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Assessment of ethnic differences in sunitinib outcome between Caucasian and Asian patients with metastatic renal cell carcinoma: a meta-analysis

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ABSTRACT

Background: An increasing number of studies have reported ethnic differences in sunitinib outcome in metastatic renal cell carcinoma (mRCC) patients. However, a comprehensive analysis is still lacking. Therefore, we systematically collected available published data and performed a meta-analysis to compare sunitinib efficacy and toxicity in Asian and Caucasian mRCC patients.

Methods: Data were extracted from published results from clinical trials, expanded access program and real-world clinical practice. Progression-free survival (or time to tumor progression), overall survival, objective response rate and adverse events were used as endpoints to evaluate the differences of sunitinib outcome between the two ethnicities. For adverse events, we focused the following clinically relevant side effects: diarrhea, fatigue, mucositis/stomatitis, hand-foot syndrome, hypertension, leukopenia, neutropenia and thrombocytopenia.

Results: A total of 33 publications including 9977 patients were available for meta-analysis. The efficacy of sunitinib in Asian patients was similar to that in Caucasian patients. However, Asian patients showed a higher incidence of all grades toxicity of hand-foot syndrome, $>$ grade 2 fatigue, $>$ grade 2 hand-foot syndrome and $>$ grade 2 thrombocytopenia.

Conclusion: Ethnic differences in adverse events of sunitinib in mRCC patients existed and dose adjustment in Asian patients may be considered.

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Renal cell carcinoma (RCC) is the most common type of kidney cancer, accounting for nearly 2% of adult malignancies. About 25–30% of patients have metastatic spread by the time they are diagnosed with RCC [1]. During the past two decades, the therapy for metastatic renal cell carcinoma (mRCC) has undergone a major evolution. Treatment strategies have changed from interleukin-2 and interferon-alpha to targeted therapy including tyrosine kinase inhibitors (TKIs, such as sorafenib, sunitinib, pazopanib, axitinib, cabozantinib and lenvatinib), mammalian target of rapamycin (mTOR) inhibitors (temsirolimus and everolimus), and the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab. More recently, a novel immunotherapeutic drug, nivolumab, has been added to the armamentarium of drugs to treat mRCC.

Sunitinib, an oral TKI, is primarily metabolized by cytochrome P450 (CYP) 3A4 into an active metabolite, SU12662. It received accelerated approval in January 2006 by the Food and Drug Administration (FDA) for the treatment of mRCC. The US approval of sunitinib was based on two single-arm, multicenter studies of single sunitinib treatment in mRCC. Both trials were conducted in the US, and the percentage of Caucasian patients in these studies was 94% and 86%, respectively. In the two studies, sunitinib-treated patients presented an objective response rate of 25.5% (95% CI 17.5–34.9%) and 36.5% (95% CI 24.7–49.6%) [2]. Subsequently, the European Medicines Agency approved sunitinib for RCC in 2007, followed by approval for treatment of RCC in Japan and China in 2008. Sunitinib has become the first-line treatment for mRCC patients in the US, Europe, Australia, Japan, South Korea and Taiwan. Due to the strict reimbursement policies in some Asian countries, sunitinib has so far not yet been widely used as first-line treatment option for mRCC patients [3].

Generally, drug trials for market approval are conducted in western countries first and evaluations in other ethnicities are performed subsequently. It is well known that for certain drugs efficacy and toxicity vary greatly among different ethnicities. One example is that, in 2005, the FDA approved the first race-based drug BiDil for the treatment of heart failure in black patients [4]. Moreover, it was reported that of 167 drugs approved by the FDA between 2008 and 2013, 21% reported some racial or ethnic differences in pharmacokinetics, safety, efficacy or pharmacogenomics in the label [5].

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Supplemental data for this article can be accessed here.

Ample examples of ethnic differences in drug response in the field of oncology are known. Ye et al. [6] compared sorafenib outcomes between Chinese and Caucasian RCC patients. Sorafenib appeared to be more effective in patients of Chinese ethnicity than in Caucasian patients. However, Chinese patients more frequently experienced hand-foot syndrome. Similarly, ethnic differences in the frequency of axitinib-related hand-foot syndrome were found between Japanese and Caucasian patients [7].

Until now, differences in sunitinib outcomes among ethnicities have been investigated in two studies. In 2013, Motzer et al. [8] retrospectively collected data from six clinical trials and reported that there was no significant difference in survival in Caucasian (n = 884) versus Asian mRCC patients (n = 70). However, several sunitinib-induced adverse events such as hand-foot syndrome occurred significantly more often in Asian patients compared to Caucasian patients (70% vs. 28%, $p < 0.001$). In addition, evidence from a global expanded access program (EAP) with 4371 mRCC patients reported a comparable sunitinib efficacy between Asian (n = 325) and non-Asian patients (n = 4046), and major differences in the incidence of all grade stomatitis (39% vs. 26%, Asian and non-Asian patients, respectively), hand-foot syndrome (39% vs. 23%), asthenia (12% vs. 22%), and skin discoloration (25% vs. 9%) [9]. Recently, a prospective, post-marketing study, including 1689 Japanese patients with mRCC, was performed to investigate sunitinib efficacy and toxicity in real-world clinical practice. Hand-foot syndrome as well as thrombocytopenia was observed at higher frequencies and with greater severity in Japanese as compared with Caucasian patients [10].

Although several studies investigated ethnic differences in sunitinib efficacy and toxicity, no comprehensive analysis is available at present. Therefore, we systematically collected available published data and performed a meta-analysis to compare sunitinib efficacy as well as toxicity in Asian and Caucasian mRCC patients.

Materials and methods

Systematic literature search strategy and selection process

A systematic search for publications archived in MEDLINE, EMBASE and Web of Science prior to 9 October 2015 was conducted. A search syntax was compiled by combining 'renal cell carcinoma' AND 'sunitinib' AND 'ethnicity'. Various synonyms and related terms for all subjects were used (the search syntax is supplied in Supplementary document 1). Duplicate articles were removed after manual curation. Initially, articles were scanned by title and abstract. Meeting abstracts, case reports, reviews and meta-analyses were excluded. Reference lists were carefully evaluated to identify additional relevant papers. Only full-text articles published in English, reporting on efficacy and toxicity in single sunitinib treatment were included. The treatment had to consist of an initial regimen of 50 mg daily dose (4-week on/2-week off) or continuous 37.5 daily regimen in mRCC patients.

Endpoints and data extraction

The primary endpoints of this meta-analysis were progression-free survival (PFS), objective response rate (ORR, only complete and partial response have been considered) and adverse events (AEs) in mRCC patients. Overall survival (OS) was regarded as secondary endpoint as PFS more closely reflects drug effects.

From the included articles, the following data were collected: first author, year of publication, sample size, median age, percentage of males, ethnicity (or country, region), sunitinib initial regimen (50 mg daily dose with 4/2 schedule or continuous 37.5 mg daily dose), tumor histology, study setting (clinical trial, EAP, real-world clinical practice), prior treatment percentage, ORR, median OS, median PFS (or time to tumor progression if PFS was not reported), follow-up period, and incidence of AEs. Based on the existing literature [11], we focused on the following clinically relevant AEs, i.e., diarrhea, fatigue, mucositis/stomatitis, hand-foot syndrome, hypertension, leukopenia, neutropenia and thrombocytopenia. AEs higher than grade 2 as well as all grades of AEs were obtained.

Statistical analysis

Meta-analysis was performed based on the survival outcomes coming from the included studies. Individual patient data were reconstructed from the estimated PFS and OS probabilities. Data in each study consisted of PFS or OS and probabilities every five months for the first two or three years after treatment. Details concerning the reconstruction of the data were described in the Appendix (Supplementary document 2). Further technical details were discussed in Fiocco et al. [12,13]. A multivariate random-effects model for a joint analysis of survival proportions reported at different times in the individual studies was used to combine all available information in each article included in the meta-analysis on the endpoint of PFS and OS. Moreover, a series of separate meta-analysis on toxicity data were performed for Caucasian and Asian patients as well. A random effect model was used to pool specific proportion in order to estimate an overall proportion and its associated confidence intervals. Inverse variance method which gives more weight to larger trials was used to pool outcomes for different studies [14]. All statistical analyses were performed in R environments version 2.18 (http://cran.rproject.org/).

Results

Search results

Our systematic search identified 1514 publications. After selecting by title, abstract, inclusion and exclusion criteria, 30 articles remained. Manual curation of reference lists identified three additional papers [15–17]. Finally, a total of 33 publications, including 9977 patients, were available for meta-analyses [2,8–10,15–43]. Of these 33 publications, 19 were eligible for survival analyses, 28 for AEs analysis and 20 for ORR.

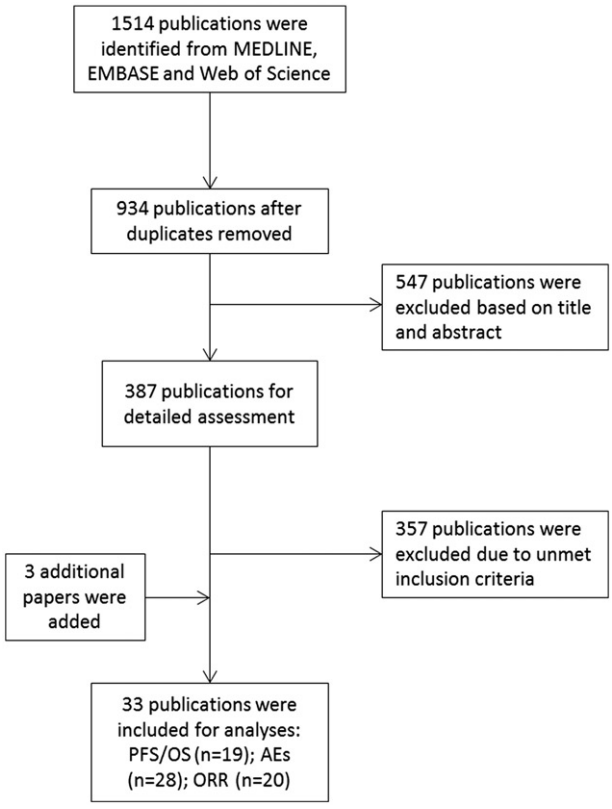


Figure 1. Flowchart of study selection. The original search on the 9 October 2015 resulted in a total of 1514 publications. Three additional publications were included based on manual curation of reference lists. In total 1484 publications were excluded due to duplication (n = 580), title and abstract (n = 547), data were not from single sunitinib treatment or included patients with multiple tumor types (n = 349), dosing regimen was not 50 mg 4/2 schedule or continuous 37,5 mg daily (n = 2), duplicate cohort (n = 3), only elderly or renal insufficient or sunitinib treatment more than 1 year patients were included (n = 3). Finally, 33 publications were included in our paper.

Figure 1 represents a flowchart on the study selection process.

Study characteristics

All studies included were published between 2006 and 2015 (details were provided in Supplementary Table 1). A total of 21 publications included patients from real-world clinical practice (n = 3869), another 11 publications included 1737 patients enrolled in clinical trials, and a large study included 4371 patients who participated in an EAP. In the subgroup of clinical trials and the EAP, Caucasian patients represent >90% of the patients. The median age of the patients per study ranged from 55 to 66 years. Of these patients, more than 70% were males.

Meta-analysis of sunitinib outcomes between Caucasian and Asian mRCC patients

The results of the meta-analysis for all grade toxicities in Asian and Caucasian mRCC patients were displayed in Figure 2. The incidence of hand-foot syndrome in Asian patients (52%, 95% CI 45–60%) was found to be two times higher than that in Caucasian patients (24%, 95% CI 19–29%). Asian and Caucasian patients had a similar incidence of toxicity other than hand-foot syndrome. Pooled incidence of toxicities higher than grade 2 was shown in Figure 3. Asian patients showed a higher percentage of > grade 2 fatigue, hand-foot syndrome and thrombocytopenia of 17 (95% CI 11–13)%, 13 (95% CI 9–17)% and 25 (95% CI 18–32)%, in comparison to Caucasian patients for whom the results were 8 (95% CI 6–9)%, 5 (95% CI 3–7)% and 6 (95% CI 2–10)%, respectively. There were no significant differences of other > grade 2 toxicities.

Figure 4 displayed the estimated pooled mean survival for PFS and OS in Asian and Caucasian patients, respectively. No significant difference was found between Asian and Caucasian patients. For PFS, the hazard ratio for Caucasian patients was 0.900 (95% CI 0.018–1.345, p-value = 0.280). For OS, the hazard ratio was 1.330 (95% CI 0.912–1.330, p-value =0.314).

Results for ORR were shown by ethnicity and stratified by setting (clinical trial, EAP and real-world clinical practice); the results were displayed in Figure 5. ORR for all Asian patients ranged from 14% to 52.4%, and 14% to 47% for Caucasian patients. No ORR data could be found in publications including Asian patients from clinical trials.

An overview of primary and secondary outcome parameters at individual study level was shown in Supplementary Tables 2–4.

Discussion

In the current meta-analysis, we systematically collected available data to compare sunitinib outcomes between Asian and Caucasian mRCC patients. Our results showed that the efficacy of sunitinib in mRCC patients from Caucasian and Asian origin was similar. However, a higher incidence of all grades hand-foot syndrome, > grade 2 fatigue, > grade 2 hand-foot syndrome and > grade 2 thrombocytopenia was observed in Asian patients. In addition, we compared the ORR among three patient settings. The range of ORR of patients from real-world clinical practice appeared to be larger than that from the clinical trial setting. However, the difference of ORR is not as large as we had expected, because the patients from real-world clinical practice usually were more heterogeneous than those enrolled in a clinical trial.

A potential explanation for the observed higher risk of toxicity in Asian patients may be increased drug exposure. As to the pharmacokinetics of sunitinib, Houk et al. assessed the population pharmacokinetics of sunitinib and SU12662 including patients with mRCC, gastrointestinal stromal tumor and other solid tumors. It was shown that the dug exposure (indicated as AUC) and the maximal plasma drug concentration (Cmax) for both sunitinib and SU12662 in Asian patients were about 15% higher compared to other ethnical groups [44]. In addition, Nagata et al. [45] reported that the total trough level of sunitinib in six Japanese RCC patients using 50mg daily 4/2 schedule was higher than 100 ng/ml, whereas the average concentration of total sunitinib in Caucasian male patients (body weight: 77 kg, 50 mg daily dose) stated by Houk et al. [44] was 30–90 ng/ml. Of note, in the studies

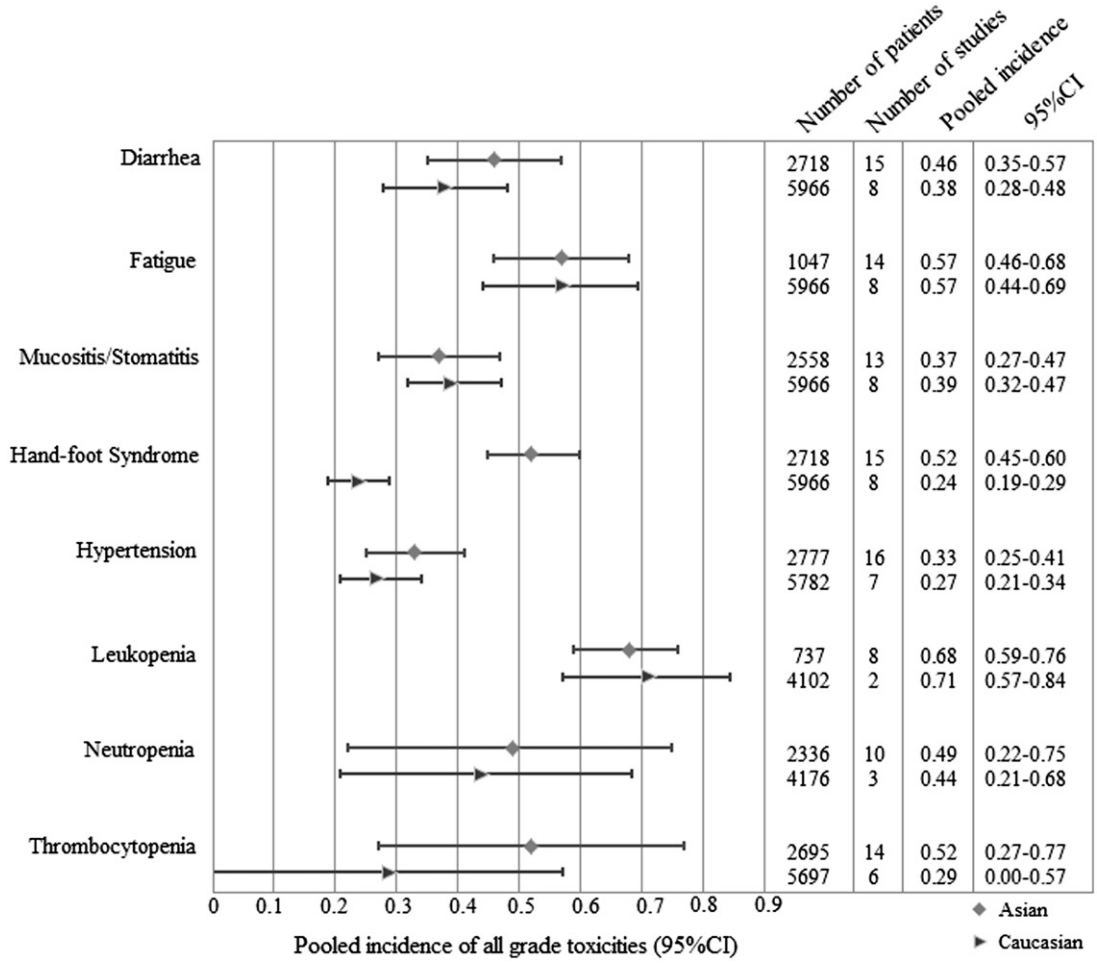


Figure 2. Pooled incidence of all grade toxicities.

included in our meta-analysis, sunitinib was administrated as a standard daily dose of 50 mg in a 4-week on/2-week off schedule. Compared to the Caucasian population, Asian people in general have a relatively lower body surface area (BSA), and as a result drug exposure in Asian patients may be higher after a standard dose. However, no or only a relatively small effect of BSA on sunitinib pharmacokinetics was identified in both Caucasian [44] and Japanese patients [46]. In contrast, the lean body mass (LBM) has recently been identified to be related with sunitinib and SU12662 exposure in 92 patients with solid tumors. The authors reported that patients with a lower LBM had a higher sunitinib and SU12662 exposure [47]. Compared to Caucasians, Asian patients in general have a lower LBM [48], and therefore might have higher exposure of sunitinib and SU12662.

The ethnic differences in sunitinib pharmacokinetics and toxicity incidence may at least in part be explained by the diversity in allele frequencies of variants in genes encoding enzymes and transporters involved in drug absorption and metabolism. The association of sunitinib-induced toxicities with pharmacogenetic determinants was studied by Kim et al. in 65 Korean mRCC patients [49]. Compared to C-allele carriers, patients with the AA variant genotype of the drug transporter *ABCG2* rs2231142 had an increased risk for grade 3 or 4 thrombocytopenia, neutropenia and hand-foot syndrome [49]. As to the relation of this SNP with pharmacokinetic parameters, Mizuno et al. clarified the effect of the *ABCG2* rs2231142 genotype in 19 Japanese RCC patients [50,51]. The clearance/F estimated in A-allele carriers of rs2231142 was approximately 50% of that in patients with CC genotype. Compared to CC-genotype patients, the dose-adjusted $AUC_{0\text{-}24}$ of sunitinib was significantly higher in A-allele carriers. It was shown that the steady-state plasma concentrations in A-allele carriers on the daily dose of 25 mg were in the same concentration range (60–80 ng/ml) as seen in CC-genotype patients on the standard 50 mg daily dose. In another cohort with 66 mRCC patients from France, the association of *ABCG2* rs2231142 with sunitinib and SU12662 has been confirmed [47]. Considering that the variant allele A is more common in Japanese, Korean and Chinese (about 30%) than in Caucasian (10%) [52], the ethnic difference in minor allele frequency (MAF) of this SNP might be an underlying cause of the higher sunitinib toxicity reported in Asian patients. In addition, the genetic variant rs776746 G > A in the drug-metabolizing enzyme CYP3A5 is associated with the defective CYP3A5 expression, resulting in a decreased conversion of sunitinib into SU12662. It has been reported that sunitinib exhibited more dermatological toxicities (among which hand-foot syndrome) compared to SU12662 [53]. Garcia-Donas et al. reported the association of *CYP3A5**3 with toxicity-related dose reduction in 101 Spanish mRCC patients [54]. *CYP3A5**3 is common is Asian (34%), but rare in

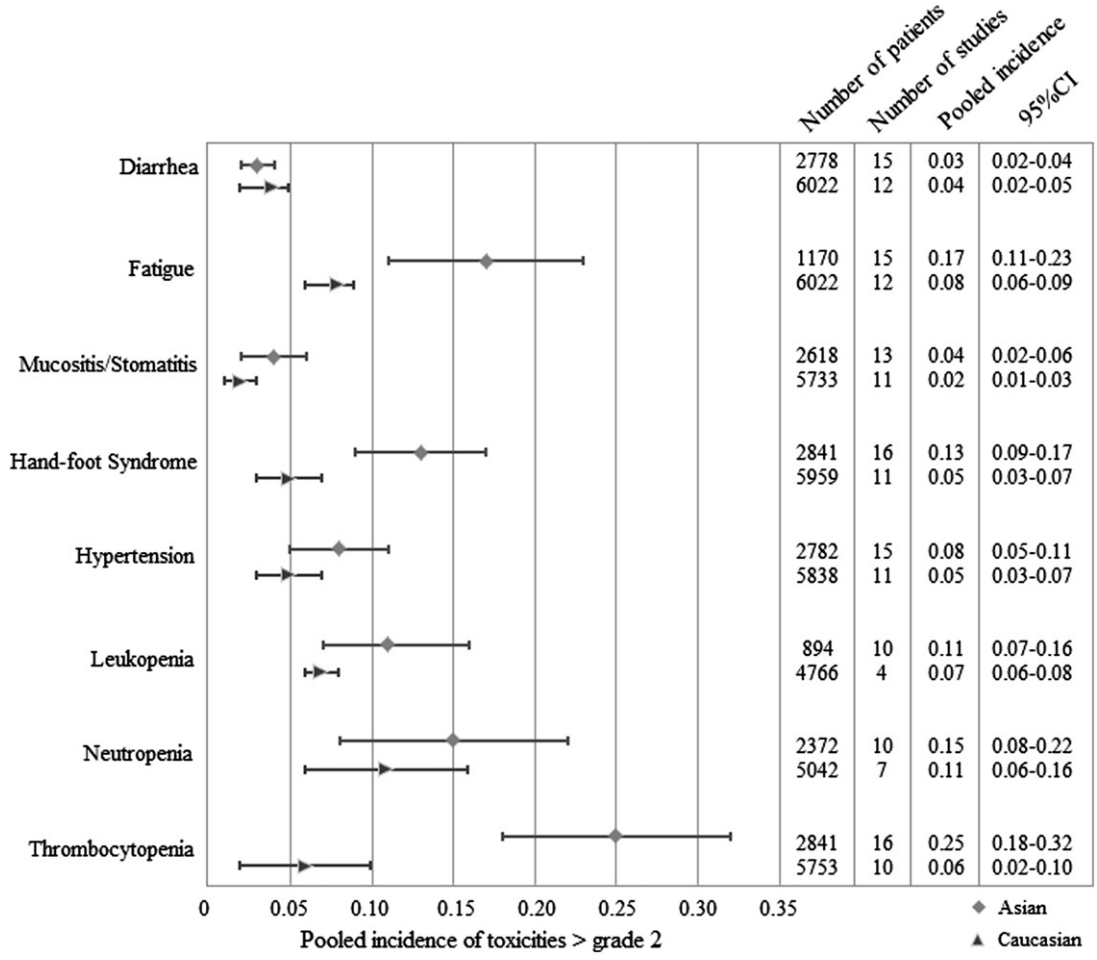


Figure 3. Pooled incidence of higher than grade 2 toxicities.

Caucasians (4%), implying the potential effect of this SNP on the different incidence of hand-foot syndrome between two ethnical groups. It has been assumed that *CYP3A5**3 is linked with higher sunitinib exposure. The potential association has been explored in Caucasian [55] and Asian mRCC patients [56]. However, no clear correlations between *CYP3A5**3 and sunitinib exposure were observed in either population.

Moreover, a recent retrospective study in 114 Caucasian patients with sunitinib treatment showed that *CYP3A4**22 (rs35599367 C > T) was associated with decreased sunitinib clearance [55]. It has been reported that activity of CYP3A4 enzyme is particularly sensitive to dietary effects [57]. Although the potential effect of food on sunitinib pharmacokinetics was not supported by the phase I study in healthy subjects, in which no difference of sunitinib and SU12662 pharmacokinetics was found between patients with single dose of sunitinib after either 10-hour fast or a high-fat meal, the effect of long-term cooking habit, such as the frequently used CYP3A4-inhibiting spices [58], could not be ignored.

The effect sizes of above-mentioned factors are relatively small compared to the inter-individual variability of pharmacokinetic characteristics of 32.2% and 42.9% in clearance of sunitinib and SU12662 reported by Diekstra et al. [55], and even higher variability published by Houk et al. (37.9% and 52.2%, respectively) [44].

Besides the comparison between Asian and Caucasian patients, an interesting subgroup analysis is the comparison between Asian patients from Asian sites (Asian-A) and Asian patients from non-Asian sites (Asian-O) performed by Lee et al. [9]. It was shown that Asian-O patients had lower incidence of toxicity compared to Asian-A, but had a similar incidence of toxicity as non-Asian patients. This observation points towards the direction of diet and body weight being a major determinant of sunitinib toxicity. Indeed, Park et al. reported that Asians living in the US have a comparable amount of visceral fat to that of European Americans [59]. Moreover, a meta-analysis showed that visceral fat in Japanese population was significantly lower than that in Caucasians [60]. Obviously, visceral fat may modify drug distribution and thus decrease drug exposure in the tumor [61].

In a real-world clinical setting, reimbursement policies in different countries may indirectly contribute to ethnic differences of sunitinib efficacy and toxicity. For example, even though five agents (sorafenib, sunitinib, everolimus, interferon-alpha and interleukin-2) are currently approved by Chinese Food and Drug Administration for mRCC treatment, reimbursement is only available for interferon-alpha and interleukin-2 [62]. This may imply that sunitinib is more frequently used as a second-line treatment of advanced disease patients in some Asian countries compared to Caucasian countries. However, this potential effect does not play a role

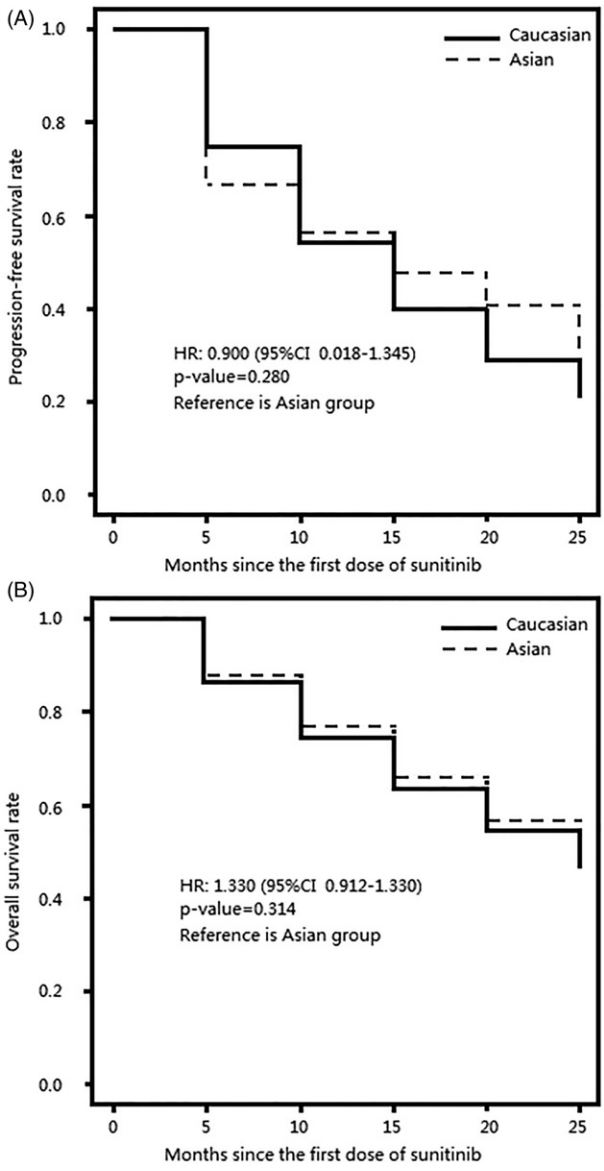
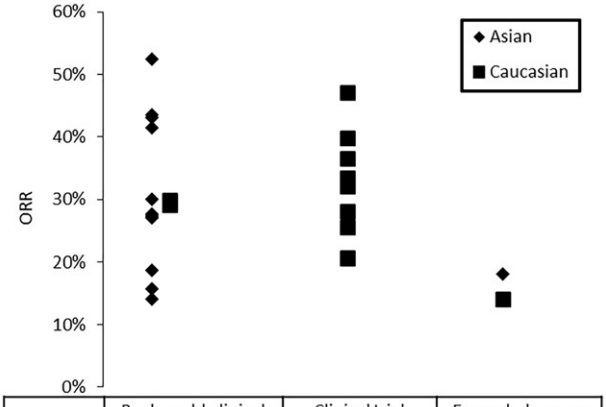


Figure 4. Pooled progression-free survival (A) and overall survival (B).



	Real-world clinical practice	Clinical trial	Expanded access program
Asian	14-52.4%	NA	18%
Caucasian	29-29.8%	20.6-47%	14%

Figure 5. Objective response rate (ORR) stratified by setting. NA: not available.

in our meta-analysis, as no differences in the percentage of patients with prior treatment from Asian or Caucasian countries was observed (Supplementary Table 1).

The present meta-analysis pooled all available data from three different patient settings (clinical trial, EAP and real-world clinical practice). Due to the strict and homogeneous patient selection criteria, drug effects in clinical trials may not be fully representative of real-world clinical practice and data from various types of drugs suggest the existence of a 'trial effect' [63]. Patients from EAP were those who were not eligible to participate in clinical trials due to exclusion criteria or were from countries where regulatory approval had not yet been granted. Therefore, the results from EAP may better reflect, to some extent, the results found in real-world clinical practice. Subgroup analyses could give some insight into inter-setting differences of sunitinib efficacy and toxicity between ethnicities, but the data available at present do not allow for performing such subgroup analyses. However, the comparison of sunitinib efficacy between clinical trial participants and a matched cohort of non-participants was explored by Keizman et al., but no significant difference was observed [63].

Available data indicate that Asian patients more frequently need a toxicity-related dose reduction or discontinuation compared to Caucasian patients with 35–76% versus 24–32%, respectively [20]. It has been suggested that Asian patients should start their treatment with a lower initial sunitinib dose. This approach was evaluated in a prospective study comparing the conventional dose regimen (50 mg daily, 4-week on/2-week off) with an attenuated dose regimen (37.5 mg daily, 4-week on/2-week off) in 160 Singapore mRCC patients. The results showed that patients with attenuated dose regimen had comparable PFS and OS, but had significantly lower incidence of toxicity compared to those with conventional dose regimen. From this study, it seems that Asian patients, with a reduced initial dose, have reached a balance of minimum toxicity and maximum efficacy [20].

The authors would like to point out that this study has some limitations that ought to be considered. There is a lack of standard definition of Asian and Caucasian origin, and it is difficult to designate a multiracial identity. Indeed, the majority of included publications did not report detailed information of ethnicity. Even though we contacted the authors of included studies, no full ethnic data appeared to be available. Therefore, we decided to regard the patients enrolled in Asian countries as Asian and patients enrolled in European and American studies as Caucasian, except when the ethnic data were presented otherwise. Moreover, although sunitinib is a standard-of-care treatment in clear cell RCC, it is acknowledged that efficacy is dependent of histological tumor type [64]. Therefore, we excluded two papers [25,36] with a high percentage of non-clear cell RCC patients, from efficacy analysis.

In conclusion, at a standard dose, Asian patients more frequently experience sunitinib-induced toxicity, such as hand-foot syndrome, fatigue and thrombocytopenia compared to Caucasian patients. No significant ethnic difference of sunitinib efficacy in mRCC patients was found in the present study.

Therefore, dose adjustment in Asian patients may be considered.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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