EDITORIAL

The More, the Better? Predicting Prognosis in Primary Biliary Cholangitis

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Primary biliary cholangitis (PBC; formerly primary biliary cirrhosis) is an autoimmune liver disease characterized by non-supprative inflammation and destruction of small bile ducts. The incidence and prevalence of PBC vary by ethnicity and geographic region. In South Korea, incidence and prevalence are relatively low, estimated as 8.57/million and 47.5/million, respectively.[1]

For decades, ursodeoxycholic acid (UCDA) has been the only drug approved for treatment of PBC, having been shown to slow disease progression and curb needed liver transplants in affected patients. Although response to UDCA is pivotal in various prognostic models of PBC, each model has its own criteria for determining biochemical responses to UDCA. Such models typically require a 12-month interval after initiating UDCA therapy to then measure responses, although recent reports suggest that responses after 6 months of treatment may also reflect long-term outcomes with no less accuracy.[2]

According to the Barcelona criteria, a biochemical response is marked by >40% decline (vs baseline) in alkaline phosphatase (ALP) level or ALP normalization after 1 year of UDCA treatment.[3] In the Paris-I criteria,[4] biochemical response (assayed after 1 year of UDCA treatment) is defined as ALP <3 times upper limit of normal (ULN), aspartate aminotransferase (AST) <2 times ULN, and bilirubin ≤1 mg/dL; whereas Paris-II criteria[5] call for ≤1.5 times ULN in ALP and AST levels and bilirubin within normal range. Rotterdam criteria equate biochemical response with normalization of albumin and/or bilirubin levels 1 year after UDCA is initiated.[6]

Unlike the dichotomous criteria of the above prognostic models, the GLOBE and UK-PBC models incorporate continuous scoring systems. The GLOBE score hinges on five indices: age at start of UDCA therapy and four determinants (bilirubin, ALP, albumin, and platelet count) assessed after 1 year of treatment.[7] GLOBE scores are calculated as follows: $0.044378 \times$ age at start of UDCA therapy $+ 0.93982 \times \ln$(bilirubin $\times$ ULN at 1-year follow-up)$+0.335648 \times \ln$(ALP $\times$ ULN at 1-year follow-up) $- 2.266708 \times$ albumin level $\times$ the lower limit of normal (LLN) at 1 year follow-up $- 0.002581 \times$ platelet count per 10^9/L at 1-year follow-up $+ 1.216865$.[7] In patients with GLOBE scores ≤0.30, life-expectancy is presumed comparable to that of matched general population members.[7]

The UK-PBC score is determined by baseline albumin and platelet levels, as well as ALP, transaminase, and bilirubin levels, after 12 months of UDCA therapy.[8] UK-PBC scores are calculated as follows: $1 -$ baseline survival functionˆexp($0.0287854 \times$ [ALP after 12 months of UDCA $\times$ ULN $- 1.722136304$] $- 0.0422873 \times$ [{(transaminase [ALT where available, otherwise AST] after 12 months of UDCA $\times$ ULN/10)ˆ-1} $- 8.675729006$] $+ 1.4199 \times$ [ln{bilirubin after 12 months of UDCA $\times$ ULN/10} $+ 2.709607778$] $- 1.960303 \times$ [albumin $\times$ LLN $- 1.17673001$] $- 0.4161954 \times$ [platelet $\times$ LLN $- 1.873564875$]).[8] Both GLOBE and UK-PBC scores surpass binary models in predicting death or liver transplantation, albeit more variables and complicated formulas are introduced.[7,8] Furthermore, they enable calculation of transplant-free survival probability or risk of developing hepatic failure at selected time points.

Most prognostic models focus solely on factors signaling treatment response. As such, it is notable that the UK-PBC model includes baseline data (albumin level and platelet count) roughly approximating hepatocellular synthetic function/hepatic fibrosis and offering a gauge of hepatic functional reserves in patients at treatment onset. These added variables (indicative

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of core liver functions) may indeed be advantageous. However, albumin levels and platelet counts may not change substantially after 12 months of UDCA therapy, as the UK-PBC authors concede.[8] The GLOBE model similarly utilizes albumin and platelet levels 1 year after UDCA initiation.[7] Hence, performance gains by both models are likely attributable to intrinsic parameters of liver function and not merely therapeutic response.

In this issue of *Gut and Liver*, Yoo *et al*.[9] retrospectively reviewed 271 patients with PBC whose laboratory data were retrievable after 1 year of UDCA therapy. Corresponding 5 and 10-year transplant-free survival rates were 91% and 77%, respectively. These authors validated all six prognostic models (Barcelona, Paris-I, Paris-II, Rotterdam, GLOBE, and UK-PBC) and investigated the neutrophil-to-lymphocyte ratio (NLR) as yet another prognosticator of patients with PBC. In doing so, they confirmed the better performance of GLOBE and UK-PBC scores relative to binary models, corroborating previous reports.[7,8,10]

The NLR (i.e., ratio of absolute neutrophil count to absolute lymphocyte count) is high in patients with neutrophilia and/or lymphopenia. Neutrophils play an active role in inflammatory conditions; and once an inflammatory response is mounted, neutrophils are the first immune cells recruited to infected or injured sites. The NLR may thus serve as a surrogate marker for intensity of inflammation. Accumulating evidence indicates that high NLR is associated with a poor prognosis in a variety of malignancies and in inflammatory diseases, despite meager understanding of related mechanisms.[11,12]

Yoo *et al*.[9] have also demonstrated that a high NLR (>2.46) negatively impacts the risk of liver transplantation or death. By combining this index of systemic inflammation, stratification of patients with PBC is enhanced even more. Of note, these authors relied on baseline data for NLR determinations, whereas most prognostic models utilize follow-up data after UDCA therapy. This implies that the degree of inflammation at start of treatment may influence long-term prognosis, regardless of UDCA responsiveness. Ultimately, extent of inflammation, response to UDCA, and hepatic reserves may all impact the prognosis of patients with PBC.

Understandably, these authors now encourage the use of NLR in this setting, suggesting its annexation to prognostic models of PBC to aid patient stratification. The question then becomes one of diminishing returns. Additional variables can improve the predictive performance, but the complexities entailed may at some point imperil the ease of model usage. Further external-validation is clearly needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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