Systematic Review and Meta-Analysis

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Efficacy and safety of HDACIs in the treatment of metastatic or unresectable renal cell carcinoma with a clear cell phenotype

A systematic review and meta-analysis

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Abstract

Background: In this study, we evaluated the efficacy and safety of histone deacetylase inhibitors (HDACIs) in the treatment of renal cell carcinoma (RCC).

Methods: PubMed, EMBASE, the Cochrane Library, CNKI, and the Wanfang database were searched to retrieve studies describing the use of HDACIs for the treatment of RCC published between January 1, 2009, and January 1, 2021. Relevant studies were selected, and data were extracted. Then, a meta-analysis was performed using R 3.5.2 software.

Results: The results showed that the objective response rate (ORR) of HDACIs used to treat RCC was 26% [95% confidence interval (95% CI): 0.19~0.34] and that the 1-year progression-free survival (PFS) rate was 29% (95% CI: 0.14~0.59). The ORR and PFS rate of the combination group were better than those of the monotherapy group, and the ORR and PFS rate of the selective HDACI group were better than those of the pan-HDACI group. The incidences of neutropenia and thrombocytopenia were higher and the incidence of fatigue was lower in the selective HDACI group than in the pan-HDACI group.

Conclusion: This study initially confirmed the efficacy and safety of HDACIs for the treatment of RCC. Due to the limitations of the included studies, more high-quality studies are needed to validate the conclusions.

Abbreviations: AEs = adverse effects, ccRCC = clear cell renal cell carcinoma, HDACIs = histone deacetylase inhibitors, NAD^+ = nicotinamide adenine dinucleotide, ORR = objective response rate, PFS = progression-free survival, RCC = renal cell carcinoma, RCTs = randomized controlled trials.

Keywords: efficacy, histone deacetylase inhibitors (HDACIs), meta-analysis, renal cell carcinoma (RCC), safety

Editor: Ahmed Salah Naser.

This project was supported by Sanya Medical and Health Science and Technology Innovation Project (No. 2019YW13).

All the data derived from the employed databases. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

This research is a meta-analysis of published studies and did not need informed consent. Ethics approval and consent to participate were not applicable to this study.

All authors meet the ICMJE criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

Consent for publication was not necessary, as this study was a "systematic review and meta-analysis." There are no data on individual persons in any form in this article.

No potential conflicts of interest were disclosed.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Chen J, Ren JJ, Cai J, Wang X. Efficacy and safety of HDACIs in the treatment of metastatic or unresectable renal cell carcinoma with a clear cell phenotype: a systematic review and meta-analysis. Medicine 2021;100:31(e26788).

Received: 6 April 2021 / Received in final form: 30 June 2021 / Accepted: 10 July 2021

http://dx.doi.org/10.1097/MD.0000000000026788

1. Introduction

Renal cell carcinoma (RCC) accounts for approximately 85% of primary malignant renal tumors.[1] In the United States, approximately 63,000 new RCC cases and approximately 14,000 deaths due to RCC occur each year.[2] RCC includes clear cell renal cell carcinoma (ccRCC), papillary renal cell carcinoma, and chromophobe RCC. The most common subtype of RCC is ccRCC, accounting for approximately 75% of cases.[3] The main treatment for early-stage RCC is surgical resection, while comprehensive treatment is used for advanced RCC. On the basis of a deepening understanding of the molecular biology of RCC, the treatment of RCC has changed, prompting the development of a large number of targeted drugs.[4]

Recent studies have shown that histone deacetylases (HDACs) play an important role in tumorigenesis.[5–7] HDACs are divided into Class I (HDAC1, HDAC2, HDAC3, and HDAC8), Class IIa (HDAC4, HDAC5, HDAC7, and HDAC9), Class IIb (HDAC6 and HDAC10), Class III (Sirt1–7), and Class IV (HDAC11). Class I and IV HDACs are located in the nucleus, Class IIb HDACs are located in the cytoplasm, and Class IIa HDACs shuttle between the nucleus and cytoplasm.[8,9] Class I, II, and IV HDACs require Zn^{2+}, whereas Class III HDACs require nicotinamide adenine dinucleotide (NAD^+).[10] The main functions of HDACs are to catalyze the deacetylation of histone and nonhistone proteins, inhibit transcriptional activity, and promote the proliferation, invasion and metastasis of cancer cells.[11,12] In addition, RCC has been confirmed to be associated with abnormal expression of HDACs. The expression of HDAC1, HDAC2, and HDAC3 is increased in ccRCC tissues, HDAC4 and HDAC5 levels are decreased in most ccRCC tissues, and HDAC6 is overexpressed in a small percentage of ccRCC tissues; knockdown of HDAC1 or HDAC6 inhibits the proliferation and invasion of ccRCC cells.[13] The loss of the primary cilium, the hallmark of ccRCC, was verified to be associated with increased activities of HDAC6.[14] In addition, lower expression of HDAC10 in RCC tissues than in normal tissues has been observed, and the downregulation of HDAC10 significantly increases the proliferation and invasion of RCC cells.[15] Therefore, histone deacetylase inhibitors (HDACIs) targeting HDACs have become promising drugs for the treatment of RCC.

In general, HDACIs contain a capping group, a zinc-binding domain, and a straight chain linker connecting the 2 domains, and HDACIs inhibit the activity of HDACs by binding to Zn^{2+} in HDACs.[9,16] To date, 4 HDACIs (vorinostat, romidepsin, belinostat, and panobinostat) have been approved by the US Food and Drug Administration (FDA) for the treatment of cutaneous T-cell lymphoma, peripheral T-cell lymphoma, and multiple myeloma.[17] However, pan-HDACIs exert obvious adverse effects, such as thrombocytopenia, diarrhea, and fatigue, and the efficacy of HDACIs in solid tumors is limited, mainly because these tumors are resistant to pan-HDACIs.[18] The focus of current research is on the development of selective HDACIs and their combination with chemotherapy, radiotherapy, and immunotherapy to improve efficacy while reducing tumor resistance to HDACIs.[19]

Through a meta-analysis, we evaluated the efficacy and safety of HDACIs in the treatment of RCC. Then, according to the therapeutic regimen and drug species, subgroup analyses were performed to further explore the administration of HDACIs in RCC. Our study provides preliminary insight into whether HDACs could become new targets for the treatment of RCC and suggestions for drug research and HDACI development, and it can help clinicians individualize the treatment of RCC patients.

2. Methods

Our single-arm meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[20] and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019140055).

2.1. Search strategy

We systematically searched PubMed, EMBASE, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and the Wanfang database for noncomparative clinical studies and randomized controlled trials (RCTs) published from January 1, 2009, to January 1, 2021, without any language restrictions. The primary search terms were as follows: "renal neoplasm, renal cancer, renal carcinoma, renal tumor, kidney cancer, kidney neoplasms, kidney carcinoma, kidney tumor, renal cell neoplasm, renal cell cancer, renal cell carcinoma, renal cell tumor" and "histone deacetylase inhibitors, HDACIs." The integrated searches used for PubMed were as follows: ("Carcinoma, Renal Cell" [Mesh] OR "Kidney Neoplasms" [Mesh] OR "Carcinoma, Renal Cell" [All fields] OR "Kidney Neoplasms" [All fields] OR renal tumor [All fields] OR kidney tumor [All fields] OR kidney carcinoma [All fields]) AND ("Histone Deacetylase Inhibitors" [Mesh] OR "Histone Deacetylase Inhibitors" [All fields] OR HDACIs [All fields]). In addition, the references of the selected studies were reviewed to determine whether any other qualified studies had been missed. The flow chart of the search strategy is shown in Figure 1.

2.2. Selection criteria

The following inclusion criteria were used: adult patients with histologically confirmed metastatic or unresectable RCC with a clear cell phenotype, a life expectancy of at least 12 weeks without any autoimmune diseases, and an Eastern Cooperative Oncology Group performance status ≤ 2, with no restrictions established and no significant differences observed based on sex, race, region, nationality, and pretreatment; the use of HDACI treatment; the performance of comparisons; the objective response rate (ORR), progression-free survival (PFS) rate, and any-grade adverse effects (any-grade AEs) reported as the primary outcomes; and noncomparative clinical study (noncomparative open-label study) or RCT as the study type.

The exclusion criteria were as follows: letters, meta-analyses, reviews, and animal trials; HDACIs not the main treatment for patients with RCC; patients comprising pregnant or lactating women; serious diseases, such as severe cardiac insufficiency, untreated hypertension, severe infection or thromboembolism; fewer than 5 patients in each group; and a lack of usable data.

2.3. Data extraction

The relevant data were extracted from the eligible studies by 2 investigators and included the following variables: name of the first author, publication year, region, age of patients, number of patients in each study, phase of the clinical study, therapeutic regimen, drug type, clinical setting, endpoint, and corresponding

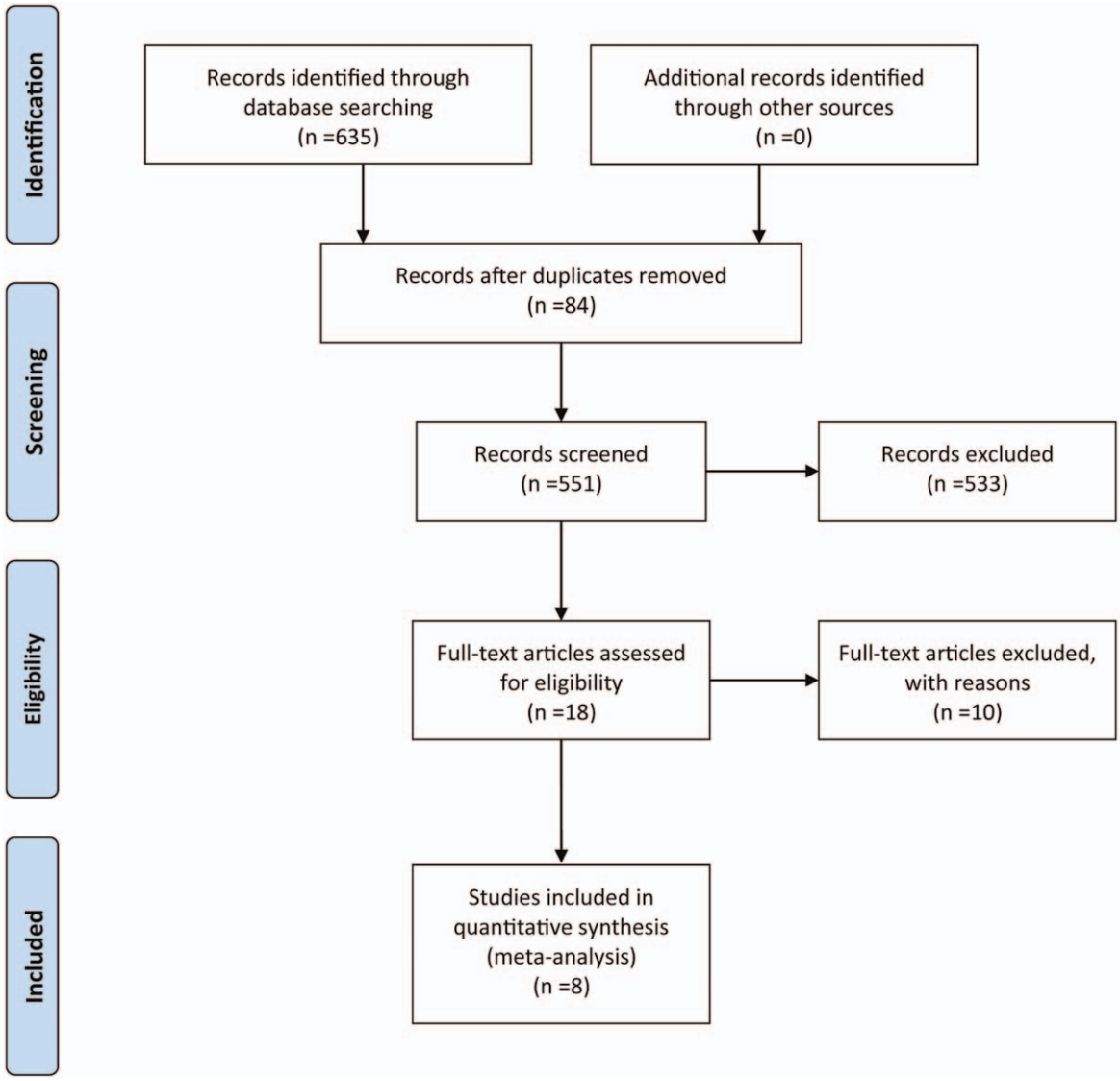

Figure 1. PRISMA flow diagram of studies using HDACIs.

outcome. The main outcomes were the ORR, PFS rate, and any-grade AEs. All of the obtained information and original data were entered into standardized collection tables and checked by a third investigator. Disagreements were settled by consensus after discussion with a third investigator.

2.4. Quality assessment

The Cochrane risk of bias tool was applied to assess the methodological quality of the only randomized controlled study. In addition, the first 8 items on the MINORS scale were used to assess the quality of the single-arm studies that lacked control groups, and the highest score was 16 points.[21]

2.5. Statistical analysis

All statistical analyses were performed using R software (version 3.5.2), and $P < .05$ was considered statistically significant. The total primary outcome rates, numbers of patients and corresponding standard errors calculated by R were then used to assess the efficacy and safety of HDACIs. The final pooled effect sizes were modified by abandoning studies with large variability based on the results of the sensitivity analysis. Heterogeneity among studies was evaluated by the Cochran Q Chi-square test and I^2 statistic, and $P < .10$ indicated apparent heterogeneity. Heterogeneity was classified as low ($I^2 < 50\%$) or high ($I^2 > 50\%$). When P was $< .1$ for the Q test and I^2 was $> 50\%$, which indicated substantial heterogeneity, a random-effects model was used; otherwise, a fixed-effect model was used. Subgroup analyses were performed according to the therapeutic regimen and drug species for the ORR, PFS rate, and any-grade AEs. We used funnel plots to visualize potential publication bias.

3. Results

3.1. Inclusion of articles

The search in PubMed, EMBASE, the Cochrane Library, CNKI, and the Wanfang database and the retrieval of relevant citations yielded 635 potentially relevant articles; 84 duplicate articles

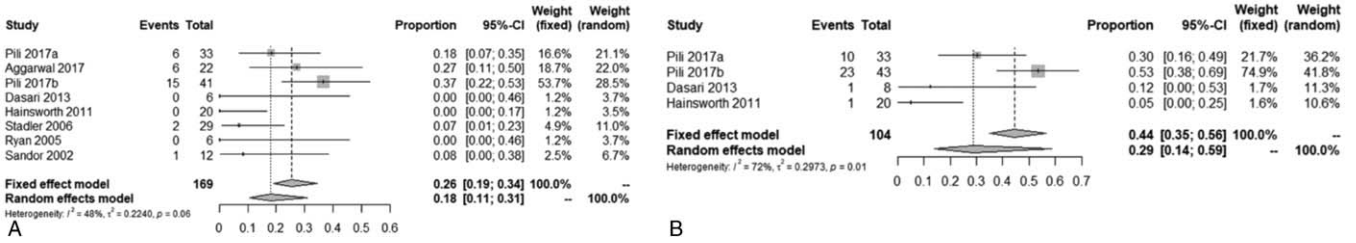

Figure 2. The objective response rate (ORR) and 1-year progression-free survival (PFS) rate were used to investigate the efficacy of histone deacetylase inhibitors (HDACIs) for renal cell carcinoma (RCC) treatment. (A) ORR results for RCC patients treated with HDACIs; (B) 1-year PFS rate results for RCC patients treated with HDACIs.

were deleted. After reading the titles and abstracts, 533 articles were excluded. Then, we fully reviewed 18 articles, and 10 articles (5 with duplicate participants and 5 with fewer than 5 patients) were excluded. Eight articles were included in the meta-analysis, all of which were single-arm studies.[22–29] Basic information on the included articles is provided in Supplementary Table 1, http://links.lww.com/MD/G315.

3.2. Meta-analysis of the ORR

The ORR of HDACIs for the treatment of RCC was reported in 8 studies (I^2 = 48%), and a fixed-effects model was used. The meta-analysis revealed an ORR of HDACIs for the treatment of RCC of 26% (95% CI: 0.19–0.34) (Fig. 2A).

3.3. Meta-analysis of PFS

The 1-year PFS rate of patients receiving HDACIs as a treatment for RCC was reported in 4 studies (I^2 = 72%) and was analyzed using a random-effects model. In the meta-analysis, the 1-year PFS rate of patients receiving HDACIs for the treatment of RCC of 29% (95% CI: 0.14–0.59) (Fig. 2B).

3.4. Meta-analysis of safety

Five studies reported the incidence of fatigue (I^2 = 91%), which was analyzed with a random-effects model. The meta-analysis yielded an incidence of fatigue of 52% (95% CI: 0.33–0.82) (Fig. 3A). The incidence of anemia was reported in four studies (I^2 = 0%); a fixed-effects model was used for analysis. In the meta-analysis, the incidence of anemia was 23% (95% CI: 0.16–0.34) (Fig. 3B). Five studies reported the incidence of neutropenia (I^2 = 62%), which was investigated with a random-effects model. The meta-analysis revealed a neutropenia incidence of 17% (95% CI: 0.08–0.35) (Fig. 3C). The incidence of thrombocytopenia was reported in 5 studies (I^2 = 55%) and was analyzed with a random-effects model. The incidence of thrombocytopenia revealed by the meta-analysis was 35% (95% CI: 0.24–0.51) (Fig. 3D). The incidence of dehydration was reported in 3 studies (I^2 = 0%); a fixed-effects model was used for analysis. The meta-analysis revealed an incidence of dehydration of 16% (95% CI: 0.10–0.26) (Fig. 3E).

3.5. Subgroup analyses

Subgroup analyses were performed based on the therapeutic regimen, with patients divided into a combination group and a monotherapy group. The ORR was higher in the combination group than in the monotherapy group (P = .003), as was the 1-year PFS rate (P = 0.047). However, there were no significant differences in the incidences of AEs between the combination group and the monotherapy group (Table 1).

Subgroup analyses were also performed based on the drug species, with patients divided into a selective HDACI group and a pan-HDACI group. The ORR (P = .017), 1-year PFS rate (P = .042), incidence of neutropenia (P < .001), and incidence of thrombocytopenia (P = .007) were higher in the selective HDACI group than in the pan-HDACI group, while the incidence of fatigue was lower in the selective HDACI group than in the pan-HDACI group (P = .012) (Table 2).

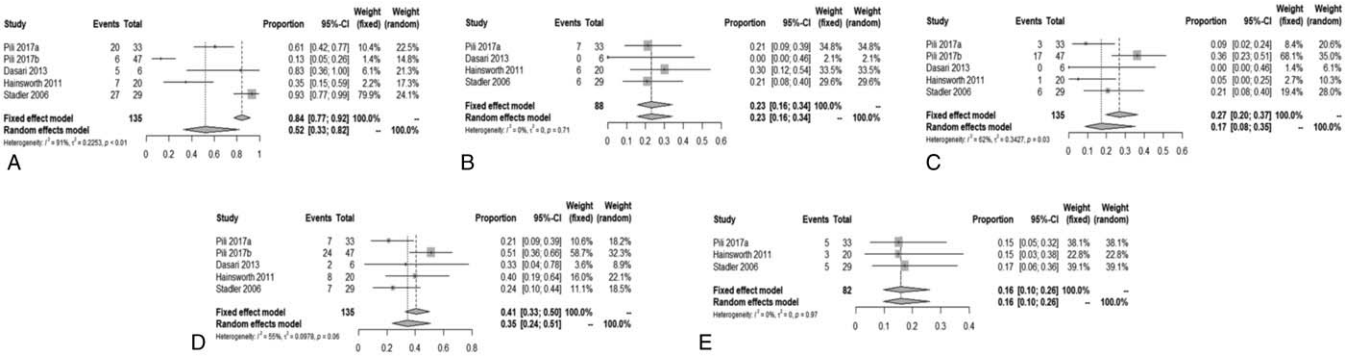

Figure 3. The incidences of fatigue, anemia, neutropenia, thrombocytopenia, and dehydration were used to investigate the safety of histone deacetylase inhibitors (HDACIs) for renal cell carcinoma (RCC) treatment. (A) the incidence of fatigue; (B) the incidence of anemia; (C) the incidence of neutropenia; (D) the incidence of thrombocytopenia; (E) the incidence of dehydration.

Table 1

Subgroup analysis based on regimen were performed to assess the differences in the efficacy and safety between the 2 groups.

	Monotherapy		Combination		M vs C
	Rate	95% CI	Rate	95% CI	*P*
ORR	6%	0.03~0.17	30%	0.22~0.40	.003
PFS rate	5%	0.01~0.34	38%	0.21~0.67	.047
Fatigue	44%	0.21~0.93	60%	0.23~1.00	.619
Neutropenia	18%	0.05~0.57	14%	0.04~0.48	.766
Anorexia	20%	0.11~0.38	25%	0.15~0.41	.573
Thrombocytopenia	35%	0.19~0.66	32%	0.19~0.52	.831
Dehydration	16%	0.09~0.31	15%	0.07~0.34	.881

C = combination, M = monotherapy.

3.6. Publication bias

We registered with PROSPERO. The number of trials included in our study was fewer than 10, and no publication bias test was performed.

3.7. Sensitivity analysis

The sensitivity analysis of the ORR, PFS rate, and incidences of fatigue, neutropenia, and thrombocytopenia showed that the results were stable (Fig. 4).

4. Discussion

New drugs have emerged to treat metastatic ccRCC. The mechanism underlying the activity of these drugs is mainly the inhibition of angiogenesis (bevacizumab, lenvatinib, cabozantinib, pazopanib, axitinib, sorafenib, and sunitinib) or the mTOR pathway (everolimus and temsirolimus).[30] However, it is rare for patients to experience definite benefits of targeted therapy, and drug resistance and economic burden remain serious problems for patients.[31,32] Therefore, other drugs with new mechanisms of action are necessary to improve the treatment of patients with advanced RCC. With the development of epigenetic treatments, research on HDACIs has become a hot topic. According to their chemical structure, HDACIs are divided into 5 categories: hydroxamic acids, short-chain fatty acids, benzamides, cyclic tetrapeptides, and SIRT inhibitors. In the future, epigenetic modifying drugs is expected to play a vital role in the treatment of urological tumors. Currently, the most commonly used epigenetic drugs are the HDACIs.[33] HDACIs exert antitumor activity by inducing cell cycle arrest, apoptosis, and autophagy and inhibiting angiogenesis, the activation of oxidative stress, and mitotic cell death.[9,34] A number of preclinical studies have confirmed that HDACIs alone or in combination with other drugs exert strong anti-RCC effects.[35–39] HDACIs alone inhibit the growth of RCC cells by increasing the acetylation of histone 3 and tubulin, whereas the combination of HDACIs with sorafenib [a small molecular multikinase inhibitor of vascular endothelial growth factor receptor (VEGFR)] reduces cell viability by activating caspases and decreasing the levels of myeloid leukemia cell differentiation protein (MCL1), phospho-extracellular signal-regulated kinase (ERK), and secreted VEGF.[35] HDACIs or 5-aza-2'-deoxycytidine (5-Aza) (an inhibitor of DNA methyltransferases) alone suppresses the proliferation of RCC cell lines by promoting apoptosis and inducing cell cycle arrest, and the 2 drugs administered in combination exert a synergistic antiproliferation effect.[36] In other studies, HDACIs combined with programmed cell death protein 1 (PD-1) inhibitors, receptor tyrosine kinase (RTK) inhibitors, or 5-fluorouracil significantly restrained RCC cell growth, and the effect of the combination was significantly better than that of HDACIs alone.[37–39] However, due to the different expression of HDACs in tumors and the resistance of tumors to HDACIs, the therapeutic effect of pan-HDACIs on solid tumors is limited in clinical practice.[16,18,40] Furthermore, the effects of different subtypes of HDACs on RCC are not the same.[13–15,41] The administration of pan-HDACIs may have the dual effects of promoting and suppressing tumorigenesis, affecting their effectiveness and safety.

A total of 8 articles were included in this study. Through a preliminary review of these articles, it was found that when HDACIs were used in combination with other drugs, anti-RCC therapeutic effects could occur, and most of the drugs used in combination with HDACIs were related to the inhibition of angiogenesis. However, the anti-RCC effect of HDACIs alone was unsatisfactory, which may be related to the complex

Table 2

Subgroup analysis based on HDACIs were performed to assess the differences in the efficacy and safety between the 2 groups.

	Pan-HDACIs		Selective HDACIs		P vs S
	Rate	95% CI	Rate	95% CI	*P*
ORR	15%	0.09~0.27	30%	0.11~0.83	.017
PFS rate	17%	0.06~0.49	53%	0.40~0.71	.042
Fatigue	68%	0.50~0.97	13%	0.06~0.27	.000
Neutropenia	14%	0.08~0.25	36%	0.24~0.52	.007
Thrombocytopenia	29%	0.21~0.41	51%	0.39~0.68	.012

HDACIs = histone deacetylase inhibitors, P = pan-HDACIs, S = selective HDACIs.

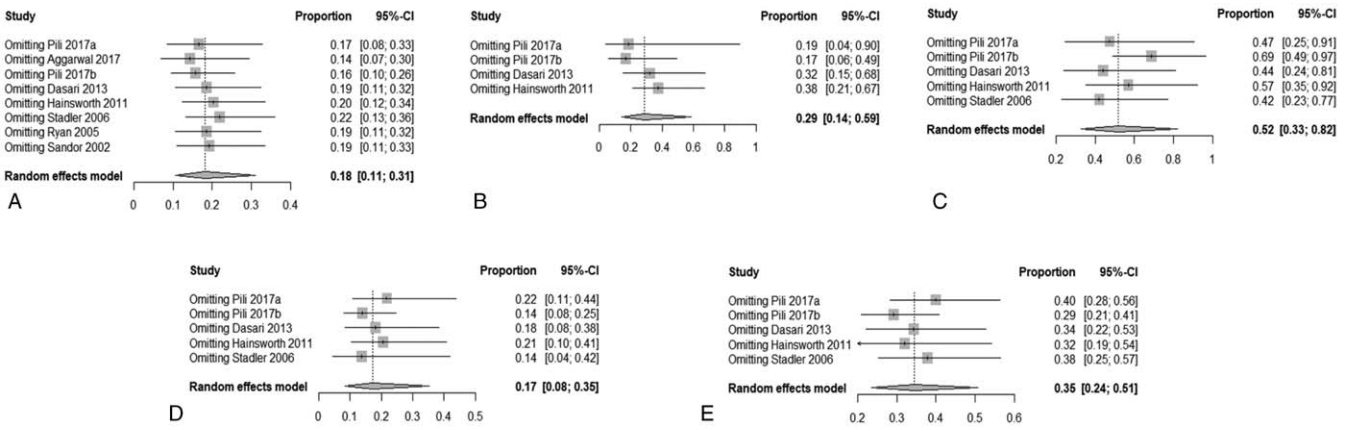

Figure 4. Sensitivity analyses of the objective response rate (ORR), 1-year progression-free survival (PFS) rate, and the incidences of fatigue, neutropenia, and thrombocytopenia. (A) sensitivity analysis of ORR; (B) sensitivity analysis of 1-year PFS rate; (C) sensitivity analysis of fatigue incidence; (D) sensitivity analysis of neutropenia incidence; (E) sensitivity analysis of thrombocytopenia incidence.

functions of HDACs in the human body. Therefore, a meta-analysis of these 8 articles was performed. The meta-analysis showed that the ORR of HDACIs for RCC treatment was 26% (Fig. 2A), the 1-year PFS rate was 29% (Fig. 2B), and the efficacy of combined treatment was greater than that of monotherapy (Table 1). Furthermore, the efficacy of selective HDACIs was greater than that of pan-HDACIs (Table 2). The safety of HDACIs was assessed by calculating the incidences of fatigue (52%) (Fig. 3A), neutropenia (17%) (Fig. 3B), anemia (23%) (Fig. 3C), dehydration (16%) (Fig. 3D), and thrombocytopenia (35%) (Fig. 3E). There were no significant differences in the incidences of AEs between the combination group and the monotherapy group (Table 1). However, the incidences of neutropenia and thrombocytopenia in the selective HDACI group were higher than those in the pan-HDACI group, and the incidence of fatigue was lower in the selective HDACI group than in the pan-HDACI group (Table 2). The results showed that combination therapy and selective HDACIs are more effective than monotherapy and pan-HDACIs, respectively; however, safety needs to be further assessed through additional, comprehensive clinical trials. The development of selective HDACIs and their combination with chemotherapy, radiotherapy, and immunotherapy have promise for the future and should improve the safety and effectiveness of HDACIs for the treatment of RCC.

The results of the present study reveal that HDACIs could be used as emerging drugs and have great development potential for the treatment of RCC. The utilization of selective HDACIs in combination with other drugs appears to be more effective than monotherapy, which may help guide urologists' treatment decisions. However, we acknowledge that the understanding of HDACIs is still incomplete and that research comparing the effects of HDACIs with those of other targeted drugs is lacking; therefore, further research is needed. Moreover, in addition to the combination of HDACIs with other drugs, the combination of multiple HDACIs might become an interesting research direction. HDACs play dual roles in RCC; HDAC1, HDAC2, and HDAC6 can promote tumor development, and HDAC9 and HDAC10 can inhibit tumor development.[13,15,41,42] The combination of multiple selective HDACIs might be more effective than the use of single HDACIs and could avoid the inactivation of tumor suppressor factors in the HDAC family.

The present study has some limitations. First, the sample size of RCC patients in some studies was small. Second, the included studies were all single-arm studies lacking control groups and were unable to be further analyzed to draw conclusions about efficacy and safety. Third, there are few studies evaluating the safety of HDACIs for the treatment of RCC, and few AEs could be included in the meta-analysis. Fourth, some important confounding factors were unable to be eliminated, including patient characteristics (such as sex and age), inhibitor dose, timing of medication, and follow-up duration, which may have affected the outcomes.

5. Conclusion

This meta-analysis preliminarily showed that HDACIs are an effective treatment for RCC, that the anti-RCC effect of HDACIs combined with other drugs was better than that of monotherapy, and that the anti-RCC effect of selective HDACIs was better than that of pan-HDACIs. However, the safety of HDACIs should be further evaluated. Because of the limitations of the quantity and quality of the included literature, large-scale and multicenter RCTs are needed to validate the conclusions of this study.

Author contributions

Conceptualization: Juan Chen, Jia-Ju Ren.
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Formal analysis: Juan Chen, Jia-Ju Ren, Xiaoli Wang.
Funding acquisition: Juan Chen.
Methodology: Juan Chen, Jia-Ju Ren, Jiangxia Cai, Xiaoli Wang.
Software: Jia-Ju Ren, Jiangxia Cai, Xiaoli Wang.
Writing – original draft: Juan Chen, Jia-Ju Ren, Jiangxia Cai, Xiaoli Wang.
Writing – review & editing: Juan Chen, Jia-Ju Ren, Jiangxia Cai, Xiaoli Wang.

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