EVALUATION OF HEPATITIS C DIRECT ACTING ANTIVIRAL TREATMENTS USING FUZZY PROMETHEE

A THESIS SUBMITTED TO THE GRADUATE SCHOOL OF APPLIED SCIENCES OF NEAR EAST UNIVERSITY

By

FUNSHO DAVID ALIM

In Partial Fulfillment of the Requirements for the Degree of Master of Science in Biomedical Engineering

NICOSIA, 2020

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Approval of Director of Graduate School of Applied Sciences

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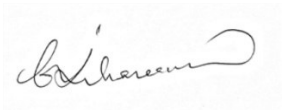
We certify that this thesis satisfactory for the award of the degree of Masters of Science in Biomedical Engineering

Examining Committee in charge



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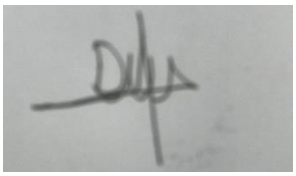

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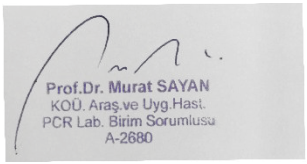

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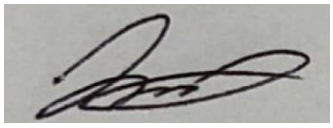

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To God Almighty and my Family

ABSTRACT

Hepatitis C virus (HCV) which research has shown to be a prominent cause of chronic liver disease and a major reason for liver transplant globally. The need to understand the genetics of the HCV had been confirmed to be very important to the effective treatment of the virus. The proposed Fuzzy PROMETHEE method of selection was aimed at ranking the HCV drugs use based on the following criteria; Previous treatments, Treatment Duration, Compliance, Age, Practicability, Glomerular Filtration Rate (GFR), Member of key population, Drug resistance (RAV), Mental disorder, HCV Genotype, False prescription, HCV subtype, Drug-drug interaction, Number of tablets, Inefficient drug combination, Coinfection, Limitations, Size of table, Dose frequency, Decompensated Cirrhosis, Post liver transplant with Cirrhosis, Working condition, and Side effects. The ranking clearly suggested based on this research that a particular drug will probably be the most preferred for a patient. The Fuzzy Promethee analysis of HCV drug combination treatment ranked and show that GLE/PIB could the most preferred option in the oral treatment HCV and OBV/PTV/RTV/DSV + RBV may be a last resolve when making decisions.

Keywords: Hepatitis C virus (HCV); Fuzzy PROMETHEE; oral treatment HCV; decision-making.

ÖZET

Hepatit C virüsü (HCV), kronik karaciğer hastalığının önde gelen bir nedeni ve global olarak karaciğer nakli için önemli bir neden olduğunu göstermiştir. HCV'nin genetiğini anlama ihtiyacının, virüsün etkili tedavisi için çok önemli olduğu doğrulandı. Önerilen Bulanık PROMETHEE seçim yöntemi, HCV ilaçlarının kullanımının aşağıdaki kriterlere göre sıralanması; Önceki tedaviler, Tedavi Süresi, Uygunluk, Yaş, Uygulanabilirlik, Glomerüler Filtrasyon Hızı (GFR), Anahtar popülasyonun üyesi, İlaç direnci (RAV), Zihinsel bozukluk, HCV Genotipi, Yanlış reçete, HCV alt tipi, İlaç-ilaç etkileşimi, Tablet sayısı , Verimsiz ilaç kombinasyonu, Koinfeksiyon, Sınırlamalar, Tablonun büyüklüğü, Doz sıklığı, Dekompanse Siroz, Sirozlu karaciğer nakli sonrası, Çalışma koşulu ve Yan etkileri. Sıralama, bu araştırmaya dayanarak belirli bir ilacın muhtemelen bir hasta için en çok tercih edileceğini önerdi. HCV ilaç kombinasyon tedavisinin Fuzzy Promethee analizi sıralandı ve GLE / PIB'nin HCV ve OBV / PTV / RTV / DSV + RBV'nin oral tedavisinde en çok tercih edilen seçenek olabileceğini gösterdi ve karar verirken son çözüm olabilir.

Anahtar Kelimeler: Hepatit C virüsü (HCV); Fuzzy PROMETHEE; oral tedavi HCV; karar verme.

TABLE OF CONTENTS

ACKNOWLEDGEMENT ..... **ii**

ABSTRACT ..... **iv**

ÖZET ..... **v**

LIST OF FIGURES ..... **viii**

LIST OF TABLE ..... **ix**

LIST OF ABBREVIATIONS ..... **x**

CHAPTER 1: INTRODUCTION

1.1 Thesis Problem 2
1.2 Aims of the Study..... 2
1.3 Significance of the Study..... 2
1.4 Limitations of the Study 3
1.5 Overview of the Thesis..... 3

CHAPTER 2: LITERATURE REVIEW

2.1 Overview 4
2.2 HCV Genotypes..... 4
2.2.1 History of HCV infection 4
2.2.2 Extrahepatic infections 5
2.3 HCV Disease 6
2.3.1 Challenge of hcv elimination..... 6
2.3.2 HCV transmission routes..... 7
2.3.3 Acute hepatitis c 7
2.3.4 Chronic hepatitis..... 7
2.4 Standard Care For Chronic HCV Patients 8
2.4.1 The Treatment of Special Population 9

CHAPTER 3: LITERATURE REVIEW

3.1 FDA Approved HCV Drug Treatment 10
3.1.1 GLE/PIB (Glecaprevir/Pibrentasvir) 12
3.1.2 SOF/LDV (Sofosbuvir/Ledipasvir) 12
3.1.3 SOF/VEL/VOX (Sofosbuvir/Velpatasvir/Voxilaprevir)..... 12
3.1.4 SOF/VEL (Sofosbuvir/Velpatasvir) 13
3.1.5 SOF/LDV + RBV (Sofosbuvir/Ledipasvir + Ribavirin) 13
3.1.6 SOF/VEL + RBV (Sofosbuvir/Velpatasvir +Ribavirin) 13
3.1.7 DCV + SOF (Daclatasvir + Sofosbuvir) 14
3.1.8 DCV + SOF + RBV (Daclatasvir + Sofosbuvir + Ribavirin)..... 14

3.1.9 GZR/EBR (Grazoprevir/Elbasvir) 15
3.1.10 OBV/PTV/RTV/DSV: (Omibitasvir/Paritaprevir/Ritonavir/Dasabuvir) 16
3.1.11 Paritaprevir/Ritonavir/Ombitasvir Plus Dasabuvir ± Ribavirin 16

CHAPTER 4: METHODOLOGY

4.1 Multi-criteria Decision-Making 18
4.2 Fuzzy PROMETHEE 19
4.2.1 Implementation of fuzzy promethee to project 22

CHAPTER 5: RESULTS 24

CHAPTER 6: CONCLUSION AND DISCUSSION

6.1 Discussion 33
6.2 Conclusion 33

REFERENCES 35

APPENDICES

APPENDIX 1: ETHICAL APPROVAL DOCUMENT 44

APPENDIX 2: SIMILARITY REPORT..... 45

LIST OF FIGURES

Figure 2.1: Chronic HCV histologic depiction of chronic hepatitis…… 6
Figure 2.2: Worldwide distribution of HCV genotypes…… 7
Figure 2.3: The putative viral and host cellular factors interacting in HCV life cycle…. 10
Figure 4.1: Types of Generalized Criteria……. 22
Figure 4.2: DAA alternatives along-side creteria……. 24
Figure 5.1: Ranking of each DAA combination…… 26
Figure 5.2: Action Profile for GLE/PIB…… 27
Figure 5.3: Action Profile for SOF+LDV……. 27
Figure 5.4: Action Profile for SOF+VEL+VOX……... 28
Figure 5.5: Action Profile for SOF+VEL…….. 28
Figure 5.6: Action Profile for SOF+LDV+RBV……... 29
Figure 5.7: Action Profile for SOF+VEL+RBV…….. 29
Figure 5.8: Action Profile for DCV+SOF…….. 30
Figure 5.9: Action Profile for DCV+SOF+RBV……..... 30
Figure 5.10: Action Profile for GZR+EBR……..... 31
Figure 5.11: Action Profile for OBV+PTV+RTV+DSV…… 31
Figure 5.12: Action Profile for OBV+PTV+RTV+DSV+RBV…….. 32
Figure 5.13: Rainbow Ranking of All HCV DAA drugs……. 33
Figure 5.14: Network Ranking View of DAAs…… 33

LIST OF TABLES

Table 4.1: Linguistic scale of importance……. 23
Table 5.1: Complete Ranking of DAAs…….. 28

LIST OF ABBREVIATIONS

ELECTRE:	Elimination and Choice Expressing Reality
MCDM:	Multi-Criteria Decision-Making
PROMETHEE:	Preference Ranking Organization Method for Enrichment of Evaluations
WHO:	World Health Organization
AST:	Aspartate Transaminase
ALT:	Alanine Aminotransferase

CHAPTER 1

INTRODUCTION

Hepa is associated with the liver while *Titis* refers to inflammation. The word Hepatitis then means an inflamed liver (CDC, 2016). Liver inflammation is the swollen, redness, painful and sometimes hot condition of a liver. This inflammation may as a result of excessive alcohol intake, drug use and other medical condition (David and Hamilton, 2010). It can also be caused by a virus known as viral hepatitis A, B, C, D, E and G (Kumar et al, 2010). A laboratory investigation of Alanine Aminotransferase (ALT) and Aspartate Transaminase (AST) with elevated results points to the presence of abnormal functioning of a Liver (George and Hans, 2016). When AST is greater than ALT, it could be an indicator of an alcohol-related Liver inflammation while a greater ALT compared to AST most times points to viral related liver condition (George and Hans, 2016). The condition could be acute, chronic or fulminant (Lindemann et al, 2014).

Hepatitis virus A, E and G are spread through faecal or oral routes. They are referred to as enteral Hepatitis virus. Hepatitis B Virus is transmitted intravenously, through sexual intercourse, and vertical transmission {Mother to Child} (CDC, 2020). Hepatitis C virus is spread by direct blood contact e.g. Intravenous Venous drug use, blood transfusion (if blood is not properly screened), sharing of sharp objects, and sexual intercourse (rate of this transmission is little) (CDC, 2020). Hepatitis D viruses are transmitted through the same route as B. Hepatitis D sole depends on Hepatitis B i.e. a person may not have Hepatitis D without B (WHO. Hep D, 2019). One major reason for liver transplant globally is HCV which has been discovered to be a prominent reason for chronic liver disease. The WHO (World Health Organization) estimated that 71 million people get chronic hepatitis virus infection globally. (WHO. Hep C, 2019). HCV is an RNA virus Hepacivirus with single strand in the Flaviviridae family. In 1989, it was cloned to be the agent causing non-A or B hepatitis (Kim & Chang, 2013). The infection can be acute or chronic. An untreated chronic HCV viral infection has the tendency of progressing to liver cirrhosis and if the cirrhosis is not properly managed it may lead to hepatocellular carcinoma (HCC),

which a terminal disease condition if it cannot be salvaged (Lindemann et al, 2014). Literature on hepatitis C and the current direct acting-antivirals (DAA's) are discussed in the next chapters, followed by the methods employed in the study with results and discussion in the subsequent chapters. The work would show the rankings of seeks to evaluate the DAA's using a fuzzy based ranking method (fuzzy PROMETHEE).

1.1. Thesis Problem

- A number of combination DAA's treatment exist making the prescription process cumbersome for doctors especially for new medical practitioners.
- There is a high chance of prescribing the same type of DAA's multiple times.

1.2. Aims of the Study

- To identify, evaluate and rank the DAA's using fuzzy-PROMETHEE.
- To reduce the incidence of repeated prescriptions.
- To increase confidence in the DAA's while simplifying the process

1.3. Significance of the Study

- The study would increase the awareness on HCV and its long term effects on bodily functions.
- The study seeks to implement new methods for prescription with more confidence in the system.
- The study would increase the rate of desired results from DAA's.
- correctly provide an outflow ranking of the DAA's according to positive and negative effects simultaneously

1.4. Limitations of the Study

- The consistency of the obtained data may vary depending on the clinician with regards to the weight of each parameter.
- More tools asides from VISUAL PROMETHEE software may be required in the future for improving the validity of results.
- Although the simplicity of the fuzzy PROMETHEE method shows promise, many medical practitioners may be slow to accepting it.

1.5. Overview of the Thesis

Chapter 1 would include an introduction to the thesis work while providing a summary of the study. Chapter 2 shows an explanation of what HCV is, mode of transmission, available DAA's and more. In Chapter 3 and Chapter 4, early studies made on HCV and DAA's and the method used for the analysis are highlighted. Chapter 5 and 6 both present the results of the study, the discussion and the conclusion respectively.

CHAPTER 2
LITERATURE REVIEW

2.1 OVERVIEW

This section presents the pathology hepatitis and the existing treatments available for the diseases. Brief illustration of studies on the advantages and limitations of the drugs would be provided.

2.2 HCV genotypes

The need to understand the genetics of the HCV has been proven to be very important to the effective treatment of the virus. Regardless of the race, a person could be infected with any of the genotypes (Kumar et al, 2018). Travelers are likely to be exposed to different HCV genotype which may result in mixed infection (Kumar et al, 2018). HCV genotypes 1, 2, 3, 4, 5, and 6 are six existing genotypes (Kumar et al, 2018) each of these genotypes responds differently to medicines that cures or treats the HCV as the case may be. These genotypes play an important role in assisting doctors to find the most effective treatment. Though, the genotypes are capable of damaging the liver at the same rate (Kumar et al, 2018).

2.2.1 History of HCV infection

HCV is a hepatotropic RNA virus of the genus hepacivirus in the *flaviviridea* family (Chang Wook and Kyong-Mi, 2013). In the 70's several studies carried out on blood samples showed that ten percent of the blood recipient showed evidence of non-A, non-B hepatitis and consequently the cases were found to be caused by a hepatitis C virus (Roger, 2007).

In humans 5 viruses from 5 different families' causes hepatitis, two of which can be gotten mainly through water or food that is fecal contaminated. These two hepatitis viruses are hepatitis A virus and hepatitis E virus (Strickland and El-Kamary, 2013) both cause self-limited acute illness. The other hepatitis viruses (hepatitis B, C and D) are transmitted in

different forms such as through sexual relations, peri-natal exposures and the blood (Strickland and El-Kamary, 2013). These cause acute hepatitis with frequent infections that further cause chronic hepatitis and more complications (Strickland and El-Kamary, 2013). The impact of hepatitis virus is related to the human ecology and socio-economic status. In developed countries HBV and HCV transmission have been significantly reduced due to improved blood screening procedures, however it still remains a huge health issue in developing countries. The incidence rates of post transfusion hepatitis C infections have since reduced due to implementation of more sensitive tests. With HBV and HCV infections the persistence of the virus may cause chronic hepatitis, lymphoid aggregation and lymphocytic inflammation in portal tracts. Long term effects of chronic infections of HBV and HCV are chronic liver failure, hepato-cellular carcinoma and cirrhosis for patients with persistent active infection (Strickland and El-Kamary, 2013). The risk of cirrhosis is between 15-30 percent after twenty years of HCV infection. At first cirrhosis may be compensated but decompensation can occur in later years causing encephalopathy or hemorrhages. The behaviors and characteristic of a HCV infected person has varying degrees of risks associated with disease progression.

2.2.2 Extrahepatic infections

Extrahepatic manifestation or secondary health problems are co morbidities such as diabetes mellitus depression and chronic renal disease directly related to HCV. According to the guidelines for the care and treatment of persons diagnosed with chronic hepatitis c virus infection of 2018, extra hepatic manifestations can be caused by HCV infections.

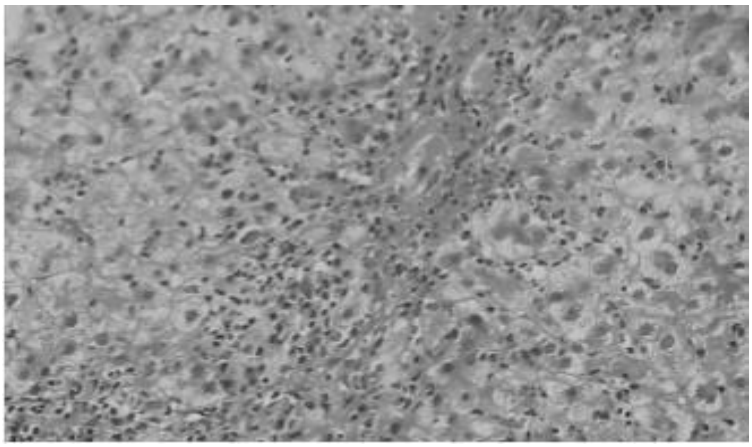


Figure 2.1: Chronic HCV histologic depiction of chronic hepatitis (Strickland and El-Kamary, 2013)

2.3 HCV disease

2.3.1 Challenge of HCV elimination

The world health organization estimated that 71 million people were infected with chronic HCV in 2015, with over 400 thousand deaths due to hepatocellular carcinoma or cirrhosis. Unsafe health care and injecting drug use has led to new HCV infection worldwide. There are 6 major HCV genotype causing HCV infection however the distribution of genotype in several countries are yet to be known.

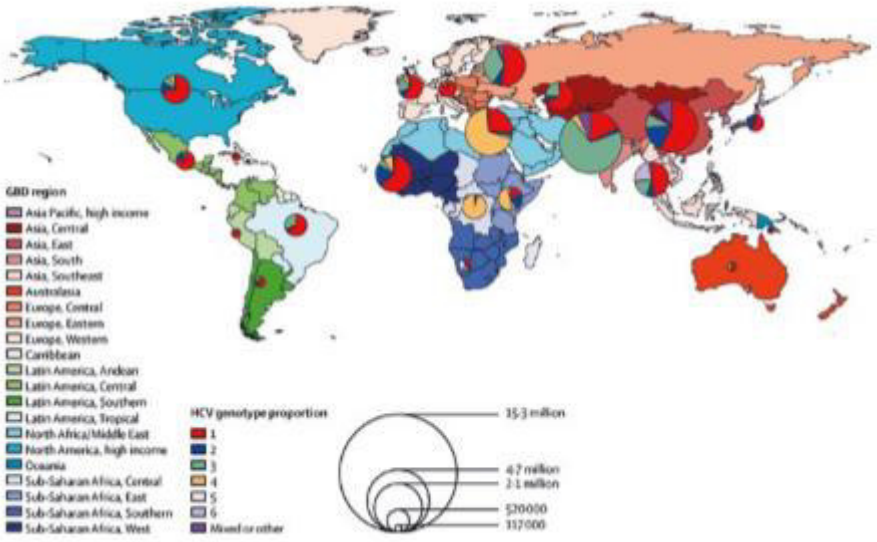


Figure 1.2: worldwide distribution of HCV genotypes. Source: The Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol. 2017; 2:161–76. Disclaimer: This map is reproduced as originally published.

The World Health Assembly approved a global health sector strategy in 2016 for a period of 5 years on HBV and HCV infection. The strategy seeks to eliminate viral Hepatitis as a public health threat by the year 2030. The target was set to reduce new chronic infection and mortality by 90 and 65 percent respectively in comparison with the baseline of 2015. The main issue regarding the elimination of HCV infection is in the large deficit in diagnosis and treatment of the identified 71 million people infected with HCV.

2.3.2 HCV transmission routes

***Injection drug use*:** this accounts for about 23 percent of new HCV cases and people who inject drugs (PWID) infected with HCV are at a high risk of all cause mortality.

Health care: unsafe injection practices in countries with insufficient control measures for HCV. Other health care practices such as dental care, unsafe blood transfusion, surgery and renal dialysis. Reuse and non-sterilization of injection have been shown to be a large contributor to an estimated 315 thousand new cases of HCV infection every year. To curb

trend, newer devices and health care practices that involve the use injections should be reviewed.

Others: percutaneous methods such as body piercing, needle stick injuries in health care workers and transmission through mother and child are modes through which HCV can be transmitted. Sexually transmitted HCV are less common with heterosexual couples and more in HIV positive people especially in homosexual couples.

2.3.3 Acute Hepatitis C

The acute hepatitis C infection is rarely diagnosed due to the asymptomatic nature of the infected. In about 20 to 30 percent of acute HCV infected adults the clinical symptoms start to show and range from three to twelve weeks from exposure. The symptoms are; jaundice, weakness, malaise and anorexia. HCV RNA can be detected with serum alanine amino transferase (ALT) levels within the first two weeks after exposure. This HCV RNA level rapidly increases during the first few weeks and reaches a peak of 10^5 to 10^7 IU/ml just before the peak levels of serum aminotransferase and onset of acute HCV symptoms. Fulminant liver failure is rare in cases of acute HCV, and the HCV antibody can be detected by an immunoassay enzyme.

2.3.4 Chronic Hepatitis

The persistence of the HCV RNA within the blood for a period of at least 6 months after the onset of acute HCV infection. Several factors affect the rate of chronic HCV infection such as; gender, age, ethnicity and jaundice development in the acute HCV period.

i. ***Race and age at time of infection***: the development of complications, response to treatment and different rates of infection of HCV within the different races are somewhat unclear. Such as in the case of African American's, seemingly have a higher rate of chronic HCV infection more than Hispanic white and Caucasians. The rate of chronic HCV is lower in younger persons with recent data showing that people infected with HCV within 25 years were less likely to be infected with chronic HCV at older ages.

ii. ***Jaundice and immune response***

There are lower rates if chronic HCV infection in patients with a history of jaundice from acute HCV. The long term follow up study for women infected with contaminated Rh immune globin in Germany showed a chronic rate in 43percent of those with a history of jaundice compared to 60 percent of those who are anicteric.

2.4 Standard care for chronic HCV patients

In the past dual therapy with pegylated interferon (IFN) alpha and ribavirin (PEG IFN/riba) were used in most countries as a standard care for chronic HCV patients. The sustained virological response (SVR) with the dual therapy was 50 percent in infected patients of genotype 1 compared to the 80 percent SVR in HCV infected patients genotype 2 or 3 (Chang et al., 2013). However the dual therapy was expensive and had several intolerable adverse effects with prolonged treatment.

In later years a new standard therapy were made available; two inhibitors with virally encoded NS3/4A protease mostly for HCV genotype 1. A triple therapy using the first generation protease inhibitors alongside PEGIFN/riba therapy improved the SVR rate for about 50 to 70 percent indifferent clinical trial. Transplant, hemodialysis, cirrhotic patients and primary non-responders were populations in which the new therapy had limited efficacy. This was due to the IFN resistance, increased drug toxicity and or emergence of protease inhibitors resistance mutation. There are however efforts to create better therapeutic options with less toxicity and drug resistance and shorter treatment duration mostly as oral combination regimens (Chang et al., 2013).Knowledge of every step of the HCV life cycle has offered a number of potential targets for therapeutic.

HCV life cycle step	Viral factors	Host cellular factors
Viral attachment, entry, and fusion	Envelope glycoprotein E1	Heparan sulfate proteoglycans
	Envelope glycoprotein E2	Scavenger receptor B type I
		CD81
		Claudin-1
		Occludin
		Epidermal growth factor receptor
		Ephrin receptor A2
		LDL receptor
		Niemann-Pick C1-like 1 cholesterol uptake receptor
HCV RNA translation	Internal ribosome entry site	Ribosomal subunits
	5' nontranslated region	Eukaryotic initiation factors 2 and 3
	HCV open reading frame	tRNA
	3' nontranslated region	
	NS4A and NS5B	
Posttranslational processing	NS2 zinc-dependent metalloprotease	Signal peptidase
	NS3/4A serine protease	Signal peptide peptidase
HCV replication	NS5B RNA-dependent RNA polymerase	ER membranes
	NS5A	Cyclophilin A
	NS4B	Phosphatidylinositol 4 kinase IIIα
	NS3 helicase-NTPase	MicroRNA122
Virus assembly and release	Core protein	Lipid droplets
	envelope glycoproteins	ER membranes
	HCV RNA genome	Golgi apparatus
	NS5A	VLDL secretion pathway
	NS2	Apolipoproteins (apoB, apoE)
	P7	

Figure 2.3: the putative viral and host cellular factors interacting in HCV life cycle (Chang wook Kim et al, 2013) HCV virology and life cycle

2.4.1 The Treatment of Special Populations

The treatment of the acute hepatitis C should consider the period for the start of therapy and the duration therapy. Some studies have shown good outcomes with patients who were given early therapy than patients who were observed with spontaneous clearance. In one of the studies the therapy offered contained high doses of conventional IFN (5-10 mil units per day for 12 weeks) which achieved an SVR of 85 to 100 percent. The dose of

CHAPTER 3

LITERATURE REVIEW

3.1 FDA approved HCV drug treatment

DAAs, the acronym for direct-acting antivirals are the recent HCV oral treatments that are made of combined drugs (Pacific Hepatitis B Network, 2020). Some of the most significant achievements of DAAs are pangenetic properties, reduction the duration of therapy, an improvement on the sustained virologic response (SVR), also to create the possibility of interferon (IFN)-free treatment (Pacific Hepatitis B Network, 2020).

Four classes of DAAs are combined in different ways to produce a therapy for HCV treatments.

1. NS3/4A Protease Inhibitors (PIs): The mechanism of action is blocking a protease which the viral enzyme responsible for the duplication and survival in host cells.

2. Nucleoside and Nucleotide NS5B Polymerase Inhibitors: The mechanism of action is targeting directly the HCV to prevent it from duplication in the liver. This prevents the proliferation of the virus, and attachment to RNA.

3. NS5A Inhibitors: The mechanism of action is blocking NS5A which is the virus protein that is needed by HCV at different stages of infection and reproduction.

4. Non-Nucleoside NS5B Polymerase Inhibitors: The mechanism of action is stopping reproduction of HCV through the insertion of the inhibitor into the virus for the avoidance of more HCV attachments.

After the emergency of the DAAs, there had been a significant improvement in the treatments of HCV though there are still some limitations. Despite the uncompromising programs to development drug, effective therapy for all genotypes of HCV was still indescribable until the US FDA approval of SOF/ VEL (sofosbuvir/velpatasvir) in June 2016 (Abutaleb et al, 2018). But recently a study from Japan had showed that deletion of

NS5A-P32 in genotype 1b infection may be a risk factor for failure in treatment (Hayato and Tetsuo 2019). This is a clear indication that there is still room for improvement on the DAAs.

Based on the goal of this research, 11 DAAs drugs was put up for comparison to assist patients in the selection of the most effective DAAs Drug.

According to the EASL recommendation HCV treatment encompasses the delivery of treatment in terms of experience in HCV therapy and assessment, proper assessment of the clinical side effects of direct-acting antiviral drugs.

3.1.1 GLE/PIB (Glecaprevir/Pibrentasvir)

Glecaprevir (GLE) is a pangenotypic antiviral inhibitor that has shown efficacy in HCV genotype 1 to 6 treatment (Wyles et al., 2018). PIB is an inhibitor of NS5A, it is a novel pangenotypic DAAs (Wyles et al., 2018). Glecaprevir confomulated with Pibrentasvir (G/P) provides treatment for HCV patient which is well-tolerated with high efficacy in genotype 3 HCV even though patient diagnosed of this ailment are harder to cure according to research investigations in the past because they are at greater risk of fibrosis progression, hepatocellular carcinoma and steatosis. HCV genotype 3 has been known to be amongst the most prevalent infection in 71-81 million people worldwide and experiencing 25-30% death rate yearly.DAA therapy for HCV has been shown by research to be a standard of care treatment since it took it the place of pegylated interferon and ribavirin due to the high rate of SVR at post-treatment levels. HCV genotype 3 patients who have concomitant cirrhosis or patients with prior HCV treatment experience are usually difficult to cure. Chronic HCV GT3 patients received treatment for 12 to 16 weeks. Also patients without cirrhosis or compensated were placed on 16weeks treatment.

G/P was well tolerated, efficacious for patients with chronic HCV GT3 infection regardless of cirrhosis status or before treatment experience. 8weeks treatment duration was effective for naïve with cirrhosis, without Cirrhosis were responded either treatment-naive at 95% of 8 weeks 198/208. 12 weeks 280/294 12 weeks treatment duration was efficacious for naive patients with compensated cirrhosis. Experience with interferon 97% 12 weeks 67/69 Glecaprevir/Pibrentasvir Non-cirrhotic patients at 90% 12 weeks 43/49 16weeks

administration of G/P were efficacious in patients with prior treatment experience irrespective of cirrhosis status at 95% 12-16 weeks 21/22Sofosburir bases regimen were well tolerated and sustained biologic response of 12 weeks post-treatment response.

***Adverse Effect*:** No serious adverse effect was attributed to Glecaprevir/pibrentasvir. Adverse effects lead to the discontinuation of G/P drugs were rated at 1% which are based on physical examination, vital signs, laboratory assessment and electrocardiogram over a 30days of drugs administration leading to discontinuation.

The combination drug was well tolerated and efficacious for chronic HCV GT3 patients with or without prior treatment of cirrhosis experience. However, the integrated analysis according to data pooled across five phases in 3 trials to evaluate the safety and efficacy of 8, 12 and 16 weeks of GP treatment in all HCV GT3 patients with or without cirrhosis or patients with prior treatment experience.

Although, treatment adherence was rated according to the percentage of drugs received during the 4 to 6 weeks span where applicable and a 16 week treatment span relative to the total expected number of tablets administered.

***Side Effects*:** Across all patients, side effects occurring at 10%were headaches, fatigue, and nausea and rate 0.4% discontinuation

3.1.2 SOF/LDV (Sofosbuvir/Ledipasvir)

The drug is administered orally as a single tablet in a combination of ledipasvir (NS5A) and sofosbuvir (NS5B) polymerase inhibitors (Gillian M, 2015). It has shown efficacy and the high SVR rate for the treatment of the chronic HCV infection (1, 3 and 4) over 12 weeks. Also eliminated through renal excretion or biliary excretion for the unchanged ledipasvir and sofosbuvir. The adverse events experienced are usually fatigue and headache.

3.1.3 SOF/VEL/VOX (Sofosbuvir/Velpatasvir/Voxilaprevir)

The drug combination sofosbuvir, velpatasvir and voxilaprevir are NS5B, NS5A and macrocyclic NS 3/4A nucleotide polymerase inhibitors (Rebecca V. and Ira M., 2017). The absorption reaches a peak concentrate for 30 to 60 minutes.

3.1.4 SOF/VEL (Sofosbuvir/Velpatasvir)

Sofosbuvir is an HCV non-structural polypeptide (NS5B) inhibitor used in combination with velpatasvir an HCV non-structural polypeptide inhibitor (NS5A) for the treatment of chronic HCV (Sarah L. Greig, 2016). It is administered orally as a single tablet once per day which has been approved by the US FDA. One of the major routes of elimination is by biliary excretion of the parent drug. Adverse events of the drug include fatigue, headache and nausea. The drug may be taken along with many antiretroviral drugs. Sofosbuvir and velpatasvir have been shown to perform exceptional antiviral activity against resistance-associated variants that are related to DAA's of different mechanisms of actions such as NS3 protease and NS5B non-nucleotide inhibitors. It has also recorded high SVR rates in some study trials Brau, et al. 2016 and Feld J et al, 2015. The clinical interactions occur during concomitant use of sofosbuvir/velpatasvir with acid-reducing agents. The cost of the drug reduces its use for many patients but it is a relevant and valued treatment option for chronic hepatitis patients.

3.1.5 SOF/LDV + RBV (Sofosbuvir/Ledipasvir + Ribavirin)

William S, et al. 2017 performed a met criterion for sofosbuvir, ledipasvir and a combination of sofosbuvir. ledipasvir and ribavirin.and it showed that the adverse events in the combination without ribavirin were low compared to the one with ribavirin over 12 weeks. Common adverse effects include rash, cough anaemia, insomnia and diarrhoea etc.

3.1.6 SOF/VEL + RBV (Sofosbuvir/Velpatasvir +Ribavirin)

This a second-generation combination DAAs for HCV treatments. Sofosbuvir is a nucleotide inhibitor NS5B, it has a low risk of resistance development and it has a safe history (Cronberg et al., 2014). The mechanism of action is blockage of the NS5B polymerase which results in the extinction of the RNA chain through the inhibition of Hep B virus RNA synthesis. Velpatasir, on the other hand, is NS5A protein inhibitor, it is known to be potent for all genotypes of Hep B virus while Ribavirin is one of the earliest treatment regimes for HCV. According to (Ahmed et al., 2018) the combination of

Ribavirin with SOL/VEL produced no significant difference from the efficacy of SOL/VEL on all genotypes of HBV. (Ahmed et al., 2018)

3.1.7 DCV + SOF (Daclatasvir + Sofosbuvir)

DACLATASVIR NS5A inhibitor - SOFOSBUVIR NS5B RNA polymerase inhibitor is one of the most effective combined treatment regimens for patients with hepatitis C genotype 4 infections. 12 weeks of daclatasvir/sofosbuvir 60/400mg regimen works effectively on patients with and without liver cirrhosis, hepatitis genotype 4. Longer treatment duration is recommended for patients with genotype 3 to get a better result. These two combined drugs were the first world's first pan-genotype hepatitis C treatment of 12 weeks regimen. It is advisable to take this oral single-dose drug with a small amount of food and water, in other to ensure maximum time for absorbing its active ingredients. This treatment is considered efficacious through BYHCV RNA level screening carriedout at the expiration of 12 weeks prescription with a lower concentration than 25IU/ML primary virological outcome as non-relapse. The clinical trial assesses the administration of phase II and phases III single aimed at testing the pharmacokinetics and pharmacodynamics safety tolerance and efficacy in naive patients, non-cirrhotic adolescent and patient with chronic HCV GT4 infection. The result shows below a pharmacological profile at 60/400mg DACLATASVIR/ SOFOSBUVIR oral once daily 12 weeks regimen achieved as; 93% cure rate at genotype 3, 100% cure rate at genotype 2, 5, 6, 97% cure rate at genotype 1, 95% cure rate at genotype 4.

However, a single dose of Daclatasvir and Sofosbuvir demonstrate that the therapy is effective and safe with or without ribavirin regardless of the baseline HCV RNA level on previous experience patient. It is advised that this drug should not be administered as monotherapy treatment because it may lead to drug resistance.

3.1.8 DCV + SOF + RBV (Daclatasvir + Sofosbuvir + Ribavirin)

One of the highly effective direct-acting antiviral treatments for HCV is the integration of daclatasvir, ribavirin and sofosbuvir (Antonio Rivero et al, 2018). These are recent treatment combinations that have shown very short therapy and higher sustained virological response rates, interferon-free treatment and fewer toxicity rates (Antonio

Rivero et al, 2018). This treatment combination is used for treatment-experienced and treatment naïve HCV patients as recommended by expert opinion for its excellent pharmacodynamics and pharmacokinetic efficacy when ingested with/without food. It is also recommended for patients' with HIV1 co-infection, compensated cirrhosis, or post-transplant recurrence (Antonio Rivero et al, 2018). The usage of sofosbuvir and daclatasvir in the treatment of HCV stems from the mechanism of HCV in the hepatocytes. The viral genome of HCV translates into a single polypeptide that splits into viral non-structural proteins (Marleen H et al. 2016). The non-structural proteins NS3,4A,5B and NS5B RNA dependent RNA polymerase are important for the replication and assemblage of the virus hence the inhibitors made available was sofosbuvir and daclatasvir for NS5B RNA dependent RNA polymerase and NS5B respectively (Marleen H et al. 2016). SVR as the goal in the treatment of HCV is undetectable HCV RNA for 12 or more weeks after completion of treatment. The SVR rates in treatment with the combination of sofosbuvir and daclatasvir have been high compared to other combination treatment of peginterferon and ribavirin which achieved a 40 to 80 % SVR rate (Marleen H et al. 2016). The sofosbuvir combination with peginterferon and ribavirin showed an efficacy rate of 50 to 93% however compared to a 94 to 100 % SVR rate of the sofosbuvir and daclatasvir combination with lesser toxicity and not genotype-dependent. This drug combination provides tolerable side effects such as headache, nausea, insomnia, and fatigue.

3.1.9 GZR/EBR (Grazoprevir/Elbasvir)

This combination is an orally administered drug for the treatment of HCV in treatment-experienced and treatment naïve HCV patients. Grazoprevir and elbasvir are potent direct-acting and a protease inhibitor NS3/4A and NS5A inhibitor respectively. Regardless of factors such as previous treatment failure, cirrhosis, renal failure, genotype and HIV co-infection, the combination records a high SVR rate. The efficacy of the drug was proven by several studies with controlled, uncontrolled, randomized and non-randomized patient groups. In treatment naïve patients the grazoprevir and elbasvir combination a randomized study by (Lawitz et al 2015), to determine the efficacy with or without ribavirin. They observed that ribavirin addition to the combination showed no significant benefit and two other related studies (Sulkowski et al 2015 and Zeuzem et al. 2015) high rates of SVR were observed with grazoprevir and elbasvir irrespective of the genotype. For treatment-

experienced patients, the combination exhibits significant SVR rates and also does not show any benefits when ribavirin is added or not. The grazoprevir and elbasvir drug combination in HIV coinfection in non-genotype 1 HCV have shown the efficacy of treatment (Duminda et al. 2016) in the presence of resistance-associated variants.

The side effects of the drug combination are tolerable and only drug-related adverse cases are common, such as headache, asthenia and fatigue. In the (Sulkowski et al 2015) study nopatients died or discontinued the treatment process due to the adverse events observed. The EASL guideline recommends a fixed-dose combination of the grazoprevir and elbasvir for 12 weeks for patients with treatment naïve and treatment-experienced patients infected with genotype 1b with or without cirrhosis.

3.1.10 OBV/PTV/RTV/DSV: OMIBITASVIR, PARITAPREVIR, RITONAVIR, DASABUVIR

The coadministration of PrOD with ribavirin had relatively a minimal identifiable impact on the liver kinetics of HCV RNA decline during the first 2 weeks regimen of the treatment irrespective of Ribavirin dosing. The regimen is considered highly efficacious and well-tolerated in patients with chronic hepatitis C virus genotype 1 infection. If this treatment is combined with a high dose of armamentarium, it will have a high chance of curing several other types of hepatitis virus infections. Similarly, clinical phase I, II, III studies of PrOD achieve high rate of SVR regardless of the presence or absence of RAS, The administration of this combined antiviral on non-cirrhotic patients with HCV genotype 1b on 12 weeks regimen sustained high virological response at 96%-100% on completion Non-cirrhotic patient HCV genotype 1a undergo same 12 weeks treatment regimen with ribavirin and responded at 75%-95% virologically Child-Pugh Class A Cirrhosis patients experienced 91.8% on 12 weeks virological response. Cirrhosis patients with HVC genotype 1a respond to 24weeks treatment at 94.2% vs 88.6% of 12 weeks treatment immediate discontinuation of PrOD is advised if patients experience some side effects which may lead to significant life-threatening cases such as decompensation of the liver and many others. However, some of the patients may still achieve viral eradication despite shorter time treatment regimen. Placing the first-line patient on the PrOD based regimen treatment should be an excluded criterion.

3.1.11 Paritaprevir/Ritonavir/Ombitasvir plus Dasabuvir ± Ribavirin

Paritaprevir/ritonavir, ombitasvir and dasabuvir (PrOD) in the presence or absence of ribavirin has shown significant efficacy and safety in the treatment of HCV 1 patients. PrOD regimen was approved by the U.S food and drug administration FDA in 2006. PrOD is a combination of non-structural NS3/4A protein inhibitor enhanced by ritonavir (Michael A, 2015). Paritaprevir tested in the presence of HCV genotype 1a and 1b virus showed a high degree of resistance. Ombitasvir also as an NS5A inhibitor showed a low genetic barrier to the resistance and hence needs a coadministration of other agents to reduce the development of resistance. Dasabuvir in the presence of HCV colonies also showed significant virologic resistance. In Chun-Hsei et al, (2019) patients with HCV 1b were given PrOD for 12 weeks and a combination of PrOD + ribavirin with or without cirrhosis. The study observed a 98.8% SVR efficacy in patients with HCV1b and100% in patients with HCV without cirrhosis and 96.4% in HCV with cirrhosis however the drug had adverse effects that caused the withdrawal of some patients from the study. PrOD is recommended for HCV treatment in HIV co-infected patients. Adverse events such as insomnia, dry skin, vomiting and nausea, pruritus, diarrhoea and anaemia are commonly associated with the drug. It records a high efficacy with or without ribavirin. The combination is favourable for the special patient population such as in post-liver transplant HCV genotype 1 infections, renal diseases and HCV in HIV co-infection. The EASL recommendation treatment for HCV 2018 recommends precautions before the administration of the drug to avoid issues from drug interaction due to the elevated plasma exposure from the ritonavir booster.

CHAPTER 4

METHODOLOGY

Chapter 4 shows the method used in the study, and it also uses secondary, hospital and expert data to provide parameters and criteria for proper analysis in the study. A multi-criteria decision making tool was applied to the parameters and criteria sourced for the study as it has been used in several analysis due to its easy to use function for comparison and quantification.

4.1 Multi-criteria Decision-Making Method and PROMETHEE (Preference Ranking Organization Method for Enrichment Evaluations)

Different research studies involve decision making with a number of criteria, and the vast use of Multi-criteria decision-making (MCDM) tools have shown good results for analysis involving a multiple criteria (Zionts, 1979 and Mardani et al., 2015) either qualitatively or quantitative and in several cases both (Seyed et al, 2015). The multi criteria decision making tools have been categorized based on the weighing method used for the evaluation of the alternatives used in a study (Majumder, 2015). The MCDMs are discussed below;

a. The compensatory decision making method: this uses weight assignment to the parameters evaluated. Further computation of the overall score of the alternatives by weight allows the one with the best score to be picked (Seyed et al, 2015) due to the disparity and difference in the evaluated alternatives. TOPSIS (technique for order of preference by similarity to ideal solution) is an MCDM software with this method.

b. The Outranking methodfor the simulteneaous evaluation of criteria and parameters to produce the best ranking criteria (Yang and wang, 2012) an example is ELECTRE (elimination and choice expressing reality)

Although described as an MCDM method for weak comparisons and real decision representation (Gelderman et, al,. 2000) improvements have been made with some

softwares such as ELECTRA and PROMETHEE which compares alternatives using generalized preference values as shown in Figure 4.1.

PROMETHEE enables its user to rank alternatives according to the criteria of each and it has been used largely due to its;

- Intuitive multi criteria decision nature and simplicity of use.
- Selection preferences for models are simple
- It easily adapts to a finite number of action with respect to criteria

Several versions of PROMETHEE were developed for combining fuzzy sets and PROMETHEE such as; FPROMTHEE, FPROMETHEE2T, PROMETHEE III and PROMETHEE V (Galindo Hose, 2008).

4.2 Fuzzy PROMETHEE

Several studies involve data which are crisp and often times vague, however a fuzzy environment composed of fuzzy numbers and functions have been used to model the randomness and vagueness of such studies. Hence this fuzzy set theory developed has been used in multi-criteria decision making processes (Galindo Hose, 2008).

Fuzzy PROMETHEE is a new simple multi criteria decision making theory that can be applied in various field of decision making. This research used fuzzy promethee to compare HCV drugs based on very important and not very important parameter analysis.

The combination of the fuzzy logic concept and promethee is called Fuzzy promethee. Fuzzy logic is a form of multi-valued logic that allows intermediate values in the form of multi-valued logic, in which the truth values of variables may be any number between 0 and 1. Fuzzy logic is distinct in concept due to different interpretations involved where binary sets have true or false valued logic. The variables may have a truth-value that ranges in degree, where the truth values can range between completely true and completely false.

Promethee (Preference Ranking Organization Method for Enrichment Evaluations) is a modern multicriteria decision making method used in different fields of study. Promethee uses a mutual comparison of related alternatives with regards to their related and selected

criteria. Promethee is quite more advantage over other modern multicriteria decision making methods due to its simple and effective concepts and applications. (Bran and Mareschal. 1986; Bran et al., 2018) were the first to conceive the concept of promethee, the same authors further developed the concept in 1986. There have been different applications of Fuzzy PROMETHEE method such as (D. Uzun Ozsahin, 2018; Ozsahin, Ozsahin, & Uzun, 2019; Yahya, Gökçekuş, Ozsahin, & Uzun, 2020). The steps expressed by Brans et al (1986) for the PROMETHEE method are as follows;

Step I determining a function f_k as the general preference of $p_k(d)$of each criterion

Step II the weight of each criterion

$$w^T = (w_1,\dots, w_k) \tag{4.1}$$

can be normalized by making the weights equal or by using

$$\sum_{k=1}^{K} w_k = 1 \tag{4.2}$$

Step III determine the outranking relation π for every alternative a_t, $a_{t'} \in$ A equation;

$$\begin{cases} AXA \rightarrow [0,1] \\ \pi(a_t, a_{t'}) \end{cases} = \sum_{k=1}^{K} w_k.\left[p_k\left(f_k(a_t) - f_k(a_{t'})\right)\right] \tag{4.3}$$

Step IV determine the strength of the positive and negative outflows equation 4.4 and 4.5 where T is the number of alternatives. The positive outflow shows the superiority of the alternatives a_t and each and the reverse for a negative outflow character.

Positive outflow a_t:

$$\Phi^+(a_t) = \frac{1}{T-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_t, a_{t'}) \tag{4.4}$$

Negative outflow a_t:

$$\Phi^-(a_t) = \frac{1}{T-1}\sum_{\substack{t'=1 \\ t' \neq t}}^{n} \pi(a_{t'}, a_t) \tag{4.5}$$

Step V the higher positive outflow and lower negative outflow depicts the best alternative a_t. In PROMETHEE I if a_t is superior compared to $a_{t'}$ $(a_t P a_{t'})$

$$\begin{cases} \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) < \Phi^{-}(a_{t'}) \; or \\ \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) = \Phi^{-}(a_{t'}) or \\ \Phi^{+}(a_t) = \Phi^{+}(a_{t'}) \; and \Phi^{-}(a_t) < \Phi^{-}(a_{t,}a_{t'}) \end{cases} \tag{4.6}$$

PROMETHEE I weighs the probable incomparabilibilty in the analysis and hence partial rankings found may be used. When incomparability or indifferences ($a_t I a_{t'}$) are found the positive and negative outflows are identical.

$$(\, a_t I a_{t'}) \text{ if: } \Phi^{+}(a_t) = \Phi^{+}(a_{t'}) \;\; and \; \Phi^{-}(a_t) = \Phi^{-}(a_{t'}) \tag{4.7}$$

When a_t is superior to$a_{t'}$ with respect to the positive outflow then both alternatives are incomparable $(a_t R a_{t'}\,)$ and the reverse applies to the negative outflow.

$$(a_t R a_{t'}\,), \text{if} \begin{cases} \Phi^{+}(a_t) > \Phi^{+}(a_{t'}) \; and \; \Phi^{-}(a_t) > \Phi^{-}(a_{t'}) \\ \Phi^{+}(a_t) < \Phi^{+}(a_{t'}) \quad and \; \Phi^{-}(a_t) < \Phi^{-}(a_{t'}) \end{cases} \tag{4.8}$$

Step VI: PROMETHEE II gives a complete ranking through the netflow. A high netflow for $a_t$indicates that $a_t$is superior to $a_{t'}$

$$\Phi^{net}(a_t) = \Phi^{+}(a_t) - \Phi^{-}(a_t) \tag{4.9}$$

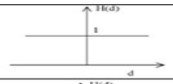
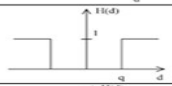
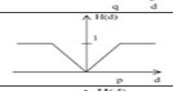
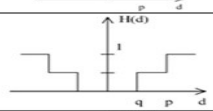
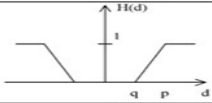
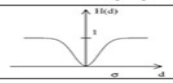
Type of genera- lazed criteria	Analytical definition	Shape	Parameters to define
Type I. Usual criterion	$H(d) = \begin{cases} 0, & d = 0; \\ 1, & \lvert d \rvert > 0. \end{cases}$		--
Type II. Quasi-criterion	$H(d) = \begin{cases} 0, & \lvert d \rvert \le q; \\ 1, & otherwise. \end{cases}$		q
Type III. Criterion with linear preference	$H(d) = \begin{cases} \dfrac{\lvert d \rvert}{p}, & \lvert d \rvert \le p; \\ 1, & \lvert d \rvert > 0. \end{cases}$		p
Type IV. Level-criterion	$H(d) = \begin{cases} 1, & \lvert d \rvert \le q; \\ 1/2, & q < \lvert d \rvert \le p; \\ 1, & otherwise. \end{cases}$		q, p
Type V. Criterion with linear preference and indifference area	$H(d) = \begin{cases} 1, & \lvert d \rvert \le q; \\ \dfrac{\lvert d \rvert - q}{p - q}, & q < \lvert d \rvert \le p; \\ 1, & otherwise. \end{cases}$		q, p
Type VI. Guassian criterion	$H(d) = 1 - \exp\{-\dfrac{d^2}{2\sigma^2}\}$		σ

Figure 4.1: Types of Generalized Criteria

4.2.1 Implementation to the project

Table 4.1: Linguistic scale of importance

Linguistic scale for evaluation	**Triangular fuzzy scale**	**Importance ratings of criteria**
Very high (VH)	(0.75, 1, 1)	Number of tablet, dose frequency, decompensated cirrhosis, post liver transplantation without cirrhosis, side effects, practicability, limitations, drug-drug interaction, compliance, previous treatment, member of key population, drug resistance, HCV genotype
Important (H)	(0.50, 0.75, 1)	Treatment duration, size of tablet, age, working condition, GFR, HCV subtype, mental disorder
Medium (M)	(0.25, 0.50, 0.75)	False prescription
Low (L)	(0, 0.25, 0.50)	Inefficient drug combination, coinfection
Very low (VL)	(0, 0, 0.25)	-

Since the advent of a complete oral regime for HCV, it has become important that patient/doctor should be able to select an accurate or a more effective drug for treatments. There some basic factors that influence the choice of treatments for HCV, this includes but not limited to Genotype, prior treatments, decompensated cirrhosis, renal disease (i.e. presence of hemodialysis), and health insurance because the treatment is not exactly cheap. In a way to easily assist patient/doctors birth this research.

The Fuzzy PROMETHEE method of selection was aimed at ranking the HCV drugs use based on the following criteria; Previous treatments, Treatment Duration, Compliance, Age, Practicability, Glomerular Filtration Rate (GFR), Member of key population, Drug resistance (RAV), Mental disorder, HCV Genotype, False prescription, HCV subtype, Drug-drug interaction, Number of tablets, Inefficient drug combination, Coinfection,

Limitations, Size of table, Dose frequency, Decompensated Cirrhosis, Post liver transplant with Cirrhosis, Working condition, and Side effects. This ranking may clearly show based on this research, a particular drug will probably be the best for a patient.

The decision making methods used (fuzzy promethee), comparatively analyze the various drug combination therapy considering the criteria mentioned earlier. Fuzzy Promethee analyzed to choose which criteria were more important than others and to determine the important weight of each criterion value. This procedure was repeated for all the drug combination to obtain positive (Phi +) and negative (Phi-) outranking and netflow (Phi). The Phi + displays the more important parameter while the Phi- displayed the less important creteria. The parameters are text against each other to get the weight.

Criterias	No. of tablet	Dose frequency	Decompensated cirrhosis	Post liver transplant with cirrhosis	Treatment Duration	Side effects	Practibility	Limitations	Size of tablet	Drug-drug interaction	Inefficient drug combination	False prescription	Compliance	Age	Working condition	Previously treatment	GFR	Coinfection	Mental disorder	Member of key population	Drug resistance (RAV)	HCV genotype	HCV subtype
Minimum	2	0.0	0.0	0.00	2.00	2.00	0.00	0.00	0.00	2.00	0.00	0.00	2.00	2.00	2.00	2.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Maximum	4	1.0	1.0	1.00	4.00	4.00	1.00	0.00	1.00	4.00	1.00	1.00	4.00	4.00	4.00	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Average	3	0.5	0.5	0.55	3.00	2.64	0.45	0.00	0.38	2.82	0.27	0.45	3.36	3.36	3.36	2.82	0.36	0.82	0.73	0.55	0.55	0.73	0.73
Standard Dev.	1	0.5	0.5	0.50	0.60	0.77	0.50	0.00	0.48	0.72	0.45	0.50	0.77	0.77	0.77	0.72	0.48	0.39	0.45	0.50	0.50	0.45	0.45
Preference parameters																							
Min/Max	max	max	max	max	max	max	max	max	min	max	min	min	max	max	min	max	max	min	max	max	max	max	min
Weight	0.92	0.92	0.92	0.92	0.75	0.92	0.92	0.92	0.75	0.92	0.25	0.50	0.92	0.75	0.75	0.92	0.75	0.25	0.75	0.92	0.92	0.92	0.75
Preference Fn.	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian	Gaussian
Thresholds	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute	absolute
Indifference	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Preference	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Gaussian	3	3.0	3.0	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Evaluations																							
GLE/PIB	3	0.0	0.0	0.00	4.00	2.00	1.00	0.00	0.00	3.00	0.00	0.00	4.00	4.00	4.00	4.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
SOF/VEL/VOX	4	0.0	0.0	0.00	3.00	2.00	1.00	0.00	0.00	2.00	0.00	0.00	4.00	4.00	4.00	4.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00
SOF/LDV	4	0.0	1.0	1.00	3.00	2.00	0.00	0.00	0.00	3.00	0.00	0.00	4.00	4.00	4.00	3.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00
SOF/LDV + RBV	3	1.0	1.0	1.00	3.00	3.00	0.00	0.00	1.00	3.00	1.00	1.00	3.00	3.00	3.00	3.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00
SOF/VEL	4	0.0	1.0	1.00	2.00	2.00	1.00	0.00	0.00	2.00	0.00	0.00	4.00	4.00	4.00	3.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00
SOF/VEL + RBV	3	1.0	1.0	1.00	2.00	3.00	0.00	0.00	1.00	3.00	1.00	1.00	3.00	3.00	3.00	3.00	0.00	1.00	0.00	0.00	1.00	1.00	1.00
OBV/PTV/RTV/DSV	2	1.0	0.0	0.00	4.00	4.00	0.00	0.00	0.00	4.00	0.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00
OBV/PTV/RTV/DSV + RBV	2	1.0	0.0	0.00	3.00	4.00	0.00	0.00	1.00	4.00	1.00	1.00	2.00	2.00	2.00	2.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00
GZR/EBR	2	0.0	0.0	0.00	3.00	2.00	1.00	0.00	0.00	3.00	0.00	0.00	4.00	4.00	4.00	3.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00
DCV + SOF	2	0.0	1.0	1.00	3.00	2.00	1.00	0.00	0.00	2.00	0.00	0.00	4.00	4.00	4.00	2.00	0.00	0.00	1.00	1.00	0.00	1.00	1.00
DCV + SOF + RBV	3	1.0	1.0	1.00	3.00	3.00	0.00	0.00	1.00	2.00	0.00	1.00	3.00	3.00	3.00	2.00	0.00	0.00	0.00	0.00	0.00	1.00	1.00

Figure 4.2: DAA alternatives along-side criteria using VISUAL PROMETHEE

CHAPTER 5

RESULTS

The HCV drugs analyzed in the study using fuzzy PROMETHEE presents the results in the table below. The table specifies the order of importance for the criterion evaluated including the triangular fuzzy number which was later implemented to rank the HCV drugs.

Table 5.1: Shows a complete ranking of the treatment drug combination, showing the positive, negative and net outranking flow values.

No	Combination of direct-acting antiviral	Net outflow ranking	Positive outflow ranking	Negative outflow ranking
1	GLE+PIB (Glecaprevir + Pibrentasvir)	0.0132	0.0252	0.012
2	SOF+LDV (Sofosbuvir + Ledipasvir)	0.0106	0.0217	0.0111
3	SOF+VEL+VOX (Sofosbuvir + Velpatasvir + Voxilaprevir)	0.0085	0.0238	0.0153
4	SOF+VEL (Sofosbuvir + Velpatasvir)	0.0065	0.0218	0.0153
5	SOF+LDV+RBV (Sofosbuvir + Ledipasvir + Ribavirin)	-0.0016	0.0142	0.0159
6	SOF+VEL+RBV (Sofosbuvir + Velpatasvir + Ribavirin)	-0.0028	0.0166	0.0194

7	DCV+SOF (Daclatasvir + Sofosbuvir)	-0.0033	0.0278	0.0311
8	DCV+SOF+RBV (Daclatasvir + Sofosbuvir + Ribavirin)	-0.0048	0.0138	0.0186
9	GZR+EBR (Grazoprevir + Elbasvir)	-0.0057	0.0153	0.0210
10	OBV+PTV+RTV+DSV (Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir)	-0.0097	0.0239	0.0337
11	OBV+PTV+RTV+DSV+RBV (Ombitasvir + Paritaprevir + Ritonavir + Dasabuvir + Ribavirin)	-0.0108	0.0116	0.0224

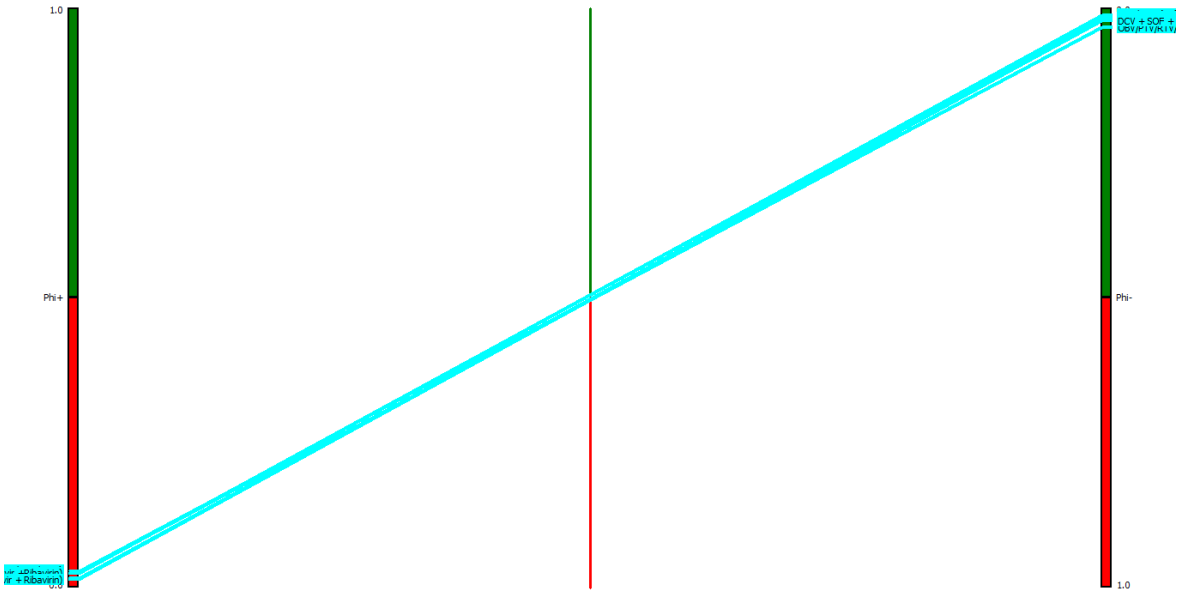


Figure 5.1: Shows the ranking of each DAA combination on a net flow-ranking pole of -1 to +1

Action profile of the high and low points for each of the evaluated DAA combination are shown below

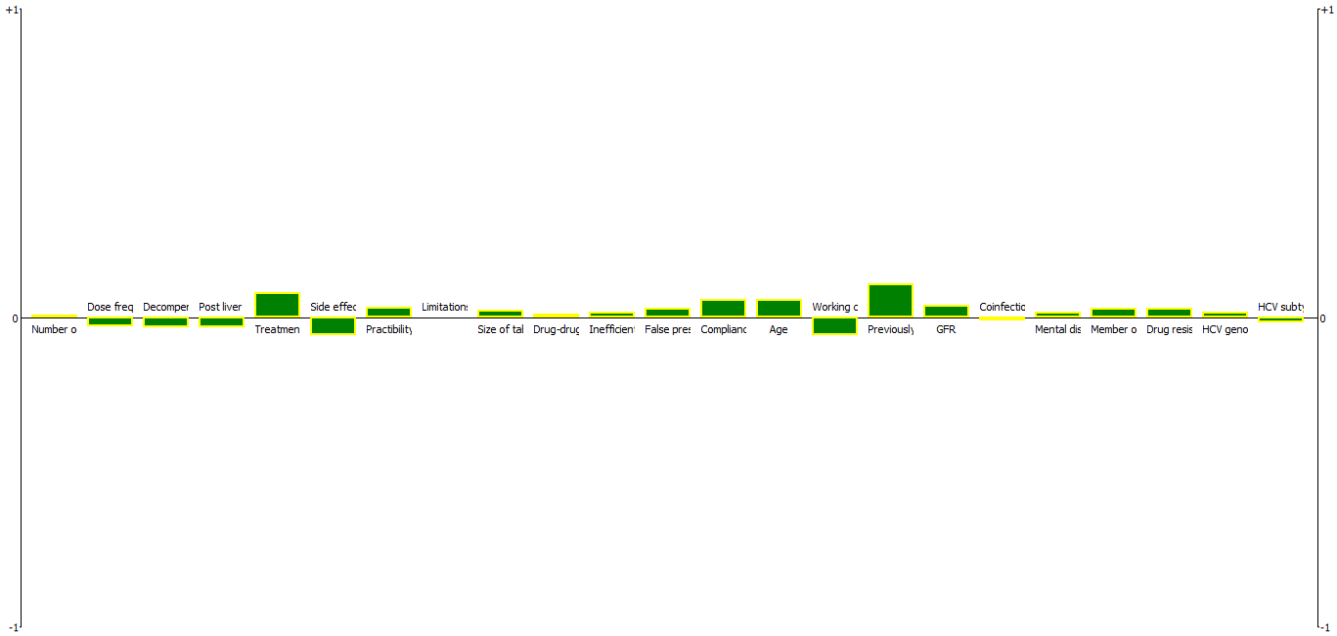


Figure 5.2: Action Profile for GLE/PIBwith a net flow of 0.0132

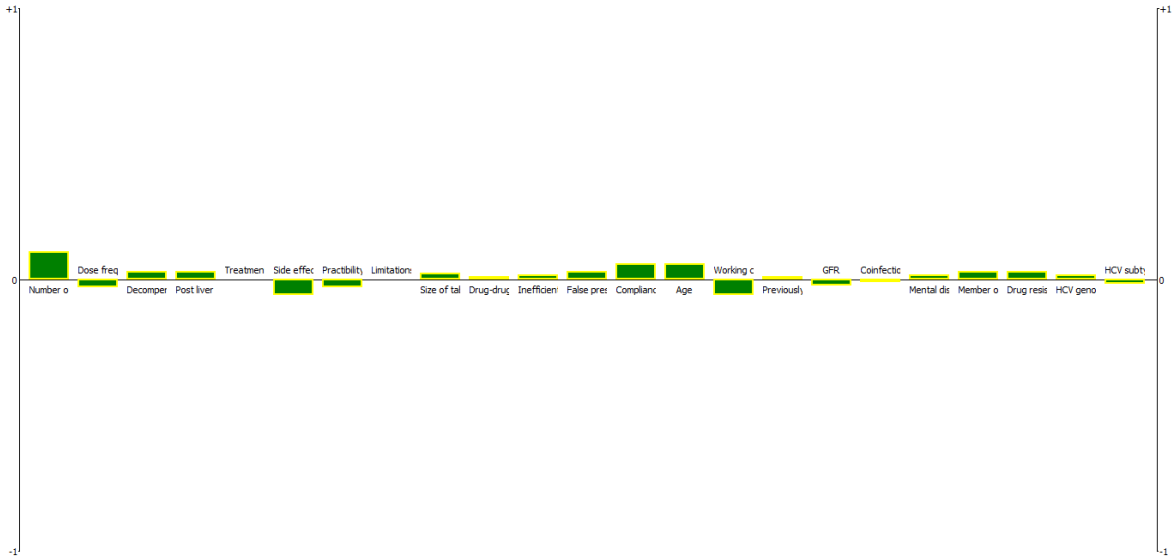


Figure 5.3: Action Profile for SOF+LDV with a net flow of 0.0106

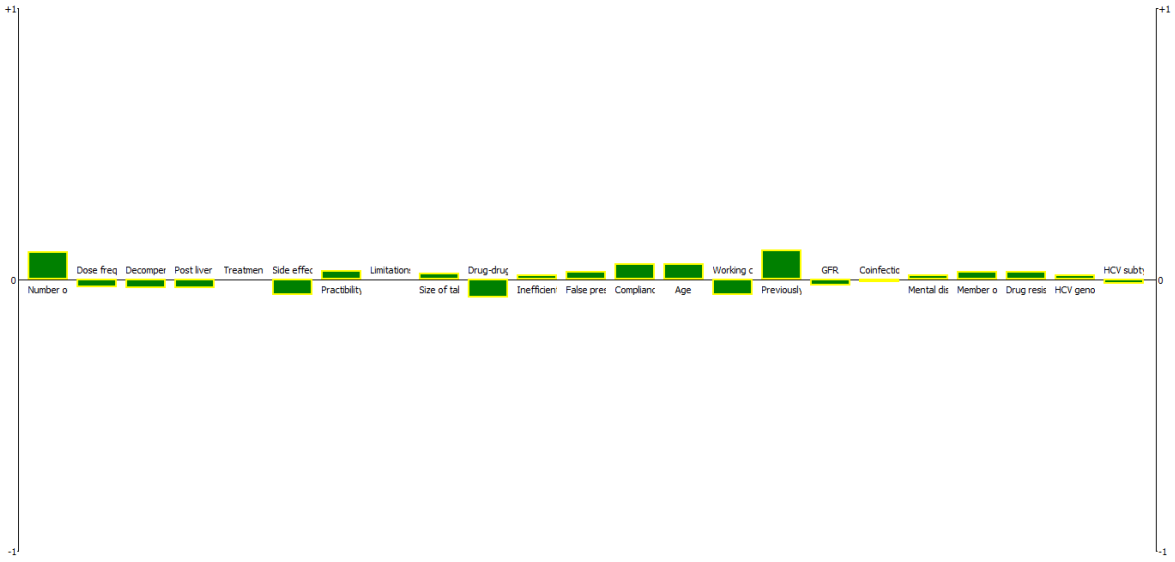


Figure 5.4: Action Profile for SOF+VEL+VOX and net-flow of 0.0085

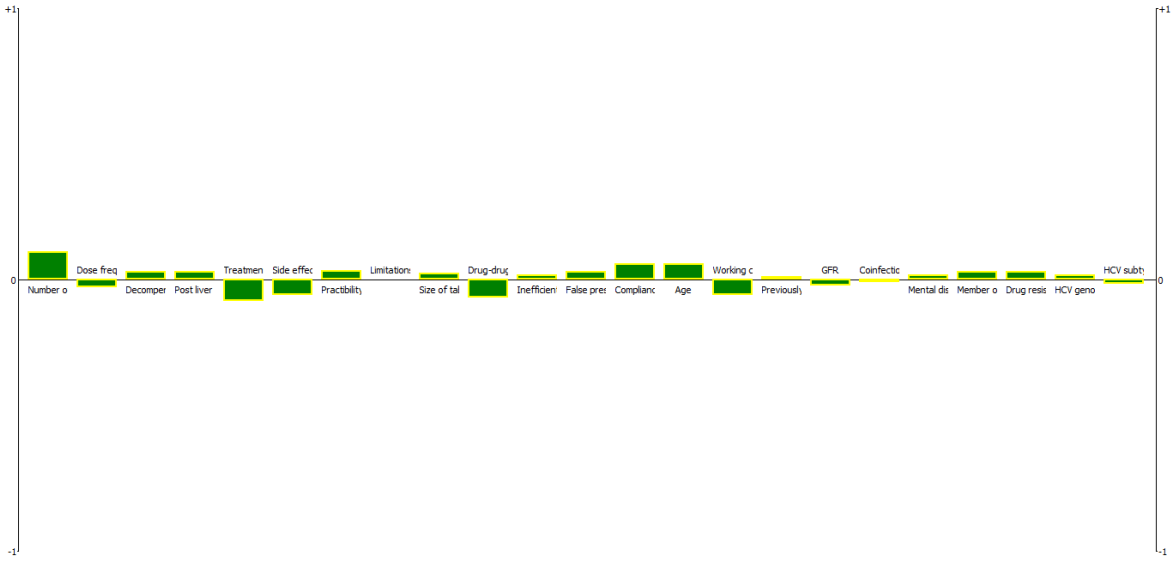


Figure 5.5: Action Profile for SOF+VEL with a net-flow discover is 0.0065

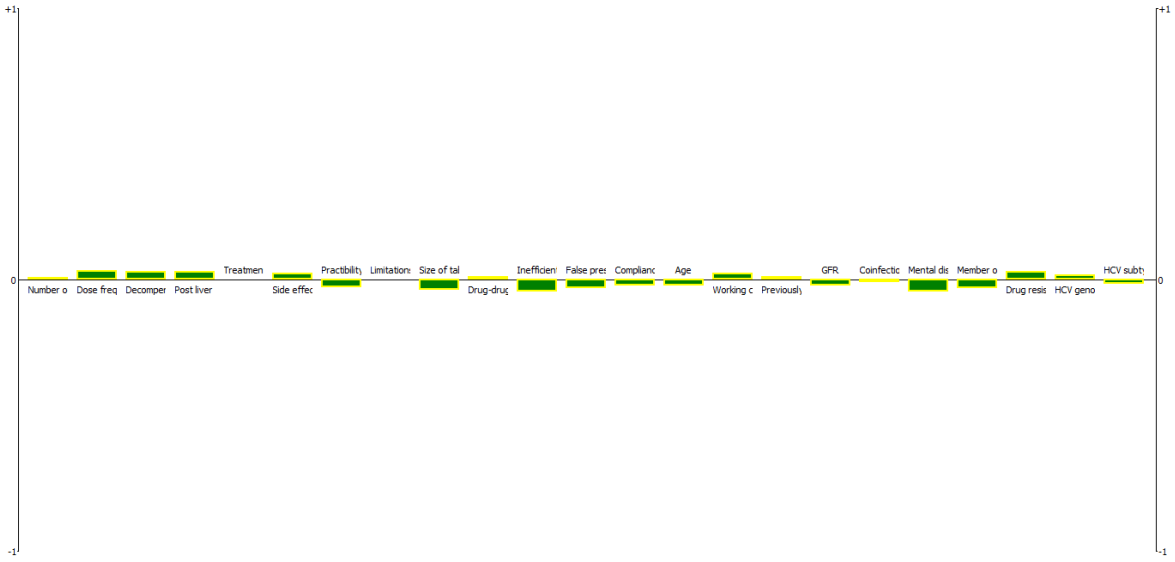


Figure 5.6: Action Profile for SOF+LDV+RBV with a net flow of -0.0016

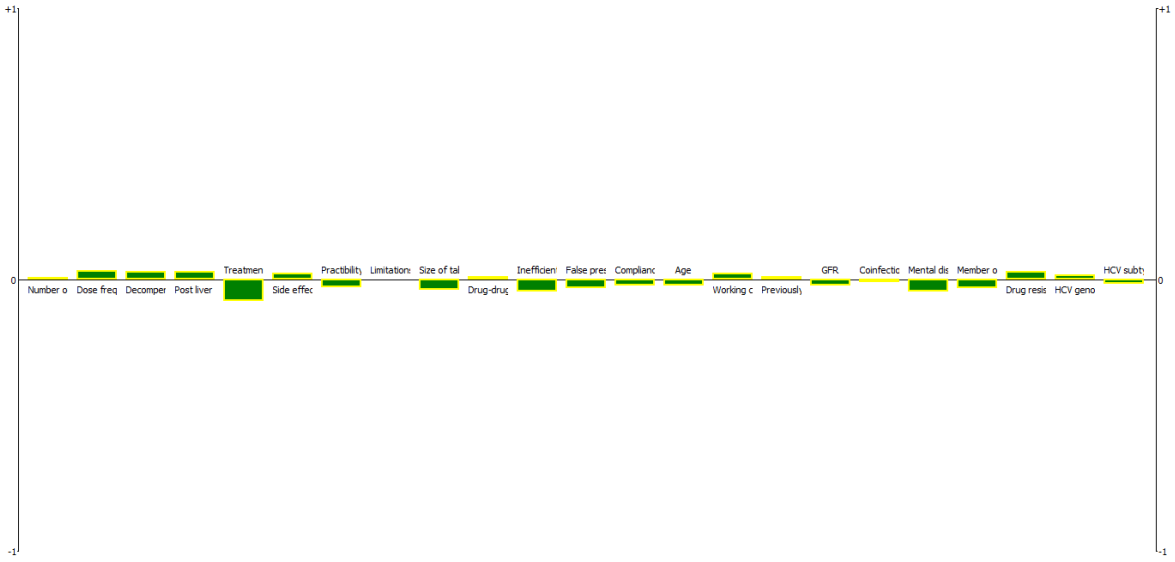


Figure 5.7: Action Profile for SOF+VEL+RBV with a net flow of -0.0028

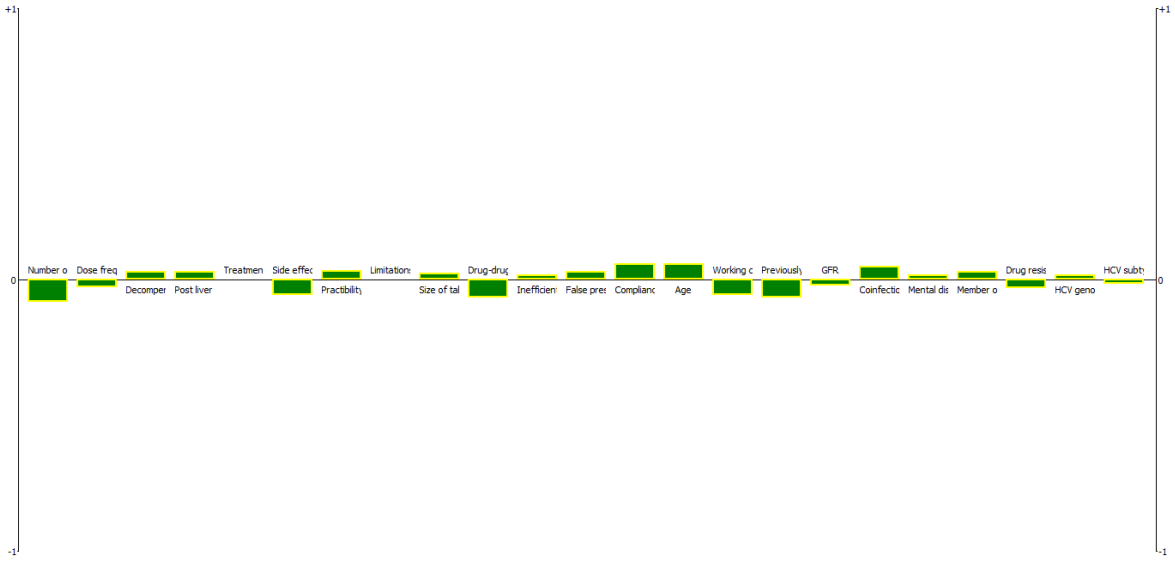


Figure 5.8: Action Profile for DCV+SOF with a net flow of 0.0033

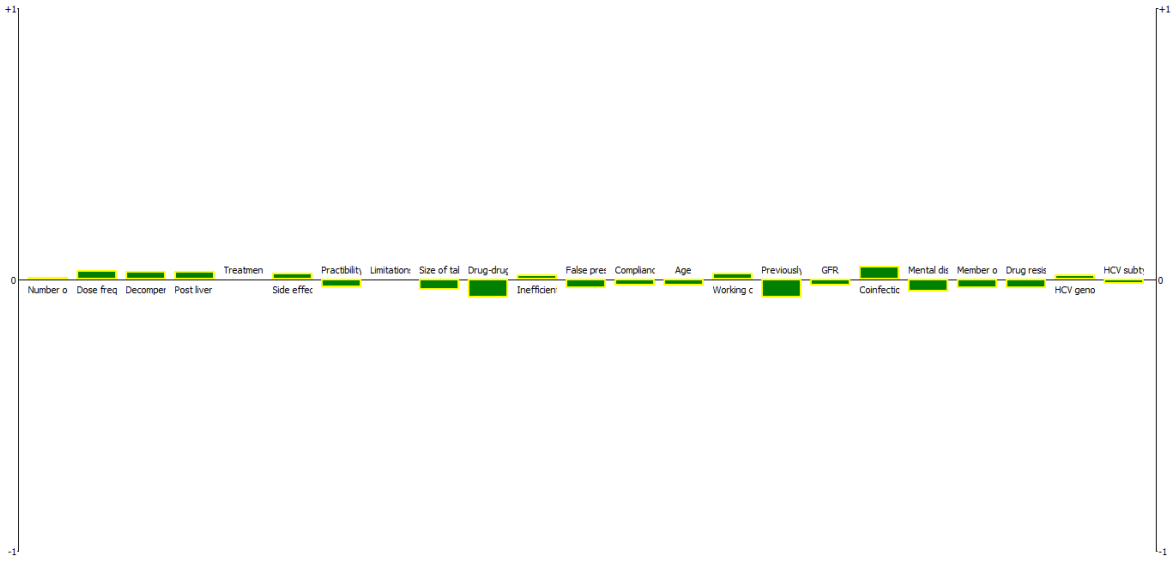


Figure 5.9: Action Profile for DCV+SOF+RBV with a net flow of -0.0048

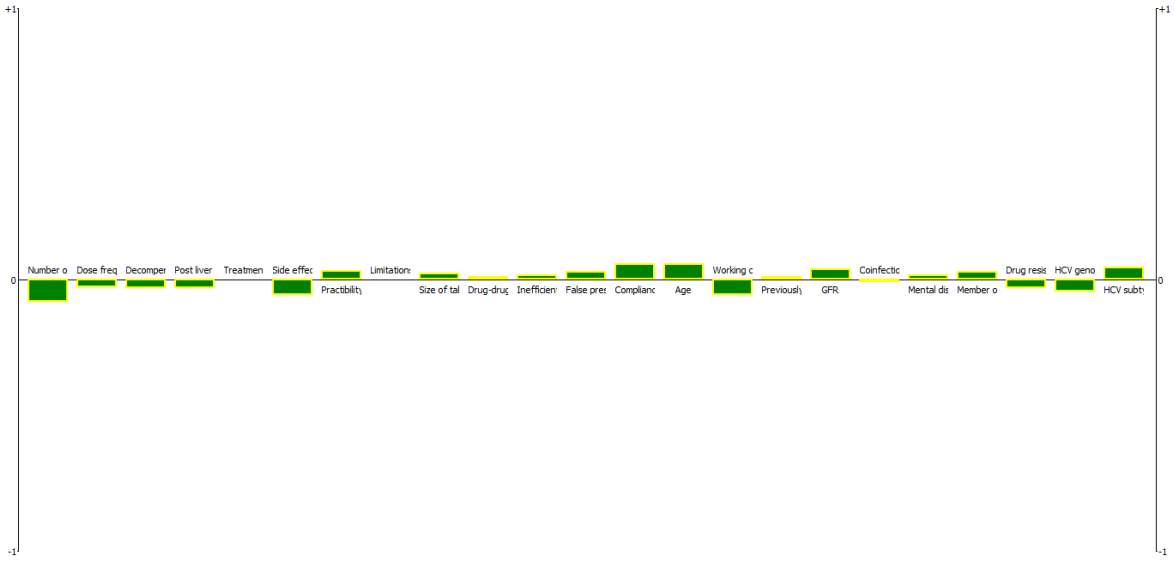


Figure 5.10: Action Profile for GZR+EBR with a net flow of -0.0057

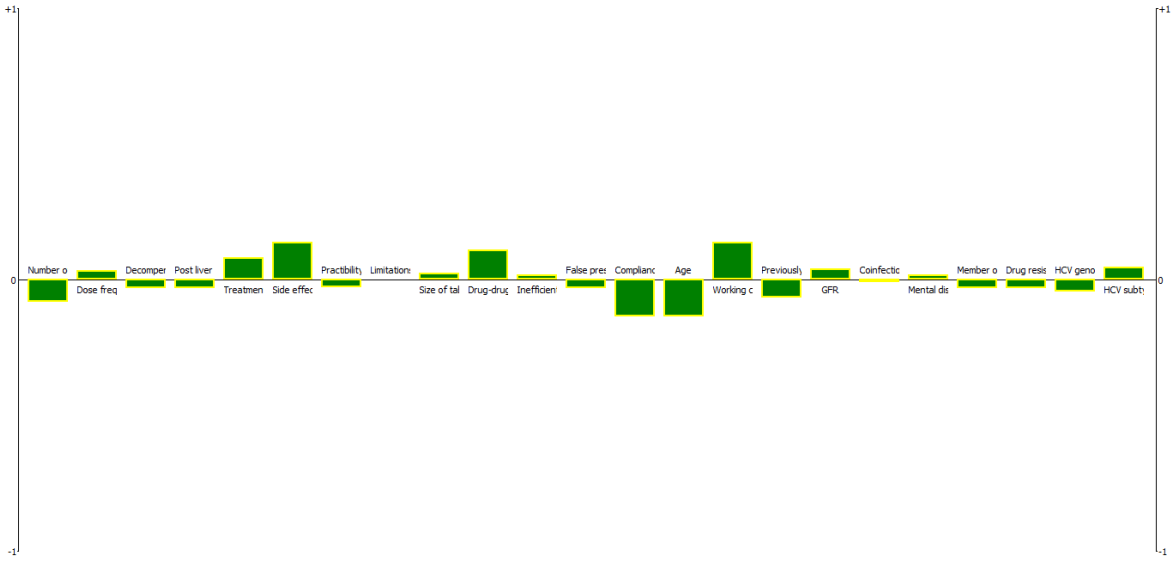


Figure 5.11: Action Profile for OBV+PTV+RTV+DSVwith a net flow of -0.0097

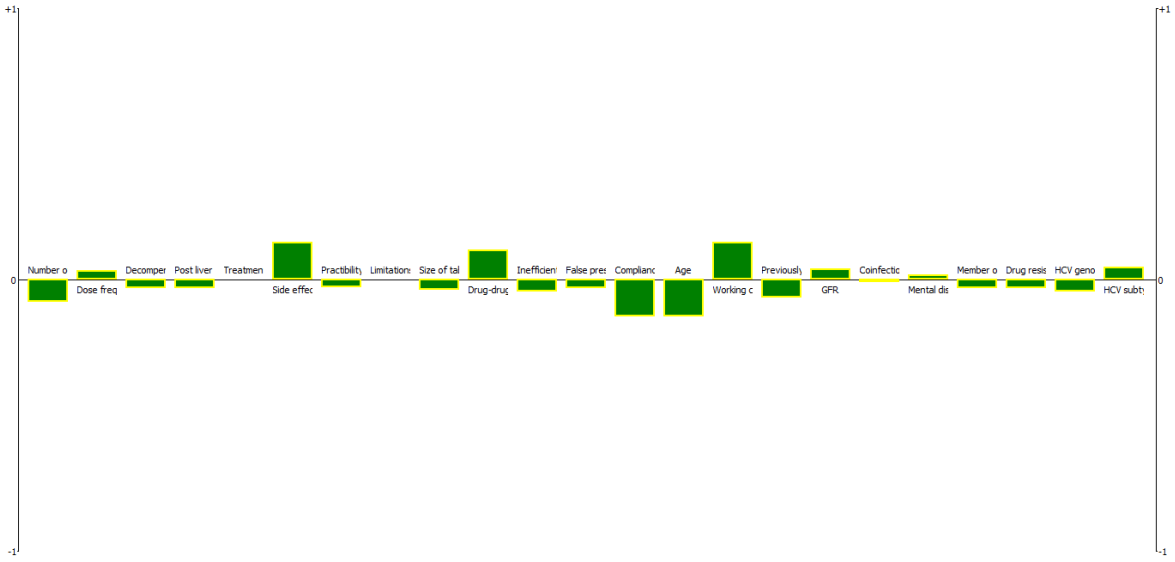


Figure 5.12: Action Profile for OBV+PTV+RTV+DSV+RBV with a net flow of -0.0108

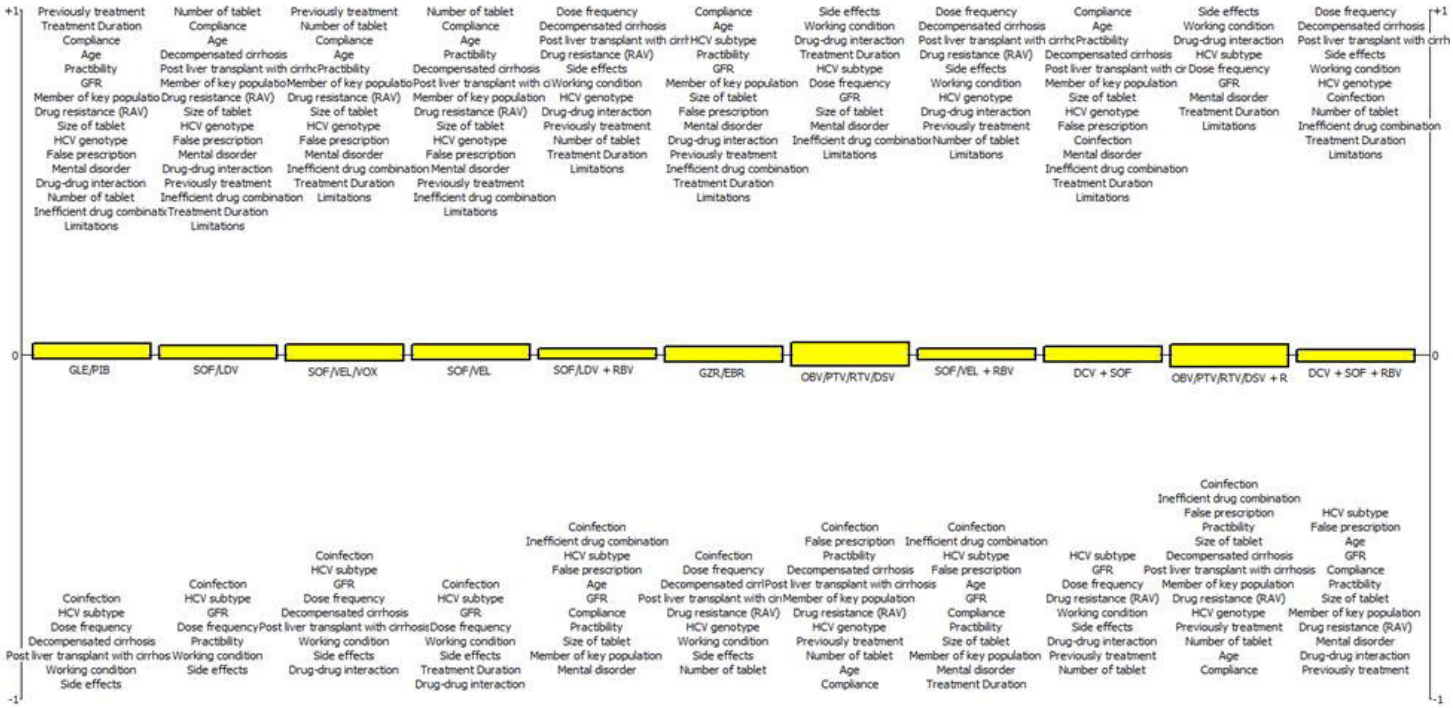


Figure 5.13: Rainbow ranking of all HCV drugs

Figure 5.14 is a network ranking view of the treatment alternatives with the negative and positive outranking values. This network view can be used to clearly outline how the device alternatives are ranked and the order in which they can be undertaken, from the most favorable, to the least favorable.

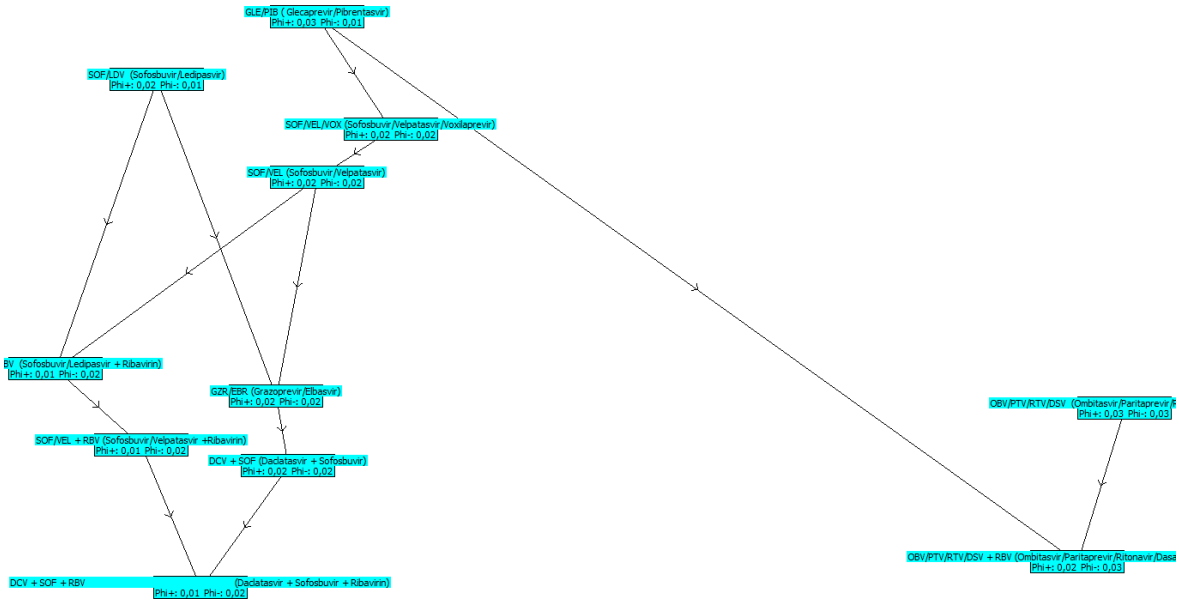


Figure 5.14: Network Ranking View of DAAs

CHAPTER 6

DISCUSSION AND CONCLUSION

6.1 Discussion

From the tabulated result (Table 1) GLE/PIB was ranked number one based on the Fuzzy Promethee analysis which gave the combination values as follows Phi: 0.0132, Phi+: 0.0252 and Phi-: 0,0120. The results showed that GLE/PIB had more of the very important parameter (previous treatments, treatment duration, compliance, age, practicability, GFR), drug resistance, member of key population, mental disorder, HCV genotype, false prescription, HCV subtype, drug-drug interaction, number of tablets, inefficient drug combination, and coinfection) and less important parameters (size of tablet, dose frequency, decompensated cirrhosis, post liver transplantation with cirrhosis, working condition, and side effects). Other drug combinations from 2 – 10 could be considered based on this analysis. However, OBV/PTV/RTV/DSV + RBV was ranked at the bottom with Phi: -0.0108, Phi+: 0.0116 and Phi-: 0.0224. And based on this research finding the combination may be least in consideration where all above are available.

6.2 Conclusions

The fuzzy PROMETHEE analysis of HCV DAAs combination treatment ranked and shows that GLE/PIB could the most preferred option in the oral treatment HCV and OBV/PTV/RTV/DSV + RBV may be a last resolve when making decisions.

Fuzzy PROMETHEE is a simplistic method for decision making in DAAs treatment. The guides for EASL and AASDL should be used every year however the method is tedious and fuzzy PROMETHEE reduces the need for reliance on both guides. The method assessed in this study for HCV treatment would help new physicians to select appropriate DAAs regimes for HCV patients without long considerations on the type of DAAs. GLE, SOF/LDV, SOF/VEL/VOX and SOF/VEL are more alike and closely ranked in the result hence based they are preferred compared to the other combination evaluated.

The essence of this comparison is borne out of the difficulty experienced by physicians in the selection of the most appropriate DAAs for a patient due to too much and still evolving DAAs.

This research work analysing with promethee is the first of its kind to simplify the method of selection of HCV DAAs regimes. It is believed that, the process will conveniently serve for new HCV drugs as they emerge in the nearest future.

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YAKİN DOĞU ÜNİVERSİTESİ

ETHICAL APPROVAL DOCUMENT

Date: 02/07/2020

To the **Graduate School of Applied Sciences**

The research project titled "Evaluation of Direct Acting Antiviral Treatments for Chronic Hepatitis C Using Fuzzy PROMETHEE" has been evaluated. Since the researcher will not collect any data from human, animal, plant or earth, this project does not need to go through the ethics committee.

Title: Assoc. Prof. Dr.

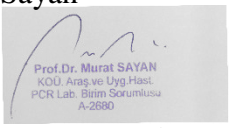
Name: Dilber Uzun Ozsahin

Signature: 

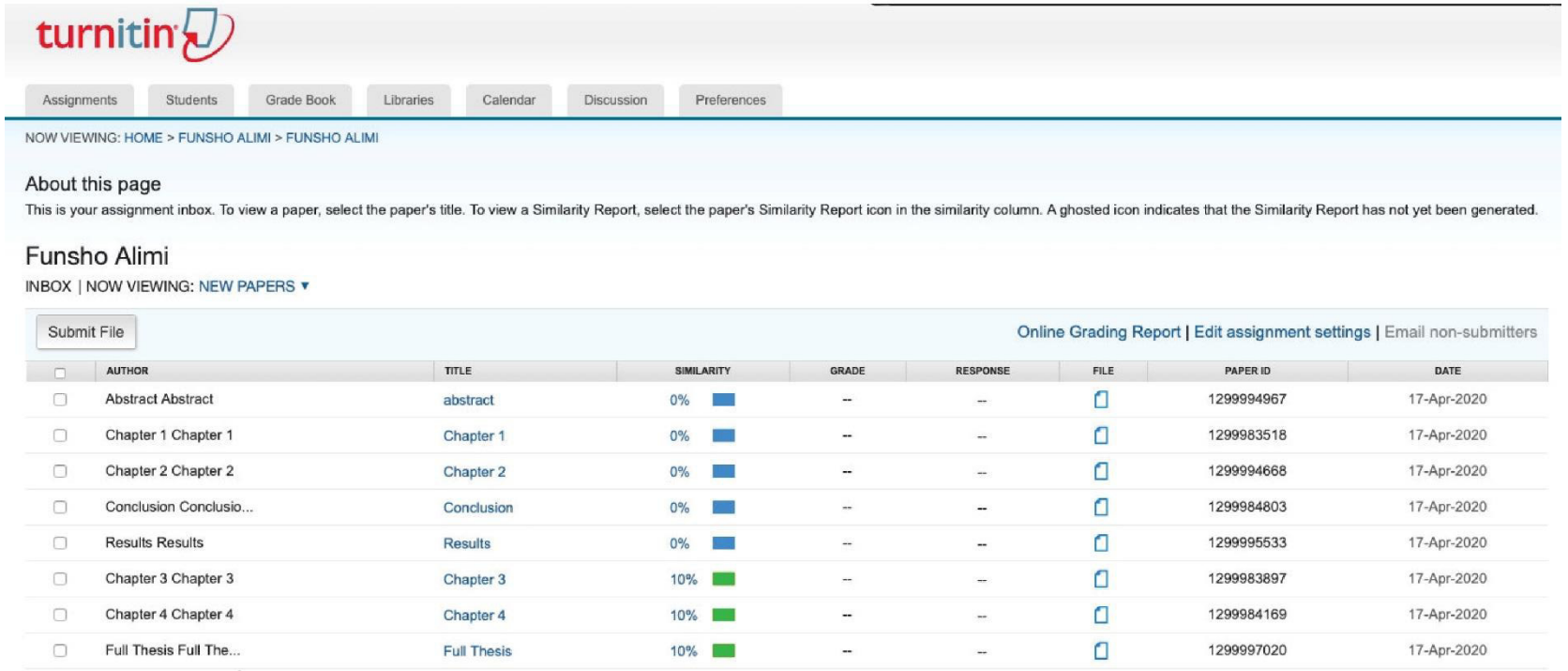
Role in the Research Project: Supervisor

Title: Prof. Dr.

Name: Murat Sayan

Signature: 

Role in the Research Project: Co-Supervisor



Assoc. Prof. Dr Dilber Uzun Ozsahin
Supervisor