



Clinicopathological and Prognostic Significance of PRMT5 in Cancers: A System Review and Meta-Analysis

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Abstract

Purpose: Since protein arginine methyltransferase 5 (PRMT5) is abnormally expressed in various tumors, in this study we aim to assess the association between PRMT5 and clinicopathological and prognostic features.

Methods: Electronic databases including PubMed, Web of Science, Scopus, ScienceDirect, and the Cochrane Library were searched until July 25, 2021. The critical appraisal of the eligible studies was performed using the Newcastle–Ottawa Quality Assessment Scale. Pooled hazard ratios (HR) and pooled odds ratios (OR) were calculated to assess the effect. Engauge Digitizer version 12.1, STATA version 15.1, and R version 4.0.5 were used to obtain and analysis the data.

Results: A total of 32 original studies covering 15,583 patients were included. In our data, it indicated that high level of PRMT5 was significantly correlated with advanced tumor stage (OR = 2.12, 95% CI: 1.22-3.70, $P = .008$; $I^2 = 80.7\%$) and positively correlated with poor overall survival (HR = 1.59, 95% CI: 1.46-1.73, $P < .001$; $I^2 = 50\%$) and progression-free survival (HR = 1.53, 95% CI: 1.24-1.88, $P < .001$; $I^2 = 0\%$). In addition, sub-group analysis showed that high level of PRMT5 was associated with poor overall survival for such 5 kinds of cancers as hepatocellular carcinoma, pancreatic cancer, breast cancer, gastric cancer, and lung cancer.

Conclusion: For the first time we found PRMT5 was pan-cancerous as a prognostic biomarker and high level of PRMT5 was associated with poor prognosis for certain cancers.

Keywords

PRMT5, cancers, prognosis, clinicopathology, meta-analysis

Background

As a major public health issue, malignant tumor has become the focus of attention. The latest global cancer data showed that cancer burden rose to 19.3 million new cases and 10.0 million cancer deaths in 2020.¹ Although various therapeutic procedures appeared to control the development of cancers, the survival rates remained dismal, which might be relevant to the lack of early diagnostic and efficient prognostic biomarkers. That's the reason why we need to develop novel molecular biomarkers for the prediction of the survival outcome for patients.

Protein arginine methyltransferases (PRMTs) are a family of enzymes that methylate the guanidino group of the arginine

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using S-adenosyl methionine (SAM) as a methyl donor, producing mono- or dimethylated arginine residues and S-adenosyl-L-homocysteine.² By altering the stability, localization, or activity of the substrate, PRMTs regulate a variety of intracellular functions that are essential for survival.³ In addition, PRMTs are involved in cancer development through oncogenic signal transduction, cancer stem cell maintenance, and epithelial-mesenchymal transition (EMT).⁴ PRMT5 belongs to the type II PRMT family which is responsible for the generation of monomethylated arginine and enantiomeric dimethylarginine.⁵ Studies have shown that PRMT5 could inhibit the transcription of tumor suppressors to provide essential conditions for tumor occurrence,^{6,7} such as p53, cell cycle related transcription factor E2F-1, tumor suppressor gene ST7, tumor metastasis suppressor gene NM23, apoptosis related protein CASP4, etc. Moreover, studies have shown that the abnormal expression of PRMT5 is closely related to the occurrence and development of a variety of diseases, and the higher expression of PRMT5 appears in such human malignancies as breast cancer, colon cancer, lung cancer, pancreatic cancer, chronic lymphocytic leukemia, and so on.⁸⁻¹⁰ Meanwhile, high level of PRMT5 is relevant to survival outcome in cancer patients. For example, based on 118 epithelial ovarian cancer tissues, 20 benign ovarian tumor and 12 normal ovary samples, PRMT5 was reported to be highly expressed in epithelial ovarian cancer, meanwhile the level of PRMT5 was correlated with the proliferation activity and the survival of ovarian cancer patients.¹¹ For hepatocellular carcinoma, the members of the high-PRMT5 group were more likely to have a worse prognosis comparing with those in the low PRMT5 group (5-year overall survival rates, 53 and 76%, respectively).¹² Vinet, M. reported high-PRMT5 expression was associated with lower probabilities of overall survival but had no influence on distant metastasis-free survival.¹³

However, so far no study has systematically evaluated the clinicopathological and prognostic value of PRMT5 in cancers. In this study, we conducted the systematic analysis to evaluate the clinicopathological and prognostic value of PRMT5 in different malignant tumors, and for the first time we found PRMT5 is pan-cancerous as a prognostic biomarker.

Materials and Methods

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria.¹⁴ The protocol of this systematic review was registered on the PROSPERO—International Prospective Register of Systematic Reviews (registration number: CRD42021268881).

Study Strategy

We totally searched 5 electronic databases including PubMed, Web of Science, Scopus, ScienceDirect, and the Cochrane Library. Two independent reviewers (LIANG ZZ and MA

SM) searched for literatures from January 1, 2000 to July 25, 2020, with search terms “Neoplasm”, “PRMT5,” and their entry words. Detailed search strategies were shown in [Supplementary Table S1](#). Additionally, the references of relevant literature and [Supplementary Materials](#) were also screened manually to identify missing relevant publications.

Select Strategy

All articles were screened according to the inclusion and exclusion criteria by 2 independent reviewers. The inclusion criteria were as follows: (1) original studies; (2) papers published in English and focused on human beings; (3) studies performed to investigate the relationship between PRMT5 and any types of survival outcomes, which included overall survival (OS, period from diagnosis to death due to any reason); progression/disease free survival (PFS/DFS, period from first treatment to identification of cancer progression or death); relapse/recurrence free survival (RFS, period between cure from cancer and identification of cancer progression/recurrence), metastasis-free survival (MFS/DMFS, period from diagnosis cancer to diagnosis a (distant) metastatic event); (4) the levels of PRMT5 were measured through any quantitative analysis, and were divided into 2 levels: high and low; and (5) pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) should be provided, or there should be sufficient data through which HR and 95% CI could be calculated.

The exclusive criteria were as follows: (1) studies without control groups; (2) studies using duplicated data; (3) studies unable to get full-text.

Data Extraction

Two reviewers (LIANG ZZ and MA SM) independently extracted information from each study. Information were shown in detail in [Table 1](#), (1) information of articles, which contains author name, year of publication and region of study; (2) information of patients, which contains age, sex proportion, clinicopathological features, time of follow-up; (3) information of PRMT5, which contain PRMT5 detection methods, number of patients with high/low PRMT5, cut-off; (4) information of survival data, which contain survival outcome indicators (OS, PFS, DFS, and MFS), HRs, and 95% CIs. The quality of the selected studies was independently evaluated by two reviewers using the Newcastle–Ottawa Scale (NOS; star system; range, 0–9 stars), which scored each study based on the methodological items.¹⁵ Studies with a NOS score of 7 or more were thought of methodological high-quality.¹⁶

Statistical Analysis

We used pooled OR and corresponding 95% CI to estimate the relation of PRMT5 and the clinicopathological features; and used pooled HR and corresponding 95% CI to estimate the relation of PRMT5 and the survival outcomes in cancers.

Table 1. Main characteristics of literatures included.

First author	Publication year	Country	Ethnicity	Cancer type	Year of patients collection	Patients age	Males/ female	Tumor stage I + II/III + IV / unknown	Lymphation metastasis Yes/no/ unknown	Differentiation well/moderate/poor/ unknown	Tumor size	Sample size	Follow-up time	Detection method	High/low expression sample size	Cut-off	Survival analysis indicators	HR	HRL	HRH
Xiangshang Bao ¹	2013	China	Asian	Epithelial ovarian cancer	2005.1-2008.12	24-86	0/118	38/80	22/49/47	30/73/15	NA	118	32 (3-81)	IHC	98/20	4	OS	1.66	0.6	4.57
Xiangshang Bao	2013	China	Asian	Epithelial ovarian cancer	2005.1-2008.12	24-86	0/118	38/80	22/49/47	30/73/15	NA	118	32 (3-81)	IHC	98/20	4	PFS	1.84	.67	5.09
Reem Ibrahim ⁹	2014	Japan	Asian	Lung adeno carcinoma	2005.6-2008.9	34-86	75/55	100/25/5	29/101	NA	<3.38 >3.92	126	NA	IHC	47/79	5 (Supplementary Material)	OS	1.1	.16	7.41
Baohai Zhang ⁴	2015	China	Asian	Colorectal cancer	2011-2012	24-90	47/43	56/34	NA	NA	<4.30 >4.60	90	NA	IHC	56/34	4	OS	1.99	.95	4.15
Baohai Zhang ³⁵	2015	China	Asian	Hepatocellular carcinoma	NA	38-72	48/6	43/11	NA	NA	<5.27 >5.27	54	NA	IHC	31/23	4	OS	2.411	1.094	5.313
Fengting Yan ³²	2015	USA	Caucasian	Glioblastoma	2003.2-2007.10	52-71	24/19	NA	NA	NA	NA	43	NA	IHC	15/28	3 (Supplementary Material)	OS	1.4	1.18	1.66
Mitsuro Kanda ³⁴	2016	Japan	Asian	Gastric cancer	2001-2010	<65.79 >65.100	137/42	69/110	27/152	71/108	<5.74 >5.105	179	NA	PCK array	90/89	Median expression	OS	3.9	1.59	10.2
Duohe Yang ³³	2016	China	Asian	Nasopharyngeal carcinoma	2018.12-2010.2	<50.57 >50.55	77/35	54/58	91/03	NA	NA	112	NA	Microarray	40/72	4	OS	6.39	3.06	13.32
Bhavna Kumar ³⁶	2017	USA	Caucasian	Oropharyngeal squamous cell carcinoma	2002-2009	NA	166/45	161/95	NA	NA	NA	209	NA	IHC	58/151	Nuclear positive	OS	1.73	1.13	2.66
Dai Shimizu ¹²	2017	Japan	Asian	Hepatocellular carcinoma	1998.1-2012.1	34-84	121/23	127/17	NA	35/109	<3.46 >3.98	144	NA	qRT-PCR	72/72	Median level	OS	1.91	1.1	3.38
Madhumitha Ranganay ²⁷	2017	USA	Caucasian	Breast cancer	METABRIC data	NA	NA	NA	NA	NA	NA	1714	NA	RNA-seq/microarray	192/1522	90% quantile	OS	2.14	1.81	2.53
Ying Wu ³¹	2017	China	Asian	Breast cancer	GEO database	NA	NA	NA	NA	NA	NA	1660	NA	RNA-seq/microarray	462/1198	Median expression	RFS (relapse free survival)	1.73	1.47	2.05
Ying Wu ³¹	2017	China	Asian	HER-2 positive breast cancer	GEO database	NA	NA	NA	NA	NA	NA	66	NA	RNA-seq/microarray	40/26	Median expression	OS	.39	.16	1
Ying Wu ³¹	2017	China	Asian	triple negative breast cancer	GEO database	NA	NA	NA	NA	NA	NA	132	NA	RNA-seq/microarray	63/69	Median expression	OS	2.53	1.15	5.56
Anamaria Gullig ²⁹	2017	USA	Caucasian	Multiple Myeloma	NA	NA	NA	NA	NA	NA	NA	320	NA	qRT-PCR	80/240	Top 25%	OS	1.69	.63	4.52
Anamaria Gullig ³¹	2017	USA	Caucasian	Multiple Myeloma	NA	NA	NA	NA	NA	NA	NA	320	NA	qRT-PCR	80/240	Top 25%	PFS	1.55	1.07	2.25
Xinyu Liu ³⁶	2018	China	Asian	Gastric cancer	2001.1-2010.12	<60.284 >60.318	400/ 202	288/314	56/546	43/207/352	NA	602	NA	IHC	433/169	3	OS	1.22	.98	1.51
Pengyu Jing ²³	2018	China	Asian	Lung cancer	2006-2013	>60.89	118/91	124/85	115/94	NA	NA	209	NA	IHC	88/121	NA	OS	1.53	1.09	2.16
Hai Jiang ²²	2018	China	Asian	Hepatocellular carcinoma	2005-2012	<52.74 >52.64	117/21	74/64	NA	38/101	<5.53 >5.85	138	NA	IHC	117/21	5	OS	1.893	1.113	3.219
Zhifei Lin ³⁵	2018	China	Asian	Hepatocellular carcinoma	1999-2006	26-78	175/20	154/41	NA	NA	NA	195	60 months (2-142)	IHC	106/89	3	OS	1.712	1.176	2.492
Mathilde Vinec ¹³	2019	France	Caucasian	Breast cancer	NA	NA	NA	NA	NA	NA	NA	153	NA	Microarray	76/77	Median expression	OS	1.61	.77	3.35
Mathilde Vinec ¹³	2019	France	Caucasian	Breast cancer	NA	NA	NA	NA	NA	NA	NA	145	NA	Microarray	73/72	Median expression	Distant metastasis-free survival (DMFS)	1.87	.79	4.01
Yi Qin ³⁹	2019	China	Asian	Pancreatic cancer	NA	<60.22 >60.33	32/23	NA	20/35	10/31/14	<4.34 >4.21	55	NA	IHC	37/18	2	OS	1.21	.56	2.62

(continued)

Table 1. (continued)

First author	Publication year	Country	Ethnicity	Cancer type	Year of patients collection	Patients age	Males/ female	Tumor stage I + II/III + IV /unknown	Lymphatic metastasis Yes/no/ unknown	Differentiation well-/moderate/poor/ unknown	Tumor size	Sample size	Follow-up time	Detection method	High/low expression sample size	Cut-off	Survival analysis indicators	HR statistic	HR	HRL	HRH
Yi Qin ³⁹	2019	China	Asian	Pancreatic cancer	NA	56-75	80/97	24/153	NA	NA	NA	177	NA	RNA-seq	89/88	Median expression	OS	SC	1.77	1.22	2.37
Yi Qin ³⁹	2019	China	Asian	Pancreatic cancer	NA	56-75	80/97	24/153	NA	NA	NA	177	NA	RNA-seq	89/88	Median expression	DFS	SC	1.62	1.11	2.36
Lu Ge ²⁰	2019	China	Asian	Pancreatic cancer	TCGA	NA	NA	NA	NA	NA	NA	82	NA	RNA-seq	50/32	NA	OS	SC	1.32	.81	2.51
Ann-Kathrin Schörmel ²⁸	2020	Germany	Caucasian	Chronic lymphocytic leukemia	ICGC CLLC project	NA	NA	NA	NA	NA	NA	92	NA	RNA-seq	46/46	Median expression	OS	SC	1.45	.54	3.87
Lei Tan ³⁸	2020	China	Asian	Bladder cancer	2002-2016	<65, 71-86, 61	108/24	53/78	48/84	113/19	<3.69 ≥3.63	132	NA	qRT-PCR	82/50	NA	OS	Rep	2.434	1.215	4.876
Lei Tan ³⁸	2020	China	Asian	Bladder cancer	TCGA	NA	NA	NA	NA	NA	NA	407	NA	RNA-seq	203/204	Median expression	OS	SC	1.45	1.11	1.9
Lei Tan ³⁸	2020	China	Asian	Bladder cancer	TCGA	NA	NA	NA	NA	NA	NA	407	NA	RNA-seq	203/204	Median expression	PFS	SC	1.5	1.16	1.94
Yu-Hang Li ³⁷	2020	China	Asian	Osteosarcoma	R2 Genomics Analysis and Visualization Platform	NA	NA	NA	NA	NA	NA	88	NA	RNA-seq	74/14	NA	OS	SC	.07	0	1.2
Yu-Hang Li ³⁷	2020	China	Asian	Osteosarcoma	R2 Genomics Analysis and Visualization Platform	NA	NA	NA	NA	NA	NA	88	NA	RNA-seq	78/10	NA	MFS (metastasis-free survival)	SC	.22	.01	4.39
Nan Wang ³⁰	2020	China	Asian	Laryngeal carcinoma	20101-2018.12	50, 42-50, 46	55/33	64/24	58/30	49/39	NA	88	NA	qPCR	44/44	Median expression	OS	Rep	2.112	1.213	3.821
Nan Wang ³⁰	2020	China	Asian	Laryngeal carcinoma	20101-2018.12	>50, 46-50, 46	55/33	64/24	58/30	49/39	NA	88	NA	qPCR	44/44	Median expression	DFS	SC	1.59	0.9	2.79
Xiao Han ⁸	2020	China	Asian	Breast cancer	2014.7-2016.3	≥51, 41-51, 39	NA	47/33	22/58	29/51	≥3.34 <3.46	80	NA	RT-PCR	45/35	the average expression of PRMT5 mRNA (1.83)	OS	SC	1.37	.65	2.92
Geo roy Walbrecc ²⁹	2020	Luxembourg	Caucasian	Melanoma	TCGA	NA	NA	NA	NA	NA	NA	335	NA	RNA-seq	166/169	NA	OS	SC	1.45	1.15	1.82
Zhaona Fan ¹⁹	2020	USA	Caucasian	Head and neck squamous cell carcinoma	2004-2018	<50, 31-50, 62	58/35	52/41	31/62	40/53	NA	93	NA	IHC	54/39	2	OS	SC	3.2	1.48	6.89
Zhaona Fan ¹⁹	2020	USA	Caucasian	Head and neck squamous cell carcinoma	TCGA	NA	NA	NA	NA	NA	NA	486	NA	RNA-seq	313/173	NA	OS	SC	1.72	1.01	2.92
Ming Liu ⁵	2020	China	Asian	Gastric cancer	NA	>60, 52-560, 38	63/28	15/75	69/21	NA	<5, 37-≥5, 53	90	NA	PCR	45/45	Median expression	OS	SC	1.13	.67	2.27
Wojciech Barczak ¹⁰	2020	UK	Caucasian	Pancreatic cancer	TCGA	NA	NA	NA	NA	NA	NA	166	NA	RNA-seq	83/83	Mean expression	OS	SC	1.6	1.07	2.38
Khaloud Bajbou ⁴⁰	2021	United Arab Emirates	Asian	Lung adeno carcinoma	caBIG, GEO, and TCGA	NA	NA	NA	NA	NA	NA	672	NA	RNA-seq	255/417	NA	OS	Rep	1.31	1.03	1.68
Khaloud Bajbou ⁴⁰	2021	United Arab Emirates	Asian	Lung squamous cell carcinoma	caBIG, GEO, and TCGA	NA	NA	NA	NA	NA	NA	524	NA	RNA-seq	168/356	NA	OS	Rep	1.29	1	1.66
Liu ⁴¹	2021	China	Asian	Lung adeno carcinoma	2008.2-2013.7	>60, 50-560, 52	56/46	71/31	43/59	NA	NA	102	4-83 months	IHC	52/50	3	OS	SC	1.78	1.23	2.38

(continued)

Table 1. (continued)

First author	Publication year	Country	Ethnicity	Cancer type	Year of patients collection	Patients age	Males/female	Tumor stage I + II/III + IV /unknown	Lymphatic metastasis Year/No/unknown	Differentiation well-moderate/poor/unknown	Tumor size	Sample size	Follow-up time	Detection method	Highlow expression sample size	Cut-off	Survival analysis indicators	HR statistic	HR	HRL	HRH
Liu Liu ¹	2021	China	Asian	Lung adeno carcinoma	2008.2-2013.7	>60, 50-60, 52	56/46	71/31	43/59	NA	NA	102	NA	IHC	48/54	3	OS	SC	1.44	1.14	1.81
Jie Gao ²	2021	China	Asian	Cervical cancer	Oncomine	NA	NA	NA	NA	NA	NA	304	NA	RNA-seq/ microArray	170/134	NA	OS	Rep	2	1.21	3.32
Jie Gao ²	2021	China	Asian	Breast cancer	Oncomine	NA	NA	NA	NA	NA	1764	NA	RNA-seq/ microArray	546/1218	NA	OS	Rep	1.67	1.42	1.95	
Jie Gao ²	2021	China	Asian	Lung cancer	Oncomine	NA	NA	NA	NA	NA	1926	NA	RNA-seq/ microArray	537/1389	NA	OS	Rep	1.35	1.34	1.75	
Jie Gao ²	2021	China	Asian	Liver cancer	Oncomine	NA	NA	NA	NA	NA	364	NA	RNA-seq/ microArray	200/164	NA	OS	Rep	1.59	1.11	2.26	
Jie Gao ²	2021	China	Asian	Gastric cancer	Oncomine	NA	NA	NA	NA	NA	641	NA	RNA-seq/ microArray	335/306	NA	OS	Rep	1.28	1.05	1.57	
Xiangwei Li ³	2021	China	Asian	Colorectal cancer	NA	NA	NA	NA	NA	NA	99	NA	IHC	50/49	NA	OS	SC	1.82	1.01	3.29	

NA: not available; IHC: Immunohistochemistry; OS: overall survival; PFS: progression-free survival; DFS: disease free survival; RFS: relapse free survival; MFS: metastasis-free survival; DMFS: distant metastasis-free survival; Rep: reported; SC: survival curve; HR: hazard ratio; HRL: Lower limit of 95% confidence interval; HRH: Upper limit of 95% confidence interval; cut-off means the threshold for distinguishing high/low expression of PRMT5.

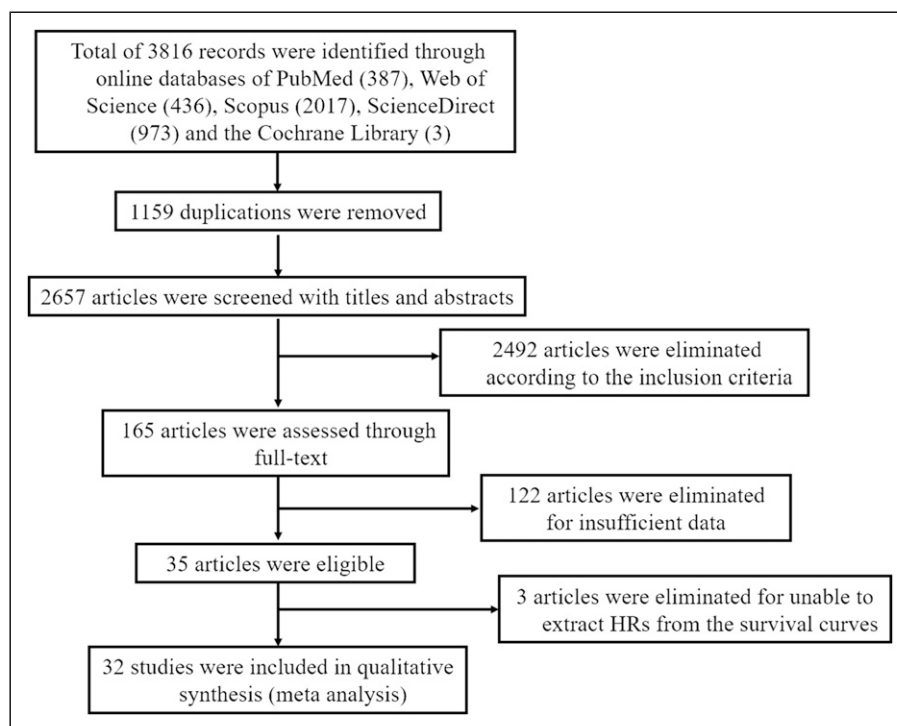


Figure 1. Flow diagram of the study selection in the meta-analysis.

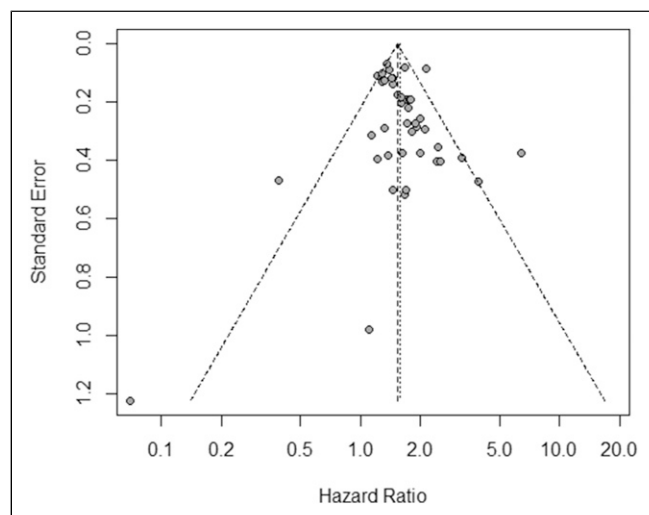


Figure 2. Begg's Funnel plot for publication bias.

We extracted HRs on the basis of the methods reported in several articles.^{17,18} If HRs were reported in the studies, we extracted the HRs directly. If both of the data from univariate analysis and multivariate analysis could be extracted, we chose multivariate analysis to improve data accuracy. If there was no direct information about HRs, then we retrieved HRs by extracting some survival rates at specified times from Kaplan-Meier Curves using Engauge Digitizer version 12.1. When pooled HR>1, we could reach the conclusion that the aberrant level of PRMT5 was associated with poor prognosis.

As included studies showed differences in some characteristics, we used the random-effects model to calculate pooled effect sizes. Publication bias was assessed by *Begg's* funnel plots asymmetry test and *Egger's* test, if the *Begg's* Funnel plot graphics were symmetrical and $P > .05$, it suggested no significant publication bias. Forest plots were used to display the results and sensitivity analyses were also performed to assess the effect of each study. Heterogeneity was evaluated by P -value of Cochran- Q test and I -square statistic. If P -value $> .05$ and $I^2 < 50\%$, studies were thought to be free of significant heterogeneity; If P -value $< .05$ and $I^2 > 50\%$, studies were thought to be of heterogeneity, and sub-groups analyses were performed to seek covariates that contributed to heterogeneity. Statistical significance was considered whenever P -values $< .05$. Engauge Digitizer version 12.1, STATA version 15.1 and R version 4.0.5 were used to obtain the data and analysis above.

Results

Study Selection

According to the search strategy, 3816 articles were found, including 387 from PubMed, 436 from Web of Science, 2017 from Scopus, 973 from ScienceDirect, and 3 from Cochrane Library. After elimination of 1159 duplications, 2657 were left. 2492 of them were removed after title and abstract scan according to inclusion and exclusion criteria. 165 of them were eliminated after full-text scan according to inclusion and

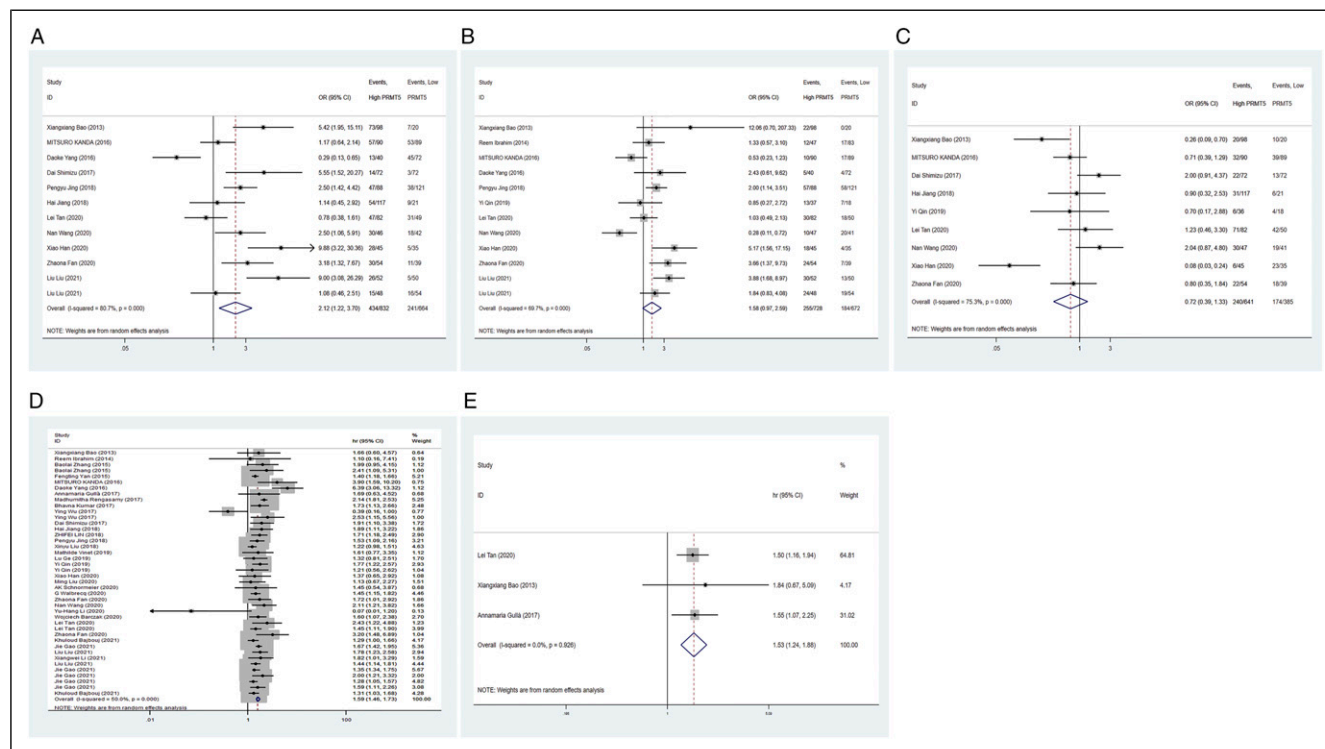


Figure 3. Forest plot of studies evaluating the associations between the PRMT5 high level and clinicopathological and prognostic features. A. tumor stage; B. lymph node metastasis; C. tumor differentiation; D. overall survival; E: progression-free survival.

exclusion criteria. 122 articles were eliminated for insufficient data. Among the left 35 articles, 3 articles could not be used to extract HRs and 95% CIs from the survival curves. Finally, 32 articles were included,^{5,8-13,19-43} those articles were published between January 1, 2013 and July 25, 2021. The flow diagram was shown in Figure 1.

Study Characteristic

A total of 50 studies were included in the 32 articles. Among them, 13 articles provided relatively complete clinicopathological data, which was enough to obtain a pooled OR to assess the relationship between PRMT5 and tumor stage, lymphatic metastasis and degree of differentiation.

The survival indicators involved in the 50 studies included OS, PFS, RFS, DFS and DMFS (42 studies were OS, 3 studies were PFS, 2 studies were DFS, 1 study was RFS, 1 study was MFS, and 1 study was DMFS). Of all the 50 studies, for the detection of PRMT5 16 studies used immunohistochemistry (IHC), 17 studies used PCR technology (RT-PCR, qPCR, and microarray), 11 studies used The Cancer Genome Atlas (TCGA) data which took RNA-Seq as PRMT5 detection method, 1 study used METABRIC data, 2 studies used caBIG, TCGA, and Gene Expression Omnibus (GEO) database simultaneously, and 3 studies used 26 datasets from GEO. The sample size of each study

is between 43 and 1926. Among the 50 studies, 7 studies were about breast cancer, 7 studies were about lung cancer, 5 studies were about hepatocellular carcinoma, 5 studies were about pancreatic cancer, 4 studies were about gastric cancer, and so on. As for the study location, excluding studies based on TCGA, GEO, METABRIC data, caBIG data, or ICGC CLLE project, the remaining 30 studies include 20 from China, 3 from Japan, 5 from the United States, and 2 from France. Detailed information was shown in Table 1 and Supplementary Table S2.

Assessment of Methodological Quality

The ranking of each study is shown in Supplementary Table S3. The NOS scores in the column titled “Comparability of Cohorts on the Basis of the Design or Analysis” indicate that some of the studies provided details regarding their design. In the studies by M Rengasamy,²⁷ Y Wu,³¹ Lu Ge²⁰, YH Li,³⁷ AK Schnormeier,²⁸ G Walbrechq,²⁹ W Barczak,¹⁰ Bajbouj K,⁴⁰ and Gao J,⁴² authors used RNA-Seq data from public database, such as TCGA, GEO, METABRIC data, but the authors did not provide study design of the included patients as well as the follow-up time, hence, a star could not be awarded. According to the assessment results, the studies included in this meta-analysis were considered high-quality studies.

Table 2. The Prognostic Effects of Sub-Groups About Overexpression of PRMT5 and OS for Cancer Patients.

Subgroup analysis	No. of studies	No. of patients	Pooled HRs (95% CI)			Heterogeneity	
			Pooled HRs (95% CI)	Z value	P-value	I ² (%)	P-value
Ethnicity							
Asian	20	2790	1.73 (1.49, 2.00)	7.29	<.001	39.6	.036
Caucasian	5	818	1.59 (1.27, 1.97)	4.13	<.001	18.0	.300
PRMT5 level							
RNA	27	11238	1.60 (1.42, 1.80)	7.69	<.001	61.9	<.001
Protein	15	2133	1.49 (1.36, 1.63)	8.46	<.001	0	.508
Cancer type							
BC	6	3909	1.63 (1.22, 2.19)	3.28	.001	70.4	.005
GC	4	1512	1.32 (1.04, 1.69)	2.26	.024	48.9	.118
HCC	5	895	1.75 (1.42, 2.17)	5.19	<.001	0	.899
PC	4	480	1.57 (1.24, 1.98)	3.78	<.001	0	.752
LC	7	3661	1.35 (1.22, 1.50)	5.95	<.001	0	.982

BC: breast cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; LC: lung cancer; PC: pancreatic cancer.

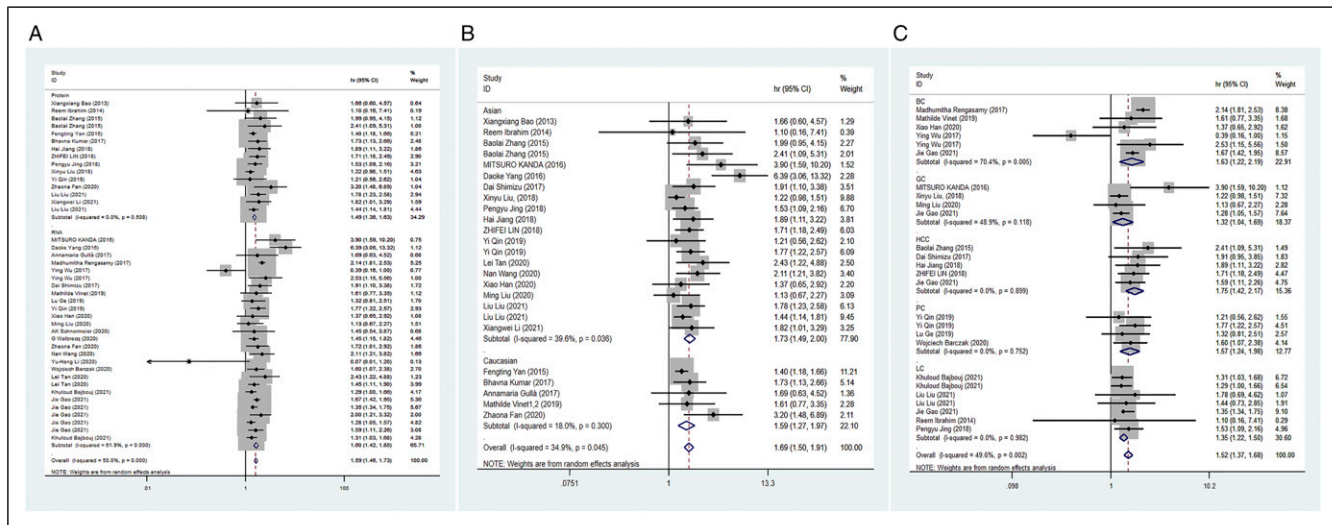


Figure 4. Meta-analysis results for the overall survival of sub-groups. A: detection method; B: ethnicity; and C: different cancer type.

Publication Bias and Heterogeneity

In this study, only when the number of studies on survival indicators is greater than or equal to 3, we conduct a meta-analysis. Thus, we only conducted on OS and PFS.

Publication bias was evaluated by *Begg's* Funnel plot and the *Egger's* test when the number of studies included was over 10. However, the number of studies on PFS was less than 10, which was not suitable for publication bias testing. Therefore, we only tested the OS publication bias. *Begg's* Funnel plot graphics were symmetrical and $P > .05$, which suggested no significant publication bias. (Figure 2)

For heterogeneity, there was moderate heterogeneity in OS group for $I^2 = 50.0\%$ and $P < .001$, and no significant heterogeneity was found in the group of PFS for $I^2 = 0\%$ and $P = .926$.

PRMT5 and Clinicopathological Parameters

Among the 32 articles, 11 articles investigated the associations between PRMT5 and tumor stage. There were 832 cases with high level of PRMT5 and 664 cases with low level of PRMT5. Of all the 832 PRMT5-overexpressed patients, 434 patients were of III-IV stage and 241 patients were of III-IV stage among 664 PRMT5 low expressed patients (Supplementary Table S2). The pooled data showed that high level of PRMT5 was significantly associated with advanced tumor stage (OR = 2.12, 95% CI: 1.22-3.70, $P = .008$) (shown in Figure 3A). Similarly, 11 researches investigated the associations between PRMT5 and lymphatic metastasis. And 9 researches investigated the associations between PRMT5 and tumor differentiation. The pooled results showed that

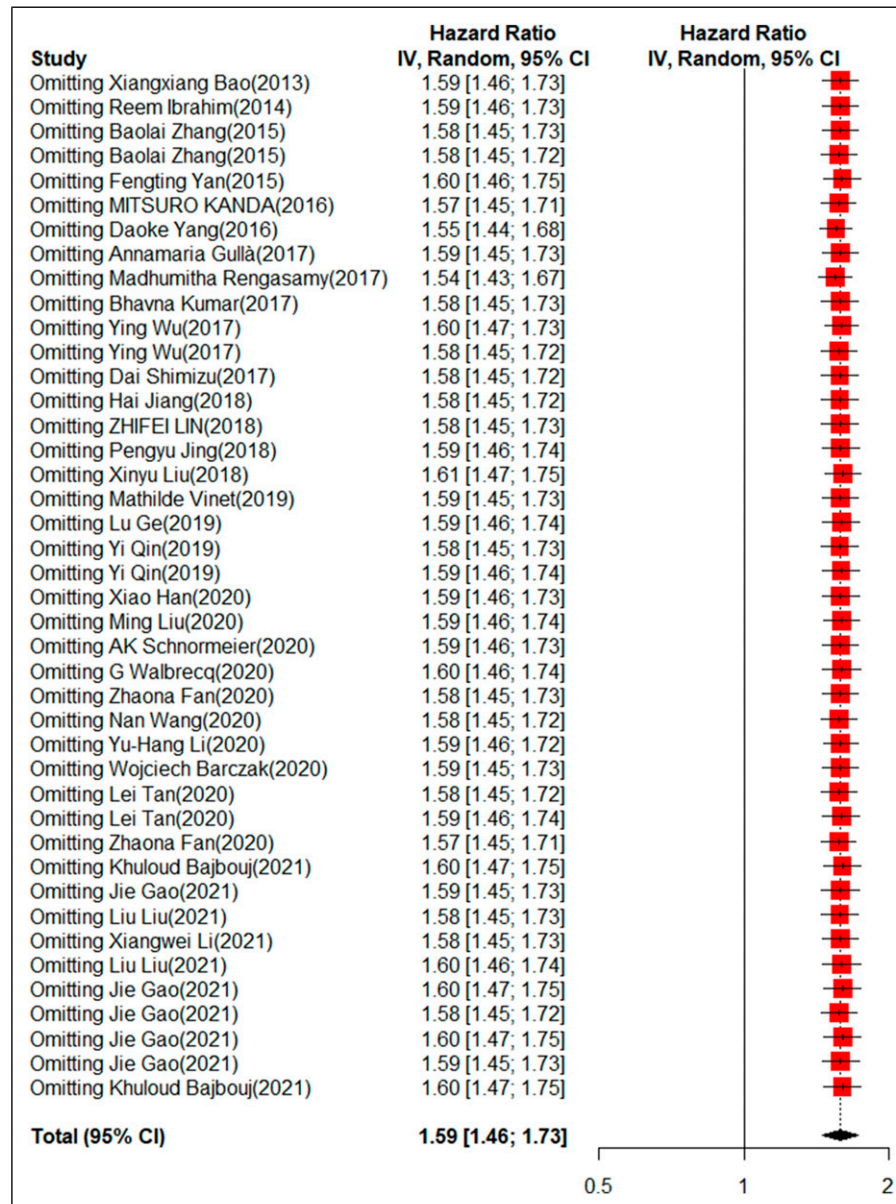


Figure 5. Sensitivity analysis for the evaluation of survival outcomes.

PRMT5 has no significant correlation with positive lymph node metastasis and tumor differentiation (OR = 1.58, 95% CI: .97–2.59, $P = .069$; OR = .72, 95% CI: .39–1.33, $P = .297$). (shown in [Figure 3B and C](#))

Overall Survival Analysis

There were 42 studies, comprising a total of 13371 patients, provided data for us to analyze the correlation between PRMT5 and OS. As shown in [Figure 3D](#), the data indicated

that the high level of PRMT5 had an obvious impact on OS (HR = 1.59, 95% CI: 1.46–1.73). And the pooled estimated HR for all studies showed a significant difference ($z = 10.57$, $P < .001$). The overall results suggested that high-PRMT5 expression is an indicator of poor OS in patients with cancer.

Progression-Free Survival Analysis

HRs for PFS were available in 3 studies for a total of 845 patients. As shown in [Figure 3E](#), the data indicated that the

high expression of PRMT5 had an obvious impact on PFS (HR = 1.53, 95% CI: 1.24–1.88). And the pooled estimated HR for all studies showed a significant difference ($z = 4.02$, $P < .001$). The overall results suggested that high-PRMT5 expression was an indicator of poor PFS in patients with cancer.

Sub-group Analysis for Overall Survival

Because of heterogeneity in samples for calculating pooled OS ($I^2 = 50.0\%$ and $P < .001$), sub-group analyses were performed for PRMT5 detection method, ethnicity and different cancer type. As mentioned previously, qPCR, RT-PCR, microarray, RNA-Seq, and IHC were used to detect PRMT5. It can be seen that the detection of PRMT5 is mainly from the RNA level (qPCR, RT-PCR, microarray, and RNA-Seq) and the protein level (IHC). Therefore, we classify the detection of PRMT5 into 2 categories: RNA level and protein level. Of all the 42 studies, 27 studies were from RNA level and 15 studies were from protein level. Regardless of RNA level or protein level, high expression of PRMT5 was associated with a poor OS, for HR=1.60, 95%CI:1.42–1.80 (RNA level) and HR = 1.49, 95% CI:1.36–1.63 (protein level), respectively. Meanwhile, we found that I^2 for RNA level was 61.9% while I^2 for protein level was 0%, suggesting that different PRMT5 detection methods might be one of the sources of heterogeneity, and the stability of the detection result of PRMT5 protein level was better than that of RNA level. As for ethnicity, considering that the PRMT5 expression data obtained from the public databases (TCGA, GEO, METABRIC, Oncomine, and caBIG) contains different ethnicity, and the ethnic information of the included population was not clarified in the original article, in the sub-group analysis based on ethnicity, we excluded the studies based on public databases. Among the remaining 25 studies, 20 were for Asian populations and 5 were for Caucasians. The results showed that whether Asian populations or Caucasian, high expression of PRMT5 was associated with poor prognosis (HR = 1.73, 95% CI:1.49–2.00; HR = 1.59, 95% CI:1.27–1.97). It also showed that the heterogeneity between studies from Asians was higher than that from Caucasians for $I^2 = 39.6$, $P = .036$ and $I^2 = 18.0$, $P = .300$, respectively. In addition, we also conducted a sub-group-analysis based on different cancer types. We analyzed tumors with more than 3 studies and the results showed that high expression was associated with poor prognosis for all of the following 5 kinds of cancers: hepatocellular carcinoma, pancreatic cancer, breast cancer, gastric cancer, and lung cancer, suggesting that PRMT5 is pan-cancerous as a prognostic biomarker. In addition, the heterogeneity among studies about breast cancer is high ($I^2 = 70.4$, $P = .005$), which might be caused by complex subtyping of breast cancer; the heterogeneity among studies about gastric cancer is moderate ($I^2 = 48.9$, $P = .118$); and there was no heterogeneity for hepatocellular carcinoma, pancreatic cancer and lung cancer ($I^2 = 0$). Therefore, different cancer type was also the source of heterogeneity for OS (Table 2 and Figure 4).

Sensitivity Analysis

Sensitivity analysis was performed to assess the influence of sequential omission of each individual study on the overall survival. The results suggested that there was no significant influence of the pooled HR by removing any study, indicating our analysis was robust (shown in Figure 5).

Discussion

Why Is PRMT5 Chosen?

PRMT5 is an enzyme which is acquiring increased prominence in cancer.⁴⁴ It is the major symmetric arginine methyltransferase in mammalian cells, and has been reported to be a novel therapeutic target molecule for human tumors.⁴⁵ PRMT5 could be regulated the expression of a wide spectrum of cellular events, including cell growth/proliferation,⁴⁶ cell invasion/metastasis,⁴⁷ epithelial-mesenchymal transition,²⁰ alternative splicing,⁴⁸ altering DNA replication and genomic instability⁴⁹ and dysregulation of cell cycle progression.⁵⁰ PRMT5 was considered to be involved in the occurrence and development of tumors, and high level of PRMT5 was thought to be associated with aggressive clinicopathological parameters, such as poor differentiation, higher incidence of vein invasion and larger tumor size.⁵¹ Thus, as an oncoprotein, PRMT5 has gained increasing attention in terms of cancer prevention and therapy in recent years. Meanwhile, PRMT5 is under investigation as a potential therapeutic target for cancer in clinical practice.⁸ In addition, we also found that the level of PRMT5 in whole blood is related to the prognosis of liver cancer in our multi-center study of liver cancer cases. Considering the important role of PRMT5, we searched for studies on PRMT5 and found that there are many literatures reporting the relationship between PRMT5 and clinical features or patient survival outcomes, then we did this systematic review and meta-analysis to clarify the relationship between the level of PRMT5 and the clinicopathological features and prognostic value of patients with tumors comprehensively and systematically.

What Did We Find and the Significance of the Phenomena

In this study, we included 32 articles with a total of 15583 patients to clarify the relationship between PRMT5 and tumor prognosis. We confirmed that (1) there were remarkable positive associations between PRMT5 and advanced clinical tumor stage; (2) high level of PRMT5 was related to poor OS and PFS, and increased the risk of death in cancer patients. These results indicated that PRMT5 might serve as a clinicopathological and prognostic biomarker for malignancy. Furtherly, by sub-group analysis, we found that in breast cancer, the relationship between PRMT5 and tumor prognosis is quite heterogeneous and it has good consistency in the prognosis of liver cancer, pancreatic cancer and lung cancer.

Through tracing the original researches, the main reason, to some extent, attributes to sub-types of breast cancer. Some of the included literatures are for triple negative breast cancer, some are HER-2 positive breast cancer, and some do not specifically list the sub-types; in addition, PRMT5 expression based on protein level detection, compared with RNA level, has a more consistent effect on the prognosis of cancer patients, which might be derived from the reason that the detection of RNA are diverse (RNA-Seq, qPCR, RT-PCR, and microarray) and the detection results have a wide distribution range, while protein detection has only one method of IHC, and the score distribution range is narrow. All in all, these results indicated that PRMT5 might serve as a clinicopathological and prognostic biomarker for malignancy, but the detection method of PRMT5 and tumor types, especially breast cancer subtyping, have a great impact on the relationship between PRMT5 and OS.

As above-mentioned, tumors are still a major global public health problem. With the development and the advancement of medicine, cancer treatment methods have become more diverse, but the incidence and mortality of malignant tumors have not been well controlled. From 10 million new cases, 6 million deaths, and 22 million people living with cancer in 2000⁵² to an estimated 19.3 million new cancer cases and almost 10.0 million cancer deaths occurred in 2020,¹ cancer is still the main killer threatening the lives and health of all human beings. The proposal of precision medicine makes clinicians pay more attention to individualized prevention, treatment and disease monitoring. This requires more biomarkers to feed back the patient's condition in a timely and effective manner, and to change prevention or treatment measures as soon as possible. In our study, by summarizing the data of various original studies, we have clarified that the high level of PRMT5 is related to tumor stage, poor OS and PFS. This provides a basis for tumor monitoring.

Possible Mechanism of PRMT5 as a Tumor Biomarker

There is evidence indicating that PRMT5 can silence tumor suppressor genes and act as an oncogene, accelerating tumor growth and metastasis.²³ This may explain why PRMT5 can act as a biomarker for advanced stage tumors and lymphatic metastasis. Mechanistically, PRMT5 is a pleiotropic enzyme involved in diverse processes. (1) It is an established regulator of RNA biogenesis, in particular RNA splicing, which frequently becomes aberrant in cancer.¹⁰ For example, PRMT5 regulates DNA repair by controlling the alternative splicing of histone-modifying enzymes⁵³; PRMT5 deficiency mainly interferes with the deletion of introns. This impaired splicing affects proliferation genes, meanwhile, its down-regulation is consistent with cell cycle defects and apoptosis.⁵⁴ (2) PRMT5 performs its function mainly through epigenetic silencing or direct methylation of histone and non-histone molecules,⁵⁵ thereby regulating

cellular processes, including transcription, proliferation, apoptosis and metabolism.⁵⁶ For example, PRMT5 regulates cell invasion by inducing transcriptional activation and inhibition through methylating histones H3 and H4⁵⁷; PRMT5 enhances the methylation of PDCD4, thereby promoting tumor cell viability, allowing the tumor to grow more aggressively⁵⁸; Inhibition of PRMT5 changes the methylation status of E2F-1, leading to attenuated DNA damage repair, cell cycle arrest, and increased apoptosis flux⁵⁹. In addition, as a co-factor in a DNA damage responsive co-activator complex that interacts with p53, PRMT5 is responsible for methylating p53. PRMT5 depletion triggers p53-dependent apoptosis.⁶⁰

Above all, PRMT5 is related to cell death, overexpression of PRMT5 enhances the cell proliferation and weakens the ability of apoptosis, and high level of PRMT5 is associated with poor prognosis, which makes PRMT5 a potential prognostic biomarker.

Limitations

There are several limitations in this study that should be acknowledged. Firstly, the articles included in the meta-analysis were from only 5 available databases (PubMed, Web of Science, Scopus, ScienceDirect, and Cochrane Library) and limited to written in English, thus, the data collection might be incomplete. Although we tried to include all published literatures, and there was no significant publication bias, most of the articles included were from Asian, which might attribute to the decreased generality and heterogeneity; Secondly, different criteria were applied in these studies for defining PRMT5 high or low level, because of the lack of uniform cut-off values in PRMT5 detection. This makes it impossible for us to give a clear threshold for distinguishing high level of PRMT5 in our study; Thirdly, HRs with 95% CIs were calculated by digitizing and extracting from the survival curves in most of the including papers, which inevitably brought minor statistical deviations. Furthermore, the effects of some factors, such as treatment strategy and family history, were not considered in this analysis due to the insufficient data. Therefore, high-quality studies are urgently needed to draw more accurate conclusions.

Our meta-analysis provided credible evidence that high level of PRMT5 was significantly related to advanced tumor stage and the poor prognosis for cancer patients. In addition, given the important prognostic factor of survival for cancer patients, PRMT5 might serve as an attractive therapeutic target in the treatment of malignant tumors.

Conclusion

For the first time we found PRMT5 was pan-cancerous as a prognostic biomarker, and high level of PRMT5 was associated with poor prognosis for certain cancers.

Appendix

Abbreviations

PRMT5	protein arginine methyltransferase 5
HR	hazard ratios
OR	pooled odds ratios
95% CI	95% confidence interval
PRISMA	the Preferred Reporting Items for Systematic Reviews and Meta-analysis
OS	overall survival
PFS/DFS	progression/disease free survival
RFS	relapse/recurrence free survival
MFS/DMFS	metastasis-free survival
IHC	immunohistochemistry
TCGA	The Cancer Genome Atlas
GEO	Gene Expression Omnibus

Author Contributions

Liang Z was in charge of the writing of manuscript. Liu L and Wen C were in charge of editing the manuscript. Jiang H and Ye T were in charge of data analysis. Ma S was in charge of the revision of manuscript. Liu X conceived and designed this study, reviewed the manuscript and was responsible for the overall content as guarantor.

Declaration of Conflicting Interests

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Ethical approval

This article does not contain any studies with human or animal subjects performed by the any of the authors.

Data availability

The data used to support the findings of this study are available from the corresponding author upon request.

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Supplemental Material

Supplemental material for this article is available online.

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