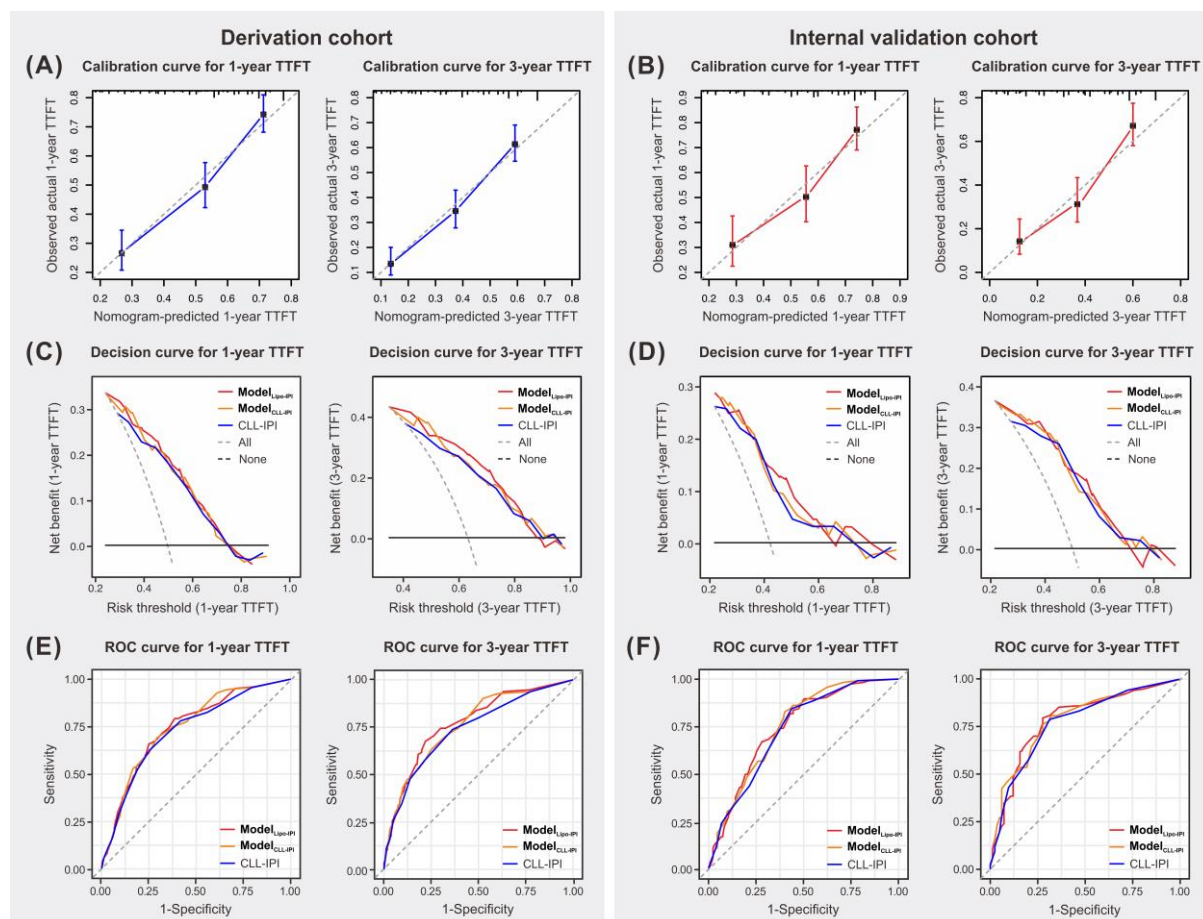
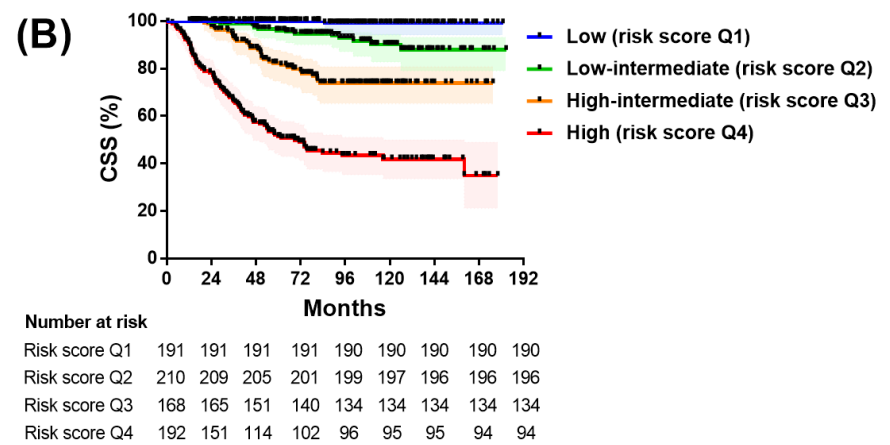
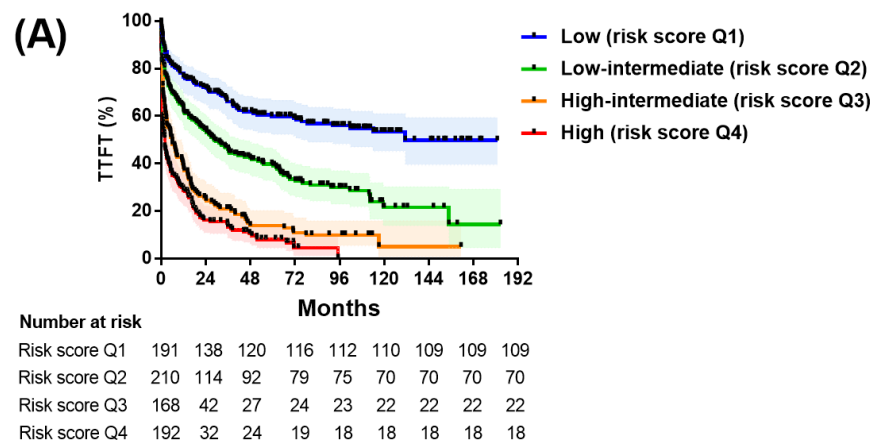


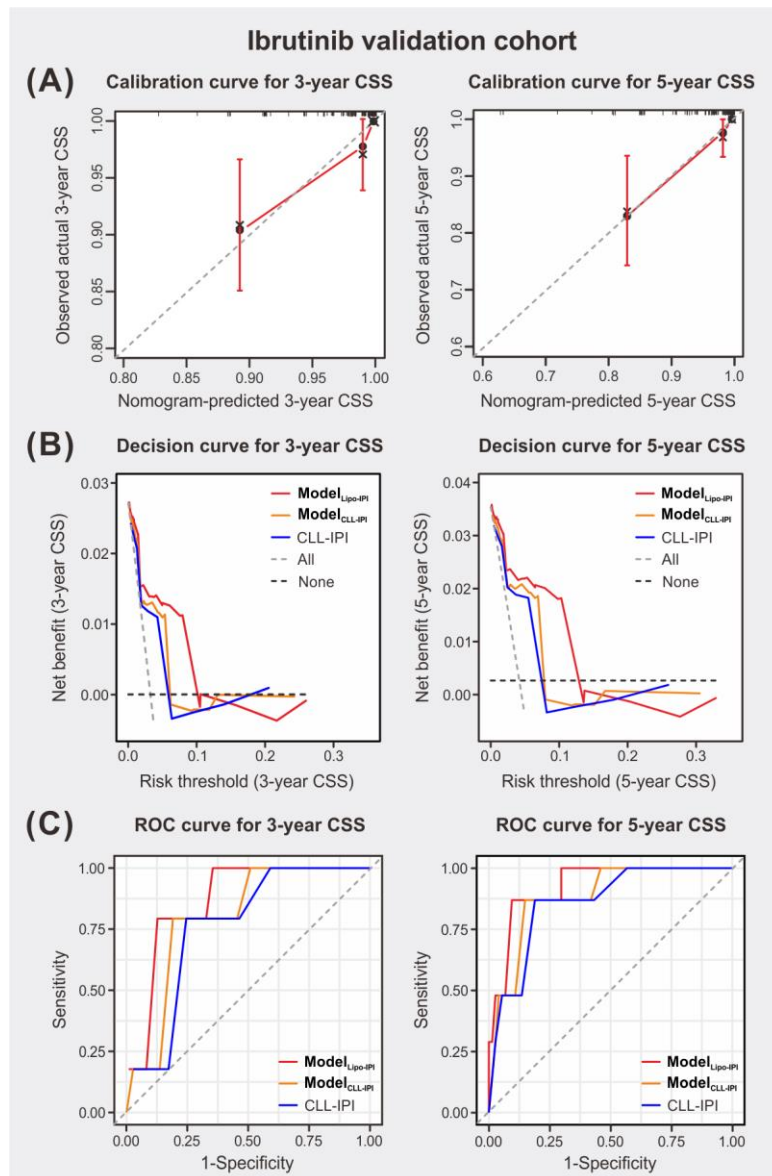
**Supplemental Figure S1.** Prognosis of four subgroups categorized by high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) cut-off values. **(A)** Kaplan-Meier survival curves of time-to-first-treatment (TTFT). **(B)** Kaplan-Meier survival curves of cancer-specific survival (CSS).



**Supplemental Figure S2.** Prognostic performance of Model<sub>Lipo-IPI</sub> for time-to-first-treatment (TTFT). **(A, B)** Calibration curves of Model<sub>Lipo-IPI</sub> for predicting 1-year and 3-year TTFT in the derivation **(A)** and internal validation **(B)** cohorts. **(C, D)** Decision curve analyses of different models for predicting 1-year and 3-year TTFT in the derivation **(C)** and internal validation **(D)** cohorts. **(E, F)** Receiver operating characteristic (ROC) curves of different models for predicting 1-year and 3-year TTFT in the derivation **(E)** and internal validation **(F)** cohorts. **Abbreviations:** CLL-IPI, international prognostic index for chronic lymphocytic leukaemia.



**Supplemental Figure S3.** Prognosis of four risk grades stratified by quantiles of Model<sub>Lipo-IPi</sub>. **(A)** Kaplan-Meier survival curves of time-to-first-treatment (TTFT). **(B)** Kaplan-Meier survival curves of cancer-specific survival (CSS).



**Supplemental Figure S4.** Prognostic performance of Model<sub>Lipo-IPI</sub> for cancer-specific survival (CSS) in the ibrutinib validation cohort. **(A)** Calibration curves of Model<sub>Lipo-IPI</sub> for predicting 3-year and 5-year CSS. **(B)** Decision curve analyses of different models for predicting 3-year and 5-year CSS. **(C)** Receiver operating characteristic (ROC) curves of different models for predicting 3-year and 5-year CSS. **Abbreviations:** CLL-IPI, international prognostic index for chronic lymphocytic leukaemia.

**Supplemental Table S1.** Pairwise comparisons of four serum cholesterol groups for TTFT and CSS in the derivation cohort.

Log-rank test (Mantel-Cox)	Serum cholesterol group	Normal HDL-C and LDL-C		Only low HDL-C		Only low LDL-C		Low HDL-C and LDL-C	
		Chi- square	p-value	Chi- square	p-value	Chi- square	p-value	Chi- square	p-value
TTFT (Overall <i>p</i> <0.001)	Normal HDL-C and LDL-C	–	–	1.038	0.308	1.045	0.307	49.374	<0.001
	Only low HDL-C	1.038	0.308	–	–	0.012	0.914	25.976	<0.001
	Only low LDL-C	1.045	0.307	0.012	0.914	–	–	19.251	<0.001
	Low HDL-C and LDL-C	49.374	<0.001	25.976	<0.001	19.251	<0.001	–	–
CSS (Overall <i>p</i> <0.001)	Normal HDL-C and LDL-C	–	–	0.575	0.448	0.002	0.962	34.523	<0.001
	Only low HDL-C	0.575	0.448	–	–	0.414	0.520	18.709	<0.001
	Only low LDL-C	0.002	0.962	0.414	0.520	–	–	15.585	<0.001
	Low HDL-C and LDL-C	34.523	<0.001	18.709	<0.001	15.585	<0.001	–	–

**Abbreviations:** TTFT, time-to-first-treatment; CSS, cancer-specific survival; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

**Supplemental Table S2.** Post-chemoimmunotherapeutic cholesterol fluctuation stratified by different treatment regimens and response to treatment.

Treatment regimens	Response to treatment	Total	Pre- or post-therapeutic	TC (mmol/L)	p-value	HDL-C (mmol/L)	p-value	LDL-C (mmol/L)	p-value
Fludarabine + cyclophosphamide ± rituximab	CR or PR	104	Before	3.94±1.05	0.006	0.99±0.3	<0.001	2.48±0.67	0.005
			After	4.22±0.97		1.09±0.31		2.70±0.70	
	SD or PD	79	Before	3.95±1.03	0.028	0.86±0.25	0.093	2.51±0.78	0.002
			After	3.72±1.02		0.82±0.24		2.26±0.74	
Bendamustine ± rituximab	CR or PR	28	Before	3.89±0.88	0.266	0.95±0.30	0.154	2.44±0.67	0.384
			After	4.13±1.03		1.06±0.39		2.57±0.70	
	SD or PD	9	Before	3.95±1.05	0.447	0.92±0.17	0.145	2.32±0.37	0.231
			After	3.62±0.53		0.83±0.12		2.13±0.33	
Chlorambucil ± rituximab	CR or PR	52	Before	4.09±0.90	0.453	0.93±0.26	0.114	2.47±0.66	0.128
			After	4.20±1.19		1.00±0.31		2.61±0.78	
	SD or PD	64	Before	3.99±1.03	0.005	0.94±0.28	0.001	2.51±0.71	0.027
			After	3.63±1.00		0.81±0.25		2.32±0.73	
Ibrutinib ± rituximab	CR or PR	78	Before	4.05±0.91	<0.001	0.96±0.29	<0.001	2.52±0.65	<0.001
			After	4.48±1.08		1.08±0.31		2.79±0.76	
	SD or PD	41	Before	3.90±1.04	0.065	0.93±0.20	0.708	2.53±0.84	0.036
			After	3.61±1.00		0.91±0.27		2.27±0.75	
Ibrutinib + fludarabine + cyclophosphamide + rituximab	CR or PR	18	Before	4.19±1.30	0.755	1.05±0.33	0.566	2.62±0.90	0.874
			After	4.27±1.22		1.10±0.29		2.59±0.93	
	SD or PD	5	Before	3.67±0.60	0.950	0.96±0.25	0.619	2.35±0.36	0.660
			After	3.69±1.10		0.90±0.27		2.21±0.77	
Other treatments	CR or PR	21	Before	4.08±1.12	0.013	1.03±0.34	0.104	2.50±0.88	0.071
			After	4.71±1.00		1.15±0.34		2.98±0.86	
	SD or PD	22	Before	4.00±1.11	0.034	1.00±0.31	0.004	2.46±0.89	0.028
			After	3.55±0.94		0.83±0.29		2.15±0.72	

**Abbreviations:** TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

**Supplemental Table S3.** Post-chemoimmunotherapeutic cholesterol fluctuation stratified by different biological variables and response to treatment.

Biological variables	Status	Response to treatment	Total	Pre- or post-therapeutic	TC (mmol/L)	p-value	HDL-C (mmol/L)	p-value	LDL-C (mmol/L)	p-value
<i>TP53</i> disruption	Absence	CR or PR	237	Before	4.06±1.01	<0.001	0.98±0.29	<0.001	2.54±0.67	0.001
				After	4.34±1.06		1.07±0.32		2.71±0.74	
	Presence	SD or PD	153	Before	3.99±1.04	<0.001	0.94±0.27	<0.001	2.53±0.80	<0.001
				After	3.40±1.06		0.85±0.26		2.24±0.71	
		CR or PR	64	Before	3.84±1.03	0.002	0.95±0.32	0.001	2.31±0.79	0.001
				After	4.22±1.19		1.08±0.33		2.70±0.87	
<i>ATM</i> deletion	Absence	SD or PD	67	Before	3.86±1.01	0.007	0.86±0.24	0.090	2.41±0.67	0.101
				After	3.58±1.07		0.81±0.24		2.30±0.77	
	Presence	CR or PR	248	Before	4.01±1.04	<0.001	0.98±0.30	<0.001	2.48±0.72	<0.001
				After	4.31±1.12		1.08±0.32		2.71±0.79	
		SD or PD	183	Before	3.94±1.03	<0.001	0.91±0.26	<0.001	2.49±0.77	<0.001
				After	3.48±1.10		0.84±0.26		2.28±0.74	
<i>IGHV</i>	unmutated	CR or PR	53	Before	4.06±0.94	0.070	0.96±0.27	0.001	2.56±0.61	0.101
				After	4.31±0.91		1.08±0.30		2.71±0.66	
	mutated	SD or PD	37	Before	3.98±1.05	<0.001	0.92±0.28	0.013	2.53±0.76	0.002
				After	3.33±0.90		0.81±0.25		2.16±0.65	
		CR or PR	167	Before	4.04±1.08	<0.001	0.98±0.29	<0.001	2.52±0.73	<0.001
				After	4.36±1.06		1.10±0.31		2.72±0.72	
<i>IGHV</i>	unmutated	SD or PD	108	Before	3.92±1.07	<0.001	0.96±0.29	0.009	2.44±0.80	0.069
				After	3.47±1.08		0.89±0.25		2.31±0.71	
	mutated	CR or PR	134	Before	3.98±0.94	0.004	0.97±0.31	0.004	2.45±0.67	0.001
				After	4.25±1.12		1.05±0.33		2.69±0.82	
		SD or PD	112	Before	3.98±0.99	<0.001	0.86±0.23	<0.001	2.55±0.73	<0.001
				After	3.44±1.06		0.78±0.25		2.21±0.75	

CD38	<30%	CR or PR	224	Before	4.00±1.05	<0.001	0.97±0.31	<0.001	2.49±0.72	<0.001
				After	4.28±1.13		1.08±0.33		2.71±0.77	
		SD or PD	144	Before	3.89±0.99	<0.001	0.91±0.26	0.001	2.45±0.73	<0.001
				After	3.46±1.08		0.85±0.26		2.25±0.72	
	≥30%	CR or PR	77	Before	4.07±0.91	<0.001	0.97±0.27	<0.001	2.50±0.65	0.004
				After	4.39±0.97		1.05±0.30		2.71±0.76	
		SD or PD	76	Before	4.06±1.09	<0.001	0.91±0.27	0.003	2.59±0.83	0.001
				After	3.44±1.05		0.82±0.24		2.27±0.75	

**Abbreviations:** TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; *IGHV*, immunoglobulin heavy chain variable region.



**Supplemental Table S4.** Pairwise comparisons of four nomogram risk score groups for TTFT and CSS in the entire cohort.

Log-rank test (Mantel-Cox)	Risk group	Low (risk score Q1)		Low-intermediate (risk score Q2)		High-intermediate (risk score Q3)		High (risk score Q4)	
		Chi- square	p-value	Chi- square	p-value	Chi- square	p-value	Chi- square	p-value
TTFT (Overall <i>p</i> <0.001)	Low (risk score Q1)	–	–	27.125	<0.001	107.082	<0.001	163.966	<0.001
	Low-intermediate (risk score Q2)	27.125	<0.001	–	–	37.906	<0.001	86.515	<0.001
	High-intermediate (risk score Q3)	107.082	<0.001	37.906	<0.001	–	–	8.306	0.004
	High (risk score Q4)	163.966	<0.001	86.515	<0.001	8.306	0.004	–	–
CSS (Overall <i>p</i> <0.001)	Low (risk score Q1)	–	–	11.312	0.001	43.024	<0.001	134.991	<0.001
	Low-intermediate (risk score Q2)	11.312	0.001	–	–	17.145	<0.001	108.364	<0.001
	High-intermediate (risk score Q3)	43.024	<0.001	17.145	<0.001	–	–	41.233	<0.001
	High (risk score Q4)	134.991	<0.001	108.364	<0.001	41.233	<0.001	–	–

**Abbreviations:** TTFT, time-to-first-treatment; CSS, cancer-specific survival.

**Supplemental Table S5.** Univariate and multivariate analyses of CSS including regimen types in treated patients of the entire cohort.

Variables	CSS			
	Univariate analyses		Multivariate analyses	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Male	1.165 (0.796–1.706)	0.432	–	–
Age >65 years	1.604 (1.124–2.288)	0.009	1.577 (1.103–2.255)	0.013
Binet B/C	3.472 (1.762–6.842)	<0.001	1.423 (0.713–2.841)	0.317
ECOG PS >1	1.435 (0.897–2.295)	0.132		
B symptoms	0.881 (0.582–1.335)	0.550	–	–
Novel targeted therapies*	0.100 (0.037–0.272)	<0.001	0.095 (0.035–0.257)	<0.001
ALC >50×10 <sup>9</sup> /L	1.184 (0.806–1.738)	0.390	–	–
Hb <100 g/L	1.745 (1.211–2.515)	0.003	0.999 (0.661–1.511)	0.998
PLT <100×10 <sup>9</sup> /L	1.809 (1.274–2.570)	0.001	1.150 (0.793–1.668)	0.462
LDH >ULN (271 U/L)	1.750 (1.214–2.522)	0.003	1.022 (0.679–1.539)	0.916
β <sub>2</sub> -MG >3.50 mg/L	2.073 (1.427–3.011)	<0.001	1.209 (0.823–1.775)	0.334
<i>TP53</i> disruption	4.416 (3.102–6.287)	<0.001	3.221 (2.255–4.600)	<0.001
<i>ATM</i> deletion	0.707 (0.418–1.196)	0.196	–	–
<i>IGHV</i> unmutated	3.053 (2.082–4.477)	<0.001	3.239 (2.199–4.772)	<0.001
CD38 ≥30%	1.453 (1.006–2.099)	0.047	1.103 (0.755–1.614)	0.612
Low HDL-C and LDL-C	3.735 (2.517–5.543)	<0.001	3.437 (2.302–5.131)	<0.001

**Abbreviations:** CSS, cancer-specific survival; HR, hazard ratio; 95% CI, 95% confidence interval; ECOG, eastern cooperative oncology group; PS, performance status; ALC, absolute lymphocytic count; Hb, haemoglobin; PLT, platelet; LDH, lactate dehydrogenase; β<sub>2</sub>-MG, β<sub>2</sub>-microglobulin; *IGHV*, immunoglobulin heavy chain variable region; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ULN, upper limit of normal.

\*Novel targeted therapies refer to ibrutinib ± rituximab, ibrutinib + fludarabine + cyclophosphamide + rituximab and part of the other treatments.

**Supplemental Table S6.** Comparisons of C-indexes, 3-year and 5-year AUC between models and CLL-IPI in the ibrutinib validation cohort.

Models	CSS	
	Ibrutinib validation cohort	
	C-index (95% CI)	p-value
Model <sub>Lipo-IPI</sub>	0.889 (0.846–0.932)	
Model <sub>CLL-IPI</sub>	0.835 (0.776–0.894)	<b>0.002</b>
CLL-IPI	0.807 (0.742–0.872)	<b>0.001</b>
	3-year AUC (95% CI)	p-value
Model <sub>Lipo-IPI</sub>	0.864 (0.757–0.972)	
Model <sub>CLL-IPI</sub>	0.797 (0.653–0.942)	<b>0.005</b>
CLL-IPI	0.760 (0.606–0.914)	<b>&lt;0.001</b>
	5-year AUC (95% CI)	p-value
Model <sub>Lipo-IPI</sub>	0.926 (0.852–1.000)	
Model <sub>CLL-IPI</sub>	0.882 (0.774–0.990)	<b>0.028</b>
CLL-IPI	0.860 (0.737–0.982)	<b>0.015</b>

**Abbreviations:** C-index, concordance index; AUC, area under the curve; CLL, chronic lymphocytic leukaemia; IPI, international prognostic index; CSS, cancer-specific survival; 95% CI, 95% confidence interval; Model<sub>Lipo-IPI</sub>, model generated by nomogram with cholesterol profile; Model<sub>CLL-IPI</sub>, model generated by nomogram without cholesterol profile.