Supplementary Materials

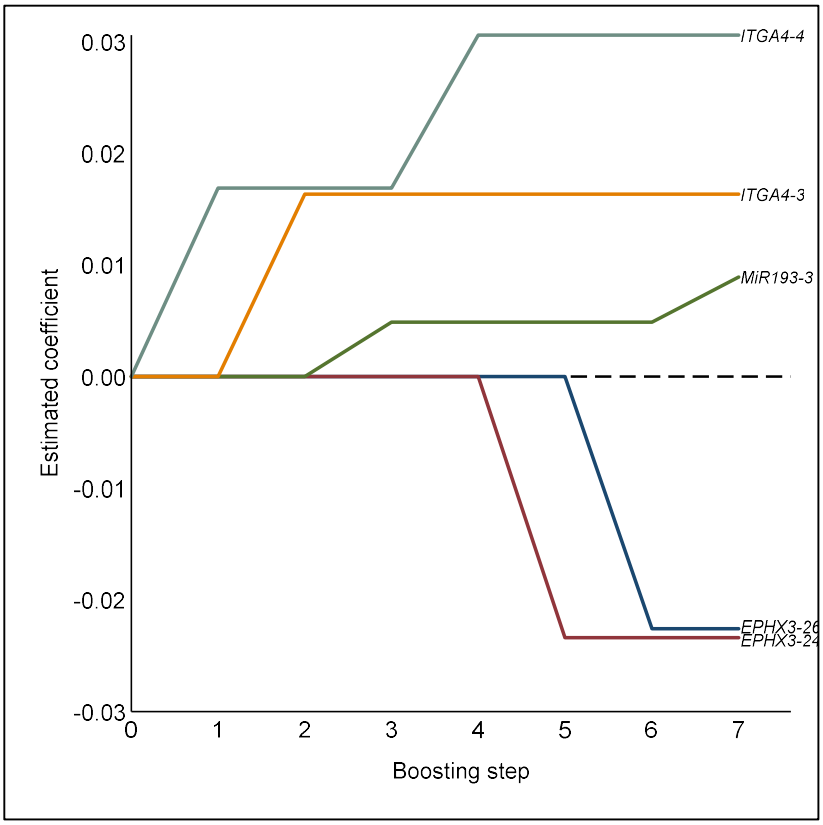

Figure 1. Coefficient paths of the five CpG sites included in the final Cox proportional hazards model. The coefficient estimates are plotted against the boosting steps as obtained from the likelihood-based component-wise algorithm. Coefficients are scaled to be at the level of the original methylation Beta-values.

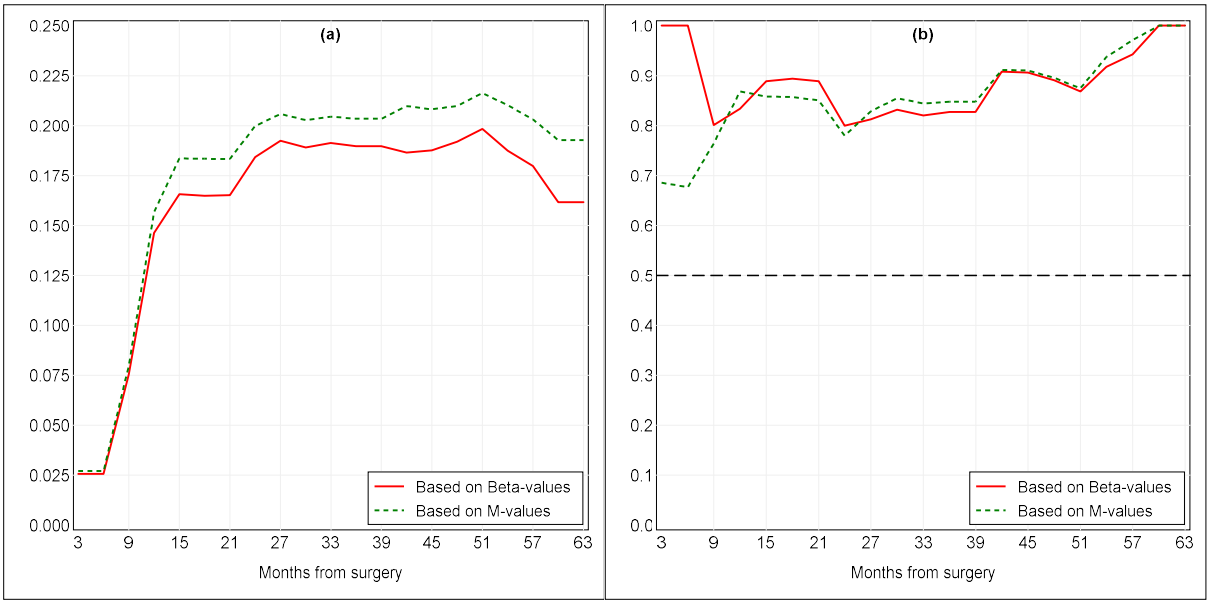

Figure S2. Time-dependent Brier score (a) and area under the receiver operator characteristic curve (AUC) (b) for the final Cox proportional hazards model fitted by component-wise likelihood-based boosting. The dashed line represents a non-discriminatory model (random guessing). M-values were computed as the binary logarithm of the intensities of methylated probes versus non-methylated probes. Performance and predictive accuracy of the model were estimated using the original training set of 36 patients.

Table S1. Permutation-based *P*-value estimations for all candidate methylation data (238 CpG sites). Covariates are ordered from smallest to largest *P*-value.

CpG site	*P*-value	CpG site	*P*-value	CpG site	*P*-value
ITGA4-4	0.0027	*PARP15-1*	0.4634	*GP1BB-7*	0.7680
ITGA4-3	0.0078	*PARP15-15*	0.4635	*KIF1A-6*	0.7686
MiR193-3	0.0099	*EPHX3-29*	0.4638	*KIF1A-20*	0.7732
EPHX3-24	0.0157	*MiR193-18*	0.4720	*MiR296-3*	0.7737
EPHX3-26	0.0172	*LRRTM1-10*	0.4733	*LINC0059-2*	0.7751
EPHX3-23	0.0196	*MiR296-7*	0.4804	*LRRTM1-18*	0.7780
ITGA4-1	0.0234	*MiR193-22*	0.4821	*KIF1A-3*	0.7864
EPHX3-18	0.0240	*PARP15-19*	0.4854	*LINC0059-19*	0.7889
EPHX3-20	0.0268	*ZAP70-9*	0.4887	*MiR296-13*	0.7965
MiR296-10	0.0286	*TERT-5*	0.5093	*NTM-15*	0.8033
TERT-2	0.0326	*EPHX3-7*	0.5105	*LRRTM1-16*	0.8086
ITGA4-2	0.0350	*GP1BB-3*	0.5157	*KIF1A-14*	0.8093
ITGA4-5	0.0404	*NTM-4*	0.5166	*LRRTM1-21*	0.8108
ITGA4-9	0.0411	*NTM-5*	0.5187	*KIF1A-26*	0.8114
EPHX3-21	0.0427	*ZAP70-17*	0.5277	*LINC0059-4*	0.8136
ITGA4-7	0.0451	*ZAP70-14*	0.5418	*LRRTM1-8*	0.8177
EPHX3-12	0.0455	*GP1BB-17*	0.5450	*PARP15-3*	0.8233
EPHX3-17	0.0476	*MiR296-15*	0.5481	*LRRTM1-1*	0.8245
EPHX3-16	0.0495	*LRRTM1-3*	0.5496	*PARP15-17*	0.8251
ITGA4-6	0.0511	*NTM-14*	0.5572	*KIF1A-22*	0.8268
TERT-1	0.0555	*ZAP70-15*	0.5578	*MiR296-12*	0.8280
ITGA4-8	0.0578	*PARP15-9*	0.5698	*LRRTM1-22*	0.8301
EPHX3-25	0.0629	*MiR193-25*	0.5704	*KIF1A-12*	0.8306
MiR296-14	0.0747	*NTM-11*	0.5734	*MiR193-8*	0.8331
EPHX3-4	0.0766	*NTM-3*	0.5735	*LRRTM1-17*	0.8351
ITGA4-12	0.0800	*GP1BB-8*	0.5813	*LRRTM1-19*	0.8377
MiR296-9	0.0831	*TERT-3*	0.5829	*KIF1A-8*	0.8411
EPHX3-14	0.0878	*ZAP70-18*	0.5844	*MiR193-4*	0.8419
ITGA4-11	0.0888	*ZAP70-8*	0.5846	*MiR193-24*	0.8423
ITGA4-10	0.0921	*PARP15-5*	0.5849	*LINC0059-7*	0.8429
EPHX3-22	0.0947	*GP1BB-12*	0.5884	*MiR193-19*	0.8432
EPHX3-28	0.1005	*GP1BB-11*	0.5920	*MiR193-5*	0.8452
EPHX3-2	0.1084	*MiR296-6*	0.5962	*LINC0059-15*	0.8499
ITGA4-14	0.1151	*ZAP70-11*	0.5963	*KIF1A-23*	0.8525
EPHX3-5	0.1257	*LRRTM1-2*	0.6014	*TERT-4*	0.8543
GP1BB-18	0.1270	*ZAP70-12*	0.6058	*MiR193-11*	0.8573
EPHX3-10	0.1311	*PARP15-13*	0.6058	*LINC0059-13*	0.8635
ITGA4-13	0.1439	*LRRTM1-11*	0.6077	*KIF1A-25*	0.8646
EPHX3-15	0.1526	*NTM-12*	0.6098	*LRRTM1-4*	0.8683
EPHX3-13	0.1570	*NTM-10*	0.6101	*LINC0059-3*	0.8739
FLI1-4	0.1646	*GP1BB-13*	0.6184	*KIF1A-27*	0.8751
EPHX3-8	0.1838	*NTM-1*	0.6185	*MiR193-14*	0.8755
EPHX3-11	0.1859	*MiR296-1*	0.6238	*MiR193-17*	0.8756
EPHX3-3	0.1942	*PARP15-6*	0.6246	*LINC0059-6*	0.8822
ZAP70-3	0.2019	*PARP15-10*	0.6255	*KIF1A-1*	0.8872
MiR296-8	0.2043	*GP1BB-4*	0.6269	*LINC0059-16*	0.8888
FLI1-5	0.2044	*MiR193-23*	0.6295	*MiR193-21*	0.8938
ZAP70-1	0.2079	*LRRTM1-13*	0.6313	*LINC0059-14*	0.8938
GP1BB-15	0.2102	*NTM-9*	0.6337	*LRRTM1-20*	0.8959
EPHX3-6	0.2151	*GP1BB-5*	0.6341	*TERT-6*	0.8997
FLI1-8	0.2152	*MiR193-20*	0.6383	*PARP15-12*	0.9038

EPHX3-1	0.2245	*NTM-13*	0.6433	*MiR193-12*	0.9053
EPHX3-19	0.2249	*MiR193-26*	0.6471	*LRRTM1-9*	0.9065
MiR193-1	0.2291	*GP1BB-9*	0.6609	*PARP15-4*	0.9077
MiR193-2	0.2408	*GP1BB-10*	0.6669	*KIF1A-19*	0.9104
ZAP70-4	0.2448	*MiR296-4*	0.6688	*KIF1A-11*	0.9121
ZAP70-20	0.2449	*NTM-7*	0.6735	*LINC0059-9*	0.9164
GP1BB-1	0.2457	*GP1BB-6*	0.6745	*KIF1A-18*	0.9180
FLI1-2	0.2493	*LRRTM1-5*	0.6773	*LRRTM1-15*	0.9207
ZAP70-7	0.2696	*MiR193-16*	0.6790	*LINC0059-17*	0.9239
ZAP70-5	0.2987	*LINC0059-5*	0.6813	*LRRTM1-14*	0.9253
MiR296-5	0.3060	*PARP15-18*	0.6904	*LINC0059-8*	0.9267
EPHX3-9	0.3064	*ZAP70-10*	0.6918	*MiR296-2*	0.9290
PARP15-8	0.3078	*LRRTM1-6*	0.7063	*LINC0059-11*	0.9304
FLI1-3	0.3314	*LINC0059-18*	0.7180	*ZAP70-13*	0.9321
ZAP70-2	0.3380	*MiR193-9*	0.7213	*LINC0059-12*	0.9366
ZAP70-19	0.3542	*KIF1A-16*	0.7251	*MiR193-6*	0.9426
MiR193-7	0.3586	*KIF1A-5*	0.7267	*LINC0059-10*	0.9448
FLI1-1	0.3613	*MiR193-15*	0.7278	*KIF1A-15*	0.9475
EPHX3-27	0.3950	*LRRTM1-12*	0.7339	*PARP15-7*	0.9476
FLI1-7	0.4166	*MiR193-13*	0.7360	*KIF1A-17*	0.9559
PARP15-2	0.4192	*LINC0059-1*	0.7434	*LRRTM1-7*	0.9565
GP1BB-2	0.4205	*KIF1A-2*	0.7456	*KIF1A-4*	0.9586
ZAP70-16	0.4322	*PARP15-16*	0.7515	*KIF1A-10*	0.9608
NTM-6	0.4449	*PARP15-14*	0.7570	*KIF1A-24*	0.9674
ZAP70-6	0.4470	*GP1BB-16*	0.7573	*KIF1A-21*	0.9674
NTM-2	0.4508	*KIF1A-9*	0.7578	*KIF1A-13*	0.9689
GP1BB-14	0.4545	*NTM-8*	0.7583	*KIF1A-7*	0.9760
MiR296-11	0.4580	*PARP15-11*	0.7603		
MiR193-10	0.4625	*LINC0059-20*	0.7622		

Table S2. Cox proportional hazards model resulting from likelihood-based component-wise boosting with no information on connection among same-gene CpG sites (optimal number of steps = 10), and after conversion of Beta-values into M-values (optimal number of steps = 4). Non-zero regression coefficients (ln HR) are presented along with hazard ratios (HRs) and permutation-based *P*-values. Coefficients are scaled to be at the level of the original methylation data.

CpG site	Beta-values, no pathway connection information		M-values*	
	Ln HR	HR	Ln HR	HR
EPHX3-18	·	·	–0.3940	0.6744
EPHX3-23	–0.0195	0.9807	·	·
EPHX3-24	–0.0235	0.9768	·	·
EPHX3-25	·	·	–0.4256	0.6534
ITGA4-4	0.0577	1.0594	0.1884	1.2073
MiR193-3	0.0176	1.0178	0.2192	1.2451
Integrated Brier score	*0.089*		*0.070*	
C-index	*0.805*		*0.806*	
Integrated AUC	*0.847*		*0.834*	

* Pathway connection information had no impact on variable selection.