ASSESSMENT OF THE EFFICACY OF HEPATITIS C TREATMENT IN HOSPITAL UNIVERSITI SAINS MALAYSIA (HUSM)

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ABBREVIATION

AFP	alpha-fetoprotein
ALT	alanine aminotransferase
Anti-HCV	HCV antibody
APRI	AST-to-platelet ratio index
AST	aspartate aminotransferase
BOC	boceprevir
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CTP	Child-Turcotte-Pugh (see below)
CYP	cytochrome P450
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA US	Food and Drug Administration
HBsAg	Hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HUSM	Hospital Universiti Sains Malaysia
IVDU	intravenous drug user
INR	international normalized ratio
MELD	model for end-stage liver disease
MSM	men who have sex with men

NAT	nucleic acid testing
NIH	National Institute of Health
NS3	HCV nonstructural protein 3
NS5A	HCV nonstructural protein 5A
PCR	polymerase chain reaction
RBC	red blood cell(s)
RBV	ribavirin
SMV	simeprevir
SOF	sofosbuvir
SVR12 (or 24)	sustained virologic response at 12 weeks (or at 24 weeks)
TVR	telaprevir

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ABSTRACT (ENGLISH VERSION)

Assessment of the efficacy of Hepatitis C treatment in Hospital Universiti Sains Malaysia (HUSM).

Background : Management of Hepatitis C virus (HCV) infection has been evolved in the last few years. Currently, the newer treatment direct acting antivirals (DAAs) promise a higher rate of efficacy to compare to previous treatment, pegylated interferon. The goal of HCV treatment is to eradicate the virus and to avoid the progression of liver fibrosis and HCV-related disease. Sustained virologic response (SVR) is the most widely used efficacy endpoint in clinical studies of hepatitis C and represents the eradication of HCV from the body. We conduct a study to compare the efficacy of Hepatitis C treatment between pegylated interferon and DAA, it effects towards liver function and its associated factors in our cohort of patient therefore, support our continuing use of DAA in the treatment of Hepatitis C virus infection in HUSM.

Methodology: This is a retrospective record review done by reviewing a record of 88 patients who were either on Pegylated Interferon or on DAAs during the period of 2011 till 2018. Subjects were who achieved undetectable viral load in serum after 12 or 24 weeks after completed therapy was taken as a sustained virological response (SVR). We also evaluated the variation of ALT at baseline and 12 weeks after completed therapy. All relevant data are gathered and recorded in statistical software for analysis.

Result: Between January 2011 and September 2018, 35 patients started a DAA treatment and 53 patients had completed pegylated interferon treatment. Overall proportion of SVR12 was 92% (n=32) for DAAs and 69.8%(n=37) for interferon-based treatment. Analysis of ALT showed that the level normalized in the most patients who had achieved

SVR (68%). Factors such as gender, genotype, race, pre-treatment HCV RNA level and liver cirrhosis are shown not to be associated with the efficacy of treatment.

Conclusion : Achievement of the high rate of SVR represents the goal for HCV treatment and has implications to reduce risk of liver disease progression and extrahepatic disease. However, further studies are needed to include more patients in order to improve power of the study. Based on the higher rate of SVR associated with DAA therapy, this should be the first choice of treatment.

ABSTRAK (VERSI BAHASA MELAYU)

Penilaian terhadap keberkesanan rawatan Hepatitis C virus di Hospital Universiti Sains Malaysia (HUSM)

Latar Belakang : Pengurusan rawatan untuk jangkitan Hepatitis C telah berubah sejak kebelakangan ini. Sekarang, rawatan terbaru menggunakan *Direct Acting Antiviral (DAA)* telah menjanjikan keberkesan yang lebih tinggi berbanding rawatan terdahulu yang menggunakan *pegylated interferon*. Matlamat perawatan adalah untuk menghapuskan virus dan menghalang proses fibrosis hati dan penyakit-penyakit berkaitan Hepatitis C. *Sustained virological response (SVR)* atau respon penahanan virus adalah istilah yang digunapakai untuk keberkesan terakhir di dalam pelajaran klinikal mengenai Hepatitis C dan melambangkan kehapusan virus di dalam badan. Kami telah menjalankan satu kajian untuk menunjukkan tahap keberkesanan rawatan di antara Pegylated interferon dan DAA, kesan terhadap fungsi hati dan factor-faktor berkaitan di kalangan pesakit di HUSM dan seterusnya menyokong penggunaan DAA di dalam rawatan Hepatitis C di HUSM.

Metodologi : Ini merupakan kajian retrospektif yang merekod data-data pesakit seramai 88 orang yang telah mendapat perawatan sepanjang 2011 sehingga 2018. Subjek-subjek yang telah mencapai tahap virus tidak dikesan di dalam darah telah diambil sebagai *sustained virological response (SVR)* atau respon penahanan virus. Kami juga menilai fungsi hati variasi pada permulaan dan selepas 12 minggu selesai mendapatkan rawatan. Semua data-data yang sesuai telah dikumpulkan dan direkodkan di dalam perisian komputer statistik.

Keputusan : Di antara Januari 2011 sehingga September 2018, seramai 35 orang pesakit telah mendapat rawatan DAA and seramai 53 orang telah mendapat rawatan *pegylated interferon.* Secara keseluruhan daripada Sustained virological response (SVR12) atau respon penahanan virus adalah 92% (n=32) untuk DAA dan 69.8% (n=37) untuk perawatan interferon. Analisa berkenaan enzim fungsi hati , ALT juga menunjukkan tahap normal setelah mencapai SVR (68%). Faktor-faktor seperti jantina, genotype , bangsa, kadar virus sebelum rawatan dan bengkak hati tidak menunjukkan perhubungan di antara tahap keberkesan rawatan.

Kesimpulan : Tahap kecapaian *sustained virological response (SVR12)* atau respon penahanan virus melambangkan matlamat di dalam perawatan Hepatitis C dan implikasi untuk mengurangkan risiko progress penyakit hati dan penyakit berkaitan hati. Walau bagaimanapun, untuk membuat sebarang cadangan dalam menentukan tahap keberkesanan , kajian lanjut dengan lebih banyak penglibatan subjek diperlukan. Berdasarkan tahap keberkesanan yang tinggi melibatkan DAA, pilihan rawatan untuk Hepatitis C perlulah diutamakan.

CHAPTER 1 : INTRODUCTION

1.1 Epidemiology of Adult Hepatitis C Virus Infection.

Hepatitis C virus (HCV) is a single-stranded RNA virus belonging to the family of flaviviridae. In 1989, the Centers for Disease Control and Prevention first recognized Hepatitis C virus as a blood-borne human pathogen. Currently, on a global level, it was estimated infected over 3% of the population world population, which corresponds to an analysis that concludes from the total of 1217 studies that represent 117 countries and cover almost 90% of the global population that bring the result of total approximately 180 million people worldwide are chronically infected. (Messina *et al.*, 2015)

Centers from Disease Control and Prevention (CDC), had labeled 6 most common HCV genotypes and more than 50 subtypes had been identified. HCV genotype 1 is the most common infected worldwide, a total of 83.4 million out of 180 million cases (46.2%), followed by genotype 3 is 54.3 million cases that contributing 30.1% (Messina *et al*., 2015). Other genotypes that least common are genotypes 2, 4, 5 and 6 are responsible for a total 23.8% of all cases (Messina *et al*., 2015). HCV is mostly transmitted through percutaneous exposure such as injecting drug use, needlestick injuries, hemodialysis and inadequate screening of blood product control in the health centre. Less frequently, HCV transmission occurs among human immunodeficiency virus (HIV)-positive men who have sex with men (MSM), unsafe sexual intercourse and among infants born to HCV-infected mothers (Lavanchy D. 2011).

1.2 Hepatitis C Virus in Malaysia.

In Malaysia, it is estimated 453,700 people infected with HCV infection in 2009 contributes to 2.5% among the population aged from 15 to 64 year-old (Raihan *et al*., 2016.). Figure 1 shows seroprevalence for HCV infection trend in Malaysia. From 1998 to 2014, it shows that there is a steadily increasing trend. This rises again was due to the awareness campaign for early detection campaign. In 2000, there were 550 reported cases of HCV infection, with an incidence rate of 2.5/100,000 population; in 2004 incidence rate was increased to 2.9/100,000 population, and in the year 2013 the rate became 6.77/100,000 (Raihan *et al*., 2016).

There are 4 genotypes commonly found in Malaysia, with a distribution of genotype (56%) followed by genotype 1 (39%), genotype 2 (4%) and genotype 4 (1%) (Raihan *et al*., 2016). This distribution of HCV genotypes has remained unchanged for past 15 years.

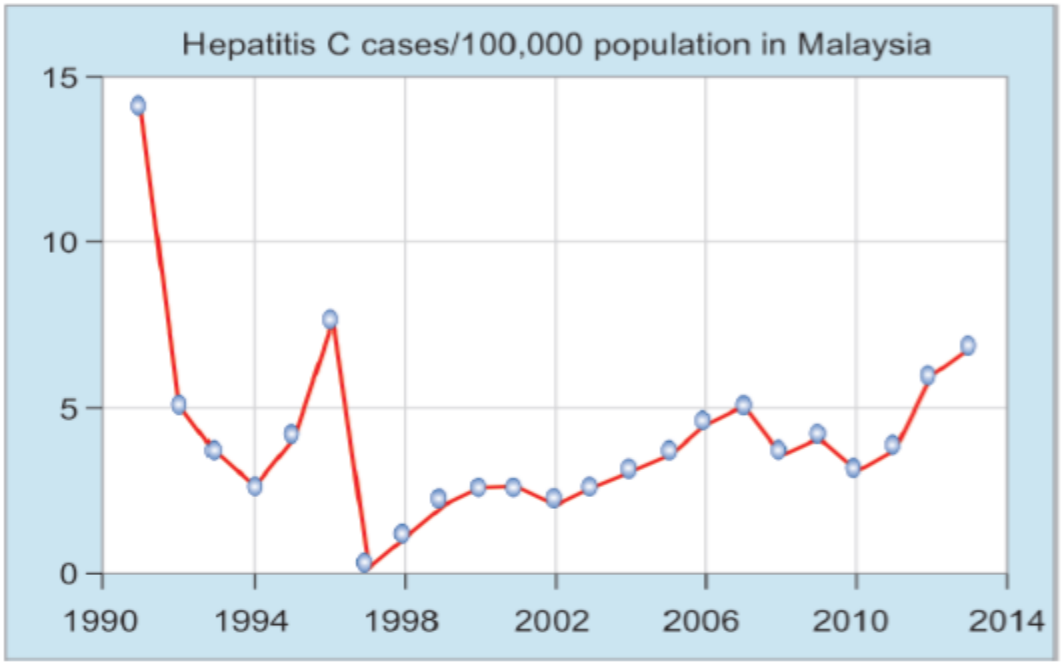

Figure 1 : Hepatitis C virus infection prevalence in Malaysia from 1990 – 2014 ***(Adapted from Raihan 2016)***

1.3 Natural History of Hepatitis C virus infection in Human.

In understanding the natural history of HCV infection, it is important to acknowledge that the disease phases and evolution of HCV treatment. HCV infections can affect in different form of severity from a mild illness that usually lasts only a few weeks to serious illness or chronic infection. The acute illness infrequently diagnosed due to mild clinically, 20% of patient will experience flu-like symptoms, malaise, weakness and anorexia and most of the patients often asymptomatic (Mohd Hanafiah K. 2013). The incubation period for HCV is 14–180 days (average is 45 days), and currently, no single vaccine is available. Then HCV is slowly progressive over a period of years and becomes chronic hepatitis. The most common outcome usually characterized by raised serum aminotransferases and sequence may lead to cirrhosis in the liver. About 20-30% of those infected will develop liver cirrhosis and hepatocellular carcinoma as explained in Figure 2 over period of 20-50 years (Trepo c., 1998).

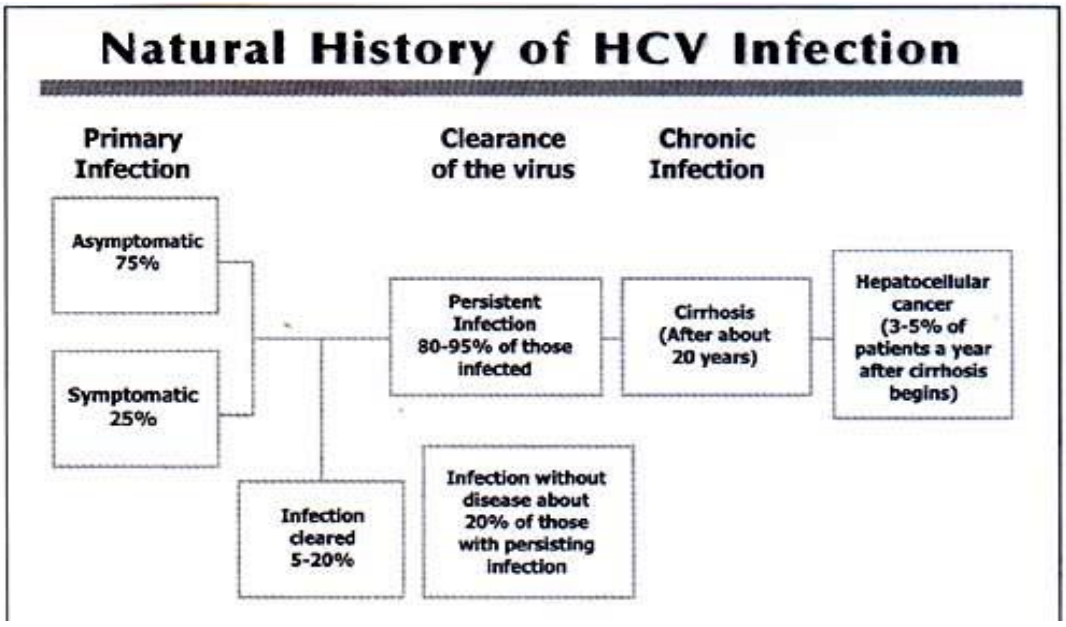

Figure 2 : Understanding the natural history of HCV (Adapted from Trepo c. 1998)

1.4 Diagnosis of Hepatitis C infection.

Most of the patients with HCV infection have anti-HCV antibodies in serum detectable by enzyme immunoassay (EIA) but this result may be negative in the early phase of infection and in immunosuppressed patients. Once the patient had achieved sustained virological response (SVR) or viral clearance, anti-HCV antibodies will persist but may decline and disappear later (Takaki a *et al.*, 2000). EIA test will be reported as positive or negative based on an absorbance signal compared with a cut-off value as shown in figure 3 below and it has sensitivity approximately 98% (Gretch DR et al., 1997). The absolute diagnosis of Hepatitis C is based on the detection of HCV RNA in plasma exclusively molecular method (EASL 2018). The result will be showed in quantitative or quantitative. For qualitative HCV RNA test will provide yes or no answer. While quantitative HCV RNA assays will generate an actual HCV RNA level and will be used to monitor response to HCV therapy (Scott JD, 2007).

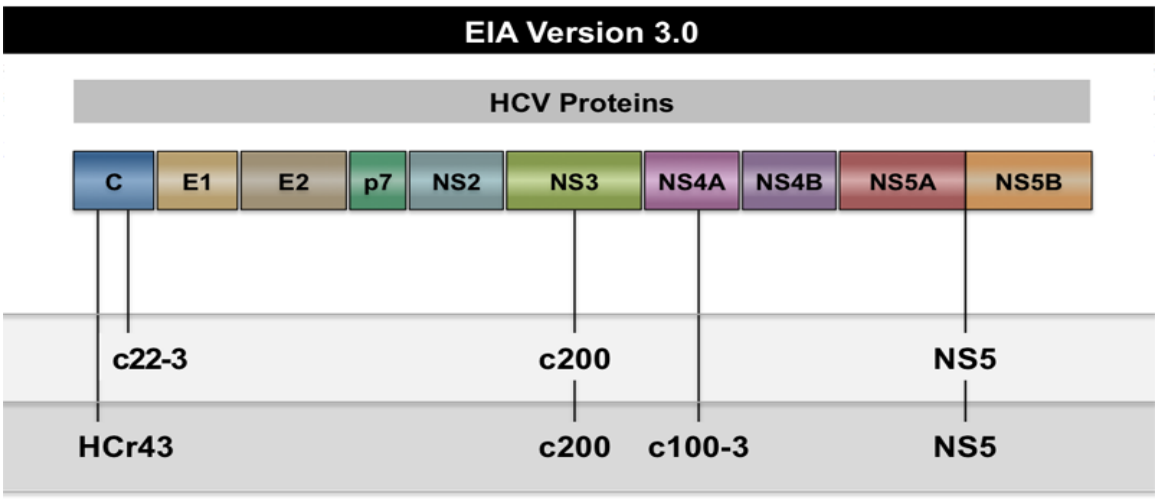

Figure 3 : combinations of proteins used in different third-generation HCV EIA tests (*Adapted from Gretch DR 1997*)

1.5 Hepatitis C Virus infection therapy.

The primary goal for therapy is a cure in order to prevent any related complications of HCV and extra-hepatic disease including liver cirrhosis, decompensated liver disease, hepatocellular carcinoma (HCC) and death. In other, once hepatitis C virus had been eradicated it will improve quality of life and most important is to prevent transmission (EASL 2018). Sustained virological response (SVR) is the endpoint of therapy. It defined as undetectable HCV RNA in serum after 12 weeks completed treatment as SVR12 and after 24 weeks completed treatment as SVR24.

The SVR also corresponds to a definitive cure of HCV infection after long-term follow up in most of the patient who received and completed the treatment (Swain MG *et al*., 2010). But once pateint had achieved SVR, surveillance for hepatocellular carcinoma should be continued in a patient with advanced fibrosis and cirrhosis since it will reduce the rate of decompensation but not abolish the rate of progression (EASL 2018).

All patients with HCV infection had been suggested to start the therapy including treatment naive or treatment experienced without delay especially in a patient with liver fibrosis or cirrhosis including decompensated cirrhosis. The treatment is only not recommended in pateints with expected life expectancy that is short due to multiple non liver related comorbidities (EASL 2018)

CHAPTER 2 : LITERATURE REVIEW

2.1 Rate of sustained virological response (SVR) in interferon-base and direct acting antiviral (DAA) therapy.

In May 2016, the World Health Assembly had endorsed the Global Health Sector Strategy (GHSS) for 2016–2021 on viral hepatitis, which proposes to eliminate viral hepatitis by 2030 as defined as 90% reduction in new chronic infections and a 65% reduction in mortality compared to previous guideline in 2015 (Geneva: World Health Organization; 2016). The future for Hepatitis C treatment is very bright since the evolution of treatment strategies by progressively improving the efficacy and reducing therapy-induced side effects. The cure rate indicator measured by sustained virologic response (SVR) have increased significantly from just 10% treated with interferon monotherapy in early 1990 to 80% in 2010 after combination interferon based treatments and are expected to climb to 90% or more with the adoption of DAA regimens (Lawitz E, Poordad F, Kowdley K, *et al*., 2012)

Multiple studies and data showed that patient who achieved SVR after treatment have virologic remission for years and experience reversal of liver fibrosis and better liver related outcomes (Swain *et. al.,* 2010). It also has been linked to a decrease liver related morbidity incidence of hepatocellular carcinoma and decreased in all cause of liver related mortality (Zator and Chung, 2013). Before this, conventional IFN monotherapy was the main treatment for HCV that required the patient to fully comply with almost daily

injection. After 2002, PEG-IFN/RBV was introduced. This therapy showed varies of SVR ranging 40–65% that differ in genotype (Nguyen NH *et al*., 2010) Furthermore, these therapies required 24–48 weeks of injections with interferon and ribavirin and too many of the patients were reluctant to accept the treatment due to intolerable severe adverse effects (Nguyen NH *et al*., 2010).

After 2011, this had been changed to the new era of direct-acting antivirals (DAA) as current standard of care but in Malaysia the DAA treatment started since 2015. Direct-acting antiviral agents (DAAs), respectively increase SVR rate as high as 90% and more for different group of genotypes (Sulkowski M *et al*., 2012).

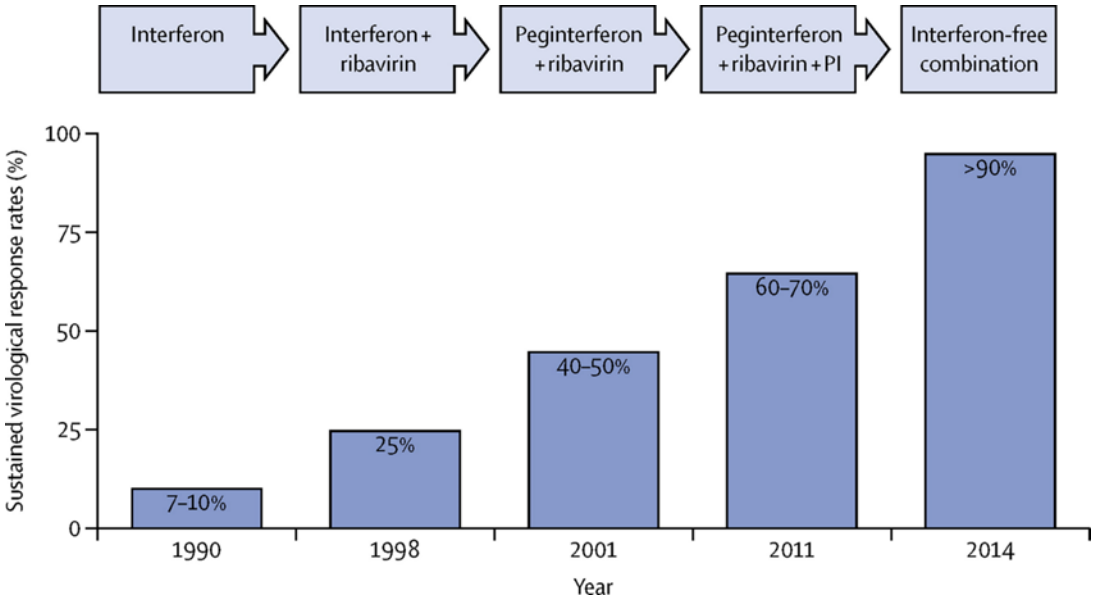

Figure 4 : Evolution of Hepatitis C treatment efficacy (Adapted from Gretch DR 1997)

The first DAA introduce was the combination of the NS5A inhibitor, ledipasvir and the polymerase inhibitor sofosbuvir (LDV/SOF) known as HARVONI, as the first single pill with interferon-free regimen in early 2014. Real-world efficacy data are presented in Table 1 and show that DAA treatment resulted in an SVR rate of between 91% and 98% in different group of genotypes. As a comparison, the SVR rate was higher in phase 2 clinical trials (n=421, SVR=96%) than in real-world studies (n=503, SVR=91%) in DAA therapy (Curry et al., 2017).

Table 1 : Overview on efficacy in real-world studies with DAA in HCV infection.

Reference	Country	Number of patients, n	Cirrhosis, n	SVR 12 in all patients, n (%)	SVR 12 in cirrhosis, n (%)
Terrault et al.	USA	1044		1008 (96)	
Afdhal et al.	USA	1979	679	1936 (98)	654 (96)
Buggisch et al.	Germany	1956		1923 (98)	
Crespo et al.	Spain	1504	814	1436 (95)	779 (96)
Latt et al.	USA	1053		983 (93)	
Qureshi et al.	USA	338		331 (98)	
Flisiak et al.	Poland	86	43	81 (94)	37 (86)
Fuchs et al.	USA	273	167	249 (97)	161 (96)
Backus et al.	USA	5390	1641	4911 (91)	1436 (88)
Cheung et al.	UK	162	162	147 (91)	147 (91)
Aghemo et al.	Italy	73		68 (93)	
Overall		13858	3506	13073 (94)	3214 (92)

2.2 Impact of sustained virological response towards liver functions.

Liver function represent the liver condition. Inflamed or injured liver cells leak higher than normal amounts of certain chemicals, including liver enzymes, into the bloodstream, which can result in elevated liver enzymes on blood tests. Here, we tested ALT as represent the liver enzyme that will release in response of damage or disease. Based on Lanini et al. BMC Infectious Diseases (2018), data analysis was carried out on a convenient sample of 3179 pateints who had measured ALT level both before started of therapy and after 12 weeks completed treatment. They found more than 75% patients had ALT levels above the upper normal limit (45 U/L) before started the treatment. In contrast, after 12 weeks completed therapy and achieved SVR, ALT levels normalized in more than 75%. This analysis from Lanini et al provides strong evidence that ALT significantly decreased in all patients who achieve SVR. However, the degree of liver function profile reduction was more than 2 times higher in those who achieved SVR12 compare to those who did not achieve SVR (Journal Hepatol 2018).

2.3 Contributing factors that associate with sustained virological response.

The success of the antiviral therapy hepatitis C patients depends on the factors related to the virus and the host. The viral category includes the HCV genotype, baseline viral load, and virological response during treatment and the host category includes age, gender, race, obesity and degree of liver fibrosis (Kumada H *et al.,* 2016). Study by Todorovska *et. al* demonstrated total of 226 patients, comparing those who achieve sustained virological response and patients without sustained virological response in terms of the genotype, viral load, gender, age and inflammatory and fibrotic changes in the liver. The factors that significantly contribute to sustained virological response are related to the age ($p = 0.0001$), genotype ($p = 0.002$), inflammatory changes in the liver ($p = 0.028$), pre treatment HCV RNA ($p = 0.022$) and duration of treatment ($p = 0.039$) (Todorovska *et al.*, 2014).

2.4 Rationale of study

HUSM is currently one of two tertiary health centres in Kelantan which has Gastroenterologist specialty. There were many studies done in Europe, US, India, China and all over the world regarding efficacy of current treatment for hepatitis C by using DAA drugs for a different group of Hepatitis C genotypes. So far, no similar studies done yet been published in Malaysian population for DAA efficacy since it is a new generation of medications that is believed to cure the illness and eradicate hepatitis C by 2030 (EASL ,2018), specifically in HUSM no yet data had been collected for pegylated interferon based treatment before and current DAA treatment that been used widely since 2015. Hopefully this study will help to guide clinician practice in determine the efficacy of current treatment for Hepatitis C benefit for liver function once achieve SVR and to identify associated factors that contribute to the efficacy of Hepatitis C treatment that later will become a baseline for better knowledge to treat patient locally.