blood

# To the editor:

## In CLL, comorbidities and the complex karyotype are associated with an inferior outcome independently of CLL-IPI

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Chronic lymphocytic leukemia (CLL) represents the most common form of leukemia in Western countries.[1] The clinical course of the disease is quite heterogeneous with some patients living for years with asymptomatic disease and others experiencing early progression and requiring therapeutic interventions.

To allow rationale management of patients with CLL in clinical practice and in clinical trials, an international prognostic index (CLL-IPI) was defined, based on the relative contribution of the major prognostic parameters, that is, *TP53* status, *IGHV* mutational status, serum β2-microglobulin, clinical stage, and age.[2]

However, CLL is mainly a disease of the elderly with many patients presenting at diagnosis with significant comorbidities that may affect treatment decisions and outcome.[3] Moreover, in recent years, the complex karyotype (CK) emerged as a prognostic biomarker associated with an inferior outcome[4,5] and worse response to treatments including novel drugs.[6,7]

We therefore set out to analyze the prognostic relevance of comorbidities and of CK in relation to the CLL-IPI.

The study cohort consisted of 335 untreated CLL patients diagnosed and followed at our center between 2006 and 2016 as previously described.[8] All patients were diagnosed and treated according to National Cancer Institute criteria.[9] The study was approved by the local ethics committee. Fludarabine- or bendamustine-containing regimens, with or without rituximab, were used as first-line treatment in fit patients; chlorambucil with or without rituximab was used in elderly and/or unfit patients according to the treatment policy adopted at our center. Since 2015, ibrutinib or idelalisib plus rituximab were offered to relapsed/refractory patients. Coexisting medical conditions were evaluated according to the Cumulative Illness Rating Scale (CIRS) scores as described.[10] Creatinine clearance was assessed with the use of the Cockcroft-Gault formula.[11]

The CK was defined by the presence of at least 3 chromosome aberrations by cytogenetic analysis as described.[12]

The principal clinical and biological characteristics of the patients are reported in supplemental Table 1 (available on the *Blood* Web site). The median age of these CLL patients was 68.7 years (range, 33-96 years)

**Table 1. Univariate and multivariate analysis for OS and TTFT**

| | Univariate analysis | | Multivariate analysis, n = 228 | | | |
|---|---|---|---|---|---|---|
| | | | | | After bootstrapping | |
| Variable | HR (95% CI) | *P* | HR (95% CI) | *P* | HR (95% CI) | *P* |
| **OS** | | | | | | |
| CLL-IPI | | | | | | |
| Low | 1 | | 1 | | 1 | |
| Intermediate | 2.593 (1.121-6.001) | .026 | 2.074 (0.853-5.237) | .108 | 2.074 (0.822-5.049) | .122 |
| High | 4.828 (2.152-10.834) | <.001 | 5.716 (2.434-13.423) | <.001 | 5.716 (2.516-12.989) | <.001 |
| Very high | 13.628 (4.742-39.166) | <.001 | 4.875 (1.399-16.984) | .013 | 4.875 (1.161-20.477) | .031 |
| CIRS ≤6/>6 | 3.843 (2.433-6.071) | <.001 | 2.899 (1.521-5.523) | .001 | 2.899 (1.352-6.217) | .006 |
| CK, yes/no | 3.176 (1.882-5.359) | <.001 | 3.572 (1.572-8.116) | .002 | 3.572 (1.341-9.515) | .011 |
| **TTFT** | | | | | | |
| CLL-IPI | | | | | | |
| Low | 1 | | 1 | | 1 | |
| Intermediate | 6.640 (2.993-14.729) | <.001 | 6.214 (2.788-13.853) | <.001 | 6.214 (2.171-17.790) | .001 |
| High | 20.831 (9.588-45.260) | <.001 | 22.308 (10.214-48.720) | <.001 | 22.308 (7.718-64.480) | <.001 |
| Very high | 25.637 (9.748-67.425) | <.001 | 15.811 (5.611-44.555) | <.001 | 15.811 (4.425-56.502) | <.001 |
| CIRS ≤6/>6 | 1.151 (0.794-1.669) | .407 | — | — | — | — |
| CK, yes/no | 2.521 (1.606-3.958) | <.001 | 2.157 (1.185-3.926) | .012 | 2.157 (1.177-3.952) | .013 |

TTFT was calculated as the interval between diagnosis and the start of first-line treatment. OS was calculated from the date of diagnosis until death due to any cause or until the last patient follow-up. Proportional hazards regression analysis was used to identify the significant independent prognostic variables on TTFT. The stability of the Cox model was internally validated using bootstrapping procedures.[4] Statistical analysis was performed using Stata 14.0 (Stata Corp, College Station, TX).

—, not applicable; CI, confidence interval; HR, hazard ratio.

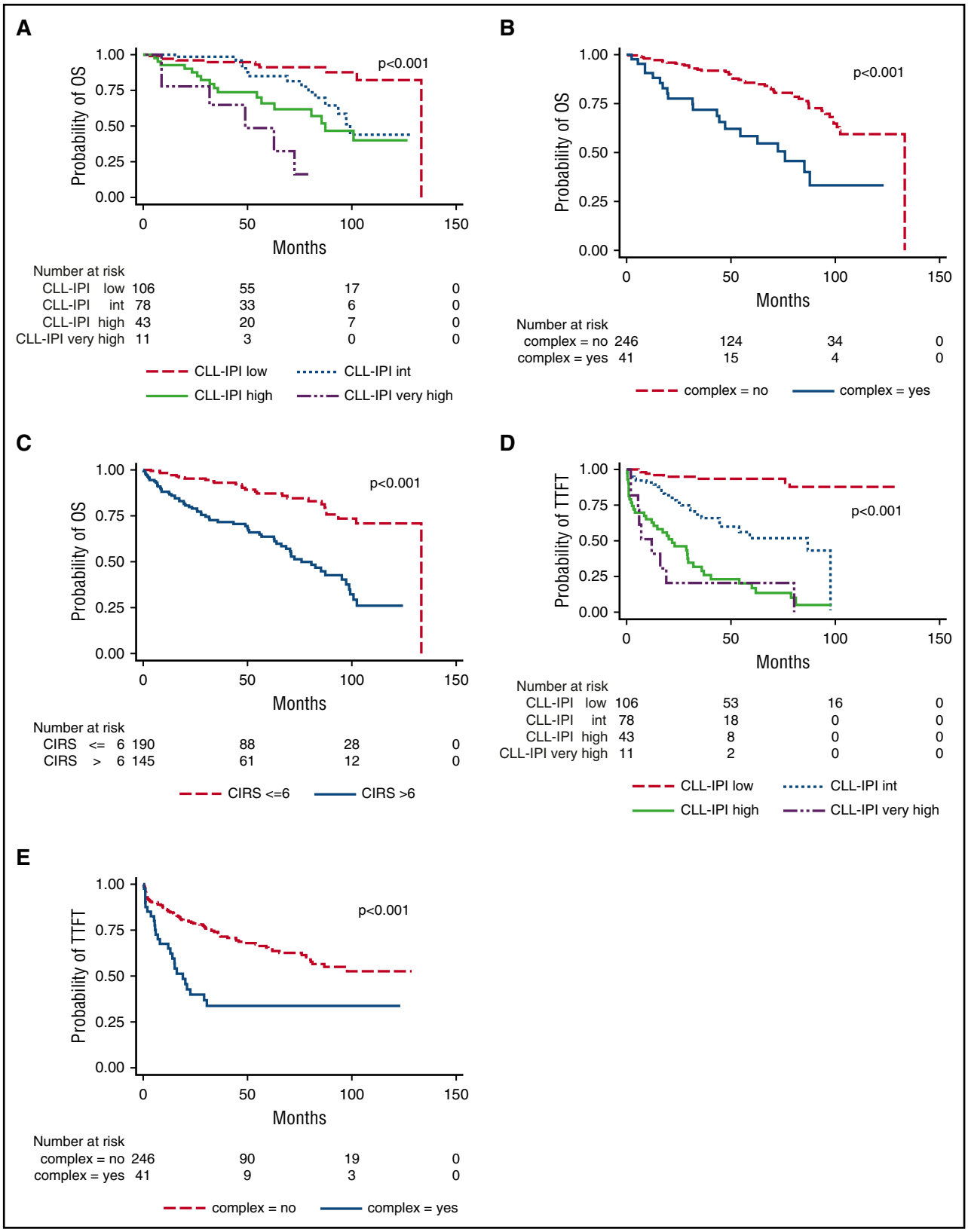


**Figure 1. OS and TTFT according to CLL-IPI, CIRS, and CK.** OS according to (A) CLL-IPI, (B) CK, and (C) CIRS. TTFT according to (D) CLL-IPI and (E) CK.

with 61.5% of the patients older than 65 years. Patients' distribution according to CLL-IPI was as follows: 106 low (44.5%), 78 intermediate (32.8%), 43 high (18.1%), and 11 very high (4.6%). Interestingly, these figures are very similar to those observed for the Mayo cohort of newly diagnosed CLL patients in the original CLL-IPI report[2] and reflect, in our region, a series of patients

diagnosed in a center that has a >90% capture of incident CLL cases therefore allowing for meaningful analyses of time to first treatment (TTFT) and overall survival (OS) in a real-world scenario. When considering coexisting medical conditions, 145 of 335 patients (43.3%) had a CIRS score > 6. CIRS distribution is reported in supplemental Table 2. A creatinine clearance lower than 70 mL per minute was present in 136 cases (40.6%). By combining CIRS and creatinine clearance, 199 of 335 of our patients (59.4%) would have been enrolled in the CLL11 trial for CLL patients with coexisting conditions.[13] As expected, a CIRS score > 6 was associated with age > 65 years ($P < .001$), creatinine clearance < 70 mL per minute ($P < .001$), Eastern Cooperative Oncology Group (ECOG) ≥ 2 ($P < .001$), and also with β2-microglobulin concentration > 3.5 mg/L ($P = .005$) (supplemental Table 3).

A CK was observed in 41 of 287 of the cases (14.3%), a figure in keeping with data from recently published series of patients.[5] The CK was significantly associated with advanced Binet stage ($P = .013$), CD38 positivity ($P = .003$), β2-microglobulin concentration > 3.5 mg/L ($P = .010$), TP53 deletion or mutation ($P = .001$), higher CLL-IPI ($P = .002$), and intermediate unfavorable fluorescence in situ hybridization results ($P < .001$) (supplemental Table 4).

In this analysis, we confirmed the prognostic impact of CLL-IPI on OS (Table 1; Figure 1A) and TTFT (Figure 1D).[14-16] In univariate analysis, an inferior OS was also associated with the CK ($P < .001$; Figure 1B) and a CIRS score > 6 ($P < .001$; Figure 1C). In multivariate analysis, both CK ($P = .002$) and CIRS score > 6 ($P = .001$) confirmed their negative prognostic impact on OS, independently of CLL-IPI. In univariate analysis, an inferior TTFT was associated with CK ($P < .001$; Figure 1E) but not with CIRS > 6. In multivariate analysis, the CK retained its negative prognostic impact on TTFT ($P = .012$), independently of CLL-IPI. The independent prognostic significance of the CK on TTFT and OS and of comorbidities on OS was also confirmed when CLL-IPI variables were considered separately (supplemental Table 5).

Although larger independent series of patients with longer follow-up are needed to confirm these observations, our findings reinforce the notion that, in CLL patients, comorbidities and the CK represent novel important prognostic markers. Indeed, relevant comorbidities may shorten life expectancy and may reduce treatment tolerance,[3,17] and modern treatment algorithms recommended evaluating not only age, clinical staging, and disease-specific prognostic biomarkers, but also comorbidities to guide clinical decisions,[13,18] particularly in the era of novel drugs.[19] However, the prognostic impact of comorbidities and of the CK in the era of mechanism-based treatment needs to be specifically addressed in larger series of patients treated for longer periods of time because in our cohort of CLL, these agents were offered only in more recent years.

Although no comorbidity score has been prospectively validated in CLL, the CIRS score is the most frequently used in CLL clinical trials.[13] Furthermore, with the use of effective mitogens, cytogenetic abnormalities and, in particular, CK recently emerged as one of the novel biomarkers associated with an inferior outcome[4-8,12,20] and with the development of chemorefractoriness.[21]

In conclusion, we showed for the first time that comorbidities and CK were associated with a worse outcome independently of CLL-IPI. We therefore suggest that comorbidities and CK might be considered as additional parameters to be included in CLL prognostic scores for better management of patients with CLL in clinical practice and in trials evaluating new drugs.

*G.M.R. and M.C. contributed equally.

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**Contribution:** G.M.R., M.C., and A.C. conceived and designed the study; G.M.R., M.C., F.M.Q., E.L., A.U., D.F., C.L., L.F., E.G., E.V., E.T., M.A.B., and A.M. acquired data and provided patient follow-up; G.M.R., M.C., M.N., F.C., and A.C. analyzed and interpreted data; and all of the authors contributed to the writing, approval, and review of the manuscript.

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# To the editor:

## Platelet factor 4/heparin complexes present epitopes differently on solid-phase vs platelet surfaces

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The immune response to complexes of the chemokine platelet factor 4 (PF4) and polyanions[1,2] results in anti–PF4/polyanion (anti–PF4/P) antibodies, which can induce one of the most frequent immune-mediated adverse drug reactions: heparin-induced thrombocytopenia (HIT). Immune complexes composed of anti–PF4/P antibodies and PF4/P complexes on the platelet surface induce platelet aggregation via

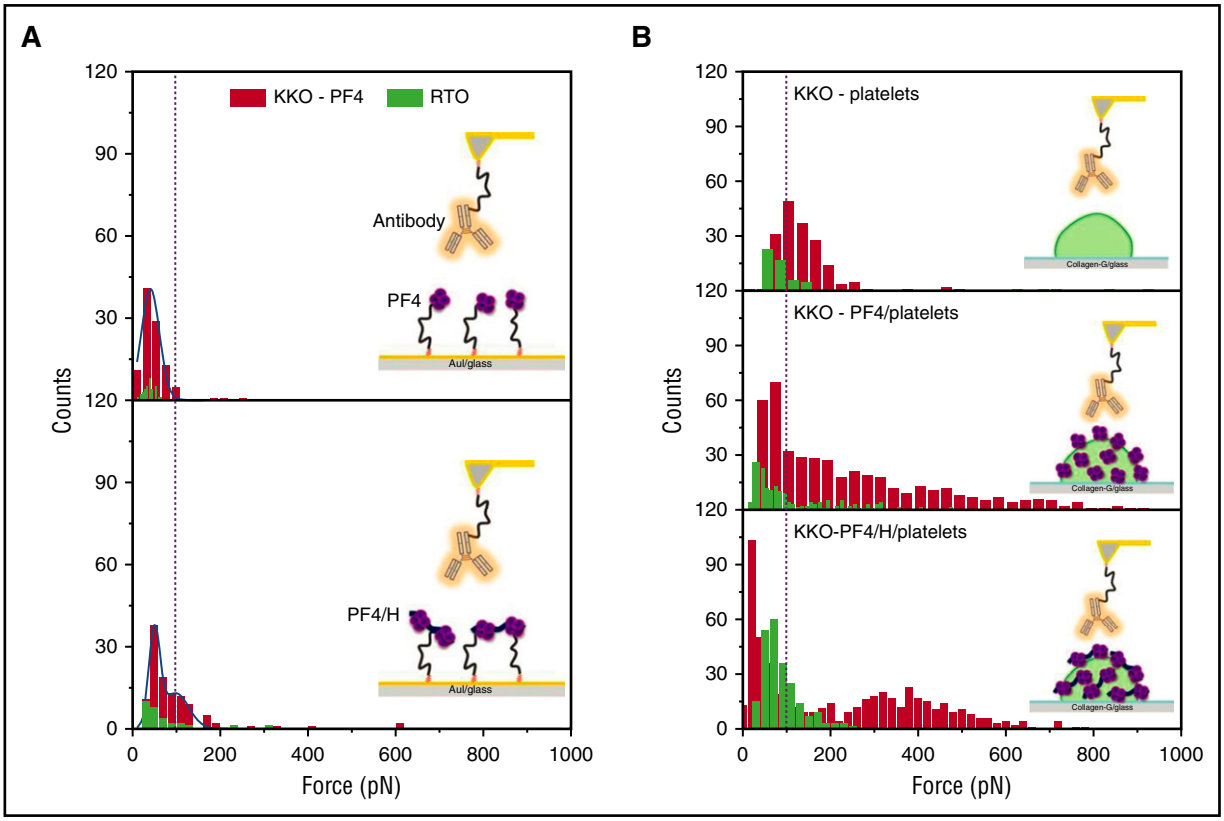


**Figure 1. The binding strength of KKO (red) vs RTO (green) to PF4 or PF4/H complexes coated on different surfaces.** (A) When PF4 (top) or PF4/H complexes (bottom) were immobilized on a gold surface, the reaction between KKO (red) and PF4 is weaker (rupture force up to 100 pN) than that between KKO and PF4/H complexes (rupture force up to 200 pN), while RTO (green) shows much weaker interactions, as evidenced by the low binding "counts." (B) When PF4 (middle) or PF4/H complexes (bottom) were coated on platelet surfaces, both KKO (red; rupture force up to 800 pN) and RTO (green; rupture force up to 200 pN) show stronger interaction forces than on the solid phase (A) or on noncoated platelets (top). The broad distribution of binding forces indicates that the binding site of KKO is presented very variably, allowing weak to very strong binding of KKO.