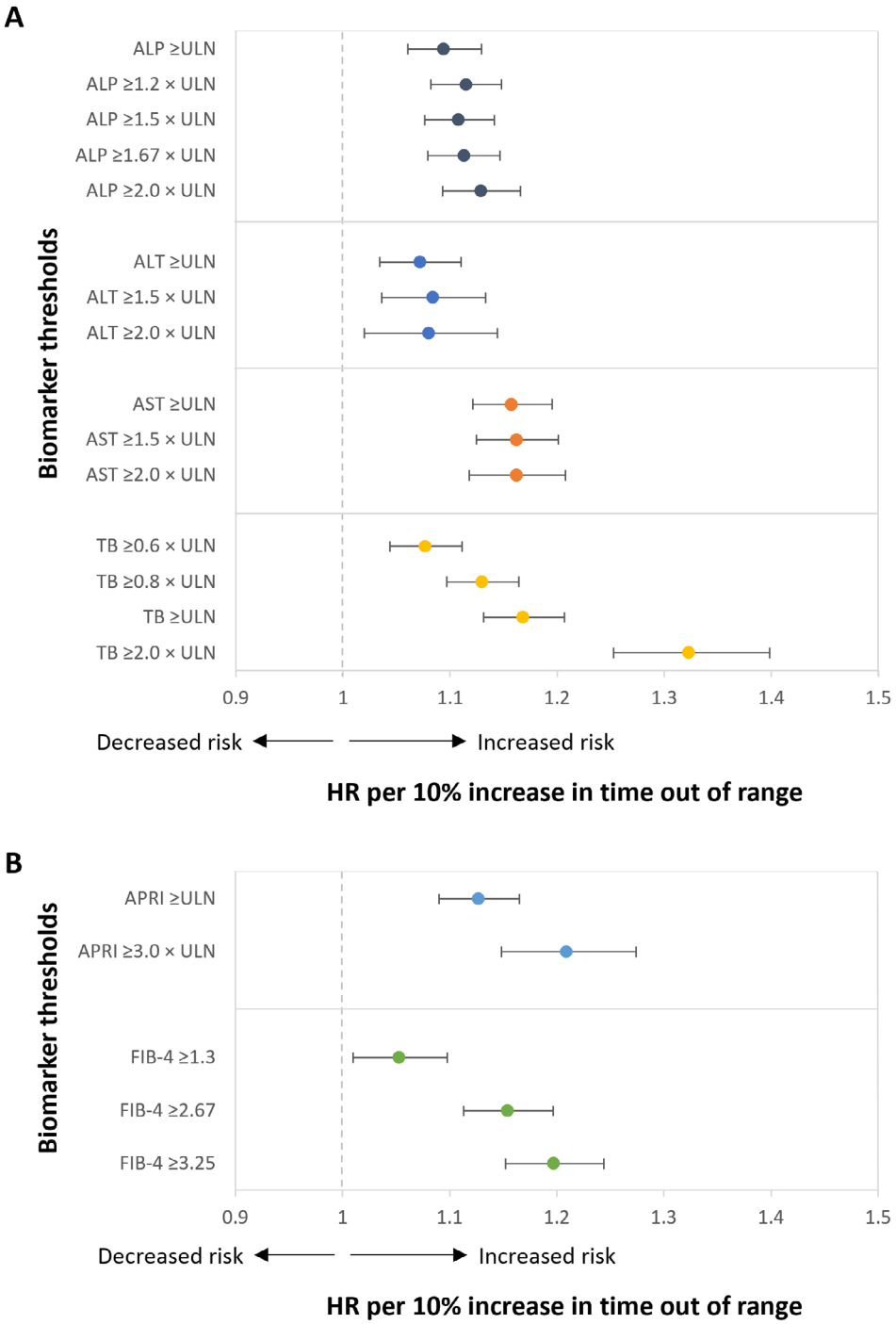

FIGURE 2 | Impact of magnitude and time spent beyond clinical thresholds for (A) hepatic biomarkers and (B) fibrosis scores on the risk of hospitalisation for hepatic decompensation, liver transplantation or death. ALP ULN defined as 120 U/L; ALT ULN defined as 40 U/L; APRI ULN defined as 0.5; AST ULN defined as 35 U/L for males and 30 U/L for females; TB ULN defined as 1 mg/dL. ALP, alanine phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis 4 score; HR, hazard ratio; TB, total bilirubin; ULN, upper limit of normal.

inclusion of additional variables in assessments may be needed to better inform timely treatment decisions and affect the risk of negative clinical outcomes in patients with PBC.

The number, geographic scope, and diversity of patients in the Komodo Health database support the generalisability of the study findings among patients with PBC. However, our study has limitations. Biomarker levels and fibrosis scores were assumed to remain constant between recorded measurement time points. Fluctuations between measurements may have led to overestimating or underestimating the proportion of time beyond established thresholds and the risk of negative outcomes. The study findings reflect trends in the insured population only, and uninsured patients with PBC may have a different disease burden and progression than those observed in this analysis. Additionally, the Komodo Healthcare

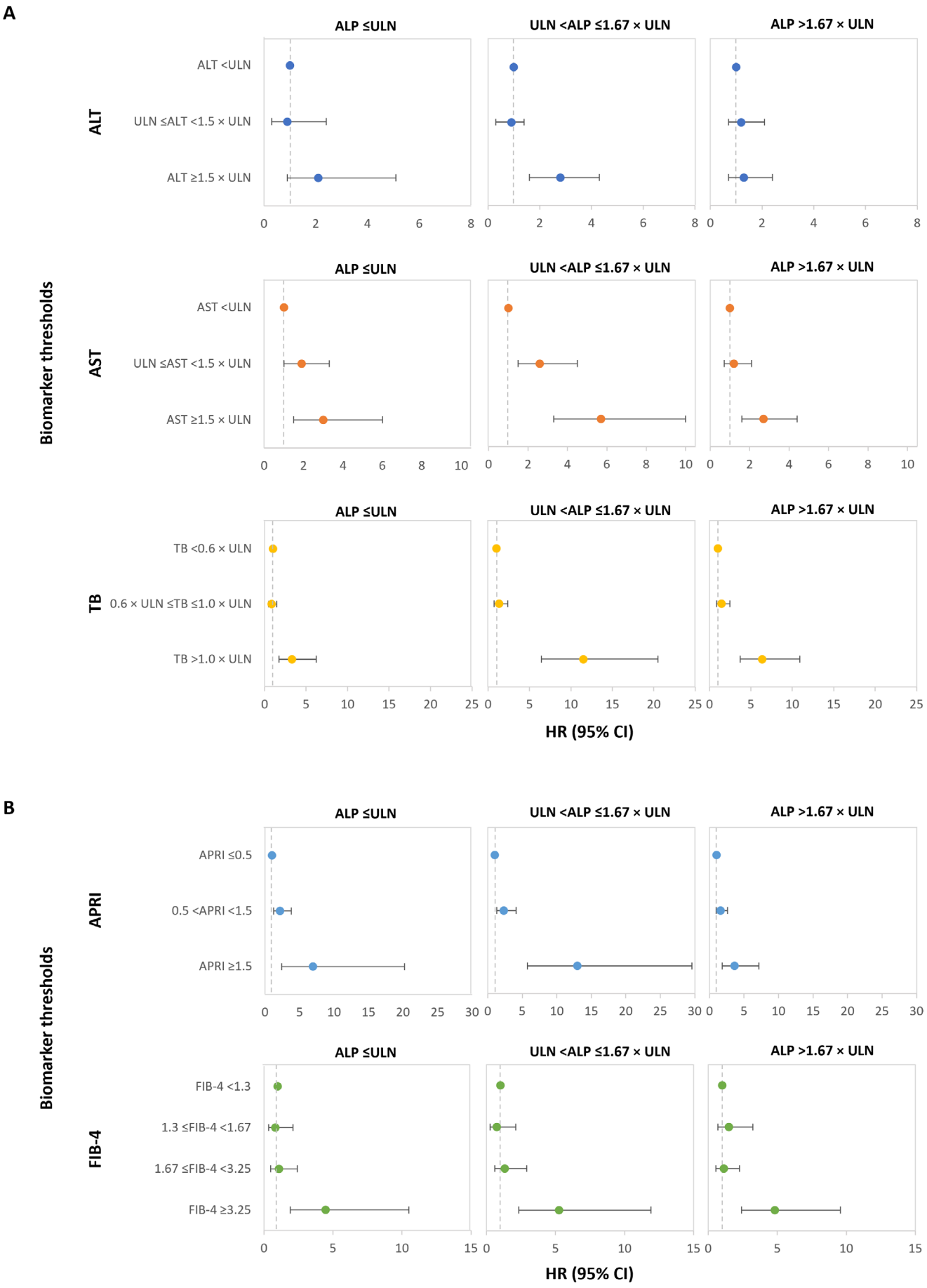

FIGURE 3 | Legend on next page.

FIGURE 3 | HRs for the risk of hospitalisation for hepatic decompensation, liver transplantation, or death as a function of time above (A) serum hepatic biomarkers and (B) fibrosis score thresholds within each ALP strata. ALP ULN defined as 120 U/L; ALT ULN defined as 40 U/L; AST ULN defined as 35 U/L for males and 30 U/L for females; TB ULN defined as 1 mg/dL. ALP, alanine phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; FIB-4, fibrosis 4 score; HR, hazard ratio; TB, total bilirubin; ULN, upper limit of normal.

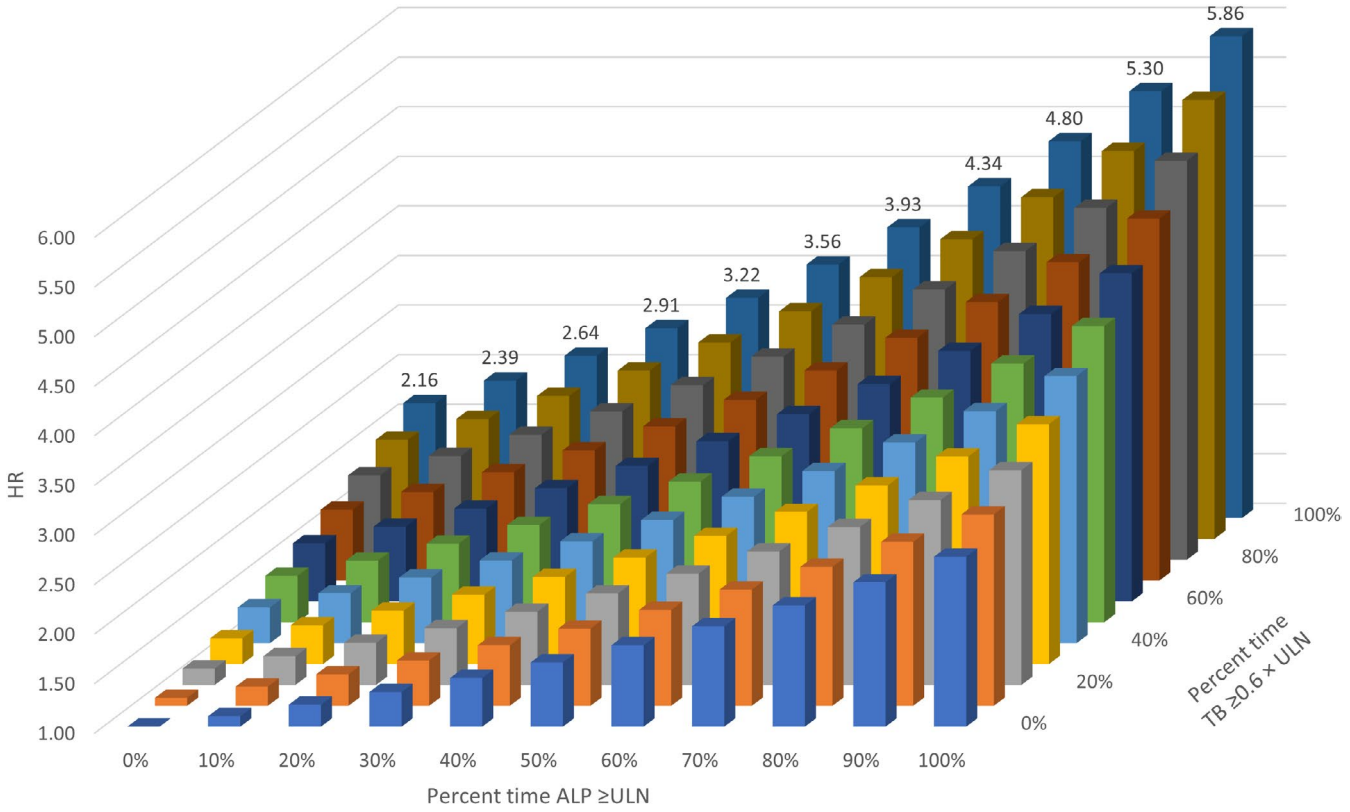

FIGURE 4 | Risk of hospitalisation for hepatic decompensation, liver transplantation, or death by proportion of 5-year follow-up with ALP ≥ ULN and TB ≥ 0.6 × ULN. ALP, alkaline phosphatase; HR, hazard ratio; TB, total bilirubin; ULN, upper limit of normal.

Map may not capture all laboratory values for all patients, and factors such as insurance coverage changes, data censoring and the time frame in which patients remain within the same healthcare system can impact follow-up duration. The median follow-up period of 2.5 years, combined with the 6-month pre-index continuous enrolment, provides a total observation period of 3.0 years, which is similar to other claims database analyses, especially for those using data for patients with commercial insurance [38]. A longer follow-up period could offer even greater insights into long-term disease progression and outcomes for PBC.

In conclusion, our data suggest an increased risk of negative outcomes across multiple hepatic biomarkers and composite fibrosis scores, with a greater risk for patients whose biomarkers and fibrosis scores remain above thresholds for longer periods of time. These findings support the importance of continued monitoring of ALT, AST, FIB-4 and APRI, along with ALP and TB, when assessing the need to initiate first- and second-line therapies. Furthermore, guidelines should consider routine monitoring of liver biomarkers and fibrosis scores beyond 1 year to better utilise available therapies and potentially reduce the overall risk of negative clinical outcomes. Timely monitoring and intervention are crucial for improving the prognosis and management of appropriate patients with PBC.

Author Contributions

Kris V. Kowdley: conceptualization, writing – review and editing, visualization, methodology, supervision. **David W. Victor III:** conceptualization, writing – review and editing, visualization, supervision. **Joanna P. MacEwan:** conceptualization, data curation, formal analysis, writing – original draft, writing – review and editing, visualization, methodology, supervision. **Radhika Nair:** conceptualization, visualization, writing – review and editing, methodology, funding acquisition, supervision. **Alina Levine:** conceptualization, writing – review and editing, data curation, formal analysis, visualization, supervision. **Jennifer Hernandez:** conceptualization, data curation, writing – review and editing, formal analysis, visualization, supervision. **Leona Bessonova:** conceptualization, writing – review and editing, visualization, methodology, funding acquisition, supervision. **Jing Li:** conceptualization, writing – review and editing, formal analysis, visualization, methodology, supervision. **Darren Wheeler:** conceptualization, writing – review and editing, visualization, methodology, supervision. **Gideon Hirschfield:** conceptualization, writing – review and editing, visualization, supervision.

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Conflicts of Interest

Kris V. Kowdley: Recipient of honoraria, fees, equity, research support or clinical trial grants for AbbVie, Corcept, CymaBay, Enanta, Genfit, Gilead, GSK, Hanmi, HighTide, Inipharm, Intercept, Madrigal, Mirum, Novo Nordisk, NGM Bio, Pfizer, Pliant, Terns, Viking and 89bio. David W. Victor III Current activity with scientific or clinical advisory boards: Intercept. Consulting: Intercept and Sebela. Speakers' fees: Gilead and Intercept. Leona Bessonova, Radhika Nair, and Jing Li: Employees of Intercept Pharmaceuticals Inc. Darren Wheeler: Former employee of Intercept Pharmaceuticals Inc. Joanna P. MacEwan, Alina Levine, and Jennifer Hernandez: Employees of Genesis Research. Gideon Hirschfield: Consultant for Intercept, Ipsen, CymaBay, Gilead, Pliant, HighTide, Escient, Mirum, and GSK.

Data Availability Statement

Questions regarding data availability should be directed to joanna.macewan@genesisrg.com.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.