JHEP|Reports

Ductular reaction is a prognostic factor in primary biliary cholangitis

To the Editor:

We read with great interest Diletta Overi *et al.*'s study[1] recently published in the *Journal*. Ductular reaction (DR) in patients with primary biliary cholangitis (PBC) is associated with disease stage and hepatic fibrosis, and extensive DR is associated with response to ursodeoxycholic acid (UDCA) and estimated survival of the individual, independent of other histological parameters. Reactive tubules were associated with timid duct articulation and fibrotic cell activation in patients with PBC. However, the survival of patients with PBC has not yet been investigated. Our study showed that baseline DR is a prognostic factor in PBC. A retrospective study was conducted on 138 patients with PBC who underwent liver histological examination, including 95 patients with simple PBC and 43 with PBC-autoimmune hepatitis (AIH) overlap syndrome (112 and 26 patients with Ludwig stages I–II and III–IV, respectively). Decompensated cirrhosis, liver transplantation, and death were considered serious adverse liver events (SAE). The median follow-up time was 68.5 months. During follow-up, decompensated cirrhosis, liver transplantation, and death occurred in nine, one, and two patients, respectively. Interestingly, we did not find a linear correlation between DR and alkaline phosphatase (ALP)(r = 0.029, p = 0.728), but we observed a close correlation between DR and Ludwig stages and PBC-AIH overlap (r = 0.29, p = 0.001; r = 0.21, p = 0.011). Kaplan-Meier survival analysis showed that ALP level was not a predictive risk factor for SAE (log-rank, p = 0.405, Fig. 1A), and no significant prognostic difference was observed for response to UDCA or the presence/absence of PBC-AIH overlap (log-rank, p all >0.05), while Ludwig stage and DR were risk factors for the development of clinical SAE (log rank, p <0.05, Fig. 1B,C).

DR is a repair response to hepatobiliary cell injury,[2] characterized by pathological changes including interlobular bile duct hyperplasia, matrix changes, and inflammatory cell infiltration.[3] DR plays a key role in the pathogenesis of various liver diseases and is related to the stage of liver fibrosis and mortality.[4,5] DR is usually prominent in patients with PBC, but the clinical significance of its appearance and its significance in the pathogenesis of the disease have not been fully determined.[6]

We demonstrated DR using cytokeratin (CK) 7 immunohistochemical staining, which revealed the composition of hepatic progenitor cells, intermediate hepatocytes, and bile duct reactions. CK19 is positive in transitional cells and bile duct cells, but negative in hepatic progenitor cells, hepatocyte lines, and hepatocytes.[7] Therefore, CK7 is more responsive to DR than CK19. Some studies suggest that CK7 reflects the Ludwig stage of PBC and can better predict its progression.[8,9] Our study found that DR in PBC was related to the Ludwig stage and PBC-AIH overlap syndrome, indicating that DR is involved in the progression of PBC and can lead to poor prognosis.

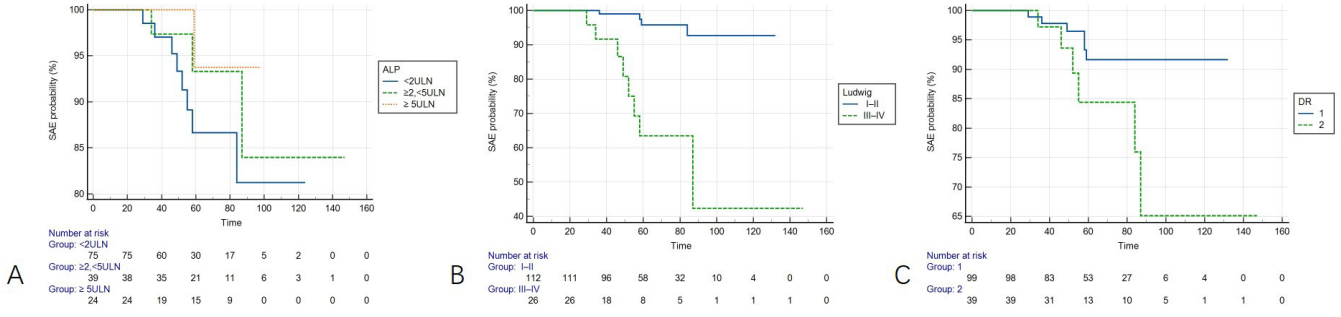

Fig. 1. Kaplan-Meier analysis of the risk of serious adverse liver-related events. (A) Kaplan-Meier survival analysis of ALP level (ALP level stratification: <2x ULN: ≥2x ULN; <5x ULN: ≥5x ULN). (B) Kaplan-Meier survival analysis of Ludwig stage (Ludwig I – II; Ludwig III – IV). (C) Kaplan-Meier survival analysis of DR (DR 1: Ductular profiles are largely limited to the portal mesenchyme, with little extension into the lobules; 2: Extensively proliferating ductules with invasive lobules.). ALP, alkaline phosphatase; DR, ductular reaction; SAE, serious adverse liver event (decompensated cirrhosis, liver transplantation and death); ULN, upper limit of normal.

Received 5 March 2023; accepted 14 March 2023; available online 6 April 2023

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Financial support
This work was supported by the social development project of Jiangsu Province, China (BE2020775), Chinese Federation of Public Health foundation (GWLM202002).

Conflict of interest
All authors declare that there is no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
YW Tan and LP Liu designed the research; LP Liu and ZH Lu collected and analyzed the data, and drafted the manuscript; YW Tan and LP Liu wrote and revised the manuscript; all authors have read and approved the final version to be published.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100750.

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