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ABSTRACT N. CO16

CHRONIC LYMPHOCYTIC LEUKEMIA AND CHRONIC LYMPHOPROLIFERATIVE DISORDERS

CLINICAL AND BIOLOGICAL IMPACT OF PLASMA CYTOKINE LEVELS IN NEWLY DIAGNOSED CHRONIC LYMPHOCYTIC LEUKEMIA

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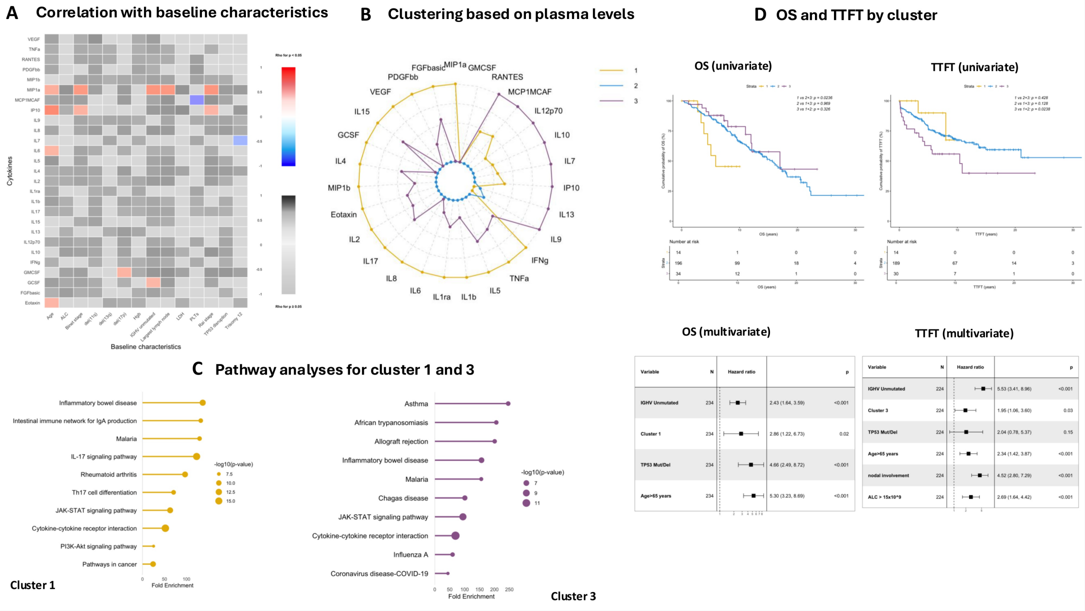
Introduction: In the context of chronic lymphocytic leukemia (CLL), the impact of baseline cytokine levels on biological features and clinical outcomes remains poorly understood.

Methods: Plasma from 244 newly diagnosed CLL patients was extracted and then analyzed using a bead-based 27-plex enzymatic assay. Different optimal cut-offs for overall survival (OS) and probability of Richter transformation (RT) risk analyses were defined using maximally selected rank statistics for every specific cytokine/chemokine. The machine-learning algorithms self-organizing map (SOM) and K-means were applied to divide patients into clusters based on cytokine/chemokine levels.

Results: Median age at diagnosis was 68.9 years; 73 patients (29.9%) had unmutated immunoglobulin heavy chain variable region (IGHV) genes, and 16 (6.6%) had *TP53* disruption. After a median follow-up of 13.4 years, the median OS was 15.7 years. By correlating cytokines/chemokines with patient baseline clinical and molecular features, elevated MIP-1α levels were significantly associated with unmutated IGHV genes ($p<0.0001$), greater lymph node diameter ($p<0.0001$), and advanced Rai and Binet stages (both $p<0.0001$) (Figure 1A). Higher IP-10 levels significantly associated with advanced Rai ($p=0.02$) and Binet ($p=0.01$) stages (Figure 1A). Elevated GM-CSF levels were associated with del(17p) ($p=0.03$) (Figure 1A). At diagnosis, patients with IL-4 levels exceeding the cut-off of 5.78 pg/mL displayed shorter OS ($p=0.02$), also in multivariate analysis adjusted for age, IGHV, and TP53 status (HR 2.2, $p=0.008$). Regarding RT, high levels of GM-CSF (cut-off: 0.86 pg/mL) were significantly associated with increased risk of RT in univariate ($p<0.0001$) and multivariate analyses (HR 9.3, $p=0.009$). Unsupervised clustering identified 3 patient groups, namely clusters 1, 2, and 3, with distinct cytokine/chemokine profiles (Figure 1B). In the pathway gene enrichment analysis, cluster 1 displayed higher activation of inflammation-related pathways, while cluster 3 was characterized by the activation of autoimmunity and infection response pathways (Figure 1C). Survival analysis demonstrated that patients in cluster 1 had significantly worse OS ($p=0.02$), a finding confirmed in multivariate analysis (HR 2.9, $p=0.02$) (Figure 1D). Furthermore, Binet A and B patients in cluster 3 exhibited a significantly shorter time to first treatment (TTFT) compared to the other clusters ($p=0.02$), even when adjusted for the IPS-E staging items (HR 2, $p=0.03$) (Figure 1D).

Conclusions: Plasma levels of immunomodulatory cytokines/chemokines are associated with unfavorable clinical and biological features at the time of CLL diagnosis and might predict lower OS and higher risk of RT and second malignancies. Moreover, patients can be divided into groups based on their plasma cytokine/chemokine profile to better stratify OS and TTFT. Consistently, if confirmed in other patient cohorts, cytokine/chemokine levels might integrate current prognostic biomarkers in CLL.

Chronic lymphocytic leukemia and Chronic Lymphoproliferative Disorders



OS (multivariate)

Variable	N	Hazard ratio		p
IGHV Unmutated	234		2.43 (1.64, 3.59)	<0.001
Cluster 1	234		2.86 (1.22, 6.73)	0.02
TP53 Mut/Del	234		4.66 (2.49, 8.72)	<0.001
Age>65 years	234		5.30 (3.23, 8.69)	<0.001

TTFT (multivariate)

Variable	N	Hazard ratio		p
IGHV Unmutated	224		5.53 (3.41, 8.96)	<0.001
Cluster 3	224		1.95 (1.06, 3.60)	0.03
TP53 Mut/Del	224		2.04 (0.78, 5.37)	0.15
Age>65 years	224		2.34 (1.42, 3.87)	<0.001
nodal involvement	224		4.52 (2.80, 7.29)	<0.001
ALC > 15x10^9	224		2.69 (1.64, 4.42)	<0.001