

Supplementary Materials

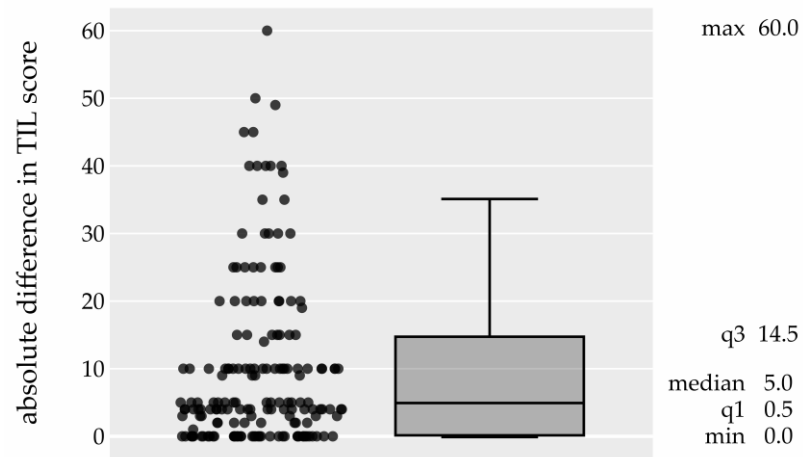


Figure S1: Absolute difference between TIL scores of two pathologists, boxplot.

Abbreviations: min: minimum; max: maximum; q3: 3rd quartile; q1: 1st quartile; TIL: tumor-infiltrating lymphocytes.

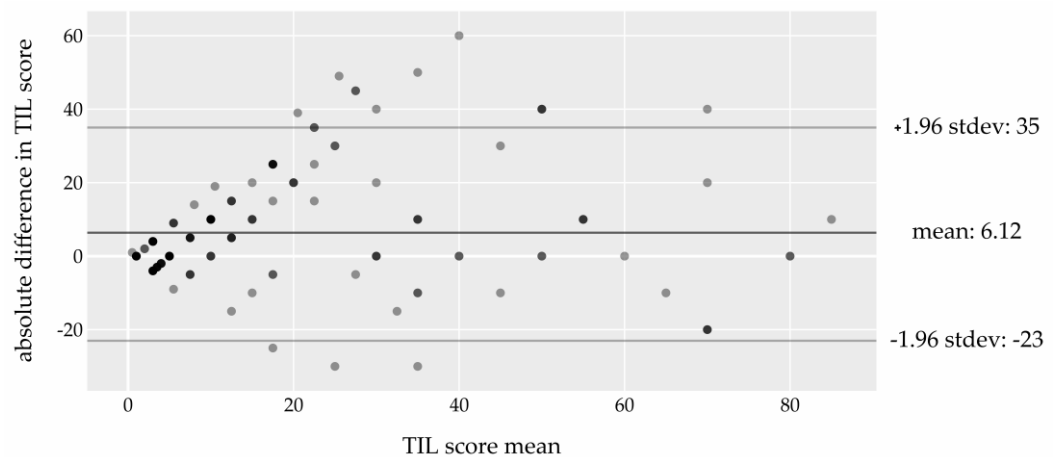


Figure S2: Bland-Altman plot for TIL measurements by two pathologists (solid line represents the mean difference, the dashed lines represent the 95% limits of agreement).

Abbreviations: TIL: tumor-infiltrating lymphocytes; stdev: standard deviation.

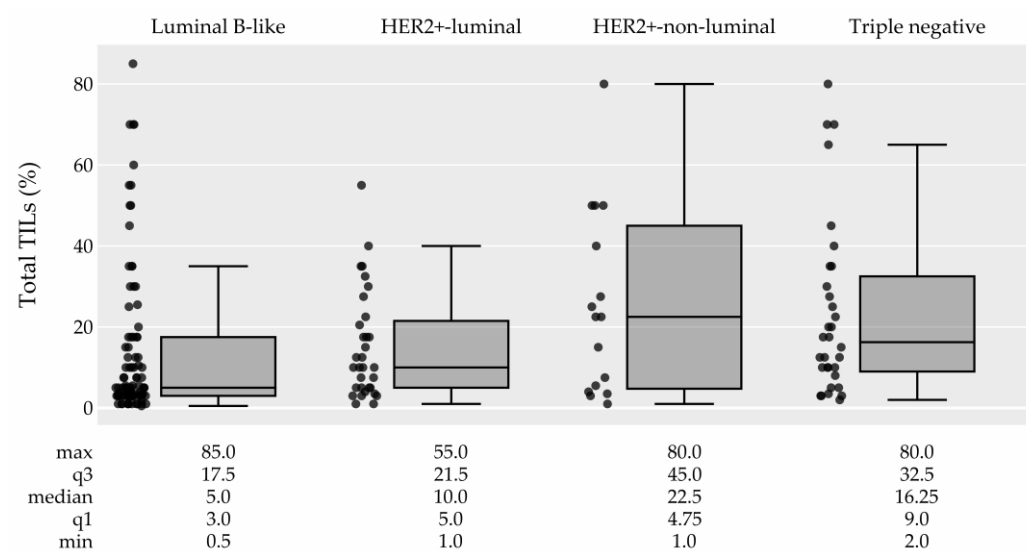


Figure S3: Distribution of tumor-infiltrating lymphocytes in breast cancer according to the four breast cancer subtypes, boxplots. The difference in TIL between breast cancer subtypes on our sample ($p=0.004$) could not be generalized to the population (adjusted $p=0.085$), see Table S1. Abbreviations: min: minimum; max: maximum; q3: 3rd quartile; q1: 1st quartile; TIL: tumor-infiltrating lymphocytes; HER-2: human epidermal growth factor receptor 2.

Table S1. Association of TIL and its subtypes (CD8+ TILs, CXCL13+ TILs, PD-1+ TILs, FOXP3+ TILs) with other clinicopathological characteristics. 1

Clinicopathologic characteristics	total TILs median (IQR)	p*	ad-justed p-value †	total TILs n(%) low (<60%) high (≥60%)	p #	ad-justed p-value †	CD8+ TILs median (IQR)	p *	ad-justed p-value †	CXCL13+ TILs median (IQR)	p *	ad-justed p-value †	PD-1+ TILs median (IQR)	p *	ad-justed p-value †	FOXP3+ TILs median (IQR)	p *	ad-justed p-value †
Grade 3	12.5 (4.0-30.0)	<0.001	0.002	115 (93.0%)	0.290	1.0	40.0 (30.0-50.0)	0.077	1.0	1.0 (0.0-2.0)	0.302	1.0	2.0 (0.0-7.0)	0.001	0.015	5.0 (2.0-7.5)	<0.001	0.012
Grade 2	5.0 (3.0-7.5)			45 (98.0%)			30.0 (20.0-50.0)			1.0 (1.0-1.0)			0.0 (0.0-2.0)			2.0 (1.0-5.0)		
Ki-67 10-20%	5.0 (3.0-10.0)	<0.001	0.002	45 (98.0%)	0.224	1.0	40.0 (30.0-50.0)	0.420	1.0	1.0 (0.5-2.0)	0.800	1.0	0.0 (0.0-2.0)	0.001	0.024	2.5 (1.0-5.0)	0.021	0.487
Ki-67 20-40%	10.0 (3.8-20.0)			63 (95.0%)			40.0 (30.0-50.0)			1.0 (0.0-2.0)			1.0 (0.0-5.0)			4.0 (1.0-8.0)		
Ki-67 >40%	17.5 (5.5-35.0)			52 (90.0%)			40.0 (27.5-50.0)			1.0 (1.0-2.0)			3.0 (2.0-8.0)			5.0 (2.0-7.0)		
Lymph nodes positive	10.0 (3.5-25.0)	0.284	1.0	117 (94.0%)	1.000	1.0	40.0 (30.0-50.0)	0.259	1.0	1.0 (1.0-2.0)	0.546	1.0	2.0 (0.0-5.0)	0.740	1.0	5.0 (1.0-7.0)	0.840	1.0
Lymph nodes negative	6.5 (3.0-20.0)			44 (96.0%)			40.0 (20.0-50.0)			1.0 (0.0-2.5)			1.5 (0.0-6.0)			3.0 (1.0-7.0)		
Tumor ≤20 mm (MRI)	30.0 (5.0-50.0)	0.051	1.0	22 (88.0%)	0.305	1.0	40.0 (25.0-50.0)	0.887	1.0	1.0 (1.0-2.0)	0.002	0.051	3.0 (0.0-8.0)	0.609	1.0	5.0 (1.0-10.0)	0.709	1.0
Tumor 20-50 mm (MRI)	10.0 (3.0-22.5)			106 (94.0%)			40.0 (30.0-50.0)			1.0 (0.0-2.0)			2.0 (0.0-5.0)			4.0 (1.5-7.0)		
Tumor >50 mm (MRI)	6.5 (4.0-11.2)			18 (100.0%)			40.0 (30.0-50.0)			2.0 (2.0-5.0)			1.0 (0.0-7.0)			5.0 (3.0-7.0)		
Luminal B-like	5.0 (3.0-17.5)	0.004	0.085	86 (95.0%)	0.173	1.0	40.0 (30.0-50.0)	0.346	1.0	1.0 (1.0-2.0)	0.499	1.0	1.0 (0.0-5.0)	0.062	1.0	3.0 (1.0-6.5)	0.027	0.598
HER2+ -luminal	10.0 (5.0-21.5)			32 (100.0%)			45.0 (30.0-50.0)			1.0 (1.0-1.0)			1.0 (0.0-2.5)			3.0 (1.0-5.0)		
HER2+ -non-luminal	22.5 (4.8-45.0)			15 (94.0%)			40.0 (30.0-60.0)			2.0 (0.0-3.0)			2.5 (0.0-8.5)			6.0 (3.5-9.0)		
Triple negative	16.2 (9.0-32.5)			28 (88.0%)			40.0 (30.0-40.0)			1.0 (0.5-2.0)			3.0 (2.0-8.0)			6.0 (3.0-7.5)		

*Mann-Whitney test (if 2 categories) or Kruskal-Wallis test (if 3 categories or more); # Fisher's exact test; † p-values were adjusted for all comparisons in this table. Statistically significant adjusted p-values are presented in bold.

Abbreviations: TIL: tumor-infiltrating lymphocytes; HER-2: human epidermal growth factor receptor 2; IQR: interquartile range; n: number

Table S2: Multivariable logistic model of prognostic factors for pathological complete response (AUC= 0.807, loglikelihood ratio test p<0.001).

Characteristic	OR (95% CI)	p-value
CD8+ TILs (per 10%)	1.31 (1.01-1.72)	0.045
Age	0.98 (0.95-1.02)	0.351
Ki-67 (per 10%)	1.44 (1.18-1.79)	<0.001
Negative lymph nodes	2.34 (1.03-5.42)	0.042
HER2+-luminal, HER2+-non-luminal, TN vs lumB	4.93 (2.31-11.09)	<0.001

Statistically significant p-values are presented in bold.

TIL: tumor-infiltrating lymphocytes; TN: triple negative subtype; lumB: luminal B subtype; HER-2: human epidermal growth factor receptor 2; OR: odds ratio; CI: confidence interval; AUC: area under the curve

Table S3: Multivariable logistic model of prognostic factors for pathological complete response (AUC= 0.796, loglikelihood ratio test p<0.001).

Characteristic	OR (95% CI)	p-value
CXCL13+ TILs (per 10%)	1.01 (0.18-5.35)	0.934
Age	0.98 (0.95-1.01)	0.235
Ki-67 (per 10%)	1.39 (1.14-1.71)	0.001
Negative lymph nodes	1.93 (0.85-4.39)	0.114
HER2+-luminal, HER2+-non-luminal, TN vs lumB	4.79 (2.26-10.66)	<0.001

Statistically significant p-values are presented in bold.

TIL: tumor-infiltrating lymphocytes; TN: triple negative subtype; lumB: luminal B subtype; HER-2: human epidermal growth factor receptor 2; OR: odds ratio; CI: confidence interval; AUC: area under the curve

Table S4: Multivariable logistic model of prognostic factors for pathological complete response (AUC= 0.801, loglikelihood ratio test p<0.001).

Characteristic	OR (95% CI)	p-value
PD-1+ TILs (per 10%)	1.56 (0.87-2.83)	0.131
Age	0.98 (0.95-1.01)	0.262
Ki-67 (per 10%)	1.37 (1.12-1.69)	0.002
Negative lymph nodes	2.20 (0.97-5.08)	0.059
HER2+-luminal, HER2+-non-luminal, TN vs lumB	4.79 (2.26-10.67)	<0.001

Statistically significant p-values are presented in bold.

TIL: tumor-infiltrating lymphocytes; TN: triple negative subtype; lumB: luminal B subtype; HER-2: human epidermal growth factor receptor 2; OR: odds ratio; CI: confidence interval; AUC: area under the curve

Table S5: Multivariable logistic model of prognostic factors for pathological complete response (AUC= 0.807, loglikelihood ratio test p<0.001).

Characteristic	OR (95% CI)	p-value
FOXP3+ TILs (per 10%)	1.83 (0.73-4.61)	0.193
Age	0.98 (0.95-1.01)	0.213
Ki-67 (per 10%)	1.38 (1.13-1.70)	0.001
Negative lymph nodes	2.08 (0.92-4.72)	0.076
HER2+-luminal, HER2+-non-luminal, TN vs lumB	4.65 (2.21-10.27)	<0.001

Statistically significant p-values are presented in bold.

TIL: tumor-infiltrating lymphocytes; TN: triple negative subtype; lumB: luminal B subtype; HER-2: human epidermal growth factor receptor 2; OR: odds ratio; CI: confidence interval; AUC: area under the curve

Table S6: Multivariable logistic model of prognostic factors for pathological complete response (AUC= 0.811, loglikelihood ratio test p<0.001).

Characteristic	OR (95% CI)	P-value
CD8+ TILs (per 10%)	1.29 (0.96-1.76)	0.086
CXCL13+ TILs (per 10%)	0.55 (0.07-3.68)	0.533
PD-1+ TILs (per 10%)	1.31 (0.66-2.66)	0.429
FOXP3+ TILs (per 10%)	1.21 (0.39-3.63)	0.708
Age	0.98 (0.95-1.02)	0.328
Ki-67 (per 10%)	1.37 (1.12-1.71)	0.002
Negative lymph nodes	2.04 (0.88-4.78)	0.096
HER2+-luminal, HER2+-non-luminal, TN vs lumB	5.19 (2.40-11.92)	<0.001

Statistically significant p-values are presented in bold.

TIL: tumor-infiltrating lymphocytes; TN: triple negative subtype; lumB: luminal B subtype; HER-2: human epidermal growth factor receptor 2; OR: odds ratio; CI: confidence interval; AUC: area under the curve