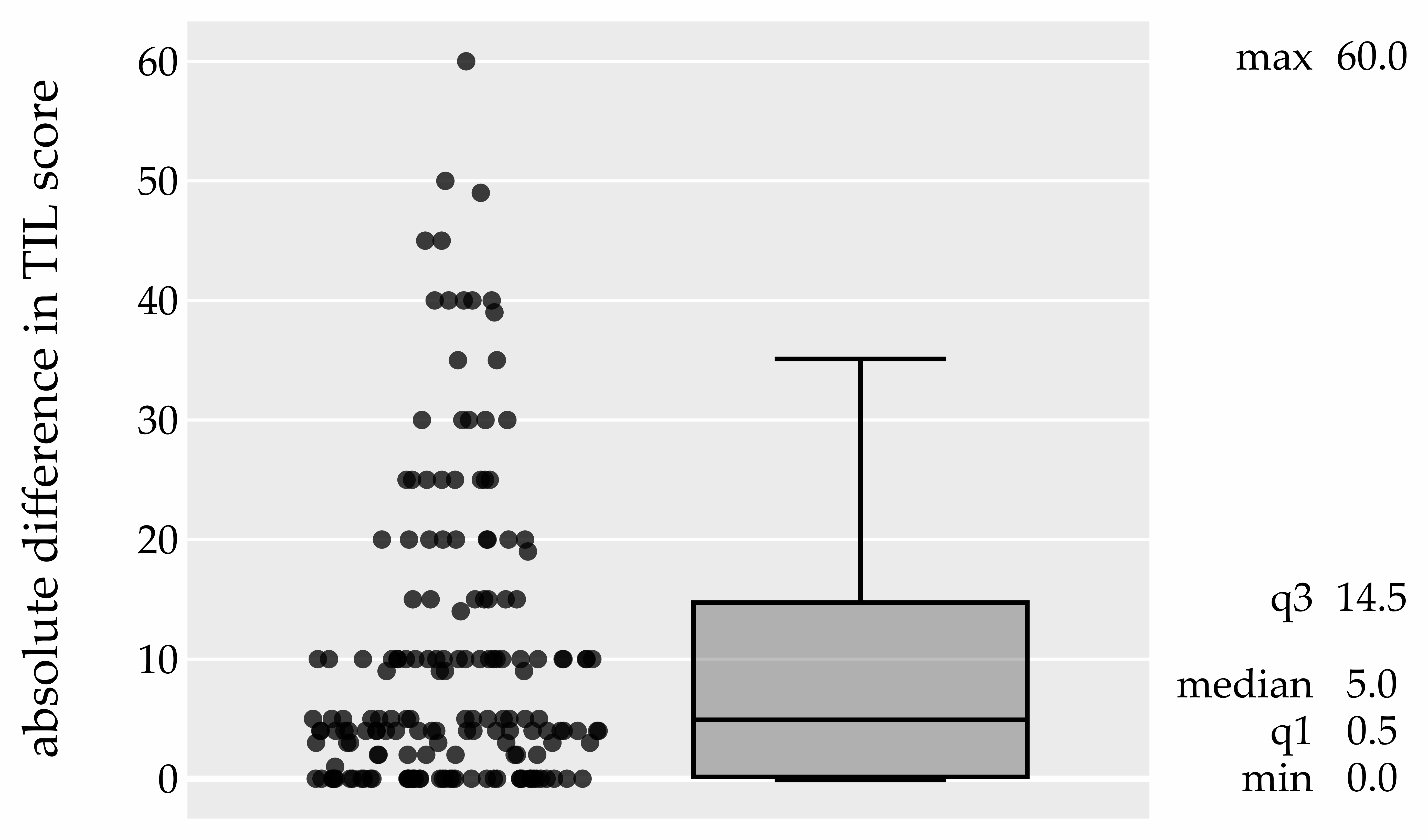
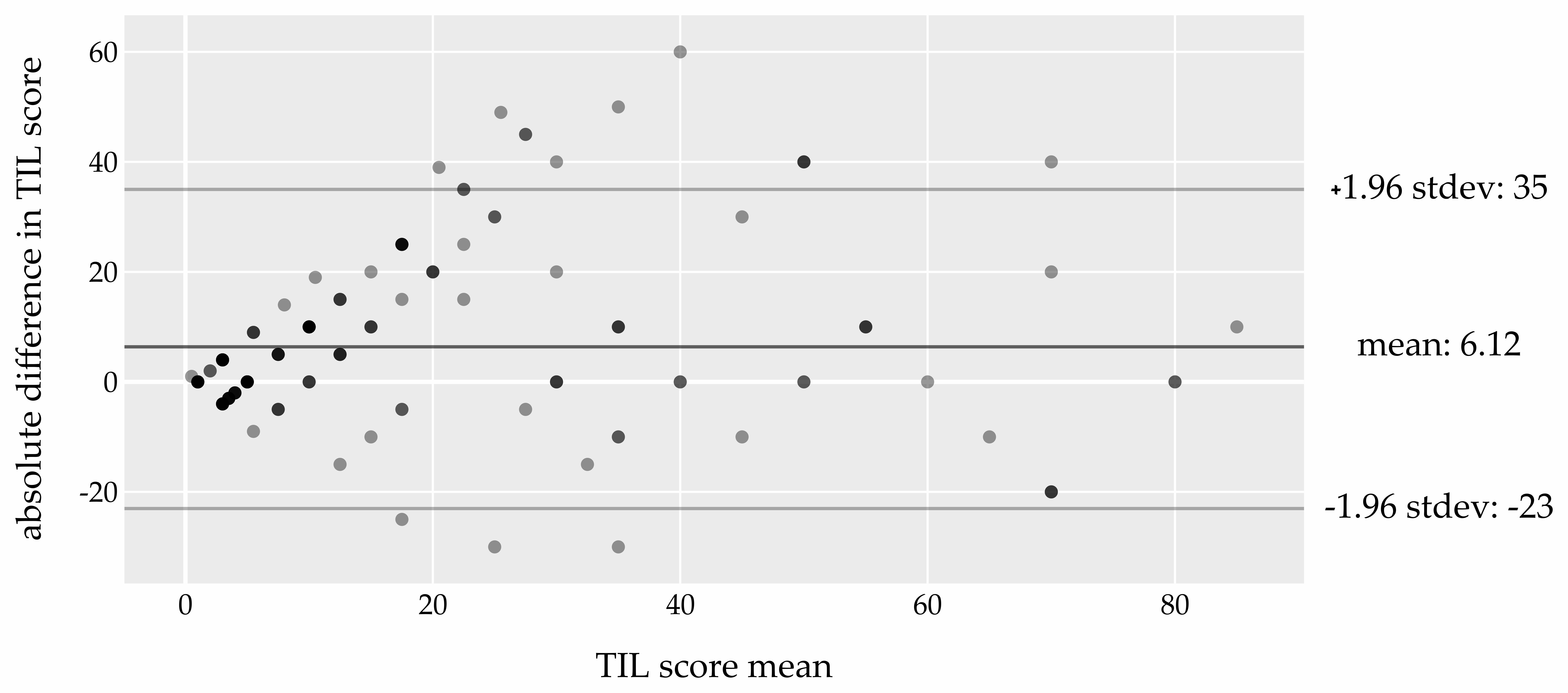
Supplementary Materials:

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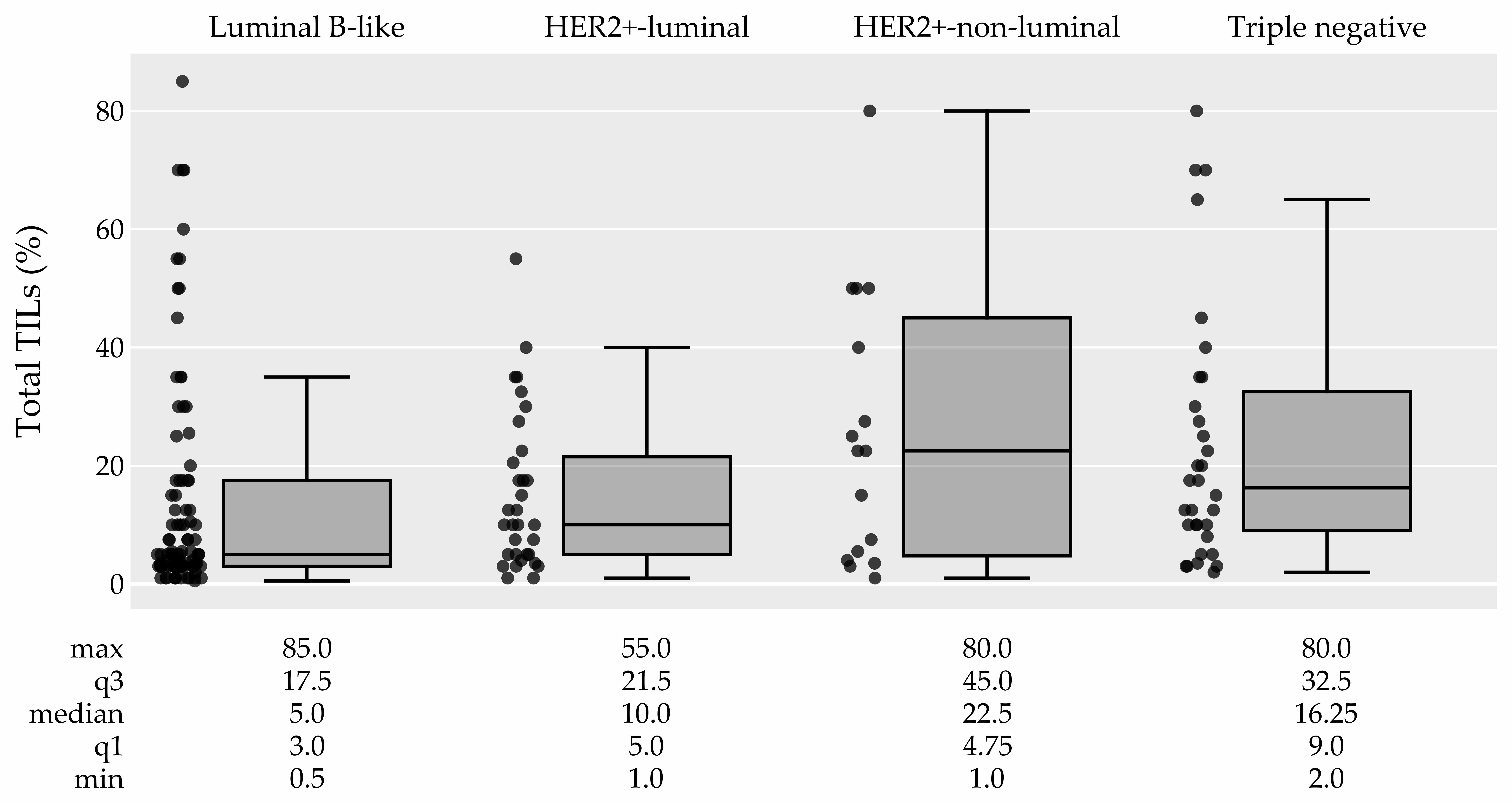
**Figure S1:** Absolute difference between TIL scores of two pathologists, boxplot.

*Abbreviations: min: minimum; max: maximum; q3: 3rd quartile; q1: 1st quartile; TIL: tumour-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: tumour-infiltrating lymphocytes; stdev: standard deviation.*

****

**Figure S3:** Distribution of tumour-infiltrating lymphocytes in breast cancer according to the four breast cancer subtypes, boxplots.

*Abbreviations: min: minimum; max: maximum; q3: 3rd quartile; q1: 1st quartile; TIL: tumour-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.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinicopathologic characteristics** | **total TILs median (IQR)** | **p\*** | **adjusted p-**  **value †** | **total TILs**  **n(%)** | | **p #** | **adjusted p-value †** | **CD8+ TILs**  **median (IQR)** | **p \*** | **adjusted p-value †** | **CXCL13+ TILs**  **median (IQR)** | | **p \*** | **adjusted p-value †** | **PD-1+ TILs median (IQR)** | **p \*** | **adjusted p-value †** | **FOXP3+ TILs**  **median (IQR)** | **p \*** | **adjusted p-**  **value †** |
| **low (<60%)** | **high (≥60%)** |
| **Grade 3** | 12.5 (4.0-30.0) | <0.001 | **0.002** | 115 | 9 | 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** |
| (93.0%) | (7.0%) |
| **Grade 2** | 5.0 (3.0-7.5) | 45 | 1 | 30.0 (20.0-50.0) | 1.0  (1.0-1.0) | 0.0  (0.0-2.0) | 2.0  (1.0-5.0) |
| (98.0%) | (2.0%) |
| **Ki-67 10-20%** | 5.0  (3.0-10.0) | <0.001 | **0.002** | 45 | 1 | 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 |
| (98.0%) | (2.0%) |
| **Ki-67 20-40%** | 10.0 (3.8-20.0) | 63 | 3 | 40.0 (30.0-50.0) | 1.0  (0.0-2.0) | 1.0  (0.0-5.0) | 4.0  (1.0-8.0) |
| (95.0%) | (5.0%) |
| **Ki-67 >40%** | 17.5 (5.5-35.0) | 52 | 6 | 40.0 (27.5-50.0) | 1.0  (1.0-2.0) | 3.0  (2.0-8.0) | 5.0  (2.0-7.0) |
| (90.0%) | (10.0%) |
| **Lymph nodes positive** | 10.0 (3.5-25.0) | 0.284 | 1.0 | 117 | 8 | 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 |
| (94.0%) | (6.0%) |
| **Lymph nodes negative** | 6.5  (3.0-20.0) | 44 | 2 | 40.0 (20.0-50.0) | 1.0  (0.0-2.5) | 1.5  (0.0-6.0) | 3.0  (1.0-7.0) |
| (96.0%) | (4.0%) |
| **Tumor ≤20 mm (MRI)** | 30.0 (5.0-50.0) | 0.051 | 1.0 | 22 | 3 | 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 |
| (88.0%) | (12.0%) |
| **Tumor 20-50 mm (MRI)** | 10.0 (3.0-22.5) | 106 | 7 | 40.0 (30.0-50.0) | 1.0  (0.0-2.0) | 2.0  (0.0-5.0) | 4.0  (1.5-7.0) |
| (94.0%) | (6.0%) |
| **Tumor >50 mm (MRI)** | 6.5  (4.0-11.2) | 18 | 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) |
| (100.0%) | (0.0%) |
| **Luminal**  **B-like** | 5.0  (3.0-17.5) | 0.004 | 0.085 | 86 | 5 | 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 |
| (95.0%) | (5.0%) |
| **HER2+**  **-luminal** | 10.0 (5.0-21.5) | 32 | 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) |
| (100.0%) | (0.0%) |
| **HER2+**  **-non-luminal** | 22.5 (4.8-45.0) | 15 | 1 | 40.0 (30.0-60.0) | 2.0  (0.0-3.0) | 2.5  (0.0-8.5) | 6.0  (3.5-9.0) |
| (94.0%) | (6.0%) |
| **Triple**  **negative** | 16.2 (9.0-32.5) | 28 | 4 | 40.0 (30.0-40.0) | 1.0  (0.5-2.0) | 3.0  (2.0-8.0) | 6.0  (3.0-7.5) |
| (88.0%) | (12.0%) |
| \*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 adjustet p-values are presented in bold.*  *Abbreviations: TIL: tumour-infiltrating lymphocytes; HER-2: human epidermal growth factor receptor 2; IQR: interquartile range; n: number* | | | | | | | | | | | | | | | | | | | | | |

**Table S2:** Multivariable 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 adjustet p-values are presented in bold.*  *TIL: tumour-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 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 adjustet p-values are presented in bold.*  *TIL: tumour-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 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 adjustet p-values are presented in bold.*  *TIL: tumour-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 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 adjustet p-values are presented in bold.*  *TIL: tumour-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* | | |