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Research Article

Enhanced Drug Classification for Cancers of the Liver with Multi-Criteria Decision-Making Method-PROMETHEE

Basil B. Duwa[1,2], Natacha Usanase[1,2], Berna Uzun[1]
[1]*Operational Research Center in Healthcare, Near East University, TRNC Mersin 10, Turkey*
[2]*Department of Biomedical Engineering Near East University, TRNC Mersin 10, Turkey*

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ABSTRACT

The combination of multi-criteria decision-making (MCDM) methods and fuzzy logic technique offers novel approaches to decision-making in the treatment planning of liver cancer; hepatocellular carcinoma (HCC), particularly the decision on how to propose the right therapeutic approach depending on multiple criteria. Since none of the treatment methods can provide fully satisfactory results for liver cancer when considering different patients, it is crucial to identify the optimal therapeutic method tailored for each individual, based on certain pertinent criteria. This study provides insight into the various factors that are likely to influence HCC pharmacological treatments. All the chosen drugs were assessed based on their effectiveness in meeting each of the criteria considered. To achieve this, we applied an MCDM-fuzzy hybrid model that combines both fuzzy logic and the Preference Ranking Organization Method for Enrichment Evaluation (PROMETHEE) technique. We evaluated eight FDA-approved medications for HCC treatment alternatives. These drugs include, Cabozantinib, sorafenib, Lenvatinib, Atezolizumab, Tivantinib, Nivolumab and Pembrozumab. Similarly, based on the multiple criteria approach, five alternatives were adopted such as efficacy, cost, safety, drug development stage and side effects. The ranking result revealed that Sorafenib ranked the highest and Tivantinib ranked the least. The study offers a structured and data-driven approach in the classification of drugs which provides valuable insights for health practitioners and policy makers and HCC treatment optimization.

1. INTRODUCTION

Liver cancer poses a serious global health threat as it is the sixth most prevalent cancer type and the third most common cause of cancer-associated mortality globally in both genders of all ages, with Asia recorded for more than 70% of global liver cancer occurrence and mortality cases [1]. Hepatocellular carcinoma (HCC); a common form of liver cancer, derived its nomenclature from Hēpar, meaning "liver" in Greek, cellular, meaning "compartment" in Latin, and "carcinoma" which means cancer in Greek. HCC is a term that describes a tumor that starts in the hepatic or liver cells and is responsible for about 80% of recorded liver cancer cases globally making it the most prevalent kind of liver cancer [2]. Thus, creating a major negative impact on both health and the economy. This disease primarily affects people who have chronic liver disorders, notably those who have cirrhosis or fibrosis, which

*Corresponding author. Email: basil.barthduwa@neu.edu.tr

are caused by prolonged liver damage and infection. The common risk factors of this disease are primarily associated with exposure to toxins, alcoholic liver disease, non-alcoholic steatohepatitis (NASH), and hepatitis infection in its various forms. Furthermore, certain genetic conditions, such as hemochromatosis and alpha-1 antitrypsin deficiency, have been reported to elevate the risk of HCC development significantly [3].

Figure 1: Global incidence rate [7]

A similar report ranked China with the highest mortality rate globally with a record of 391, 152, followed by Japan (28,155), Thailand (26,704), and Vietnam (25,272) as shown in Figure 2 [8].

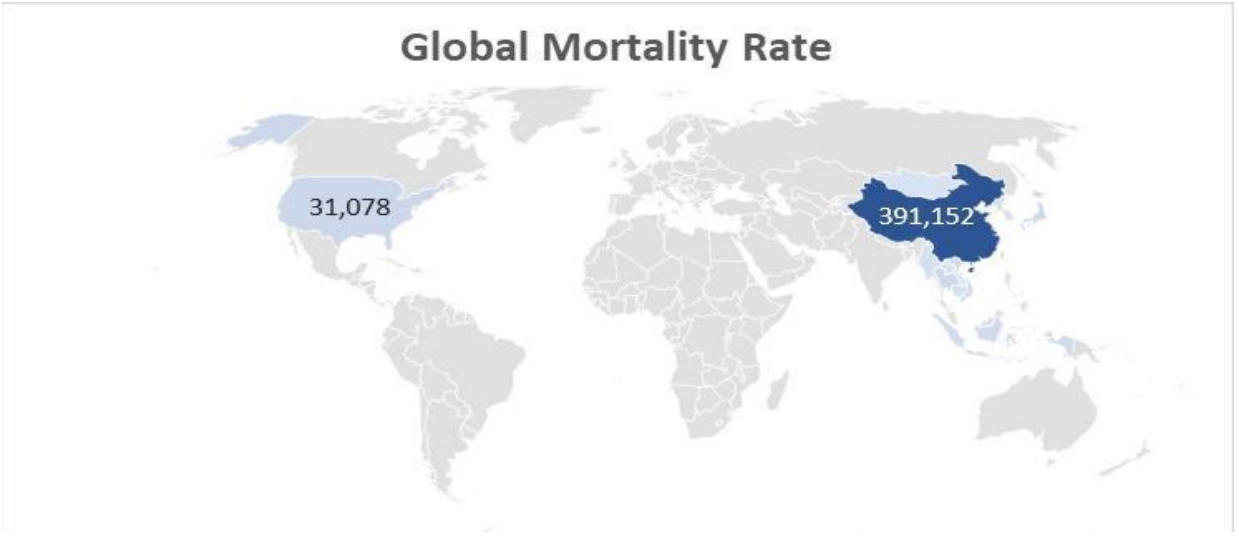

Figure 2: Global Mortality Rate [9]

The incidence and death rates of HCC exhibit significant global variations, which can be attributed to various factors such as the timing and degree of exposure to both environmental and transmissible risk factors, availability to medical facilities, and the capacity to identify HCC in its early stages and provide potentially curative treatments. It was reported that in 2020, Asian countries like Vietnam,

Cambodia, and Thailand recorded high cases and fatality rates of about 24 per 100,000 people, while the highest death rates were recorded in Mongolia with more than 80 per 100,000 individuals[4]. China is recorded to have the highest number of incident cases of HCC as presented in Figure 1, with over 400, 000 cases, followed by Japan with 45, 000 cases, Thailand, and Vietnam. GLOBOCAN 2020 data shows that over the past two years, the number of cases has sharply increased among nations such as Iran, Azerbaijan, Qatar, Afghanistan, Iraq, and Nepal which previously had a low prevalence of HCC [5]. Similarly, the growing number of people with persistent hepatitis C has probably contributed to the threefold increase in the rate of HCC in the USA over the past forty years. In the next twenty years, it is anticipated that there will be 22 million instances of HCC [6].

Surgical resection is effective for early-stage HCC, but advanced HCC is mostly treated by drug therapy, which includes chemotherapy, immunotherapy, targeted therapy, and combination therapy, most of which are mainly in the category of proteins/peptides, small molecular compounds, and nucleic acids. Initially, these therapies consisted of multi-kinase inhibitors including Sorafenib and monoclonal antibodies but later MTL-CEBPA was also approved for clinical use [10]. Many genes such as small interfering RNAs (siRNAs), short hairpin RNAs (shRNAs), microRNAs (miRNAs), and others have also been targeted as therapeutic agents for HCC treatment. Therefore, the clinical application of these highly effective therapies has led to a progressive 2% year decrease in HCC mortality rate [11]. However, several studies have also identified the effects of primary and secondary drug resistance and tumor microenvironment on the efficacy of the pharmacological treatment of HCC [12]. Therefore, increasing the treatment effectiveness of advanced HCC is the key factor in improving the prognosis of HCC.

A lot of progress has been made in the systemic therapies of HCC following the approval of Sorafenib in 2007. No effective systemic treatments were available until sorafenib, a TKI, showed significant improvement over placebo [13]. HCC is a highly vascularized mass, and angiogenetic molecular pathways responsible for the formation of novel blood vessels are critical for HCC tumor growth and spread [14]. Regarding its antitumor effects on HCC, the small molecule's effects include the regulation of multiple detailed processes including tumor growth, cell proliferation, differentiation, and angiogenesis. In the SHARP trial [15], the patients with advanced HCC were randomized to receive first-line treatment with Sorafenib 400 mg orally twice daily or placebo. The key endpoints were overall survival rate and time to develop symptomatic progression, while the secondary endpoints were time to develop radiographic progression and safety and tolerability. The primary endpoint-overall survival-showed that the median survival was 10.7 months in the Sorafenib group compared with 7.9 months in the placebo group. Another phase III trial comparing Sorafenib to placebo also confirmed the benefit of Sorafenib in HCC [16]. This trial showed only a slightly improved PFS (2.8 months vs. 1.4 months) but no difference in TSP between the two groups. Sorafenib showed toxicities in 80 % of patients as compared to placebo in 52% but mostly these side effects were of low grade. Diarrhea, fatigue, HFS, alopecia, and anorexia were the frequent adverse events in the Sorafenib group. Among all side effects, diarrhea and hand-foot syndrome were the most severe. Sorafenib was considered tolerable in the majority of patients.

Although Sorafenib has been licensed for use over the past 10 years, many phase III trials employing various drugs or their combinations for the same HCC failed to show non-inferior or superior efficacy to the drug. Until 2018 when Lenvatinib, a highly effective MKI, was included in the therapy option, Sorafenib was the only option for first-line therapy [13]. Sorafenib and Lenvatinib were compared in the first-line, non-randomized open-label phase 3 REFLECT trial for US-HCC [17]. Lenvatinib outperformed Sorafenib as demonstrated by the significant difference in the secondary endpoints including PFS, TTP, and ORR. As for progressive disease, more patients were reported in the Sorafenib group, while the disease control rate was higher in the Lenvatinib group. The adverse event rates were

similar between both groups despite the differences in the side effect profiles of the two groups. Patients who received Lenvatinib had more significant hypothyroidism, proteinuria, and hypertension compared to the placebo group, whereas, diarrhea, anorexia, and fatigue were common adverse effects in both groups who received therapy [17].

The FDA approved bevacizumab coupled with atezolizumab in May 2020, and it is the first systemic therapy that enhanced survival outcomes over Sorafenib in more than a decade [13]. Compared with sorafenib, the combination has a longer mean treatment duration and is safe and effective. The rate of proteinuria and hepatitis is higher in bevacizumab coupled with atezolizumab, while the rate of diarrhea and PPE is comparatively higher in Sorafenib [13]. Although the COSMIC-312 clinical study LBA2 [18] (atezolizumab with cabozantinib) and the LEAP-002 clinical trial LBA2 [19] (pembrolizumab with Lenvatinib) did not meet the anticipated overall survival endpoint outcomes, but they showed a certain level of efficacy and reported acceptable therapeutic performance. As a result of the continuous investigations into the pathophysiology of HCC, more phase III randomized controlled clinical studies were then conducted for second-line therapies including Donafenib [20], Regorafenib [21], Capozantinib [22], Ramucirumab [23], and Apatinib [24]. Currently, there are various therapeutic methods for HCC however, their efficacy varies, and therefore, there is a lack of comparative data concerning these treatments. As a result, determining the optimal first and second-line treatment approaches represents an urgent clinical challenge that requires resolution.

In clinical practice, physicians may come across patients whose cases are challenging in choosing the right therapeutic approach owing to various factors that may influence the treatment decision, and every patient has their own choice, which has to be weighed carefully [25]. In such cases, computational algorithms can help patients in the process of choosing a treatment plan. A clinical decision-making system is an information system designed to improve healthcare through the integration of clinical knowledge, patient information, and other health information in decision-making. Most of these systems have been utilized in disease diagnosis and to choose the first-line therapy of different health conditions, in the prognosis of post-treatment consequences of patients [26]. In contrast, others are designed to forecast post-treatment years of life expectancy. To deliver effective healthcare support, applying these computational models incorporates the knowledge of experts from different disciplines such as data scientists, researchers, and medical specialists; including radiation oncologists, hepatologists, oncologists, transplant, hepatobiliary, surgeons, diagnostic, and operational radiologists [27].

Even though HCC management has advanced significantly, traditional therapeutic and preventive approaches have some obvious drawbacks that restrict their long-term efficacy. Preventive measures such as the hepatitis B vaccine and early hepatitis C therapy have been effective in lowering the incidence of liver cancer worldwide, nevertheless, in low-resource communities, vaccination coverage is still uneven, and chronic hepatitis infections continue to occur despite advances in antiviral treatments, especially in areas with limited access to healthcare. In addition, even though they are important to culture, traditional herbal medicines frequently lack rigorous scientific confirmation, which results in unpredictable results. Consequently, many patients are diagnosed at a late stage with advanced HCC, which limits the efficacy of curative therapies such as liver transplants. Moreover, current therapies are not widely available, and even when they are accessible, these treatments may be intrusive, cause serious adverse effects, or offer only modest advantages for long-term survival [28].

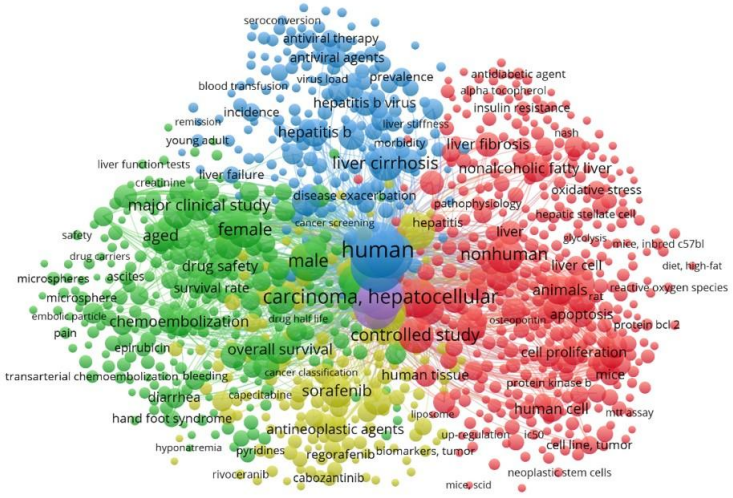

Figure 3: Major keywords used for HCC pharmacological treatment in scientific publications

Thorough research within different databases like Scopus, web of Science, and others, indicates that there have been several scientific studies on HCC treatment in the past years (Figure 3 highlights some of the common keywords found in such articles), however, considering the challenges associated with the traditional HCC treatment modalities and with the ongoing advancement of existing and development of new treatment techniques in conjunction with the advances in technology recently, a growing number of scientists has suggested that to improve HCC management, new technical solutions are required to tackle all the possible challenges that are related with HCC treatment methods. As a result, this study aims to show how multi-criteria decision-making (MCDM) methods can assist in the comparative analysis of HCC pharmacological treatments and enhance the management and prognosis of HCC. Additionally, this article will examine how the MCDM-PROMETHEE technique can improve drug delivery, offer more precise prognoses for the course of the illness, and provide tailored therapy suggestions.

2. MATERIALS AND METHODS

The MCDM problem identifies the most preferred treatment out of the feasible alternatives given that they are appraised against two or more conflicting criteria [29]. Therefore, we begin by collecting the important data, defining the criteria for the selection, evaluating their significance, and determining the best preferable pharmacological treatment with the help of one of the MCDM methodologies; fuzzy PROMETHEE [29].

2.1 Fuzzy PROMETHEE

The main objective of PROMETHEE is to deliver a comprehensive evaluation of different alternatives ranging from the most beneficial to the least when multiple criteria are considered. The fundamental concept of PROMETHEE is a pair-wise assessment on alternatives across every defined criterion. To use this approach, only two pieces of information are necessary: the relative importance of the criteria and a preference function that determines how valuable every alternative is, considering each criterion. A preference function measures the difference in the evaluation of different alternatives with the help

of a preference degree between 0 and 1, whereas a triangular fuzzy scale is used to determine the relative weights of the various criteria for the evaluation.

Fuzzy theory development has resulted in several types of fuzzy numbers such as triangular, trapezoidal, pentagonal, hexagonal, heptagonal, nanogonal, decagonal, hexadecagonal, sequential, diamond, and pictorial [29]. We focused on triangular fuzzy numbers, which are defined as $\tilde{F} = (f_1, f_2, f_3)$, which is demonstrated in Figure 4.

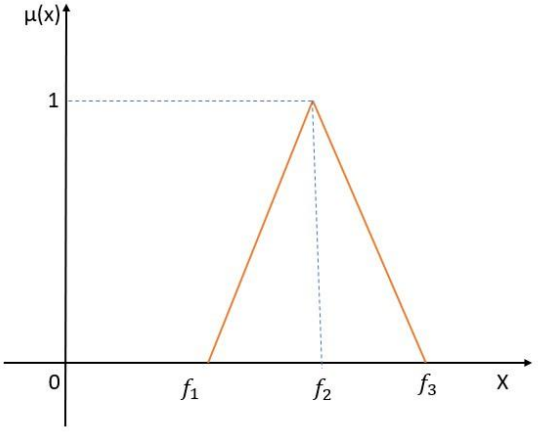

Figure 4: Triangular fuzzy numbers

Symbols f_1 and f_3 represent the left and right distribution of the confidence interval of the fuzzy number $\tilde{F}$, while f_2 represents the point at which $\mu(x)$; a membership function, is at its highest point which is 1. The membership function of the fuzzy number $\tilde{F}$ is defined by the following formulas [29]:

$$\mu_{\tilde{F}}(x) = \begin{cases} 0, & x < f_1 \\ \frac{x - f_1}{f_2 - f_1}, & f_1 \le x \le f_2 \\ 1, & x = f_2 \\ \frac{f_3 - x}{f_3 - f_2}, & f_2 \le x \le f_3 \\ 0, & x > f_3 \end{cases}$$

The degree of expert confidence (σ) as the basis for a new fuzzification is based on a variable confidence range (Equation (2)).

$$\tilde{F} = (f_1, f_2, f_3) = \left\{ \begin{array}{l} f_1 = \sigma f_2,\ f_1 \le f_2,\ f_1 \ge 1 \\ f_2 = f_2, \\ f_3 = (2 - \sigma) f_2, \quad f_3 \ge f_2 \end{array} \right\}$$

The certainty level in the current study context is measured in the closed interval of $\sigma \in [0,1]$, whereby the value *1* means that the expert is 100% sure of the statement he or she is making. The fuzzification described above will be used to define the fuzzy PROMETHEE.

Following the identification of the criteria, the assigning of their corresponding weights, and the determination of the evaluation preferences, the outranking flows (positive outranking flow; "Phi^+" and negative outranking flow; "Phi^-") are defined. The outranking flows are computed to determine how one alternative outperforms or is outranked by any other alternatives. Thus, the best alternative is one with a higher Phi^+ and a smaller Phi^-. Phi^- is the alternative's weakness and outranked character, whereas Phi^+ is the alternative's strength and outranking character. Once the outranking flows have

been determined, PROMETHEE I is used to analyze the partial ranking of the alternatives, while PROMETHEE II is used to assess the net ranking based on the net flow.

The calculation for the net flow $Phi(a_t)$ for both alternative a_t and alternative $a_{t'}$ is as follows:

$(Phi(a_t)) = (Phi^{+}(a_t) - Phi^{-}(a_t)$

$$(Phi(a_{t'})) = (Phi^{+}(a_{t'}) - Phi^{-}(a_{t'})$$

As illustrated below, PROMETHEE II is utilized to derive a final ranking based on net flow.

a_t is preferred to $a_{t'}$ $(a_t P a_{t'})$ if $Phi(a_t) > Phi(a_{t'})$

a_t is indifferent to $a_{t'}$ $(a_t I a_{t'})$ if $Phi(a_t) = Phi(a_{t'})$

The superiority of an alternative increases with its net $Phi(a_t)$ value.

A hybrid method that combines fuzzy logic and the PROMETHEE outranking technique (fuzzy PROMETHEE) was built considering the foundation of the PROMETHEE algorithm with the advantages of fuzzy logic in handling ambiguous data. Due to the ability to solve complex and nonsystematic problems with just the data provided by the decision-makers, the application of the fuzzy PROMETHEE technique has proven to be of high efficiency in various fields [30], [31], [32], [33].

2.2 Fuzzy PROMETHEE Application in HCC Treatments

The current study used scientific research reports from peer-reviewed publications, clinical trials, and regulatory approval procedures to build an extensive dataset (refer to Table 1). The dataset includes information on HCC drugs according to several important factors, including cost, research stage, safety profile, efficacy, and side effects. When evaluated alongside their brands, Atezolizumab, Sorafenib, Lenvatinib, and Pembrolizumab exhibit differences in cost (high to very high), safety (moderate to good), and efficacy (moderate to high). Tivantinib is still undergoing clinical studies, however, the majority of medications are approved. Through the integration of these factors, this data supports the fuzzy PROMETHEE technique for drug ranking, enabling well-informed choices for the prioritization of HCC treatment.

Table 1: Data from different sources reporting on the HCC pharmacological treatments

Drugs	Brand	Side Effects	Efficacy	Safety	Cost	Drug development Stage (DDS)	Ref
Atezolizumab	Tecentriq	Fatigue, liver enzyme abnormalities	High	Moderate	High	Approved	[34]
Sorafenib	Nexavar	Diarrhea, hand-foot syndrome	Moderate	Good	Moderate	Approved	[35]
Lenvatinib	Lenvima	Hypertension, fatigue	High	Good	Low	Approved	[36]
Cabozantinib	Cabometyx	Diarrhea, fatigue, hypertension	High	Good	Moderate	Approved	[37]
Regorafenib	Stivarga	Hand-foot syndrome, diarrhea	Moderate	Moderate	Moderate	Approved	[38]
Nivolumab	Opdivo	Fatigue, rash	High	Moderate	High	Approved	[39]
Tivantinib	Tivantinib	Anemia, fatigue	Promising	Unknown	High	Clinical Trials	[40]
Pembrolizumab	Keytruda	Fatigue, rash	High	Moderate	High	Approved	[41]

Normalizing the data is necessary to make it comparable across various parameters. Qualitative ratings were transformed into numeric scores for qualitative parameters such as "Side Effects." Numerical values for the other criteria are normalized as follows: Side Effects: High = 3, Moderate = 2, Low/Unknown = 1. Efficacy: Low = 1, Moderate/Promising = 2, High = 3. Safety: Poor/unknown: 1, Moderate: 2, Good: 3. Cost: High = 3, Low = 1, Moderate = 2. Drug development stage: approved = 3, clinical trials = 2, Not approved=1. The overall normalization of the data can be seen in Table 2.

Table 2: Normalized dataset

Alternatives / **Drug**	**Side Effects**	**Efficacy**	**Safety**	**Cost**	**Drug Development Stage**
Preference	*Min*	*Max*	*Max*	*Min*	*Max*
Atezolizumab	3	3	2	3	3
Sorafenib	3	2	3	2	3
Lenvatinib	2	3	3	1	3
Cabozantinib	3	3	3	2	3
Regorafenib	2	2	2	2	3
Nivolumab	2	3	2	3	3
Tivantinib	2	2	1	3	2
Pembrolizumab	2	3	2	3	3

As shown in Table 3, the linguistic scales were applied to the weight of the criteria together with the associated triangular fuzzy numbers. The Yager index [42] was used for the defuzzification of these numbers, and a Gaussian preference function is selected for each criterion to measure the preference of the alternatives followed by the PROMETHEE analysis.

Preference Score=(Side Effects Score×Weight)+(Efficacy Score×Weight)+(Safety Profile Score×Weight)+(Cost Score×Weight)+(Stage of Development Score×Weight)

Table 3 The Linguistic Fuzzy Scale and Importance

Linguistic scale	**Triangular fuzzy scale**	**Criteria**
(VH)	(0.75,1,1)	-
(H)	(0.50,0.75,1)	Efficacy, Safety, drug development stage
(M)	(0.25,0.50,0.75)	Side Effects
(L)	(0,0.25,0.50)	Cost
(VL)	(0,0,0.25)	-

VH: Very High, H: High, M: Moderate, L: low, VL: Very Low

Expert reviews including pharmacologists, hepatologists, and oncologists confirmed the final rankings, by assessing how well the rankings matched clinical expectations and the effectiveness of actual treatments. The study did not include direct patient interactions and was carried out using clinical data

that was made publicly accessible. Ethical approval was considered unnecessary; nonetheless, the study followed ethical standards for medical research and safeguarded data privacy. The applied model provides a reliable decision-support system for selecting HCC pharmaceutical treatments while balancing effectiveness, safety, cost, and other key criteria.

3. RESULTS AND DISCUSSIONS

Table 4 shows the ranking of the eight HCC drugs based on the Phi, Phi+ and Phi- values. These analyses revealed the Sorafenib to rank the highest (Phi = 0.0346) followed by Lenvatinib and Regorafenib. In addition, these three HCC drugs have shown Positive Phi values which indicates an increased effectiveness. Contrastingly, Cabozantinib has a relatively good Phi+ value (0.0263) but a significantly negative Phi- value (0.0206), which indicates high disadvantages. Furthermore, Atezolizumab, Nivolumab, and Pembrolizumab all revealed identical results (Phi = -0.0107) which indicates lower efficacy with high negative impacts. Tivantinib however, has the lowest Phi (-0.0477) and the highest Phi- (0.0884), indicating that it has the least favorable profile of the medicines studied.

Table 4: Complete Ranking of Drug alternatives in HCC treatment

Rank	HCC drugs	Phi	Phi+	Phi-
1	Sorafenib	0.0346	0.0372	0.0026
2	Lenvatinib	0.0254	0.0364	0.011
3	Regorafenib	0.0142	0.0226	0.0084
4	Cabozantinib	0.0056	0.0263	0.0206
5	Atezolizumab	-0.0107	0.0103	0.0211
5	Nivolumab	-0.0107	0.0103	0.0211
5	Pembrolizumab	-0.0107	0.0103	0.0211
8	Tivantinib	-0.0477	0.0407	0.0884

Based on the fuzzy PROMETHEE methodology ranks, Figure 5 represents the PROMETHEE Net flow score visualisation of individual HCC medications according to a number of factors, which includes side effects, cost, safety, efficacy, and drug development stage. According to the visualisation, there is a compromise between major side effects and efficacy for Sorafenib, Lenvatinib, and Regorafenib, which have moderate preference flows. Atezolizumab, Nivolumab, and Cabozantinib exhibit balanced performance across all parameters, suggesting that they provide a decent balance between safety and efficacy, however there may be cost problems.

The results offer a thorough evaluation of liver cancer medication substitutes based on the fuzzy PROMETHEE methodology. Because of their proven effectiveness and regulatory authorisation for primary treatment of HCC, Sorafenib and Lenvatinib emerge as the most advantageous alternatives in the ranking system, which is complies with current clinical standards. Despite worries about side effects and expense, Regorafenib and Cabotazinib, which are placed third and fourth, respectively, are acknowledged as good second-line treatment alternatives because of their positive effectiveness profiles.

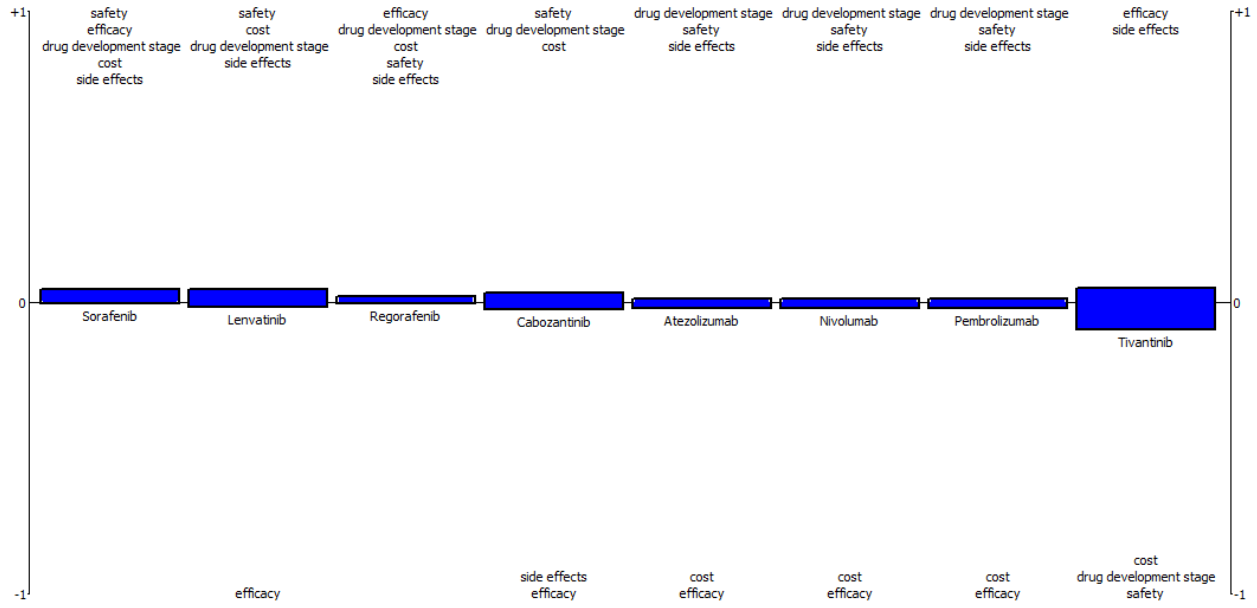

Figure 5: PROMETHEE evaluation of HCC drugs

Interestingly, immune checkpoint inhibitors (Nivolumab, Pembrolizumab, and Atezolizumab) were ranked at rank 5, indicating a comparatively lesser preference than kinase inhibitors. Although these medications have demonstrated encouraging outcomes when used in combination, their middling ranking is a result of their cost, side effect profiles, and efficacy when used alone.

Tivantinib's poor performance (Rank 8, Phi = -0.0477) is notable and consistent with clinical trial data [43], which show that MET inhibition does not provide significant survival advantages in large-scale investigations. This emphasizes the significance of rigorous clinical validation before using experimental medicines.

3. CONCLUSION

This study effectively proved the application of fuzzy PROMETHEE method in evaluating HCC pharmaceuticals. Exploiting the fuzzy PROMETHEE technique, we offered an analytical and unbiased approach to assessing different treatment alternatives according to multiple significant variables. The study highlighted both the positive and negative impacts of the medications in treatment of HCC and also revealed the preferred alternatives in the treatment of the disease. Furthermore, the study incorporates MCDM framework-based decision-support technologies which greatly improves clinical decision-making and guarantees that HCC patients receive the most individualized and efficient therapies. However, future developments in analytical models will improve the applied technique even further, opening the door to more specialized and accurate cancer treatments and more guided decision-making.

Conflicts of Interest

No conflict of interest.

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