Economic analysis of HCV different screening algorithms in Egypt

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Introduction:

Viral hepatitis is a major public health problem, ranked the 7th leading cause of mortality globally [1]. Hepatitis C virus (HCV) infection contributes to almost half of this mortality [2, 3]. Affecting as many as 170 million individuals globally, and about 350,000 die annually from HCV-related diseases [4]. Progressive nature of HCV infection, lead to a higher risk of developing complicated liver diseases among infected individuals, where chronic HCV infection accounts for 27% and 25% of the worldwide prevalence of cirrhosis and hepatocellular carcinoma (HCC) [5].

Hepatitis C is present worldwide. However, Egypt, Bolivia, Mongolia and Cameroon have the highest HCV prevalence (>10%), and other areas of South America, Southeast Asia, and Sub-Saharan Africa regions report high to intermediate HCV prevalence of 2.5-10% [6]. According to The Egypt Demographic and Health Surveys (EDHS), antibody prevalence among the adult population aged 15–59 years was 14.7% [7] in 2009 and reached 10.0% [8] in 2015, substantially higher than global levels [2,3,9].

Since most chronic HCV infections are asymptomatic, screening during the long pre-symptomatic period, may allow patients to receive treatment before chronic complications develop [10]. In the same context development of highly efficacious oral direct-acting antivirals (DAAs) provides a vision for reducing HCV disease burden and its onward transmission, with the potential for eliminating this blood-borne virus as a public health concern [4, 11, 12]. Hepatitis C can be completely cured with direct acting antivirals (DAAs) within 3 months [13].

The World Health Organization (WHO) has recently formulated the 'Global Health Sector Strategy on Viral Hepatitis, 2016–2021 [14] with service coverage targets to eliminate HCV as a public health threat by 2030 [14,15]. Targets where set to be reached by 2020, to Increase the number of diagnosed tests performed for hepatitis by 100% and to test 80% of all health care workers for HBV and HCV [16]. WHO is working to ensure that DAAs are affordable and accessible to those who need them. Prices have dropped dramatically in some countries (primarily in some high-burden, low-and lower middle income countries), facilitated by the introduction of generic versions of these medicine [13].

To achieve this challenge, Egypt developed a national strategy for HCV control and established HCV prevention and treatment programs [17–19]. Following successful negotiations for 99% discounted DAAs prices [20], Egypt launched an ambitious national HCV treatment program aiming to treat over 250,000 chronically infected individuals per year, with the goal of achieving a national chronic infection prevalence of <2% by 2025 [21].

Despite this progress, existing evidence suggests ongoing HCV transmission in Egypt, with higher incidence levels relative to other countries [11, 22]. The economic impact of screening and treatment for chronic HCV in higher prevalence countries has not been well studied. Previous economic analyses have primarily focused on the U.S. population. Those studies did not recommend screening for HCV in the general population and suggested targeted birth-cohort or high-risk population screening only due to the low prevalence of HCV in the United States [23-25].

Thus, in anticipation of the need for supporting evidence on the health and economic consequences of hepatitis C screening this research is aiming to evaluate screening algorithms among different population groups as proposed by Egypt national plan.

General Objectives:

The study is aiming at providing evidence on the cost effectiveness of adopting a selective one-time hepatitis C screening program among different population strata (based on their risk probability of acquiring HCV infection).

Specific Objectives:

1. Construct a Markov model to follow-up the two cohorts of apparently healthy individuals (with different HCV risk probabilities) through transitional health states till death (from liver related causes) after diagnosis by the screening program.
2. Calculate Incremental Cost Effectiveness Ratio (ICER) of adopting the screening program for the two cohorts of population.
3. Prepare a policy brief to summarize the available evidence to clarify the size and nature of the HCV problem ,and describe the likely impacts of adopting the screening program on different population strata

Methodology:

1- Study Design:

A Full Economic evaluation, Cost –Utility analysis study, was conducted using a tailored, validated decision tree model linked to a Markov Model, to compare the Incremental Cost Effectiveness ratio of two **Policy scenarios;**

The Alternative Policy scenarios were; examining 2 screening regimens ***1) "No screening"; or 2) "Screen-and-treat with direct-acting antiviral agents (DAA)*** **ON two Egyptian population subgroups** (**categorized according to their risk of acquiring HCV infection**):

i. **Group I: Populations at high risk:** these include people who inject drugs (PWID), and populations exposed to frequent medical injections and/or blood transfusions such as hemodialysis, thalassemia, hemophilia, and multi-transfused patients, among others [26].

ii. **Group II: General populations:** include populations at relatively low risk of exposure to HCV such as blood donors, healthy children, antenatal clinic (ANC) attendees, pregnant women, and participants in household- based surveys, among others.

2) Sampling and study population

Two hypothetical cohorts of 1000 individuals, each, **assumed to be unaware of their HCV infection state**

- **Cost effectiveness of Screening versus No screening among each of the 2 cohorts, was evaluated using a decision tree model, as Illustrated in Annex (1).**

A. Screening then treating with DAA: Screening involves a blood test for HCV antibody. All positive antibody tests will be followed by an HCV RNA test to confirm infection. Our analysis assumes that all individuals who are tested positive for both tests will be referred to a hepatologist, to be offered treatment according to the Egyptian guidelines [27].

Treatment and monitoring for CHC

According to the Egyptian guidelines, diagnosed patients were categorized as either *eligible to treatment or ineligible to treatment* and in turn, eligible patients were further classified into *easy to treat group or difficult to treat group as illustrated in **Fig (2)*** [28] This classification significantly vary in the treatment prognosis, where patients who achieve **No SVR** after treatment were 0.035 among difficult to treat group, versus 0.073 among easy to treat group [29] with more probability of progressing to cirrhotic, decompensated liver disease and HCC.

Monitoring of HCV viral load estimation is required, at any time-point between12 and 24 weeks post-treatment to confirm successful eradication of the virus.

B. NON-screening, where accidental diagnosis is assumed to happen in merely 5 % of the population [30] while the rest will seek medical advice when complications appear (Cirrhosis, Decompensated Liver Cirrhosis or HCC). **We assumed that 100% undiagnosed chronic infected patients, were unaware of their situation.**

- **The decision tree (for each policy scenario) is linked to a Markov Process model to project** patients' out-comes (Fig 1). The structure of the model reflects the natural history of the disease. The cycle length of the ***model was 1 year*** to allow for an accurate estimation of the timing of the different health states and related costs [31].

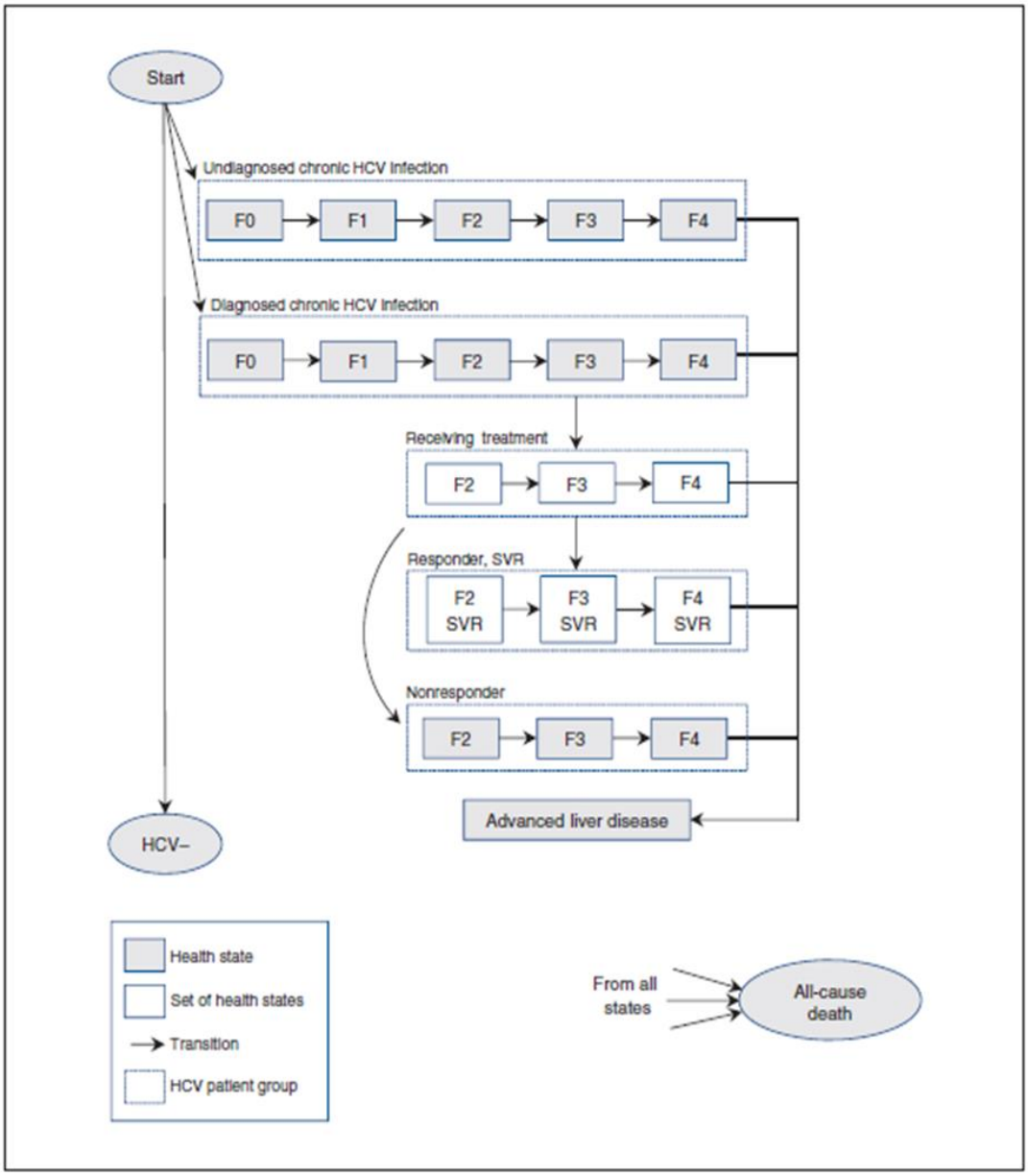

Fig (1): illustrating the used Transition heath states from F0 to F4 then progressing to advanced health state (DCC, HCC and Liver transplant).

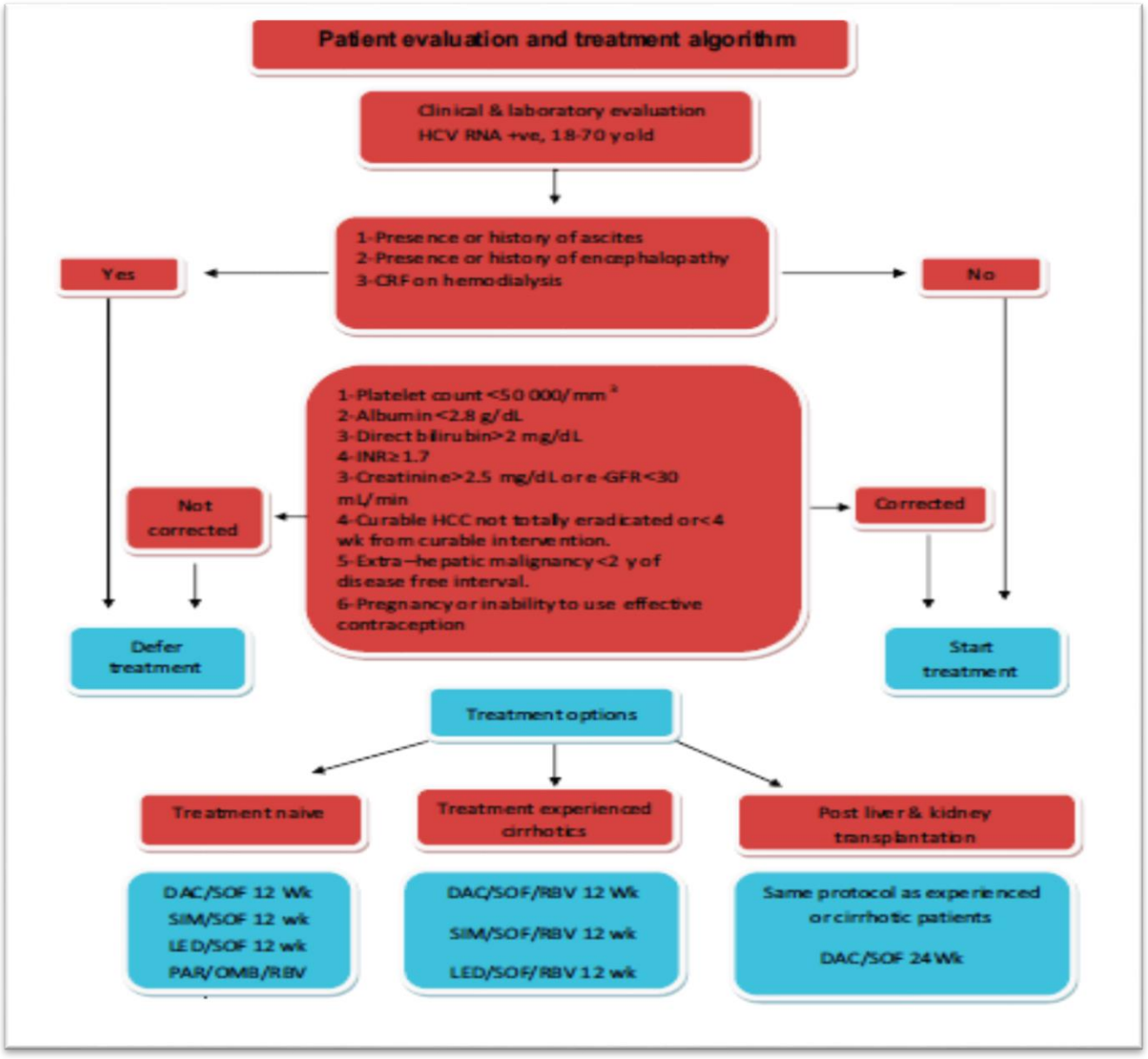

Fig (2): Journey of Chronic Hepatitis C Virus (HCV) patient through the Egyptian HCV model of care. DAC: daclatasvir; SIM, simeprevir; LED, Ledipasvir; SOF, sofoprevir, REV, ribavirin, PAR, paritaprevir; OMB, ombitasvir;

3) Study setting: The National Liver institute was the site of data collection of model inputs in addition to holding the capacity building workshop for preparing a policy brief

4) Data collection methods:

The study was conducted in 4 Phases:

Phase (I):

Extensive literature search together with critical appraisal of relevant studies (published meta-analyses of clinical trials, cohort studies, and systematic reviews) to **construct the decision Tree and the linked Markov model, and perform extraction of Model parameters as following:**

❖ **Model parameters**

A comprehensive search of PubMed and Google scholar was conducted for English articles published in the last 5 years to retrieve the available published data, regarding the probabilities of the health states, SVR rates of the combination therapy and the quality of life over the different health states [32, 33]. Published Egyptian guidelines were used for different treatment scenarios [27].

❖ **Clinical Parameters**:

Mutually exclusive health states were studied: ***F0***; defined as ***Normal liver*** of infected HCV patients, minimal fibrosis in the portal areas and the walls of central veins. ***F1***, chronic hepatitis results in fibrous expansion of portal tracts, which may maintain a rounded contour or develop short spike-like septa involving ***only*** a few portal tracts, ***F2*** chronic hepatitis eventually involves all portal tracts [34].

Fibrosis score ***F3***, defined as patients who had been infected with HCV without developing cirrhosis; fibrosis score ***F4,***which was defined by the patients who had been infected with HCV and had cirrhosis ;***DCC*** ,in which patients were at high risk of dying from ascites, bleeding varices, encephalopathy, and jaundice; ***HCC***, which was defined by the type of primary liver cancer that develops in patients with chronic liver disease; ***LT***, which was defined by patients who had undergone liver replacement because of life-threatening decompensated complications ;and death ,which was defined as death from any liver related causes [35].

Several assumptions were incorporated to simplify the model. First, the population was assumed to be treatment-naive. *Second,* all infections were caused by HCV Genotype IV. *Third,* all patients with chronic HCV infection who are offered antiviral therapy would be treated SOF and LDV. *Fourth*, we assumed that HCV patients who achieved SVR would not develop relapse to No SVR [36, 37].

All model input variables, their ranges, and sources are noted in **Table (1),** sensitivity of third generation enzyme-linked immunosorbent assay (ELISA) used for HCV screening is 98.6% , followed by confirmation with polymerase chain reaction (PCR) with 100% sensitivity [38].

Prevalence rate of HCV infection among general populations and high risk population were retrieved from a meta-analysis and systematic review studying Hepatitis C virus epidemiology in Egypt, 0.119 (± 0.06) and 0.556 (± 0.062) [26].

Transition probabilities for HCV natural history patients ***with and without SVR*** were derived from a decision-analytic model that assessed the cost-effectiveness of telaprevir plus pegIFN-2a and RBV (PR) compared with PR alone in adults with chronic HCV genotype 1 [33].

Phase II:

Determination of primary outcomes, Total (QALYs) accrued per patient

- **Health Outcomes**

The health outcomes of each intervention were evaluated in terms of quality-adjusted life-years (QALYs).This generic measurement weighs the length of life by the quality of life a patient experiences while in a specific health state. QALYs combine both morbidity and mortality into a single parameter. The utility value of F3,F4, DCC, HCC, and post-LT health states and the disutility value of the SOF þ LDV regimen that were incorporated into the model were derived from a decision-analytic model that assessed the cost-effectiveness of boceprevir þ RBV þ peg IFN compared with that of SOF þ pegIFN þ RBV and three peg IFN-free regimens (SOF þ simeprevir, SOF þ DCV, and SOF þ LDV) in treatment-naive patients with chronic HCVgenotype1 [32]. Each health state in the model was assigned a utility score between 0 (death) and 1 (perfect health) to quantify patient utilities for residing in that state. The utility measure of the LT health state that was incorporated into the model was derived from an observational, cross-sectional cohort study of 751 patients with HCV from several tertiary care settings in Canada evaluating health-related quality of life across the HCV disease spectrum using preference-based (utility) and non–preference-based (psychometric) methods, adjusted for socio-demographic factors and comorbidity [39].

Utility decrements that were specific to each treatment regimen were assigned during treatment to account for reduced health-related quality of life associated with treatment-related adverse events. Utility decrements during treatment course were derived from a study to estimate the utility associated with treatment administration and adverse events of hepatitis C treatments using general population valued health states in time trade-off interviews with10-and1-year time horizons in182 participants [40]. A utility increment, assigned to patients who achieved SVR, that was derived from a multicenter, randomized, controlled, and non-blinded trial assessed the efficacy of the combination therapy of interferon and RBV versus no treatment for 204 patients with chronic hepatitis C [41].

- **Cost Items**

-The direct medical care costs of HCV (drug regimen, treatment monitoring, adverse events, and health state complications) from the **Hospital perspective** were obtained from the National Liver Institute database and supplemented with the information that was available from the authors' institutions (**Table 1**).

-This secondary research method provided the best available evidence for the valuation of health service resources in terms of their unit costs.

-No capital costs were included. Cost data for the base-case represent the public scheme to reflect the actual circumstances in Egypt.

-.A macro-costing approach was used to determine the costs. Calculated costs of drug regimens were based on the indicated drug dosing, mean clinical trial therapy duration, and unit drug costs.
-Monitoring costs varied by treatment regimen and cirrhosis status.
-Adverse event costs were estimated on the basis of the incidence of each event and related costs associated with their management.
-Pharmacy costs for the management of each adverse event in the model were based on Egyptian drug-treatment algorithms [42].

This study adopted the **Hospital perspective** seeking to maximize the health gains of the population while representing the most efficient allocation of the finite resources available to Egyptian government hospitals. All costs and health consequences were discounted at 3.5% annually as recommended by Egyptian guidelines [43].

❖ **Time Horizon:**

Our cohort members transitioned between predefined health states in yearly cycles and was followed for **37years** (based on average life expectancy of Egypt to capture the detailed events occurring during the course of disease [44]. With every cycle, the patients could remain in their current health state or could experience the following: fibrosis score ***F4, DCC, HCC, LT,*** or death from any cause [45].

Phase (III)

Two incremental cost effectiveness ratios (ICER) were calculated for **Screening versus No screening** scenarios among BOTH cohorts; High Risk population and Population with Low risk of acquiring HCV infection.

Phase (IV)

A two days capacity building workshop, on Policy Brief Writing was held on 13th and 14th November, at National Liver Institute in Cairo. The instructor was a reputable political science and public policy researcher at The American University in Cairo. Fifteen, young to middle age researchers, actively participated; all of them are Master and/or MD holders of Public Health.

5) Data collection tools

CAPS quality checklists for critical appraisal of cohort and RCT and systematic Literature Reviews studies were used to ensure the quality of the used studies for retrieving data. The reports for Data Quality Check are provided in Annex 2 and 3.

6) Data management and statistical analysis

-The data was collected on Microsoft Excel sheets. Data was entered, cleaned and revised through Microsoft Excel 2010 software. Data was presented by tables and Graphs.

-the primary data analysis was done using Microsoft Excel and SPSS

-the decision making tree and Markov Model were constructed using Microsoft Excel software for Window 10.

7) Quality Control and monitoring:

- Attendance sheets for the capacity building workshop were completed, including names of the participants, their IDs the workshop successfully ended by preparing a policy paper for advocating for Screening of the whole population.

- ***Deterministic and Probabilistic sensitivity analyses will be done using Tree age software.*** They were not accomplished yet due to time constrain and some administrative issues concerning Purchasing Tree age software.

Results:

Total cost of monitoring of patients before treatment/first year including cost of PCR every 3 mon., cost of fibroscan /ultrasound every 3 mon., cost of serum albumin/3mon….etc was estimated to be 732 EGY (± 146).

The total discounted costs of the 2 alternative policies and the corresponding outcomes as experienced QALY values were recorded.

Concerning Policy (I); of High Risk population. Total discounted costs of "Screen and Treat" **scenario** was estimated to be 5687357.42 EGY compared to 513815.33 EGY for **"No screening" scenario. In addition; the total Discounted QALYs** of "Screen and Treat" **scenario was 1367.06 QALYs compared to 39.17** for **"No screening" scenario.**

The calculated "Incremental Cost Effectiveness Ratio" for this policy was 3895.31 EGY/ QALY where it is considered to be cost effective as it is below the Egyptian Threshold of Cost Effectiveness Ratio determined to be 1 GDP/ capita, approx. 46000 EGY/ QALY.

On the Other hand,

Concerning the Policy (II); of General population. Total discounted costs of "Screen and Treat" ***scenario*** was estimated to be 1513586.61 EGY compared to 1921742.56 EGY for ***"No*** **screening" scenario. In addition; the total Discounted QALYs** of "Screen and Treat" **scenario was 1125.42 QALYs compared to 6.10** for **"No screening" scenario.**

The calculated "Incremental Cost Effectiveness Ratio" for this policy was -34.64 EGY/ QALY where it is considered Dominant (cost saving strategy).

Table (1) shows Model Input parameters:

Parameter	Base Case	Range		Source of data
		Lower Limit	Upper Limit	
Population-related model Probabilities				
1- General populations: with relatively low risk of exposure to HCV	0.119	0.111	0.126	[26]
2- Populations at high risk: e.g. people who inject drugs	0.556	0.494	0.617	[26]
Annual screening rate (no screening arm)	0.05	**0.045**	**0.055**	[30]
Easy to treat (according to Egyptian classification)	0.98	**0.96**	**1**	[28]
Sensitivity of (ELISA) used for HCV screening	98.6%	**0.96**	**1**	[38]
Proprotion of Eligible patients to ttt (according to Egyptian classification)	0.82	**0.79**	**0.85**	[46]
Proportion of No SVR 12 among Easy to treat (non response(according to Egyptian classification)	0.035			[29]
Proprotion of SVR among difficult to treat (according to Egyptian classification)	0.9			[29]
Proportion of different fibrosis states among chronic infected HCV patients				
F0	0.199			[47]
F1	0.263			
F2	0.177			
F3	0.1			
F4	0.261			
Natural history of CHC Transition probabilities				
F0 to F1	0.117	0.041	0.155	[48]
F1 to F2	0.085	0.044	0.111	[48]
F2 to F3	0.12	0.092	0.201	[48]
F0, F1, F2 to Death	0.001			[48]
F3 to F4	0.16	0.13	0.19	[33]
F3 to HCC	0.001	0.0001	0.002	[33]
F3 to Death	0.079	0.06	0.1	[33]
F4 to DCC	0.039	0.03	0.05	[32]
F4 to HCC	0.027	0.02	0.02	[32]
F4 to Death	0.1	0.08	0.12	[33]

DCC to HCC	0.02	0.018	0.21	[32]
DCC to LT	0.05	0.04	0.06	[32]
DCC to Death	0.26	0.21	0.31	[32]
HCC to LT	0.15	0.12	0.18	[32]
HCC to Death	0.43	0.38	0.48	[33]
LT(1 y) to death	0.14	0.139	0.142	[32]
LT(2 y) to death	0.057	0.05	0.06	[32]
Transitionprobabilitiesfor cirrhotic patients (without SVR)				
F4 → DCC	0.031	0.0248	0.0372	[33]
F4 → HCC	0.027	0.0216	0.0324	[33]
Transitionprobabilitiesfor cirrhotic patients (with SVR)				
F4 → DCC	0.001	0.0001	0.002	[33]
F4 → HCC	0.008	0.006	0.01	[33]
Utilities of Health States				
F0, F1, F2	0.79	0.87	0.72	[49]
F3	0.85	0.66	0.96	[32]
F4	0.79	0.46	0.95	[32]
DCC	0.72	0.26	0.91	[32]
HCC	**0.72**	**0.15**	**0.95**	[32]
LT	**0.65**	**0.59**	**0.72**	[39]
Post LT	**0.83**	**0.64**	**0.95**	[32]
Utility decrement during treatment	**0.17**	**0.04**	**0.19**	[32]
Utility increment for achieving SVR	**0.05**	**0.047**	**0.06**	[41]
Annual costs of health states				
Fibrosis scoreF3	**4,000**	**3200**	**4800**	**[42]**
Fibrosis scoreF4	**4797**	**38838**	**5756**	**[42]**
DCC	**21,832**	**17458**	**26188**	**[42]**
HCC	**30750**	**24600**	**36900**	**[42]**
LT	**250000**	**200000**	**300000**	**[42]**
Post LT	30,000	24,000	36,000	**[42]**
Costs of monitoring				
Cost ofalfafetoprotein/1m	**40**	**32**	**48**	**[42]**
Cost ofPCR/3mo(0,3,6)	**350**	**280**	**420**	**[42]**
Cost of fibroscan/ultrasound/3mo	**200**	**160**	**240**	**[42]**
Cost ofINR/3mo	**30**	**24**	**36**	**[42]**
Cost ofserumalbumin/3mo	**12**	**10**	**14**	**[42]**
Cost ofbilirubin/3mo	**27**	**22**	**32**	**[42]**
Cost ofSGOT/3mo	**14**	**11**	**17**	**[42]**

Cost ofSGPT/3mo	**14**	**11**	**17**	**[42]**
Cost ofcreatinine/1mo	**20**	**16**	**24**	**[42]**
Cost ofCBC/3mo	**25**	**20**	**30**	**[42]**
Total costofmonitoringbeforetreatment/first year	**732**	**586**	**878**	**[42]**
Annual totalcostofmonitoring/secondyear2	**2196**	**1757**	**2635**	**[42]**
cost of screening	**90**	80	100	**[42]**
Costs of interventions				
SOF+LDV	**3000**	**2400**	**3600**	[50]
Discount Rate of Costs and QALYs	**0.035**			[43]

Table 2: Costs, Consequences and Incremental Cost Effectiveness Ratio (ICER) of "Policy I" screening versus no screening among Populations at high risk of HCV infection.

Policy I	Total Discounted costs (EGY)	Total Discounted QALYs	ICER
Screening	**5687357.42**	**1367.06**	**3895.31**
No screening	**513815.33**	**39.17**	

Table 3: Costs, Consequences and Incremental Cost Effectiveness Ratio (ICER) of "Policy II" screening versus no screening among General populations at low risk of HCV infection.

Policy II	Total Discounted costs (EGY)	Total Discounted QALYs	ICER
Screening	**1513586.71**	**1125.42**	**-364.64**
No screening	**1921742.56**	**6.10**	

Discussion:

This study was conducted in Egypt as an example of a country with high prevalence of hepatitis C in the developing world. We found implementing hepatitis C screening and treatment for asymptomatic, average-risk Egyptian adults would be cost-saving for the general population and highly cost-effective among high-risk population. Worldwide, countries with higher HCV prevalence, lower costs of treatment, and a higher SVR rate after treatment may find it cost-effective to implement HCV screening and treatment programs.

The immediate plans in Egypt after registering the new drug are to focus on treating HCV patients with liver cirrhosis identified in the past few years, eventually followed by screening and treatment programs for at-risk groups. The last stage will include national screening and treatment of patients from the general population.

On the national level, screening and treatment for HCV in Egypt could have substantial costs, but with corresponding large health benefits. If a screening and treatment program were implemented

"No screening" and "Screen-and-treat with direct-acting antiviral agents (DAA) for the high risk population in Egypt, the screening and treatment program would have a cost of 5687357.42 EGY compared to 513815.33 EGY for **"**No screening" scenario, and saving 1367.06 QALYs in "Screen and Treat" scenario compared to 39.17 QALYs in "No screening" scenario. Regarding the implementation in General population, costs of "Screen and Treat" scenario was estimated to be 1513586.61 EGY compared to 1921742.56 EGY for "No screening" scenario. The total Discounted QALYs of "Screen and Treat" scenario was 1125.42 QALYs compared to 6.10 for "No screening" scenario.

This was in accordance with the study done in Canada, one-time hepatitis C screening and treatment program save lives and be cost effective, at $31 468/QALY to $34 614/QALY gained over the lifetime of the cohort. The screening strategies that are most likely to be cost-effective are those focusing on immigrant populations with high prevalence (scenario 2), a birth cohort aged 25–64 years (scenario 3) and a birth cohort aged 45–64 years (scenario 4). On the other hand, screening and treatment programs targeting very low-risk populations (e.g., prevalence of 0.2%) would be only marginally cost-effective, at $50 490/QALY gained over the lifetime of the cohort [51].

Regarding the limitations of our study, it relied on the international literature to identify the clinical progression of HCV infection to chronic liver diseases and depended on clinical experts' opinions. Having more information on this for Egyptian patients would have added to the strength of the conclusions for Egypt. Although using Egyptian data is a strength for making conclusions about Egypt, it also may be a limitation to making broader conclusions about other developing countries with intermediate-to-high prevalence. Also, due to the lack of data on future treatments for HCV, we had to predict future events based on current data and treatment algorithms. Changes such as advances in treatment options or an unprecedented reduction of HCV prevalence could change our results.

Policy Recommendations:

- Our study is the first modeling study in Egypt to investigate the potential effects on the health system, examining 2 screening scenarios for diagnosis of HCV infection on 2 population subgroups based on their Risk of acquiring infection. ***The calculated "Incremental Cost Effectiveness Ratio" for implementing screening program on High risk population policy was 3895.31 EGY/ QALY where it is considered to be cost effective as it is below the Egyptian Threshold of Cost Effectiveness Ratio determined to be 1 GDP/ capita, approx. 46000 EGY/ QALY.***

- ***Whereas concerning Policy (II);*** of implementing HCV screening on the General population. ***The calculated "Incremental Cost Effectiveness Ratio" was -34.64 EGY/ QALY where it is considered Dominant (cost saving strategy).***

- Our results **came in accordance with the National Screening Program of HCV** that was launched in 2018 that aims to screen 62 million adults and 15 million adolescents by 2020.

A- On Macro level (National level):

1- Continuing the National HCV screening (on General population) is proven according to this study to be cost saving (Dominant strategy compared to no screening program) thus providing more QALYs and less cost
2- More studies needed to be implemented in Egypt to measure the quality of life among Egyptians in addition to studies that address the prevalence of complications.

B-On Micro Level (Unit Level):

1. It is recommended to conduct cost of illness studies on HCV infection, including all the probable health states, they experience throughout the course of infection. This could be through cost analysis of each preventive or curative service provided to HCV patients throughout their course of illness.

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