Cost Minimization of Pre-Enrolment Investigations in Treating HCV Infected Patients

[1]Arwa El Shafei, [2,3]Wafaa Elakel, [4]Mohamed Fathi Sakr, [2,3]Wahid Doss, [2,3]Gamal Esmat and [3]Mohamed Hassany

[1]Public Health and Community Medicine Department, [2]Endemic Medicine & Hepatology Faculty of Medicine Cairo University. [3]National Committee for Control of Viral Hepatitis NCCVH, Ministry of Health & population, Egypt. [4]Health Economics Department, Economic and Political Science, Cairo University

Abstract

Background: A screening program was launched in Egypt in 2018, targeting adult population for HCV and hypertension, diabetes, and obesity. **Objective**: To assess the financial impact of reducing cost of pre-enrolment investigations before treatment allocation. **Method:** 6771 adult patients, recently diagnosed with anti-HCV antibody positive during screening campaigns were included. Scenario-1: patients were categorized into 2 groups; Difficult and Easy to treat. Scenario-2: Patients were categorized by Fib-4 score into 2 groups with score ≤3.25 and score >3.25. Costs of pre-enrolment data obtained from National Committee for Control of Viral Hepatitis (NCCVH) administrative records. Cost minimization (CM) analysis compared the 2 scenarios with incremental analysis in Egyptian pounds. **Results:** Direct medical costs of both scenarios, pre-enrolment costs, direct treatment costs in scenarios 1 and 2 were 2528 and 3866 L.E respectively. Total costs in scenario-1 is 18,536,706 L.E. Comparing the 2 scenarios, 502 patients would have discordant results of both scenarios. Based on 89% SVR response expected from chronic HCV patients in previous literatures, supposing 11% treatment failure in patients with discordant results, 55 patients would need retreatment with Direct antivirus agents (DAAs) with 24 weeks duration. Total cost of scenario 2 is 18,087,772 L.E. Incremental cost minimization analysis per patient is 66 Egyptian pounds (LE). **Conclusion**: In limited resources countries with high prevalence of HCV as in Egypt, cost minimization in pre-enrolment setting would be preferable.

Key words: *HCV, Cost minimization analysis, Incremental analysis, Chronic liver disease, Screening*

Corresponding author: Arwa El Shafei; arwashafei@yahoo.com

Introduction

Hepatitis C virus (HCV) infection forms a load facing Egyptian governments, as it represents the greatest prevalence rate all over the world.[1] Treatment of Schistosomiasis (Bilharziasis) was introduced on a mass scale, starting from the middle of the last century till the 1980s, applying tartar emetic injections of as an implemented mass treatment by the Egyptian Ministry of Health (MOH) with the instruction and supervision of the World Health Organization (WHO).[2,3] Two million injections were given yearly to an average of quarter a million of patients. So that, in about 18 years of treatment, more than thirty six million injections were given to more than six million patients, with limited sterilization and injection safety procedures concerning syringes and other sharps leading to the highest healthcare worker malpractice with spreading of blood-borne infection.[3]

For estimating the prevalence of HCV in Egypt an algebraic model was used in 2014, it revealed new infection of about 150,000 annually causing 100,000 chronic HCV infections with 7.4% prevalence.[4,5]

Thus, the greatest prevalence of HCV infection was estimated by mathematical model in Egypt with estimated collective mean HCV prevalence at 12.5% in year 2008 within the general population and the viremic prevalence was 8.5% and that 6.3 (5.7-7.0) million people were living with HCV infection.[6,7]

Owed to the HCV remarkable economic and health status burden, in 2006 Egyptian government launched the National Committee for Control of Viral Hepatitis (NCCVH) to present nationwide strategies aiming to present both care of HCV patients and ensuring treatment accessibility. A digitally connected network of all centres presenting HCV treatment boosting treatment accessibility was launched. All health care providers were trained upon the practice guidelines.[8-11]

In 2014, NCCVH discussed pharmaceutical company to supply oral direct antiviral agents (DAAs) Sovaldi with a cost around $300 per one-month supply, or $900 for the whole 12-week course of treatment. Generic manufacturers lead to reduction of the cost in Egypt to be $84 per patient.

With this financial affordability, MOH created an online site for those infected by HCV to register for treatment. Within three days, about one quarter of HCV patients had signed up. Within the following three years, more than 1.6 million took hepatitis C treatment, according to World Bank reports.

The speed of eliminating HCV depends on how fast it diagnoses infected population, and the capability to present a screening program and ensuring sustainability of the needed resources.

Consequently, in early 2018, the Egyptian government decided to embark on an effort to detect all HCV infected population and treat them to ensure HCV elimination over the shortest time period possible. The MOH and the NCCVH planned and execute the largest population disease presidential screening campaign/initiative in history. The government and the MOH set goals to screen everyone in Egypt above the age of 18 (a population of 61 Million out of 98 Million) and treat all those who prove HCV viremic.

At screening locations, rapid test for HCV antibody (anti-HCV) testing was conducted. People who test positive for anti-HCV were confirmed by testing for the presence of virus and are referred for medical evaluation.

On medical evaluation at treatment centres, patients who are assigned for treatment by direct antiviral agents (DAAs) have to undergo a full list of investigations before starting treatment. Results of those investigations categorize the patients into 2 groups; easy to treat and difficult to treat groups. The “easy to treat” group include patients who have early infection and or minimal liver fibrosis. This group of patients need therapy only for 12 weeks. The “difficult to treat” group are those who might have chronic liver disease group with more than minimal fibrosis. They need treatment for 24 weeks.[12]

Many studies' data compared DAA response rates found that patients who are known to be difficult to treat have lower SVR rates than those who are categorized as easy to treat.[13-15]

On this stage, discrimination between Easy to treat and Difficult to treat patients with the least costs is a big challenge. In such discrimination, a 12 or 24 weeks duration for the same treatment protocol is decided. Minimization of the cost from MOH perspectives, of pre-enrolment is our scope.

Minimization of the direct cost for HCV treatment is needed in the current health setting in Egypt without affecting the

expected effectiveness of DAAs. Reducing the cost of pre-enrollment investigation would partially reduce the heavy financial burden of the disease and optimizes the efficient use of limited resources. Thus, the current study compared the same treatment regimens with assessment of reduction of pre-treatment investigations.

Cost minimization analysis (CMA) is an economic analysis seeking the least costly substitutes when the outcomes of two or more therapies are almost identical.

This is why, we chose CMA for the current study. The focus is on measuring cost of pre-enrolment investigations, while the treatment pathway outcome is assumed to be the same [16].

Is reducing the cost of pre enrollment investigations, would reduce costs or would increase the cost by missing patients who need longer duration of therapy. Failure of treatment in those patients would necessitate repetition of the treatment with longer duration for 24 weeks with extra costs.

The goal of the current study is optimizing the efficiency of NHCV program with effective control HCV patients

Objectives of the current study is to assess the financial impact of reducing the cost of pre-enrollment investigations before starting the treatment regimens prescribed for the patients. Those candidates' labs are total and direct bilirubin, albumin, International normalized ratio INR, and Alfa feto protein AFP and to evaluate the clinical consequences of the medical decision based on fib-4 when reduction of some labs had been performed.

Method

Study population: Patients were recruited from treatment centers affiliated to NCCVH, MOH, during the Presidential Initiative for screening of adult Egyptian population. The screening initiative was launched from October 2018 till April 2019. Choice of those patients during that time period was planned to exclude chronic HCV patients who came previously electively for HCV treatment. Patients who came during screening initiative were recently diagnosed with HCV infection.

Table (1): Planned Cross Tabulation of Both Scenarios

Scenario 2	Scenario 1	
	Easy to treat	**Difficult to treat**
Fib-4 ≤3.25	Treatment duration 12 weeks (concordant)	Treatment duration 12 weeks (discordant with *11% failure probability)
Fib-4 >3.25	---	Treatment duration 24 weeks (concordant)

Inclusion criteria: 18 years old and above, HCV antibody (Ab) positive

Exclusion criteria: Patients knowing they are infected with HCV or previously received treatment of HCV were excluded from screening campaign, therefore they will not be included.

All patients were subjected to medical examination, HCV RNA testing, in addition to laboratory investigations: Complete blood count CBC, Liver function tests; which include Liver enzymes: Alanine transaminase ALT, Aspartate transaminase AST, bilirubin (total and direct), INR and the serum albumin level, Kidney functions tests including urea and creatinine, in addition to :Alpha feto protein

Patients were categorized into 2 groups; "Easy to treat group" which include patients who fulfilled the following criteria: They have not been treated before by DAAs or Interferon and/or Fib-4 ≤3.25, Serum albumin level above 3.5, Serum total bilirubin less than or equal to 1.2, INR =<1.2, Serum Alfa feto protein less than or equal to 10, and "Difficult to treat group" include patients who have been treated with previous failure, and/or Fib-4 >3.25, Serum albumin less than or equal to 3.5, Serum total bilirubin above 1.2, INR >1.2, Serum Alfa feto protein AFP more than 10

Table (2): Baseline Characteristics of The Enrolled Patients (N=6771) with the 2 Scenarios

		Scenario 1			Scenario 2		
		Easy to treat	Difficult to treat	P value	Fib-4 ≤3.25	Fib-4 >3.25	P value
Total	**N (%)**	5710 (84)	1061 (16)		6212 (92)	559 (8)	
Gender: N (%)	**Female**	3332 (58)	591 (56)	0.11	3636 (59)	287 (51)	<0.01
	Male	2378 (42)	470 (44)		2576 (41)	272 (49)	
Age (years) N (%)	**=<30**	599 (11)	38 (4)	<0.01	636 (10)	1 (0)	<0.01
	31-40	1075 (19)	77 (7)		1144 (18)	8 (1)	
	41-50	1248 (22)	144 (14)		1346 (22)	46 (8)	
	51-60	1549 (27)	303 (29)		1680 (27)	172 (31)	
	61-70	970 (17)	336 (32)		1090 (18)	216 (39)	
	>70	269 (5)	163 (15)		316 (5)	116 (21)	
Fib-4 N (%)	**Mean±SD**	1.4±0.68	2.94±2	<0.01	1.4±0.7	4.7±2.1	<0.01
	=<3.25 (n=6212)	5701 (100)	502 (47)	<0.01	6212 (100)	0	---
	>3.25 (n=559)	0 (0)	559 (53)		0	559 (100)	
S. Albumin N (%)	**Mean ± SD**	4.3±0.4	3.85±0.6	<0.01	4.29±0.47	4.01±0.52	<0.01
	>3.5	5710 (100)	659 (62)	<0.01	5910 (95)	459 (82)	<0.01
	=<3.5	0 (0)	402 (38)		302 (5)	100 (18)	
T. Bilirubin N (%)	**Mean ± SD**	0.6±0.2	1.0±0.9	<0.01	0.67±0.48	0.83±0.52	<0.01
	=<1.5	5710 (100)	912 (86)	<0.01	6097 (98)	525 (94)	
	>1.5	0 (0)	149 (14)		115 (2)	34 (6)	<0.01
AFP N (%)	**median (IQR)**	3.5 (2.1)	12.1(17.2)	<0.01	3.3 (3.3)	5.8 (8.3)	<0.01
	=<10	714 (100)	121 (56)	<0.01	769 (92)	66 (71)	<0.01
	>10	0 (0)	97 (45)		70 (8)	27 (29)	
INR N (%)	**Mean±SD**	1.1±0.1	1.1±0.3	<0.01	1.07±0.15	1.11±0.15	<0.01
	=<1.5	5710 (100)	1010 (95)	<0.01	6167 (99)	553 (99)	0.31
	>1.5	0 (0	51 (5)		45 (1)	6 (1)	
Number of abnormal tests N (%)	**0 test**	0 (0)	5710 (84)	<0.01	5710 (92)	0 (0)	<0.01
	1 test	0 (0)	887 (13)		**474 (8)	413 (74)	
	2 tests	0 (0)	151 (2)		**26 (0)	125 (22)	
	3 tests	0 (0)	23 (0.3)		**2 (0)	21 (4)	

BMI: Body mass index, PC: Prothrombin concentration, INR: International normalized ratio, AFP: Alpha fetoprotein, TSH: Thyroid stimulating hormone, WBC: White blood cell count, E-CrCl: Estimated creatinine clearance

*Operational definitions***:**

Chronic infected HCV patients: Patients who are known to have chronic liver disease, have been treated before from HCV, or they know they have liver cirrhosis.

Recently diagnosed: Patients who were accidentally diagnosed in the screening campaign.

Treatment duration 12 weeks: 12 weeks of therapy. This choice is for easy to treat group of patients

Treatment duration 24 weeks: 24 weeks of therapy. This choice is for difficult to treat group of patients

Sustained Virological Response SVR: Negative test for HCV RNA (HCV viremia) 12 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection.

Table (3): Concordance of Both Scenarios

Scenario 2	Scenario 1	
	Easy to Treat (n=5710)	Difficult to Treat (n=1061)
Fib-4 =<3.25 Easy to Treat (n=6212)	5710 (84%)	**502 (7%)
Fib-4 >3.25 Difficult to Treat (n=559)	0	559 (9%)

Negative predictive value is the probability that subjects with a fib-4 =<3.25 truly fulfill easy to treat criteria group; considering that The gold standard is the easy to treat criteria; having albumin =>3.5, total bilirubin =<1.2, AFP=<10.

Sample size calculation: On designing the current study, number of patients who came for treatment after being screened through the presidential initiative was

Table (4): Comparison of the patients based on both scenarios New Format as required

		Easy to treat		Difficult to treat		Different results by Scenario 2
		Sc 1 (gold standard) (a)	Fib-4 ≤3.25 (c)	Sc 1 (gold standard) (b)	Fib-4 >3.25 (d)	
Total	**N (%)**	5710 (84)	6212 (92)	1061 (16)	559 (8)	502 (7)
Gender N (%)	**Female**	3332 (58)	3636 (59)	591 (56)	287 (51)	304
	Male	2378 (42)	2576 (41)	470 (44)	272 (49)	198
Age (years) N (%)	**=<30**	599 (11)	636 (10)	38 (4)	1 (0)	37
	31-40	1075 (19)	1144 (18)	77 (7)	8 (1)	69
	41-50	1248 (22)	1346 (22)	144 (14)	46 (8)	98
	51-60	1549 (27)	1680 (27)	303 (29)	172 (31)	131
	61-70	970 (17)	1090 (18)	336 (32)	216 (39)	120
	>70	269 (5)	316 (5)	163 (15)	116 (21)	47
Fib-4 N (%)	**Mean±SD**	1.4±0.68	1.4±0.7	2.94±2	4.7±2.1	
	=<3.25 (n=6212)	5701 (100)	6212 (100)	502 (47)	0	502
	>3.25 (n=559)	0 (0)	0	559 (53)	559 (100)	0
S. Albumin N (%)	**Mean±SD**	4.3±0.4	4.29±0.47	3.85±0.6	4.01±0.52	
	>3.5	5710 (100)	5910 (95)	659 (62)	459 (82)	200
	=<3.5	0 (0)	302 (5)	402 (38)	100 (18)	302
T. Bilirubin N (%)	**Mean±SD**	0.6±0.2	0.67±0.48	1.0±0.9	0.83±0.52	
	=<1.5	5710 (100)	6097 (98)	912 (86)	525 (94)	387
	>1.5	0 (0)	115 (2)	149 (14)	34 (6)	115
AFP N (%)	**median (IQR)**	3.5 ±2.1	3.3 (3.3)	12.1±17.2	5.8 (8.3)	
	=<10	714 (100)	769 (92)	121 (56)	66 (71)	55
	>10	0 (0)	70 (8)	97 (45)	27 (29)	70
INR N (%)	**Mean±SD**	1.1±0.1	1.07±0.15	1.1±0.3	1.11±0.15	
	=<1.5	5710 (100)	6167 (99)	1010 (95)	553 (99)	457
	>1.5	0 (0)	45 (1)	51 (5)	6 (1)	45
Number of abnormal tests N (%)	**0 test**	0 (0)	5710 (92)	5710 (84)	0 (0)	
	1 test	0 (0)	**474 (8)	887 (13)	413 (74)	474
	2 tests	0 (0)	**26 (0)	151 (2)	125 (22)	26
	3 tests	0 (0)	**2 (0)	23 (0.3)	21 (4)	2

***Representing the 502 patients with discordant results of the 2 scenarios*

143,000 patients. As we are not sure of the actual proportion of difficult to treat patients among screened group, we hypothesized them to be 50% ±5%. With confidence interval 95%%, and design effect (for cluster surveys-DEF) of 1. Thus, we defined 6000 patients to be enrolled.

Random selection of the patients' data from the central database were done by automatic random generator using SPSS 20.0.

Collected Data include demographic features; age, gender, governorate, body mass index (BMI),

Clinical parameters include complete blood count CBC (includes Hemoglobin level HB, White blood cells count WBCs, Platelets count, Liver function tests LFTs (include Total and direct bilirubin, ALT, AST), KFTs (includes urea, creatinine), Alpha feto protein AFP, serum albumin level, International neutralization rate (INR), Imaging findings were included as Ultrasonographic data , if available

The Fib- 4 score was considered for all patients. It is a safe easy scoring technique which is calculated through entering many laboratory data that enables estimating the amount of liver scarring. This score has been functioned to evaluate the liver condition after Hepatitis C

Table (5): Comparison of The Patients Based on Both Scenarios Old Format

		Scenario 1			Scenario 2			Different results by Scenario 2
		Easy to treat (a)	Difficult to treat (b)	P value	Fib-4≤3.25 (c)	Fib-4 >3.25 (d)	P value	
Total	**N (%)**	5710 (84)	1061 (16)		6212 (92)	559 (8)		502 (7)
Gender N (%)	**Female**	3332 (58)	591 (56)	0.11	3636 (59)	287 (51)	<0.01	304
	Male	2378 (42)	470 (44)		2576 (41)	272 (49)		198
Age (years) N (%)	**≤30**	599 (11)	38 (4)	<0.01	636 (10)	1 (0)	<0.01	37
	31-40	1075 (19)	77 (7)		1144 (18)	8 (1)		69
	41-50	1248 (22)	144 (14)		1346 (22)	46 (8)		98
	51-60	1549 (27)	303 (29)		1680 (27)	172 (31)		131
	61-70	970 (17)	336 (32)		1090 (18)	216 (39)		120
	>70	269 (5)	163 (15)		316 (5)	116 (21)		47
Fib-4 N (%)	**Mean ± SD**	1.4±0.68	2.94±2	<0.01	1.4±0.7	4.7±2.1	<0.01	
	≤3.25 (n=6212)	5701 (100)	502 (47)	<0.01	6212 (100)	0	---	502
	>3.25 (n=559)	0 (0)	559 (53)		0	559 (100)		0
S. Albumin N (%)	**Mean ± SD**	4.3±0.4	3.85±0.6	<0.01	4.29±0.47	4.01±0.52	<0.01	
	>3.5	5710 (100)	659 (62)	<0.01	5910 (95)	459 (82)	<0.01	200
	≤3.5	0 (0)	402 (38)		302 (5)	100 (18)		302
T. Bilirubin N (%)	**Mean ± SD**	0.6±0.2	1.0±0.9	<0.01	0.67±0.48	0.83±0.52	<0.01	
	≤1.5	5710 (100)	912 (86)	<0.01	6097 (98)	525 (94)		387
	>1.5	0 (0)	149 (14)		115 (2)	34 (6)	<0.01	115
AFP N (%)	**median (IQR)**	3.5 ±2.1	12.1±17.2	<0.01	3.3 (3.3)	5.8 (8.3)	<0.01	
	≤10	714 (100)	121 (56)	<0.01	769 (92)	66 (71)	<0.01	55
	>10	0 (0)	97 (45)		70 (8)	27 (29)		70
INR N (%)	**Mean ± SD**	1.1±0.1	1.1±0.3	<0.01	1.07±0.15	1.11±0.15	<0.01	
	=<1.5	5710 (100)	1010 (95)	<0.01	6167 (99)	553 (99)	0.31	457
	>1.5	0 (0)	51 (5)		45 (1)	6 (1)		45
No of abnormal tests N (%)	**0 test**	0 (0)	5710 (84)	<0.01	5710 (92)	0 (0)	<0.01	
	1 test	0 (0)	887 (13)		**474 (8)	413 (74)		474
	2 tests	0 (0)	151 (2)		**26 (0)	125 (22)		26
	3 tests	0 (0)	23 (0.3)		**2 (0)	21 (4)		2

infection. Fib-4 score results were a reflection of liver fibrosis status. It is calculated as follows:

$$\boldsymbol{Fib-4} = \frac{\boldsymbol{age} \times \textbf{AST (ULN40)}}{\textbf{platelets}(\times \mathbf{10^3})\sqrt{\textbf{ALT}}\textbf{(ULN40)}}$$

FIB-4 score <1.45 has a negative predictive value results of 95% for advanced fibrosis. While, a FIB-4>3.25 has a 98% specificity and a positive predictive value results of 65% for advanced fibrosis.[17]

Statistical Analysis

Quantitative data were expressed by mean and standard deviation (SD) and median and inter quartile range (IQR). Qualitative data were presented by number and percent

Two Scenarios were considered in the statistical analysis; Based on clinical features, lab results and / or fib-4 scores; (table 1)

First scenario: Assuming all lab tests will be done. Upon these full investigations, medical decision would be applied with the appropriate duration of treatment. Patients were categorized into: (1) Difficult to treat Patients; They would be treated for 24 weeks. (2) Easy to treat patients; Patients with no chronic liver disease stigmata as previously mentioned. Those patients would be treated for 12 weeks only.

Second scenario: Based on results of Fib-4 scores only, patients were classified

Table (5): Pre-Enrolment Investigations and Treatment Costs For Both Scenarios

	cost LE/unit	Sc 1	Sc 2
CBC	60	60	60
ALT	20	20	20
AST	20	20	20
T Bil	10	10	
D bil	10	10	
Albumin	15	15	
Creatinine	15	15	15
INR	50	50	
AFP	50	50	
HBsAg	75	75	75
Bl glucose	10	10	10
(a) Pre enrolment cost		335	200
(b) Medication cost		1473	2946
(c) Follow up *PCR (#2)		720	720
Total cost/case (a+b+c)	360	2528	3866

**PCR=HCV RNA quantitative by PCR*

into: (1) Less than or equal 3.25 and (2) More than 3.25 groups.

In each group, results of other lab tests were assessed in each group number of lab tests were saved (unnecessary), and number of necessary tests

Number of proper medical decision were conducted in both groups. Comparisons of both groups were done by student t-test for quantitative variables, and by Chi-square test for qualitative variables. All p values less than 0.05 are considered significant.

Referring to Pernner SB study 2017, Ahmed OA study in 2018 and El Sharkawy A study in 2017 all have agreed upon that the treatment failure probability due to discordant between the two scenarios is on average 11% (13-15)

Determination of medical costs, other costs: Medical cost classified as pre enrollment costs, treatment costs, follow up costs. Only direct costs were considered in this study. Indirect costs and follow up costs were not included. They are the same in both scenarios in both groups.

All costs for all pre enrollment investigations, medication, and follow up costs were obtained from NCCVH administrative records.

Cost Minimization Analysis CMA

Two scenarios were assumed; (1) Scenario 1 based on easy and difficult to treat categorization (base case): Medical costs in terms of pre-enrollment, medical and follow up costs for 12 weeks DAAs treatment duration for easy to treat group and for 24 weeks DAAs treatment duration for difficult to treat group. (2) Scenario 2 (based on Fib-4 score); medical costs in terms of pre-enrollment,

Table 6: Total costs in both scenarios

		12 wks	24 wks	total
Scenario 1	**no of patients**	5710	1061	6771
	total cost/patient (LE)	2528	3866	
	Total costs (LE)	14,434,880	4,101,826	18,536,706
Scenario 2	**no of patients**	6212	559	6771
	***Additional treatment courses required**		(0.11*502) 55	
	Total cost/patient (LE)	2528	3866	
	Overall costs (LE)	15,714,048	2,373,724	18,087,772

**for 89% SVR expected from the 502 patients who were missed as difficult to treat, we would get 55 patients with failed treatment outcome, will need retreatment with 24 weeks duration*

Table (7): Both Scenarios in Different Age Groups

Age groups	Scenario		12 wks	24 wks	Total	ICM/pt In LE	NPV
≤30 yrs	Sc 1	no of patients	599	38	637	53	0.94
		total cost (LE)/patient	2528	3866			
		Overall costs (LE)	1,514,272	146,908	1,661,180		
	Sc 2	no of patients	636	1	637		
		*Additional treatment courses required		4			
		total cost (LE)	2528	3866			
		Overall costs (LE)	1,607,808	19,601	1,627,409		
31-40 yrs	Sc 1	no of patients	1075	77	1152	55	0.94
		total cost (LE)	2528	3866			
		Overall costs (LE)	2,717,600	297,682	3,015,282		
	Sc 2	no of patients	1144	8	1152		
		*Additional treatment courses required		8			
		total cost (LE)	2528	3866			
		Overall costs (LE)	2,892,032	60,271	2,952,303		
41-50 yrs	Sc 1	no of patients	1248	144	1392	64	0.93
		total cost (LE)	2528	3866			
		Overall costs (LE)	3,154,944	556,704	3,711,648		
	Sc 2	no of patients	1346	46	1392		
		*Additional treatment courses required		11			
		total cost (LE)	2528	3866			
		Overall costs (LE)	3,402,688	219,511	3,622,199		
51-60 yrs	Sc 1	no of patients	1549	303	1852	65	0.92
		total cost (LE)	2528	3866			
		Overall costs (LE)	3,915,872	1,171,398	5,087,270		
	Sc 2	no of patients	1680	172	1852		
		*Additional treatment courses required		14			
		total cost (LE)	2528	3866			
		Overall costs (LE)	4,247,040	720,661	4,967,701		
61-70 yrs	Sc 1	no of patients	970	336	1306	84	0.89
		total cost (LE)	2528	3866			
		Overall costs (LE)	2,452,160	1,298,976	3,751,136		
	Sc 2	no of patients	1090	216	1306		
		*Additional treatment courses required		13			
		total cost (LE)	2528	3866			
		Overall costs (LE)	2,755,520	886,087	3,641,607		
>70 yrs	Sc 1	no of patients	269	163	432	99	0.85
		total cost (LE)	2528	3866			
		Overall costs (LE)	680,032	630,158	1,310,190		
	Sc 2	no of patients	316	116	432		
		*Additional treatment courses required		5			
		total cost (LE)	2528	3866			
		Overall costs (LE)	798,848	468,443	1,267,291		

**Additional treatment courses required =0.11*number of patients with discordant results on cross tabulation of the 2 scenarios. ICM/Pt= Incremental cost minimization per patient in each age group. NPV=Negative Predictive Value.*

medical and follow up costs for 12 weeks DAAs treatment duration for group =<3.25 in Fib-4 score and 24 weeks DAAs treatment duration for >3.25 in Fib-4 score. In addition, medical costs of re-treatment of the probable failing treatments (11% of the discordant group between the two scenarios) see table 1.

Incremental cost analysis by comparison of both scenarios

For international interpretation sixteen Egyptian pounds are equivalent to 1 USD

Results

A total number of 6771 subjects were enrolled in this study. Their baseline characteristics are shown in table (2). Scenario 1 (based on easy to treat and difficult to treat categorization that was based on all labs available): Group of "Easy to treat" (n=5710, 84%) which considers all lab as well as fib-4 score being less than <3.25, albumin >3.5, INR <1.5, Total bil<1.5, and AFP <10 were 5710 patients (84% of total enrolled population).

Group of "*Difficult to treat*" included patients with any of abnormal labs results were presented in three labs only in the current study (albumin <3.5, INR >1.5, Total bilirubin >1.5 or AFP >10)

Scenario 2; classification of patients into 2 groups according to fib-4 results. Based on fib-4 scores considering patients' age, AST, ALT values and platelets levels, patients were classified into ≤3.25 and >3.25 fib scores groups. Comparison of results of both groups is shown in table (table 2), there was significant difference in fibrosis surrogate markers such as total bilirubin, albumin, and AFP between the two groups. But there was no significant difference in INR.

Comparison of quantitative variables was assessed by t-student test. Qualitative variables were compared by Chi-square test.

Table 3 shows there was concordance between the 2 scenarios in most of the patients (n=6269, 93%). Negative predictive value NPV of fib-4 was 92% (5710/6212). considering that the gold standard is the easy to treat criteria, having albumin ≥3.5, total bilirubin ≤1.2, AFP≤10.

As shown in table 3, only 502 (7%) patients who showed discrepancies in their results. Fib-4 ≤3.25 failed to predict the abnormality in some lab results that might denote chronic liver disease status. It is to say that 502 patients with discordant results of the 2 scenarios.

Table 4 displays the comparison of the studied groups considering both scenarios. Among the 502 patients with discordant results of both scenarios; AFP was elevated >10 in 70 patients, serum albumin was low in 302 patients, total bilirubin was elevated >1.5 in 115 patients, and INR was prolonged >1.5 in 45 patients.

Unfortunately we cannot conduct inferential tests cannot be interpreted for comparison between 2 groups easy to treat and fib-4 less than or equal to 3.25 at one hand; and difficult to treat and fib -4 more than 3.25 one the other hand as both classifications include almost the same patients (categorized by 2 different ways)]

Table 4, displays the comparison between easy to treat (a) and difficult to treat (b) by scenario 1 and between the 2 Fib-4 groups by scenario 2 (c) and (d) (≤3.25 and >3.25)

The comparison between (a) and (b) in scenario 1 and between (c) and (d) in scenario 2, both comparison is valid as each group include different patients.

Patients in group (a) are almost the same in group (c), the difference in number of patients is the number of discordant results between the fib-4 and the gold standard. This was shown in last column in the table (total=502 patients, and are shown in table 4)

Cost Minimisation analysis

By calculating the direct medical costs of both scenarios; Pre-enrollment Costs, treatment costs are shown in table 5

Incremental cost minimization analysis

Incremental cost minimization is calculated by subtracting the costs of the 2 scenarios 18,536,706 -18,087,772= 448934 L.E for the whole population. Incremental cost minimization per patient would be 448,934/6771= 66 L.E (table 6)

Considering Age groups, cross tabulation of the 2 scenarios showed that young group with age≤30 years has discordance in 37 patients, group with 31-40 years old has discordance in 69 patients, group with 41-50 years old has discordance in 98 patients, group with 51-60 years old has discordance in 131 patients, group with 31-40 years old has discordance in 120 patients, and group with >70 years old has discordance in 47 patients

Stratification of patients based on age groups showed that the older age, the more discordant results, the more additional treatment courses needed for non-responders (table 6). Thus, incremental cost minimization is increased with older age.

Discussion

Egypt, presenting the greatest prevalence of HCV all over the world, has remarkable effort compacting the disease from its population at an extraordinary speed. The effort was made achievable by innovative

drugs. Therefore a screening program was launched in 2018, targeting to screen all adult population and treat who would been proved HCV infected. A mass screening and treatment program is considered to be an expensive step. Public accessibility to both diagnosis and treatment is considered a national target facing Egyptian Governments, in addition to ensuring their affordability.[18]

Treatment cost by generic locally-manufactured DAAs ranges from 10,545 to 1,527 L.E per 12 weeks of the treatment course.[19, 20]

The national plan of the screening program that any patient showing HCV Ab positive, they should have pre-enrolment investigations for medical evaluation in treatment centres.

One of surrogate markers for assessing the liver condition is FIB-4 score which considers patient's age and levels of both AST and ALT and platelets count. Although, there are other lab tests that were conducted for all patients.

The current study aimed to assess the effect of reducing the pre-enrolment lab tests and compare the costs of full medical investigations as base case scenario (scenario 1) with the other scenario (scenario 2), with reduced cost, which consider fib-4 is the factor that categorise patients regarding liver fibrosis status rather than full medical investigations.

Fib-4 has objectively great diagnostic importance for assessing liver fibrosis in hepatitis patients.[21] In previous studies, Fib-4 was used as a surrogate indicator for levelling liver fibrosis, a cut-off point at 3.25 was taken to as the best interpretations of Fib-4 with NPV up to 92%.[22]

Applying a cut off (3.25) in our study, most of the patients (92%) had minimal liver fibrosis, while only 8% had fib-4 score above the cut off levels denoting advanced liver disease. Male Gender was significantly associated with more fib-4 scores. This observation is in agreement with many studies which reported same significant association concerning gender.[23] Other fibrosis status indicators (serum albumin, total bilirubin, AFP and INR) are significantly different between the 2 groups based on fib-4 cut off values. This finding confirms more advanced liver disease in the group with fib-4 >3.25. In addition, it validates good interpretation for fib-4 score.

On assessing the concordance of the whole lab set tests (scenario 1) with the fib-4 score only (scenario 2), we could find only 502 patients with conflicting results; while they are considered as difficult to treat patients, their fib-4 score was below the cut off value 3.25.

However, most of those patients (474/502) had only one abnormal test. This observation would raise the probability of having milder liver disease rather than advanced liver fibrosis. Nevertheless, low serum albumin as a surrogate marker for more chronic liver insult, was low in 302 (60%) of the 502 patients.

Considering the stratification of the patients according to their age groups; it is well observed that application of scenario 2 is safer in younger age groups less than 50 years old. While, the older age, the more discordant between the 2 scenarios. This would increase the probability of treatment failure among the patients who were given shorter duration than required. This observation is in agreement with other studies.[24] It was concluded that FIB-4 scores have sound precision for advanced fibrosis in patients aged >35 years. However, the specificity for advanced fibrosis is unsatisfactorily low in patients aged ≥65 years, resulting in a high false positive rate considering that The gold standard is the easy to treat criteria; having albumin ≥3.5, total bilirubin ≤1.2, AFP≤10. New cut off levels are recommended to be employed for use in patients aged ≥65 years to correct this issue.

The individual cost of the laboratory investigations was estimated in previous

studies by assuming that clinics first use the enzyme immunoassay (EIA), then retesting through applying recombinant immunoblot assay (RIBA) test for those with a low EIA signal-to-cut off ratio (1.0 to 3.8).[25] Aiming to costs reduction and improving the reliability, CDC conditioned the use of RIBA to confirm low-positive EIAs.[26]

It was almost the same in our study the per-patient cost of the laboratory test was estimated by assuming that people came to screening sites to conduct the rapid test for HCV. After proven positive, patients were referred to HCV treatment clinics to start their pre-enrolment investigations. In addition, other lab tests were done after positive HCV RNA is proven.

In our study, reduction of some pre enrolment investigations such as total, direct bilirubin, INR, serum albumin and AFP, may reduce the cost in one hand and increase it in another. The reduction in pre-enrolment investigations reach up to 135 L.E per patient. Other costs are not included in this comparison as they are the same in both scenarios.

On the other hand, a small percent of patients (7%) may be wrongly diagnosed (false negative) as "easy to treat" and given 12 weeks duration treatment while they would have given 24 weeks duration of therapy.

Based on 89% in SVR results in chronic liver disease[13], supposing this scenario, a 11% failure probability to achieve virus cure (SVR), in this group of patients, is suspected would theoretically produce around smaller percent of patients who might need retreatment with additional treatment courses.

In another setting, the cost for retreatment of this proportion of patients may minimize the reduction of the pre enrolment investigation that was suggested. The balance was addressed by the incremental analysis. In our setting; on applying the second scenario, the incremental analysis concluded that a 66 L.E would be saved per patient.

In such a big mass screening and treatment campaigns and need to rapidly diagnose and treat patients with HCV in Egypt, such small reduction of the pre-treatment cost would make difference.

However, considering comparing the 2 scenarios, with age groups stratification; fib-4 score gave most specific results for patients younger than 50 years old. This comes in agreement with other previous studies.[27] This observation would encourage applying the second scenario on younger population. Egyptian population pyramids, shows the most prevalent age groups are the groups below 50 years.[27] This fact would augment saving approach with applying fib-4 scores on screened patients below 50 years.

Conclusion

From the previous notes, we can conclude, in limited resources countries with high prevalence HCV as in Egypt, cost minimization in pre-enrolment setting would be preferable. This statement may bear some precautions to be considered, if we could overcome the drawbacks of its consequences.

One of the main drawbacks of this strategy is to get treatment failure group who would be given shorter duration of treatment. In this case, a stricter follow up of treatment outcome is needed. This would be achieved by increase patients' awareness of importance of checking the treatment outcome by PCR testing 12 weeks post treatment and the importance of retreatment with physician consultation.

It is of utmost importance, as well, to consider setting the pathway for this group of patients among the massive flow of screened and treated patients.

The other drawback of this approach is to consider the false negative results of fib-4 in older age. A more careful assessment for older age is recommended in pre and post treatment.

Cost minimization of pre-enrolment in treating HCV in Egypt is recommended with some considerations. More research is needed to set the proper cut off values of fib-4 among elderly patients. In addition, careful monitoring and well planned flow pathways for patients who would need retreatment, if failed of treatment and needed additional treatment course of therapy with longer duration.

Study limitation

Direct cost only were considered, we have not considered the per-client clinic costs. No indirect cost was considered

No discounting of inflation, as the time zone of the study is less than one year

Prices calculated in L.E according to perspectives of MOH and their price lists. Private prices were not considered. Other societal costs are not considered

Public private partnership PPP were not calculated as all treatment expenses are supported for free with governmental support.

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Conflict of interest

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