Commentary

New kid on the block: C-reactive protein-to-albumin ratio as a new prognostic marker for chronic lymphocytic leukemia: Comment on "C-reactive protein-to-albumin ratio is an independent poor prognostic factor in newly diagnosed chronic lymphocytic leukaemia: A clinical analysis of 322 cases"

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Chronic lymphocytic leukemia (CLL) is an indolent disease of CD5-positive mature *B* cells and it is the most common lymphoid malignancy of adulthood in the Western world. The clinical course and outcome of patients with CLL may vary, and parameters were needed in order to determine the treatment need and prognosis in CLL patients [1].

In this regard, two groups historically performed two prognostication systems, the Rai (later modified) and Binet staging systems, which are simple, inexpensive and practical, based on physical examination and complete blood count (Table 1). Both systems define three main prognostic groups: low, intermediate, and high risk [2,3]. Symptomatic or high risk CLL patients require therapy, and the choice of treatment is mainly based on comorbidities and functional status as well as the genetics of the disease.

Genetic and chromosomal aberrations can be used to predict disease biology. Among others, deletion of the short arm of chromosome 17 (del17p) and/or mutations of the *TP53* gene and immunoglobulin heavy chain (IGHV) mutation status are the most commonly used markers in order to predict outcome in patients with CLL. Del17p and/or *TP53* mutation, are associated with resistance to standard chemoimmunotherapy and an aggressive course. The *B* cell receptor signaling plays a notable role in the survival of CLL cells and it is regulated by IGHV somatic hypermutation and stereotype status. It also serves as a therapeutic target in CLL. The mutational status of the IGHV gene is a powerful prognostic marker that does not vary over time. The unmutated status is associated with an inferior prognosis and unresponsiveness to standard chemoimmunotherapy [1].

The Rai and Binet systems, which do not incorporate molecular biomarkers, may lack in predicting the course of disease. In addition to the clinical stage and known genetic and chromosomal abnormalities, there are many potential biomarkers, and comprehensive prognostic scoring systems have been created aiming to blend these clinical, biological, and genetic information (Table 1). The purpose of prognostic models in CLL is to accurately predict the clinical course of patients with low- and high-risk diseases. Also, these parameters should be affordable, widely accessible, and easy to use [1,4].

The most accepted of these newer scoring systems is CLL - International Prognostic Index (CLL-IPI), which consists of five independent prognostic factors; del17p and/or *TP53* mutation status, serum β2-microglobulin, IGHV mutational status, clinical stage of Rai and Binet, and age to identify four risk groups with significantly different estimated rates of overall survival (OS) [5] (Table 1). Patients with low-risk CLL-IPI (0–1) and asymptomatic disease do not require treatment [1,5].

In this issue of the *Journal*, Tang et al. [6] evaluated the impact of pretreatment *C*-reactive protein-to-albumin ratio (CAR) on prognosis in 322 newly diagnosed CLL patients. Also, they evaluated the prognostic effects of adding CAR to CLL-IPI. The study cohort had a median age

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Table 1

Characteristics of some prognostic models in CLL.

Selected Prognostic Model, [Reference number]	Patient Population	Total Number of Variables	Clinical Parameters	Laboratory Parameters	Genetic Parameters	Endpoints
Rai et al. [2]	At diagnosis treated with CIT	5	Lymph node involvement, Organomegaly (HM, SM)	Absolute lymphocyte count, Hemoglobin, Platelet	N/A	Median Survival
Binet et al. [3]	At diagnosis treated with CIT	3	Enlarged areas (Lymph node involvement, Organomegaly)	Hemoglobin, Platelet	N/A	Median Survival
CLL-IPI [5]	At diagnosis treated with CIT	5	Age, Rai/Binet stage	Beta-2 microglobulin	TP53 status, IGHV mutational status	OS
MDACC 2007ᵖ [9]	At diagnosis treated with CIT	6	Age, Sex, Rai stage, Lymph node involvement	Beta-2 microglobulin, Absolute lymphocyte count	N/A	OS
Barcelona-Brno modelʳ [9]	At diagnosis treated with CIT	2	N/A	N/A	IGHV mutational status, adverse FISH cytogenetics status (del17p, del11q)	OS
BALL scoreˢ [9]	R/R with TT	4	Time from the initiation of last therapy <24 months	Beta-2 microglobulin, Lactate dehydrogenase, Hemoglobin	N/A	OS
4-factor score [10,11]	Treatment naïve and R/R during ibrutinibtherapy	4	Disease status (treatment naïve or R/R)	Lactate dehydrogenase, Beta-2 microglobulin	TP53 aberration	PFS, OS
CAR with CLL-IPI* [6]	At diagnosis treated with mostly CIT	6	Age, Rai/Binet stage	Beta-2 microglobulin, CAR	TP53 status, IGHV mutational status	TFS, OS

CAR, C-reactive protein-to-albumin ratio; CIT, chemoimmunotherapy; CLL-IPI; Chronic lymphocytic leukemia - International Prognostic Index; HM, hepatomegaly; IGHV, immunoglobulin heavy chain; MDACC 2007, M. D. Anderson Cancer Center 2007; N/A, not applicable; OS, overall survival; PFS, progression free survival; R/R, relapsed refractory; SM, splenomegaly; TFS, treatment free survival; TT, targeted therapy.

* CAR with CLL-IPI has not been validated yet. ᵖWierda WG, et al. *Blood.* 2007;109(11):4679–85. ʳGentile M, et al. *Am J Hematol.* 2018;93(2):E35-e37. ˢSoumerai JD, et al. *Lancet Haematol.* 2019;6(7):e366-e374.

of 59 with a male predominance (65.2%). Although the median age at diagnosis in CLL is approximately 70 in the Western countries [1], the CLL population in the study of Tang et al. [6] is a decade younger, that is consistent with previous CLL studies coming from China [7]. Also, 222 patients (68.9%) had Binet stage *B* or *C* disease.

In this new prognostic factor, the authors used two parameters mainly related to inflammation and malnutrition. It was stated that they excluded patients with known inflammation and infection, however, these confounding factors might set a barrier in using CAR in daily clinical practice, although it seems quite practical. They determined a cut off value for the CAR (which was 0.6166), and 10.9% ($n = 35$) and 89.1% ($n = 287$) of patients had high and low CAR, respectively [6]. During a follow-up of 65 months, 82.8% (29/35) and 70.7% (203/287) of the patients with high and low CAR required treatment, respectively, and CAR was found to be an independent prognostic factor for OS in this Chinese CLL cohort [6].

In this study, 20.4% and 39.4% of patients had a TP53 disruption and unmutated IGHV, respectively [6]. Seventy two percent of the patients ($n = 232$) received treatment, of which 88.8% ($n = 206$) received chemoimmunotherapy as a frontline therapy and only 3.8% ($n = 9$) had ibrutinib. Adding CAR enabled CLL-IPI to work more accurately in this study cohort, where the vast majority of patients received upfront chemoimmunotherapy [6].

The therapeutic landscape of CLL is rapidly evolving in the era of targeted therapies, and the use of Bruton's tyrosine kinase, phosphoinositide 3-kinase, and BCL2 inhibitors and anti CD20 antibodies may overcome the adverse biological features and provide long-term disease control. It is known that patients with CLL harboring del17p and/or TP53 mutation are at high risk for not responding to chemoimmunotherapy [1], and in the recent ESMO recommendations, patients with a del17p and/or *TP53* mutation should be treated with targeted agents [8]. Chemoimmunotherapy (e.g. FCR) is especially recommended to patients < 65 years, fit, and with mutated IGHV and without del17p and/or TP53 mutation. Novel agents (ibrutinib, acalabrutinib, venetoclax, obinutuzumab) are preferred in patients with unmutated IGVH and with/without del17p and/or *TP53* mutation, as they

were shown to improve progression-free survival (PFS) in some studies [8].

Since CLL-IPI was developed in the era of chemoimmunotherapy, the prognostic value of CLL-IPI needs to be re-evaluated in studies with novel agents and still a longer follow-up is needed [5,9]. Also, the combination of CLL-IPI and CAR needs to be tested among patients receiving novel targeted therapies.

Recently, Molica et al. [9] published a meta-analysis evaluating the performance of 4 prognostic models (CLL-IPI, MDACC 2007 and Barcelona–Brno models, and BALL score) validated in at least 3 studies in CLL for predicting OS (Table 1). Discrimination, which is the capacity to distinguish low- and high-risk patients, is an important factor in determining the prognostic power of a model. Concordance statistic (C-statistic), a measure of accuracy, is used for discrimination [9]. The closer a *C*-statistic to 1, the better a model to classify outcomes correctly. The pooled *C*-statistics for CLL-IPI, MDACC 2007 and Barcelona-Brno models, and BALL score were 0.73, 0.67, 0.65, 0.71 respectively, and CLL-IPI found to be having the best performance especially in discrimination of individuals with good prognosis at diagnosis [9].

With the increasing use of targeted therapies in CLL, validated scoring systems begin to emerge for those receiving these agents. The National Institutes of Health (NIH) CLL group collected information on CLL patients treated with ibrutinib and developed a novel scoring system, 4-factor score, which was then validated in a multi-center Italian study [10,11] (Table 1). This scoring system was shown to be superior to CLL-IPI, especially in those receiving ibrutinib, with knowing the fact that CLL-IPI was developed in previously untreated patients, however these patient cohorts consisted of both newly diagnosed and relapsed/refractory patients [10,11].

In conclusion, there are many prognostic scoring systems in order to predict clinical outcomes in CLL. An ideal prognostic model should be able to differentiate low- and high-risk patients and make a proper risk assessment with a reasonable number of parameters. According to the present study by Tang et al. [6], baseline CAR seems to be an economic, accessible, useful prognostic parameter for previously untreated CLL patients receiving upfront chemoimmunotherapy. The combination

of CAR with CLL-IPI, also seems to improve the prognostic effectiveness of CLL-IPI.

Having said that, since the parameters used in CAR can be affected by inflammation and/or infection, in CLL patients with inflammatory conditions, this new prognostic marker should be used with caution. And what's more, the prognostic impact of CAR and CLL-IPI combination should be validated in other patient cohorts receiving both chemoimmunotherapy and novel agents. Finally, in the future, CAR can most probably be mounted on the newer scoring systems other than CLL-IPI in order to evaluate its effectiveness.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Selin Küçükyurt: Conceptualization, Methodology, Investigation, Writing - original draft. **Furkan Bahar:** Investigation, Writing - original draft. **Ahmet Emre Eşkazan:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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