PERIPHERAL BLOOD INFLAMMATORY MARKERS AS PROGNOSTIC INDICATORS IN CHRONIC LYMPHOCYTIC LEUKEMIA

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is shaped by interactions between leukemic cells and the tumor microenvironment. Peripheral blood inflammatory markers are simple, low-cost surrogates of systemic inflammation that may help guide treatment decisions.

With BTK inhibitors now used across multiple lines of CLL therapy, identifying routinely available biomarkers that flag patients at higher risk of early progression is clinically relevant.

METHODS

Retrospective, single-center cohort study.

- ROC curves (Youden index) identified optimal cut-offs for progression/death at 12 months; AUC was additionally estimated at 6, 24 and 36-month PFS landmarks (supplementary analysis).
- Associations with TTFT were assessed by Spearman correlation.
- Event rates were compared with Fisher's exact test.
- BTK+BCL2 combination patients were analyzed separately and are not included here.

PATIENTS

Characteristic	BTKi, any line (n=134)	First-line, all therapies (n=110)
Patients	134	110
Age at diagnosis, median (IQR)	70 y (61–76)	69.5 y (62–76)
Male sex	86 (63.7%)	72 (65.5%)
Binet A / B / C	66% / 22% / 12%	72% / 18% / 11%
Line / regimen	1st 63% · 2nd 31% · ≥3rd 6% (Ibrutinib 64% · Acalabrutinib 21% · Zanubrutinib 15%)	1st line only, by design (BTKi 42% · Chemo±IO 37% · Ven-combo 19% · other 1%)
TTFT, median (IQR)	21.0 mo (0–87)	26.2 mo (5.5–59.9)
Endpoints assessed	TTFT, PFS (6/12/24/36 mo), OS	TTFT only (PFS/OS not evaluated)

AIM

In CLL/SLL patients treated with BTK inhibitors, to evaluate whether pre-treatment inflammatory markers — NMR (ANC/AMC), RDW/albumin ratio, and ESR — are associated with:

- time from diagnosis to BTK inhibitor initiation (TTFT),
- progression-free survival (PFS) on BTK therapy,
- overall survival (OS).

MATERIALS

Two-step, retrospective design. Two dedicated, partially overlapping databases were analyzed sequentially.

Step 1 — Population-level analysis (TTFT). The full first-line cohort (n=110), including all first-line regimens (BTK inhibitors, chemoimmunotherapy, BCL2i-based combinations), was used to test whether inflammatory markers at diagnosis (NMR, CD4/CD8 ratio, RDW/albumin, ESR) were associated with time to first treatment (TTFT), by Spearman correlation.

Step 2 — BTKi subgroup analysis (PFS/OS). Within the subgroup of patients treated with a BTK inhibitor at any line (n=134), the same markers were re-evaluated for their association with progression-free survival (PFS) and overall survival (OS) on BTK therapy, using ROC-derived cut-offs (Youden index) at the 12-month landmark.

This sequential design first characterizes TTFT determinants at the population level, then focuses on the BTKi-treated subgroup to test whether the same markers also carry prognostic value for PFS/OS.

Baseline characteristics in BTKi cohort	
Patients	134
Age at diagnosis, median (IQR)	70 y (61–76)
Male sex	86 (63.7%)
Rai 0–I / II / III–IV	44% / 39% / 18%
Binet A / B / C	66% / 22% / 12%
1st / 2nd / ≥3rd line	63% / 31% / 6%
Ibrutinib / Acalabrutinib / Zanubrutinib	64% / 21% / 15%
Alive / Dead	87 (65%) / 47 (35%)
PFS events (progression/death)	49 (36%)
OS follow-up, median (IQR)	45.3 mo (16.8–71.2)

RESULTS

STEP 1 — TTFT IN THE FULL FIRST-LINE POPULATION (n=110)

TTFT in the full first-line population (n=110). Median time to first treatment 26.2 months (IQR 5.5–59.9). None of the inflammatory markers assessed at diagnosis were associated with TTFT: NMR (ρ=0.14, p=0.21), RDW/albumin (ρ=−0.12, p=0.30), ESR (ρ=−0.10, p=0.51), CD4/CD8 (ρ=0.14, p=0.26).

Exploratory signal in the BTKi subgroup. Restricted to BTK inhibitor–treated patients (n=134; time to BTK initiation, median 21.0 months, IQR 0–87), **ESR** correlated with shorter TTFT (ρ=−0.27, **p=0.033**); NMR and RDW/albumin did not. As this did not replicate in the full population above, it should be treated as hypothesis-generating.

Overall survival (BTKi subgroup). 47 deaths / 124 patients with follow-up (median 45.3 months). None of the three markers were associated with OS, either as a continuous correlate with survival time or as a binary cut-off (all p>0.30, including at the 12-month landmark).

STEP 2 — BTKi SUBGROUP (n=134): PFS & OS — KEY FINDING

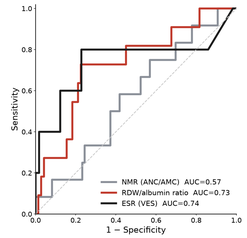

Fig. 1. ROC curves for PFS at 12 months.

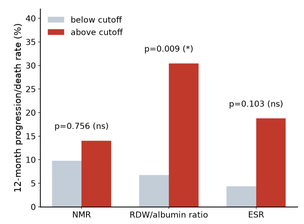

Fig. 2. 12-month event rate by cut-off.

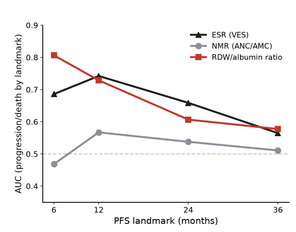

Fig. 3 (supplementary). AUC vs. PFS landmark (6/12/24/36 mo).

PATIENT COHORTS AT A GLANCE — BTKi (any line) vs. first-line, all therapies

Marker	AUC	Cut-off	Event rate ↑ vs ↓	OR	p
NMR (ANC/AMC)	0.57	> 3.59	14.0% vs 9.8%	1.5	0.76
RDW/albumin	**0.73**	**> 4.06**	**30.4% vs 6.8%**	**6.0**	**0.009**
ESR	0.74	> 33 mm/h	18.8% vs 4.3%	5.1	0.10

Key finding: an elevated **RDW/albumin ratio (>4.06)** at BTK initiation was associated with a **6-fold higher risk** of progression or death within 12 months (30.4% vs 6.8%, OR 6.0, **p=0.009**). ESR showed a concordant, non-significant trend; NMR was not discriminative.

Supplementary landmark analysis (6/12/24/36 months, Fig. 3): AUC for RDW/albumin and ESR was highest early (6–12 months) and declined progressively by 36 months, while NMR remained uninformative at every landmark — indicating the signal is strongest for near-term progression risk.

CONCLUSIONS

- Inflammatory markers **do not predict** time from diagnosis to BTK initiation.
- An elevated **RDW/albumin ratio** identifies patients at higher risk of early (12-month) progression or death on BTK therapy.
- **ESR** shows a concordant trend; **NMR** (ANC/AMC) is not informative.
- None of the markers were associated with overall survival.
- These simple, inexpensive biomarkers may support **early risk stratification** in patients starting BTK inhibitors.

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