The Prognostic Value of DNA Methylation Markers in Renal Cell Cancer: A Systematic Review

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Abstract.

Introduction: DNA methylation is an epigenetic event that occurs in normal tissues but changes in both the early and late stages of multiple tumor entities, including renal cell cancer (RCC). Many studies have shown that DNA methylation markers are relevant to RCC prognosis, but none of these markers have entered into clinical routine. Furthermore, because of its potential reversibility, DNA methylation might provide a new target for RCC therapy strategies.

Materials and methods: Following PRISMA guidelines, we performed a systematic literature search up to February 2019. After selection for eligibility, a total of 56 studies were identified for analysis. Each study was categorized and the level of evidence assessed. Only articles reporting on DNA methylation markers and their association with survival were included. Descriptive statistical analyses were conducted with R statistical software.

Results: We identified promoter methylation of SFRP1, GATA5, NEFH, GREM1, and BCN1 as associated with survival in RCC. Moreover, we found evidence that methylation signatures, i.e., grouping of different potential gene markers, might be of better prognostic value than single gene marker investigations. Nevertheless, because of the heterogeneous features of the studies in terms of design, methodology, patient cohorts, and statistics, the true clinical impact of these methylation markers for prognosis in RCC patients remains uncertain.

Conclusion: This systematic review elucidates the potential impact of DNA methylation on survival of patients with RCC. Several promising prognostic markers, especially methylation signatures, were identified, which is encouraging, but prospective validations are necessary to establish their true clinical value.

Keywords: DNA methylation, kidney cancer, renal cell carcinoma, prognosis, survival, biomarkers, outcome

INTRODUCTION

Renal cell cancer (RCC) is the twelfth most common cancer worldwide. In 2012, it accounted for about 338,000 new cases [1]. Clear cell RCC (ccRCC) represents 75%–80% of all RCCs and is the major histological subtype. Currently, the University of California Los Angeles (UCLA) Integrated Staging System (UISS) and the Stage, Size, Grade, Necrosis (SSIGN) Score are clinical models used for estimating prognosis and survival for patients with localized RCC. Both models are based on clinicopathological features rather than molecular-based biomarkers, and despite their high predictive
competence [2, 3], they carry the risk of omit-
ting important patient-dependent factors. Numerous 
molecular markers are currently under investigation 
with the aim of improving these models. A main focus 
is on epigenetic alterations, such as DNA methyla-
tion.

DNA methylation is the covalent addition of a 
 methyl group to a cytosine adjacent to a guanine (CpG 
dinucleotide), which changes the chemical proper-
ties of the DNA without altering the DNA sequence. 
Gene promoter regions often contain a high density 
of CpG dinucleotides, or so-called CpG islands, and 
methylation in these regions is frequently linked to 
gene silencing because it renders them inaccessible 
for transcription [4]. In addition to DNA hyperme-
thylation, global and gene-specific hypomethylation 
represents a second frequent aberration. This pro-
cess can lead to proto-oncogene activation and 
genomic instability in repetitive sequences if there 
is a decrement in genome-wide methylation (global 
hypomethylation) [5, 6].

The Cancer Genome Atlas (TCGA) Kidney 
consortium recently conducted a comprehensive 
characterization of the molecular alterations associ-
ated with RCC. In addition to genetic mutations, the 
consortium found, along with multiple other reports, 
that ccRCC [7] and papillary RCC (PRCC) [8] char-
acteristically display DNA hypermethylation of gene 
promoters and concurrent loss of gene function from 
transcriptional silencing. Of interest, this group found 
only limited associations between gene mutations and 
RCC prognosis. These data are in line with previously 
conducted genetic studies demonstrating inconsistent 
results regarding survival [9].

In contrast, for a significant number of genes, DNA 
hypermethylation occurs with high frequency and to 
a degree that correlates with clinicopathological fea-
tures and survival in RCC [10]. For example, the 
tumor suppressor genes RAS-associated domain fam-
ily 1 (RASSF1A) and secreted frizzled-related protein 
1 (SFRP1) are each found in 30% to >70% of tumors. 
These tumor suppressors are associated with both 
clinical pathological features and outcomes [12–15].
A recent study showed that tumor-specific hyperme-
thylation in RCC correlated with adverse pathology 
and was associated with overall survival (OS) among 
patients undergoing targeted therapy [16]. Detecting 
DNA methylation–based biomarkers is therefore of 
substantial interest because these markers could serve 
diagnostic, prognostic, and predictive purposes [17].

In the last two decades, several published studies 
have focused on the prognostic and predictive value 
of DNA methylation markers in RCC. Because of 
widespread heterogeneity among them in (i) design, 
(ii) materials and methods, and (iii) statistical analy-
ses, a direct comparison and proof of reproducibility 
is unfortunately not possible.

This systematic review provides an overview of 
the current literature on DNA methylation and its 
role as a prognosticator in RCC. Included articles 
were categorized and graded using the level of evi-
dence (LOE) approach. We also critically discuss 
the studies in terms of methodology and perform 
a descriptive statistical analysis to reveal the most 
 promising methylation markers for future clinical 
evaluation.

MATERIALS AND METHODS

Search strategy

We conducted this review according to PRISMA 
guidelines [18, 19]. A systematic literature search 
was performed on PubMed, including Medline, and 
EMBASE from 2005 through February 2019. The 
following terms were used for the search: renal cell 
carcinoma, kidney cancer, renal cell cancer, DNA 
methylation, prognosis, survival, and methylation. 
Either one term or several combinations were used 
for screening all relevant publications. Titles and 
abstracts were screened to identify eligible articles. 
Step two continued with scanning all bibliographies 
of articles identified to retrieve additional impor-
tant publications that were not listed in PubMed, 
EMBASE, or Medline.

Inclusion criteria and study selection

We included all articles reporting on DNA methyla-
tion of one or more genes and their association with 
patient survival. In this review, DNA methylation 
refers to genome-wide evaluations. DNA methylation 
is found in so-called CpG islands that are typically 
located in the promoter region of genes and show 
a high density of CpG dinucleotides. Articles meet-
ing the following inclusion criteria were included: 
original articles (not included: reviews, case reports, 
editorials, conference abstracts); English language; 
biomarker research performed on RCC tissues or on 
body fluids from patients with RCC; and inclusion 
of statistical analysis on patient survival. Analyses not 
reporting on DNA methylation of a specific gene or 
marker were excluded. Studies investigating marker
panels or methylation signatures were included if the analyzed genes were specified.

**Data extraction**

Two authors (IP and CVK) initially extracted the data independently and collected the information in a standardized registration form. This form included the following information: first author, year of publication, PubMed identifier (PMID), gene/marker, source of material, study design, tumor subtype, sample size (total), sample size (survival), method used for detection of methylation, outcome measures (hazard ratio [HR], 95% confidence interval [CI]), and reported association of the marker with patient outcome. The term “patient outcome” refers to progression free survival (PFS), OS, cancer-specific survival (CSS), and recurrence free survival (RFS). Summarized results and characteristics of data extraction are shown in Supplementary Table 1.

**Assessment of study categories and level of evidence**

Studies were categorized as A) prospective randomized controlled trials specifically designed to address tumor markers, B) prospective randomized controlled trials not specifically addressing tumor markers, C) prospective, observational studies, and D) retrospective, observational studies. LOE was assessed as follows: briefly, studies from category A or one or more studies from category B with concordant results were defined as LOE I; one study from B or two or more studies from C were defined as LOE II; one study from category C was LOE III; and studies from category D were designated as LOE IV/V, as proposed by Hayes et al. [20].

**Statistical analysis**

For descriptive analyses, we created a three-dimensional (3D) matrix using numbers at risk, HRs, and p values as primary parameters. The functions scatter3D and box3D from the R-package plot3D were used to visualize data in a 3D scatterplot. The function forest plot from R-package forest plot [21] was used to visualize HRs and corresponding 95% CIs. Data management and data visualization were conducted using R statistical software version 3.5.0 [22].

**RESULTS**

**Results of electronic database search**

Figure 1 shows a diagram of the selection process of the included studies. The initial database search revealed 633 papers in total. After removal of duplicates and articles with irrelevant titles or abstracts, 170 eligible full-text articles were identified. Out of these, 114 articles were excluded after the second assessment. The final selection comprised 56 studies.

**Study characteristics and level of evidence**

Supplementary Table 1 summarizes the basic characteristics of reported studies. Included articles were published between 2003 and 2019. The majority were retrospective, whereas four studies were conducted using a prospective trial design. Sample sizes ranged from 18 to 993 patients in total, and the sample sizes of patients with follow-up data and who therefore were eligible for survival analyses ranged from 10 to 445. In one study, the sample size was not provided. In 19 studies, authors investigated various subtypes of RCC (mixed RCC). The term “mixed RCC” described tissues originating from patients suffering from ccRCC, PRCC, or chromophobe RCC. Thirty-six articles exclusively studied ccRCC and one study analyzed the tissues of PRCC.

Fifty-four articles involved investigations of tissue from primary tumors (PT), one study used preoperative blood serum of patients, and another one used blood-based cell-free DNA for analyses. For outcome measurements, PFS, RFS, CSS, and OS were...
assessed. Most studies \((n = 39)\) reported on only one parameter, and only 17 reported on two and more.

Only six studies reached LOE grade III; all other studies were classified as LOE grade IV/V, as defined above. Category A or B studies (LOE I and II) were not identified. An internal or external validation of study findings was found for 28 studies. Figure 2A illustrates the distribution of studies with validated and non-validated outcome findings. In Fig. 2B, the 3D plot focuses exclusively on internally or externally validated outcome results.

**Outcome reports**

All relevant data on the reported methylation markers and their associations with survival are summarized in Supplementary Table 2 and illustrated in the corresponding forest plots in Figs. 3A–D. Promoter regions of multiple genes were found to be tumor-specifically methylated in various subtypes of RCC, but for ccRCC in most cases. For our descriptive statistical analysis of reported outcomes, we focused on studies in which results were externally or internally validated. **SFRP1**, **GATA5**, **BNC1**, **GREM1**, **LAD1**, and **NEFH** showed frequent promoter methylation, which was associated with survival. Morris et al. found promoter methylation of **SFRP1**, along with **BNC1** and **COL14A1**, to be associated with poorer CSS and OS (HR: 4.44; 95% CI: 2.75–86.2; and HR: 4.88; 95% CI: 2.76–87.95, respectively) in univariate Cox regression analyses. In multivariate analyses, **SFRP1** \((p = 0.4)\) was not an independent predictor of OS, but **BNC1** (HR(multi): 4.87; 95% CI: 1.14–20.88) and **COL14A1** (HR: 6.56; 95% CI: 1.69–25.38) were independently associated with survival [12]. These results were confirmed by Ricketts and colleagues [23] in a large study with two independent cohorts from the TCGA KIRC dataset. In both cohorts, **SFRP1** promoter methylation was statistically associated with worse OS and an independent predictor for OS (HR(multi): 2.40; 95% CI: 1.25–4.64) and HR(multi): 1.92; 95% CI: 1.05–3.50).

On the other hand, our research group found an association of **SFRP1** methylation with prolonged RFS for patients (HR: 0.13; 95% CI: 0.03–0.58) [14]. **GATA5** promoter methylation in ccRCC was associated with OS (HR: 2.82; 95% CI: 1.02–7.82), RFS (HR: 13.00; 95% CI: 3.57–47.4), and PFS (HR: 4.59; 95% CI: 1.57–13.4) in univariate Cox regression analysis [23–25]. **GREM1**, which encodes gremlin 1, a protein that directly binds to VEGFR2 and consecutively stimulates neoangiogenesis, is frequently methylated in RCC. Ricketts et al. identified **GREM1** promoter methylation as an independent predictor of OS (HR: 3.05; 95% CI: 1.36–6.86) [23]. Van Vlo-
In contrast, Morris et al. found no association of GREM1 methylation with survival [12]. Dubrowinskaja and colleagues, as well as van Vlodrop et al., found NEFH methylation to be statistically associated with OS (HR(multi): 2.6; 95% CI: 1.5–4.6) [26] in patients with ccRCC and with PFS (HR: 8.61, 95% CI: 3.03–24.5) [16] in patients within an overall RCC cohort.

Methylation signatures, i.e., combinations of markers with potential prognostic value, seem to be of special interest. Van Vlodrop’s group showed a robust association of hypermethylation of a four-gene panel consisting of NEFH, GREM1, LAD1, and NEURL with worse OS in patients with ccRCC (HR(multi): 6.6; 95% CI: 2.1–20.1) [26]. Furthermore, a methylation signature reported by Wei et al. consistently showed a strong association with OS in various test and validation cohorts with sample sizes >150 patients, and a high-risk score was correlated with a poorer outcome (Fig. 3A) [27]. Tian et al. investigated 23 CpG units out of a seven-gene panel in a ccRCC cohort. A positive methylation status, i.e., more than 16 CpG methylated units, was correlated...
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**B**

**RFS**

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>HR (CI95%)</th>
<th>Method</th>
<th>Marker (Source)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autschkezel (2012)</td>
<td>0.34 (0.03–0.58)</td>
<td>univar.</td>
<td>SFRP1 (PT)</td>
</tr>
<tr>
<td>Hildebrandt (2010)</td>
<td>2.74 (0.78–9.6)</td>
<td>multivar.</td>
<td>LEPR (PT)</td>
</tr>
<tr>
<td>Mendoza–Perez (2017)</td>
<td>3.15 (1.23–8.07)</td>
<td>multivar.</td>
<td>GATA5 (allRCC)</td>
</tr>
<tr>
<td>Peters (2014)</td>
<td>17.8 (4.89–65.1)</td>
<td>univar.</td>
<td>GATA5 (ccRCC)</td>
</tr>
<tr>
<td>Peters (2014)</td>
<td>13 (3.57–47.4)</td>
<td>univar.</td>
<td>NELL1 (PT)</td>
</tr>
<tr>
<td>Peters (2018)</td>
<td>4.15 (1.1–15.6)</td>
<td>univar.</td>
<td>Marker panel* (PT)</td>
</tr>
<tr>
<td>Tian (2014)</td>
<td>10.6 (2.81–40.2)</td>
<td>univar.</td>
<td></td>
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</table>

**C**

**PFS**

<table>
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<th>Author (Year)</th>
<th>HR (CI95%)</th>
<th>Method</th>
<th>Marker (Source)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubrowinskaja (2014)</td>
<td>8.61 (3.03–24.5)</td>
<td>univar.</td>
<td>NEFH1 (PT)</td>
</tr>
<tr>
<td>Lin (2014)</td>
<td>3.061 (1.439–6.513)</td>
<td>univar.</td>
<td>PCDH8 (PT)</td>
</tr>
<tr>
<td>Lin (2014)</td>
<td>2.292 (1.544–6.031)</td>
<td>multivar.</td>
<td>PCDH8 (PT)</td>
</tr>
<tr>
<td>Peters (2012)</td>
<td>3.48 (1.38–8.83)</td>
<td>univar.</td>
<td>GATA5 (allRCC)</td>
</tr>
<tr>
<td>Peters (2012)</td>
<td>4.59 (1.57–13.4)</td>
<td>univar.</td>
<td>GATA5 (ccRCC)</td>
</tr>
</tbody>
</table>

**D**

**CSS**

<table>
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<th>Author (Year)</th>
<th>HR (CI95%)</th>
<th>Method</th>
<th>Marker (Source)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fisel (2015)</td>
<td>0.018 (0.003–0.119)</td>
<td>univar.</td>
<td>SLC16A3 (TCGA)</td>
</tr>
<tr>
<td>Fisel (2015)</td>
<td>0.0068 (0.0002–0.3022)</td>
<td>univar.</td>
<td>SLC16A3 (PT)</td>
</tr>
<tr>
<td>Gu (2017)</td>
<td>0.594 (0.385–0.915)</td>
<td>multivar.</td>
<td>CA9 (TCGA)</td>
</tr>
<tr>
<td>Kawai (2010)</td>
<td>1.49 (1.02–2.26)</td>
<td>univar.</td>
<td>RASSF1A (PT)</td>
</tr>
<tr>
<td>Kawai (2010)</td>
<td>1.78 (1.18–2.78)</td>
<td>multivar.</td>
<td>RASSF1A (PT)</td>
</tr>
<tr>
<td>Morris (2010)</td>
<td>3.69 (1.27–10.93)</td>
<td>univar.</td>
<td>BNC1 (PT)</td>
</tr>
<tr>
<td>Morris (2010)</td>
<td>4.86 (2.76–87.95)</td>
<td>univar.</td>
<td>SFRP1 (PT)</td>
</tr>
<tr>
<td>Tian (2014)</td>
<td>75.8 (7.81–735)</td>
<td>univar.</td>
<td>Marker panel* (PT)</td>
</tr>
</tbody>
</table>

Fig. 3. Forest plots. Forest plot for 58 publications on epigenomic markers in renal cell carcinoma (RCC) with regard to: A) overall survival (OS), B) recurrence-free survival (RFS), C) progression-free survival (PFS), and D) cancer-specific survival (CSS). Only publications that were internally or externally validated were included. Studies with cohort sample sizes of <150 and ≥150 are illustrated with small and large squares, respectively (■, ■). HR = hazard ratio; 95% CI = 95% confidence interval; PT = primary tumor; marker panel* = CpG island methylator phenotype (CIMP) with more than >16CpG sites methylated.

in univariate Cox regression analysis with shorter RFS and CSS (Fig. 3B and D) [28]. CpG island methylator phenotype (CIMP) positivity and its associations with outcome were also shown in a TCGA PRCC analysis. In a cohort of 159 PRCC patients, OS was significantly decreased in patients with CIMP positivity (suppl. Table 2) [8]. Of interest, methylation of PARVG (HR: 0.09; 95% CI: 0.00027–0.29), RAC2 (HR: 0.016; 95% CI: 0.00059–0.061), PLCB2 (HR: 0.047; 95% CI: 0.0039–0.57), and VAV1 (HR: 0.0226; 95% CI: 0.0013–0.372) was associated with longer OS in patients from a TCGA KIRC dataset, both solely and in a four-gene panel risk score (p = 0.00163) (Fig. 3A, suppl. Table 2) [29].

**DISCUSSION**

With an increasing number of incidentally detected small renal masses (<4 cm), treatment stratification in terms of surgical options vs. surveillance can be difficult, especially among older patients. For this reason, predictive tools are needed to estimate prognosis and tumor aggressiveness on an individual basis. As a cancer biomarker, DNA methylation is attractive for several reasons, including the fact that it is a stable event, and analysis is time and cost-effective compared with most of genetic analyses. Meanwhile,
multiple studies support and underline the importance of epigenetic changes in RCC development and disease progression.

Exome-wide sequencing approaches have revealed only a few genes that are frequently mutated (frequency >10%) in sporadic RCC, among them PBRM1 with about 20%–41% [30, 31], BAP1 with 8%–15% [30, 32, 33], and SETD2 with 3%–12% [34–36]. In contrast, DNA hypermethylation occurs as a frequent and more homogeneous event in RCC [27, 37]. Therefore, epigenetic changes as potential drivers for RCC tumorigenesis have moved into the focus of current research activities. In addition to DNA methylation, post-translational histone modification and non-coding RNAs are the main epigenetic regulatory processes. The underlying mechanism of DNA methylation, especially de novo methylation of distinct areas in the genome, is not yet fully understood. Nevertheless, a vast number of studies have investigated the single locus methylation status of promoter regions of candidate methylation markers and identified some statistically significant associations with clinical and histopathological factors and with survival [10, 38–40].

In this systematic review, we performed an electronically based literature search on DNA methylation markers with potential prognostic value. We identified SFRP1, GATA5, BNC1, GREM1, LADI, and NEFH as promising individual prognostic methylation markers that have been internally or externally validated and therefore are of interest for further investigations. Moreover, van Vlodrop and colleagues tested the combination of putative markers (GREM1, LADI, NEURL, and NEFH) in three independent patient cohorts and found that performing analysis with methylation signatures leads to more robust statistical results [26]. Wei et al. also demonstrated that a CpG-based classifier consisting of five genes (PITX1, FOXE3, TWF2, EHBP1L1, and RINI) predicted OS in ccRCC patients in a cohort of almost 1000 patients [27]. However, prospective validations in randomized trials are urgently needed to transfer these results into clinical practice.

The total increase in DNA methylation across a CpG island is designated as a CIMP. In a cohort of 100 ccRCC patients, CIMP positivity was associated with worse outcome in terms of CSS (p = 0.0001) and OS (p < 0.0001) [28]. Furthermore, analysis of a TCGA PRCC dataset also demonstrated an association between OS and CIMP positivity in non-ccRCC patient [8]. The TCGA PRCC dataset includes 159 patients with PRCC and is currently the largest comprehensive molecular characterization of non-ccRCC. A CIMP was observed in a subcohort with PRCC type II showing methylation of the CDKN2A promoter. This CIMP was also associated with mutations in the fumarate hydratase gene and with poor OS [8]. This study emphasizes the need for further analyses of distinct DNA methylation patterns in non-ccRCC cohorts, likely revealing them as possible drivers of tumorigenesis in these subtypes. Moreover, CIMP positivity in ccRCC was linked to a defect in the spindle checkpoint pathway, so targeting this pathway might be of clinical interest [41].

As noted, DNA hypomethylation also plays a relevant role in RCC tumorigenesis. A retrospective case–control study from Mendoza-Pérez and colleagues revealed a significantly lower 5-methyldeoxycytosin content in peripheral blood samples from RCC patients compared to healthy individuals [42]. Furthermore, in a TCGA KIRC analysis, an association between SETD2 mutations and promoter region–independent global DNA hypomethylation was linked to histone H3K36 trimethylation, which sustains the heterochromatin structure [7, 43]. Nevertheless, most studies found that DNA hypermethylation, rather than global hypomethylation, was associated with RCC [44].

In addition to these encouraging findings, we found some inconsistent results. These inconsistencies included heterogeneity in terms of methodology, clinical, and statistical factors. More than eight methylation analysis techniques were used, including non-quantitative methods, precluding the need for cut-off calculations. Ideally, in clinical routine, a practicable test relies mainly on three aspects: costs, applicability, and reliability. In recent years, DNA methylation detection approaches have made considerable improvements. A review by Umer et al. nicely summarizes the most frequently used methods. These authors also explain the underlying mechanisms of the different methods for DNA methylation analysis and describe the advantages and disadvantages of each method in detail [45]. For example, bisulfite-treated DNA in combination with array-based assays like GoldenGate or Illumina Infinium Bead Chip assays are widely used. Their coverage rate is high, but the need for bisulfite pretreatment may cause bisulfite PCR bias and higher costs because of handling. All methods have their shortcomings: if the genome coverage is excellent, as for the shotgun bisulfite sequencing on high-throughput platforms, which is the current gold standard for DNA methylation analysis, the costs and efforts per patient are
still immense. Recent approaches in next-generation sequencing will prospectively allow sufficient DNA methylation analyses in a near-patient and cost-effective way.

In terms of clinical factors, more than 90% of the studies were retrospective. Matched paired cohorts or complete survival data were often not available. Also, the numbers of patients were relatively small in most studies (<100 patients in about 50% of the studies). Because retrospective trial designs mostly involved no predefined inclusion or exclusion criteria and inclusion was often based on availability of tissues, a variety of studies were prone to selection bias, resulting in a non-representative study population.

Furthermore, almost all studies investigated various RCC subtypes, but subgroup analyses by RCC type were subsequently not performed or reported in most cases. Methylation markers and their prognostic values can vary among different subtypes, so it is prognostically relevant to perform subgroup analyses [46, 47]. Nevertheless, subtypes other than ccRCC are actually underrepresented in the research activities concerning DNA methylation markers or other epigenetic alterations.

We also recognized serious statistical differences among the articles, including differing endpoints. Inconsistency in the definition of outcome measures leads to distortion. A direct comparison between studies was not viable given the absence of standardized and predefined clinical endpoints.

In conclusion, our systematic review of DNA methylation in RCC reveals a number of promising candidates with prognostic value, but none of them are ready for transfer into clinical practice. Therefore, the clinical management of RCC patients based on distinct DNA methylation markers remains unchanged. We urgently need prospective biomarker trials that are ideally incorporated into clinical trials with randomized controlled patient cohorts, homogeneous and standardized analytical and statistical methods, and clearly defined clinical endpoints. Results should be reported according to the REMARK (Reporting Recommendations for Tumor Marker Prognostic Studies) guidelines, enabling comparative analyses and meta-analyses.

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None.

COMPETING INTERESTS

The authors declare no competing interest.

SUPPLEMENTARY MATERIAL

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