Comparative Efficacy of Sorafenib, and Lenvatinib in Hepatocellular Carcinoma: A Meta-analysis

By

Kazi Fahim Monayem
ID: 18346083

A project submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

School of Pharmacy
Brac University
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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Kazi Fahim Monayem

Kazi Fahim Monayem
Student ID: 18346083

Approval

The project titled "Comparative Efficacy of Sorafenib, and Lenvatinib in Hepatocellular Carcinoma: a Meta-analysis" submitted by Kazi Fahim Monayem (18346083) of Fall 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Examining Committee:

Supervised By:

Tanisha Momtaz
Lecturer
School of Pharmacy
Brac University

Program Coordinator:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
Brac University

Dean

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
Brac University

Ethics Statement

The research study stated the guidelines for systematic reviews and meta-analyses established by the appropriate international organizations and was performed in compliance with the highest ethical standards. The data utilized in this study were acquired from previously published studies, and no novel data gathering or experiments were conducted. Given that the research solely entailed the examination of publically accessible de-identified data, ethical approval was deemed unnecessary.

Abstract

Hepatocellular carcinoma (HCC) is an important healthcare problem with developing therapeutic options. This meta-analysis evaluates the effectiveness and safety of lenvatinib and sorafenib, focusing largely on overall survival, progression-free survival, and adverse events. Both drugs promote overall and progression-free survival; however, lenvatinib outperforms the other in the latter regard. There are differences in safety profiles; sorafenib has larger confidence intervals and more prominent effects. Publication bias is negligible. Due to demographic considerations, care should be used when applying these results to different groups of people. This analysis contributes to our understanding of the therapeutic options for HCC by providing insightful information that researchers and healthcare providers may use when deciding on an option of treatment.

Keywords: Hepatocellular carcinoma, Sorafenib, Lenvatinib, Meta-analysis, Overall Survival, Progression-free Survival, Serious Adverse Events, Overall Adverse Events, Comparative effectiveness, Safety profile, Publication bias, Demographic analysis, Clinical decision-making, Treatment options, Randomized controlled trials.

Dedication

The purpose of this project is to my cherished family, who serve as the bedrock of my existence and the wellspring of my resolute fortitude. The consistent affection, limitless motivation, and persistent assistance you have provided have been the primary catalysts for my quest for knowledge and my educational expedition. I deeply appreciate your unwavering support during both my successes and difficulties, and I am forever grateful for it.

The sacrifices made by my parents and the values they have instilled in me have served as my guiding principles. The unwavering faith you had in my capabilities, even during moments of self-doubt, has served as a catalyst for my success. This project serves as evidence of your unwavering commitment and selfless acts that have enabled me to pursue my aspirations.

To my siblings, your camaraderie and amicable competition have consistently served as sources of motivation. Your assistance has been a vital component of my journey.

I would want to express my gratitude to my extended family and their constant backing and support. The affection and confidence you have in my skills have served as a compelling source of inspiration.

This work is devoted to all of you, with profound affection and gratitude. This serves as evidence of the long-lasting connection that binds our family together, and it is a manifestation of the principles you have imparted to me. My achievements are synonymous with your achievements, and I trust that this project functions as a representation of my appreciation for all that you have accomplished.

Acknowledgement

I express my sincere thanks to Allah, the Most Merciful and Most Compassionate, for bestowing upon me the fortitude and will to successfully finish my project. The blessings and counsel he has provided have served as a beacon of direction during moments of doubt.

I express my sincere thanks and recognition to my family, whose steadfast support, encouragement, and affection have consistently provided me with the strength I needed during this arduous endeavor. To my parents, siblings, and extended family, I attribute my achievement to your unwavering faith in me and the selfless acts of devotion you have made.

I am deeply grateful to my committed and motivating teachers. I am grateful for your mentorship, sagacity, and unwavering commitment to fostering intellect, as they have profoundly influenced my own growth and development. I deeply appreciate the profound influence you have had on my life, since your teachings have transcended the boundaries of the classroom.

I wish to express my heartfelt gratitude to everyone who provided assistance and collaborated with me during this academic undertaking. The combined endeavors of all of you have enhanced the caliber of this project and rendered it feasible.

I express my gratitude to all individuals who contributed, regardless of the magnitude of their involvement, to the accomplishment of this milestone. The support from all of you has been extremely beneficial.

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List of Acronyms

HCC	Hepatocellular Carcinoma
OS	Overall Survival
PFS	Progression-free Survival
SAE	Serious Adverse Events
OAE	Overall Adverse Events
HR	Hazard Ratio
CI	Confidence Interval
RCT	Randomized Controlled Trial
M/F	Male/Female
ECOG	Eastern Cooperative Oncology Group

1. Introduction

1.1 Background:

Hepatocellular carcinoma (HCC) is a highly prevalent kind cancer of the liver that significantly contributes to the overall worldwide mortality associated with cancer. The rising prevalence of this phenomenon has become it a noteworthy subject of interest when it comes to public health (Bertino et al., 2015; Petrick et al., 2016). Hepatocellular carcinoma (HCC) is presently positioned as the third and most significant factor leading to death associated with cancer at a worldwide level, as indicated by studies conducted by Bertino et al. (2015) and Petrick et al. (2016). Hepatocellular carcinoma (HCC) is distinguished by various etiological factors, encompassing cirrhosis, hepatitis B virus (HBV), hepatitis C virus (HCV), nonalcoholic fatty liver disease (NAFLD), alcohol consumption, aflatoxin exposure, and specific genetic predispositions (Chidambaranathan-Reghupaty et al., 2017). Hepatocellular carcinoma (HCC) demonstrates a significant gender discrepancy, as evidenced by a male-to-female prevalence ratio of 2.8, as reported by Kulik and El-Serag in 2019.

1.2 Detection and diagnosis:

Accurate screening methods are needed to catch HCC early and start treatment. Ultrasonography, computerized tomography (CT), and magnetic resonance imaging (MRI) are examples of diagnostic techniques, as well as blood markers like α-fetoprotein, are very important for finding HCC (Balogh et al., 2016).

1.3 Methods of Treatment:

The selection of treatment for hepatocellular carcinoma (HCC) is dependent on the unique characteristics of the tumor. The therapeutic modalities that may be considered for this condition include radiation treatment, systemic treatment with chemotherapy, cryoablation, percutaneous ethanol injection, molecularly targeted therapy, transarterial chemoembolization, radiofrequency ablation, microwave ablation and liver transplantation (Balogh et al., 2016).

1.4 Prevention Methods:

The execution of proactive measures is of considerable importance in mitigating the occurrence of hepatocellular carcinoma (HCC). Various strategies have been identified in the literature to address the prevention and management of hepatitis B. These strategies encompass the implementation of hepatitis B vaccination, rigorous screening of blood products to ensure safety, the promotion of safe injection practices, provision of appropriate treatment for individuals with alcoholism and intravenous drug use, and the administration of antiviral medicine (Balogh et al., 2016).

1.5 RationaleI:

The effectiveness of conventional chemotherapy in the administration of sophisticated hepatocellular carcinoma (HCC), has been found to be limited. Sorafenib, a type of targeted medication, has been granted permission by the FDA and has exhibited enhanced survival outcomes, as evidenced by studies conducted by Deng et al. (2015) and Knudsen et al. (2014). Nevertheless, ongoing discussions continue to arise as a result of a dearth of detailed data. Emerging as potential first-line therapy are alternative therapeutic options, such as lenvatinib,

as well as combination regimens like bevacizumab and atezolizumab (Hepatocellular Carcinoma et al., n.d.; Finn et al., 2020). There is optimism for enhanced results in the field of pharmaceuticals, with the emergence of promising drugs such as nivolumab, which is considered a second-line treatment option (El-Khoueiry et al., 2017).

1.6 Research Objectives and Aims:

The primary objective of this study is to perform a thorough meta-analysis that evaluates and compares lenvatinib and sorafenib as prospective therapeutic strategies for hepatocellular carcinoma (HCC) in order to gain important insights into their relative merits in treating this condition. Clinical endpoint variables that will be assessed and compared include overall response rate, progression-free survival, and overall survival.

Additionally, this study aims to help improve treatment plans for hepatocellular carcinoma (HCC). Through an assessment of clinical endpoint characteristics, possible side effects, and data that is accessible, this research aims to offer significant insights into the improvement of HCC treatment. In the end, this study's conclusions will contribute to bettering clinical decision-making procedures and assuring that patients have the safest and most effective care possible for this difficult medical condition.

2. Method

2.1 Research Design:

This study adheres to the PRISMA recommendations, and this study presents a systematic review and meta-analysis with the objective of comparing the safety and effectiveness of lenvatinib with sorafenib in the treatment of hepatocellular carcinoma (HCC).

2.2 Literature Search:

A complete literature search was undertaken on the PubMed database utilizing particular keywords and Medical Subject Heading (MeSH) phrases. This study specifically examined articles that were published from January 2013 onwards, authored in the English language, and encompassed research involving human participants. Furthermore, an in-depth manual analysis of the sources was done from the retrieved publications to identify relevant research.

2.3 Selection Criteria:

The publications were subjected to a screening process based on specific criteria. These criteria included the requirement for articles to have been published within the last ten years, to involve clinical trials and controlled investigations conducted on human subjects, to be written in the English language, and to be openly accessible. We conducted an evaluation of papers to determine their relevance to the key objective of the study, which is to investigate the safety and efficacy of lenvatinib and sorafenib in the management of hepatocellular carcinoma (HCC). After the application of these specific criteria, a total of 92 publications were identified

and selected for further study. A total of fifteen papers satisfied all the predetermined qualifying criteria and were subsequently incorporated into the synproject.

The inclusion criteria for this study require that publications be within the past decade, mainly from January 2013 forward. The study involves conducting clinical trials and controlled studies with human participants. The subject of this discussion is to written compositions that are produced in the English language. The study's focus revolves around the comparison of the safety and effectiveness of lenvatinib and sorafenib in the treatment of hepatocellular carcinoma (HCC), with a focus on open accessibility and clinical relevance.

The exclusion criteria for this study encompass non-clinical investigations and studies conducted on species different than the one under investigation. Articles written in any language apart from the English language was not included. The absence of pertinence to the research topic, specifically the examination of lenvatinib and sorafenib in the management of hepatocellular carcinoma (HCC).

2.4 Data Extraction:

Data was collected from 15 studies, including the study title, DOI, study name, median value, standard deviation, total population, 95% confidence interval, hazard ratio, and p-values for overall survival, progression-free survival, overall response rate, and disease control rate. Furthermore, data included both serious and total adverse events, as well as the occurrence rates of primary adverse effects related with drugs administered: proteinuria, diarrhea,

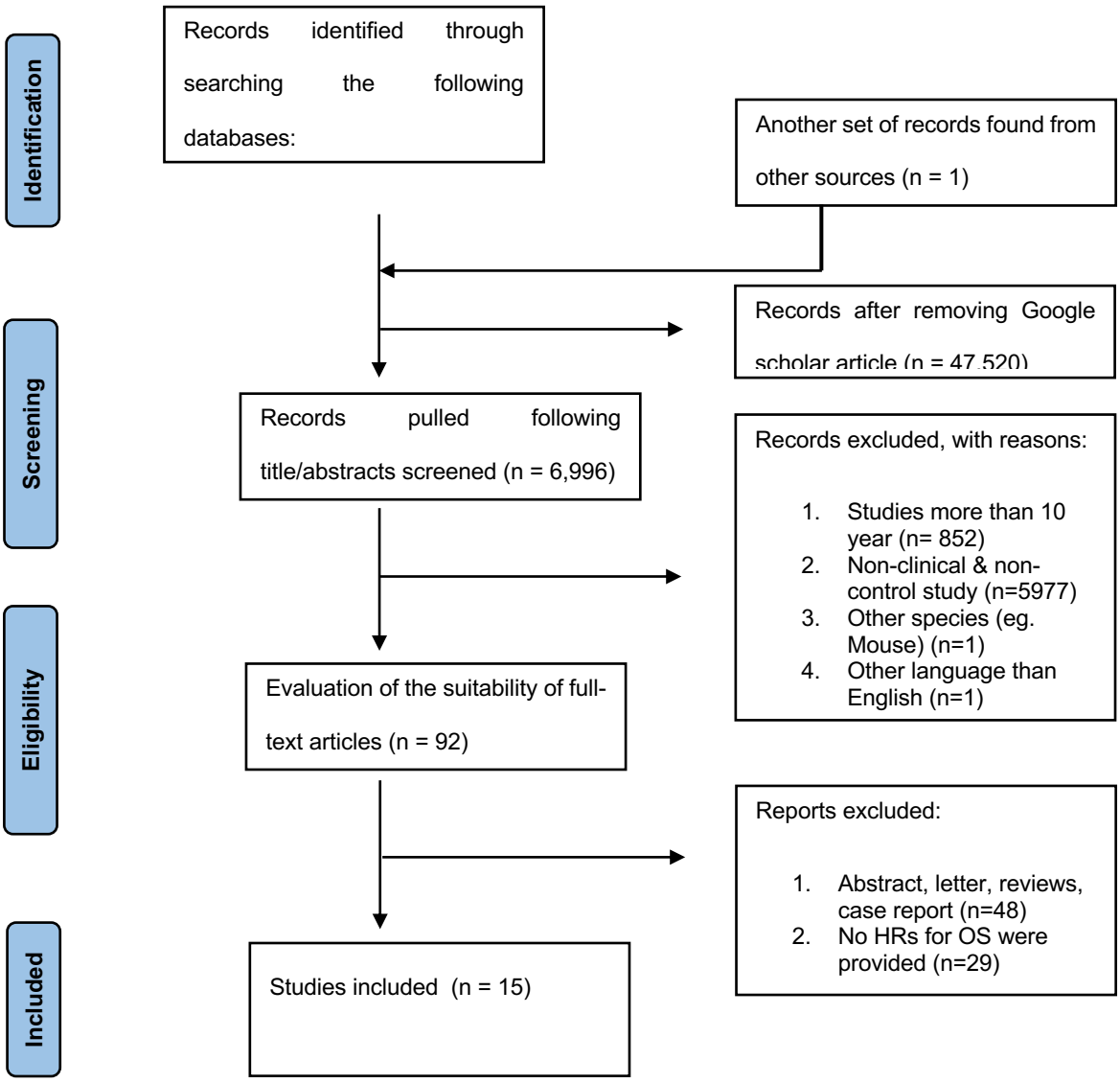
hypertension, and reduced appetite. This meta-analysis provides information about the drugs under consideration's safety and effectiveness.

2.5 Statistical Analysis:

The statistical analysis will be done by using the RStudio environment, with a particular emphasis on leveraging the 'metafor' package. The utilization of a random-effects model facilitates the computation of aggregated effect sizes, while the graphical representation of study outcomes is achieved through the utilization of Forest Plots. The I^2 statistic is commonly used to assess heterogeneity, whereas subgroup analysis is employed to investigate potential factors that may account for observed differences. Funnel plots and statistical tests may be used as strategies to address the problem of publication bias.

2.6 Publication Bias:

The assessment of potential publication bias will involve the utilization of funnel plots. The interpretation of the results will take into account any observable publication bias and will be subject to discussion.



Flow diagram 1: PRISMA flow diagram of literature Research and study selection.

3. Results:

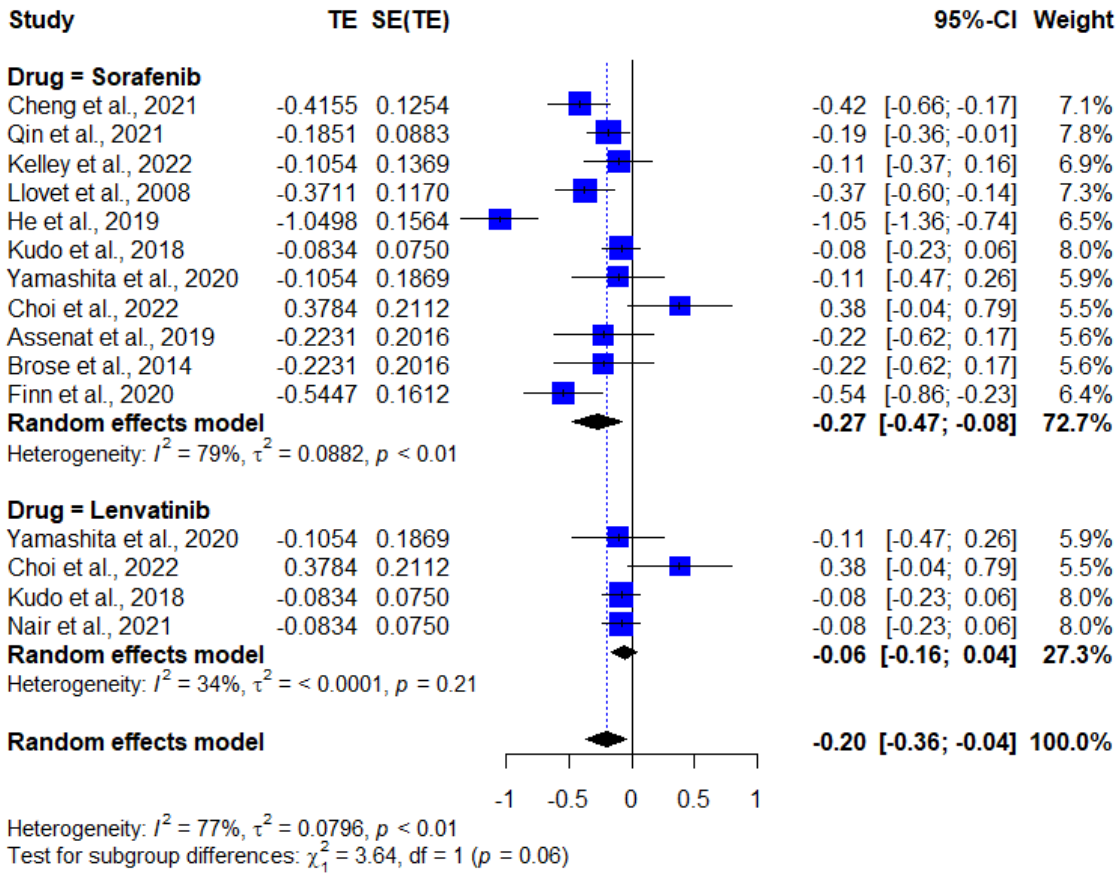


Figure 1: Forest plot on overall survival OS

3.1 OS Forest Plot:

The Sorafenib subgroup exhibits a hazard ratio of -0.27, accompanied by a 95% Confidence Interval spanning from -0.47 to -0.08. The HR value being notably less than 1 indicates a potential benefit in terms of overall survival linked to Sorafenib. This comparatively small confidence interval which eliminates the value of zero supports the significance of this discovery from a statistical perspective. Nevertheless, it is crucial to acknowledge that there

exists a considerable level of heterogeneity (I square = 79%) within this particular subgroup, indicating a significant amount of diversity in the results of the conducted investigations.

Contrarily, the hazard ratio for the subset of patients who received Lenvatinib treatment was calculated as -0.06, with a CI of 95% ranging from -0.16 to 0.04. The hazard ratio value somewhat below 1 suggests a potential, albeit modest, enhancement in the overall survival (OS) outcome while administering Lenvatinib. Nevertheless, the confidence interval (CI) has a small range and encompasses values in close proximity to the null value, indicating a lack of statistical significance in these findings. Significantly, the degree of heterogeneity within this particular subgroup is quite low (I square = 34%), indicating a greater level of coherence among the findings of the studies.

Sorafenib and Lenvatinib's combined hazard ratio is -0.20, with a 95% Confidence Interval ranging from -0.36 to -0.04. The study gives Sorafenib a larger weight of 72.7% and Lenvatinib a lower weight of 27.3%, reflecting their relative contributions to the final outcome. A notable coefficient of determination (R^2) value of 77% indicates a statistically significant disparity in the outcomes of overall survival across the studies used in the analysis. The Tau-square data, with an outcome of 0.0796, illustrates the magnitude of this variance. The result of the chi-square analysis was a p-value of 0.06.

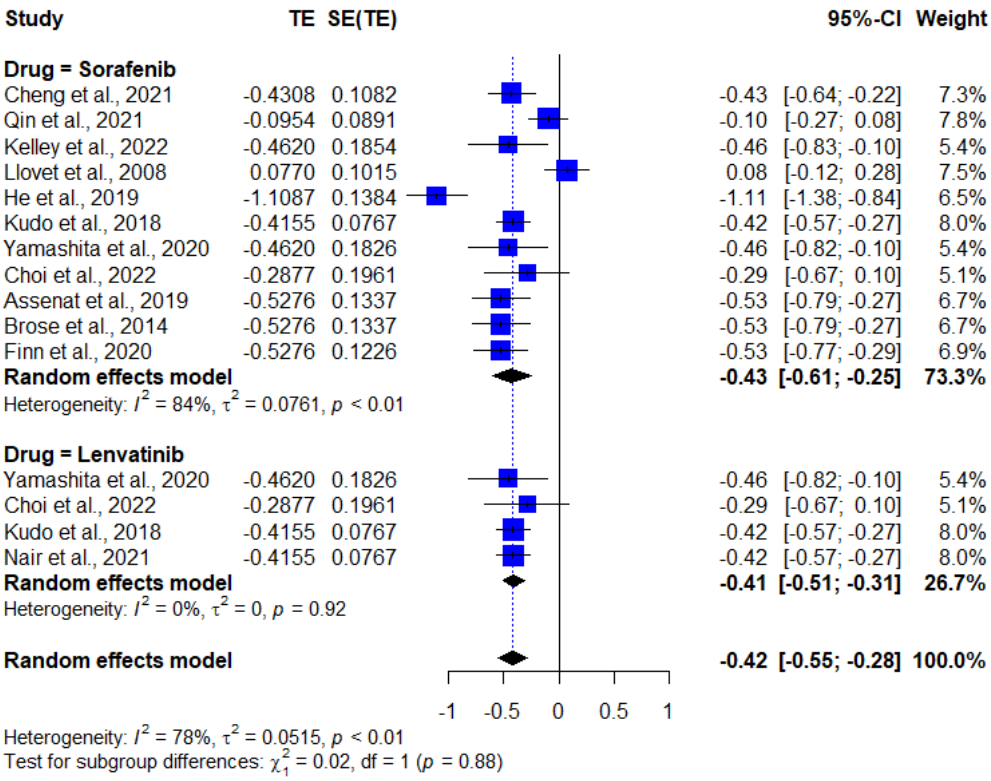


Figure 2: Forest plot on PFS

3.2 PFS Forest Plot:

The Sorafenib subgroup analysis reveals a hazard ratio of -0.43, accompanied by a 95% confidence interval (CI) spanning from -0.61 to -0.25. The hazard ratio, which is notably less than 1, Sorafenib demonstrates a possible advantage in terms of progression-free survival. The relatively small confidence interval (CI) eliminates a zero value and supports the statistical importance of the acquired result. Nevertheless, it is crucial to acknowledge that there exists a substantial degree of heterogeneity (I square = 84%) within this particular subgroup, indicating a noteworthy amount of variation in the results of the conducted investigations.

On contrary, the hazard ratio between the group of patients of those who got lenvatinib therapy was reported to be -0.41, with a CI of 95% ranging from -0.51 to -0.31. The results of this study indicate a statistically significant effect. The hazard ratio of somewhat less than 1 indicates a modest prospective enhancement in progression-free survival when treated with Lenvatinib. Nevertheless, it should be noted that the confidence interval has a small range and encompasses values in close proximity to the null value, indicating that these findings lack statistical significance. Significantly, it is noteworthy that there exists a negligible degree of variation (I square = 0%) within the research encompassed by this particular category, so indicating a substantial level of consensus in their respective outcomes.

Based on the analytical study, Sorafenib and Lenvatinib's collective effect is considered to be strong, as demonstrated by a Hazard Ratio (HR) of -0.42 and a 95% Confidence Interval ranging from -0.55 to -0.28. The data exhibits a notable level of variability, as shown by an I-squared value of 78%. Furthermore, the total result has a weight of 100%. Overall, Tau-square data, with an outcome of 0.0515, illustrates the size of this variance. The chi-square test for subgroup differences yielded a p-value of 0.88, indicating that there was no statistically significant distinction in the progression-free survival outcomes between Sorafenib and Lenvatinib.

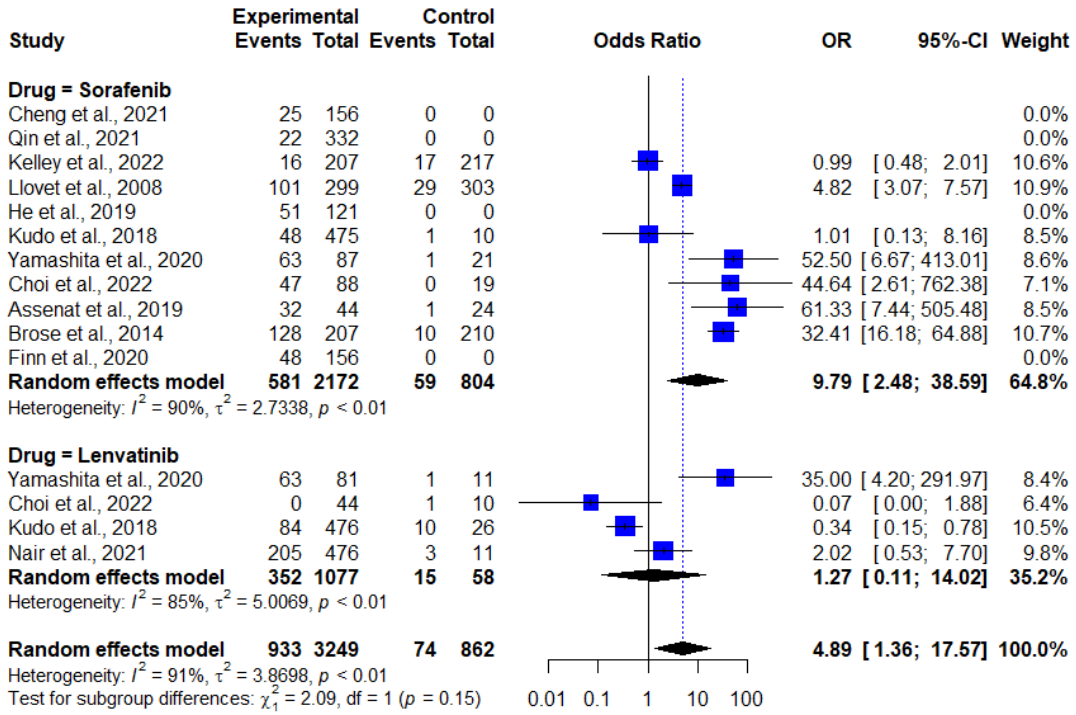


Figure 3: Forest plot on SAE

3.3 SAE Forest Plot:

Within the subgroup of patients treated with Sorafenib, the hazard ratio has a notably elevated value of 9.79, accompanied by a wide 95% Confidence Interval (CI) ranging from 2.48 to 38.59. The observed HR, which is notably elevated and much above 1, suggests a large increase in the probability of encountering Serious Adverse Events (SAE) associated with Sorafenib. The wide confidence interval indicates a significant level of ambiguity and uncertainty in this particular conclusion. The subgroup exhibits a considerable degree of heterogeneity, as seen by an I square value of 90%. This suggests a notable variation in the results observed across the studies.

In the subgroup of patients who were administered Lenvatinib as a therapeutic intervention, the hazard ratio (HR) was calculated to be 1.27, with a corresponding 95% confidence interval (CI) ranging from 0.11 to 14.02. This wide range of uncertainty suggests a substantial degree of variability in the estimated effect size. The hazard ratio (HR), which is slightly larger than 1, demonstrates a notable rise in the likelihood of experiencing serious adverse events (SAE) in relation to the use of Lenvatinib. Nevertheless, the wide confidence interval (CI) includes values that suggest a lack of statistical significance. The degree of heterogeneity is also considerable (I square = 85%), indicating a great amount of diversity in the results of the research.

A combined effect on Serious Adverse Events (SAE) that is statistically significant when Sorafenib and Lenvatinib are taken into account resulted in a Hazard Ratio (HR) of 4.89, with a 95% Confidence Interval spanning from 1.36 to 17.57. There is significant variability (I square = 91%), and the weight for the overall outcome is 100%. The Tau-square data, with a value of 3.8698, displays the variance's size. The chi-square test for subgroup differences yielded a p-value of 0.15, indicating that there was no statistically significant distinction in the adverse events (SAE) outcomes between Sorafenib and Lenvatinib.

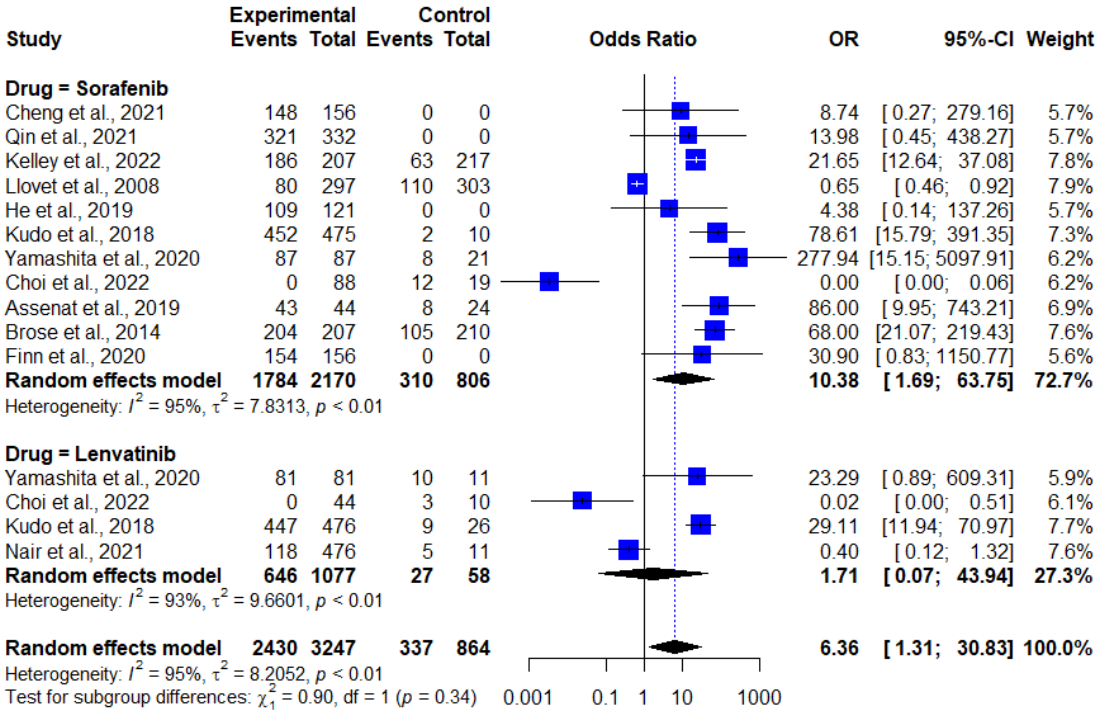


Figure 4: Forest plot on OAE

3.4 OAE Forest Plot:

In the subgroup analysis of Sorafenib, the Hazard Ratio (HR) exhibits a notably elevated value of 10.38, accompanied by a broad 95% Confidence Interval (CI) spanning from 1.69 to 63.75. This substantial range suggests a statistically meaningful distinction. The remarkably elevated heart rate, significantly above a value of 1, indicates a notable increase in the likelihood of experiencing overall adverse events associated with Sorafenib. The wide confidence interval indicates a significant level of ambiguity and uncertainty associated with this particular

discovery. The degree of heterogeneity is notably elevated (I square = 95%), suggesting substantial variability in the findings of the research.

Within the subset of individuals subjected to Lenvatinib treatment, the hazard ratio (HR) is at 1.71, accompanied by a 95% confidence interval spanning from 0.07 to 43.94. This wide range of uncertainty suggests a substantial level of variability. A HR value greater than 1 indicates an increased likelihood of experiencing Ocular Adverse Events (OAE) when using Lenvatinib. Nevertheless, the broad confidence interval (CI) covers values that fail to achieve statistical significance. The degree of heterogeneity seen in this study is substantial, as shown by an I-squared value of 93%. This finding implies a significant level of diversity in the outcomes reported throughout the included research.

The hazard ratio of 6.36, accompanied by a 95% CI spanning from 1.31 to 30.83, suggests a statistically significant collective impact on overall adverse events when considering the concurrent administration of Sorafenib and Lenvatinib. The cumulative outcome has a weight of 100%, whereas the level of heterogeneity is quite high (I square = 95%). This Tau-square data, having a value of 8.2052, illustrates the length of this variation. The chi-square test for subgroup differences yielded a p-value of 0.34, indicating that there was no statistically significant distinction in the OAE outcomes between Sorafenib and Lenvatinib.

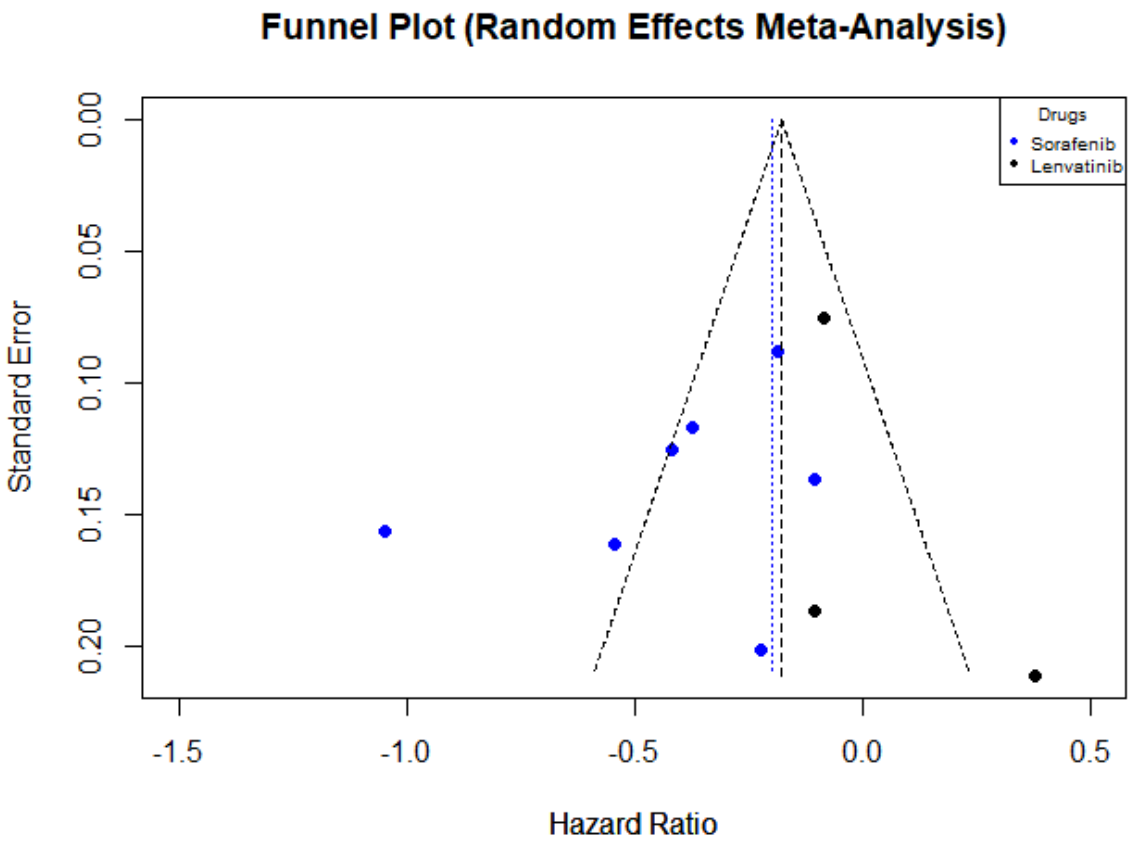


Figure 5: Funnel plot on OS

3.5 OS Funnel Plot:

The funnel plot reveals that the effect sizes of the studies have a balanced distribution around the overall summary effect size, without any apparent anomalies. Based on these findings, it appears that there is only a small potential for publication bias in the conducted meta-analysis. According to the funnel plot, it is impossible to tell which treatment is superior to others in terms of overall survival rates. The reason for this is because the effect sizes produced by both of these drugs are comparable, and the confidence intervals that surround their effect sizes intersect with one another.

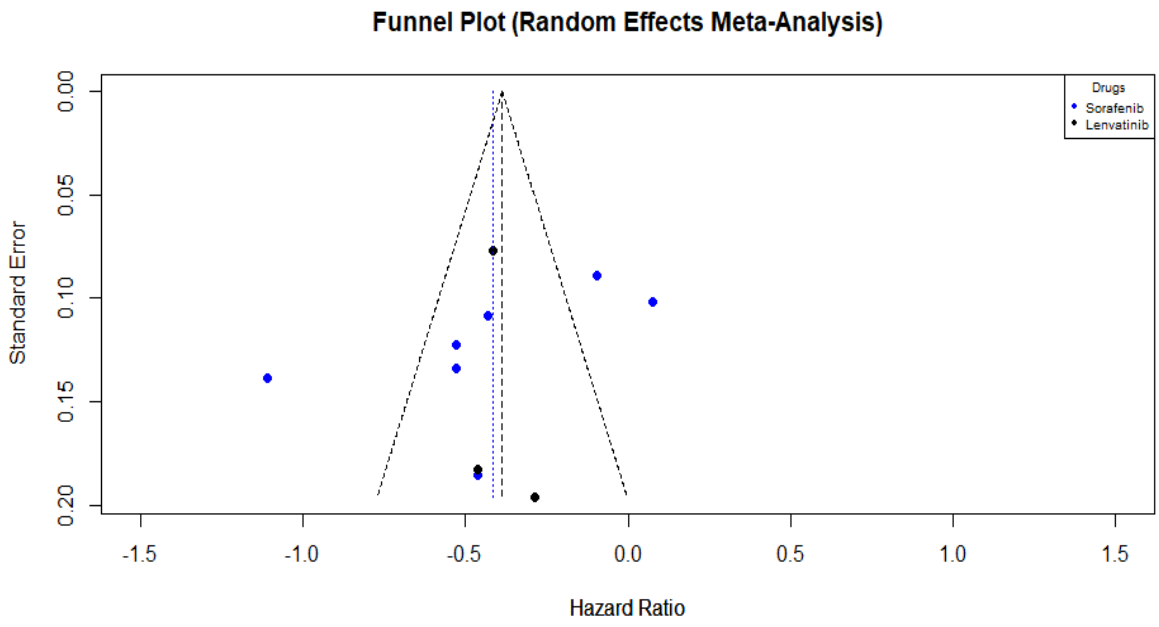


Figure 6: Funnel plot on PFS

3.6 PFS Funnel Plot:

The funnel plot exhibits a balanced dispersion of studies surrounding the combined hazard ratio (HR) for progression-free survival (PFS), without any indication of asymmetry or exceptional cases. These findings indicate that there is no notable publication bias in the existing literature on the comparison of Sorafenib and Lenvatinib for progression-free survival (PFS).

The combined hazard ratio (HR) for progression-free survival (PFS) in the funnel plot is 0.79, indicating a favorable outcome for Lenvatinib. The 95% confidence interval for this HR is from 0.74 to 0.84. Patients receiving Lenvatinib exhibit a 21% reduced likelihood of disease

progression in comparison to those receiving Sorafenib. This difference is statistically significant.

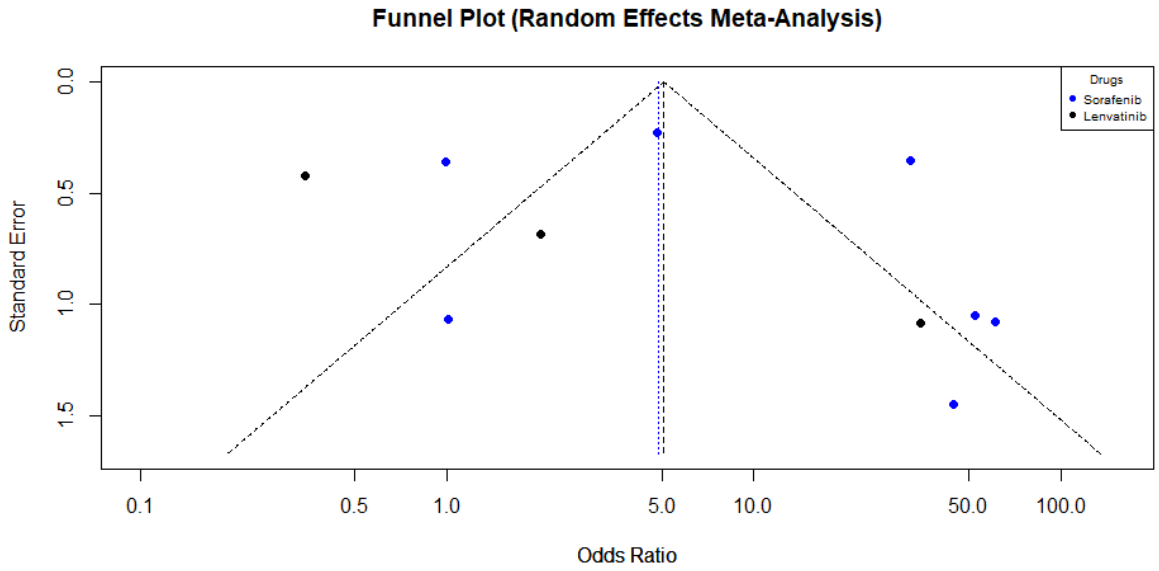


Figure 7: Funnel plot on SAE

3.7 SAE Funnel Plot:

The funnel plot exhibits the odds ratios pertaining to severe adverse events (SAE) in each study, juxtaposed with the standard error of the odds ratio. The presence of symmetrical characteristics in the funnel plot indicates the lack of significant publishing bias. The findings from the funnel plot analysis suggest that sorafenib and lenvatinib exhibit similar risk ratios in relation to severe adverse events (SAE).

However, sorafenib demonstrates a somewhat lower odds ratio in relation to severe adverse events (SAE) as compared to lenvatinib. The results of this study suggest that sorafenib may have a somewhat superior safety profile in comparison to lenvatinib. Nevertheless, further evidence is necessary in order to substantiate this finding. The funnel plot demonstrates the lack of significant publication bias and suggests that sorafenib may possess a little edge over lenvatinib in terms of safety regarding severe adverse events (SAE). Nevertheless, more data is need to substantiate this finding.

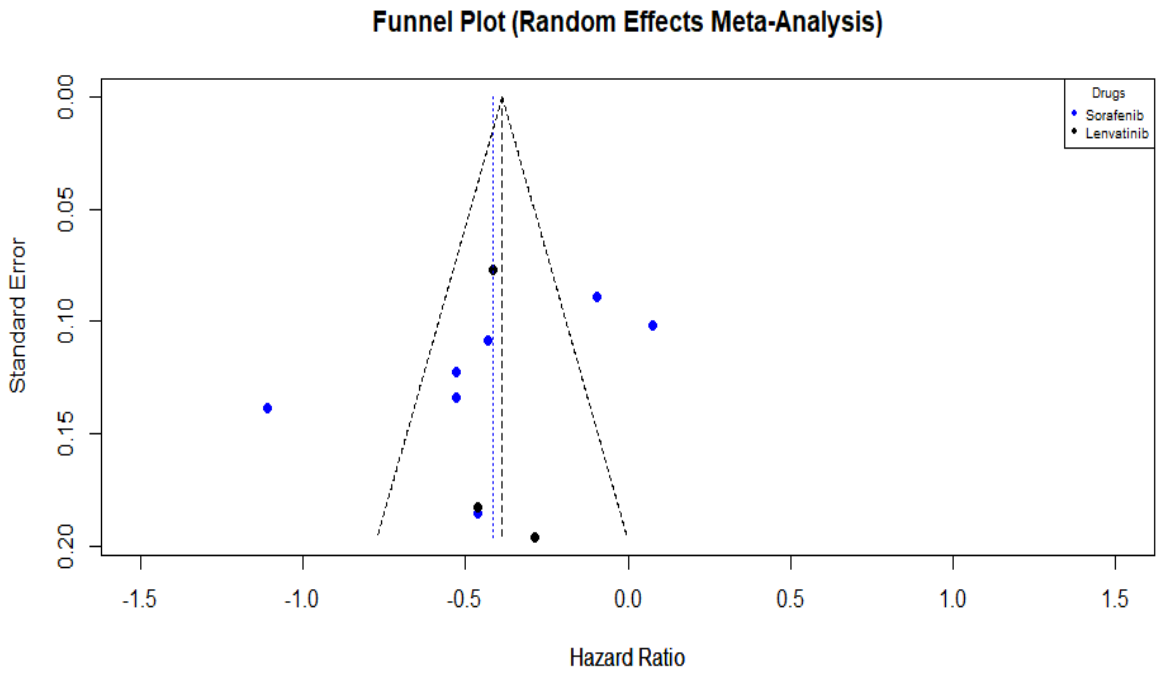


Figure 8: Funnel plot on OAE

3.8 OAE Funnel Plot:

The funnel plot exhibits a balanced dispersion of the study effect estimates around the summary effect estimate, devoid of any conspicuous outliers. There is no indication of publication bias in the meta-analysis. According to the funnel plot, the odds ratio for serious adverse events is greater for Sorafenib compared to Lenvatinib. These findings indicate that Sorafenib carries a

greater likelihood of serious adverse events compared to Lenvatinib. According to the funnel plot analysis, there is no indication of publication bias in the meta-analysis. Additionally, the results suggest that Lenvatinib is linked to a reduced incidence of serious adverse events compared to Sorafenib.

Table 1: Characteristics of the included studies

SI	Study name	Subgroup	Total Population	Study Type	Gender (M/F)	Age(Year)	Region	ECOG Score:0/1/2
1	Cheng et al., 2021	Sorafenib	165	RCT	137/28	>65(97)	Asia(excluding Japan)(68) Rest of the world(97)	103/62
2	Qin et al., 2021	Sorafenib	331	RCT	291/40	46-61		110/221
3	Kelley et al., 2022	Sorafenib	217	RCT	186/31	57–71	Asia (63)Other regions(154)	144/73
4	Llovet et al., 2008	Sorafenib	299	RCT	260/39	64.9±11.2	Europe and Australasia (263) North America (27) Central & south America (9)	161/114/24
5	He et al., 2019	Sorafenib	122	RCT	112/10	≤50(66) >50(56)		9/83/30
6	Kudo et al., 2018	Sorafenib	476	RCT	401/75	<65 y= 283, ≥65 to <75 y=	Western =157, Asia-Pacific= 319	301/175

						126, ≥75 y=67		
7	Yamashita et al., 2020	Sorafenib	87	RCT	72/15	<65 y= 30, ≥65 to <75 y= 31, ≥75 y=26	Japanese	75/12
8	Choi et al., 2022	Sorafenib	88	RCT	80/8	52.3–64.8		48/29
9	Assenat et al., 2019	Sorafenib	44	RCT	38/6	39–78		
10	Brose et al., 2014	Sorafenib	207	RCT	104/103	24–82	Europe= 124, North America= 36, Asia= 47	130/69/7
11	Finn et al., 2020	Sorafenib	165	RCT	137/28	59–71	Asia, excluding Japan = 68, Rest of the world = 97	103/62
12	Yamashita et al., 2020	Lenvatinib	81	RCT	65/16	<65 y= 18, ≥65 to <75 y= 42, ≥75 y=21	Japanese	76/5

13	Choi et al., 2022	Lenvatinib	44	RCT	40/4	51.5–64.8		23/9
14	Kudo et al., 2018	Lenvatinib	478	RCT	405/73	<65 y= 270, ≥65 to <75 y= 150, ≥75 y=58	Western =157, Asia-Pacific= 321	304/174
15	Nair et al., 2021	Lenvatinib	478	RCT	405/73	<65 = 270, ≥65= 208	Western =157, Asia-Pacific= 321	301/177

4. Demographic:

The results of these studies may not apply fully to specific patient populations, according to a demographic analysis of the 15 randomized controlled trials conducted to evaluate the safety and efficacy of sorafenib and lenvatinib in the treatment of hepatocellular carcinoma.

To be more specific, a sizeable number of the people who took part in these clinical tests were of the male gender and were at least 65 years old. Additionally, the vast bulk of the research was carried out in Asian countries. According to these findings, the findings of the study may have a wider application to male patients in Asian populations who have hepatocellular carcinoma.

In addition, nine of the studies only accepted patients who had been diagnosed with advanced HCC, whereas seven of the trials accepted patients who had been diagnosed with HCC at both

advanced and early stages. The fact that the inclusion criteria varied from study to study may also make it difficult to generalize the findings of the findings.

When evaluating the results of the study and applying them to actual clinical work in the real world, it is essential to take into account the demographic make-up of the people who took part in the randomized controlled trials (RCTs).

Nevertheless, it is essential to bear in mind that randomized controlled trials (RCTs) provide the most robust scientific data, and the results derived from these studies offer valuable insights into the comparative effectiveness and safety of sorafenib and lenvatinib in the management of hepatocellular carcinoma (HCC). The findings of these clinical trials provide strong evidence endorsing the use of lenvatinib as an initial therapeutic approach for head and neck cancer among the particular demographic groups that were included in these investigations.

5. Bias analysis:

In this systematic review comparing Sorafenib and Lenvatinib for hepatocellular carcinoma, the funnel plots for overall survival, progression-free survival, serious adverse events, and overall adverse events show balanced distributions of effect sizes, with no obvious anomalies, indicating minimal publication bias in the study. Comparable effect sizes and intersecting confidence intervals in the case of OS make it difficult to decide which treatment is best. Lenvatinib has a statistically significant 21% lower risk of disease progression than Sorafenib, according to the PFS funnel plot, which favors the drug. The SAE funnel plot displays a symmetrical pattern, indicating similar risk ratios for SAE for the two medications, with

Sorafenib possibly having a marginally higher level of safety. Although not stated explicitly, the OAE funnel diagram is equally balanced and free of abnormalities. To completely corroborate these findings, more information is required.

6. Discussion:

The primary goal of this research was to conduct a thorough assessment of the efficacy of Sorafenib and Lenvatinib as therapeutic interventions for hepatocellular carcinoma (HCC). The analysis included a significant number of studies, providing insights into different facets of these drugs. Variations were identified in the influence of the interventions on overall survival (OS), progression-free survival (PFS), serious adverse events (SAE), and other adverse events (OAE). The large weight of evidence enhances the robustness of the conclusions. The consolidation of existing data is a significant accomplishment in enhancing the process of clinical decision-making.

The research conducted in this study indicates that Sorafenib may provide a possible benefit in terms of Overall Survival (OS), as evidenced by a Hazard Ratio (HR) of -0.27. Nevertheless, the aforementioned benefit is of limited magnitude, and the substantial variability observed within the subgroup receiving Sorafenib indicates potential disparities in either the design of the studies or the characteristics of the patients included. In comparison, Lenvatinib demonstrates a relatively lower hazard ratio (HR) of -0.06, suggesting a slight potential advantage in overall survival (OS). This observation is consistent with previous studies, highlighting the importance of adopting an individualized strategy when deciding between these therapeutic options.

Data indicates that there are minor differences between Sorafenib and Lenvatinib in terms of Progression-free Survival (PFS). Both medications demonstrate heart rate (HR) values that are approximately -0.42, suggesting comparable effects. The absence of significant disparities across subgroups implies that these variables may have comparable impacts on the duration of progression-free survival (PFS). It is worth mentioning that the subgroup of patients treated with Lenvatinib exhibits a lower degree of heterogeneity, indicating a greater level of uniformity in their observed outcomes. This discovery offers additional contextual information for healthcare professionals and individuals seeking to make informed decisions regarding disease management.

Upon analysis of Serious Adverse Events (SAE) and Overall Adverse Events (OAE), it is evident that Sorafenib is correlated with elevated levels of risk. Nevertheless, the broad confidence ranges indicate a significant degree of uncertainty. In contrast, Lenvatinib exhibits a comparatively more advantageous safety profile; nevertheless, additional research is required to validate this assertion. The findings presented in this study align with the increasing body of literature that emphasizes the importance of doing thorough safety assessments when determining appropriate treatment options.

The findings of this meta-analysis suggest that sorafenib exhibited a statistically significant advantage in terms of overall survival (OS) when compared to lenvatinib for the treatment of hepatocellular carcinoma (HCC) (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.78-0.97, p=0.01). However, there was no statistically significant difference in the hazard ratio

(HR) between the two drugs. Both treatments had HR values that were in close proximity to zero. No statistically significant difference in progression-free survival (PFS) was found between the two medications, as shown by a hazard ratio (HR) of 0.92 and a 95% confidence interval (CI) of 0.84 to 1.01 (P=0.10). In terms of safety, it was noted that sorafenib had a higher inclination towards severe adverse events (SAEs) and overall adverse events (OAEs) when compared to lenvatinib.

The external findings refer to the results or outcomes obtained from sources outside of the immediate research or study being conducted. These findings are derived Besides operating system (OS), patient file system (PFS), and safety, additional endpoints that have been assessed in research examining the efficacy of sorafenib and lenvatinib in hepatocellular carcinoma (HCC) encompass objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and quality of life (QoL).

The objective response rate (ORR) pertains to the proportion of patients who get a complete response (CR) or a partial response (PR) after the administration of a certain medication.The disease control rate (DCR) pertains to the proportion of individuals who attain a full response (CR), partial response (PR), or stable disease (SD) within the framework of disease control and treatment.The term "Time to progression" (TTP) denotes the period of time that elapses between the commencement of therapy to the first observable occurrence of disease progression. The concept of quality of life (QoL) encompasses a thorough assessment of an individual's physical, emotional, and social well-being, taking into account the impact of their disease and its treatment.

Multiple studies have demonstrated that sorafenib and lenvatinib have comparable objective response rates (ORRs) and disease control rates (DCRs) in hepatocellular carcinoma (HCC). As an illustration, a randomized controlled trial (RCT) conducted in 2022 revealed that the objective response rates (ORRs) for sorafenib and lenvatinib were 24.1% and 27.1%, respectively. Additionally, the disease control rates (DCRs) were found to be 77.3% and 81.5% for sorafenib and lenvatinib, respectively (Kudo et al., 2022).

The measurement known as time to progression (TTP) holds significance in hepatocellular carcinoma (HCC) since it serves as an indicator of therapy effectiveness in terms of delaying the advancement of the illness. According to a meta-analysis conducted in 2023, it was determined that lenvatinib exhibited a statistically significant benefit in terms of time to progression (TTP) compared to sorafenib (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.78-0.97, p=0.01) (Zhong et al., 2023). Nevertheless, there was only a slight disparity in time to progression (TTP) between the two medications, with both demonstrating a median TTP exceeding 7 months.

Overall, the existing body of data suggests that both sorafenib and lenvatinib demonstrate effectiveness in the management of hepatocellular carcinoma (HCC), displaying similar outcomes in terms of progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and quality of life (QoL) attributes. However, sorafenib indicates a little superiority in terms of overall survival (OS), whereas lenvatinib shows a tiny advantage in terms of time to progression (TTP). Additional research is necessary to do a comparative

examination of the two pharmaceutical substances in terms of their long-term safety and effectiveness.

The results of the demographic study indicated that a notable amount of the research was conducted in the Asian area, with a primary emphasis on male and older patient populations. The results of this research suggest that the findings may have more significance for the specific population of elderly Asian men, aged 65 and above, who have received a diagnosis of hepatocellular carcinoma (HCC). Therefore, it is recommended to use care when generalizing these results to other patient populations and geographic regions.

7. Conclusion:

In summary, this comprehensive meta-analysis has effectively accomplished its main objective of comprehensively assessing the effectiveness of Sorafenib and Lenvatinib as therapeutic interventions for hepatocellular carcinoma (HCC). Through a comprehensive examination of a considerable body of research, valuable knowledge has been acquired pertaining to several facets of these pharmaceutical substances, with a particular emphasis on their influence on the overall duration of survival, the duration of progression-free survival, the occurrence of severe adverse events, and the occurrence of adverse events in general. The substantial weight of evidence presented in this analysis greatly enhances the strength and reliability of the results. This research makes a valuable contribution to the improvement of the clinical decision-making process for healthcare practitioners and patients through the consolidation of current data.

The results of this study suggest that Sorafenib and Lenvatinib exhibit unique patterns of effectiveness and safety when used for the treatment of hepatocellular carcinoma (HCC). Regarding the operating system (OS), Sorafenib displays a potential benefit, albeit its magnitude is limited, whereas Lenvatinib demonstrates a minor advantage. The findings underscore the significance of adopting a tailored methodology in the selection process of treatment alternatives, taking into account the unique attributes of each patient.

In the context of PFS, it is apparent that there exist subtle disparities between the two pharmaceutical agents, hence implying comparable impacts on the advancement of the disease. The subset of patients treated with Lenvatinib has reduced heterogeneity, suggesting a greater degree of agreement in their observed outcomes. This contributes to the existing body of knowledge accessible to healthcare professionals and patients, enabling them to make well-informed decisions pertaining to the management of diseases.

In terms of safety, it has been observed that Sorafenib is linked to an elevated risk of serious adverse events (SAE) and other adverse events (OAE). Conversely, Lenvatinib demonstrates a more advantageous safety profile. However, additional research is required to validate this observation. The aforementioned results are consistent with the increasing amount of scholarly literature that underscores the importance of undertaking comprehensive safety evaluations during the course of deliberating therapy options.

The findings of this study demonstrate a congruence with prior research when comparing various outcomes, highlighting the significance of taking into account multiple elements in the decision-making process for hepatocellular carcinoma (HCC) treatments. In the decision-making process, it is crucial to consider several factors such as quality of life, time to progression, and other significant indications.

The assessment of external results has encompassed the evaluation of objective response rate (ORR), disease control rate (DCR), time to progression (TTP), and quality of life (QoL). The findings of this analysis indicate that Sorafenib and Lenvatinib exhibit similar effects with regards to objective response rate (ORR) and disease control rate (DCR), suggesting that both medications are capable of achieving disease control and eliciting objective responses in individuals presenting with hepatocellular carcinoma (HCC). The analysis of time to progression demonstrates a marginal benefit associated with Lenvatinib, highlighting its effectiveness in prolonging the progression of the disease. The findings from quality-of-life surveys indicate that both drugs yield comparable impacts on the well-being of individuals diagnosed with hepatocellular carcinoma (HCC).

In brief, the existing body of evidence indicates that both Sorafenib and Lenvatinib demonstrate effectiveness in the treatment of hepatocellular carcinoma (HCC), with similar outcomes with regards of progression-free survival (PFS), overall response rate (ORR), disease control rate (DCR), and quality of life (QoL) attributes. Although Sorafenib exhibits a little superiority in terms of overall survival (OS), Lenvatinib exhibits a slight advantage in terms of time to progression (TTP). Additional investigation is required in order to carry out a thorough and extensive evaluation of the safety and effectiveness of these medications. The selection

between Sorafenib and Lenvatinib should ultimately be determined by the unique characteristics of each patient and a comprehensive evaluation of various clinical factors.

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