Abbreviations used in this supplement

NR = Not reported
NP = Not performed
OS = Overall Survival
DFS = Disease Free Survival
PFS = Progression Free Survival
K-M = Kaplan-Meier
ROC = Receiver operating characteristic
AUC = Area under curves
MSI = Microsatelite instability
MSS = Microsatelite stable
PROBAST = Prediction model risk of bias assessment tool

Supplementary Methods

Systematic review and quality assessment

We selected eligible studies from a 2019 systematic review summarizing prognostic DNA methylation biomarkers among patients with gastrointestinal cancer.[1] Besides, we conducted an updated systematic search in PubMed and Web of Science for studies published between July 2019 and February 2022. We used a combination of Medical Subject Headings (MESH) and key words related to colon and rectum, cancer, epigenetic signatures, and prognosis, respectively. We included studies that were peer-reviewed articles, reported in English, included patients with CRC, performed an epigenome-wide methylation array on tumor tissue samples, and reported CpGs associated with survival in CRC patients. We extracted the following study-level information onto pre-designed spreadsheets: first author, year of publication, patient characteristics (mean or median age, the percentage of females, tumor site, and the percentage of patients with tumor stage III/IV), size of training set, endpoint, event rate, and the name of prognostically relevant CpGs. For studies that additionally constructed prognostic models based on CpGs, we also extracted the equation of these prognostic models and the model performance reported in the development study. We contacted the corresponding author of the study to request information when necessary.

We additionally assessed the methodological quality of each prognostic model based a tool to assess the risk of bias and applicability of prediction model studies (PROBAST).[2] PROBAST assesses the risk of bias (ROB) of prediction model studies in four broad domains: participants (2 signaling questions), predictors (3 signaling questions), outcome (6 signaling questions), and analysis (9 signaling questions). Each domain is rated as high (the answer to any of the signaling question in that domain is "No" or "Probably no"), low (the answer to all signaling questions is "Yes" or "Probably yes"), or unclear (relevant information is missing for some of the signaling questions, and the answer to all remaining questions is "Yes", or "Probably yes") risk of bias.[2] The overall ROB for a prognostic model was rated as high (the model is rated as high ROB for at least one domain), low (the model is rated as low ROB on all domains), or unclear (the model is rated as unclear ROB for at least one domain and was rated as low ROB in the remaining domains).[2] The rationale for rating each criterion was recorded for each prognostic model.

Data collection of the DACHS cohort

At baseline, patients provided extensive information regarding sociodemographic characteristics, lifestyle, family and medical history, and symptoms of the disease during a face-to-face interview, carried out by trained interviewers using a standardized questionnaire. Tumor characteristics and stage of disease (6th edition of the TNM staging manual) were obtained from medical records and pathology reports. Molecular tumor tissue analyses were performed based on DNA extracted from formalin-fixed, paraffin- embedded tumor samples from the patients enrolled.[3,4] Microsatellite instability (MSI) status was determined using a mononucleotide marker panel (BAT25, BAT26, and CAT25).[5] The presence of KRAS mutation was determined by single-stranded conformational polymorphism technique.[5] The expression of BRAF V600E was determined independently by two experienced pathologists using immunohistochemical analyses in tissue microarray blocks.[5] CpG Island methylator phenotype (CIMP) status was determined using a five-marker methylation panel (MLH1, MINT1, MINT2, MINT31 and MGMT), and classified based on the number of hypermethylated loci: CIMP negative (none), CIMP-low (1 or 2 loci), or CIMP-high (3 or more loci).[5] Genome-wide methylation analysis was performed on tissue DNA using the Illumina Human Methylation 450 Bead-Chip (Illumina, San Diego, CA, USA), which interrogated over 485000 CpG sites.[3] At scheduled follow-up visits (3, 5, and 10 years after diagnosis), standardized information on CRC therapy, comorbidities, and recurrence were obtained from the physicians of the patients. Vital status, date and cause of death were collected from the local population registries and health authorities. Details regarding data collection and follow up could be found elsewhere.[3-7]

DNA methylation pre-processing

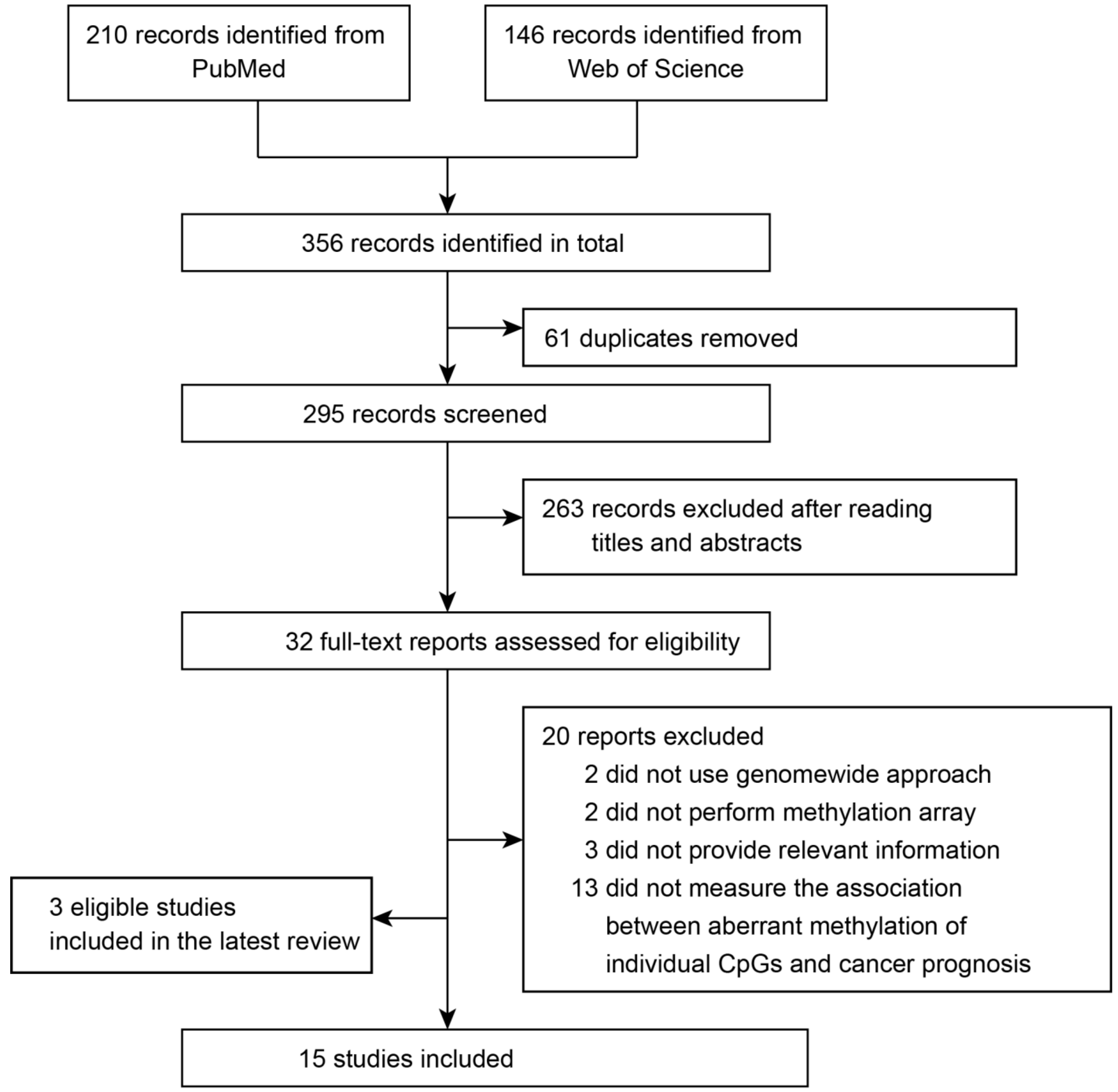
We filtered failed probes based on a detection p-value threshold of 0.01, and probes with a bead count less than three. Normalization procedure was performed to correct for technical difference between the type I and type II probes, and then the ComBat method was used to correct for batch effects. Next, all the prognostically relevant CpGs reported in included studies were selected from the genome-wide methylation array.

Multiple imputation

We used multiple imputation to impute (20 times) missing information in all patient characteristics. The multiple imputation process generated 20 plausible datasets accounting for the uncertainty associated with missing values. All analyses, except for the sensitivity stratified analyses, were performed in the 20 imputed datasets in parallel, and results obtained from each dataset were combined based on Rubin's rule. Two imputation models were created to separately impute clinical variables and four molecular characteristics (microsatellite instability [MSI], BRAF mutation, KRAS mutation, and CIMP mutation). Variables included in the first imputation model included year of diagnosis, age, gender, TNM stage at diagnosis, CRC location, treatment, and the primary outcome (i.e., the Nelson-Aalen estimator of the baseline cumulative hazard and the outcome indicator).[8] Predictive mean matching, logistic regression, and proportional odds model were used to impute continuous, binary, and ordered variables, respectively. For the second imputation model, 1852 CpGs related with CIMP genes based on a systematic search,[9] age, gender, TNM stage at diagnosis, CRC location, primary outcome, MSI, BRAF mutation, KRAS mutation, and CIMP mutation were included, and the random forest method was used to impute the four molecular variables.[3]

Supplementary Table 1: Search strategy

Keywords		Pubmed	Web of science[1]
Colon and rectum	#1	((colon*(Title/Abstract)) OR (rect*(Title/Abstract))) OR (colorect*(Title/Abstract))	((AB=(colon*)) OR AB=(rect*)) OR AB=(colorect*)
Cancer	#2	((((neoplasms(MeSH Terms)) OR (cancer(Title/Abstract))) OR (tumor*(Title/Abstract))) tumour*(Title/Abstract)))OR (carcinoma*(Title/Abstract))) OR (adenocarcinoma*(Title/Abstract))	((((((TI=(neoplasms)) OR TI=(cancer)) OR TI=(tumor)) OR TI=(tumour)) OR TI=(carcinoma)) OR TI=(pan-cancer)) OR TI=(adenocarcinoma))
Epigenetic signatures	#3	((((((((((methylation(MeSH Terms)) OR (dna methylation*(MeSH Terms))) OR (methylat*(Title/Abstract))) OR (epigenetic*(Title/Abstract))) OR (epigenetic marker*(Title/Abstract))) OR (DNA-methylation(Title/Abstract))) OR (hypermethylat*(Title/Abstract))) OR (hypomethylat*(Title/Abstract))) OR (CpG(Title/Abstract))) OR (epigenome-wide(Title/Abstract))) OR (methylation-based(Title/Abstract))	((((((((((AB=(methylation)) OR AB=(dna methylation)) OR AB=(methylat*)) OR AB=(epigenetic*)) OR AB=(epigenetic marker*)) OR AB=(DNA-methylation)) OR AB=(hypermethylat*)) OR AB=(hypomethylat*)) OR AB=(CpG)) OR AB=(epigenome-wide)) OR AB=(methylation-based)
Prognosis	#4	((((((((mortality(MeSH Terms)) OR (survival(MeSH Terms))) OR (survival analysis(MeSH Terms))) OR (mortality(Title/Abstract))) OR (survival(Title/Abstract))) OR (prognos*(Title/Abstract))) OR (predict*(Title/Abstract))) OR (outcome*(Title/Abstract))) OR (recurr*(Title/Abstract))	((((((TI=(mortality)) OR TI=(survival)) OR TI=(survival analysis)) OR TI=(prognos*)) OR TI=(predict*)) OR TI=(outcome*)) OR TI=(recurr*)
Study design	#5	((((database(Title/Abstract)) OR (dataset*(Title/Abstract))) OR (case-control(Title/Abstract))) OR (cohort(Title/Abstract))) OR (trial(Title/Abstract))	((((AB=(database)) OR AB=(dataset*)) OR AB=(case-control)) OR AB=(cohort)) OR AB=(trial)
Final	#5	#1 AND #2 AND #3 AND #4 AND (humans(Filter)) AND (2019/7/1:2022/10(pdat)) AND (english(Filter)))	(#1 AND #2 AND #3 AND #4 AND #5) AND Articles (Documents Types) AND English (Languages) AND DOP =(2019-07-01 -2022-10-31)



Supplementary Figure 1: Inclusion of studies for validation

Supplementary Table 2. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement Checklist

Section/Topic	n	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	p1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	p3
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	p5
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	p6
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	p6-7
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	p6-7
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	p7
	5b	Describe eligibility criteria for participants.	p7
	5c	Give details of treatments received, if relevant.	Not applicable
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	Supplement, p8
	6b	Report any actions to blind assessment of the outcome to be predicted.	Not applicable
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	Supplement, p7
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable
Sample size	8	Explain how the study size was arrived at.	p7
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Supplement, p8
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	p9
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	p9-10
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	p10
Risk groups	11	Provide details on how risk groups were created, if done.	Not applicable
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	p10-11
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	p11

Section/Topic	n	Checklist Item	Page
Title and abstract			
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	p11-12, table2
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	p12, table1 and table2
Model performance	16	Report performance measures (with CIs) for the prediction model.	p13-14, figure3
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	Not performed
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	p19
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	p17
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	p19-20
Implications	20	Discuss the potential clinical use of the model and implications for future research.	p20
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	supplementary
Funding	22	Give the source of funding and the role of the funders for the present study.	p21

Supplementary Table 3. Characteristics of studies to be validated.

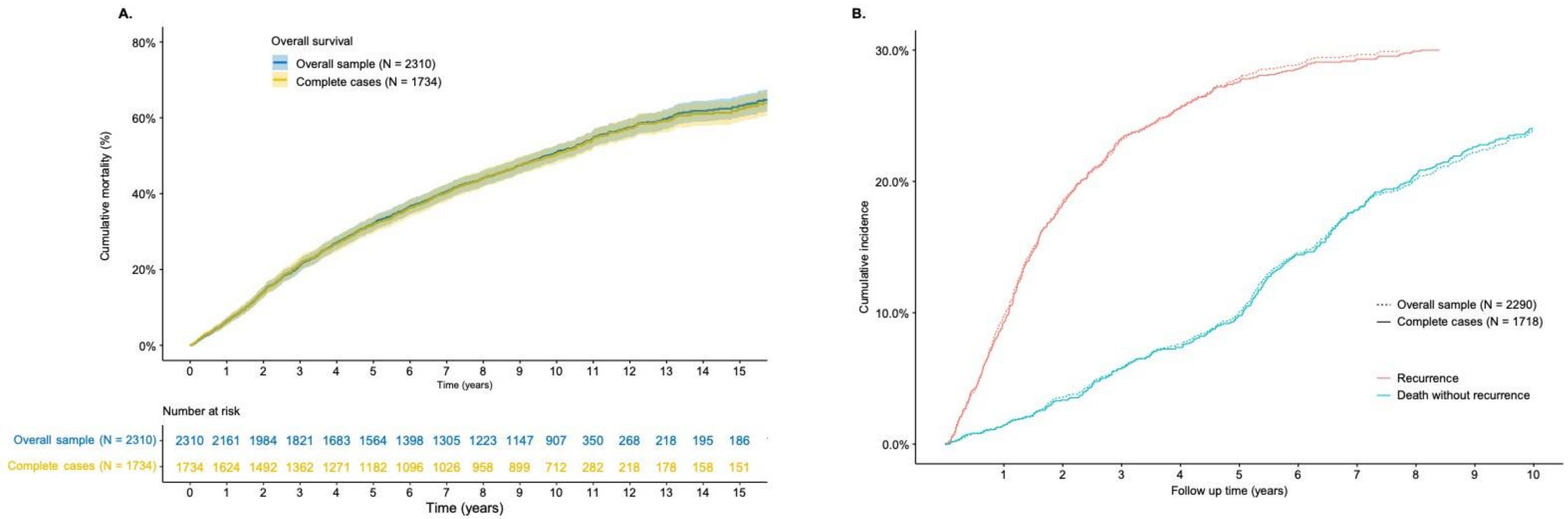
Study	Mean/median Age (year)	Female (%)	Tumor stage III/IV (%)	Cancer site	Source of patients	Size of training set	Endpoint	Event rate	Construct prognostic score based on CpGs
Yang et al, 2017[10]	NR	NR	NR	Colon adenocarcinoma	TCGA	301	OS	NR	Yes, but NR
Hou et al, 2018[11]	64	46%	43%	Colon and rectum	TCGA	379	OS	NR	NP
Gündert et al, 2019[3]	69	46%	41%	Colon and rectum	DACHS cohort	572	OS, DSS[1]	NR	Yes
Yang et al, 2019[12]	67	45%	43%	Colon adenocarcinoma	TCGA	272	OS	Overall deaths: 14%	Yes
Gong et al, 2020[13]	NR	46%	NR	Colon and rectum	TCGA	320	OS	NR	Yes
Wang X et al, 2020[14]	66	43%	45%	Colon and rectum	TCGA	249	OS, PFS[1]	Cumulative incidence, OS: 3-year: 36.3%, 5-year: 61; PFS: 3-year: 57.9%, 5-year: 76.7%	Yes
Wang XY et al, 2020[15]	67	48%	41%	Colon	TCGA	461	OS	Overall deaths: 19.3%	NP
Wang Y et al, 2020[16]	>64, 60%	49%	17%	Colon	TCGA	143	OS	NR	Yes
Xiang et al, 2020[17]	67	47%	40%	Colon adenocarcinoma	TCGA	385	OS	NR	Yes
Yang et al, 2020[18]	NR	NR	NR	Colon	TCGA	225	OS	NR	Yes, but NR
Yin et al, 2020[19]	>65, 55%	NR	NR	Colon adenocarcinoma	TCGA	337	OS	NR	NP
Chen et al, 2021[20]	≥65, 61%	46%	43%	Colon and rectum	TCGA	127	OS	Overall deaths: 23.6%	Yes
Huang et al, 2021[21]	66	46%	47%	Colon and rectum	TCGA	376	OS, DFS[1]	NR	Yes
Li et al, 2021[22]	NR	NR	NR	Colon and rectum	TCGA	327	OS	NR	Yes
Xin et al, 2022[23]	NR	46%	42%	Colon and rectum	TCGA	621	OS	Overall death: 20.5	NP

NR = Not reported; TCGA = the Cancer Genome Atlas Program; NP = Not performed; OS = Overall survival; DDS = Disease-specific survival; DFS = Disease-free survival; PFS = Progression-free survival. [1] In the three studies, prognostic CpGs were selected based on their associations with OS only, and were additionally validated for the other outcome.

Supplementary Table 4: Outcomes of validation cohort

	All-cause death		Recurrence	
	Overall sample *N* **= 2310**	**Complete cases[1]** *N* **= 1734**	**Overall sample** *N* **= 2290**	**Complete cases[1]** *N* **= 1718**
Median follow-up (years, IQR)	10.43 (10.05-12.40)	10.51 (10.08-13.01)	9.81 (5.27-10.23)	9.84 (5.32-10.24)
Total follow-up (person-years)	17622	13535	13362	10195
Event per 1000 person-years (95% CI)	71.05 (67.17-75.09)	70.19 (65.80 -74.80)	57.03 (53.05-61.23)	55.32 (50.85-60.08)
Number of events	1252	950	762	564
3-year cumulative incidence	21.10%	21.45%	23.20%	23.33%
5-year cumulative incidence	32.02%	31.72%	27.85%	27.56%
10-year cumulative incidence	50.73%	50.33%	31.35%	31.10%

[1] Excluding sample with any missing values in covariables presented on Table 2.



Supplementary Figure 2: K-M survival curves for OS (A) and cumulative incidence curves for DFS (B) comparing the overall sample and complete cases

Supplementary Table 5: Cox regression analyses for individual CpGs

		Endpoint in	OS						DFS					
		development	Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
Study	**CpG name**	**study**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	**p value**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**
Chen et al, 2021[20]	cg11621464	OS	1.08 (1.02, 1.14)	0.008	1.03 (0.97, 1.09)	0.375	1.03 (0.97, 1.09)	0.394	1.08 (1.00, 1.17)	0.037	1.01 (0.94, 1.1)	0.716	1.01 (0.93, 1.09)	0.798
	cg13565656	OS	1.01 (0.96, 1.07)	0.724	1.01 (0.95, 1.08)	0.708	1.02 (0.95, 1.09)	0.56	0.92 (0.85, 1.00)	0.041	1 (0.91, 1.09)	0.947	1.03 (0.94, 1.13)	0.514
	cg18976437	OS	1.00 (0.95, 1.06)	0.865	1.01 (0.96, 1.07)	0.657	1.01 (0.96, 1.07)	0.653	0.90 (0.84, 0.97)	0.007	0.97 (0.9, 1.04)	0.386	0.97 (0.9, 1.04)	0.385
	cg20505223	OS	1.00 (0.95, 1.06)	0.972	0.96 (0.91, 1.01)	0.145	0.96 (0.91, 1.01)	0.141	0.92 (0.86, 0.99)	0.020	0.94 (0.88, 1.01)	0.116	0.94 (0.88, 1.01)	0.106
	cg20528583	OS	1.02 (0.96, 1.08)	0.53	1 (0.94, 1.06)	0.956	1 (0.94, 1.06)	0.949	0.91 (0.84, 0.97)	0.008	0.96 (0.89, 1.04)	0.313	0.96 (0.89, 1.04)	0.302
Gong et al, 2020[13]	cg00110724	OS	1.08 (1.01, 1.15)	0.016	1.07 (1.01, 1.15)	0.026	1.08 (1.01, 1.15)	0.025	1.14 (1.04, 1.25)	0.004	1.13 (1.03, 1.23)	0.011	1.13 (1.03, 1.23)	0.011
	cg09353563	OS	0.87 (0.83, 0.92)	<0.001	0.97 (0.92, 1.03)	0.292	0.97 (0.92, 1.03)	0.341	0.80 (0.75, 0.86)	<0.001	0.93 (0.86, 0.99)	0.033	0.94 (0.87, 1.01)	0.083
	cg14660573	OS	0.98 (0.93, 1.04)	0.582	1.01 (0.95, 1.06)	0.857	1.01 (0.95, 1.06)	0.841	0.96 (0.88, 1.03)	0.257	0.97 (0.9, 1.05)	0.472	0.98 (0.9, 1.05)	0.534
Gündert et al, 2019[3]	cg00832644	OS and DSS	0.91 (0.86, 0.97)	0.002	0.96 (0.9, 1.02)	0.164	0.95 (0.89, 1.02)	0.16	0.88 (0.81, 0.94)	0.001	0.91 (0.84, 0.99)	0.033	0.9 (0.83, 0.98)	0.016
	cg01131395	OS and DSS	0.84 (0.79, 0.89)	<0.001	0.9 (0.85, 0.96)	0.002	0.9 (0.85, 0.96)	0.002	0.72 (0.67, 0.78)	<0.001	0.83 (0.76, 0.9)	<0.001	0.84 (0.77, 0.91)	<0.001
	cg05646575	OS and DSS	0.79 (0.74, 0.84)	<0.001	0.85 (0.8, 0.9)	<0.001	0.85 (0.79, 0.9)	<0.001	0.71 (0.65, 0.76)	<0.001	0.8 (0.74, 0.87)	<0.001	0.8 (0.74, 0.86)	<0.001
	cg08617020	OS and DSS	0.88 (0.83, 0.94)	<0.001	0.92 (0.86, 0.98)	0.007	0.92 (0.86, 0.98)	0.007	0.86 (0.80, 0.93)	<0.001	0.9 (0.83, 0.98)	0.01	0.89 (0.82, 0.96)	0.004
	cg08729279	OS and DSS	0.88 (0.82, 0.93)	<0.001	0.9 (0.85, 0.96)	0.002	0.9 (0.85, 0.96)	0.002	0.82 (0.76, 0.89)	<0.001	0.87 (0.8, 0.94)	0.001	0.86 (0.8, 0.94)	<0.001
	cg08804626	OS and DSS	0.85 (0.80, 0.90)	<0.001	0.86 (0.81, 0.92)	<0.001	0.85 (0.8, 0.91)	<0.001	0.81 (0.76, 0.86)	<0.001	0.84 (0.78, 0.9)	<0.001	0.81 (0.75, 0.87)	<0.001
	cg10758824	OS and DSS	0.88 (0.83, 0.94)	<0.001	0.94 (0.88, 1)	0.068	0.94 (0.88, 1)	0.068	0.78 (0.72, 0.85)	<0.001	0.89 (0.82, 0.97)	0.008	0.9 (0.83, 0.98)	0.011
	cg11056055	OS and DSS	0.87 (0.82, 0.92)	<0.001	0.9 (0.84, 0.95)	0.001	0.89 (0.84, 0.95)	<0.001	0.84 (0.78, 0.91)	<0.001	0.85 (0.79, 0.92)	<0.001	0.84 (0.77, 0.9)	<0.001
	cg12510999	OS and DSS	0.83 (0.78, 0.88)	<0.001	0.88 (0.82, 0.94)	<0.001	0.88 (0.82, 0.94)	<0.001	0.72 (0.67, 0.78)	<0.001	0.83 (0.77, 0.9)	<0.001	0.83 (0.77, 0.9)	<0.001
	cg14270346	OS and DSS	0.84 (0.79, 0.89)	<0.001	0.9 (0.84, 0.96)	0.001	0.9 (0.84, 0.96)	0.001	0.78 (0.72, 0.84)	<0.001	0.84 (0.78, 0.92)	<0.001	0.84 (0.77, 0.91)	<0.001
	cg14983135	OS and DSS	0.91 (0.85, 0.97)	0.002	0.94 (0.88, 1)	0.052	0.94 (0.88, 1)	0.05	0.84 (0.77, 0.91)	<0.001	0.86 (0.8, 0.94)	0.001	0.86 (0.79, 0.93)	<0.001
	cg16336556	OS and DSS	0.82 (0.77, 0.88)	<0.001	0.92 (0.86, 0.98)	0.013	0.92 (0.86, 0.98)	0.013	0.72 (0.66, 0.79)	<0.001	0.87 (0.8, 0.95)	0.001	0.87 (0.8, 0.95)	0.002
	cg16399624	OS and DSS	0.89 (0.84, 0.95)	<0.001	0.91 (0.86, 0.97)	0.003	0.91 (0.86, 0.97)	0.002	0.86 (0.79, 0.92)	<0.001	0.89 (0.82, 0.96)	0.002	0.88 (0.81, 0.94)	0.001
	cg17431888	OS and DSS	0.90 (0.84, 0.96)	0.002	0.97 (0.91, 1.04)	0.392	0.97 (0.91, 1.04)	0.391	0.80 (0.73, 0.88)	<0.001	0.89 (0.82, 0.97)	0.011	0.9 (0.82, 0.98)	0.015
	cg18195165	OS and DSS	0.86 (0.81, 0.92)	<0.001	0.89 (0.83, 0.94)	<0.001	0.89 (0.83, 0.94)	<0.001	0.82 (0.76, 0.89)	<0.001	0.88 (0.81, 0.95)	0.001	0.86 (0.8, 0.93)	<0.001
	cg18736676	OS and DSS	0.89 (0.84, 0.95)	<0.001	0.91 (0.86, 0.97)	0.002	0.91 (0.86, 0.97)	0.002	0.85 (0.79, 0.91)	<0.001	0.91 (0.84, 0.98)	0.012	0.91 (0.84, 0.98)	0.011
	cg19184885	OS and DSS	0.81 (0.76, 0.86)	<0.001	0.89 (0.83, 0.95)	<0.001	0.89 (0.83, 0.95)	<0.001	0.70 (0.65, 0.75)	<0.001	0.83 (0.76, 0.9)	<0.001	0.83 (0.76, 0.9)	<0.001
	cg19340296	OS and DSS	0.83 (0.78, 0.88)	<0.001	0.9 (0.85, 0.97)	0.003	0.9 (0.85, 0.97)	0.003	0.73 (0.69, 0.79)	<0.001	0.86 (0.79, 0.93)	<0.001	0.86 (0.79, 0.93)	<0.001
	cg22522598	OS and DSS	0.93 (0.87, 0.99)	0.02	0.99 (0.92, 1.05)	0.683	0.99 (0.92, 1.05)	0.683	0.82 (0.76, 0.89)	<0.001	0.94 (0.87, 1.03)	0.184	0.94 (0.87, 1.03)	0.193
	cg23750514	OS and DSS	0.81 (0.77, 0.86)	<0.001	0.83 (0.78, 0.88)	<0.001	0.82 (0.77, 0.87)	<0.001	0.79 (0.73, 0.85)	<0.001	0.83 (0.77, 0.9)	<0.001	0.82 (0.75, 0.88)	<0.001
Hou et al, 2018[11]	cg00147009	OS	0.91 (0.86, 0.96)	0.001	0.93 (0.87, 0.98)	0.013	0.93 (0.87, 0.98)	0.012	0.87 (0.81, 0.95)	0.001	0.9 (0.82, 0.97)	0.01	0.89 (0.82, 0.97)	0.008
	cg00199007	OS	0.95 (0.89, 1.01)	0.09	0.97 (0.91, 1.03)	0.371	0.97 (0.91, 1.04)	0.418	0.91 (0.83, 0.99)	0.030	0.96 (0.89, 1.05)	0.387	0.98 (0.9, 1.06)	0.592
	cg01467592	OS	1.00 (0.95, 1.06)	0.893	1.04 (0.98, 1.1)	0.175	1.04 (0.98, 1.1)	0.166	1.01 (0.94, 1.09)	0.732	1.06 (0.98, 1.15)	0.124	1.07 (0.99, 1.15)	0.097
	cg03895094	OS	1.01 (0.96, 1.07)	0.658	1 (0.94, 1.06)	0.95	1 (0.94, 1.06)	0.882	1.05 (0.97, 1.13)	0.270	1.02 (0.94, 1.11)	0.617	1.01 (0.93, 1.1)	0.8
	cg04138846	OS	1.09 (1.02, 1.16)	0.007	1.09 (1.02, 1.16)	0.009	1.09 (1.02, 1.16)	0.009	1.09 (1.01, 1.19)	0.032	1.11 (1.02, 1.21)	0.012	1.11 (1.02, 1.21)	0.014
	cg05821816	OS	0.92 (0.87, 0.98)	0.01	0.93 (0.87, 0.99)	0.015	0.93 (0.87, 0.99)	0.015	0.92 (0.85, 1.00)	0.060	0.92 (0.85, 0.99)	0.035	0.92 (0.85, 1)	0.039
	cg06328127	OS	1.08 (1.02, 1.14)	0.007	1.08 (1.02, 1.14)	0.009	1.08 (1.02, 1.14)	0.009	1.08 (1.01, 1.17)	0.035	1.11 (1.03, 1.2)	0.005	1.11 (1.03, 1.2)	0.007
	cg06882340	OS	0.94 (0.89, 0.99)	0.019	0.98 (0.92, 1.03)	0.417	0.97 (0.92, 1.03)	0.366	0.93 (0.86, 1.00)	0.042	0.97 (0.89, 1.05)	0.399	0.95 (0.88, 1.03)	0.248

Study	CpG name	Endpoint in development study	OS						DFS					
			Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
			cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR(95%CI)	*p* value	cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR(95%CI)	*p* value
	cg07206725	OS	1.00 (0.94, 1.06)	0.973	1.01 (0.96, 1.07)	0.686	1.01 (0.96, 1.07)	0.665	1.01 (0.94, 1.09)	0.713	1.02 (0.95, 1.1)	0.601	1.02 (0.95, 1.1)	0.519
	cg08021727	OS	1.13 (1.07, 1.20)	<0.001	1.1 (1.03, 1.16)	0.003	1.1 (1.04, 1.17)	0.002	1.24 (1.15, 1.35)	<0.001	1.14 (1.04, 1.24)	0.004	1.15 (1.06, 1.25)	0.001
	cg10248231	OS	1.03 (0.98, 1.09)	0.248	1.02 (0.96, 1.08)	0.549	1.02 (0.96, 1.08)	0.55	1.13 (1.05, 1.21)	0.002	1.05 (0.97, 1.13)	0.203	1.05 (0.98, 1.14)	0.185
	cg10584300	OS	0.98 (0.93, 1.04)	0.502	0.98 (0.93, 1.03)	0.444	0.98 (0.93, 1.03)	0.413	0.97 (0.90, 1.04)	0.409	0.99 (0.93, 1.06)	0.761	0.98 (0.92, 1.05)	0.635
Huang, 2021[21]	cg12751565	OS and DFS	1.11 (1.05, 1.17)	<0.001	1.08 (1.02, 1.15)	0.007	1.08 (1.02, 1.15)	0.007	1.27 (1.18, 1.38)	<0.001	1.16 (1.07, 1.25)	<0.001	1.16 (1.07, 1.26)	<0.001
	cg21614638	OS and DFS	1.09 (1.03, 1.15)	0.002	1.04 (0.98, 1.1)	0.213	1.03 (0.97, 1.1)	0.269	1.17 (1.09, 1.26)	<0.001	1.05 (0.96, 1.13)	0.28	1.02 (0.94, 1.1)	0.665
	cg21770617	OS and DFS	1.08 (1.02, 1.14)	0.01	1.11 (1.05, 1.18)	<0.001	1.12 (1.06, 1.19)	<0.001	1.18 (1.10, 1.27)	<0.001	1.13 (1.05, 1.22)	0.001	1.15 (1.07, 1.24)	<0.001
Li et al, 2021[22]	cg01408654	OS	1.02 (0.96, 1.07)	0.596	0.96 (0.91, 1.02)	0.186	0.96 (0.91, 1.02)	0.181	0.90 (0.84, 0.97)	0.006	0.94 (0.88, 1.01)	0.098	0.94 (0.88, 1.01)	0.093
	cg04035209	OS	1.03 (0.97, 1.09)	0.339	0.96 (0.9, 1.02)	0.158	0.96 (0.9, 1.02)	0.151	0.93 (0.86, 0.99)	0.034	0.94 (0.87, 1.01)	0.083	0.93 (0.86, 1)	0.063
	cg10196720	OS	1.03 (0.97, 1.09)	0.338	0.97 (0.92, 1.03)	0.311	0.97 (0.91, 1.03)	0.277	0.94 (0.87, 1.01)	0.075	0.94 (0.88, 1.01)	0.099	0.93 (0.87, 1)	0.055
	cg10379890	OS	1.08 (1.02, 1.14)	0.008	1.04 (0.98, 1.11)	0.153	1.04 (0.98, 1.1)	0.174	0.98 (0.91, 1.05)	0.524	0.99 (0.92, 1.07)	0.794	0.98 (0.91, 1.05)	0.578
	cg11097433	OS	1.07 (1.01, 1.13)	0.02	1.03 (0.97, 1.09)	0.382	1.02 (0.97, 1.09)	0.408	0.97 (0.90, 1.04)	0.365	0.98 (0.91, 1.06)	0.592	0.97 (0.9, 1.05)	0.475
	cg14675211	OS	1.06 (1.00, 1.12)	0.04	0.99 (0.94, 1.05)	0.838	0.99 (0.94, 1.05)	0.743	1.00 (0.93, 1.07)	0.943	0.97 (0.9, 1.04)	0.413	0.95 (0.88, 1.03)	0.197
	cg15428578	OS	1.06 (1.00, 1.12)	0.037	1.02 (0.96, 1.08)	0.587	1.01 (0.96, 1.07)	0.626	0.97 (0.90, 1.04)	0.366	0.99 (0.92, 1.06)	0.709	0.98 (0.91, 1.05)	0.513
	cg19343464	OS	1.04 (0.98, 1.10)	0.206	0.99 (0.93, 1.05)	0.713	0.99 (0.93, 1.05)	0.657	0.96 (0.89, 1.03)	0.278	0.97 (0.9, 1.05)	0.484	0.96 (0.89, 1.04)	0.321
	cg21384402	OS	1.07 (1.01, 1.13)	0.027	1 (0.95, 1.06)	0.936	1 (0.95, 1.06)	0.955	0.96 (0.89, 1.04)	0.308	0.97 (0.9, 1.04)	0.343	0.96 (0.89, 1.03)	0.29
	cg27404023	OS	1.10 (1.04, 1.17)	0.001	1.04 (0.98, 1.1)	0.2	1.04 (0.98, 1.1)	0.213	1.01 (0.93, 1.08)	0.886	1.03 (0.95, 1.11)	0.469	1.02 (0.95, 1.1)	0.562
Wang X et al, 2020[14]	cg03091331	OS and PFS	0.96 (0.91, 1.02)	0.161	0.99 (0.93, 1.05)	0.705	0.99 (0.93, 1.06)	0.814	0.85 (0.79, 0.92)	<0.001	0.96 (0.88, 1.04)	0.348	0.98 (0.91, 1.07)	0.712
	cg06884352	OS and PFS	1.03 (0.98, 1.09)	0.276	1.06 (1, 1.12)	0.047	1.06 (1, 1.13)	0.034	1.11 (1.03, 1.19)	0.008	1.09 (1.01, 1.18)	0.021	1.11 (1.03, 1.2)	0.006
	cg07707546	OS and PFS	0.99 (0.94, 1.05)	0.731	0.96 (0.91, 1.02)	0.21	0.97 (0.91, 1.02)	0.226	0.88 (0.82, 0.95)	0.002	0.93 (0.86, 1)	0.051	0.93 (0.86, 1.01)	0.075
	cg08081805	OS and PFS	1.04 (0.99, 1.10)	0.138	0.98 (0.93, 1.04)	0.58	0.98 (0.93, 1.04)	0.57	0.98 (0.91, 1.06)	0.624	0.97 (0.9, 1.04)	0.393	0.97 (0.9, 1.04)	0.384
	cg21347353	OS and PFS	0.99 (0.93, 1.04)	0.652	0.98 (0.93, 1.04)	0.517	0.98 (0.93, 1.04)	0.505	0.88 (0.82, 0.96)	0.002	0.94 (0.87, 1.01)	0.101	0.94 (0.87, 1.01)	0.09
	cg25164589	OS and PFS	0.95 (0.90, 1.01)	0.098	0.97 (0.92, 1.03)	0.342	0.97 (0.92, 1.03)	0.374	0.87 (0.80, 0.94)	<0.001	0.92 (0.84, 0.99)	0.037	0.93 (0.85, 1.01)	0.073
Wang XY et al, 2020[15]	cg00660989	OS	0.93 (0.88, 0.98)	0.008	0.91 (0.86, 0.96)	0.001	0.91 (0.86, 0.96)	0.001	0.86 (0.80, 0.93)	<0.001	0.88 (0.82, 0.95)	0.001	0.9 (0.83, 0.97)	0.005
	cg00929855	OS	0.96 (0.91, 1.02)	0.194	0.98 (0.93, 1.04)	0.543	0.99 (0.93, 1.04)	0.6	0.88 (0.82, 0.95)	0.001	0.92 (0.85, 0.99)	0.031	0.93 (0.87, 1.01)	0.074
	cg01340952	OS	0.93 (0.88, 0.99)	0.018	0.94 (0.88, 0.99)	0.026	0.94 (0.88, 1)	0.034	0.84 (0.78, 0.91)	<0.001	0.88 (0.82, 0.96)	0.003	0.9 (0.83, 0.98)	0.013
	cg01639032	OS	0.97 (0.92, 1.03)	0.348	0.99 (0.94, 1.05)	0.851	1 (0.94, 1.06)	0.928	0.89 (0.83, 0.96)	0.002	0.94 (0.87, 1.01)	0.087	0.95 (0.88, 1.02)	0.188
	cg02704535	OS	0.97 (0.92, 1.03)	0.301	1 (0.94, 1.05)	0.862	1 (0.94, 1.06)	0.939	0.89 (0.82, 0.95)	0.001	0.93 (0.86, 1)	0.059	0.94 (0.88, 1.02)	0.136
	cg05194618	OS	0.93 (0.88, 0.98)	0.012	0.92 (0.87, 0.97)	0.004	0.92 (0.87, 0.98)	0.005	0.85 (0.79, 0.91)	<0.001	0.88 (0.82, 0.95)	0.001	0.9 (0.83, 0.97)	0.006
	cg10598353	OS	0.97 (0.92, 1.02)	0.262	1 (0.95, 1.06)	0.907	1.01 (0.95, 1.06)	0.836	0.89 (0.83, 0.96)	0.001	0.94 (0.88, 1.02)	0.13	0.96 (0.89, 1.03)	0.254
	cg11353380	OS	0.97 (0.92, 1.03)	0.297	0.99 (0.94, 1.05)	0.854	1 (0.94, 1.06)	0.933	0.89 (0.83, 0.96)	0.004	0.93 (0.86, 1)	0.065	0.94 (0.87, 1.02)	0.149
	cg11485463	OS	0.97 (0.92, 1.03)	0.277	1 (0.94, 1.05)	0.87	1 (0.94, 1.06)	0.953	0.88 (0.82, 0.95)	0.001	0.94 (0.87, 1.01)	0.102	0.95 (0.88, 1.03)	0.222
	cg12643366	OS	0.97 (0.92, 1.02)	0.261	0.99 (0.94, 1.05)	0.736	0.99 (0.94, 1.05)	0.811	0.89 (0.83, 0.96)	0.002	0.93 (0.86, 1)	0.055	0.94 (0.87, 1.02)	0.132
	cg12883479	OS	0.97 (0.91, 1.02)	0.221	1 (0.94, 1.06)	0.926	1 (0.94, 1.06)	0.994	0.88 (0.82, 0.95)	0.001	0.93 (0.87, 1.01)	0.07	0.95 (0.88, 1.02)	0.146
	cg13413286	OS	0.96 (0.91, 1.01)	0.15	1 (0.94, 1.05)	0.923	1 (0.94, 1.06)	0.992	0.88 (0.82, 0.95)	0.001	0.94 (0.87, 1.01)	0.101	0.95 (0.88, 1.03)	0.202
	cg15174834	OS	0.97 (0.92, 1.02)	0.239	0.99 (0.94, 1.05)	0.763	0.99 (0.94, 1.05)	0.835	0.88 (0.82, 0.95)	0.001	0.92 (0.86, 1)	0.037	0.94 (0.87, 1.01)	0.089
	cg15185479	OS	0.97 (0.91, 1.02)	0.216	0.99 (0.94, 1.05)	0.754	0.99 (0.94, 1.05)	0.813	0.88 (0.81, 0.95)	0.001	0.92 (0.85, 0.99)	0.031	0.93 (0.86, 1.01)	0.067
	cg17494781	OS	0.97 (0.91, 1.02)	0.213	1 (0.94, 1.06)	0.971	1 (0.95, 1.06)	0.963	0.89 (0.82, 0.95)	0.001	0.94 (0.87, 1.01)	0.098	0.95 (0.88, 1.02)	0.189
	cg18466674	OS	0.97 (0.91, 1.02)	0.229	1 (0.95, 1.06)	0.995	1 (0.95, 1.06)	0.93	0.89 (0.82, 0.95)	0.001	0.94 (0.88, 1.02)	0.124	0.96 (0.89, 1.03)	0.23
	cg19677203	OS	0.97 (0.92, 1.03)	0.294	1 (0.94, 1.05)	0.87	1 (0.94, 1.06)	0.952	0.88 (0.82, 0.95)	0.001	0.93 (0.86, 1)	0.066	0.95 (0.88, 1.02)	0.158

			OS						DFS					
		Endpoint in development	Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
Study	**CpG name**	**study**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**
	cg20428713	OS	1.02 (0.96, 1.08)	0.481	1.06 (1, 1.12)	0.061	1.07 (1.01, 1.13)	0.034	1.06 (0.98, 1.14)	0.160	1.09 (1.01, 1.18)	0.023	1.13 (1.04, 1.22)	0.002
	cg20607287	OS	0.99 (0.94, 1.05)	0.713	1 (0.95, 1.06)	0.969	1 (0.95, 1.06)	0.914	0.92 (0.85, 0.99)	0.020	0.96 (0.89, 1.04)	0.32	0.97 (0.9, 1.05)	0.477
	cg21096966	OS	0.92 (0.87, 0.97)	0.003	0.91 (0.86, 0.96)	0.001	0.91 (0.86, 0.96)	0.001	0.86 (0.80, 0.92)	<0.001	0.89 (0.82, 0.96)	0.002	0.91 (0.84, 0.98)	0.009
	cg21122656	OS	0.97 (0.92, 1.02)	0.258	0.99 (0.94, 1.05)	0.719	0.99 (0.94, 1.05)	0.788	0.88 (0.82, 0.95)	0.001	0.92 (0.86, 1)	0.038	0.94 (0.87, 1.01)	0.09
	cg22715094	OS	0.95 (0.90, 1.01)	0.096	0.98 (0.92, 1.03)	0.427	0.98 (0.93, 1.04)	0.482	0.87 (0.80, 0.93)	<0.001	0.9 (0.84, 0.98)	0.01	0.92 (0.85, 0.99)	0.027
	cg22847691	OS	0.97 (0.91, 1.02)	0.23	0.99 (0.93, 1.04)	0.631	0.99 (0.93, 1.05)	0.697	0.88 (0.82, 0.95)	0.001	0.92 (0.85, 0.99)	0.03	0.93 (0.87, 1.01)	0.076
	cg23285774	OS	0.93 (0.88, 0.98)	0.009	0.92 (0.87, 0.97)	0.002	0.91 (0.86, 0.97)	0.002	0.90 (0.83, 0.97)	0.006	0.87 (0.81, 0.94)	0.001	0.87 (0.8, 0.94)	<0.001
	cg24888257	OS	0.95 (0.90, 1.00)	0.067	0.94 (0.89, 0.99)	0.025	0.94 (0.89, 0.99)	0.026	0.92 (0.85, 0.99)	0.026	0.94 (0.87, 1.01)	0.117	0.94 (0.88, 1.02)	0.132
Wang Y et al, 2020[16]	cg00177496	OS	1.02 (0.96, 1.08)	0.492	1.04 (0.99, 1.1)	0.131	1.04 (0.99, 1.1)	0.118	1.06 (0.99, 1.13)	0.093	1.06 (0.99, 1.14)	0.088	1.06 (0.99, 1.14)	0.081
	cg01963906	OS	0.94 (0.90, 1.00)	0.036	0.98 (0.92, 1.03)	0.367	0.97 (0.92, 1.03)	0.362	0.89 (0.83, 0.95)	0.001	0.95 (0.89, 1.02)	0.195	0.95 (0.89, 1.03)	0.205
	cg05165940	OS	1.09 (1.04, 1.15)	0.001	1.13 (1.07, 1.19)	<0.001	1.15 (1.09, 1.22)	<0.001	1.07 (1.00, 1.15)	0.055	1.14 (1.06, 1.23)	0.001	1.19 (1.1, 1.28)	<0.001
	cg12921795	OS	0.94 (0.89, 1.00)	0.053	0.99 (0.93, 1.04)	0.624	0.99 (0.93, 1.04)	0.621	0.94 (0.87, 1.02)	0.120	0.98 (0.91, 1.05)	0.557	0.98 (0.91, 1.05)	0.552
	cg19414598	OS	0.99 (0.94, 1.05)	0.723	1.01 (0.96, 1.07)	0.694	1.02 (0.96, 1.07)	0.604	0.92 (0.85, 0.99)	0.034	0.98 (0.9, 1.06)	0.565	0.99 (0.92, 1.08)	0.898
	cg25783173	OS	1.01 (0.96, 1.07)	0.654	1.03 (0.97, 1.09)	0.353	1.03 (0.97, 1.09)	0.358	0.92 (0.84, 1.02)	0.106	0.95 (0.87, 1.05)	0.331	0.95 (0.87, 1.05)	0.328
Xiang et al, 2020[17]	cg03017653	OS	1.06 (1.01, 1.12)	0.029	1.07 (1.01, 1.13)	0.032	1.06 (1, 1.13)	0.044	1.14 (1.06, 1.23)	<0.001	1.07 (0.99, 1.16)	0.08	1.04 (0.96, 1.13)	0.292
	cg03977782	OS	0.92 (0.87, 0.98)	0.008	0.93 (0.88, 0.99)	0.026	0.93 (0.87, 0.99)	0.022	0.92 (0.84, 0.99)	0.033	0.92 (0.84, 1)	0.042	0.91 (0.84, 0.99)	0.029
	cg05417950	OS	0.97 (0.91, 1.03)	0.289	1.01 (0.96, 1.08)	0.631	1.02 (0.96, 1.08)	0.614	0.92 (0.84, 0.99)	0.031	0.98 (0.91, 1.06)	0.594	0.98 (0.91, 1.06)	0.656
	cg06250108	OS	0.95 (0.89, 1.01)	0.105	0.99 (0.93, 1.05)	0.692	0.99 (0.93, 1.05)	0.68	0.93 (0.85, 1.02)	0.116	0.97 (0.89, 1.05)	0.469	0.97 (0.89, 1.05)	0.442
	cg09893305	OS	0.96 (0.91, 1.02)	0.18	1.01 (0.96, 1.08)	0.633	1.02 (0.96, 1.09)	0.467	0.87 (0.81, 0.94)	<0.001	0.95 (0.88, 1.03)	0.228	0.99 (0.91, 1.07)	0.744
	cg10414946	OS	1.00 (0.94, 1.05)	0.869	1.04 (0.98, 1.1)	0.166	1.04 (0.99, 1.11)	0.146	1.06 (0.98, 1.14)	0.150	1.04 (0.97, 1.13)	0.278	1.06 (0.98, 1.14)	0.168
	cg15170424	OS	0.95 (0.89, 1.01)	0.095	0.98 (0.92, 1.04)	0.535	0.98 (0.93, 1.05)	0.617	0.88 (0.80, 0.98)	0.016	0.97 (0.88, 1.08)	0.607	1.01 (0.91, 1.11)	0.844
	cg15639045	OS	0.99 (0.93, 1.05)	0.812	0.97 (0.91, 1.03)	0.304	0.97 (0.91, 1.03)	0.351	1.02 (0.95, 1.10)	0.574	0.97 (0.9, 1.04)	0.387	0.98 (0.91, 1.05)	0.619
	cg15786837	OS	1.04 (0.98, 1.10)	0.184	1.07 (1.01, 1.13)	0.018	1.08 (1.02, 1.15)	0.006	0.94 (0.86, 1.02)	0.151	1.02 (0.93, 1.11)	0.695	1.06 (0.98, 1.16)	0.165
	cg17329249	OS	0.98 (0.93, 1.04)	0.527	1 (0.93, 1.06)	0.89	1 (0.94, 1.06)	0.907	0.99 (0.92, 1.07)	0.772	1 (0.92, 1.08)	0.937	1 (0.92, 1.09)	0.98
	cg21212956	OS	0.99 (0.93, 1.05)	0.664	1 (0.94, 1.06)	0.949	1 (0.94, 1.06)	0.985	0.95 (0.88, 1.03)	0.210	0.95 (0.87, 1.03)	0.212	0.94 (0.87, 1.03)	0.178
	cg24206256	OS	0.99 (0.93, 1.05)	0.749	1 (0.94, 1.06)	0.975	1 (0.94, 1.06)	0.997	1.00 (0.92, 1.08)	0.963	1.02 (0.94, 1.1)	0.708	1.02 (0.94, 1.11)	0.634
Xin et al, 2021[23]	cg00117463	OS	1.03 (0.97, 1.09)	0.347	1.02 (0.96, 1.08)	0.471	1.03 (0.97, 1.09)	0.395	0.95 (0.88, 1.02)	0.175	0.95 (0.87, 1.02)	0.171	0.96 (0.89, 1.04)	0.357
	cg00688963	OS	1.03 (0.97, 1.08)	0.35	1 (0.94, 1.05)	0.871	1 (0.94, 1.06)	0.971	0.92 (0.85, 1.01)	0.073	0.95 (0.87, 1.04)	0.278	0.98 (0.89, 1.07)	0.584
	cg02333852	OS	1.02 (0.97, 1.08)	0.489	0.99 (0.94, 1.05)	0.834	1 (0.94, 1.06)	0.932	0.91 (0.83, 0.99)	0.032	0.95 (0.86, 1.04)	0.228	0.97 (0.88, 1.06)	0.491
	cg11444379	OS	1.03 (0.98, 1.09)	0.233	1.02 (0.96, 1.08)	0.577	1.02 (0.96, 1.08)	0.5	0.94 (0.87, 1.01)	0.100	0.99 (0.91, 1.07)	0.785	1.01 (0.93, 1.09)	0.89
	cg12181621	OS	1.02 (0.96, 1.08)	0.485	1.02 (0.96, 1.08)	0.599	1.02 (0.96, 1.08)	0.584	0.99 (0.92, 1.07)	0.842	0.98 (0.9, 1.06)	0.608	0.98 (0.91, 1.07)	0.687
	cg13442960	OS	0.99 (0.94, 1.05)	0.851	0.99 (0.92, 1.06)	0.743	0.99 (0.92, 1.06)	0.774	0.90 (0.83, 0.97)	0.006	0.97 (0.87, 1.07)	0.512	0.97 (0.88, 1.08)	0.59
	cg14026459	OS	1.03 (0.98, 1.09)	0.283	1.03 (0.96, 1.1)	0.383	1.03 (0.96, 1.1)	0.384	0.94 (0.87, 1.02)	0.122	0.99 (0.91, 1.09)	0.907	0.99 (0.91, 1.09)	0.88
	cg19838156	OS	0.98 (0.93, 1.04)	0.509	0.99 (0.93, 1.05)	0.667	0.99 (0.93, 1.05)	0.727	0.92 (0.85, 1.00)	0.044	0.97 (0.89, 1.05)	0.463	0.98 (0.9, 1.06)	0.627
	cg21200129	OS	1.01 (0.96, 1.07)	0.723	1.01 (0.93, 1.08)	0.881	1.01 (0.94, 1.08)	0.846	0.92 (0.85, 0.99)	0.028	1 (0.9, 1.11)	0.991	1.01 (0.91, 1.11)	0.916
	cg23849078	OS	0.97 (0.91, 1.02)	0.247	0.98 (0.92, 1.04)	0.43	0.98 (0.92, 1.04)	0.492	0.89 (0.82, 0.97)	0.007	0.95 (0.87, 1.03)	0.218	0.96 (0.88, 1.05)	0.39
	cg26592281	OS	0.99 (0.94, 1.05)	0.72	0.99 (0.94, 1.05)	0.849	1 (0.94, 1.06)	0.899	0.93 (0.85, 1.01)	0.067	0.97 (0.9, 1.06)	0.542	0.98 (0.9, 1.07)	0.654
	cg26796283	OS	0.99 (0.94, 1.05)	0.839	0.96 (0.91, 1.03)	0.27	0.96 (0.91, 1.03)	0.271	1.04 (0.96, 1.11)	0.339	0.97 (0.9, 1.06)	0.546	0.97 (0.9, 1.06)	0.53
Yang et al, 2017[10]	cg00584485	OS	1.02 (0.97, 1.08)	0.442	1.01 (0.96, 1.07)	0.634	1.01 (0.96, 1.07)	0.615	1.08 (1.00, 1.17)	0.042	1.06 (0.98, 1.14)	0.132	1.06 (0.99, 1.14)	0.104
	cg00854817	OS	0.99 (0.94, 1.05)	0.847	0.95 (0.9, 1.01)	0.114	0.95 (0.9, 1.01)	0.112	0.87 (0.81, 0.93)	<0.001	0.9 (0.84, 0.97)	0.007	0.9 (0.84, 0.97)	0.006
	cg02457680	OS	1.09 (1.03, 1.15)	0.005	1.03 (0.97, 1.09)	0.344	1.02 (0.97, 1.08)	0.386	1.00 (0.93, 1.08)	0.990	0.98 (0.92, 1.06)	0.651	0.97 (0.91, 1.04)	0.44

Study	CpG name	Endpoint in development study	OS						DFS					
			Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
			cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR(95%CI)	*p* value	cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR(95%CI)	*p* value
	cg03890037	OS	1.09 (1.03, 1.15)	0.004	1.02 (0.96, 1.09)	0.432	1.02 (0.96, 1.09)	0.447	0.97 (0.91, 1.05)	0.476	0.96 (0.89, 1.04)	0.353	0.96 (0.89, 1.04)	0.313
	cg04929703	OS	1.08 (1.02, 1.14)	0.009	1 (0.95, 1.06)	0.91	1 (0.94, 1.06)	0.986	0.97 (0.90, 1.05)	0.445	0.97 (0.9, 1.05)	0.429	0.96 (0.89, 1.03)	0.248
	cg05917460	OS	1.01 (0.96, 1.07)	0.707	1.02 (0.96, 1.09)	0.479	1.03 (0.97, 1.09)	0.392	0.93 (0.86, 1.00)	0.046	0.99 (0.91, 1.07)	0.802	1.01 (0.93, 1.09)	0.817
Yang et al, 2017[10]	cg07936950	OS	1.07 (1.01, 1.13)	0.016	1.06 (1, 1.13)	0.06	1.07 (1.01, 1.14)	0.032	0.99 (0.91, 1.06)	0.704	1.06 (0.97, 1.15)	0.186	1.09 (1.01, 1.18)	0.037
	cg08152546	OS	1.03 (0.98, 1.09)	0.258	1.01 (0.95, 1.06)	0.854	1 (0.95, 1.06)	0.887	0.95 (0.89, 1.03)	0.209	0.96 (0.9, 1.04)	0.31	0.96 (0.89, 1.03)	0.244
	cg08318726	OS	1.03 (0.98, 1.09)	0.25	0.98 (0.93, 1.04)	0.552	0.98 (0.93, 1.04)	0.552	0.90 (0.84, 0.97)	0.004	0.94 (0.87, 1.01)	0.083	0.94 (0.87, 1.01)	0.085
	cg08358166	OS	1.05 (0.99, 1.11)	0.108	1.01 (0.95, 1.07)	0.752	1.01 (0.95, 1.07)	0.784	0.94 (0.88, 1.01)	0.099	0.96 (0.9, 1.04)	0.317	0.96 (0.89, 1.03)	0.252
	cg09632907	OS	1.03 (0.98, 1.09)	0.255	1.03 (0.97, 1.09)	0.398	1.03 (0.97, 1.09)	0.362	0.92 (0.85, 0.99)	0.020	0.98 (0.91, 1.06)	0.689	0.99 (0.92, 1.07)	0.854
	cg10023272	OS	1.05 (1.00, 1.11)	0.069	1 (0.94, 1.06)	0.932	1 (0.94, 1.06)	0.904	0.93 (0.86, 1.00)	0.046	0.96 (0.89, 1.03)	0.257	0.95 (0.88, 1.03)	0.199
	cg12395205	OS	1.02 (0.97, 1.08)	0.407	1 (0.94, 1.06)	0.953	1 (0.94, 1.06)	0.95	0.91 (0.85, 0.98)	0.013	0.97 (0.9, 1.04)	0.39	0.97 (0.9, 1.04)	0.36
	cg12630714	OS	0.99 (0.93, 1.04)	0.634	1.02 (0.96, 1.08)	0.575	1.02 (0.96, 1.08)	0.479	0.89 (0.83, 0.96)	0.003	0.98 (0.91, 1.06)	0.652	1 (0.93, 1.09)	0.931
	cg13066016	OS	1.07 (1.01, 1.13)	0.02	1.05 (0.99, 1.12)	0.081	1.05 (0.99, 1.12)	0.075	0.97 (0.90, 1.05)	0.500	1.05 (0.97, 1.13)	0.259	1.05 (0.97, 1.14)	0.206
	cg13596833	OS	1.03 (0.98, 1.09)	0.279	1 (0.94, 1.05)	0.886	1 (0.94, 1.06)	0.899	0.93 (0.87, 1.01)	0.071	0.97 (0.9, 1.05)	0.512	0.98 (0.91, 1.05)	0.555
	cg14036143	OS	1.01 (0.96, 1.07)	0.606	1.02 (0.97, 1.08)	0.446	1.02 (0.97, 1.08)	0.431	0.88 (0.82, 0.95)	0.001	0.95 (0.88, 1.03)	0.204	0.96 (0.89, 1.03)	0.252
	cg15105326	OS	1.00 (0.94, 1.05)	0.898	0.95 (0.9, 1.01)	0.092	0.95 (0.9, 1)	0.072	0.91 (0.84, 0.97)	0.008	0.91 (0.85, 0.98)	0.015	0.9 (0.84, 0.97)	0.005
	cg15916004	OS	1.01 (0.95, 1.06)	0.793	0.97 (0.92, 1.03)	0.341	0.97 (0.92, 1.03)	0.286	0.93 (0.86, 1.00)	0.037	0.93 (0.86, 1)	0.037	0.91 (0.85, 0.98)	0.015
	cg17495087	OS	1.02 (0.96, 1.07)	0.599	1.02 (0.96, 1.08)	0.583	1.02 (0.96, 1.08)	0.541	0.94 (0.88, 1.01)	0.113	1 (0.93, 1.08)	0.954	1.01 (0.93, 1.09)	0.854
	cg18131582	OS	0.96 (0.91, 1.02)	0.174	0.99 (0.94, 1.05)	0.71	0.99 (0.94, 1.05)	0.808	0.94 (0.87, 1.01)	0.082	1 (0.93, 1.08)	0.907	1.02 (0.95, 1.1)	0.569
	cg18443359	OS	1.07 (1.01, 1.13)	0.024	1.01 (0.96, 1.07)	0.639	1.01 (0.95, 1.07)	0.702	0.98 (0.91, 1.05)	0.531	0.96 (0.89, 1.03)	0.283	0.95 (0.88, 1.02)	0.153
	cg19624849	OS	1.00 (0.95, 1.06)	0.922	1.01 (0.96, 1.07)	0.637	1.02 (0.96, 1.08)	0.613	0.88 (0.82, 0.94)	<0.001	0.95 (0.88, 1.03)	0.197	0.96 (0.89, 1.03)	0.257
	cg20661138	OS	1.03 (0.97, 1.09)	0.347	1 (0.94, 1.06)	0.969	1 (0.94, 1.06)	0.981	0.93 (0.87, 1.00)	0.051	0.98 (0.91, 1.06)	0.598	0.98 (0.91, 1.05)	0.576
	cg21695661	OS	1.06 (1.00, 1.12)	0.06	1.03 (0.97, 1.09)	0.331	1.03 (0.97, 1.09)	0.323	0.93 (0.87, 1.01)	0.079	0.99 (0.91, 1.07)	0.738	0.99 (0.92, 1.07)	0.796
	cg22488797	OS	1.07 (1.01, 1.13)	0.026	1.03 (0.97, 1.09)	0.293	1.03 (0.97, 1.09)	0.342	1.00 (0.92, 1.07)	0.897	1.01 (0.93, 1.08)	0.876	0.99 (0.92, 1.06)	0.775
	cg24804195	OS	1.08 (1.02, 1.14)	0.007	1.01 (0.96, 1.07)	0.676	1.01 (0.96, 1.07)	0.674	0.98 (0.91, 1.06)	0.631	0.98 (0.91, 1.06)	0.663	0.98 (0.91, 1.06)	0.682
Yang et al, 2019[12]	cg02196655	OS	0.93 (0.88, 0.99)	0.015	0.98 (0.92, 1.03)	0.436	0.98 (0.92, 1.04)	0.444	0.88 (0.81, 0.95)	0.002	0.95 (0.88, 1.03)	0.215	0.95 (0.88, 1.03)	0.242
	cg03763616	OS	0.98 (0.92, 1.03)	0.393	1.01 (0.96, 1.07)	0.687	1.02 (0.96, 1.08)	0.586	0.89 (0.82, 0.96)	0.004	0.95 (0.88, 1.03)	0.225	0.97 (0.89, 1.06)	0.515
	cg03944089	OS	0.97 (0.92, 1.03)	0.345	1.02 (0.96, 1.08)	0.517	1.02 (0.96, 1.08)	0.477	0.95 (0.88, 1.03)	0.218	0.99 (0.92, 1.07)	0.877	1 (0.93, 1.08)	0.901
	cg06117855	OS	1.01 (0.96, 1.07)	0.725	1.04 (0.98, 1.1)	0.175	1.04 (0.98, 1.1)	0.161	0.94 (0.87, 1.02)	0.126	0.96 (0.88, 1.04)	0.279	0.97 (0.89, 1.04)	0.382
	cg07173760	OS	0.97 (0.91, 1.02)	0.213	1.02 (0.97, 1.08)	0.465	1.03 (0.97, 1.09)	0.381	0.93 (0.86, 1.00)	0.064	0.99 (0.92, 1.07)	0.878	1.02 (0.94, 1.1)	0.66
	cg07293947	OS	1.01 (0.95, 1.07)	0.704	1.04 (0.98, 1.1)	0.194	1.04 (0.99, 1.11)	0.147	1.03 (0.95, 1.11)	0.457	1.06 (0.99, 1.13)	0.109	1.07 (1.01, 1.15)	0.035
	cg07509155	OS	0.91 (0.86, 0.97)	0.002	0.99 (0.93, 1.04)	0.605	0.99 (0.93, 1.05)	0.708	0.87 (0.80, 0.94)	0.001	0.96 (0.89, 1.04)	0.344	0.99 (0.91, 1.07)	0.724
	cg09244244	OS	0.93 (0.87, 0.98)	0.008	0.98 (0.93, 1.04)	0.466	0.98 (0.93, 1.04)	0.525	0.87 (0.81, 0.95)	0.001	0.94 (0.87, 1.01)	0.113	0.95 (0.88, 1.03)	0.201
	cg10451565	OS	1.05 (1.00, 1.11)	0.065	1.04 (0.98, 1.1)	0.202	1.04 (0.98, 1.1)	0.186	1.06 (0.98, 1.14)	0.150	1.01 (0.94, 1.09)	0.765	1.02 (0.95, 1.1)	0.608
	cg12582008	OS	1.00 (0.95, 1.06)	0.954	1 (0.95, 1.06)	0.983	1.01 (0.95, 1.06)	0.86	0.97 (0.90, 1.05)	0.476	0.97 (0.9, 1.04)	0.36	0.99 (0.92, 1.07)	0.833
	cg13796218	OS	1.02 (0.97, 1.08)	0.451	1 (0.94, 1.06)	0.99	1 (0.95, 1.07)	0.874	0.94 (0.86, 1.02)	0.147	0.95 (0.88, 1.04)	0.256	0.98 (0.9, 1.07)	0.622
	cg20247048	OS	1.08 (1.02, 1.13)	0.005	1.04 (0.99, 1.1)	0.129	1.04 (0.99, 1.1)	0.141	1.16 (1.09, 1.24)	<0.001	1.06 (0.99, 1.14)	0.108	1.05 (0.98, 1.13)	0.133
	cg21481775	OS	0.93 (0.88, 0.99)	0.024	0.96 (0.91, 1.02)	0.205	0.96 (0.91, 1.02)	0.23	0.85 (0.78, 0.93)	<0.001	0.9 (0.83, 0.98)	0.02	0.91 (0.84, 0.99)	0.038
	cg23829949	OS	0.96 (0.90, 1.01)	0.113	1.01 (0.96, 1.07)	0.617	1.02 (0.97, 1.09)	0.435	0.96 (0.89, 1.03)	0.259	1.01 (0.93, 1.08)	0.877	1.05 (0.97, 1.13)	0.244
	cg23964386	OS	1.01 (0.95, 1.07)	0.781	1.03 (0.97, 1.09)	0.346	1.03 (0.97, 1.09)	0.299	0.95 (0.88, 1.03)	0.234	0.99 (0.92, 1.07)	0.799	1 (0.93, 1.08)	0.926
	cg24127989	OS	1.05 (0.99, 1.11)	0.084	1.02 (0.97, 1.08)	0.364	1.03 (0.97, 1.08)	0.341	1.07 (1.00, 1.15)	0.050	1.03 (0.96, 1.09)	0.456	1.03 (0.96, 1.1)	0.406
	cg24674703	OS	1.10 (1.04, 1.17)	<0.001	1.09 (1.03, 1.15)	0.004	1.09 (1.03, 1.15)	0.003	1.20 (1.11, 1.29)	<0.001	1.09 (1.01, 1.18)	0.023	1.1 (1.02, 1.18)	0.014

		Endpoint in	OS						DFS					
		development	Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
Study	**CpG name**	**study**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**
	cg24938727	OS	0.94 (0.89, 1.00)	0.043	0.97 (0.92, 1.03)	0.278	0.97 (0.92, 1.03)	0.311	0.95 (0.88, 1.03)	0.197	0.98 (0.9, 1.06)	0.564	0.99 (0.91, 1.07)	0.763
Yang et al, 2020[18]	cg00817367	OS	1.04 (0.99, 1.11)	0.131	0.99 (0.93, 1.05)	0.715	0.99 (0.93, 1.05)	0.677	0.95 (0.88, 1.02)	0.173	0.94 (0.87, 1.02)	0.127	0.94 (0.87, 1.01)	0.085
	cg02037307	OS	1.06 (1.00, 1.13)	0.04	1.01 (0.95, 1.07)	0.821	1 (0.95, 1.06)	0.904	1.02 (0.95, 1.10)	0.577	1.02 (0.94, 1.1)	0.694	1 (0.93, 1.08)	0.969
Yang et al, 2020[18]	cg02245020	OS	0.99 (0.93, 1.04)	0.631	0.95 (0.9, 1.01)	0.091	0.95 (0.9, 1)	0.069	0.94 (0.87, 1.01)	0.070	0.91 (0.85, 0.99)	0.019	0.9 (0.83, 0.97)	0.005
	cg03403065	OS	1.05 (0.99, 1.11)	0.113	0.98 (0.93, 1.04)	0.505	0.98 (0.92, 1.03)	0.411	0.97 (0.90, 1.05)	0.450	0.98 (0.91, 1.05)	0.557	0.96 (0.89, 1.03)	0.25
	cg04992638	OS	1.07 (1.01, 1.13)	0.023	1.05 (1, 1.12)	0.068	1.05 (1, 1.12)	0.073	1.03 (0.96, 1.11)	0.443	1.03 (0.95, 1.11)	0.463	1.02 (0.95, 1.1)	0.549
	cg06176750	OS	0.99 (0.93, 1.04)	0.618	1.03 (0.97, 1.09)	0.303	1.03 (0.98, 1.09)	0.258	1.00 (0.93, 1.08)	0.952	1.02 (0.94, 1.09)	0.695	1.03 (0.96, 1.11)	0.453
	cg06218079	OS	0.87 (0.82, 0.92)	<0.001	0.99 (0.93, 1.05)	0.633	0.99 (0.93, 1.05)	0.692	0.82 (0.76, 0.89)	<0.001	0.97 (0.9, 1.05)	0.455	0.98 (0.91, 1.07)	0.695
	cg06531379	OS	1.03 (0.97, 1.09)	0.351	1 (0.95, 1.06)	0.988	1 (0.94, 1.05)	0.867	1.01 (0.94, 1.09)	0.825	0.98 (0.91, 1.06)	0.581	0.95 (0.88, 1.03)	0.217
	cg06952671	OS	1.09 (1.03, 1.16)	0.003	1.06 (1, 1.13)	0.036	1.06 (1, 1.13)	0.044	1.04 (0.96, 1.12)	0.352	1.05 (0.97, 1.13)	0.246	1.03 (0.95, 1.11)	0.437
	cg07162000	OS	0.95 (0.90, 1.00)	0.067	1.01 (0.95, 1.06)	0.85	1 (0.95, 1.06)	0.876	0.92 (0.85, 0.99)	0.037	1 (0.93, 1.08)	0.989	1 (0.92, 1.08)	0.951
	cg13294849	OS	1.04 (0.99, 1.10)	0.151	1 (0.94, 1.06)	0.967	1 (0.94, 1.06)	0.959	0.95 (0.88, 1.02)	0.127	0.97 (0.9, 1.05)	0.484	0.97 (0.9, 1.05)	0.459
	cg14175690	OS	1.16 (1.09, 1.23)	<0.001	1.08 (1.01, 1.15)	0.016	1.08 (1.01, 1.14)	0.019	1.07 (0.99, 1.16)	0.088	1.03 (0.95, 1.11)	0.461	1.02 (0.95, 1.11)	0.58
	cg14817541	OS	1.07 (1.01, 1.13)	0.026	1.02 (0.97, 1.08)	0.432	1.02 (0.97, 1.08)	0.447	0.98 (0.91, 1.06)	0.626	1.01 (0.93, 1.08)	0.876	1 (0.93, 1.08)	0.953
	cg14861089	OS	1.07 (1.01, 1.14)	0.018	1.03 (0.97, 1.09)	0.357	1.03 (0.97, 1.09)	0.38	0.97 (0.90, 1.04)	0.379	0.95 (0.89, 1.03)	0.213	0.95 (0.88, 1.02)	0.142
	cg15848890	OS	0.97 (0.91, 1.02)	0.222	1 (0.95, 1.06)	0.956	1 (0.95, 1.06)	0.898	1.02 (0.95, 1.10)	0.547	1.04 (0.96, 1.12)	0.339	1.05 (0.97, 1.13)	0.205
	cg16863522	OS	1.01 (0.96, 1.07)	0.693	1.02 (0.96, 1.08)	0.546	1.02 (0.96, 1.08)	0.525	1.03 (0.95, 1.10)	0.491	1.01 (0.94, 1.09)	0.822	1.02 (0.94, 1.09)	0.679
	cg17300544	OS	1.01 (0.96, 1.07)	0.673	1 (0.95, 1.06)	0.973	1 (0.94, 1.06)	0.906	1.00 (0.92, 1.07)	0.908	0.98 (0.91, 1.06)	0.6	0.96 (0.89, 1.04)	0.29
	cg19114576	OS	0.97 (0.91, 1.02)	0.227	0.99 (0.93, 1.04)	0.609	0.99 (0.93, 1.06)	0.833	0.96 (0.89, 1.04)	0.301	1.01 (0.93, 1.09)	0.793	1.07 (0.98, 1.16)	0.117
	cg27361134	OS	1.00 (0.95, 1.06)	0.911	1 (0.94, 1.06)	0.924	1 (0.94, 1.06)	0.92	0.94 (0.87, 1.01)	0.079	1 (0.93, 1.08)	0.999	1 (0.93, 1.08)	0.981
Yin et al, 2020[19]	cg01102158	OS	0.94 (0.88, 1.00)	0.059	0.97 (0.91, 1.03)	0.281	0.97 (0.91, 1.03)	0.311	0.92 (0.84, 1.01)	0.098	0.97 (0.88, 1.06)	0.486	0.98 (0.89, 1.08)	0.672
	cg02009256	OS	0.96 (0.90, 1.02)	0.21	0.97 (0.91, 1.03)	0.329	0.97 (0.91, 1.03)	0.361	0.86 (0.77, 0.96)	0.006	0.92 (0.82, 1.02)	0.103	0.93 (0.84, 1.03)	0.183
	cg02654360	OS	0.95 (0.90, 1.01)	0.105	0.95 (0.89, 1)	0.069	0.95 (0.89, 1.01)	0.08	0.87 (0.80, 0.95)	0.002	0.89 (0.82, 0.97)	0.008	0.9 (0.82, 0.98)	0.019
	cg02760766	OS	1.05 (1.00, 1.11)	0.04	1.05 (1, 1.1)	0.069	1.05 (1, 1.1)	0.075	1.08 (1.02, 1.14)	0.010	1.04 (0.98, 1.11)	0.154	1.04 (0.98, 1.11)	0.183
	cg04096096	OS	0.97 (0.92, 1.03)	0.323	0.96 (0.91, 1.02)	0.227	0.96 (0.91, 1.02)	0.216	0.92 (0.85, 1.00)	0.052	0.93 (0.86, 1.01)	0.107	0.93 (0.86, 1.01)	0.098
	cg04353251	OS	1.01 (0.96, 1.07)	0.618	1.02 (0.97, 1.08)	0.404	1.03 (0.97, 1.09)	0.335	0.98 (0.90, 1.06)	0.562	1.02 (0.94, 1.1)	0.672	1.03 (0.96, 1.12)	0.406
	cg06671690	OS	0.97 (0.92, 1.03)	0.339	0.99 (0.93, 1.05)	0.655	0.99 (0.93, 1.06)	0.826	0.89 (0.81, 0.98)	0.020	0.96 (0.87, 1.06)	0.47	1.01 (0.91, 1.12)	0.816
	cg06685724	OS	0.93 (0.88, 0.99)	0.025	0.96 (0.91, 1.02)	0.186	0.96 (0.91, 1.02)	0.198	0.91 (0.84, 0.99)	0.023	0.92 (0.84, 0.99)	0.035	0.92 (0.85, 1)	0.054
	cg11027354	OS	0.98 (0.92, 1.03)	0.418	0.98 (0.92, 1.04)	0.426	0.98 (0.92, 1.04)	0.435	0.92 (0.85, 1.00)	0.049	0.93 (0.86, 1.01)	0.076	0.93 (0.86, 1.01)	0.097
	cg12091396	OS	1.02 (0.97, 1.08)	0.394	1 (0.95, 1.06)	0.974	1 (0.95, 1.06)	0.886	0.93 (0.84, 1.02)	0.120	0.97 (0.89, 1.06)	0.512	0.99 (0.91, 1.09)	0.867
	cg13883256	OS	1.00 (0.95, 1.06)	0.978	1.04 (0.99, 1.1)	0.139	1.05 (0.99, 1.11)	0.086	0.96 (0.88, 1.05)	0.359	1.05 (0.96, 1.14)	0.274	1.1 (1.01, 1.19)	0.033
	cg15844835	OS	0.97 (0.91, 1.02)	0.245	0.97 (0.92, 1.03)	0.388	0.98 (0.92, 1.04)	0.443	0.90 (0.82, 0.98)	0.021	0.93 (0.84, 1.02)	0.112	0.94 (0.86, 1.04)	0.238
	cg18421529	OS	0.98 (0.93, 1.04)	0.538	1 (0.94, 1.06)	0.897	1 (0.94, 1.06)	0.939	0.92 (0.84, 1.01)	0.085	0.95 (0.86, 1.04)	0.234	0.96 (0.87, 1.05)	0.36
	cg19585103	OS	0.96 (0.91, 1.02)	0.214	0.96 (0.9, 1.02)	0.147	0.96 (0.9, 1.02)	0.148	0.95 (0.88, 1.03)	0.224	0.94 (0.87, 1.01)	0.102	0.94 (0.87, 1.02)	0.114
	cg20717205	OS	0.98 (0.92, 1.04)	0.536	1 (0.94, 1.06)	0.917	1 (0.94, 1.06)	0.891	0.88 (0.79, 0.97)	0.014	0.92 (0.83, 1.02)	0.127	0.92 (0.83, 1.02)	0.101
	cg22267597	OS	0.96 (0.91, 1.02)	0.213	0.95 (0.89, 1.01)	0.115	0.95 (0.9, 1.02)	0.14	0.89 (0.81, 0.97)	0.010	0.91 (0.83, 0.99)	0.033	0.92 (0.84, 1.01)	0.08
	cg22346124	OS	0.98 (0.92, 1.04)	0.497	0.99 (0.93, 1.05)	0.753	0.99 (0.93, 1.05)	0.816	0.95 (0.87, 1.03)	0.224	0.99 (0.91, 1.08)	0.793	1 (0.92, 1.09)	0.953
	cg23835677	OS	0.98 (0.92, 1.04)	0.493	0.96 (0.9, 1.01)	0.138	0.96 (0.9, 1.02)	0.152	0.92 (0.83, 1.01)	0.069	0.95 (0.87, 1.03)	0.211	0.96 (0.88, 1.04)	0.311
	cg25074185	OS	0.92 (0.87, 0.98)	0.008	0.93 (0.87, 0.99)	0.022	0.93 (0.87, 0.99)	0.021	0.89 (0.82, 0.96)	0.004	0.88 (0.81, 0.96)	0.004	0.88 (0.81, 0.96)	0.004
	cg26151087	OS	1.00 (0.94, 1.05)	0.903	0.99 (0.94, 1.05)	0.715	0.99 (0.94, 1.05)	0.723	0.94 (0.87, 1.02)	0.148	0.95 (0.88, 1.03)	0.237	0.95 (0.88, 1.03)	0.238
	cg27525037	OS	0.89 (0.84, 0.94)	<0.001	0.91 (0.85, 0.96)	0.001	0.91 (0.85, 0.96)	0.001	0.84 (0.77, 0.91)	<0.001	0.87 (0.8, 0.95)	0.002	0.87 (0.8, 0.95)	0.002

		Endpoint in development	OS						DFS					
			Unadjusted model		Model 1[1]		Model 2[2]		Unadjusted model		Model 1[1]		Model 2[2]	
Study	**CpG name**	**study**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	**p value**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**
	cg27624313	OS	1.05 (0.99, 1.10)	0.117	1.01 (0.96, 1.07)	0.624	1.01 (0.96, 1.07)	0.629	1.04 (0.97, 1.12)	0.271	0.99 (0.92, 1.06)	0.829	0.99 (0.92, 1.06)	0.822

Cells painted with green represent having a p value ≤ 0,05, and those painted with yellow represent having a *p* value above 0.05 but below 0.1. [1] Model1 refers to multivariable Cox regression analyses with adjustment of age, sex, TNM stage, treatment, and cancer location. [2] Model2 refers to multivariable Cox regression analyses with adjustment of age, sex, TNM stage, treatment, cancer location, and MSI.

Supplementary Table 6: Equations of prognostic models, their distributions in the validation cohort, and their performance in the original development study

Study	Outcome	Equation to calculate the prognostic score	PI Distribution Median (IQR)	Performance in the development study		
				Apparent performance	Internal Performance	External performance
Chen et al, 2021[20]	OS	Risk score= 1.87*cg11621464 + 1.11*cg13565656 + (-1.74*cg18976437) + (2.40*cg20505223) + (-1.97*cg20528583)	0.2 (-1.8, 2.0)	High-risk group vs low-risk group; cHR (95%CI): 3.18 (1.82–5.56) aHR (95%CI): 6.17 (2.37-16.0) AUC = 0.78	cHR (95%CI): 1.75 (1.03–4.17) aHR (95%CI): 11.35 (0.98-130.98) AUC = 0.73	NP
Gong et al, 2020[13]	OS	Risk score = 0.09*cg14660573 + −0.04*cg 09353563 + 2.06*cg00110724	0.4 (-0.5, 1.1)	log-rank test: p = 0.003, AUC (all sample) = 0.67, AUC (age<73) = 0.59, AUC (age>73) = 0.85, AUC (female) = 0.80, AUC (male) = 0.68	log-rank test: p = 0.03	NP
Gündert et al, 2019[3]	OS and DSS	Risk score = (0.18*cg23750514) + (0.15*cg01131395) + (0.26*cg12510999) + (0.19*cg18195165) + (0.3*cg05646575) + (0.24*cg11056055) + (0.21*cg10758824) + (0.31*cg16336556) + (0.22*cg19184885) + (0.12*cg19340296) + (0.22*cg22522598) + (0.29*cg17431888) + (0.15*cg18736676) + (0.23*cg08804626) + (0.19*cg08617020) + (0.31*cg14270346) + (0.07*cg16399624) + (0.22*cg14983135) + (0.24*cg00832644)	0.3 (-1.6, 1.9)	Change from the lower to the upper quartile; aHR (95%CI), OS: 0.51 (0.41-0.63), DSS: 0.50 (0.38-0.67)	NP	aHR (95%CI), OS: 0.61 (0.45-0.82), DSS: 0.55 (0.38-0.79)
Huang et al, 2021[21]	OS	Risk sore = (0.754*cg21614638) + (1.230*cg21770617) + (0.701*cg12751565	0.0 (-1.3, 1.2)	aHR (95%CI): 1.71 (1.06-2.75) AUC, 1-year: 0.61, 3-year: 0.65, 5-year: 0.64	NP	aHR (95%CI): 1.69 (1.10-2.58) AUC, 3-year: 0.63, 5-year: 0.65, 8-year: 0.63
Huang et al, 2021[21]	DFS	Risk sore = (0.573*cg21614638) + (0.888*cg21770617) + (0.477*cg12751565)	0.0 (-0.9, 0.9)	aHR (95%CI): 1.55 (1.08-2.25) AUC, 1-year: 0.61, 3-year: 0.58, 5-year: 0.65	NP	aHR (95%CI): 1.68 (1.10-2.56) AUC, 3-year: 0.61, 5-year: 0.62, 8-year: 0.61
Li et al, 2021[22]	OS	Risk score =(-2.1*cg01408654) + (-2.2*cg04035209) + (-3*cg10196720) + (-5*cg10379890) + (2.3*cg11097433) + (4.86*cg14675211) + (2.93*cg15428578) + (-4.7*cg19343464) + (2.7*cg21384402) + (3.7*cg27404023)	-0.4 (-4.2, 4.0)	Log-rank test: p<0.001 aHR (95%CI): 0.96 (1.71-2.89)	NP	NP
Wang X et al, 2020[14]	OS and PFS	Risk score = 0.919*cg03091331 + 0.963*cg06884352 + 0.703*cg07707546 + 0.721*cg08081805 + 0.587*cg21347353 + 0.528*cg25164589	-0.2 (-1.6, 1.5)	cHR (95%CI), OS: 4.13 (2.10 - 8.01), PFS: 1.99 (1.18-3.34) AUC (95% CI), 3-year: 0.68 (0.59=0.78), 5-year: 0.70 (0.60-0.81)	cHR (95%CI), OS: 2.80 (1.17 - 6.68), PFS: 2.31 (1.08-4.97)	NP
Wang Y et al, 2020[16]	OS	Risk score = (38.52*cg00177496) – (4.13*cg01963906) + (2.574*cg05165940) – (79.32*cg12921795) + (2.31*cg19414598) + (6.061*cg25783173)	11.2 (-33.6, 44.6)	Log-rank test: p<0.001 AUC: 0.83	Log-rank test: p<0.001 AUC: 0.79	NP
Xiang et al, 2020[17]	OS	Risk score = (3.02*cg03017653) + (22.84*cg03977782) + (3.00*cg05417950) + (36.54*cg06250108) + (2.18*cg09893305) + (3.12*cg10414946) + (3.06*cg15170424) + (5.77*cg15639045) + (-9.51*cg15786837) + (22.02*cg 17329249) + (8.12*cg21212956) + (−23.31*cg24206256)	-10.7 (-34.3, 21.7)	cHR (95%CI): 2.72 (2.10-3.52) aHR (95%CI): 2.87 (2.15-3.82) Log-rank test: p<0.001 AUC: 0.87	NP	Log-rank test: p<0.001 AUC: 0.68
Yang et al, 2019[18]	OS	Risk Score=0.12*cg02196655 +1.35*cg03763616+0.73*cg03944089+0.73*cg0611 78 55+0.76*cg07173760-3.96*cg07293947-0.76*cg07509 155+0.58*cg09244244+0.4*cg10451565+0.28*cg1258 2008+1.99*cg13796218+3.6*cg20247048+1.34*cg214 81775+0.42*cg23829949-0.28*cg23964386+0.96*cg 24127989-0.45*cg24674703+0.84*cg24938727	-0.4 (-3.8, 3.4)	AUC = 0.81, log-rank test: p=0.02	Log-rank test: p=0.03	NP

Supplementary Table 7: Cox regression analyses for prognostic scores

Score (outcome)	Quartiles of prognostic score	OS						DFS					
		Unadjusted model		Model 1		Model 2		Unadjusted model		Model 1		Model 2	
		cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR (95%CI)	*p* value	cHR (95%CI)	*p* value	aHR(95%CI)	*p* value	aHR(95%CI)	*p* value
	Q1	1		1		1		1		1			
	Q2	1.05 (0.90, 1.23)	0.522	0.96 (0.82, 1.13)	0.65	0.97 (0.82, 1.13)	0.677	1.01 (0.81, 1.25)	0.936	0.93 (0.75, 1.16)	0.543	0.95 (0.76, 1.19)	0.67
Chen et al, 2021[20]	Q3	1.05 (0.90, 1.23)	0.508	0.99 (0.84, 1.16)	0.911	1 (0.85, 1.17)	0.955	1.03 (0.83, 1.28)	0.780	0.94 (0.76, 1.17)	0.578	0.96 (0.77, 1.19)	0.69
(OS)	Q4	1.12 (0.95, 1.30)	0.173	1 (0.85, 1.17)	0.982	1 (0.85, 1.18)	0.994	1.23 (1.00, 1.52)	0.048	0.99 (0.8, 1.23)	0.928	1 (0.81, 1.24)	0.986
	Q1	1		1		1		1		1			
	Q2	1.05 (0.90, 1.24)	0.520	1.01 (0.86, 1.19)	0.895	1.01 (0.86, 1.19)	0.881	1.11 (0.89, 1.38)	0.352	1.05 (0.84, 1.31)	0.661	1.07 (0.86, 1.33)	0.567
Gong et al, 2020[13]	Q3	1.20 (1.02, 1.40)	0.025	1.14 (0.98, 1.34)	0.098	1.14 (0.97, 1.34)	0.1	1.25 (1.01, 1.54)	0.040	1.18 (0.95, 1.46)	0.137	1.17 (0.94, 1.45)	0.159
(OS)	Q4	1.12 (0.95, 1.31)	0.176	1.18 (1, 1.38)	0.05	1.18 (1, 1.38)	0.048	1.19 (0.96, 1.47)	0.122	1.32 (1.06, 1.65)	0.012	1.33 (1.07, 1.66)	0.011
	Q1	1		1		1		1		1			
Gündert et al,	Q2	0.79 (0.67, 0.94)	0.008	0.73 (0.61, 0.87)	<0.001	0.73 (0.61, 0.87)	<0.001	0.77 (0.63, 0.95)	0.014	0.72 (0.58, 0.89)	0.003	0.7 (0.57, 0.87)	0.001
2019[3] (OS and	Q3	0.67 (0.56, 0.81)	<0.001	0.83 (0.69, 0.99)	0.043	0.83 (0.69, 0.99)	0.04	0.55 (0.44, 0.70)	<0.001	0.81 (0.64, 1.03)	0.087	0.82 (0.64, 1.03)	0.092
DSS)	Q4	0.59 (0.49, 0.70)	<0.001	0.73 (0.6, 0.88)	0.001	0.72 (0.6, 0.87)	0.001	0.39 (0.30, 0.50)	<0.001	0.6 (0.46, 0.78)	<0.001	0.58 (0.44, 0.75)	<0.001
	Q1	1		1		1		1		1			
	Q2	1.03 (0.88, 1.22)	0.684	1.1 (0.93, 1.3)	0.255	1.1 (0.93, 1.3)	0.259	1.13 (0.89, 1.42)	0.320	1.18 (0.93, 1.49)	0.181	1.18 (0.93, 1.49)	0.178
Huang et al, 2021[21]	Q3	1.25 (1.06, 1.46)	0.007	1.13 (0.96, 1.33)	0.141	1.13 (0.96, 1.33)	0.141	1.51 (1.21, 1.88)	<0.001	1.16 (0.92, 1.45)	0.206	1.16 (0.92, 1.45)	0.202
(OS)	Q4	1.40 (1.20, 1.64)	<0.001	1.4 (1.19, 1.65)	<0.001	1.4 (1.19, 1.65)	<0.001	1.88 (1.51, 2.32)	<0.001	1.54 (1.24, 1.93)	<0.001	1.55 (1.24, 1.93)	<0.001
	Q1	1		1		1		1		1			
	Q2	1.05 (0.89, 1.24)	0.531	1.1 (0.93, 1.3)	0.25	1.1 (0.93, 1.3)	0.252	1.14 (0.90, 1.44)	0.285	1.15 (0.91, 1.46)	0.253	1.15 (0.91, 1.46)	0.25
Huang et al, 2021[21]	Q3	1.26 (1.07, 1.48)	0.004	1.16 (0.98, 1.36)	0.077	1.16 (0.98, 1.36)	0.076	1.52 (1.22, 1.90)	<0.001	1.17 (0.94, 1.47)	0.166	1.18 (0.94, 1.48)	0.158
(DFS)	Q4	1.39 (1.19, 1.63)	<0.001	1.38 (1.17, 1.62)	<0.001	1.37 (1.17, 1.62)	<0.001	1.89 (1.52, 2.34)	<0.001	1.51 (1.21, 1.88)	<0.001	1.5 (1.2, 1.88)	<0.001
	Q1	1		1		1		1		1			
	Q2	1.09 (0.93, 1.27)	0.296	1.15 (0.98, 1.35)	0.09	1.15 (0.98, 1.35)	0.082	0.96 (0.77, 1.19)	0.697	1.06 (0.84, 1.32)	0.635	1.07 (0.86, 1.34)	0.539
	Q3	1.12 (0.96, 1.32)	0.150	1.13 (0.96, 1.32)	0.146	1.13 (0.96, 1.32)	0.136	1.13 (0.91, 1.39)	0.278	1.14 (0.92, 1.41)	0.235	1.14 (0.92, 1.42)	0.221
Li et al, 2021[22] (OS)	Q4	1.13 (0.96, 1.32)	0.141	1.11 (0.94, 1.3)	0.213	1.11 (0.94, 1.3)	0.22	1.25 (1.01, 1.54)	0.036	1.15 (0.93, 1.42)	0.193	1.14 (0.92, 1.41)	0.224
	Q1	1		1		1		1		1			
Wang X et al,	Q2	0.98 (0.84, 1.15)	0.819	1.02 (0.87, 1.19)	0.832	1.02 (0.87, 1.19)	0.825	0.83 (0.68, 1.02)	0.076	0.92 (0.75, 1.13)	0.424	0.93 (0.75, 1.14)	0.479
2020[14] (OS and	Q3	0.98 (0.84, 1.15)	0.832	1.03 (0.88, 1.21)	0.718	1.04 (0.88, 1.22)	0.674	0.87 (0.71, 1.07)	0.188	1.02 (0.83, 1.25)	0.878	1.06 (0.86, 1.3)	0.61
PFS)	Q4	1.00 (0.85, 1.17)	0.969	1.03 (0.88, 1.22)	0.697	1.04 (0.88, 1.23)	0.621	0.73 (0.59, 0.91)	0.004	0.95 (0.76, 1.18)	0.62	0.99 (0.79, 1.23)	0.927
	Q1	1		1		1		1		1			
	Q2	1.01 (0.86, 1.19)	0.883	0.93 (0.79, 1.09)	0.358	0.93 (0.79, 1.09)	0.359	1.02 (0.83, 1.27)	0.825	0.94 (0.75, 1.17)	0.554	0.93 (0.74, 1.16)	0.499
Wang Y et al,	Q3	1.20 (1.03, 1.41)	0.022	1.14 (0.97, 1.34)	0.104	1.14 (0.97, 1.34)	0.101	1.19 (0.97, 1.48)	0.100	1.11 (0.89, 1.37)	0.351	1.11 (0.89, 1.37)	0.357
2020[16] (OS)	Q4	1.28 (1.09, 1.49)	0.002	1.18 (1.01, 1.39)	0.035	1.19 (1.01, 1.39)	0.033	1.25 (1.02, 1.55)	0.034	1.13 (0.91, 1.4)	0.267	1.13 (0.92, 1.4)	0.251
	Q1	1		1		1		1		1			
	Q2	0.99 (0.85, 1.15)	0.888	0.94 (0.81, 1.1)	0.443	0.94 (0.8, 1.1)	0.431	0.91 (0.75, 1.12)	0.384	0.83 (0.68, 1.02)	0.08	0.82 (0.66, 1.01)	0.057
Xiang et al, 2020[17]	Q3	0.89 (0.76, 1.04)	0.131	0.97 (0.83, 1.14)	0.735	0.97 (0.83, 1.14)	0.711	0.86 (0.70, 1.06)	0.160	0.91 (0.74, 1.12)	0.383	0.89 (0.72, 1.1)	0.295
(OS)	Q4	0.84 (0.72, 0.98)	0.029	0.86 (0.74, 1.01)	0.071	0.86 (0.73, 1.01)	0.063	0.73 (0.59, 0.91)	0.004	0.72 (0.58, 0.9)	0.004	0.71 (0.57, 0.88)	0.002
Yang et al, 2019[18]	Q1	1		1		1		1		1			
(OS)	Q2	0.94 (0.81, 1.11)	0.482	0.87 (0.74, 1.02)	0.085	0.87 (0.74, 1.02)	0.085	0.92 (0.74, 1.14)	0.446	0.8 (0.65, 1)	0.052	0.81 (0.65, 1)	0.055

Score (outcome)	Quartiles of prognostic score	OS						DFS					
		Unadjusted model		Model 1		Model 2		Unadjusted model		Model 1		Model 2	
		cHR (95%CI)	***p* value**	**aHR(95%CI)**	***p* value**	**aHR (95%CI)**	**p value**	**cHR (95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**	**aHR(95%CI)**	***p* value**
	Q3	1.09 (0.93, 1.27)	0.305	1.05 (0.9, 1.23)	0.544	1.05 (0.9, 1.23)	0.535	1.08 (0.87, 1.33)	0.483	0.98 (0.8, 1.21)	0.869	0.99 (0.8, 1.22)	0.934
	Q4	1.07 (0.92, 1.25)	0.396	1.03 (0.88, 1.21)	0.691	1.04 (0.88, 1.22)	0.657	1.02 (0.83, 1.26)	0.827	0.9 (0.73, 1.11)	0.334	0.92 (0.74, 1.14)	0.443

Supplementary Table 8: Time-dependent AUC for all scores

		OS		DFS	
	Times	Continuous score	Quartiles of score	Continuous score	Quartiles of score
Scores significant in multicox					
Gong et al, 2020[13]	1 year	0.57 (0.52, 0.62)	0.55 (0.51, 0.6)	0.57 (0.53, 0.61)	0.56 (0.52, 0.59)
	3 years	0.56 (0.53, 0.58)	0.55 (0.52, 0.58)	0.54 (0.51, 0.57)	0.53 (0.5, 0.56)
	5 years	0.54 (0.52, 0.57)	0.53 (0.51, 0.56)	0.54 (0.51, 0.57)	0.53 (0.5, 0.55)
	8 years	0.53 (0.51, 0.56)	0.53 (0.5, 0.55)	0.54 (0.51, 0.57)	0.53 (0.5, 0.56)
Gündert et al, 2019[3]	1 year	0.64 (0.59, 0.69)	0.62 (0.57, 0.67)	0.67 (0.63, 0.71)	0.65 (0.61, 0.68)
	3 years	0.63 (0.61, 0.66)	0.6 (0.57, 0.63)	0.64 (0.61, 0.67)	0.62 (0.6, 0.65)
	5 years	0.6 (0.58, 0.63)	0.58 (0.56, 0.61)	0.63 (0.6, 0.66)	0.62 (0.59, 0.65)
	8 years	0.59 (0.57, 0.62)	0.58 (0.55, 0.6)	0.62 (0.58, 0.65)	0.61 (0.57, 0.64)
Huang et al, 2021 (OS)[21]	1 year	0.57 (0.52, 0.62)	0.56 (0.52, 0.61)	0.6 (0.56, 0.64)	0.59 (0.55, 0.62)
	3 years	0.56 (0.53, 0.59)	0.55 (0.52, 0.58)	0.58 (0.55, 0.61)	0.57 (0.55, 0.6)
	5 years	0.56 (0.54, 0.59)	0.56 (0.54, 0.58)	0.59 (0.56, 0.62)	0.58 (0.56, 0.61)
	8 years	0.55 (0.52, 0.57)	0.54 (0.52, 0.57)	0.58 (0.55, 0.61)	0.58 (0.55, 0.61)
Huang et al, 2021 (DFS)[21]	1 year	0.57 (0.52, 0.62)	0.56 (0.52, 0.61)	0.6 (0.56, 0.64)	0.59 (0.55, 0.62)
	3 years	0.56 (0.53, 0.59)	0.55 (0.52, 0.58)	0.58 (0.55, 0.61)	0.57 (0.55, 0.6)
	5 years	0.56 (0.54, 0.59)	0.56 (0.53, 0.58)	0.59 (0.56, 0.61)	0.58 (0.55, 0.6)
	8 years	0.55 (0.52, 0.57)	0.54 (0.52, 0.57)	0.58 (0.55, 0.61)	0.58 (0.55, 0.61)
Wang Y et al, 2020[16]	1 year	0.59 (0.54, 0.64)	0.58 (0.53, 0.62)	0.57 (0.53, 0.61)	0.55 (0.51, 0.59)
	3 years	0.56 (0.54, 0.59)	0.56 (0.54, 0.59)	0.55 (0.52, 0.57)	0.54 (0.52, 0.57)
	5 years	0.55 (0.53, 0.58)	0.55 (0.53, 0.58)	0.54 (0.52, 0.57)	0.54 (0.52, 0.57)
	8 years	0.55 (0.53, 0.57)	0.55 (0.53, 0.57)	0.55 (0.52, 0.58)	0.54 (0.52, 0.57)
Scores not significant in multicox					
Chen et al, 2021[20]	1 year	0.53 (0.5, 0.55)	0.55 (0.5, 0.6)	0.53 (0.5, 0.55)	0.53 (0.49, 0.57)
	3 years	0.55 (0.5, 0.6)	0.54 (0.51, 0.57)	0.53 (0.49, 0.57)	0.53 (0.5, 0.56)
	5 years	0.54 (0.51, 0.57)	0.52 (0.5, 0.55)	0.53 (0.5, 0.56)	0.53 (0.5, 0.55)
	8 years	0.53 (0.5, 0.55)	0.52 (0.5, 0.54)	0.53 (0.5, 0.56)	0.51 (0.49, 0.54)
Li et al, 2021[22]	1 year	0.51 (0.49, 0.54)	0.51 (0.47, 0.56)	0.54 (0.51, 0.57)	0.52 (0.48, 0.56)
	3 years	0.52 (0.48, 0.57)	0.5 (0.47, 0.53)	0.53 (0.49, 0.57)	0.52 (0.49, 0.55)
	5 years	0.51 (0.48, 0.54)	0.5 (0.48, 0.53)	0.53 (0.5, 0.55)	0.54 (0.51, 0.56)
	8 years	0.51 (0.48, 0.53)	0.52 (0.5, 0.54)	0.54 (0.51, 0.56)	0.54 (0.51, 0.56)
Wang X et al, 2020[14]	1 year	0.51 (0.49, 0.54)	0.53 (0.49, 0.58)	0.54 (0.51, 0.57)	0.51 (0.47, 0.55)
	3 years	0.5 (0.45, 0.54)	0.5 (0.47, 0.53)	0.51 (0.47, 0.55)	0.53 (0.51, 0.56)
	5 years	0.51 (0.48, 0.54)	0.51 (0.48, 0.53)	0.53 (0.5, 0.56)	0.54 (0.51, 0.57)
	8 years	0.51 (0.49, 0.54)	0.52 (0.49, 0.54)	0.54 (0.52, 0.57)	0.53 (0.5, 0.56)
Xiang et al, 2020[17]	1 year	0.54 (0.51, 0.56)	0.56 (0.51, 0.61)	0.54 (0.51, 0.57)	0.54 (0.5, 0.58)
	3 years	0.55 (0.51, 0.6)	0.53 (0.5, 0.56)	0.54 (0.5, 0.58)	0.52 (0.5, 0.55)
	5 years	0.53 (0.5, 0.56)	0.53 (0.51, 0.55)	0.53 (0.5, 0.56)	0.53 (0.5, 0.55)
	8 years	0.53 (0.51, 0.56)	0.54 (0.51, 0.56)	0.53 (0.51, 0.56)	0.55 (0.52, 0.58)
Yang et al, 2019[18]	1 year	0.51 (0.48, 0.53)	0.51 (0.47, 0.56)	0.53 (0.5, 0.56)	0.54 (0.5, 0.57)

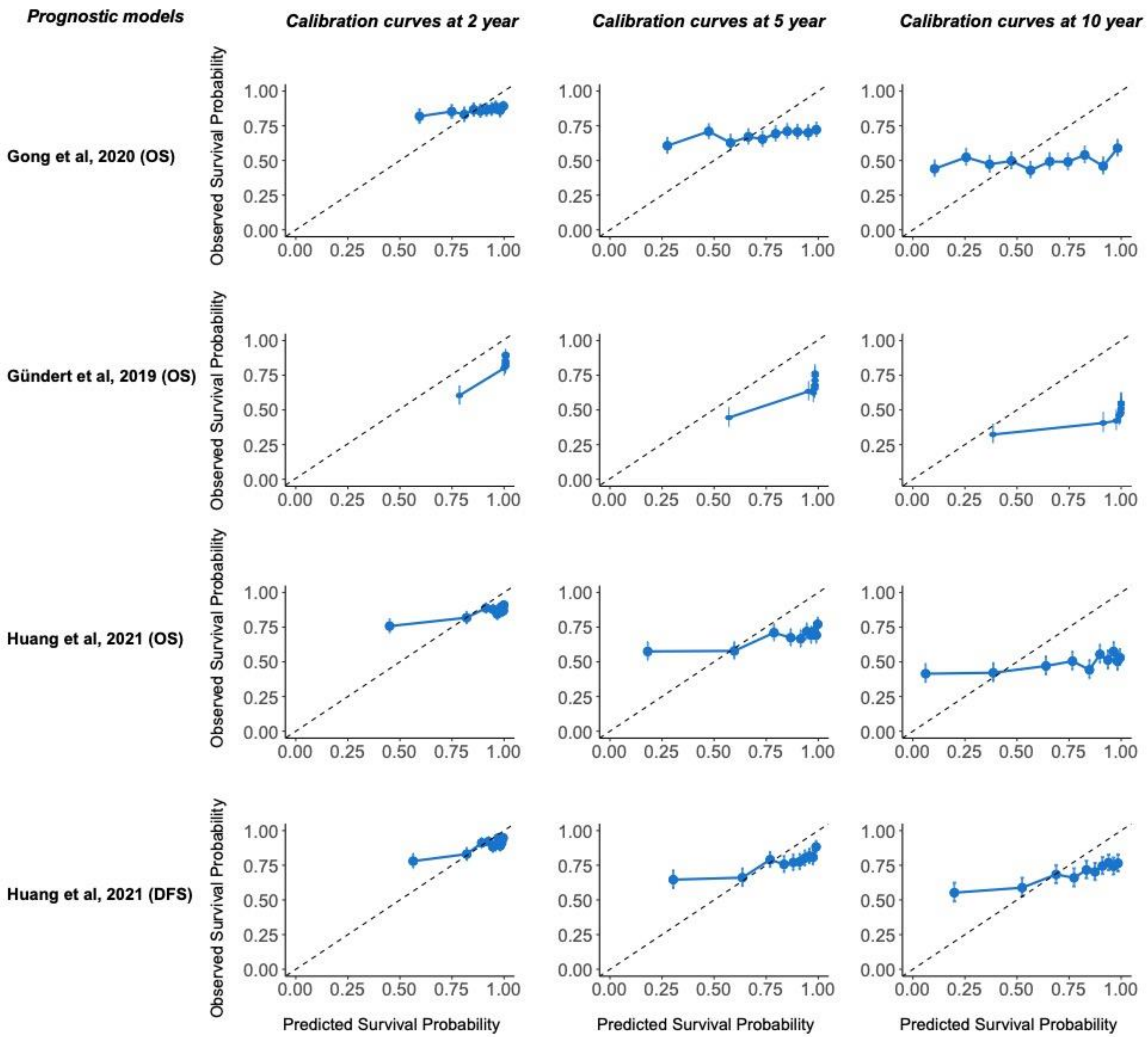
	OS		DFS	
Times	**Continuous score**	**Quartiles of score**	**Continuous score**	**Quartiles of score**
3 years	0.51 (0.46, 0.56)	0.51 (0.48, 0.54)	0.54 (0.5, 0.58)	0.53 (0.5, 0.56)
5 years	0.51 (0.48, 0.54)	0.51 (0.49, 0.54)	0.53 (0.51, 0.56)	0.53 (0.5, 0.55)
8 years	0.51 (0.49, 0.54)	0.51 (0.49, 0.53)	0.53 (0.51, 0.56)	0.53 (0.5, 0.56)

Supplementary Table 9: Stratified analyses for the AUC at mean follow-up time of prognostic scores

Score	Group	OS		DFS	
		Sample size	AUC (95%CI)	Sample Size	AUC (95%CI)
	Age (year)				
Gong et al, 2020	<70	1157	0.53 (0.49, 0.56)	1149	0.53 (0.49, 0.56)
	>=70	1153	0.55 (0.52, 0.58)	1141	0.54 (0.51, 0.58)
Gündert et al, 2019	<70	872	0.59 (0.55, 0.63)	866	0.63 (0.58, 0.67)
	>=70	866	0.59 (0.55, 0.63)	858	0.63 (0.58, 0.67)
Huang et al, 2021 (OS)	<70	1157	0.54 (0.51, 0.58)	1149	0.57 (0.53, 0.61)
	>=70	1153	0.56 (0.52, 0.59)	1141	0.6 (0.56, 0.63)
Huang et al, 2021 (DFS)	<70	1157	0.54 (0.51, 0.58)	1149	0.57 (0.53, 0.61)
	>=70	1153	0.56 (0.52, 0.59)	1141	0.6 (0.56, 0.63)
Wang Y et al, 2020	<70	1157	0.53 (0.5, 0.57)	1149	0.55 (0.51, 0.58)
	>=70	1153	0.54 (0.5, 0.57)	1141	0.53 (0.49, 0.57)
	Gender				
Gong et al, 2020	Female	964	0.53 (0.49, 0.57)	955	0.53 (0.49, 0.58)
	Male	1346	0.54 (0.51, 0.57)	1335	0.54 (0.5, 0.58)
Gündert et al, 2019	Female	699	0.61 (0.57, 0.66)	692	0.64 (0.59, 0.68)
	Male	1039	0.58 (0.54, 0.61)	1032	0.61 (0.58, 0.65)
Huang et al, 2021 (OS)	Female	964	0.55 (0.51, 0.58)	955	0.59 (0.54, 0.63)
	Male	1346	0.54 (0.51, 0.57)	1335	0.58 (0.54, 0.61)
Huang et al, 2021 (DFS)	Female	964	0.55 (0.51, 0.58)	955	0.59 (0.54, 0.63)
	Male	1346	0.54 (0.51, 0.57)	1335	0.58 (0.54, 0.61)
Wang Y et al, 2020	Female	964	0.52 (0.48, 0.56)	955	0.53 (0.48, 0.57)
	Male	1346	0.56 (0.53, 0.6)	1335	0.55 (0.51, 0.58)
	TNM stage				
Gong et al, 2020	I & II	1185	0.53 (0.49, 0.56)	1178	0.54 (0.49, 0.59)
	III	747	0.54 (0.5, 0.58)	737	0.54 (0.49, 0.59)
	IV	336	0.56 (0.5, 0.62)	333	0.56 (0.5, 0.62)
Gündert et al, 2019	I & II	850	0.54 (0.5, 0.58)	845	0.6 (0.54, 0.67)
	III	519	0.57 (0.52, 0.62)	513	0.58 (0.53, 0.64)
	IV	335	0.62 (0.56, 0.68)	332	0.61 (0.55, 0.67)
Huang et al, 2021 (OS)	I & II	1185	0.52 (0.49, 0.56)	1178	0.54 (0.48, 0.59)
	III	747	0.48 (0.44, 0.53)	737	0.53 (0.48, 0.57)
	IV	336	0.59 (0.53, 0.65)	333	0.59 (0.53, 0.65)
Huang et al, 2021 (DFS)	I & II	1185	0.52 (0.49, 0.56)	1178	0.54 (0.48, 0.59)
	III	747	0.48 (0.44, 0.53)	737	0.53 (0.48, 0.57)
	IV	336	0.59 (0.52, 0.65)	333	0.59 (0.52, 0.65)
Wang Y et al, 2020	I & II	1185	0.54 (0.5, 0.58)	1178	0.52 (0.46, 0.58)
	III	747	0.54 (0.5, 0.58)	737	0.53 (0.48, 0.58)

	IV	336	0.53 (0.47, 0.59)	333	0.53 (0.47, 0.59)
	Cancer location				
Gong et al, 2020	Distal colon	636	0.51 (0.46, 0.56)	632	0.51 (0.46, 0.56)
	Proximal colon	851	0.56 (0.53, 0.6)	844	0.58 (0.53, 0.62)
	Rectum	822	0.51 (0.47, 0.55)	813	0.52 (0.47, 0.56)
Gündert et al, 2019	Distal colon	476	0.6 (0.55, 0.65)	473	0.64 (0.59, 0.7)
	Proximal colon	617	0.61 (0.57, 0.66)	613	0.66 (0.61, 0.71)
	Rectum	822	0.57 (0.53, 0.61)	813	0.6 (0.56, 0.65)
Huang et al, 2021 (OS)	Distal colon	636	0.55 (0.5, 0.59)	632	0.56 (0.51, 0.61)
	Proximal colon	851	0.58 (0.54, 0.62)	844	0.61 (0.56, 0.66)
	Rectum	822	0.51 (0.47, 0.56)	813	0.56 (0.52, 0.61)
Huang et al, 2021 (DFS)	Distal colon	636	0.55 (0.5, 0.59)	632	0.56 (0.51, 0.61)
	Proximal colon	851	0.58 (0.54, 0.62)	844	0.61 (0.56, 0.66)
	Rectum	822	0.51 (0.47, 0.55)	813	0.56 (0.52, 0.61)
Wang Y et al, 2020	Distal colon	636	0.55 (0.51, 0.6)	632	0.56 (0.5, 0.61)
	Proximal colon	851	0.56 (0.52, 0.6)	844	0.54 (0.49, 0.58)
	Rectum	822	0.53 (0.49, 0.57)	813	0.53 (0.48, 0.57)
	Treatment				
Gong et al, 2020	No	1217	0.54 (0.51, 0.58)	1211	0.57 (0.52, 0.61)
	Yes	1087	0.53 (0.49, 0.56)	1076	0.52 (0.49, 0.56)
Gündert et al, 2019	No	885	0.57 (0.53, 0.61)	882	0.63 (0.58, 0.68)
	Yes	848	0.58 (0.54, 0.62)	839	0.58 (0.54, 0.62)
Huang et al, 2021 (OS)	No	1217	0.54 (0.5, 0.57)	1211	0.57 (0.52, 0.62)
	Yes	1087	0.53 (0.49, 0.56)	1076	0.54 (0.5, 0.57)
Huang et al, 2021 (DFS)	No	1217	0.53 (0.5, 0.57)	1211	0.57 (0.52, 0.62)
	Yes	1087	0.53 (0.49, 0.56)	1076	0.54 (0.5, 0.57)
Wang Y et al, 2020	No	1217	0.55 (0.52, 0.59)	1211	0.53 (0.48, 0.57)
	Yes	1087	0.54 (0.51, 0.58)	1076	0.54 (0.51, 0.58)
	MSI status				
Gong et al, 2020	MSI	223	0.54 (0.46, 0.62)	221	0.57 (0.46, 0.69)
	MSS	1769	0.54 (0.51, 0.56)	1751	0.54 (0.51, 0.57)
Gündert et al, 2019	MSI	153	0.57 (0.47, 0.66)	151	0.53 (0.38, 0.67)
	MSS	1303	0.6 (0.57, 0.63)	1291	0.65 (0.61, 0.68)
Huang et al, 2021 (OS)	MSI	223	0.54 (0.46, 0.62)	221	0.55 (0.42, 0.68)
	MSS	1769	0.54 (0.51, 0.56)	1751	0.57 (0.54, 0.6)
Huang et al, 2021 (DFS)	MSI	223	0.54 (0.46, 0.62)	221	0.55 (0.42, 0.68)
	MSS	1769	0.54 (0.51, 0.56)	1751	0.57 (0.54, 0.6)
Wang Y et al, 2020	MSI	223	0.6 (0.52, 0.68)	221	0.59 (0.46, 0.71)
	MSS	1769	0.54 (0.52, 0.57)	1751	0.54 (0.51, 0.57)
	BRAF mutation				
Gong et al, 2020	Yes	166	0.57 (0.48, 0.66)	163	0.63 (0.52, 0.73)
	No	1914	0.54 (0.51, 0.56)	1897	0.54 (0.51, 0.57)
Gündert et al, 2019	Yes	123	0.68 (0.59, 0.77)	120	0.72 (0.61, 0.82)

	No	1444	0.58 (0.55, 0.61)	1433	0.62 (0.58, 0.65)
Huang et al, 2021 (OS)	Yes	166	0.66 (0.58, 0.74)	163	0.74 (0.66, 0.83)
	No	1914	0.54 (0.51, 0.56)	1897	0.57 (0.54, 0.6)
Huang et al, 2021 (DFS)	Yes	166	0.66 (0.58, 0.74)	163	0.75 (0.66, 0.83)
	No	1914	0.54 (0.51, 0.56)	1897	0.57 (0.54, 0.6)
Wang Y et al, 2020	Yes	166	0.59 (0.51, 0.68)	163	0.54 (0.43, 0.65)
	No	1914	0.54 (0.51, 0.56)	1897	0.53 (0.5, 0.56)
	KRAS mutation				
Gong et al, 2020	Yes	693	0.55 (0.51, 0.59)	688	0.56 (0.51, 0.6)
	No	1388	0.53 (0.5, 0.56)	1374	0.54 (0.5, 0.57)
Gündert et al, 2019	Yes	693	0.53 (0.48, 0.57)	688	0.56 (0.51, 0.61)
	No	1388	0.56 (0.53, 0.59)	1374	0.59 (0.56, 0.63)
Huang et al, 2021 (OS)	Yes	693	0.52 (0.48, 0.57)	688	0.56 (0.51, 0.61)
	No	1388	0.56 (0.53, 0.59)	1374	0.59 (0.56, 0.63)
Huang et al, 2021 (DFS)	Yes	693	0.53 (0.49, 0.58)	688	0.54 (0.49, 0.58)
	No	1388	0.55 (0.52, 0.58)	1374	0.53 (0.5, 0.57)
Wang Y et al, 2020	Yes	532	0.6 (0.55, 0.65)	530	0.63 (0.58, 0.69)
	No	1062	0.58 (0.55, 0.62)	1050	0.63 (0.59, 0.67)
	CIMP phenotype				
Gong et al, 2020	high	388	0.59 (0.53, 0.65)	382	0.62 (0.55, 0.69)
	low	1811	0.52 (0.5, 0.55)	1797	0.53 (0.5, 0.56)
Gündert et al, 2019	high	388	0.57 (0.52, 0.63)	382	0.68 (0.61, 0.75)
	low	1811	0.54 (0.51, 0.57)	1797	0.56 (0.53, 0.59)
Huang et al, 2021 (OS)	high	388	0.58 (0.52, 0.63)	382	0.68 (0.61, 0.75)
	low	1811	0.54 (0.51, 0.57)	1797	0.56 (0.53, 0.59)
Huang et al, 2021 (DFS)	high	388	0.57 (0.51, 0.63)	382	0.56 (0.48, 0.63)
	low	1811	0.55 (0.52, 0.57)	1797	0.54 (0.51, 0.57)
Wang Y et al, 2020	high	295	0.58 (0.52, 0.65)	290	0.58 (0.5, 0.66)
	low	1346	0.59 (0.56, 0.62)	1337	0.64 (0.61, 0.68)



Supplementary Figure 3: Calibration curves for prognostic models

The baseline survival for each prognostic model was recalibrated. The calibration curves for the prognostic model developed by Wang Y et al, 2020 was unable to show, because the recalibrated baseline survival equaled to 1 at each time point.

Supplementary Table 10: *P* values for the likelihood ratio test comparing models based on clinical variables only and models based on clinical variables added with prognostic scores[1]

	OS					DFS				
Imputation dataset	Huang et al, 2021 (OS)	Huang et al, 2021 (DFS)	Wang Y et al, 2020	Gong et al, 2020	Gündert et al, 2019	Huang et al, 2021 (OS)	Huang et al, 2021 (DFS)	Wang Y et al, 2020	Gong et al, 2020	Gündert et al, 2019
#1	<0.001	<0.001	0.212	0.01	<0.001	<0.001	<0.001	0.201	0.003	<0.001
#2	<0.001	<0.001	0.188	0.008	<0.001	<0.001	<0.001	0.155	0.003	<0.001
#3	<0.001	<0.001	0.188	0.016	<0.001	<0.001	<0.001	0.174	0.005	<0.001
#4	<0.001	<0.001	0.161	0.008	<0.001	<0.001	<0.001	0.147	0.002	<0.001
#5	<0.001	<0.001	0.152	0.007	<0.001	<0.001	<0.001	0.142	0.001	<0.001
#6	<0.001	<0.001	0.142	0.01	<0.001	<0.001	<0.001	0.119	0.003	<0.001
#7	<0.001	<0.001	0.16	0.011	<0.001	<0.001	<0.001	0.142	0.004	<0.001
#8	<0.001	<0.001	0.175	0.011	<0.001	<0.001	<0.001	0.138	0.003	<0.001
#9	<0.001	<0.001	0.157	0.008	<0.001	<0.001	<0.001	0.145	0.002	<0.001
#10	<0.001	<0.001	0.117	0.013	<0.001	<0.001	<0.001	0.097	0.004	<0.001
#11	<0.001	<0.001	0.163	0.01	<0.001	<0.001	<0.001	0.154	0.003	<0.001
#12	<0.001	<0.001	0.112	0.011	<0.001	<0.001	<0.001	0.094	0.003	<0.001
#13	<0.001	<0.001	0.126	0.013	<0.001	<0.001	<0.001	0.110	0.005	<0.001
#14	<0.001	<0.001	0.123	0.017	<0.001	<0.001	<0.001	0.105	0.006	<0.001
#15	<0.001	<0.001	0.159	0.012	<0.001	<0.001	<0.001	0.127	0.005	<0.001
#16	<0.001	<0.001	0.124	0.014	<0.001	<0.001	<0.001	0.105	0.003	<0.001
#17	<0.001	<0.001	0.165	0.008	<0.001	<0.001	<0.001	0.152	0.002	<0.001
#18	<0.001	<0.001	0.121	0.01	<0.001	<0.001	<0.001	0.106	0.003	<0.001
#19	<0.001	<0.001	0.121	0.014	<0.001	<0.001	<0.001	0.108	0.006	<0.001
#20	<0.001	<0.001	0.162	0.008	<0.001	<0.001	<0.001	0.128	0.002	<0.001

[1] The two models compared are: 1) Outcome ~ age + sex + TNM stage, and 2) Outcome ~ age + sex + TNM stage + prognostic model.

Supplementary Table 11: Differences in AUC comparing models based on clinical variables only and that added with prognostic scores

		AUC difference[1]	
	Times	**OS**	**DFS**
Gong et al, 2020	1 year	0.002 (-0.001, 0.005)	0.004 (-0.001, 0.009)
	3 years	0.002 (-0.001, 0.004)	0.001 (-0.002, 0.005)
	5 years	0.001 (-0.001, 0.004)	0 (-0.003, 0.004)
	8 years	0.001 (-0.001, 0.004)	0.002 (-0.002, 0.006)
Gündert et al, 2019	1 year	-0.001 (-0.008, 0.007)	0.009 (0.001, 0.017)
	3 years	0.003 (-0.002, 0.008)	0.006 (0, 0.012)
	5 years	0 (-0.004, 0.005)	0.005 (-0.001, 0.01)
	8 years	0 (-0.005, 0.004)	0.003 (-0.003, 0.009)
Huang et al, 2021 (OS)	1 year	-0.002 (-0.007, 0.003)	0.003 (-0.003, 0.009)
	3 years	0.001 (-0.003, 0.004)	-0.001 (-0.005, 0.004)
	5 years	0.001 (-0.002, 0.005)	0 (-0.004, 0.005)
	8 years	-0.001 (-0.005, 0.002)	0 (-0.005, 0.005)
Huang et al, 2021 (DFS)	1 year	-0.002 (-0.007, 0.003)	0.003 (-0.003, 0.009)
	3 years	0.001 (-0.003, 0.004)	-0.001 (-0.005, 0.004)
	5 years	0.002 (-0.002, 0.005)	0 (-0.004, 0.005)
	8 years	-0.001 (-0.005, 0.002)	0 (-0.004, 0.005)
Wang Y et al, 2020	1 year	0.003 (0.001, 0.005)	0.003 (0.001, 0.006)
	3 years	0.002 (0.001, 0.003)	0.002 (0, 0.003)
	5 years	0 (-0.001, 0.001)	0 (-0.002, 0.002)
	8 years	0 (-0.001, 0.001)	0 (-0.002, 0.002)

[1]Compare the AUC score for the following two models: 1) Outcome ~ age + sex + TNM stage, and 2) Outcome ~ age + sex + TNM stage + continuous prognostic score; AUC difference = AUC (2) – AUC (1).

Supplementary Table 12: PROBAST risk of bias for all prognostic models to be validated

	Chen et al, 2021		Gong et al, 2020		Gündert et al, 2019		Huang et al, 2021		Li et al, 2021		Wang X et al, 2020		Wang Y et al, 2020		Xiang et al, 2020		Yang et al, 2019	
	Answer	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**
DOMAIN 1: Participants																		
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	Probably yes	Data were retrieved from the TCGA database	Probably yes	Data were retrieved from the TCGA database	Yes	Data were retrieved from the prospective database	Yes	Data were retrieved from TCGA and ArrayExpress databases	Yes	Data were retrieved from the TCGA database	Yes	Data were retrieved from the TCGA database	Yes	Data were retrieved from the TCGA database	Yes	Data were retrieved from the TCGA database	Yes	Data were retrieved from the TCGA database
1.2 Were all inclusions and exclusions of participants appropriate?	No information	182 stage II/III CRC samples with Illumina 450K methylation information were download, but more detailed inclusion/exclusion criteria were not provided.	Probably no	Only patients with complete clinical data were selected	Probably no	Patients who had received neoadjuvant therapy were excluded	Probably no	Only patients with both DNA methylation data and corresponding RNA!seq expression data were included	Probably no	Only patients with both methylation and transcriptome information were included	Probably no	Patients who had received neoadjuvant therapy were excluded	No information	Detailed inclusion/exclusion criteria were not provided.	No information	Detailed inclusion/exclusion criteria were not provided.	No information	Detailed inclusion/exclusion criteria were not provided.
Overall ROB Domain 1	***Unclear risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***Unclear risk of bias***		***Unclear risk of bias***		***Unclear risk of bias***	
DOMAIN 2: Predictors																		
2.1 Were predictors defined and assessed in a similar way for all participants?	Yes	Illumina 450 K Methylation Beadchip	Yes	Illumina 450 K Methylation Beadchip	Yes	Illumina 450 K Methylation Beadchip	Yes	DNA methylation data and RNA seq expression data were obtained with the Illumina Infinium Human Methylation 450 platform and the Illumina HiSeq 2000 RNA Sequencing platform.	No information	Methods used to measure methylation information were not reported, which could be Illumina 450 K Methylation Beadchip or Illumina 270 K Methylation Beadchip, or both.	Yes	Illumina 450 K Methylation Beadchip	Yes	Illumina 450 K Methylation Beadchip	Yes	Illumina 450 K Methylation Beadchip	Yes	Illumina 450 K Methylation Beadchip
2.2 Were predictor assessments made without knowledge of outcome data?	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Probably yes	Methylation information was measured before an outcome could occur in TCGA	Probably yes	Methylation information was measured before an outcome could occur in TCGA	Probably yes	Methylation information was measured before an outcome could occur in TCGA	Probably yes	Methylation information was measured before an outcome could occur in TCGA	Probably yes	Methylation information was measured before an outcome could occur in TCGA
2.3 Are all predictors available at the time the model is intended to be used?	Yes	Same as above	Yes	Same as above	Yes	Same as above	Yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above

	Chen et al, 2021		Gong et al, 2020		Gündert et al, 2019		Huang et al, 2021		Li et al, 2021		Wang X et al, 2020		Wang Y et al, 2020		Xiang et al, 2020		Yang et al, 2019	
	Answer	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**
Overall ROB Domain 2	***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***	
DOMAIN 3: Outcome																		
3.1 Was the outcome determined appropriately?	Probably yes	The outcome was overall survival, which is a well-established outcome	Probably yes	The outcome was overall survival, which is a well-established outcome	Probably yes	The main outcome was overall survival, which is a well-established outcome	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.	Probably yes	The outcomes of overall survival is a standardized outcome, and disease-free survival was clearly defined.
3.2 Was a pre-specified or standard outcome definition used?	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above	Probably yes	Same as above
3.3 Were predictors excluded from the outcome definition?	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur	Yes	Methylation and RNA information was measured before an outcome could occur
3.4 Was the outcome defined and determined in a similar way for all participants?	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA	Probably yes	Follow-up information was collected in a standardized manner in the TCGA
3.5 Was the outcome determined without knowledge of predictor information?	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur	Yes	Methylation information was measured before an outcome could occur
3.6 Was the time interval between predictor assessment and outcome determination appropriate?	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the outcome	Probably yes	The follow-up time (around 5 yearss) was long enough to observe the death outcome	Probably yes	The follow-up time (around 8 yearss) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome	Probably yes	The follow-up time (around 10 years) was long enough to observe the death outcome
Overall ROB Domain 3	***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***		***Low risk of bias***	
DOMAIN 4: Analysis																		

	Chen et al, 2021		Gong et al, 2020		Gündert et al, 2019		Huang et al, 2021		Li et al, 2021		Wang X et al, 2020		Wang Y et al, 2020		Xiang et al, 2020		Yang et al, 2019	
	Answer	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**
4.1 Were there a reasonable number of participants with the outcome?	No	The number of events per variable = 30 death/349 candidate CpGs = 0.085 is too small	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated	No	The number of death was unknown, but the number of events per variable is definitely very small in that genome-wide CpGs were investigated
4.2 Were continuous and categorical predictors handled appropriately?	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.	Probably yes	β values were kept as continuous variables. Though the relationship between the β values of CpGs and risk of death was unexamined, testing all CpGs is impossible, and their relationship is generally non-linear.
4.3 Were all enrolled participants included in the analysis?	Probably no	Patients with missing clinical variables were likely to be excluded.	No	Only patients with complete clinical data were selected in the analysis	Yes	All patients meeting the inclusion criteria were included in the analysis	Probably no	Patients with missing clinical variables were likely to be excluded.	Probably no	Patients with missing clinical variables were likely to be excluded.	Probably no	Patients with missing clinical variables were likely to be excluded.	Probably no	Patients with missing clinical variables were likely to be excluded.	Probably yes	Patients with missing values were also shown in Table 3	No information	No information was provided regarding whether patients with missing data/outliers were excluded
4.4 Were participants with missing data handled appropriately?	Probably no	Same as above	No	Same as above	Yes	Multiple imputation was used	Probably no	Same as above	Probably no	Same as above	Probably no	Same as above	Probably no	Same as above	No information	The 'impute' R package was used, but more details regarding handling of missing data was not reported	No information	No information was provided regarding how the missing data were handled.
4.5 Was selection of predictors based on univariable analysis avoided?	Probably yes	Selection of CpGs was partly based on gene function (immune genes)	No	Selection was entirely based on p-values in univariable and multivariable Cox analyses	Probably yes	Selection was also based on the Brier score for each predictor	Probably yes	Select CpGs located in the promoter region of genes significantly associated with survival	Probably yes	Select differently methylated CpGs associated with differently expressed genes comparing tumor and normal tissues	Probably yes	CpGs were also selected based on standard deviation and clustering methods	No	Selection was entirely based on p-values in univariable and multivariable Cox analyses	Yes	Selection was entirely based on p-values in univariable and multivariable Cox analyses	Probably no	selection was only based on differentially methylation CpGs comparing tumor and normal tissues and importance value obtained by random forest

	Chen et al, 2021		Gong et al, 2020		Gündert et al, 2019		Huang et al, 2021		Li et al, 2021		Wang X et al, 2020		Wang Y et al, 2020		Xiang et al, 2020		Yang et al, 2019	
	Answer	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**	**Answer**	**Rationale**
4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls) accounted for appropriately?	Probably yes	Cox regression analysis was used to handle censored data	Probably yes	Cox regression analysis was used to handle censored data	Yes	Cox models were used for time-to-event data, and p-values were adjusted via independent hypothesis weighting	Probably yes	Cox regression analysis was used to handle censored data	Probably yes	Cox regression analysis was used to handle censored data	Probably yes	Cox regression analysis was used to handle censored data	Probably yes	Cox regression analysis was used to handle censored data	Probably yes	Cox regression analysis was used to handle censored data	Probably no	Censored data were likely not to be accounted for when using random forest method
4.7 Were relevant model performance measures evaluated appropriately?	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated.	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated.	Probably no	Discrimination was measured by AUCs, and overall model performance was measured by Brier score. But calibration was not examined.	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated. The calibration was evaluated for another prognostic model consisting of CpG-based prognostic score and age, gender, TNM stage.	No	Only discrimination was assessed by K-M curves, whereas calibration was not evaluated.	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated. The calibration was evaluated for another prognostic model consisting of CpG-based prognostic score plus age and TNM stage.	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated.	No	Only discrimination was assessed by K-M curves and AUC, whereas calibration was not evaluated. The calibration was evaluated for another prognostic model consisting of CpG-based prognostic score plus age, TNM stage, and N stage.	No	Only discrimination was assessed by AUC, whereas calibration was not evaluated. The calibration was evaluated for another prognostic model consisting of CpG-based prognostic T stage, N stage, and lymph node metastasis
4.8 Were model overfitting and optimism in model performance accounted for?	No	Internal validation consists only of a single random split sample of participant data	No	Internal validation consists only of a single random split sample of participant data	Yes	10-fold internal cross-validation approach with three repetitions was performed	No	Internal validation consists only of a single random split sample of participant data	Probably yes	5-fold internal cross-validation approach with three repetitions was performed	Yes	The shrinkage technique (regularization) was used	No	Internal validation consists only of a single random split sample of participant data	Yes	The shrinkage technique (regularization) was used	Yes	Random forest with three-fold cross-validation was used to control overfitting
4.9 Do predictors and their assigned weights in the final model correspond to the results from multivariable analysis?	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis	Yes	Both predictors and regression coefficients in the reported final model correspond to the reported results of the multivariable regression analysis
Overall ROB Domain 4	***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***		***High risk of bias***	

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