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Vascular endothelial growth factor (VEGF) antibody significantly increases the risk of hand–foot skin reaction to multikinase inhibitors (MKIs): A systematic literature review and meta-analysis

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Summary

With the use of multikinase inhibitors (MKIs) having emerged in recent years, skin toxicities such as hand–foot skin reaction (HFSR) are primary side effects, and they lack effective prediction methods. Here, we updated a previous systematic review by establishing a meta-analysis of the risk of developing HFSR among patients receiving MKIs and antivascular endothelial growth factor antibody. Publications from PubMed and abstracts presented at the American Society of Clinical Oncology Annual Meeting up to February 5, 2015, were searched to identify relevant studies, and a total of 236 patients with metastatic tumours in nine trials were included for analysis. In the meta-analysis, the pooled incidence rates of all-grade and high-grade HFSR among patients who received the combination therapy were 56.9% [95% confidence interval (CI), 45%-71.1%] and 14.3% (95% CI, 9%-24.2%), respectively, with significant differences observed with MKI monotherapy ($P < .05$). Further subgroup analysis demonstrated that increasing the dosages of bevacizumab (77.8% vs 51.1%, $P = .04$) and MKIs (64.3% vs 52.6%, $P = .02$) significantly increased HFSR incidence. Moreover, combination with chemotherapy exerted a minimal effect on HFSR risk (61% vs 55.3%, $P = .5$). This updated review and meta-analysis confirm the increased risk of HFSR incidence due to the use of MKIs and antivascular endothelial growth factor antibody. Thus, using these therapies requires safety standards.

KEYWORDS
antivascular endothelial growth factor antibody, hand–foot skin reaction (HFSR), HFSR risk, meta-analysis, multikinase inhibitors (MKIs)

1 | INTRODUCTION

Multikinase inhibitors (MKIs) have become popular in antitumour research. Many new MKIs have emerged in recent years. Some of these MKIs have reached significant breakthroughs and revealed potential for tumour treatment. Sorafenib was approved for the treatment of metastatic renal cell cancer (RCC) in 2005 and for unresectable hepatocellular carcinoma in 2007.[1,2] Sunitinib was approved in 2006 for the treatment of both advanced RCC and imatinib-resistant gastrointestinal stromal tumours.[2,3] Other MKIs, such as axitinib, have been developed and gradually applied in tumour treatment.

However, skin toxicities such as hand–foot skin reaction (HFSR) are primary side effects of these new multityrosine kinase inhibitors. All published phase III trials, excluding abstracts without complete toxicity data, have reported grade 3 cutaneous reactions that require therapy modification and that probably affect the clinical benefits.[4-6] Although three decades have passed since HFSR was first described, the pathogenesis of and optimum therapeutic strategy for this skin toxicity remain largely unknown.

Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody that has proven beneficial in cancer therapy. It was approved by the Food and Drug Administration for the treatment of various tumours, including metastatic colorectal cancer, metastatic breast cancer, advanced non-small cell lung cancer, and metastatic renal cell carcinoma. Recent clinical trials have combined MKIs with bevacizumab. Some phase I and phase II trials showed that the combination therapy is effective against various tumours, particularly ovarian cancer, colorectal cancer, and neuroendocrine neoplasm; this finding indicates that the combination therapy may have a promising clinical application in the future.[7-10]

Although the results were encouraging, HFSR incidence was discovered to be higher when MKIs were combined with bevacizumab than when MKIs were used alone. Lee et al[11] demonstrated through a phase I trial that the HFSR incidence is higher in combination therapy with MKIs and bevacizumab than in monotherapy with MKIs, with all-grade and high-grade HFSR incidence rates of 94% and 56%, respectively. However, this finding was not conclusive because of limited enrolment of patients. Other researchers observed the same phenomenon.[8-10]

Therefore, we conducted a meta-analysis and systematic review of the risk of developing HFSR when the combination therapy of MKIs and bevacizumab was used to explore the safety of this therapy and to elucidate the pathogenesis of HFSR.

2 | RESULTS

2.1 | Search results

A total of 78 potentially relevant citations were reviewed. Of the 35 articles identified by searching PubMed, 26 were excluded after review. Our search of American Society of Clinical Oncology (ASCO) abstracts yielded 43 potentially relevant studies, but none of these abstracts met the inclusion criteria. Finally, nine studies[7-15] that met the inclusion criteria were retrieved, including five phase I trials[9-11,14,15] and four phase II trials[7,8,12,13] (Figure 1, Table 1). All were prospective single-arm studies. The sample sizes ranged from 14 to 54 (median sample size, 18 patients).

2.2 | Patients

Data from a total of 236 patients from the nine clinical trials were available for analysis. The baseline characteristics of the patients in the nine studies are listed in Table 1. The trials included various tumour types, such as colorectal cancer, breast cancer, glioblastoma, neuroendocrine tumours, melanoma, and other advanced solid tumours. All enrolled patients were Caucasians. Six trials involving 186 patients used the combination treatment of sorafenib (200 or 400 mg BID) and bevacizumab (5 or 10 mg/kg), two trials involving 34 patients used sorafenib (90-400 mg BID) plus bevacizumab (1-15 mg/kg) and chemotherapy, and one trial involving 16 patients used axitinib (5 mg BID) plus bevacizumab (1-5 mg/kg) and chemotherapy. HFSR was not listed as a pre-existing condition in any of the selected studies.

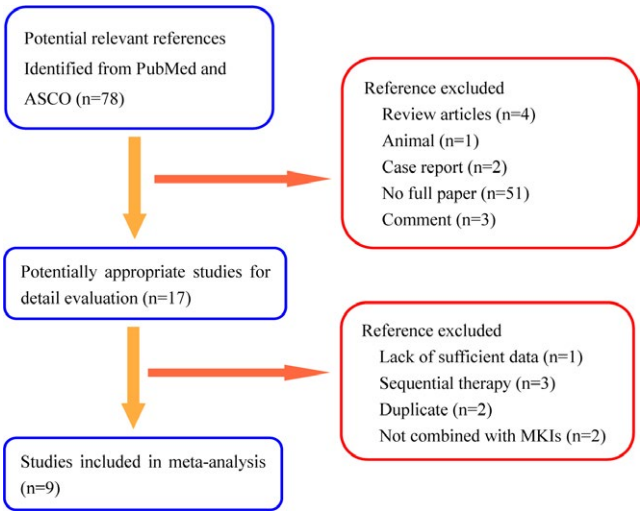


FIGURE 1 Flow chart illustrating the selection of studies

2.3 | Incidence of all-grade HFSR

All studies and all 236 patients had available data on all-grade HFSR for analysis. The reported incidences of all-grade HFSR ranged between 31.2% (5/16) and 79.4% (31/39). As shown in Figure 2A, the pooled incidence of all-grade HFSR in the 236 patients was calculated using the random-effects model (I^2 = 4.8%, P = .4) to be 56.9% (95% CI, 45%-71.1%).

2.4 | Incidence of high-grade HFSR

All studies reported data on high-grade HFSR. High-grade HFSR was defined as grade 3 or grade 4, which can significantly impair patient functioning and affect treatment by necessitating dose reductions or treatment interruption. In our research, the incidence of high-grade HFSR in these studies ranged from 2.5% (1/39) to 33.3% (5/15). As shown in Figure 2B, the pooled incidence of all-grade HFSR in the 236 patients was calculated using the random-effects model (I^2 = 28.1%, P = .2) to be 14.3% (95% CI, 9%-24.2%).

2.5 | Incidence of HFSR in patients treated with different doses of bevacizumab

Subgroup analysis on the dose of bevacizumab (≤5 or ≥10 mg/kg) was conducted to elucidate HFSR pathogenesis. Of the nine trials

TABLE 1 Characteristics of trials included in the meta-analysis

Trial	Year	Phase	Tumour type	Disease stage	Treatment	Dosage	No. cases
Azad NS	2008	I	Solid tumours	Advanced	Bev + Sora	Bev: 5, 10 mg/kg; Sora: 200, 400 mg bid	39
Sharma S	2010	I	Colorectal cancer	Metastatic	Bev + Axitinib + CT	Bev: 1, 2, 5 mg/kg; Axitinib: 5 mg bid	16
Lee JM	2010	I	Solid tumours	Advanced	Bev + Sora	Bev: 5, 10 mg/kg; Sora: 200, 400 mg bid	17
Navid F	2012	I	Solid tumours	Recurrent	Bev + Sora + CTX	Bev: 5, 10, 15 mg/kg; Sora: 90-180 mg bid	19
Schultheis B	2012	I	Solid tumours	Advanced	Bev + Sora + PTX	Bev: 1, 2, 5, 10 mg/kg; Sora: 400 mg bid	15
Mina LA	2013	II	Breast cancer	Metastatic	Bev + Sora	Bev: 5 mg/kg; Sora: 200 mg bid	18
Galanis E	2013	II	Glioblastoma	Recurrent	Bev + Sora	Bev: 5 mg/kg; Sora: 200 mg bid	54
Castellano D	2013	II	Neuroendocrine	Advanced	Bev + Sora	Bev: 5 mg/kg; Sora: 200 mg bid	44
Mahalingam D	2014	II	Malignant melanoma	Advanced	Bev + Sora	Bev: 5 mg/kg; Sora: 200 mg bid	14

included in our analysis, four involved patients treated with bevacizumab at ≤5 mg/kg and another four involved patients treated with bevacizumab at ≥10 mg/kg. The incidence of high-grade HFSR in the ≤5 mg/kg group ranged from 33.3% (4/12) to 61.1% (11/18), whereas that in the ≥10 mg/kg group ranged from 66.6% (4/6) to 80% (4/5). Through the random-effects model, this meta-analysis revealed a pooled incidence of high-grade HFSR of 51.1% in the ≤5 mg/kg group (95% CI, 34.5%-75.6%, I^2 = 0.0%, P = .8) and 77.8% in the ≥10 mg/kg group (95% CI, 38.7%-96.8%, I^2 = 0.0%, P = 1.0). The two groups were significantly different (P = .04; Table 2).

2.6 | Incidence of HFSR in patients with chemotherapy versus no chemotherapy

We explored whether chemotherapy affects the incidence of HFSR during treatment with MKIs and antiangiogenesis agents. In our search, three trials included chemotherapy in their regimen, whereas six did not. The incidence of HFSR ranged from 31.3% (5/16) to 73.6% (14/19) in the chemotherapy group and from 33.3% (18/54) to 79.4% (31/39) in the no chemotherapy group. The pooled incidence of HFSR was calculated using the random-effects model to be 61% (95% CI, 37.5%-99.1%, I^2 = 9.3%, P = .3) in the chemotherapy group and 55.3% (95% CI, 42%-72.7%, I^2 = 17.5%, P = .3) in the no chemotherapy group. The two groups were significantly different (P = .5; Table 2).

2.7 | Difference in HFSR incidence between combination therapy and MKI monotherapy

We investigated the differences in HFSR incidence between combination therapy with MKIs and antiangiogenesis agents and monotherapy with MKIs, such as sorafenib, sunitinib, and pazopanib (incidences were all reported previously).[16-18] We used combination therapy as the control [with relative risk (RR) = 1] to calculate the RR of HFSR for each MKI. As shown in Table 3, the RRs of all-grade and high-grade HFSR were significantly lower for monotherapy with any MKI than for the combination therapy. For sorafenib, the RRs of all-grade and high-grade HFSR were 0.595 (95% CI, 0.528-0.671, P < .001) and 0.618 (95% CI, 0.446-0.857, P = .004), respectively; for sunitinib, the RRs of all-grade and high-grade HFSR were 0.333 (95% CI, 0.293-0.378, P < .001) and 0.381 (95% CI, 0.273-0.533, P < .001), respectively; for pazopanib, the RRs of all-grade and high-grade HFSR were 0.080 (95% CI, 0.058-0.111, P < .001) and 0.103 (95% CI, 0.056-0.189, P < .001), respectively; for axitinib, the RRs of all-grade and high-grade HFSR were 0.513 (95% CI, 0.434-0.607, P < .001) and 0.513 (95% CI, 0.434-0.607, P < .001), respectively.

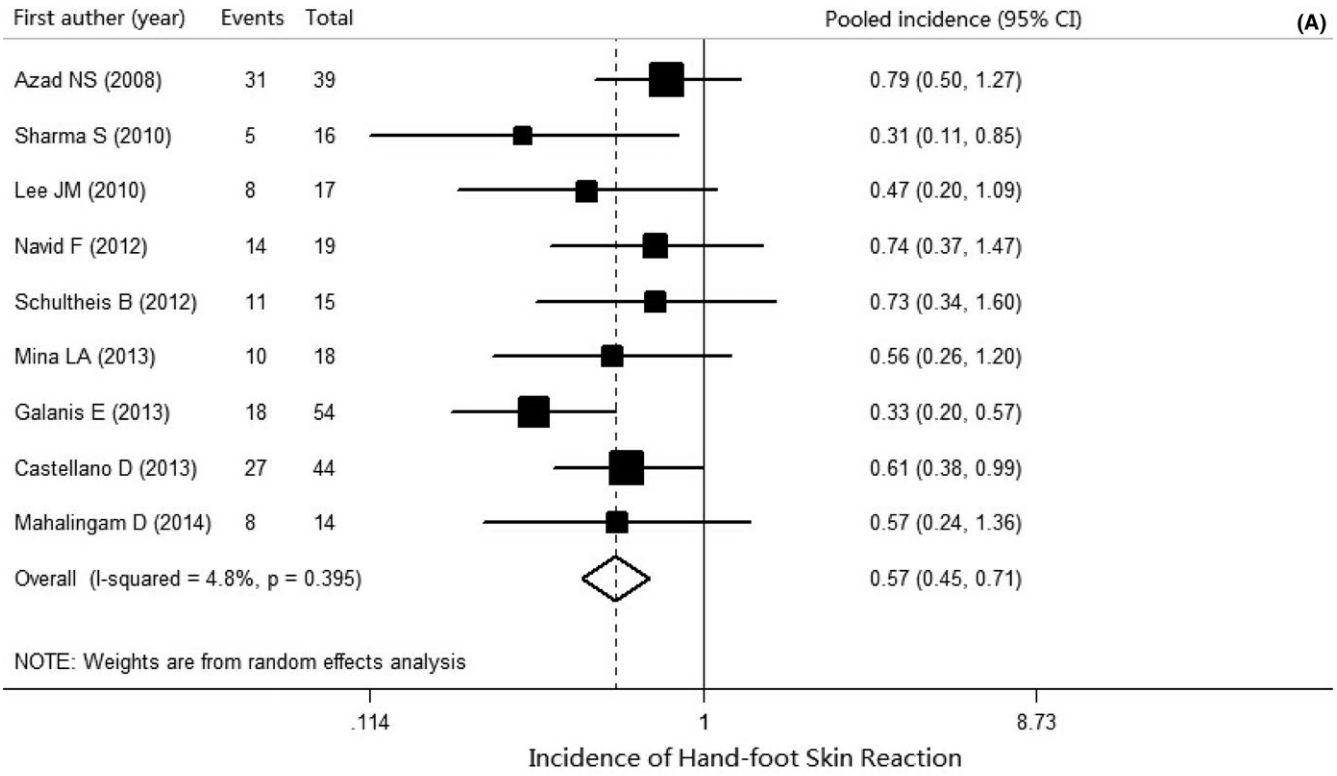
2.7.1 | Publication bias

As shown in Figure 3, the funnel plot was optically symmetrical, indicating the absence of publication bias in this analysis.

3 | DISCUSSION

Our analysis demonstrated that adding the antivascular endothelial growth factor antibody to MKI treatment significantly increases the risk of developing HFSR. The overall incidences of all-grade and high-grade HFSR (grade 3 and grade 4) with the combination therapy were 56.9% (95% CI, 45%-71.1%) and 14.3% (95% CI, 9%-24.2%), respectively. The incidences of all-grade and high-grade HFSR were significantly higher (P < .05, Table 3) with the combination therapy than with any MKI monotherapy. We can expect increased use of the combination of antivascular endothelial growth factor antibody and MKIs. Thus, clinicians must be vigilant for common dermatologic adverse events in these patients to provide timely intervention.

Further subgroup analysis demonstrated that increasing the dosages of bevacizumab (77.8% vs 51.1%, P = .036) and MKIs



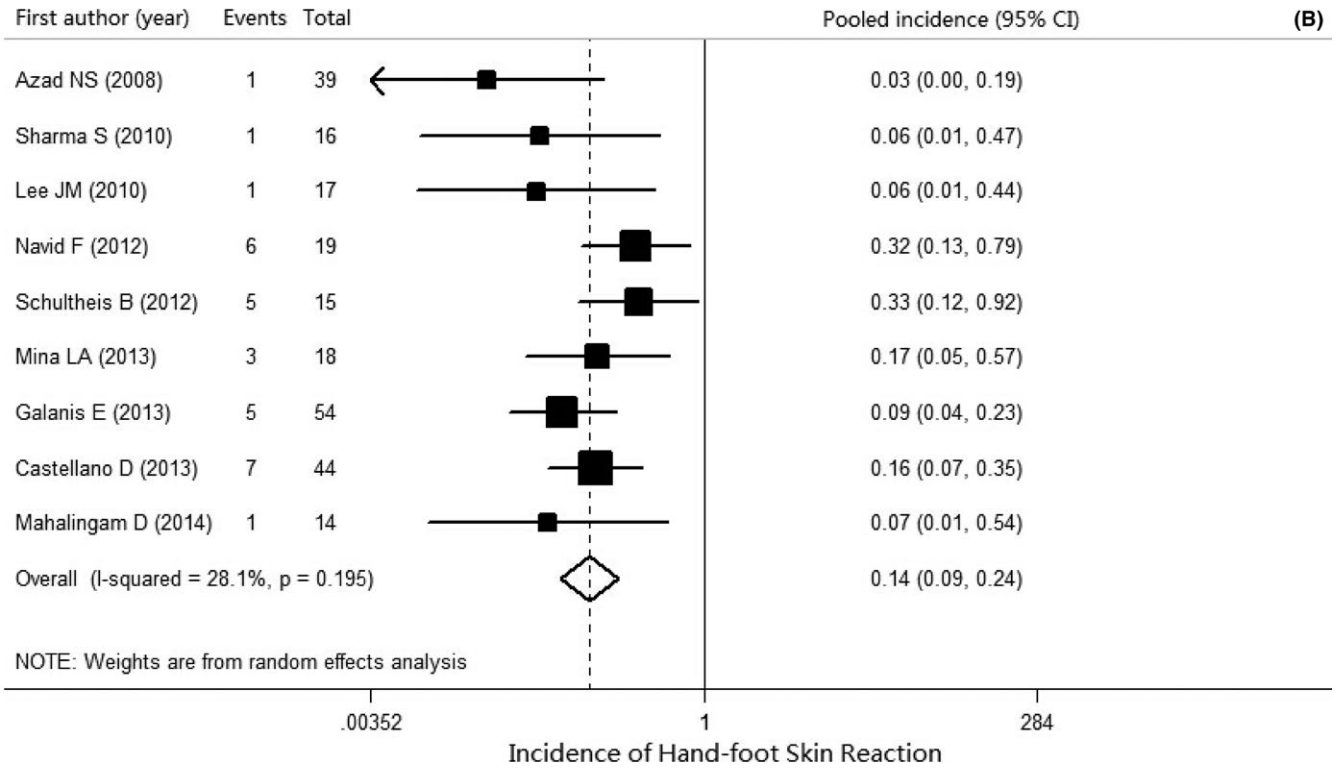


FIGURE 2 Forest plot the incidence of (A) all-grade HFRS and (B) high-grade HFSR in patients with cancer randomly treated with combination MKIs and bevacizumab

TABLE 2 Meta-analysis of incidence of HFS in subgroups on the basis of multikinase inhibitor, dosage of sorafinib, dosage of bevacizumab and combination of chemotherapy

			Pooled risk		Heterogeneity	
Factor	N	Incidence(%)	PI (95% CI)	*P*	*P*	I^2(%)
Multikinase inhibitor						
Axitinib	1	5/16 (31.3)	0.313 (0.114~0.853)	.102	-	-
Sorafinib	8	127/220 (57.7)	0.586 (0.470~0.731)		.433	0.0
Dosage of Sorafenib						
Sora <200 mg, bid	5	77/149 (51.7)	0.526 (0.395~0.699)	.016*	.383	4.2
Sora = 400 mg, bid	3	32/50 (64.0)	0.643 (0.412~1.005)		.690	0.0
Dosage of Bevacizumab						
Bev ≤ 5 mg/kg	4	38/75 (50.6)	0.511 (0.345~0.756)	.036*	.810	0.0
Bev ≥10 mg/kg	4	14/19 (73.6)	0.778 (0.387~0.968)		.984	0.0
Combination of chemotherapy						
With CT	3	30/50 (60.0)	0.610 (0.375~0.991)	.500	.332	9.3
Without CT	6	102/186 (54.8)	0.553 (0.420~0.727)		.301	17.5

CT, chemotherapy; PI, pooled incidence. * $P<0.05$

TABLE 3 Comparison of the risk of HFSR between sorafenib, axitinib, pazopanib and sunitinib relative to combination therapy *$P<0.05$; **$P<0.01$; ***$P<0.001$

Risk subset	Incidence (sample size)	Incidence (sample size)	Risk ratio (95% CI)	*P* value
Sorafinib		Combination therapy		
All-grade	33.8% (3797)	56.9% (236)	0.595 (0.528-0.671)	<.001***
High-grade	8.9% (4020)	14.3% (236)	0.618 (0.446-0.857)	.004**
Sunitinib		Combination therapy		
All-grade	18.9% (4436)	56.9% (236)	0.333 (0.293-0.378)	<.001***
High-grade	5.5% (4281)	14.3% (236)	0.381 (0.273-0.533)	<.001***
Pazopanib		Combination therapy		
All-grade	4.5% (858)	56.9% (236)	0.080 (0.058-0.111)	<.001***
High-grade	1.5% (942)	14.3% (236)	0.103 (0.056-0.189)	<.001***
Axitinib		Combination therapy		
All-grade	29.2% (597)	56.9% (236)	0.513 (0.434-0.607)	<.001***
High-grade	9.6% (577)	14.3% (236)	0.662 (0.444-0.987)	.04*

(64.3% vs 52.6%, $P = .016$) significantly increases HFSR incidence. Meanwhile, combination with chemotherapy exerts a minimal effect on HFSR risk (61% vs 55.3%, $P = .5$). We only compared the HFSR risk of sorafenib and axitinib when combined with bevacizumab because of limited data. The results showed that the HFSR risk with sorafenib treatment is obviously higher than that with axitinib. However, statistical significance was not achieved (58.6% vs 31.3%, $P = .102$), possibly because of the limited number of enrolled cases. These results may serve as a basis for further discussion of HFSR pathogenesis.

Patients receiving MKIs reportedly suffer from many skin toxicities, including mucositis, pruritus, alopecia, skin discoloration, seborrheic dermatitis-like rash, hair changes, xerosis, subungual hemorrhage, and HFSR.[1] Among these skin toxicities, HFSR usually causes dosage adjustment or even treatment interruption. Thus, HFSR is a clinical issue that should be solved because it was reported

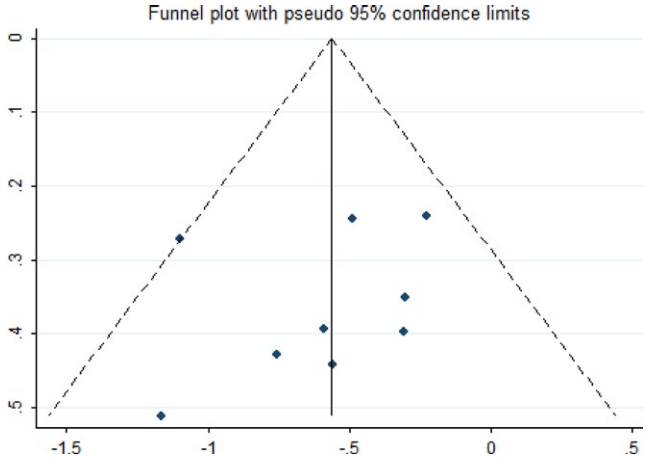


FIGURE 3 The funnel plot of risk ratio for all studies

in all MKI phase II/III trials,[4-6] with incidence rates of 33.8% for sorafenib,[16] 18.9% for sunitinib,[17] and 29.2% for axitinib.[19] The onset period of HFSR ranges from 24 hours to 10 months after taking MKIs, with median times from 6 days to 126 days, which vary widely among case series.[20,21] The clinical features of MKI-associated HFSR differ from those of traditional chemotherapy–associated HFSR, although both types of HFSR present as dysesthesia, tingling, burning sensation, red and swollen skin, and decrustation. MKI-associated HFSR may be likely to present as localized patches not only on pressure-bearing aspects of the palms and soles but also on areas that rub against neighbouring surfaces, such as lateral soles and web spaces, sometimes with simultaneous scalp dysesthesia, angular cheilitis, perianal rashes, and facial erythema resembling seborrheic dermatitis.[22-24] In histopathology, three features predominate both traditional chemotherapy–associated hand–foot syndrome (HFS) and MKI-associated HFSR, namely dyskeratotic keratinocytes at various stages of necrosis, basal layer vacuolar degeneration, and a mild perivascular or lichenoid lymphocytepredominant infiltrate.[25,26] However, HFSR due to MKIs may be associated with a greater degree of epidermal replication and acanthosis than conventional HFSR, indicating that HFSR resulting from MKI treatment may have a unique pathogenesis.[25-28]

The pathogenesis of HFSR still remains unclear, but primary theories to explain HFSR have been developed based on clinical features and histopathologic findings. The most commonly accepted theory of HFSR pathogenesis contends that MKIs cause the syndrome at acral regions via a direct toxic effect.[20] HFSR can occur as early as 24 hours after drug administration, and a correlation between HFSR and MKI dosage was observed in most of the series and trials. A cell-poor lymphocytic interface dermatitis with basilar vacuolar degeneration and dyskeratosis, which is the most common histopathologic pattern observed, is also consistent with direct cytotoxic injury to the epidermis.[22,29] However, evidence of the eccrine secretion of sorafenib and sunitinib onto the acral surface is still lacking, which argues against a direct toxic effect. Our analysis showed that HFSR incidence correlates with sorafenib dosage and that the incidence of HFSR is significantly higher with 400 mg BID than with 200 mg. However, this finding is still insufficient to prove the hypothesis of direct toxic effect.

A previous study reported that combining antiangiogenic therapy with sorafenib and the VEGFR inhibitor bevacizumab increases the incidence and severity of HFSR.[11] Thus, HFSR may be the result of the direct inhibition of target receptors, specifically the dual blockade of VEGFR and PDGFR, in healthy tissue.[30] Given their inhibitory activities against multiple targets of VEGFR and PDGFR, sorafenib, sunitinib, and axitinib increase the risk of developing HFSR; in contrast, HFSR is not common when receptors are individually inhibited, as observed with the PDGFR inhibitor imatinib[31] or with small molecules and monoclonal antibodies that specifically target VEGFR.[32] The present study revealed that the combination therapy of MKIs and bevacizumab significantly increases the risk of HFSR depending on the bevacizumab dosage. Moreover, VEGFR is a critical factor but may not be the only factor that motivates HFSR. This observation suggests that vascular endothelial injury is the leading cause of HFSR.

Although it provided useful information, this study cannot draw other conclusion aside from the fact that VEGFR contributes to the occurrence of HFSR. Chemotherapy exerted a minimal effect on HFSR incidence, suggesting that a direct toxic effect may not be the cofactor of VEGFR that leads to HFSR. This may be attributed to the concentration of drugs at acral regions being too low to stimulate injury. As mentioned previously, PDGFR may be the cofactor because both sorafenib and sunitinib, multitarget inhibitors of VEGFR and PDGFR, increase the incidence of HFSR. From the mechanistic standpoint, PDGFR promotes cell chemotaxis, division, and proliferation. Several studies have confirmed that inhibiting PDGFR can aggravate organism damage.[33,34] Nevertheless, synergetic damage may be caused by other factors, such as immunologic injury. Beard et al[35] proposed that the observed histologic findings in apoptotic keratinocytes with satellitosis of lymphocytes in the absence of spongiosis or neutrophilic infiltrate are consistent with immune-mediated responses, such as GVHD-like response, and sorafenib had a detrimental effect on the DC phenotype and inhibited cytokine secretion, migration ability, and T-cell stimulatory capacity,[36] which may result from immune pathways. Further investigation is warranted to clarify the pathogenesis of HFSR.

Given its beneficial effect on various solid tumours and its clinical potential, combination therapy should be monitored for HFSR incidence. Dose reduction and treatment interruption remain the only rigorously evaluated definitive therapies for HFSR. HFSR resolves within 2-4 weeks of drug cessation[28,37,38] Sorafenib may be used as an interruption therapy for any grade 3 HFSR or for persistent or recurrent grade 2 HFSR. Once HFSR symptoms decline to grade 0-1, therapy should be restarted at one dose level lower than the previous dose (ie, decreasing the dose from 400 mg BID to 400 mg once daily). The fourth occurrence of grade 2 HFSR or the third occurrence of grade HFSR should prompt therapy cessation. Other economical and safe options are pyridoxine,[39] cyclo-oxygenase-2 inhibitors,[40] and steroids.[41] No standard therapy for HFSR exists, and treatment guidelines have largely been based on expert opinions because of

insufficient reliable data on HFSR treatment. Understanding HFSR pathogenesis is necessary to design effective treatments.

This meta-analysis has several important limitations. First, the investigators and institutions involved in the clinical trials included in this study may have varying capacities to detect and thus report HFSR, which may lead to the underestimation of HFSR and, therefore, heterogeneity among the results. However, calculation using the random-effects model in this study possibly minimized some of these problems. Second, all the studies included in the analysis were phase I or II single-arm trials. No placebo-controlled or MKI-controlled RCT was available to determine the RR of HFSR for combination therapy. To further assess the risk, we calculated the RR via indirect comparison of HFSR incidences between combination therapy and monotherapy. Thus, these results should be interpreted with caution. Third, detailed individual data were unavailable; such data may allow for a meta-analysis of HFSR risk based on several factors, such as age, sex, ethnicity, and performance status score. Finally, the results of this study may not be applicable to patients in a private or community setting because most of the patients in enrolled studies were involved in clinical trials performed in major institutions or academic centres.

In conclusion, combination therapy with MKIs and bevacizumab significantly increases HFSR risk. Therefore, using this combination therapy requires safety standards. The understanding of the pathogenesis of HFSR remains inadequate. Nevertheless, this study revealed that HFSR incidence depends on the dosages of MKIs and bevacizumab, implicating the key role of VEGFR in HFSR development. Synergetic factors that possibly lead to HFSR include PDGFR or immune pathways. However, these factors do not present direct toxic effects. Therefore, further studies with large clinical RCTs are necessary to evaluate MKI-associated HFSR and to explore the pathogenesis of HFSR. Improved understanding of this skin toxicity is crucial to suggest novel treatments that alleviate patient discomfort, improve quality of life, and minimize treatment interruptions.

4 | METHODS

4.1 | Data sources

A systematic computerized search of the PubMed database was performed using the following keywords: multikinase inhibitor, VEGF inhibitor, sorafenib, regorafenib, axitinib, or pazopanib; antivascular endothelial growth factor, Avastin or bevacizumab; and hand–foot skin reaction or hand–foot syndrome. Abstracts presented at the ASCO Annual Meeting were also searched. Only papers published up to February 5, 2015, were considered. An independent search using the Web of Science database (a product developed by the Institute for Scientific Information, a citation database) was also conducted to ensure that no additional relevant studies were missed. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. When data were not available, efforts were exerted to contact the investigators. When the same patient population was used in several studies, only the largest and most recent publication was included in the meta-analysis.

4.2 | Study selection

The following criteria were used for study selection: (i) prospective phase I, II, and III clinical trials and expanded access programs in patients with any type of cancer; (ii) assignment of participants to treatment with a multikinase VEGF inhibitor (eg, sorafenib, regorafenib, axitinib, or pazopanib) and an antivascular endothelial growth factor agent (eg, bevacizumab); (iii) available data regarding events and incidence of HFSR; (iv) full papers published in the English language (abstracts were excluded because of insufficient data to evaluate the methodological quality of the study).

4.3 | Data extraction and clinical end point

The final articles included were independently assessed by two authors. Disagreements were resolved via discussion between these two authors. If they could not reach a consensus, another author was consulted to resolve the dispute, and a final decision was reached by majority vote. The clinical end points were extracted from the safety profile in each trial. HFSR incidence was recorded in accordance with the Common Terminology Criteria for Adverse Events, version 3.0.[42] In addition, the following data were collected from each study: the name of the first investigator, the year of publication, the study design, the cancer type, the disease stage, and the treatment protocols. We included the incidences of all patients with HFSR grade ≥1. The name of the lead investigator and the year of publication of the article were used for identification.

4.4 | Statistical analysis

For each study, the proportion of patients with HFSR was calculated, and the 95% CI was derived. The heterogeneity assumption was checked with the χ^2-based Q test. A P value of more than 0.1 for the Q test indicates a lack of heterogeneity across studies. Different evaluation tools are developed due to the characteristics of different study types. Thus, in our study, the pooled incidence of HFSR was calculated using the fixed-effects model (Mantel–Haenszel model). Otherwise, the random-effects model (DerSimonian and Laird model) was used.[43,44] Although meta-analysis has been used as an effective method to address a wide variety of clinical questions by summarizing and reviewing previously published quantitative research, several factors limit the quality of the results, due to publication bias, method of sampling, variations in genetic background of the subjects, and differences in the used protocols.[45] We aimed to minimize these limitations by using appropriate criteria to reduce selection bias, besides a funnel plot was used to estimate potential publication bias, with an asymmetric plot suggesting possible bias. A two-tailed P value < .05 was indicated statistical significance. All statistical tests were performed with STATA 13.0.

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DISCLOSURE

The authors have declared that no conflicts of interest exist.

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