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**Research Article**

# *Comparative Assessment of the Safety between Pazopanib and Sunitinib for Metastatic Renal Cell Carcinoma*

# Perbandingan Keamanan antara Pazopanib dan Sunitinib untuk Karsinoma Sel Ginjal Metastatik

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***ABSTRACT***

*Renal cell carcinoma (RCC) is the most common kidney lesion with approximately 90% of all kidney malignancies and 30% of people with RCC have developed metastasis at the time of diagnosis. Based on European Association of Urology (EAU) guideline, therapy for metastatic RCC (mRCC) patient who cannot tolerate immune checkpoint inhibitor is pazopanib or sunitinib. However, these drugs cause several uncomfortable side effects for the patient. Therefore, this meta-analysis was made, based on the available evidence base, to compare the safety of pazopanib and sunitinib as the treatment of mRCC. Systematic reviews were made in accordance with the PRISMA guideline requirements, a literature review was conducted in January 2022 used PubMed, ScienceDirect, Cochrane Library, publishing year of at least 10 years with an adult population. And the data is analyzed using RevMan V.5.4. In total 1.665 participants, there were 431 patients taking pazopanib and 1.234 patients taking sunitinib from 8 studies. The result shows that sunitinib has more frequent result of side effects than pazopanib in several occasion like hand-foot syndrome, nausea/vomiting, skin rash, stomatitis & mucosal inflammation, leucopenia and thrombocytopenia. Meanwhile, there are no significant differences between pazopanib and sunitinib in causing other side effect such as fatigue, diarrhea, hypertension, anemia, and increased liver enzymes. The conclusion is that pazopanib is better and has less frequent side effects than sunitinib.*

***Keywords:*** *Metastatic renal cell carcinoma, pazopanib, safety, sunitinib*

**ABSTRAK**

Karsinoma sel ginjal (KSG) merupakan keganasan ginjal tersering yang mencapai 90% dari semua keganasan ginjal dan 30% diantaranya telah mengalami metastasis saat terdiagnosis. Berdasarkan pedoman dari *European Association of Urology* (EAU), terapi pasien KSG metastatik yang tidak sanggup menggunakan penghambat *checkpoint* imun adalah pazopanib atau sunitinib. Namun, kedua obat ini beberapa efek samping yang mengganggu pasien. Meta analisis ini kami buat untuk membandingkan keamaan pazopanib dan sunitinib sebagai pengobatan KSG metastatik. Penelitian ini menggunakan metode tinjauan literatur sesuai pedoman PRISMA dengan menggunakan basis data PubMed, ScienceDirect, dan Cochrane Library dengan batasan 10 tahun terahir dan populasi pasien dewasa. Semua data dianalisa menggunakan RevMan V.5.4. Terdapat total 1.665 partisipan dari 8 penelitian, 431 diantaranya pasien mengkonsumsi pazopanib dan 1.234 sisanya mengkonsumsi sunitinib. Hasilnya menunjukkan bahwa sunitinib menimbulkan efek samping yang lebih sering dibanding pazopanib seperti sindrom hand-foot, mual/muntah, ruam kulit, sariawan & radang mukosa, leukopenia dan trombositopenia. Namun, efek samping lain seperti lelah, diare, hipertensi, anemia, dan peningkatan enzim hati akibat kedua obat tersebut ternyata tidak terdapat perbedaan yang berarti. Maka disimpulkan bahwa pazopanib lebih baik dan lebih jarang menimbulkan efek samping dibanding dengan sunitinib.

**Kata Kunci:** Karsinoma sel ginjal metastatik, keamanan, pazopanib, sunitinib

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## INTRODUCTION

Renal cell carcinoma (RCC) is the most common solid lesion within the kidney and accounts for approximately 90% of all kidney malignancies. It comprises different RCC subtypes with specific histopathological and genetic characteristics. There is a 1.5:1 predominance in men over women with a higher incidence in the older population (1).

Renal cell carcinoma represents around 3% of all cancers, with the highest incidence occurring in Western countries. In Europe and worldwide the highest incidence rates are found in the Czech Republic and Lithuania. Generally, during the last two decades until recently, there has been an annual increase of about 2% in incidence both worldwide and in Europe leading to approximately 99,200 new RCC cases and 39,100 kidney cancer-related deaths within the European Union in 2018 [1]. Up to 30 % of patients with RCC have metastatic disease at the time of diagnosis. According to criteria established by the Memorial Sloan-Kettering Cancer Center (MSKCC) and the advanced renal cell carcinoma (ARCC) trial, most poor-risk patients survive for less than 1 year with a median overall survival (OS) of 5–10 months (2).

Small-molecule tyrosine kinase inhibitors (TKIs) have been the standard first-line systemic treatment for metastatic renal cell carcinoma (mRCC) for over a decade, with sunitinib and pazopanib being the most commonly used drugs. Phase III trials showed progression-free survival (PFS) ranging from 8 to 11 months with either sunitinib or pazopanib, with objective response rates (ORR) of approximately 30% and acceptable tolerability profiles (3).

Invasive procedures in patients with metastatic RCC have a high risk. Fortunately, in several recent studies, such as the CARMENA study, which compared patients who underwent cytoreductive nephrectomy with sunitinib compared to patients taking sunitinib alone, that results did not find any inferiority between those two. this can provide a new choice that treatment for mRCC can be done in a non-invasive way. Beside sunitinib, there are a lot of tyrosine kinase inhibitors such as sorafenib, pazopanib, axitinib, cabozantinib, Lenvatinib, and tivozanib. But, only pazopanib from all those TKIs that European Association of Urology (EAU) therapy guideline for 1$^{st}$ line IMDC favorable mRCC patient treatment-naïve patients that can't tolerate immune checkpoint inhibitor is recommended beside sunitinib (1). This shows how important both pazopanib and sunitinib for mRCC patients. Both of these drugs also available in Indonesia.

Unfortunately, both of this TKIs drugs give some inconveniences adverse events. Some of these side effects are quite disturbing the patient's discipline in taking the drug (Table 1). This most common adverse events with sunitinib or pazopanib include fatigue, arterial hypertension, stomatitis, diarrhea, hand-foot syndrome, thrombocytopenia, and increased levels of alanine aminotransferase (3).

**Table 1. List of side effects from TKIs**

| No. | Side Effects |
|---|---|
| 1. | Fatigue |
| 2. | Hand-Foot Syndrome |
| 3. | Nausea / Vomiting |
| 4. | Diarrhea |
| 5. | Hypertension |
| 6. | Rash |
| 7. | Stomatitis |
| 8. | Mucosal Inflammation |
| 9. | Anemia |
| 10. | Leukopenia |
| 11. | Thrombocytopenia |
| 12 | Increased ALT/SGPT |

This meta-analysis was made based on the available evidence base to comparing the safety of pazopanib and sunitinib for the treatment of mRCC.

## METHOD

Systematic review was made in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Figure 1) guidelines requirements, a literature review was conducted in January 2022 using PubMed, ScienceDirect, Cochrane Library (4). Database search was limited to a minimum of 10 years of publication with adult population. Searches carried out using the terms: Pazopanib, Sunitinib, mRCC or metastatic Renal Cell Carcinoma.

Inclusion and exclusion criteria were established before searching the literature. Studies that meet the inclusion criteria were as follows: (1). Patients with metastatic Renal Cell Carcinoma diagnosis, (2). Comparing pazopanib and sunitinib, (3). Reported the results of one outcome such as: fatigue, hand-foot syndrome, nausea/vomiting, diarrhea, hypertension, skin rash, stomatitis & mucosal inflammation, hematology routine test, and elevated *Alanine Aminotransferase* (ALT) / *Serum Glutamic Pyruvic Transaminase* (SGPT), (4). The data is limited to year 2012 until 2022 of publication with retrospective study and English language. Meanwhile, the exclusions criteria from all studies mentioned above are patient who have received TKIs.

Data extraction was done by including the name of the first author and the year the article was used for identification purposes. All authors extracted data independently and held discussions to determine the problem. The results which analyzed were fatigue, hand-foot syndrome, nausea/vomiting, diarrhea, hypertension, skin rash, stomatitis & mucosal inflammation, hematology routine test, and elevated ALT/SGPT.

Newcastle-Ottawa Quality Assessment Scale Tool was used to assess the methodology quality in this meta-analysis using a scale of 1 star until 9 stars (5). The level of evidence was assessed for each study included according to criteria provided by the Oxford Center for Evidence-Based Medicine (6). This procedure was carried out independently by all reviewers. Every dissent is resolved by discussion.

Meta-analysis was carried out using software Review Manager (RevMan V.5.4, Cochrane Collaboration, Oxford, English). Combined Odds Ratio (OR) statistics summary

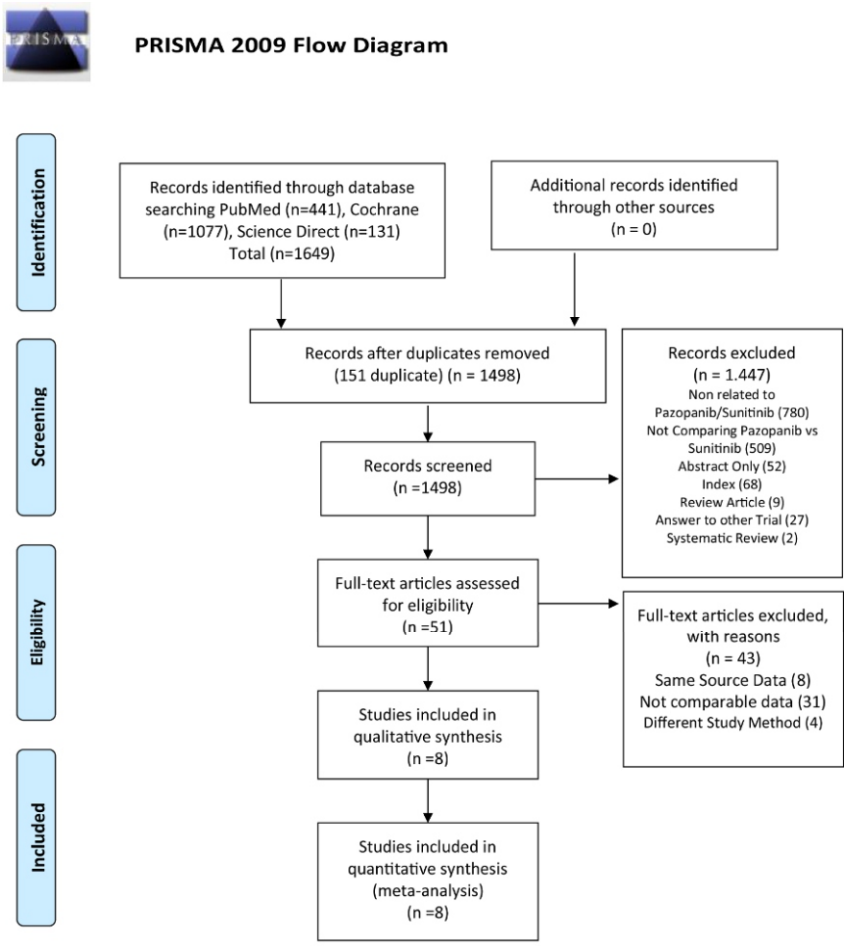


**Figure 1. Study flow diagram based on PRISMA guideline**

**Table 2. Pazopanib vs Sunitinib: Summary of comparative study**

| References | Institution | Intervention | Study Design | LE* | Inclusion Criteria | Cases (n) | |
|---|---|---|---|---|---|---|---|
| | | | | | | Pazopanib | Sunitinib |
| Ekenel, 2020 (7) | Institute of Oncology, Istanbul University, Istanbul (Turkey) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | Patients from two cancer centers in turkey between 2006-2016 that received either SUN or PAZ in the 1st line setting for mRCC | 38 | 41 |
| Hirsch, 2014 (8] | Division of Medical Oncology, Duke University Medical Center (USA) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | Data collection from 466 patients between 2007-2011 that received 1st line therapy | 25 | 270 |
| Kim, 2016 (2) | Asan Medical Center, University of Ulsan College of Medicine, Seoul (Korea) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | Data collection from all patients with mRCC in Asan Medical Center between December 2006-April 2015 that received SUN or PAZ | 72 | 100 |
| Lalani, 2017 (9) | Cross Cancer Institute, University of Alberta, Edmonton (Canada) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | Data were collected from CKCis database between January 2011-November 2015 | 93 | 577 |
| Pierantoni, 2020 (10) | Department of Oncology, Istituo Oncologica Veneto IOV IRCCS, Padova (Italy) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2 | All >70yo patients that receive SUN or PAZ as 1st line treatment with at least 6 month follow up | 37 | 49 |
| Rudresha, 2018 (11) | Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru (India) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2 | Single institutional review of mRCC patients treated between January 2012 – July 2017 | 11 | 24 |
| Uccelo, 2019 (3) | Northampton General Hospital NHS Trust, Cliftonville (UK) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | All >70yo patients that receive SUN or PAZ as 1st line treatment between March 2012 – April 2018 | 23 | 12 |
| Yuan, 2015 (12) | Dana-Farber Cancer Institute, Brookline Avenue, Boston (USA) | Pazopanib 800 mg VS Sunitinib 50 mg | Retrospective | 2b | Electronic medical record from adult cancer patients treated at Dana-Farber Cancer Institute from 2009 to 2012 | 132 | 161 |

**Note:** LE (Level of Evidence, *based on Oxford CEBM Levels of Evidence []), SUN (Sunitinib), PAZ (Pazopanib), mRCC (Metastatic Renal Cell Carcinoma), CKCis (Canadian Kidney Cancer Information System)

were calculated using dichotomous variables. OR were reported with a 95% Confidence Interval (CI). The cochrane Chi Squared Test and inconsistency ($I^2$) were used to assess heterogeneity among studies. P<0.05 was considered to indicate significancy, while $I^2$ <50% was considered to indicate acceptable heterogeneity.

The article search result steps are shown in Figure 1, which resulted in 1.649 articles on search results that had continuity or potentially relevant studies. In the end we got 8 articles that met the requirements, in the selected article we got a total of 431 patients that consume pazopanib and 1.234 patients that consume sunitinib. The case was then processed in a statistical meta-analysis based on selection criteria that have been determined previously.

The characteristic of each study included in the inclusion criteria are shown in Table 2 and 3 (Appendix). The risk of bias from this study is using Newcastle - Ottawa Quality Assessment Scale Tool (5), was shown in the Table 4.

**Table 4. Pazopanib vs Sunitinib: Risk of bias (5)**

| References | Selection | Comparability | Outcome |
|---|---|---|---|
| Ekenel, 2020 (7) | ☆☆☆☆ | ☆☆ | ☆☆☆ |
| Hirsch, 2014 (8) | ☆☆☆ | ☆ | ☆ |
| Kim, 2016 (2) | ☆☆☆☆ | ☆☆ | ☆☆☆ |
| Lalani, 2017 (9) | ☆☆☆ | ☆☆ | ☆☆☆ |
| Pierantoni, 2020 (10) | ☆☆☆☆ | ☆ | ☆☆☆ |
| Rudresha, 2018 (11) | ☆☆☆☆ | ☆☆ | ☆☆ |
| Uccelo, 2019 (3) | ☆☆☆ | ☆☆ | ☆☆☆ |
| Yuan, 2015 (12) | ☆☆ | ☆ | ☆☆ |

**Note:** Risk of Bias, *based on Newcastle - Ottawa Quality Assessment Scale Tool (5)

## RESULTS

### *Fatigue*

Comparison of the Fatigue side effect resulted (OR 0.72, 95% CI 0.42-1.24, p=0.23, Figure 2) with heterogeneity ($I^2$=48%) which means the fatigue side effect in this both drugs is same in all study conducted.

### *Hand-Foot Syndrome*

From this comparison, pazopanib clearly has less side effect than sunitinib. The Hand-Foot Syndrome comparison resulting 0.19 Odds Ratio, (95% CI 0.13 to 0.29, p<0.00001, Figure 3) with heterogeneity between studies conducted ($I^2$=0 %).

### *Nausea/Vomiting and Diarrhea*

The nausea/vomiting side effect, pazopanib group got slightly better result compared than sunitinib with result (OR 0.60, 95% CI 0.37 to 0.98, p=0.04, Figure 4a) with heterogeneity between studies conducted ($I^2$=12%). On the other hand, in the diarrhea comparison side effect neither pazopanib nor sunitinib has better result (OR 1.51, 95% CI 0.87 to 2.60, p=0.14, Figure 4b) with heterogeneity ($I^2$=60%). All studies conducted with meta-analysis results.

### *Stomatitis and Mucosal Inflammation*

Stomatitis and mucosal inflammation comparison, pazopanib is preferable than sunitinib in those both comparison all studies conducted with meta-analysis results. For the stomatitis (OR 0.29, 95% CI 0.11 to 0.74, p=0.009, Figure 7a) with heterogeneity between studies conducted ($I^2$=59%). The mucosal inflammation comparison result (OR 0.27, 95% CI 0.10 to 0.69, p=0.006, Figure 7b) with heterogeneity ($I^2$=48%).

### *Anemia, Leukopenia and Thrombocytopenia*

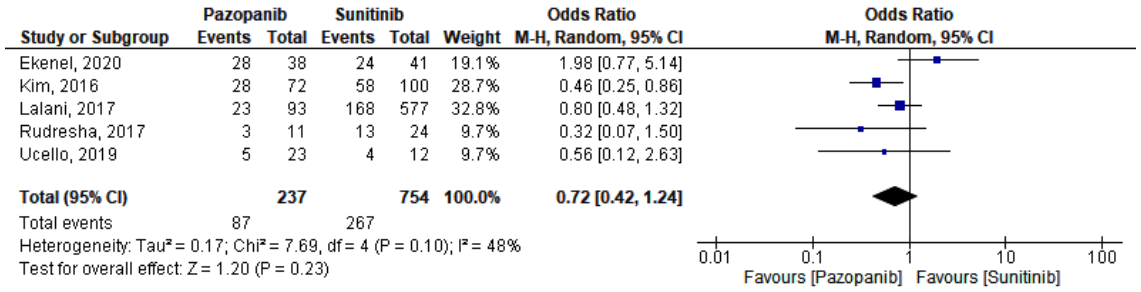


**Figure 2. Forest plot comparison of fatigue**

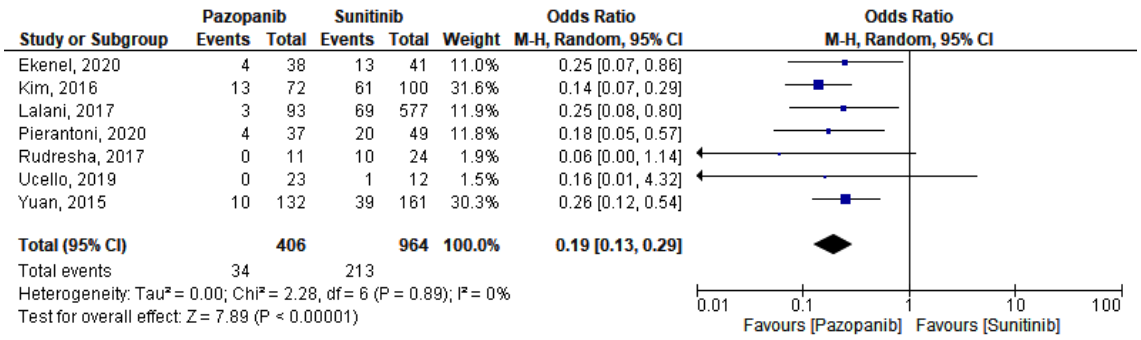


**Figure 3. Forest plot comparison of hand-foot syndrome**

The hematology laboratory comparison, pazopanib has better result except in anemia side effect result that has no significant difference in all studies conducted with meta-analysis results. For the anemia comparison (OR 0.36, 95% CI 0.05 to 2.64, p=0.31, Figure 8a) with heterogeneity between studies conducted ($I^2$=87%). The leucopenia comparison result (OR 0.43, 95% CI 0.23 to 0.79, p=0.006, Figure 8b) with heterogeneity ($I^2$=3%). Thrombocytopenia result (OR 0.19, 95% CI 0.11 to 0.33, p<0.00001, Figure 8c) with heterogeneity ($I^2$=0%).

*Increased ALT/SGPT*

The liver enzyme escalation in both groups have no significant difference, the result is (OR 2.90, 95% CI 0.90 to 9.35, p = 0.07, Figure 9) with heterogeneity ($I^2$ = 75%).

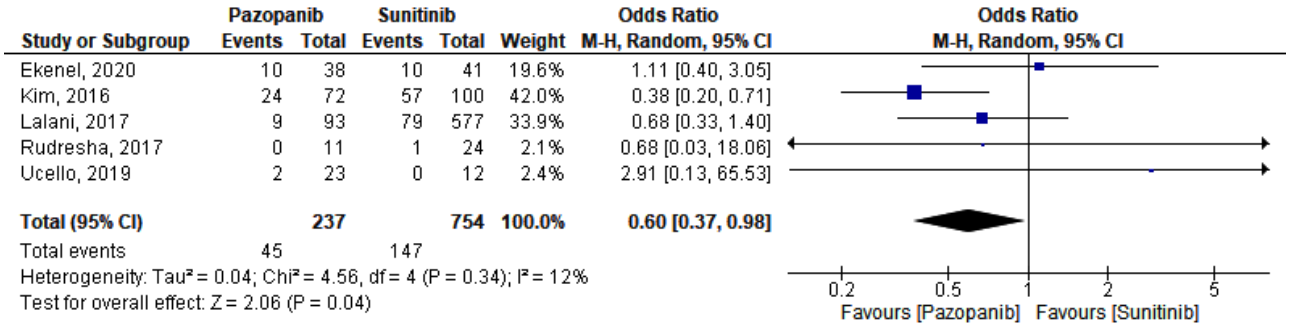


**Figure 4a. Forest plot comparison of nausea/vomiting**

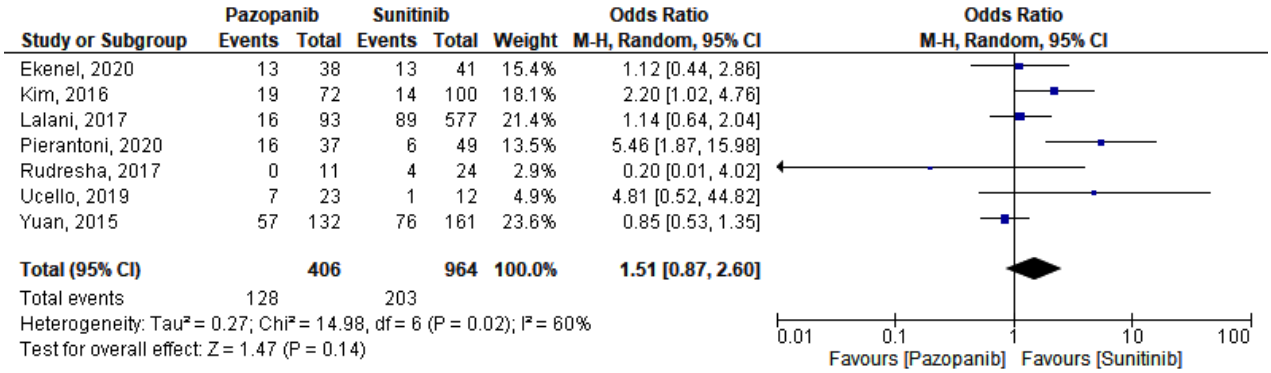


**Figure 4b. Forest plot comparison of diarrhea**

*Hypertension*

Hypertension cases in both groups have no significant difference, the result is (OR 0.76, 95% CI 0.46 to 1.25, p=0.28, Figure 5) with heterogeneity ($I^2$=16%).

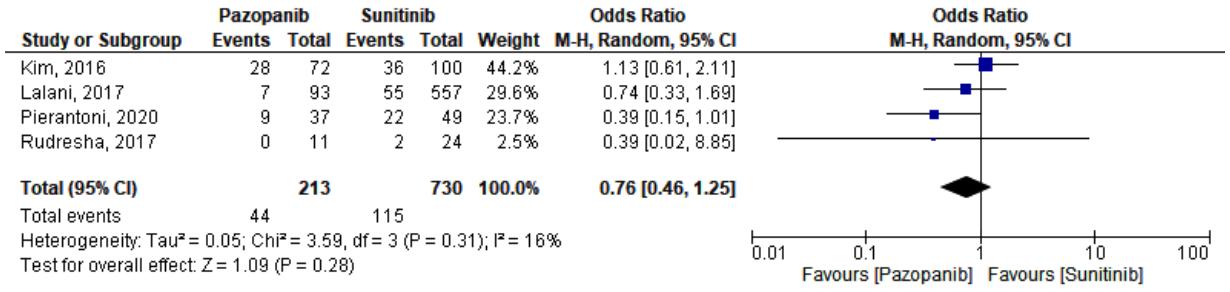


**Figure 5. Forest plot comparison of hypertension**

*Rash*

Comparison of the skin rash resulted (OR 0.37, 95% CI 0.15 -0.95, p=0.04, Figure 6) with heterogeneity ($I^2$=0%) which means pazopanib is less causing skin rash than sunitinib in all study conducted.

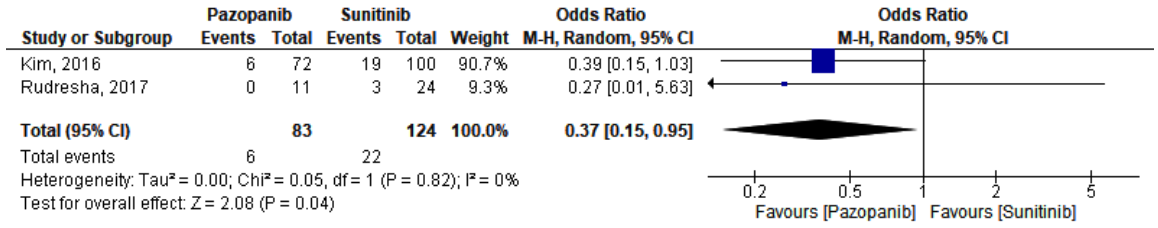


**Figure 6. Forest plot comparison of rash**

## DISCUSSION

Vascular endothelial growth factor receptor (VEGFR) is a receptor in our body that is responsible for angiogenesis and endothelial cell's survival. Inhibition on this receptor has brought new safety profiles into the clinical scenario such as bleeding, renal dysfunction, hand-foot skin reaction and hypertension. Moreover, trials with VEGFR TKIs have consistently reported to increase the incidence of fatigue, hypothyroidism and diarrhea (13). In phase 2 and 3 trials, the incidence of drug-related rash, hand-foot skin reaction, epistaxis, mouth ulceration and stomatitis

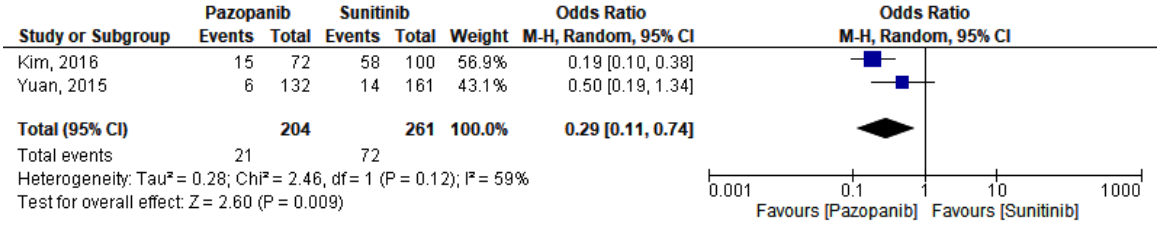


**Figure 7a. Forest plot comparison of stomatitis**

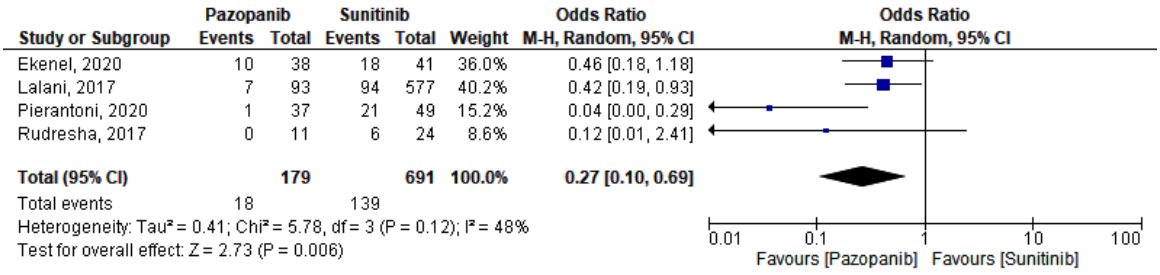


**Figure 7b. Forest plot comparison of mucosal inflammation**

seem to be infrequent and/or low-grade when it presents. It seems that pazopanib has a slightly higher incidence of high-grade ALT and AST elevation and a lower incidence of myelosuppression, rash, mucositis, hand-foot syndrome and fatigue (13). In addition, the other studies that also compare the side effects of pazopanib and sunitinib, COMPARZ and PIESCES showed that pazopanib has less frequent side effects in compare to sunitinib (14,15). There were also several studies in different countries, that comparing about the cost effectiveness between pazopanib and sunitinib. The studies that conducted in United States (16), United Kingdom (17), Canada (18) and in

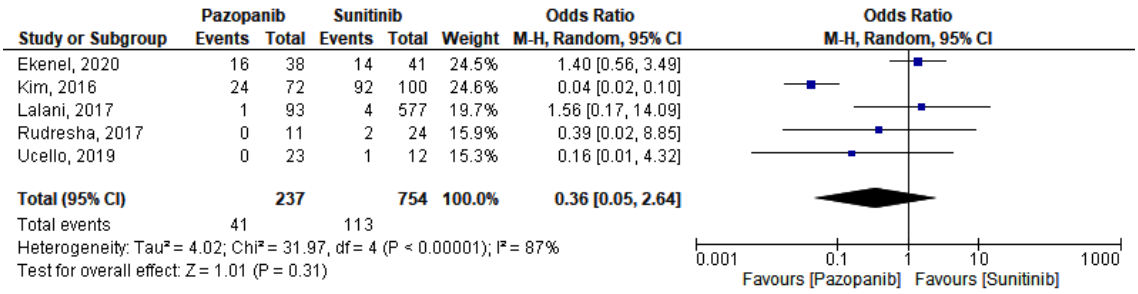


**Figure 8a. Forest plot comparison of anemia**

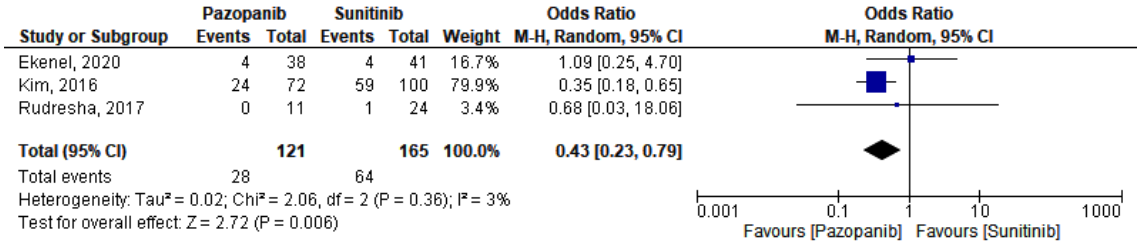


**Figure 8b. Forest plot comparison of leucopenia**

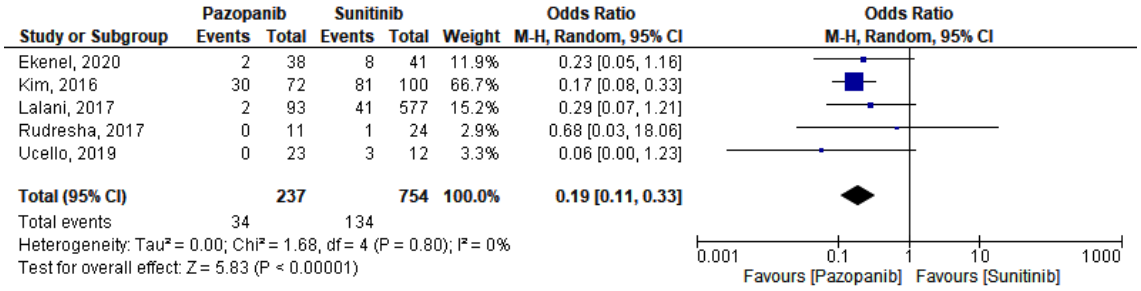


**Figure 8c. Forest plot comparison of thrombocytopenia**

the Italy shows that pazopanib is more cost-effective compared than sunitinib (19). Others studies also shows similar results that proof if pazopanib in better in the viewpoint of cost effectiveness (20-22).

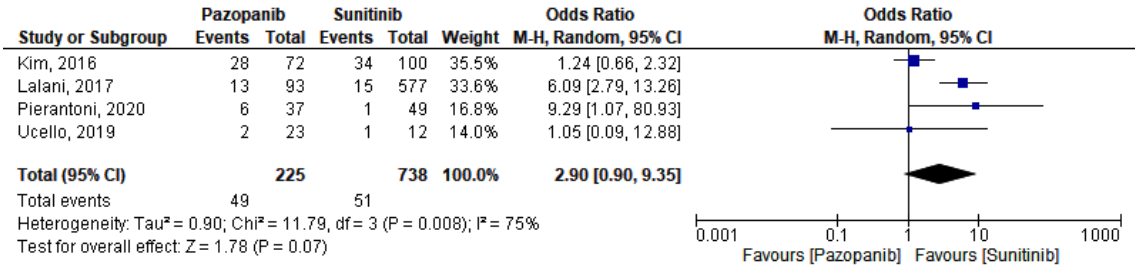


**Figure 9. Forest plot comparison of increased ALT/SGPT**

The result in this study is in line with the researches mentioned above. In our study, from 8 journals, a total of 1,665 people (consisting of 431 people taking pazopanib and 1,234 patients taking sunitinib) showed that Sunitinib caused more significant several side effects than pazopanib such as hand-foot syndrome, nausea/vomiting, skin rash, stomatitis, mucosal inflammation, leucopenia and thrombocytopenia. This can be happened because sunitinib interacted with more receptors than pazopanib. From Figure 10 above, we can conclude that sunitinib directly inhibit the *rearranged during transfection* (RET) and *colony stimulating factor 1 receptor* (CSF-1R) that different from pazopanib. Those receptors affect the angiogenesis and proliferation, so several adverse effects were occurred in sunitinib patients (23).

Meanwhile, there are not any significant differences between pazopanib and sunitinib in terms of the side effect such as fatigue, diarrhea, hypertension, anemia, and increased ALT/SGPT. However, there are slight differences with this study with COMPARZ (15), namely fatigue, anemia, and an increase in ALT/SGPT. Fatigue and anemia in the COMPARZ (15) are more common in sunitinib users, and elevated ALT/SGPT levels are more common in pazopanib users. But in our study, there is not a significant difference between these two drug groups. From above explanation we know that sunitinib interact with more receptor compared to pazopanib, but sunitinib not always give more adverse effect than pazopanib. Sunitinib has *rest period* (2 weeks off after 4 weeks consumption sunitinib), so several "slowly appear" side effects like fatigue, diarrhea, hypertension, and anemia were repaired by itself when in the *rest period* time. The subjectivity of "fatigue" sensation can make this study result different with other study. In addition, diarrhea also caused by many factors such as patient's diet and habits.

This study's limitations such as unavoidable biases of decision making and patient selection as this study is a retrospective study, limited medical records or reporting bias from physicians and patients resulting in bias of AEs evaluation, to small study that only 8 study that head-to-head comparing sunitinib and pazopanib, and inability to

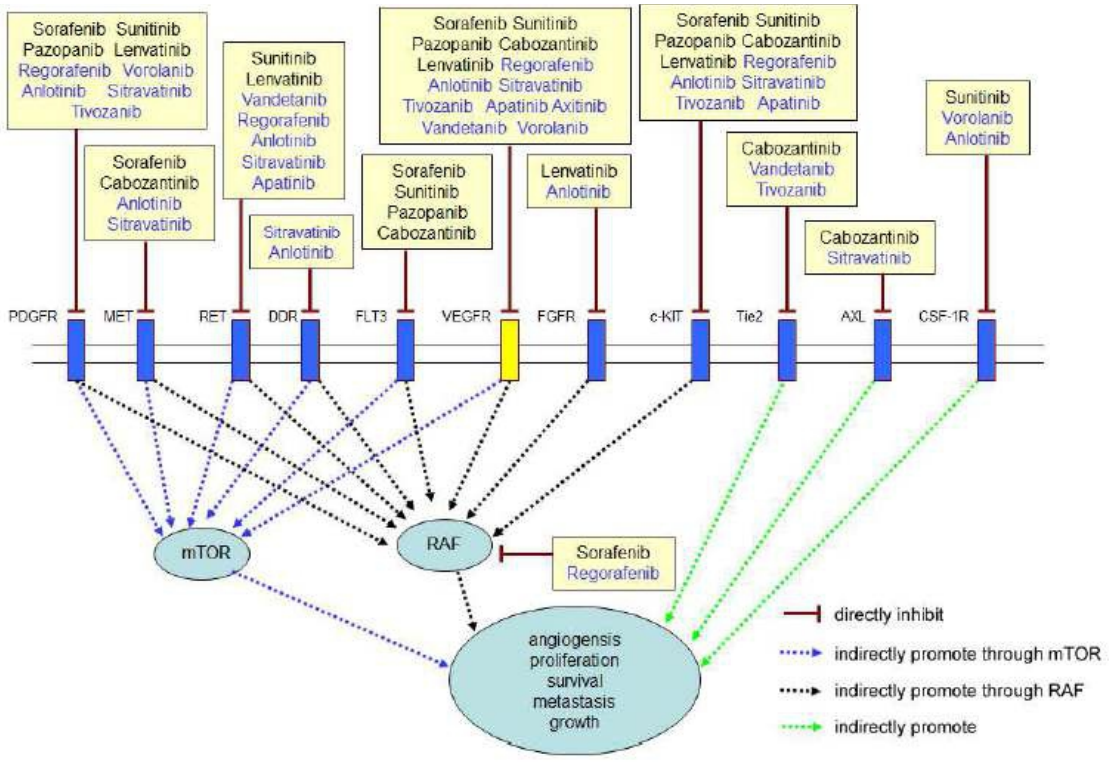


**Figure 10. Approved and under development targeted drugs effects on many target s** (Blue text highlights agents currently under development) (23)

assess the patient compliance. The heterogeneity of some of the studies that we use is still quite high in some comparisons. This can be caused by a variety of sunitinib schedule, patient compliance and health behavior models.

In the end, pazopanib shows less side effects than sunitinib in terms of hand-foot syndrome, nausea/vomiting, skin rash, stomatitis & mucosal inflammation, leucopenia and thrombocytopenia side effects.

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## Appendix

**Table 3. Pazopanib vs Sunitinib: characteristic induded in a meta-analysis**

| References | Intervention | Fatigue | Hand-Foot Syndrome | Nausea / Vomiting | Diarrhea | Hypertension | Rash | Stomatitis | Mucosal Inflammation | Anemia | Leukopenia | Thrombocytopenia | Increased ALT/SGPT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ekenel, 2020 [7] | Pazopanib | 28 | 4 | 10 | 13 | N/A | N/A | N/A | 10 | 16 | 4 | 2 | N/A |
| | Sunitinib | 24 | 13 | 10 | 13 | N/A | N/A | N/A | 18 | 14 | 4 | 8 | N/A |
| Hirsch, 2014 [8] | Pazopanib | 16 | N/A | 15 | 12 | N/A | 5 | N/A | 1 | N/A | N/A | N/A | N/A |
| | Sunitinib | 151 | N/A | 112 | 99 | N/A | 101 | N/A | 71 | N/A | N/A | N/A | N/A |
| Kim, 2016 [2] | Pazopanib | 28 | 13 | 24 | 19 | 28 | 6 | 15 | N/A | 24 | 24 | 30 | 28 |
| | Sunitinib | 58 | 61 | 57 | 14 | 36 | 19 | 58 | N/A | 92 | 59 | 81 | 34 |
| Lalani, 2017 [9] | Pazopanib | 23 | 3 | 9 | 16 | 7 | N/A | N/A | 7 | 1 | N/A | 2 | 13 |
| | Sunitinib | 168 | 69 | 79 | 89 | 55 | N/A | N/A | 94 | 4 | N/A | 41 | 15 |
| Pierantoni, 2020 [10] | Pazopanib | N/A | 4 | N/A | 16 | 9 | N/A | N/A | 1 | N/A | N/A | N/A | 6 |
| | Sunitinib | N/A | 20 | N/A | 6 | 22 | N/A | N/A | 21 | N/A | N/A | N/A | 1 |
| Rudresha, 2018 [11] | Pazopanib | 3 | 0 | 0 | 0 | 0 | 0 | N/A | 0 | 0 | 0 | 0 | N/A |
| | Sunitinib | 13 | 10 | 1 | 4 | 2 | 3 | N/A | 6 | 2 | 1 | 1 | N/A |
| Uccelo, 2019 [3] | Pazopanib | 5 | 0 | 2 | 7 | N/A | N/A | N/A | N/A | 0 | N/A | 0 | 2 |
| | Sunitinib | 4 | 1 | 0 | 1 | N/A | N/A | N/A | N/A | 1 | N/A | 3 | 1 |
| Yuan, 2015 [12] | Pazopanib | N/A | 10 | N/A | 57 | N/A | N/A | 6 | N/A | N/A | N/A | N/A | N/A |
| | Sunitinib | N/A | 39 | N/A | 76 | N/A | N/A | 14 | N/A | N/A | N/A | N/A | N/A |

**Note:** ALT (Alanine Aminotransferase), SGPT (Serum Glutamic Pyruvic Transaminase)