cancers

Functional Classification of *TP53* Mutations in Acute Myeloid Leukemia

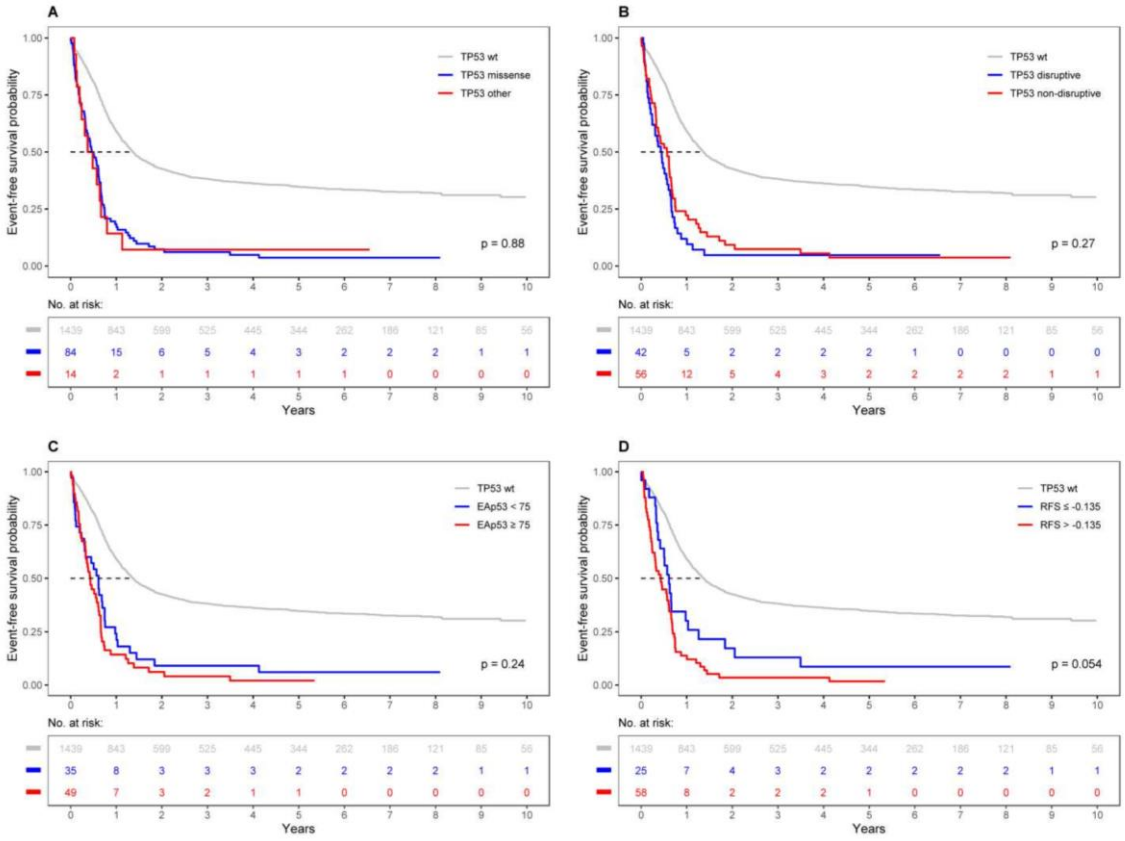

Figure S1. Event-free survival probabilities for patients with *TP53* mutated AML according to functional mutation scoring systems. (**A**) comparison of missense *TP53* mutations versus other types (nonsense and splice-site mutations, insertions and deletions). (**B**) comparison of disruptive versus non-disruptive mutations. (**C**) classification according to the "Evolutionary Action p53 Score" (EAp53). (**D**) classification based on the "Relative Fitness Score" (RFS) with the AML-specific threshold of -0.135. All P-values refer to the comparison of *TP53* mutated groups, survival of *TP53* wild-type patients is shown as a reference.

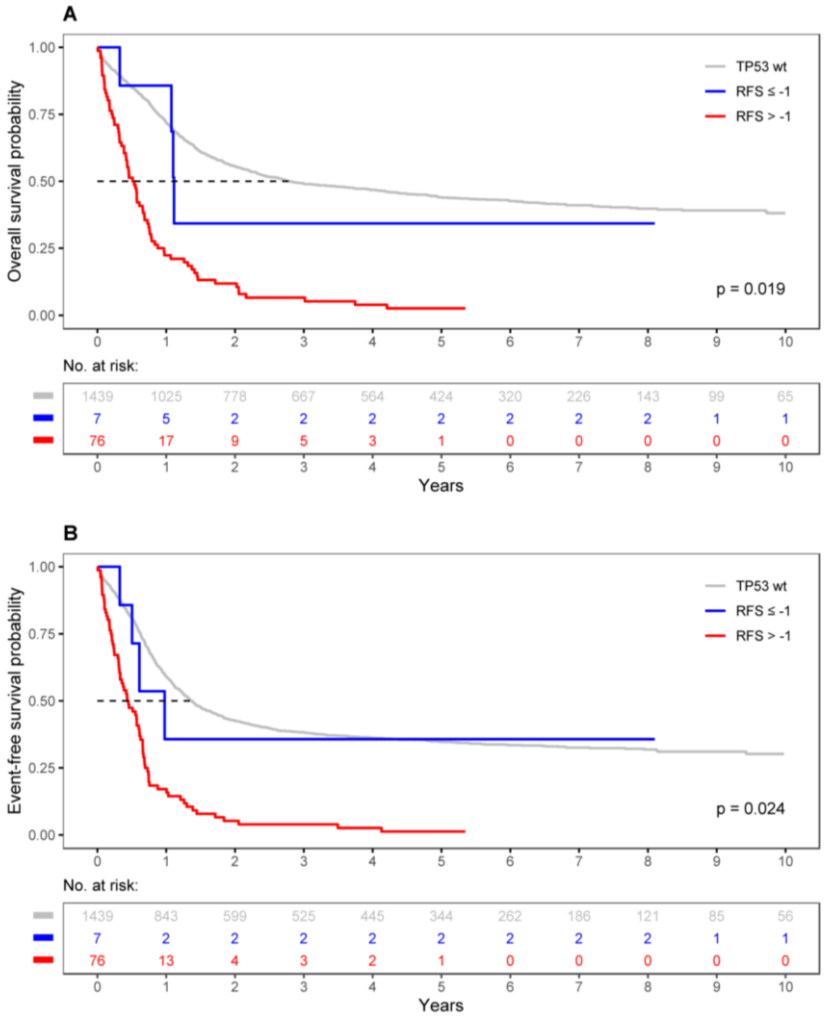

Figure S2. Overall and event-free survival probabilities for patients with *TP53* mutated AML according to the RFS with a cut-off set at -1.

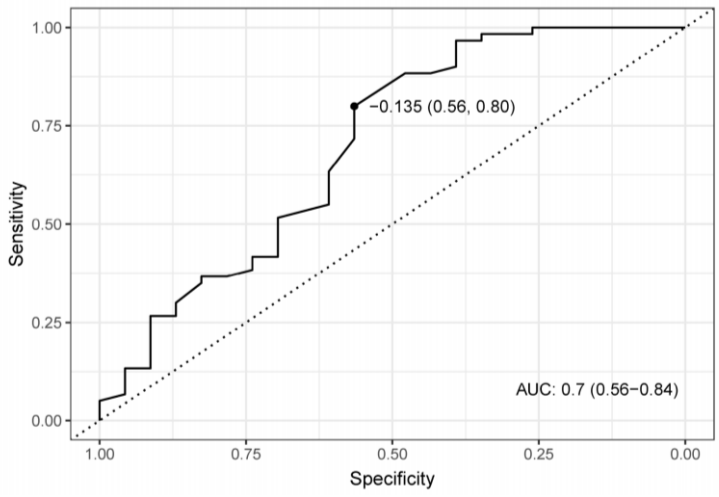

Figure S3. Receiver operating characteristics analysis for the "Relative Fitness Score" as a predictor for 1-year mortality. Abbreviation: AUC, area under the curve.

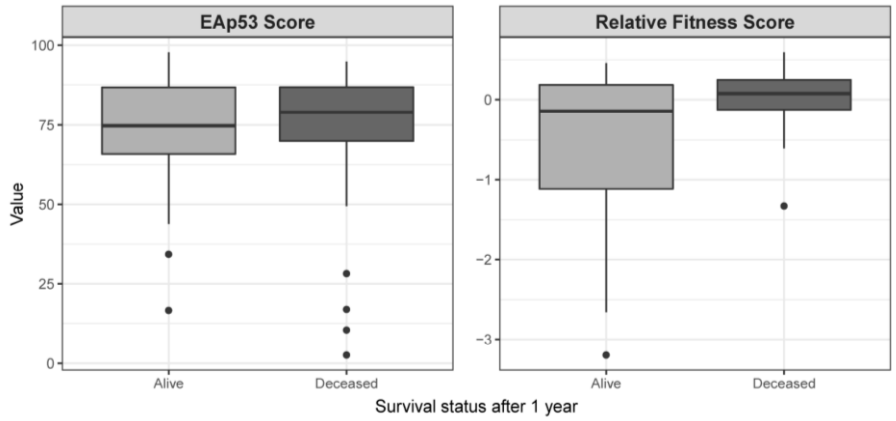

Figure S4. Box plots of the "EAp53 Score" and the "Relative Fitness Score" for patients with *TP53* mutated AML according to the survival status at 1 year.

Table S1. Median event-free survival rates of AMLSG patients with and without *TP53* mutated AML and with respect to *TP53* functional scoring systems. Abbreviations: mut, *TP53* mutated; wt, *TP53* wild-type; CI, confidence interval; EAp53, "Evolutionary Action p53 Score"; RFS, "Relative Fitness Score"; RFS AML, AML-specific RFS; NA, not applicable—median survival not reached.

Variable	Group	Median	95% CI
TP53	mut	5.7	4.3–7.4
	wt	16.5	15.0–18.2
Disruptive	no	6.8	4.0–8.0
	yes	5.3	3.0–7.7
Missense	no	5.1	2.9–13.6
	yes	5.8	4.0–7.5
EAp53	< 75	7.3	3.7–9.1
	≥ 75	5.2	4.0–7.5
RFS	≤ −1	11.7	6.0–NA
	> −1	5.3	4.0–7.4
RFS AML	≤ −0.135	7.3	5.0–15.1
	> −0.135	5.2	3.6–7.4

Table S2. Cox proportional hazards regression analysis of the different functional mutation scoring systems and patient characteristics on overall survival–univariable analysis. The *TP53* variant allele frequency (VAF) is assessed as a continuous and a binary variable. Abbreviations: HR, hazard ratio; CI, confidence interval; EAp53, "Evolutionary Action p53 Score"; RFS, "Relative Fitness Score"; RFS AML, AML-specific RFS.

Variable	Category	HR (95% CI)	*p*
Disruptive	no	1 (Ref.)	0.064
	yes	1.49 (0.98–2.26)	
Missense	no	1 (Ref.)	0.492
	yes	0.81 (0.45–1.47)	
EAp53 score	<75	1 (Ref.)	0.488
	≥75	1.17 (0.75–1.84)	
RFS	≤−1	1 (Ref.)	0.026
	>−1	3.15 (1.15–8.67)	
RFS AML	≤−0.135	1 (Ref.)	0.018
	>−0.135	1.83 (1.11–3.02)	
Age		1.05 (1.02–1.07)	<0.001
Gender	male	1 (Ref.)	0.460
	female	1.17 (0.77–1.78)	
White blood cell count		1.01 (1.00–1.02)	0.045
Cytogenetic risk	high	1 (Ref.)	0.161
	intermediate	0.47 (0.21–1.02)	
	low	0.83 (0.20–3.41)	
Type of AML	AML	1 (Ref.)	0.193
	secondary AML	1.47 (0.53–4.04)	
	Therapy-related AML	0.58 (0.30–1.13)	
VAF		1.00 (1.00–1.01)	0.428
VAF	<20	1 (Ref.)	0.398
	≥20	0.79 (0.46–1.36)	

Table S3. Cox proportional hazards regression analysis of the different functional mutation scoring systems and patient characteristics on event-free survival–univariable analysis. The *TP53* variant allele frequency (VAF) is assessed as a continuous and a binary variable. Abbreviations: HR, hazard ratio; CI, confidence interval; EAp53, "Evolutionary Action p53 Score"; RFS, "Relative Fitness Score"; RFS AML, AML-specific RFS.

Variable	Category	HR	*p*
Disruptive	no	1 (Ref.)	0.274
	yes	1.26 (0.83–1.91)	
Missense	no	1 (Ref.)	0.882
	yes	0.96 (0.53–1.72)	
EAp53 score	<75	1 (Ref.)	0.240
	≥75	1.31 (0.83–2.06)	
RFS	≤−1	1 (Ref.)	0.032
	>−1	3.05 (1.10–8.43)	
RFS AML	≤−0.135	1 (Ref.)	0.056
	>−0. 135	1.63 (0.99–2.68)	
Age		1.05 (1.03–1.08)	<0.001
Gender	male	1 (Ref.)	0.715
	female	1.08 (0.71–1.64)	
White blood cell count		1.01 (1.00–1.02)	0.004
Cytogenetic risk	high	1 (Ref.)	0.122
	intermediate	0.44 (0.20–0.97)	
	low	0.74 (0.18–3.06)	
Type of AML	AML	1 (Ref.)	0.099
	secondary AML	1.31 (0.48–3.60)	
	therapy-related AML	0.50 (0.26–0.97)	
VAF		1.00 (0.99–1.01)	0.915
VAF	<20	1 (Ref.)	0.357
	≥20	0.78 (0.46–1.33)	

Table S4. Sensitivity and specificity values of the various thresholds for the "EAp53 Score" and the "Relative Fitness Score" (RFS). For each of the investigated thresholds, we stated the number of patients that were below and above the threshold in the groups "alive" and "deceased" after 1 year. The resulting sensitivity and specificity values are presented with their respective 95% confidence intervals (CI).

Scoring System	Threshold	Below/above (deceased)	Below/above (alive)	Sensitivity (95% CI)	Specificity (95% CI)
EAp53	**75**	23/38	12/11	62.3 (49.0–74.4)	52.2 (30.6–73.2)
RFS	**−1**	1/59	6/17	98.3 (91.1–100)	26.1 (10.2–48.4)
RFS AML	**−0.135**	12/48	13/10	80.0 (70.0–90.0)	56.5 (34.8–73.9)

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