haematologica
Journal of the Ferrata Storti Foundation

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Received: August 8, 2026.
Accepted: October 30, 2026.

Citation: Julian Liebaert, Martin Neumann, Lorenz Bastian, Claudia D. Baldus, Monika Brüggemann, Stefan Habringer, Thomas Burmeister, Nicola Gökbuget, Ulrich Keller and Stefan Schwartz. Flow cytometric detection of the thymic stromal lymphopoietin receptor reliably identifies CRLF2-rearranged BCR::ABL1-like acute lymphoblastic leukemia. Haematologica. 2026 Nov 5. doi: 10.3324/haematol.2026.301773 [Epub ahead of print]

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Flow cytometric detection of the thymic stromal lymphopoietin receptor reliably identifies *CRLF2*-rearranged *BCR*::*ABL1*-like acute lymphoblastic leukemia

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Short title: TSLPR expression in B-cell ALL with *CRLF2*-rearrangement

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Data sharing statement:

Data supporting the findings of this study are available from the corresponding author upon request.

Artificial Intelligence:

ChatGPT (GPT-5.6; OpenAI, commercial software) was used to assist with formatting and revising of selected passages of the manuscript to improve clarity and conciseness. All AI-assisted content was critically reviewed and approved by the authors, who take full responsibility for the accuracy and integrity of the manuscript.

Word count:

Main text: 1500 words, 3 figures, 1 supplementary file (1 table, 2 figures)

Acknowledgments:

The authors are grateful to the staff of the flow cytometry laboratory and Thomas Bauer for graphic design support.

JL is a MD candidate at Charité Universitätsmedizin Berlin. This work is submitted in partial fulfillment of the requirement for the MD degree.

Conflicts of interest:

M.B. has received travel support and speaker honoraria from Amgen, AstraZeneca, Johnson & Johnson, Pfizer and has served as an advisory board member for Amgen, AstraZeneca, Hello Healthcare, Incyte. S. H. has served as an advisory board member and has received speaker honoraria from Incyte, Jazz, Onkowissen TV, Miltenyi, SERB SAS, Pentixapharm and travel support from AbbVie, and co-founded Moonlight AI GmbH. T.B. has received travel support and speaker honoraria from CSL Behring and Novartis. S. S. has received a research grant from Protherics Medicines Development Ltd, consultancy fees from AMGEN, Pfizer, SERB SAS, speaker honoraria from Akademie für Infektionsmedizin e.V., AMGEN, CSi Hamburg GmbH, Pfizer, SERB SAS, and travel grants from AMGEN, Pfizer, SERB SAS.

For the remaining authors, no relevant conflicts of interest were declared.

Sources of Funding

U.K. was funded by: Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) grants KE222/11-1, KE222/10-1 and the cooperative research center 1335 (CRC 1335/ SFB 1335); under Germany's Excellence Strategy – EXC 3118/1 – project number 533770413; German Cancer Consortium (DKTK) within the DKTK UPGRADE

Joint Funding grant IDENTI-T; Deutsche Krebshilfe grants 70114425, 70116097, 70111944, 70114724 (to U.K.); Hector Foundation grant M2506. S. H. was a participant in the BIH Charité Clinician Scientist Program and received funding from Else Kröner-Fresenius-Stiftung (EKFS), grant number 2022_EKEA.94.

Author contributions: J.L and S.S. conceived and designed the study. M.N., L.B., C.D.B., M.B., S.H., T.B., N.G., U.K. acquired and/or analyzed and interpreted data. J.L. and S.S. drafted the manuscript. All authors revised the manuscript for important intellectual content and approved the submitted version of the manuscript.

Main Text:

BCR::*ABL1*-like acute lymphoblastic leukemia (ALL) is a biologically distinct subtype associated with adverse outcomes and enriched for kinase-activating lesions that may provide therapeutic opportunities.[1] Cytokine receptor-like factor 2 (*CRLF2*) rearrangements represent the most frequent genetic lesion in adult *BCR*::*ABL1*-like ALL and result in overexpression of *CRLF2*, also known as thymic stromal lymphopoietin receptor (TSLPR).[2-4] *CRLF2* rearrangements mainly result from translocation to the *IGH* enhancer locus on chromosome 14 (*IGH*::*CRLF2*) or as a microdeletion within *PAR1* on chromosomes X and Y, generating *P2RY8*::*CRLF2*.[3] Comprehensive molecular classification is not universally available at diagnosis and rapid identification of *CRLF2* rearrangements could facilitate early recognition of *BCR*::*ABL1*-like ALL guiding molecular testing or therapeutic stratification. Flow-cytometric detection of TSLPR has been proposed as a screening approach, but its diagnostic performance, particularly in adults and across different *CRLF2* rearrangements, remains incompletely defined.[5, 6] We prospectively assessed TSLPR surface expression in a large cohort of adult B-ALL samples and correlated the results with RNA-sequencing based molecular classification. We demonstrate that routine flow-cytometric TSLPR assessment using clone 1F11 identifies *CRLF2*-rearranged B-ALL with high sensitivity and specificity, including potentially novel *CRLF2* fusions. Despite the historically adverse prognosis of *BCR*::*ABL1*-like and *CRLF2*-rearranged ALL, TSLPR positivity was not associated with inferior overall survival in our large cohort of adult patients.

Fresh diagnostic bone marrow or peripheral blood samples from adults with ALL were analyzed at the central reference laboratory of the German Multicenter Study Group on Adult Acute Lymphoblastic Leukemia (GMALL) between February 2018 and April 2022. The GMALL registry (NCT02872987) and associated trials were approved by the responsible ethics committees (reference no. 63/09) and all patients provided written informed consent. Leukemic cells were characterized by routine multiparametric flow cytometry as previously described.[7] TSLPR expression on CD19-positive leukemic cells was assessed prospectively using clones 1F11 and 1A6; positivity was defined as expression on ≥20% of leukemic cells. *BCR*::*ABL1* was tested by multiplex RT-PCR, as previously described.[8] RNA sequencing was performed in a subset of samples as

previously described[9] with molecular subtype assignment based on the integration of gene expression predictions with genomic driver calls.[10] Associations were assessed using Fisher exact, Wilcoxon, or Kruskal-Wallis tests as appropriate. Overall survival (OS) was assessed using the Kaplan-Meier method and log-rank test. Survival analysis was performed separately for patients aged ≤55 and >55 years according to TSLPR expression. P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure.

Overall, 686 consecutive diagnostic B-ALL samples were screened by flow cytometry and of these, 564 samples of 550 patients fulfilled the inclusion criteria for diagnosis (pre-B, common, pro-B, and mature B-ALL), viability (≥20%), and $CD45^{+}$-gating (≥20%). For patients with multiple samples, only the earliest available sample was retained for further analyses. Among the resulting 550 patients (i.e. samples), 374 were *BCR*::*ABL1*-negative by RT-PCR and RNA-sequencing and were used for further analysis (**Table S1**). Median age was 47 years (range, 18–85), 210 patients (56.1%) were male. Sixty of 374 cases (16%) were TSLPR-positive using clone 1F11 (defined as ≥20% positive cells). TSLPR positivity was enriched in common B-ALL and associated with a higher percentage of samples positive for CD10 and CD34, whereas age and sex did not differ significantly between TSLPR-positive and TSLPR-negative cases. Among 176 excluded *BCR*::*ABL1*-positive patients, one case was TSLPR-positive; notably, this sample also harbored an *IGH*::*CRLF2* fusion and was classified as *BCR*::*ABL1*-like by RNA sequencing.

Within the *BCR*::*ABL1*-negative subset analyzed by RNA-seq, 39 of 161 patients (24.2%) were classified as *BCR*::*ABL1*-like. Among these 39 *BCR*::*ABL1*-like samples, 27 (69.2%) harbored a *CRLF2*-rearrangement: 21 *IGH*::*CRLF2*, 4 *P2RY8::CRLF2* and two other *CRLF2* fusions. This predominance of *IGH*::*CRLF2* is consistent with observations in adult ALL.[4]

We next assessed the association between TSLPR expression and age according to *BCR*::*ABL1* fusion status. Among *BCR*::*ABL1*-negative cases, TSLPR positivity showed no significant association with age, whereas the prevalence of *BCR*::*ABL1*-positive/TSLPR-negative ALL increased markedly with age (**Figure S1A-B**).

Comparison of the two TSLPR antibodies revealed several discordant cases, including one *P2RY8*::*CRLF2*-positive sample detected only by clone 1F11 (**Figure 1A**). The antibody clone 1F11 was used for further analyses due to its better discrimination and sensitivity, as described below. TSLPR surface expression correlated closely with *CRLF2* gene expression values (R=0.88; p<0.001; **Figure 1B**). Two outliers harbored *P2RY8*::*CRLF2* despite not being classified as *BCR*::*ABL1*-like by the RNA-sequencing classifier. With one exception, all samples above the 20% TSLPR threshold were assigned as *BCR*::*ABL1*-like; the exceptional case was classified as *ZNF384* but nevertheless had a *P2RY8*::*CRLF2* fusion (**Figure 1C**). Conversely, all but one *CRLF2*-rearranged sample were TSLPR-positive (**Figure 1D**). The single sample carried a *IGH*::*CRLF2* fusion, but had a low CRLF2 gene expression value. Median *CRLF2* gene expression was substantially higher in both *BCR*::*ABL1*-like and *CRLF2*-rearranged samples compared to non-*BCR*::*ABL1*-like and non-*CRLF2*-rearranged samples (**Figure S2**). Noteworthy, *IGH*::*CRLF2* rearranged samples had a significantly higher percentage of TSLPR-positive cells compared to *P2RY8*::*CRLF2* rearranged samples (**Figure 1E**).

Interestingly, RNA sequencing identified two *CRLF2* fusion transcripts, *ZNF844*::*CRLF2* and *ZNF846*::*CRLF2*, not previously reported in B-ALL. Both were associated with increased TSLPR surface expression. Although their functional relevance requires further validation, these findings expand the spectrum of lesions associated with *CRLF2* overexpression and highlight the value of phenotype-based screening, as TSLPR detection is independent of the *CRLF2* fusion partner. Thus, TSLPR screening may identify uncommon or novel *CRLF2*-rearrangements missed by assays targeting canonical lesions such as *IGH*::*CRLF2* and *P2RY8*::*CRLF2*.

For detection of *CRLF2* rearrangement, clone 1F11 showed peak predictive performance at cut-off values between 15% and 25%, with an F1 score of 0.98 and an area under the receiver-operating-characteristic curve of 0.98 (**Figure 2A-B**). Sensitivity was 96.3%, specificity 100%, and the negative predictive value was 99.3% (**Figure 2C**). For *BCR*::*ABL1*-like subtype assignment, sensitivity was 64.1%, specificity 99.2%, the positive predictive value was 96.2%, and the negative predictive value was 89.7% (**Figure 2C**). Clone 1A6 showed somewhat lower sensitivity and negative predictive value for

detection of *CRLF2* rearrangement, 92.6% and 98.5%, respectively (**Figure 2C**). These findings extend previous reports of TSLPR as a suitable screening marker[5, 6] and demonstrate that a simple flow-cytometric assay can identify *CRLF2*-rearranged disease with high diagnostic accuracy. The strong specificity may partly reflect use of the predefined ≥20% threshold, which was also within the range yielding maximal F1 scores.

Clinical follow-up was available for 217 patients. TSLPR expression was not associated with inferior OS in either age group (**Figure 3**). Among patients aged ≤55 years, 3-year OS was 79% in TSLPR-negative patients (n=146) and 72% in TSLPR-positive patients (n=25; p>0.05). Among patients aged >55 years, 3-year OS was 41% and 46%, respectively (n=33 and n=13; p>0.05). These observations are consistent with two pediatric studies in which elevated surface TSLPR expression was not associated with inferior survival.[11, 12]

The absence of a significant survival disadvantage in TSLPR-positive patients is particularly noteworthy given the repeatedly reported adverse prognosis of *BCR*::*ABL1*-like and *CRLF2*-rearranged ALL.[1] This may reflect differences in molecular definitions, the distribution of co-occurring prognostic lesions, as well as variations in the applied treatment regimens. Increasing incorporation of immunotherapeutic approaches, particularly blinatumomab, into frontline and improvements in relapse management has altered the therapeutic landscape of B-ALL. Such therapies act independently of underlying kinase-activating lesions and may therefore attenuate the adverse prognostic impact of high-risk subgroups, such as *BCR*::*ABL1*-like ALL. However, given the cohort size and the treatment heterogeneity, our study is unsuitable to detect the impact of treatment variations on survival outcomes. Larger, treatment-stratified cohorts are required to clarify the prognostic significance of TSLPR positivity in the contemporary treatment era.

Our findings also highlight the complementary roles of phenotype and genotype in ALL diagnostics. A transcriptome-based classifier assigned one *P2RY8*::*CRLF2*-positive case to the *ZNF384* subtype, whereas flow cytometry identified strong TSLPR expression. Similarly, TSLPR detection captured the two novel *ZNF844*::*CRLF2* and *ZNF846*::*CRLF2* rearrangements. These observations indicate that direct assessment of cell surface

TSLPR as the biological consequence of *CRLF2* rearrangement could complement molecular classification algorithms and targeted fusion panels. Conversely, the near-complete mutual exclusivity of conventional *BCR*::*ABL1* positivity and TSLPR expression further supports the specificity of this phenotype for *CRLF2*-driven biology, although rare co-occurrence has been described.[13, 14]

Nonetheless, TSLPR expression by flow cytometry should not replace molecular characterization but may serve as a rapid and accessible screening tool to identify patients for prioritized molecular testing, particularly in resource-constrained settings or when comprehensive genomic testing is not immediately available. This may become increasingly relevant as molecularly informed treatment options evolve. Moreover, TSLPR itself represents a potential therapeutic target, including for TSLPR-directed cellular approaches.[15]

In summary, prospective flow-cytometric assessment of TSLPR using clone 1F11 identified *CRLF2* rearrangements in adult *BCR*::*ABL1*-negative-ALL with 96.3% sensitivity, 100% specificity, and a 99.3% negative predictive value. The detection of the potentially novel *ZNF844*::*CRLF2* and *ZNF846*::*CRLF2* fusions further demonstrates that TSLPR expression could serve as a fusion-partner-independent marker of *CRLF2*-rearranged B-ALL. Despite the historically adverse prognosis attributed to this biological subgroup, TSLPR positivity was not associated with inferior overall survival in our contemporary adult cohort, potentially reflecting the increasing impact of immunotherapeutic treatment strategies. Routine TSLPR assessment may therefore provide a rapid and clinically implementable bridge between diagnostic flow cytometry and refined molecular characterization of *BCR*::*ABL1*-like ALL.

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Figure Legends

Figure 1

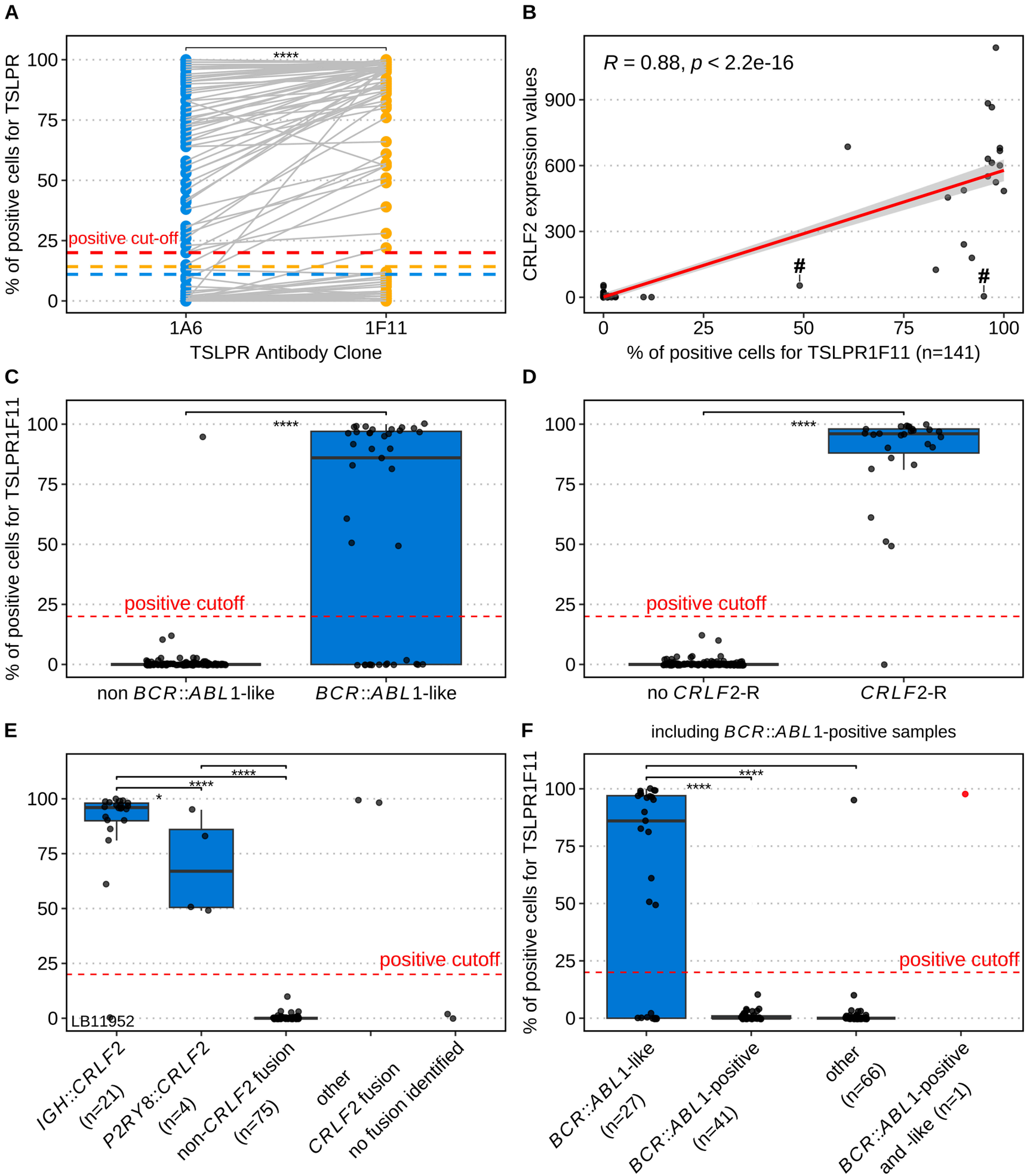
TSLPR expression according to CRLF2 status and molecular subgroups.
A) Comparison of TSLPR expression assessed by flow cytometry using antibody clones 1A6 and 1F11. Means are represented by blue and yellow dashed lines. **B**) Pearson correlation of TSLPR (1F11) expression and quantification of *CRLF2* gene expression values (n = 141). # *P2RY8*::*CRLF2* unassigned/not classified as *BCR*::*ABL1*-like **C**) TSLPR (1F11) expression in *BCR*::*ABL1*-like and non-*BCR*::*ABL1*-like cases and **D**) in patients with and without *CRLF2* rearrangement (n=161) as identified by RNA sequencing (RNAseq). **E**) TSLPR (1F11) expression according to the type of gene fusion (n = 104). **F**) TSLPR (1F11) expression according to RNAseq subgroups including *BCR::ABL1*-positive samples (n = 135). The red dot marks a single sample that was classified as *BCR*::*ABL1*-like and harbored a *BCR::ABL* fusion. The red dashed line represents the cut-off for positivity (≥ 20% positive cells). ****$p < 0.0001$, ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

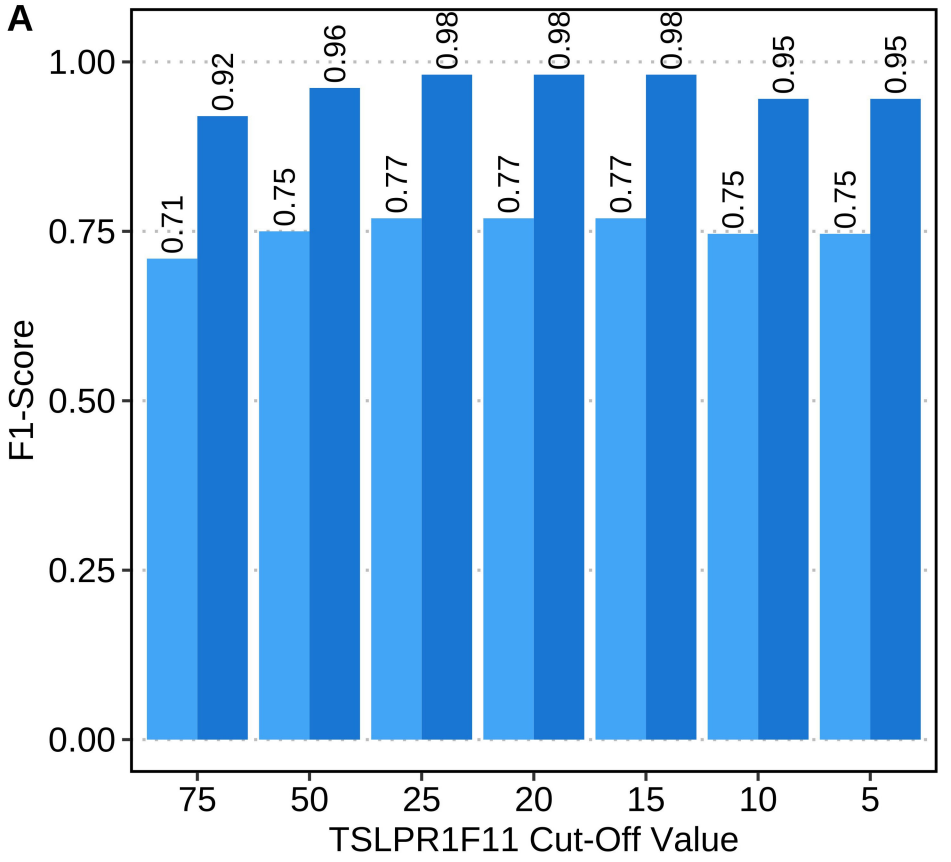
Figure 2

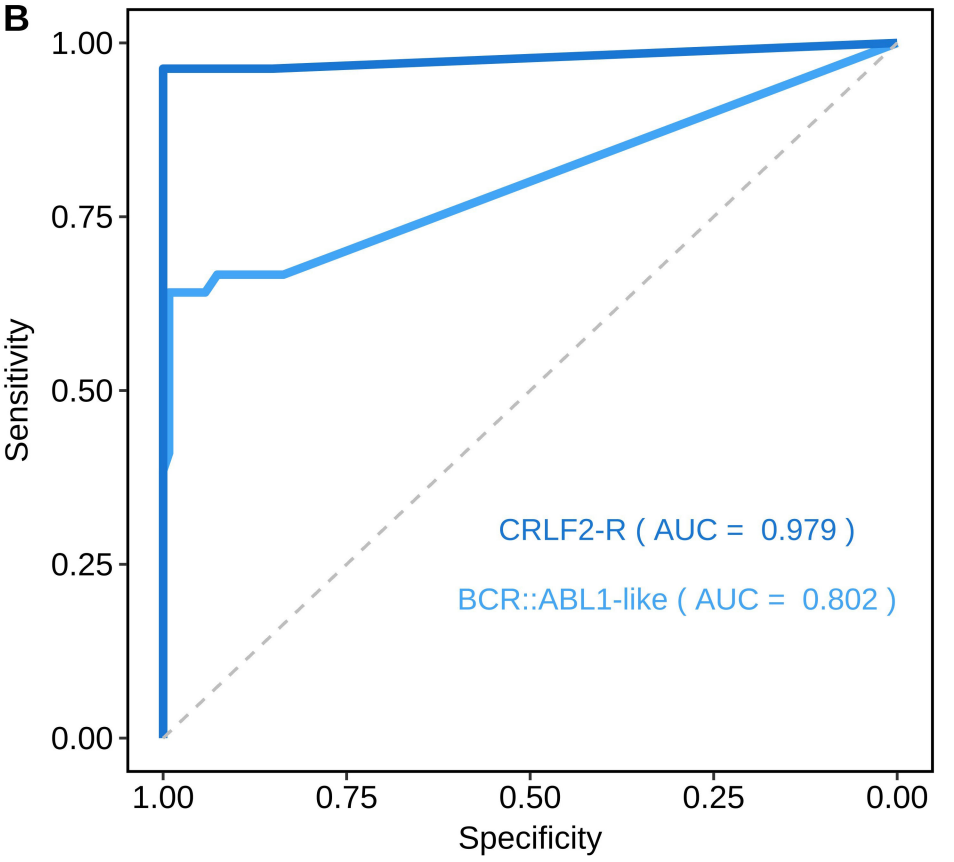
Diagnostic performance of TSLPR expression for the detection of *BCR*::*ABL1*-like ALL and CRLF2 rearrangements.
A) F1-scores for the detection of *BCR*::*ABL1*-like or *CRLF2* gene rearrangement for different cut-off values. **B)** Area under the receiver operating characteristic curve (AUROC) for the recognition of *BCR*::*ABL1*-like or *CRLF2*-rearrangement. **C)** Diagnostic scores (sensitivity, specificity, precision, positive predictive value, and negative predictive value) for thymic stromal lymphopoietin receptor (TSLPR) specific antibody clones 1F11 and 1A6 (cut-off for positivity: ≥20% positive cells).

Figure 3

Overall survival according to TSLPR status.
Overall survival (OS) in 171 younger (**A**: ≤55 years, TSLPR-negative n=146, TSLPR-positive n=25, p>0.05) and 46 elderly (**B**: >55 years, TSLPR-negative n=33, TSLPR-positive n=13, p>0.05) adult patients with *BCR*::ABL1-negative B-ALL.


A
% of positive cells for TSLPR
100
75
50
25
0
****
positive cut-off
1A6
1F11
TSLPR Antibody Clone
B
R = 0.88, p < 2.2e-16
CRLF2 expression values
900
600
300
0
#
#
0
25
50
75
100
% of positive cells for TSLPR1F11 (n=141)
C
% of positive cells for TSLPR1F11
****
positive cutoff
non BCR::ABL1-like
BCR::ABL1-like
D
****
positive cutoff
no CRLF2-R
CRLF2-R
E
****
****
*
positive cutoff
LB11952
IGH::CRLF2 (n=21)
P2RY8::CRLF2 (n=4)
non-CRLF2 fusion (n=75)
other CRLF2 fusion
no fusion identified
F
including BCR::ABL1-positive samples
% of positive cells for TSLPR1F11
****
****
positive cutoff
BCR::ABL1-like (n=27)
BCR::ABL1-positive (n=41)
other (n=66)
BCR::ABL1-positive and -like (n=1)

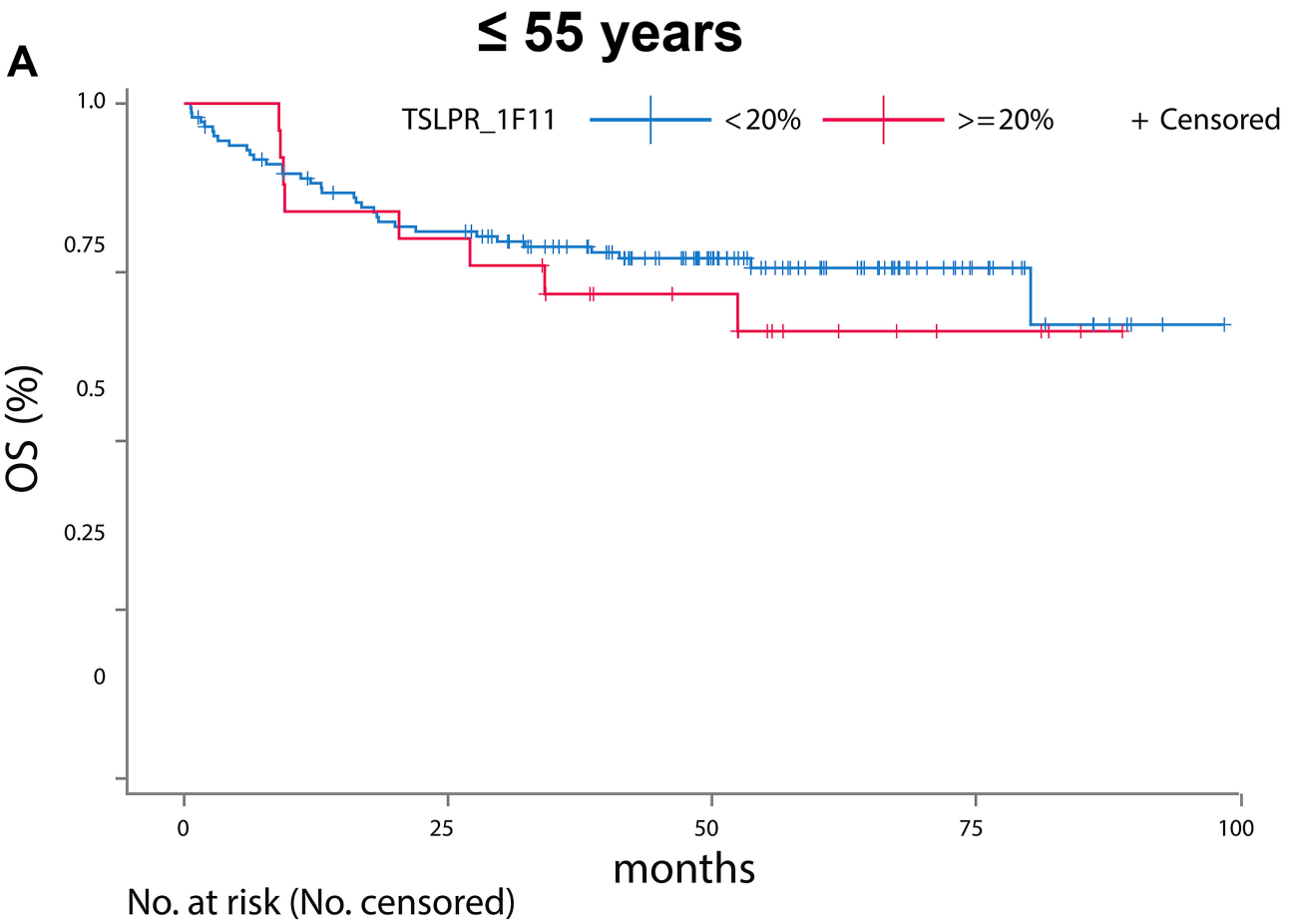




C

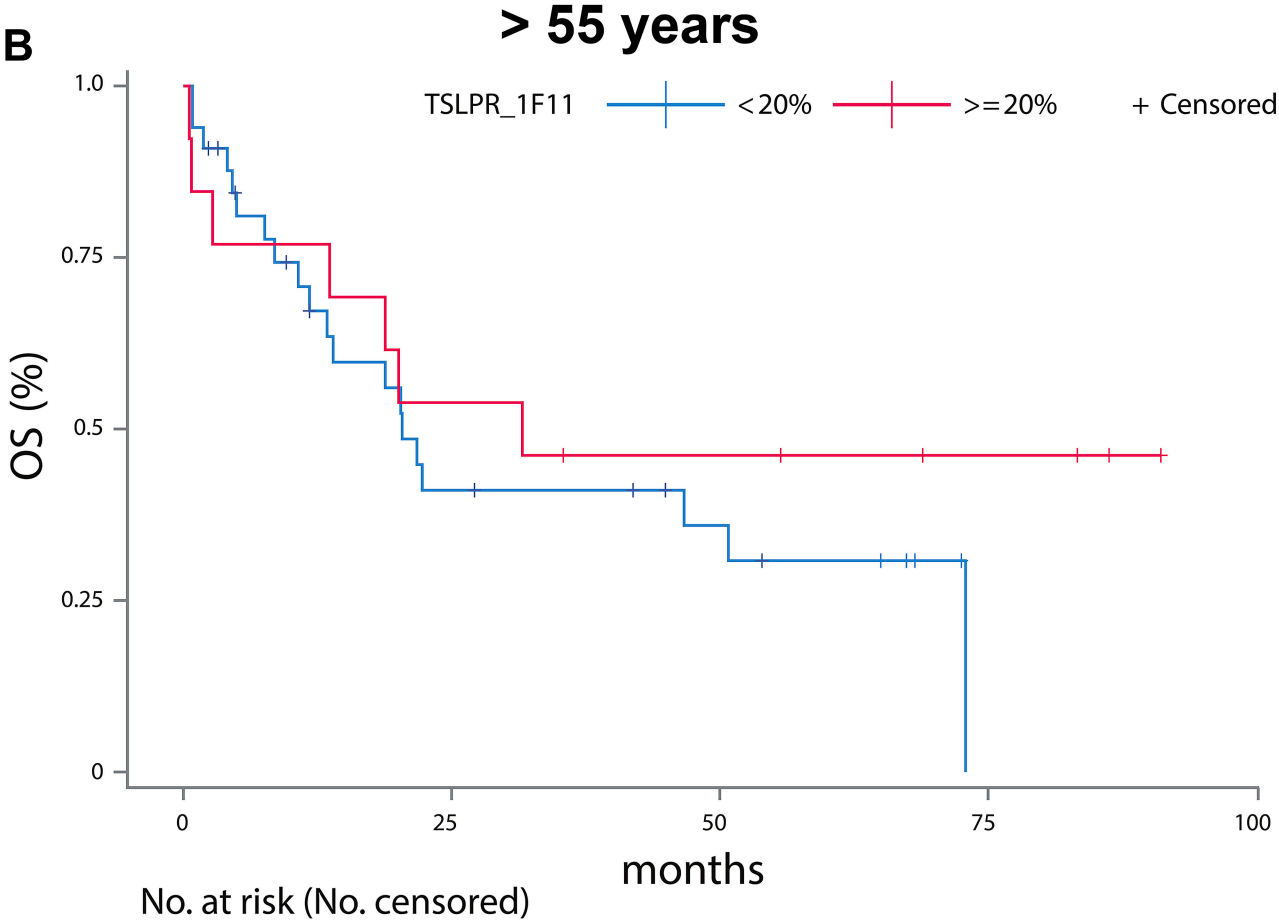
TSLPR Clone	Group	Sensitivity	Specificity	Precision	Negative Predictive Value	Positive Predictive Value
1F11	*BCR*::*ABL1*-like	64.1%	99.2%	96.2%	89.7%	96.2%
	CRLF2-R	96.3%	100%	100%	99.3%	100%
1A6	*BCR*::*ABL1*-like	61.5%	99.2%	96%	88.6%	96%
	CRLF2-R	92.6%	100%	100%	98.5%	100%

BCR::*ABL1*-like *CRLF2*-rearrangement



No. at risk (No. censored)

<20%	146 (0)	113 (6)	69 (45)	19 (94)	1 (111)
>=20%	25 (0)	20 (0)	13 (5)	4 (13)	0 (17)



No. at risk (No. censored)

<20%	33 (0)	11 (5)	7 (8)	0 (13)	0 (13)
>=20%	13 (0)	7 (0)	5 (1)	3 (3)	0 (6)

Supplementary Table and Figures

Table S1

Clinical characteristics of 374 patients with B-cell precursor acute lymphoblastic leukemia (ALL), excluding *BCR*::*ABL1* positive samples, investigated for expression of the thymic stromal lymphopoietin receptor (TSLPR).

	All* n (%)	TSLPR negative n (%)	TSLPR positive n (%)	P value	Adjusted p value**
Total no. of patients	374	314 (85.6%)	60 (16)	-	
Sex					
Male	210 (56.1)	172 (54.8)	38 (63.3)	0.28	0.39
Age					
Years, median (range)	47 (18-85)	47 (18-83)	48 (18–85)	0.91	0.91
Sample Type					
Bone Marrow	289 (77.5)	245 (78.0)	44 (73.3)	0.45	0.49
Peripheral Blood	82 (21.9)	66 (21)	16 (26.7)	0.43	0.49
Not reported	3 (0.8)	3 (1)	0 (0)	0.45	0.49
Diagnosis					
pro B-ALL	62 (16.6)	61 (19.4)	1 (1.7)	**<0.001**	**0.005**
common ALL	226 (60.4)	173 (55.1)	53 (88.3)	**<0.001**	**<0.001**
pre B-ALL	73 (19.5)	67 (21.3)	6 (10)	0.064	0.11
mature B-ALL	13 (3.5)	13 (4.1)	0 (0)	0.24	0.37
RNA sequencing (n = 161)[10]					
BCR::*ABL1*-like	39 (24.2)	14 (10.4)	25 (96.2)	**<0.001**	**<0.001**
CRLF2 rearrangement	27 (16.8)	1 (0.7)	26 (100)	**<0.001**	**<0.001**
Immunophenotype					
CD20 positive	128 (34.3)	98 (31.3)	30 (50)	0.008	0.016
CD10 positive	295 (79.1)	236 (75.4)	59 (98.3)	**<0.001**	**<0.001**
CD34 positive	271 (72.7)	215 (68.7)	56 (93.3)	**<0.001**	**<0.001**

*number (%) of patients are given if not stated otherwise
**P-values were corrected for multiple testing using the Benjamini-Hochberg procedure.

Figure S1

Age distribution according to *BCR*::ABL1 and TSLPR status. **A)** *BCR*::ABL1-negative samples by TSLPR positivity (≥20% positive cells) and negativity. **B)** *BCR*::*ABL*-negative/TSLPR-negative, *BCR*::*ABL*-positive/TSLPR-negative, and *BCR*::*ABL*-negative/TSLPR-positive. A single sample, positive for TSLPR and with a *BCR*::*ABL* fusion, was excluded.

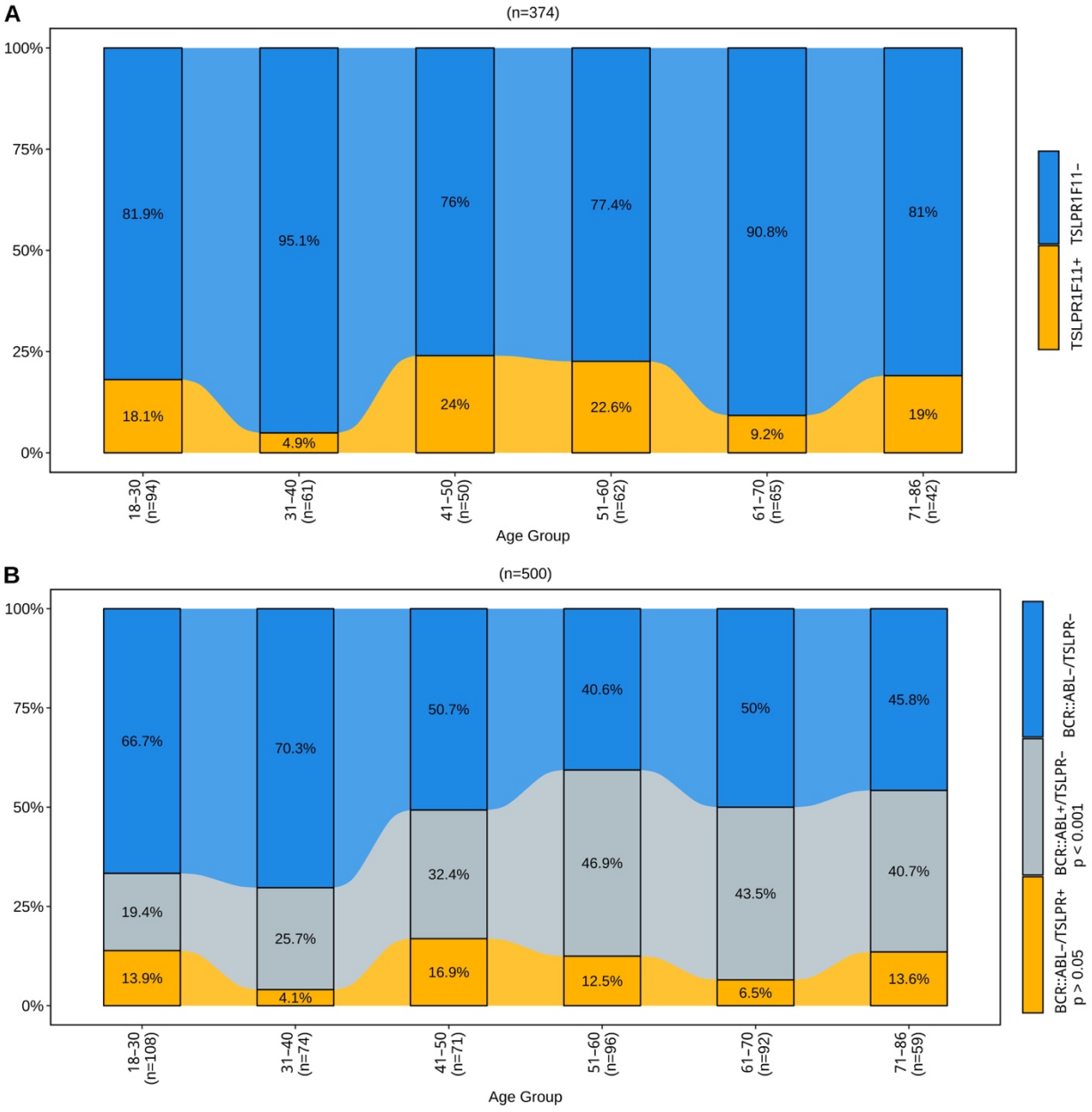


Figure S2

CRLF2 expression values according to *BCR*::*ABL1*-like (**A**) and *CRLF2*-rearrangement status (**B**). ****$p < 0.0001$.

