Introduction

Egypt had the highest prevalence of hepatitis C virus infection (HCV) in the world in 2019 [1] with high mortality from chorionic liver disease, particularly in the rural areas, estimated at prevalence 14.7% among 15 – 59 years old [2], which is attributed to the epidemic to mass campaigns of parenteral anti-schistosomiasis treatment in the 1960s – 70s. It had operated the world's most extensive national treatment system [1]; for instance, since 2006 Egyptian government had been operated 23 national treatment centres and treated 190,000 patients by 2014. However, patients treated weres still insufficient compared to the estimated 4,000,000 patients (2014) [2]. Since Egypt has one of the little overall health care spending (6%) per percentage of gross domestic product [3], running a considerable operation may put a substantial economic constraint on Egyptian health care finance each year [4]. Furthermore, HCV related morbidity and mortality are predicted to at least double in the upcoming 20 years [4]. It requires the Egyptian government to prioritise delivering cost-effective HCV treatment to manage HCV treatment interventions within the limited budget to meet the high demand and pursue allocative efficiency.

HCV is a virus that can be infected by contact with the blood of an infected person. Transmission can occur from (1) sharing the needles amongst intravenous drug users (IDU) or (2) receipt of contaminated blood products [5]. The virus can survive over many years, causing liver damage, which would lead patients to have liver cirrhosis, liver failure, and liver failure caused death [5]. Patients with chorionic HCV has a low health-related quality of life (QoL) than the general population [5]. Once the disease progressed to cirrhosis, QoL continuously

gets reduced, leading patients to have an increased risk of hepatocellular carcinoma and decompensated cirrhosis (jointly termed liver failure) and subsequent death [5].

The goal of HCV treatment is to remain in the Sustained Virological Response (SVR) and clear the virus. Once patients get into the SVR stage, the HCV virus re-infection ratio decreases, and patients would no longer require further treatment depending on the genotype [5]. However, Pegylated Interferon plus Ribavirin (PR) achieve relatively low SVR rate (around 40%) among genotype 1 and 4, which consist of the majority of the Egyptian HCV cases (>90% of genotype for patients with chronic hepatitis C in Egypt is type 4), and patients happen to experience side effects which are vomiting and diarrhoea [5].

Recent developments of treatment such as Ledipasvir and Sofosbuvir (LS) showed a relatively higher proportion of patients achieved to the SVR stages and showed effectiveness on its treatment avoiding the side effects; however, having relatively high cost compared to PR [5]. LS treatment regime can also shorten the treatment time to six months, compared to the standard PR treatment for chronic HCV patients in Egypt, that typically takes 6 to 12 months [5]. Treatment combinations can be given to people in different health states, such as moderate or cirrhosis.

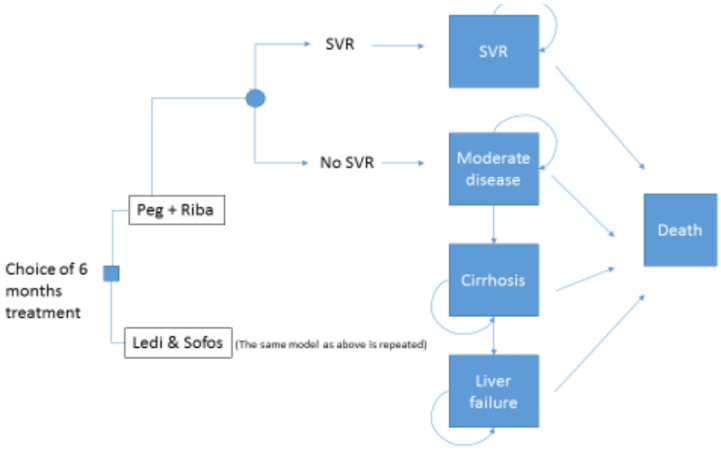
The objective of this study was to evaluate the cost-effectiveness of LS treatment regime compared to PR in Egypt for patients with chronic hepatitis C virus infection. The target population for this analysis is patients with chronic HCV at the 'moderate' health states [5], whose average age to begin the treatment is 40 years old. The study was conducted from health service perspective.

Methods

A Markov model was developed with Microsoft Excel to identify if LS treatment regime is more cost-effective than PR. Disease progression can be captured reflecting the variables.

Markov model is helpful especially modelling for chronic diseases, I.e., HCV, as it allows economic evaluation of each health stage over a certain period. Developed Markov model identified once the 12 weeks of antiviral treatment with each treatment regime cohort (1:1 treatment arm ratio) occurred; patients may enter SVR states or no SVR states [5] and continuously progress following health states and exclusively.

Several assumptions have been applied to simplify the model [5]. It assumed that patients already in the SVR stage could not get re-infected with HVC [5] and stated that health states are mutually exclusive. Patients who did not respond to treatment (No SVRs) happen to be classified as in 'moderate disease' state and moved to the following health states, which are 'Cirrhosis', 'Liver Failure', and 'Death', according to the reflected probabilities. All cause death can be occurred at any health state on any general population, while there is a specific death rate from 'Liver Failure' caused from their liver disease.



(Table 1: Markov model)

All model input variables and ranges are noted in table 2. Evidence determining the probability and effectiveness of both PR and LS has been synthesis from single-arm (non-randomised) comparisons across different Randomised controlled trials and non-randomised studies [5]. As there were no prior head-to-head two-arm RCTs conducted to compare two treatment regimes, therefore, systematic reviews of RCTs were conducted to provide the least biased and most robust evidence to set the parameters [4].

Scenario Summary		Base value	Low value	High value	Data distribution
Model inputs					
Probabilities	**Having a SVR, Pegylated Interferon and Ribavirin**	0.395	0.393	0.397	Beta distribution
	Having a SVR, Ledipasvir and sofosbuvir	0.920	0.890	0.950	Beta distribution
	Moderate – Cirrhosis	0.043	0.033	0.053	Beta distribution
	Cirrhosis – Liver failure	0.039	0.029	0.049	Beta distribution
	Liver failure – HCV related death	0.150	0.110	0.150	Beta distribution
Cost	**6 months of treatment Peg + Riba**	4245	4245.000	4245.000	Gamma distribution
	6 months of treatment Ledi + Sofos	40000	40000.000	40000.000	Gamma distribution
	Moderate	900	690.000	1110.000	Gamma distribution
	Cirrhosis	2500	1440.000	3560.000	Gamma distribution
	Liver failure	4400	2065.000	6735.000	Gamma distribution
	dead	0	0.000	0.000	Gamma distribution
Utility	**SVR**	0.71	0.660	0.760	Beta distribution
	Moderate	0.66	0.606	0.714	Beta distribution
	Cirrhosis	0.55	0.496	0.604	Beta distribution
	Liver failure	0.45	0.396	0.504	Beta distribution
All cause mortality	**40-49 years old**	0.004			
	50-59 years old	0.012			
	60-69 years old	0.027			
	70-79 years old	0.066			
	80+ years	0.189			
Discount rate	**QALY**	0.035	0.020	0.060	
	Cost	0.035	0.020	0.060	

(Table 2: base case decision parameter for input variables)

- **Time cycle and time Horizon**

The cycle length of the model is set as one year to allow the timing of health states and administration [4], considering clinical requirements as such regular blood checkups and monitoring health states. Reflecting the WHO guideline, a 10-years period of intervention implementation cycle has been applied as its one complete programme implement cycle enables more strategic cash flow planning, such as annualised start-up costs prior to 10 years of cycle period [6]. Life-time time horizon setting has been applied for the model to capture all the health effects that intervention occurred. The life expectancy of Egypt, 71.9 9 years [7], has not been adopted as the time horizon as it may exclude a significant amount of additional health effects to the model.

Synthesising all the components considered, the model set its time-horizon until 99 years to evaluate six sets of 10 years of implementation periods.

- **Cost**

The modelling could not be conducted from a societal perspective due to the limited cost data available on non-health expenditure which would allow the incorporated evaluation to estimate the impacts and trade-offs such as in welfare [6] or in the labour market that enables estimated economic analysis [8]. Instead, the modelling adopted a health service perspective

with its available dataset in drug and treatment cost and attributed to available non-medical service cost on caregiving [9] given to cirrhosis and liver failure patients.

The costs of 6 months of antiviral treatment in 2022 (both PR and LS) have been considered the one-time fixed cost that does not require further sensitivity analysis. Annual costs associated with HCV treatment in 2022 have been given per health state in both average cost and standard error. All treatments and annual treatment costs were given in the Egyptian pound, which is presented in table 2.

- **Utilities and measuring health outcome**

Due to the absence of local valuations or similar generic measurements in the different health statues, average utility and standard error have been driven from a survey of UK patients at different disease stages by completing a Europol (EQ-5D-3L) questionnaire to calculate total life years and utility gain (measured on 0 – 1 scale) [5]. All utility values, including average utility and standard error, have been suggested in table 2.

Using the UK generic measurement to measure utilities that cannot accurately reflect the context of Egyptian jurisdiction can produce a broader range of uncertainty to extrapolated modelling results over the time horizon. However, applying QALY instead of DALY, which is commonly used in LMICs context, should be encouraged as QALY can provide validity, reliability, and sensitivity on evidence [9]. Moreover, QALY is more inclusive than DALY as it can capture the impact of co-morbidities and is measured by the patient.

- **Discount rate**

All annual costs (except both antiviral treatment which is considered as sunk costs) and health outcomes were discounted at 3.5% every year as per the local guideline [3], to express decreased weights valued to the future cost and health outcome compared to the current cost and health outcome values that addressed by standard discounting model [8]. For the sensitivity analysis, the discount rate varied from 2% to 6%, as the local guideline pointed out [3], for both cost and health outcome.

Analyses

Deterministic sensitivity analysis (DSA) and probability sensitivity analysis (PSA) have been conducted to evaluate the impact of transition, utilities, and cost parameter probabilities on the results.

Two-way sensitivity analyses had not been performed, as input parameters have been firmly justified by the references [5] with sampling error which provides high certainty on its validity.

Result	Total cost	Total QALYs	ICER	Interpretation
Treatment Strategy				
Pegylated Interferon and Ribavirin	23,014,837	11,750		Base Case
Ledipasvir and sofosbuvir	42,481,962	12,830	18,036	
Ledipasvir and sofosbuvir (negotiation completed)	42,233,766	12,830	17,806	

(Table 3) Base case and result

- **Base case analysis**

PR is set as the base case on the analyses as it is the current treatment in Egyptian context. Modelling has shown that the ICER of LS is 18,038 Egyptian Pounds per QALY. In case the continuing negotiation succeeds, ICER will become 17,806 Egyptian Pounds per QALY.

- **Deterministic Sensitivity Analysis (DSA)**

A one-way deterministic sensitivity analysis was conducted and visualised by a tornado diagram below. It is to address methodological uncertainty, parameter uncertainty, and structural uncertainty by observing the magnitude of differences that. Point estimates of each parameter are set as the ICER of the mean value. 95% Confidence Interval was conducted to identify the lowest and highest range of the ICER to capture the sensitivity range of each parameter. The discount rate applied 2% and 6% as the lowest and highest value per the local guideline [11], which was also used at the previous HCV economic evaluation study in the Egyptian jurisdiction [4]. It contains structural uncertainty instead of parameter uncertainty, unlike other parameters.

- **Probabilistic Sensitivity Analysis (PSA)**

As ICER values depend on multiple parameters on the model simultaneously, a monte carol PSA was performed. 1000 simulations conducted to capture stochastic uncertainty and range of the interaction might occur, allowing varying values of each parameter simultaneously within probability distribution. By plotting ICER variables to the cost-effectiveness plane