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To the editor:

The CLL-IPI applied in a population-based cohort

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The rapid development in treatment options for patients with chronic lymphocytic leukemia (CLL) in parallel with a much more detailed understanding of the underlying pathogenesis has warranted the development of novel prognostic indices for patients with CLL to replace the clinical staging systems developed by Rai and Binet 40 years ago.[1,2]

Bahlo and colleagues from an international consortium have developed a new international prognostic index for patients with chronic lymphocytic leukemia (CLL-IPI) based on a combination of molecular and clinical baseline characteristics for patients with CLL.[3,4] The impact of previously proposed prognostic models has been limited due to omission of molecular characteristics,[5] inclusion of parameters not widely used,[6] or restriction to cytogenetic findings.[7] With an initial assessment of 27 baseline markers in patients enrolled in 8 clinical trials, they have established the CLL-IPI prognostic model based on 5 parameters becoming widely available: *TP53* aberrations (including del(17p) and *TP53* mutation), IGHV mutational status, β(2)microglobulin level, clinical stage and age. The model was validated in 2 external cohorts including patients followed from time of diagnosis.

The establishment of a robust and widely accepted international prognostic index in CLL to guide treatment decisions and assess the composition of in trial populations is an important and valuable tool.[8] The CLL-IPI was developed based on participants in clinical trials before the era of chemoimmunotherapy, with only 571 out of 3725 patients receiving chemoimmunotherapy as first-line treatment. The included patients were younger (median age, 61 years) and mainly physically fit (96% ECOG performance status [PS] 0-1) compared with the general population of newly diagnosed patients with CLL.[4] Thus, application and validation of the CLL-IPI in a population-based cohort of patients with newly diagnosed CLL in the current era of chemoimmunotherapy is warranted prior to broader implementation.

Here, we present data from the prospective Danish National CLL Registry, which is a nationwide, mandatory registry including and prospectively following all consecutive patients diagnosed with CLL in Denmark since 2008 to estimate time to event (TTE; treatment or death) and overall survival (OS) according to the 4 CLL-IPI risk groups.[9] All prognostic variables were analyzed at the time of diagnosis according to the Danish national guidelines for CLL.

In total, all 5 variables for the CLL-IPI were available for 1514 patients (861 low risk, 453 intermediate risk, 193 high risk, and 34 very high risk) diagnosed with CLL between 2008 and 2015. Excluded from the analyses were an additional 1509 patients included in the registry who were missing 1 or more of the 5 variables. The majority of patients (917 [60%]) were male, the median age was 69 years (interquartile range, 61-76 years), 306 (20%) were Binet stage B or C, 1498 (97%) were PS 0-1, and 3-year OS and 3-year event-free survival rates were 88% and 74%, respectively. 3-year OS in the low-risk, intermediate-risk, high-risk, and very high-risk CLL-IPI groups was 91%, 86%, 76%, and 62%, respectively. A total of 295 patients (19%) (60 low risk [7%], 128 intermediate risk [28%], 87 high risk [45%], and 20 very high risk [59%]) were treated for CLL, and 249 patients (16%) (89 low risk [10%], 89 intermediate risk [20%], 56 high risk [30%], and 15 very high risk [44%]) died during follow-up. The median observation time was 3.2 years, and the median survival was not reached. For patients excluded from the analysis due to ≥1 missing CLL-IPI variables, 898 (61%) were male, 71 years was the median age, 335 (24%) had Binet stage B or C, 1356 (93%) had PS 0-1, the 3-year OS was 80%, and the 3-year event-free survival was 70%.

For our analyses, the 4 different risk categories proposed by Bahlo et al[3] predicted significantly different TTE and OS ($P < .001$) for each of the 4 risk categories (Figure 1). Thus, the robustness of the CLL-IPI index in an unselected cohort of patients with newly diagnosed patients CLL in the era of chemoimmunotherapy could be confirmed.

As single-agent targeted treatment and combinations of chemotherapy- and non–chemotherapy-based options are evolving, the CLL-IPI may be used to identify at the time of diagnosis CLL patients who will likely not benefit from conventional chemoimmunotherapy, as proposed by Bahlo et al. Our data presented here provide the basis for external validation of the CLL-IPI in a population-based cohort exposed to chemoimmunotherapy. As such, the CLL-IPI could prove a critical step in predicting the time from diagnosis to a need

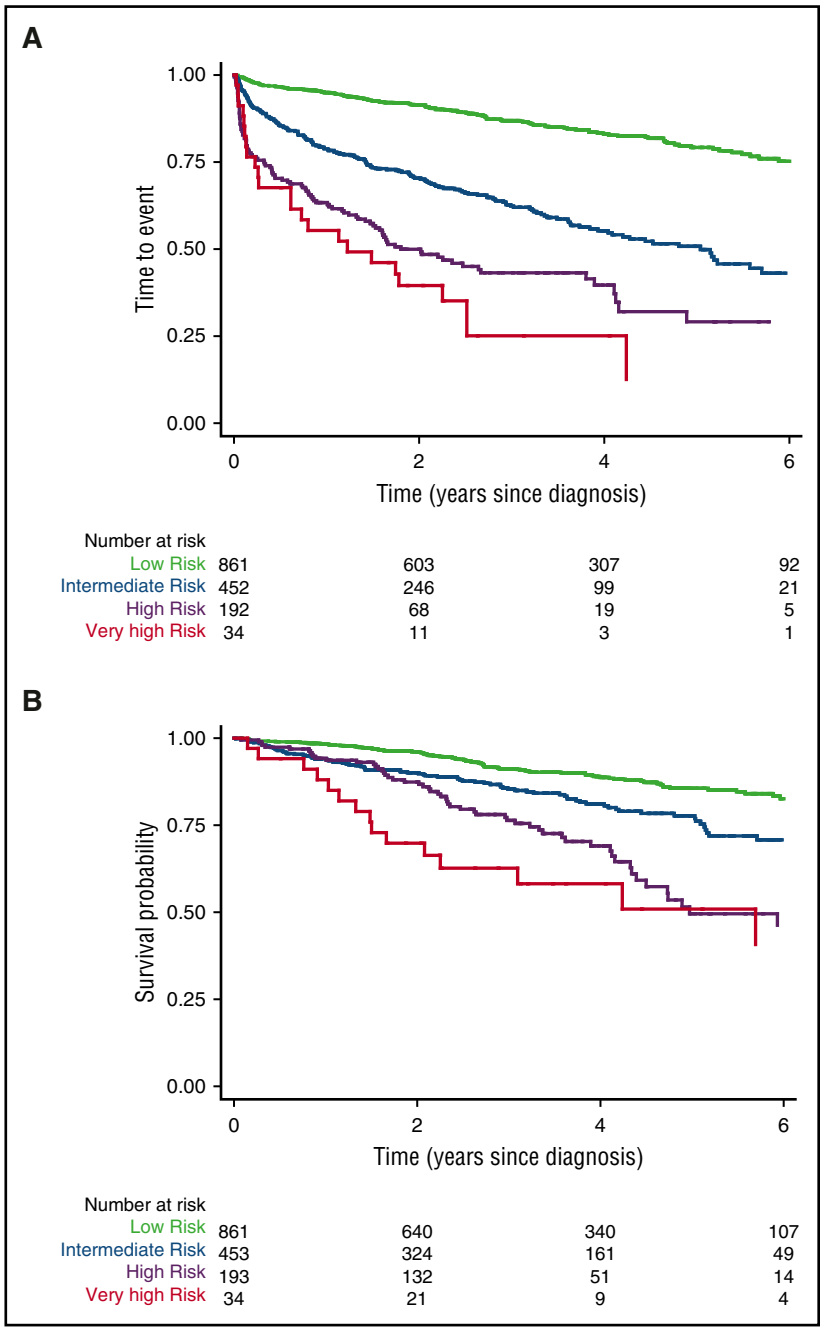

Figure 1. TTE and OS according to the CLL-IPI. (A) TTE and (B) OS according to the CLL-IPI in 1514 patients with all 5 variables available through the Danish National CLL Registry.

for treatment and help guide therapeutic decision making in the era of novel targeted treatment options for CLL. We encourage all centers caring for patients with CLL to integrate the 5 parameters as part of their routine diagnostic workup and to report the CLL-IPI risk categories for patients in clinical trials.

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To the editor:

Clinical relevance of antiplatelet antibodies and the hepatic clearance of platelets in patients with immune thrombocytopenia

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Immune thrombocytopenia (ITP) is an autoimmune disorder whose primary pathogenesis is mediated by Fc receptor (FcR) clearance of antibody-opsonized platelets by spleen macrophages.[1] Recently, however, an Fc-independent mechanism of platelet clearance mediated by antibodies recognizing the platelet membrane glycoprotein Ib molecule (anti-GPIb antibodies) and leading to hepatic clearance of platelets was proposed by Li et al.[2] More specifically, they found that both murine and human anti-GPIb antibodies induced platelet GPIb desialylation in vitro; murine in vivo studies suggested that anti–GPIb-opsonized desialylated platelets lacking sialic acid become the ligand for the Ashwell-Morell receptor (AMR) on hepatocytes[3] and are removed by endocytosis. According to the hypothesis, this mechanism may predict for failure to respond to splenectomy, a recognized highly effective ITP treatment.[4] To date, however, this hypothesis has not been tested in ITP patients.

To address this, we retrospectively analyzed 93 adult primary ITP patients who were screened for antiplatelet antibody specificities and underwent platelet survival studies (PSSs) to estimate the site of clearance. This study was approved by the hospital review board. Moreover, patients signed an informed consent to clinical data use at enrollment in a local ITP database.

Our results suggest that the specificities of the antiplatelet autoantibodies do not predict or mediate a skewed hepatic clearance pattern.

Charts of adult ITP patients who had data on both PSSs and autoantibody testing were reviewed by 2 independent reviewers (S.C. and M.C.).

Antiplatelet antibodies are routinely searched for during testing at diagnosis of ITP (or, for patients diagnosed elsewhere, at first referral to our center); PSSs are performed in patients who fail or have a suboptimal response to first-line steroid therapy and are candidates for splenectomy.

Measurements of platelet-bound (direct) and plasma (indirect) immunoglobulin G (IgG) antiplatelet activity were performed using a commercially available solid-phase enzyme-linked immunosorbent assay (PakAutoAssay, Immucor GTI Diagnostic). Blood samples were added to microwells coated with monoclonal-captured glycoprotein IIb-IIIa, Ib-IX, Ia-IIa, allowing antibodies, if present, to bind; an alkaline phosphatase–labeled secondary reagent (anti-IgG/IgM/IgA) was added and incubated for 30 minutes, and optical density was measured at 405 nm.

Patient platelets were labeled with ^{111}In-oxide by methods previously described,[5] and reinfused platelets were used for the PSSs. To determine platelet survival time, platelet-bound radioactivity was assessed from 10-mL venous blood samples taken at 30 minutes, 2 hours, and 4 hours postinfusion and daily thereafter. Sampling was maintained up to 168 hours postinjection or until platelet-bound radioactivity was $<10\%$ of the initial value. A multiple-hit method was used to calculate the mean platelet survival according to the International Committee for Standardization in Hematology.[6] Platelet clearance pattern was determined by images from a γ camera. Scintigraphic indices obtained were spleen/heart, liver/heart, spleen/liver, spleen/spleen at 30 minutes, and liver/liver at 30 minutes according to standard procedures.[7] Platelet clearance pattern was defined as splenic uptake (if splenic uptake measured on the third day was >1.2 times the splenic uptake measured at 30 minutes from platelet reinfusion), hepatic uptake (if hepatic uptake measured on the third day was >1.2 times the splenic uptake measured at 30 minutes from platelet reinfusion), or mixed uptake (if both splenic and hepatic uptakes measured on the third day were >1.2 times the splenic uptake measured at 30 minutes from platelet reinfusion).[8]

Standard descriptive statistical analysis techniques were used for all the collected variables using Stata/SE 14.1 (StataCorp, College Station, TX). The Fisher's exact test was used to assess the association between categorical variables.

Our study population comprised 93 ITP patients with a median age at diagnosis of 48 years (range, 19-86 years). Of these, 56 out of 93 (60.2%) were splenectomized; in the remaining 37 patients (39.8%), splenectomy had not been performed yet or was subsequently deemed not necessary because of a late response to medical therapy.

Table 1 summarizes antibody testing and PSSs results. The time interval between antibody testing and PSSs was ≤ 12 months in 71% of patients, with only 17.2% of patients tested at ≥ 24 months.