Validation of EGCRISC for Chronic Hepatitis C Infection Screening and Risk Assessment in the Egyptian Population

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Abstract

Chronic HCV infection, a highly endemic disease in Egypt, is usually asymptomatic for decades after infection. Prediction questionnaire tool was proofed to be a valuable, feasible and efficient instrument for the screening of several diseases. We previously developed an Egyptian HCV risk screening tool (EGCRISC). This study aims to validate/modify EGCRISC. A cross-sectional study testing 4579 individuals by EGCRISC as well as ELISA/PCR was performed. The sample was a stratified cluster sampling from urban and rural areas in Upper and Lower Egypt using a proportional allocation technique. The degree of agreement and positive and negative posttest probabilities were calculated. ROC curve was done and the cutoff points were customized for best performance. The total score was further classified into three levels according to the risk load. The mean age of the participants was 41.1 ± 12.2 in whom HCV prevalence was 8.6%. EGCRISC, particularly after modifying the cutoff points, has a good discriminating ability. The degree of agreement was at least 68.1% and the positive posttest probability ranged from 5% to 37.2% whereas the negative posttest probability was in the range 1% to 17%. We conclude that EGCRISC is a valid tool that can potentially screen for HCV infection risk in Egypt and could diminish the demand for mass serologic screening in those apparently at minimal risk. Extensive use of electronic and self- or interviewer-administered risk-based screening strategy may simplify and promote overall screening and detection of HCV dissimilar communities.

Introduction

Early detection of chronic HCV infection and eventually treatment and lifestyle/behavioral changes cannot only prevent sequelae such as cirrhosis, end-stage liver disease or HCC, but also interrupts infection transmission [1].

HCV is arguably the major public health challenge facing Egypt today. The virus shows evidence of continuous transmission in health care settings as well as within households [2]. Due to the absence of vaccines and drugs for post-exposure prophylaxis, precautionary measures preventing future spread is the cornerstone for prevention [3].
Because of the asymptomatic nature of HCV infection before diseases progression, many HCV infected individuals are not aware of their condition and therefore do not seek help or perceive a need to screen for HCV infection. As a result, a potentially large number of infected individuals remain unidentified or are identified late [3]. A major barrier to seeking HCV treatment is unawareness of HCV seropositivity [4].

People identified to be HCV infected benefit from counseling, risky behavior modification, HAV or HBV vaccinations, alcohol cessation and other interventions including the recently released effective antiviral treatment [5].

To control the epidemic in Egypt, extensive efforts should be directed towards identifying apparently healthy individuals with HCV infection. Risk calculation approaches have been widely applied in public health actions and clinical care and have even been accepted as preliminary diagnosis for some diseases [6].

The United States Preventive Services Task Force (USPSTF) concluded in 2004 that screening high-risk population would be more efficient strategy than screening average-risk population [7]. With increasing recognition of the clinical and public health benefit of early detection, a simple self-administered tool may provide means to identify infected individuals [8–10].

Few studies have evaluated screening tools for estimating risk for HCV infection to support efficient screening of the hidden population of HCV–infected individuals [11, 12]. Further research is needed to understand the effects of different strategies on clinical outcomes and to customize the tool to the target population. Accordingly, we -in a previous study [13]- developed a short version risk assessment tool for HCV infection screening in Egypt (EGCRISC). The present large scale cross-sectional study is aiming to validate and modify -if needed- the EGCRISC tool to be more effective in identifying those at increased risk of HCV infection in the Egyptian setting, a step in a road to apply this tool in the primary care settings and as an internet-based screening program.

**Methods**

**Development of the prediction model**

The risk assessment tool abstracted from the first phase [13] was developed through a multivariate model of independent predictors of HCV seropositivity, that included the significant factors detected in the bivariate analysis among two age strata (< 45 and > 45 years) for each gender. Variables were ranked by their magnitude of risk [(Odds Ratio (OR)], with an overall score represented by the simple arithmetic sum of the nearest integral values. “Table 1” summarizes the 17 overlapping predictors, ranging from 8 to 13 in each of the four stratified groups. The OR for each factor assigned its score, giving a different total score for each stratum. The cut-off value for each group was estimated using ROC curve analysis, based on Youden index criterion, to specify the discriminating point of the highest sensitivity and specificity.

**Sample size**

A sample of 4100 persons are required to estimate expected agreement with phase I scoring for predicting HCV infection status to be on average 70% with a tolerated error margin of 2%, confidence level of 95% and design effect = 2.

**Sampling technique and methods of selection**

During this validation phase, the tool was applied to a stratified cluster sampling from urban and rural areas using a proportional allocation technique in governorates representing upper
and lower Egypt considering a rural to urban ratio of 1.3:1 according to the latest national estimates [14]. In each governorate, a number of districts were selected at random where participants older than 15 years were voluntarily recruited.

Laboratory investigations

According to the pre-specified cutoff points for males and females in both age groups (above and below 45 years), the cross sectional sample individuals were classified to potentially HCV infected and potentially non-HCV infected. The actual HCV status was determined using commercial 3rd generation ELISA kits (DIALAB	extsuperscript{®}, Austria). Confirmation of ELISA results was done using a kit from a different supplier (DiaSorin Murex	extsuperscript{®}, version 4.0, Italy). Quantitative real time PCR was done for ELISA positive subjects to test for HCV-RNA. A cross validation between the predicted status by EGCRISC score and the actual status was done by calculating classification accuracy rate and the degree of agreement between both tests. A new cutoff points for EGCRISC score system was derived using c statistic of ROC curve to estimate the distance between the extracted point and the previously determined one by the case control phase as a crude measure of validity for the old score.

Zones

Being at risk of having HCV based on a total score of the risk factors was categorized into zones; low risk (green zone), moderate risk (yellow zone) and high risk (red zone) using cluster analysis depending on the very large sample size and including all scored factors for discriminating cases into 3 groups using K-Means clustering technique, then and after identifying the extracted groups (clusters) of cases, the upper and lower limit for the overall score was identified as borders for each area which showed good concordance with the actual binary classification of persons.

Table 1. Summary of EGCRISC strata, factors, scores and cut-off points.

| Risk Factor                      | Score |
|----------------------------------|-------|
|                                  | Male <45 yrs | Male >45 yrs | Female <45 yrs | Female >45 yrs |
| Blood/blood products transfusion | 9      | 8          | 4             | 2             |
| Rural Residence                  | 8      | 15         | 18            | 7             |
| Fatigue                          | 7      | 2          | 3             | 2             |
| History of jaundice              | 6      | 3          | 4             | 1             |
| History of PAT                   | 2      | 3          | 9             | 6             |
| Incarceration                    | 2      | 4          | -             | -             |
| Unsafe rout of sex               | 2      | -          | -             | -             |
| Contact with jaundice patient    | 2      | -          | -             | -             |
| Use of barber or beautician tools| 2      | -          | -             | 3             |
| Substance abuse                  | 2      | 3          | -             | -             |
| Living abroad                    | 2      | 2          | -             | -             |
| Hospitalization                  | 2      | -          | 3             | -             |
| Needle prick                     | 2      | 2          | -             | 2             |
| History of invasive procedures   | -      | 2          | 3             | -             |
| Menses during intercourse        | -      | -          | 4             | -             |
| Blood sample                     | -      | -          | 2             | -             |
| Labour and delivery at home      | -      | -          | -             | 2             |
| Total                            | 47     | 44         | 50            | 25            |
| Cut-off value                    | 11     | 8          | 11            | 7             |

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Ethical statement

The present study was approved by the ethics committee and institutional review board of the High Institute of Public Health, Alexandria University (Egypt). The research conformed to the ethical guidelines of the Declaration of Helsinki (2013) and the International Conference on Harmonization Guidelines for Good Clinical Practice. An informed written consent was signed by all participants invited after elaborating on the study aim and concerns. Data sheets were coded to ensure anonymity and confidentiality of participants’ data.

Results

The study comprised a total of 4579 participants (55.7% males, 44.3% females) recruited from different urban and rural areas in Egypt “Table 2”. The mean age was 41.1±12.2. Other sociodemographic characteristics and a list of the studied HCV risk factors are detailed in “Table 3”. Stratified analysis of HCV risk factors by age and gender is displayed in (S1 Table).

In the studied population, there was an 8.6% prevalence of HCV antibodies with HCV viremia found in 83.8% of them (7.2%).

The EGCRISC has an average discriminating ability for persons’ HCV status as the area under curve (AUC) ranged from 0.65 for older males (above 45 years) to 0.84 for older females. Based on ROC curve analysis, the best cutoff point discriminating HCV positive and HCV negative cases for each gender in the two age strata are displayed in (Fig 1). As for males above 45, we respected the use of the best cutoff point of phase I model (8 vs 7) since it had higher reported sensitivity (70% vs 66%) and specificity (80% vs 58%).

“Table 4” cross tabulates the real HCV status and the risk status based on EGCRISC old and new cutoff points. The results of the old EGCRISC show a significant association and a considerable degree of agreement with the real HCV status in each category. The highest agreement levels were mainly for males and the lowest agreement level was for females <45 years. This discrepancy in agreement levels was eliminated after the use of the new cutoff points of

| Item                  | Setting                  | Kafr Sheikh (n = 1403) | Damanhur (n = 103) | Alexandria (n = 2036) | Luxor (n = 1037) |
|-----------------------|--------------------------|------------------------|--------------------|-----------------------|------------------|
| Gender                |                          |                        |                    |                       |                  |
| Female                |                          | 730 (52.0)             | 31 (30.1)          | 679 (33.3)            | 590 (56.9)       |
| Male                  |                          | 673 (48.0)             | 72 (69.9)          | 1357 (66.7)           | 447 (43.1)       |
| Age                   |                          |                        |                    |                       |                  |
| <45                   |                          | 707 (50.4)             | 53 (51.5)          | 1329 (65.3)           | 597 (57.6)       |
| 45+                   |                          | 696 (49.6)             | 50 (48.5)          | 707 (34.7)            | 440 (42.4)       |
| Mean ± SD             |                          | 42.5 ± 15.4            | 42.7 ± 8.6         | 39.8 ± 11.2           | 41.3 ± 13.9      |
| Anti-HCV ELISA        |                          |                        |                    |                       |                  |
| Negative              |                          | 1205 (85.9)            | 98 (95.1)          | 1932 (94.9)           | 950 (91.6)       |
| Positive              |                          | 198 (14.1)             | 5 (4.9)            | 104 (5.1)             | 87 (8.4)         |
| PCR                   |                          |                        |                    |                       |                  |
| Negative              |                          | 1231 (86.9%)(12.3)*    | 98 (95.1)          | 1955 (96.0)           | 965 (93.1)       |
| Positive              |                          | 172 (13.1%)(12.3)*     | 5 (100.0%)(4.9)*   | 81 (77.9%)(4.0)*      | 72 (82.8%)(6.9)* |

*percentage from the ELISA positive subjects.
*percentage from the total.

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Table 3. Sociodemographics and HCV risk factors including those of EGCRISC.

| Factor                          | Anti-HCV ELISA |          |           | OR (95% CI) |
|--------------------------------|----------------|----------|----------|-------------|
|                                |                | Negative | Positive |             |
|                                |                | No       | %        | No          | %        |       |
| Residence                      |                | Urban    | 1834     | 95.5        | 87       | 4.5    | 2.8 (2.2–3.5) |
|                                |                | Rural    | 2351     | 88.4        | 307      | 11.6   |               |
| Education                      |                | Illiterate /read & write | 1440 | 84.7 | 261 | 15.3 | 4.4 (2.9–6.7) |
|                                |                | Basic    | 699      | 95.1        | 36       | 4.9    | 1.3 (0.74–2.1) |
|                                |                | Secondary | 1437 | 95.2 | 72 | 4.8 | 1.2 (0.76–1.9) |
|                                |                | University / more | 609 | 96.1 | 25 | 3.9 |               |
|                                |                | Single   | 465      | 98.9        | 5        | 1.1    |               |
| Marital status                 |                | Married  | 3394     | 91          | 336      | 9      | 9.2 (3.8–22.4) |
|                                |                | Divorced/widow | 326 | 86 | 53 | 14 | 15.1 (5.9–38.2) |
|                                |                | Not working | 1519 | 91.1 | 148 | 8.9 | ref |
| Job nature                     |                | Low risk | 2308     | 90.8        | 234      | 9.2    | 0.84 (0.68–1.1) |
|                                |                | High risk | 564 | 88.7 | 72 | 11.3 | 1.3 (0.97–1.8) |
| Working abroad                 |                | No       | 3615     | 91.9        | 318      | 8.1    |               |
|                                |                | Yes      | 570      | 88.2        | 76       | 11.8   | 1.5 (1.2–1.9) |
| Tattooing                      |                | No       | 3878     | 91.3        | 370      | 8.7    | 0.82 (0.53–1.3) |
|                                |                | Yes      | 307      | 92.7        | 24       | 7.3    |               |
| Ear / body piercing            |                | No       | 2308     | 90.8        | 234      | 9.2    | 0.84 (0.68–1.1) |
|                                |                | Yes      | 1877     | 92.1        | 160      | 7.9    |               |
| Shared instruments             |                | No       | 904      | 90          | 101      | 10     | 0.80 (0.63–1.1) |
|                                |                | Yes      | 3281     | 91.8        | 293      | 8.2    |               |
| Use barber tools               |                | No       | 1026     | 88.4        | 134      | 11.6   | 0.63 (0.51–0.78) |
|                                |                | Yes      | 3159     | 92.4        | 260      | 7.6    |               |
| Pierced with blood contaminated tool |            | No       | 3851     | 91.5        | 357      | 8.5    | 1.2 (0.83–1.7) |
|                                |                | Yes      | 334      | 90          | 37       | 10     |               |
| Bitten by animal               |                | No       | 3386     | 91.4        | 317      | 8.6    | 1.0 (0.79–1.3) |
|                                |                | Yes      | 799      | 91.2        | 77       | 8.8    |               |
| Exposed to blood               |                | No       | 3305     | 91.6        | 305      | 8.4    | 1.1 (0.86–1.4) |
|                                |                | Yes      | 880      | 90.8        | 89       | 9.2    |               |
| Blood / blood products transfusion |            | No       | 3858     | 92.2        | 326      | 7.8    | 2.5 (1.9–3.2) |
|                                |                | Yes      | 327      | 82.8        | 68       | 17.2   |               |
| History of jaundice            |                | No       | 3814     | 91.5        | 353      | 8.5    | 1.2 (0.99–1.7) |
|                                |                | Yes      | 371      | 90          | 41       | 10     |               |
| Family member with hepatic disease |          | No       | 3503     | 91.5        | 326      | 8.5    | 1.1 (0.82–1.4) |
|                                |                | Yes      | 682      | 90.9        | 68       | 9.1    |               |
|                                |                | No       | 591      | 93.2        | 43       | 6.8    | ref |
| Blood sampling                 |                | <10 years | 2757 | 92.2 | 234 | 7.8 | 1.2 (0.83–1.6) |
|                                |                | >10 years | 837 | 87.7 | 117 | 12.3 | 1.9 (0.89–2.7) |
| Previous hospitalization       |                | No       | 1914     | 91.2        | 185      | 8.8    | 0.95 (0.77–1.2) |
|                                |                | Yes      | 2271     | 91.6        | 209      | 8.4    |               |
| Bilharziasis                   |                | No       | 2886     | 96.1        | 116      | 3.9    | 5.3 (4.2–6.7) |
|                                |                | Yes      | 1299     | 82.4        | 278      | 17.6   |               |
| Genital ulcers                 |                | No       | 3236     | 92          | 281      | 8      | 1.4 (1.0–1.7) |
|                                |                | Yes      | 949      | 89.4        | 113      | 10.6   |               |
| Circumcision                   |                | No       | 1061     | 96.6        | 37       | 3.4    | 3.3 (2.3–4.6) |
|                                |                | Yes      | 3124     | 89.7        | 357      | 10.3   |               |

(Continued)
EGCRISC while keeping the significant association. The positive posttest probability ranged from 5% to 37.2% whereas the negative posttest probability was in the range 1% to 17%.

For applicability we used the zones classification to rate the risk score instead of having a positive/negative test result. The limits for being at risk of having HCV based on validated scoring system of the selected risk factors are shown in (S2 Table and Fig 2). The risk is classified as low (subjects lie in the Green zone), borderline (subjects lie in Yellow zone), or high (subjects lie in Red zone).

“Table 5” highlights the zones classification and performance in the four different groups. The negative predictive value (NPV) ranged from 82% for yellow and red zones in males >45 years to 99% for younger groups. Positive predictive values (PPV) were high for red zones in older age groups compared to the younger age groups.

### Discussion

Although active HCV infection has an estimated national prevalence of 4% in the population age 1–59 years[14], the present study revealed a seroprevalence of 8.6% and active infection in 7.2% of those aged > 15 years. Egypt has a large reservoir of HCV and the disease transmission is ongoing [15, 16]. However, there is no adopted strategy for HCV case finding in primary
health care settings in Egypt and the rates of detection remains beyond the CDC goals [17]. Spotting individuals at increased risk who should be screened for infection is a critical step. Our group has previously derived a simple risk assessment predication tool (EGCRISC) based on patient-reported yes/no questions to be used as a first-level screening tool in identifying subjects who should undergo serologic testing for HCV antibodies (phase I) [13]. In this study, we validated the proposed model in a sample depicting the Egyptian population.

Compared to the data derived from the first development phase and initial testing of EGCRISC, the probability threshold for HCV seropositivity based on our prediction model was increased except for the category male > 45 years, we respected the use of the old cutoff point which had better agreement and performance. These new cutoff points will oust the need for serologic HCV antibody testing in a considerable number of uninfected subjects. The testing counsel of the proposed tool agreed well with the HCV status in this study and this features its validity, high diagnostic value, and hopefully cost-effectiveness.

A number of worldwide studies (Table 6) have developed or appraised questionnaire tools for HCV infection risk assessment [5, 18–22]. Of those that evaluated accuracy and feasibility in clinical practice, a harmony between sensitivity and specificity was respected to guarantee cogency, diagnostic performance, and cost-effectiveness of the selection method.

The present study has several strengths, among which comes the internal validation of our predictive model through internal case control and cross sectional data sets. Categorizing risk factors by age and gender enhanced the properties of our scoring tool. Also, the large representative sample of 4579 participant is ideal in risk assessment. Furthermore, the use of a proportionally allocated population based sample asserts that the derived results feature the Egyptian

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**Fig 1. The scoring system for the selected risk factors.** ROC curve analysis for the best cutoff point discriminating HCV positive and HCV negative status. Old cut off value was included in the table. Cutoff values respected in our prediction model are displayed in a red color font. – old cut off value

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### Table 4. HCV status based on standard lab and extracted scoring system of selected risk factors.

| Strata          | Standard  | Score Categories (old cut off) | N          | %     | Negative Agreement (%) | PTP (%) | NPTP (%) | Score Categories (new cut off) | N          | %     | Negative Agreement (%) | PTP (%) | NPTP (%) |
|-----------------|-----------|--------------------------------|------------|-------|------------------------|---------|----------|--------------------------------|------------|-------|------------------------|---------|----------|
| Male <45 yrs    | Anti-HCV ELISA | Negative                      | 1123       | 69.9  | 72.3                   | 8.3     | 1.2      | Positive                        | 431        | 26.8  | -                      | 96.7    | -        |
|                 |           | Positive                      | 14         | 0.9   | 71.8                   | 5.7     | 1.0      | Positive                        | 443        | 27.6  | 0.001                  | 72.3    | 8.3      |
|                 | PCR       | Negative                      | 1126       | 70.1  | -                      | 1126    | 70.1     | 443 27.6 0.001                  | 71.8    | 5.7     | 0.001                  | 72.3    | 8.3      |
|                 |           | Positive                      | 11         | 0.7   | 11.0                   | 0.7     | 1.7      | Positive                        | 27        | 1.7    | -                      | 113     | 7.4      |
| Male >45 yrs    | Anti-HCV ELISA | Negative                      | 576        | 61.1  | 68.1                   | 26.5    | 16.9     | Positive                        | 183       | 19.4   | 0.0001             | 66.0    | 25.3     |
|                 |           | Positive                      | 117        | 12.4  | 113                    | 12.0    | 7.4      | Positive                        | 66        | 7.0    | 0.0001             | 66.0    | 25.3     |
|                 | PCR       | Negative                      | 593        | 63.0  | 69.1                   | 23.0    | 14.4     | Positive                        | 192       | 20.4   | 0.0001             | 66.7    | 21.7     |
|                 |           | Positive                      | 100        | 10.6  | 97                     | 10.3    | 6.4      | Positive                        | 57        | 6.1    | 0.0001             | 66.7    | 21.7     |
| Females <45 yrs | Anti-HCV ELISA | Negative                      | 329        | 30.5  | 33.2                   | 3.9     | 0.3      | Positive                        | 720       | 66.7   | 0.028               | 68.8    | 6.3      |
|                 |           | Positive                      | 1          | 0.1   | 8                      | 0.7     | 2.0      | Positive                        | 29        | 2.7    | 0.028               | 68.8    | 6.3      |
|                 | PCR       | Negative                      | 329        | 30.5  | 32.4                   | 2.7     | 0.3      | Positive                        | 729       | 67.6   | 0.026               | 68.6    | 4.6      |
|                 |           | Positive                      | 1          | 0.1   | 8                      | 0.5     | 1.5      | Positive                        | 20        | 1.9    | 0.026               | 68.6    | 4.6      |
| Females >45 yrs | Anti-HCV ELISA | Negative                      | 287        | 30.2  | 42.7                   | 18.2    | 3.0      | Positive                        | 536       | 56.4   | 0.0001             | 656    | 37.2     |
|                 |           | Positive                      | 9          | 0.9   | 29                     | 3.0     | 9.4      | Positive                        | 119       | 12.5   | 0.0001             | 660    | 33.4     |
|                 | PCR       | Negative                      | 288        | 30.3  | 41.4                   | 16.2    | 2.7      | Positive                        | 549       | 57.7   | 0.0001             | 660    | 33.4     |
|                 |           | Positive                      | 8          | 0.8   | 25                     | 2.6     | 9.4      | Positive                        | 106       | 11.1   | 0.0001             | 660    | 33.4     |

- Exact Sig. (2-sided) McNemar test
- preTP = Pre test probability (Agreement)
- PPTP = Positive posttest probability
- NPTP = Negative posttest probability

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population. The study conducted by McGinn et al., in USA was limited by surveying population coming from an inner-city primary care practice, thus the results do not represent the true community [21]. Other studies validated their tool on hospital based small samples [19, 22] or on certain risk groups [5, 20].

Internet screening appears appropriate, attainable, and more cost-effective comparing to other strategies as it abates health care consultation costs [22]. An interactive electronic version of EGCRISC is now available at www.virus-c.com. The tool is enabled with a calculator for weighing the risk score and estimating the risk. Depending on the obtained score, the subject will be given a tailored recommendation that he/she should discuss with his/her professional healthcare provider. This instrument will empower the detection of silent chronic HCV cases in Egypt. People who are concerned about their probable HCV infection state will be boosted to assess their risk and pursue diagnosis. Filling out a risk assessment questionnaire via internet

**Fig 2.** Limits for risk of having HCV based on the scoring system of the selected risk factors. The questions are not equally weighed.

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ensure anonymity and provide better chance for understanding its purpose. Individuals will therefore recall relevant information and disclose risky behaviors differently from those collected through interviewing in a survey or health care settings. However, this might result in difference in the sensitivity and specificity of our validated tool. Nevertheless, although most of individuals in Egypt can have access to internet, not all of them have sufficient literacy or mastery to employ it. According to the 2015 EHIS (Egypt Health Issues Survey)\[14\], 22% of women and 8% of men age 15–59 are illiterate. It also reported that around 37% of adult men and 22% of adult women use computer and internet at least once a week. These factors may represent a challenge for the wide use of our proposed web-based screening. Marketing the use of EGCRISC will be adequately advertised through mass media outlets. Egyptians are regularly exposed to mass media particularly the television (99%) that have been traditionally used to convey health messages to the population. Additionally, reports will be disseminated to health authorities recommending the wide use of EGCRISC in primary care settings. Training workshops for primary care providers are planned to be held after phase III (a governorate-based EGCRISC application phase).

Prediction questionnaire tool was proofed to be an adequate, feasible and conductive instrument, accomplishing the growing needs for the screening of several diseases including dementia [23], type 2 diabetes [24], osteoporosis [25], and HCV infection among high risk groups [5]. A composite screening tool was also developed for chronic kidney disease, cardiovascular disease and type 2 diabetes screening in the same individual [26]. Moreover, risk estimation approaches were envisaged as an alternative for the diagnosis of some diseases such as cancer and cardiovascular disorders and have been widely exploited in public health and clinical care decision-making process [6].

The perspectives of the current work are to assess the feasibility and potential shortcoming of risk-based screening using our proposed prediction tool in the clinical practice. Also, to address its cost effectiveness in HCV detection and the cost of treating early/minimal liver diseased populations. A future study is foreseen by our group to assess the cost-effectiveness of EGCRISC in internet-based and alternative programs compared with other strategies, such as

| Age Category | Lab. Test | Zone | Green Zone | Yellow Zone | Red Zone |
|--------------|----------|------|------------|-------------|---------|
| Male <45 years | Anti-HCV ELISA | Negative | 598 | 38.5 | 708 | 45.6 | 248 | 16.0 | 4 | 99 | 7 | 99 |
| Male >45 years | Anti-HCV ELISA | Negative | 644 | 84.8 | 105 | 13.8 | 10 | 1.3 | 12 | 82 | 75 | 82 |
| Female <45 years | Anti-HCV ELISA | Negative | 348 | 33.2 | 472 | 45.0 | 229 | 21.8 | 2 | 99 | 8 | 99 |
| Female >45 years | Anti-HCV ELISA | Negative | 493 | 59.9 | 284 | 34.5 | 46 | 5.6 | 13 | 97 | 61 | 97 |
| PCR | Negative | 350 | 33.1 | 474 | 44.8 | 234 | 22.1 | 2 | 99 | 5 | 99 |
| | Positive | 16 | 12.5 | 40 | 31.3 | 72 | 56.3 | 12 | 98 | 54 | 98 |

Table 5. EGCRISC zones classification and performance.

| Zone | 
|------|
| Green Zone | Yellow Zone | Red Zone |
| No | % | No | % | No | % |

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Table 6. Literature overview of the different HCV risk assessment tools.

| Reference | Study population                                                                 | Respondent (n) | Age (years) | HCV prevalence | Type of study | Screening tool | cut off discriminatory point | Sensitivity | Specificity |
|-----------|----------------------------------------------------------------------------------|----------------|-------------|----------------|---------------|----------------|-----------------------------|-------------|-------------|
| Lapane et al., 1998 | Top of Form database of a national hepatitis screening program that included self-referred individuals screened for viral hepatitis in 40 urban hospitals in USA | 13,997 | 20% | cross sectional | Risk Factors based Questionnaire (Model 1) | Probability 7% in a mathematical model | 65.0% | 84.0% |
| | | | | | | | | | |
| | Bottom of Form | 29% | | | | | | 69.0% | 74.0% |
| | Top of Form | 25% | | | | | | 53.0% | 77.0% |
| | Bottom of Form | 12% | | | | | | 63.0% | 92.0% |
| Nguyen et al., 2005 | patients attending general medicine practice and hepatology practice at Thomas Jefferson University hospital | 207 with unknown HCV status and 222 HCV +ve patients | 18–60 | 1.5% in general medicine patients | cross sectional | a 7 item questionnaire based on variables found significantly associated with HCV infection in multivariate model of exposures | 4 or more risk factors are present | 24.4% | 99.4% |
| Mallette et al., 2008 | Veterans presenting for care and participated in risk stratification screening program at the Providence VA Medical Center (USA) | 25,701 | 25–92 (mean = 58.7) | 7.30% | cross sectional | a self-administered questionnaire identifying common HCV risk factors | Patients who answer yes to any of risk factors are offered anti-HCV antibody testing. | 63.0% | 92.0% |
| McGinn et al., 2008 | patients attending an inner-city primary care clinic | 1000 | 55 (mean) | 8.30% | cross sectional | A 27-item questionnaire assessing 5 HCV risk factor domains: work, medical, exposure, personal care, and social history. Questions were inspired from the literature and the clinical experience | 1 or more positive domains | 90.0% | 31.0% |
| | | | | | | | | 3 or more positive domains | 34.0% | 97.0% |

(Continued)
mass screening or screening evidently high risk groups. The cost-effectiveness analysis should take into consideration not only abating eventual health care costs of identified HCV-infected individuals, but also expenditure associated with HCV patient who would not be detected using one of the aforementioned strategies. We also recommend further validation of our questionnaire tool particularly in countries and regions with comparable prevalence and setting to those in Egypt.

In conclusion, we have validated a simplified tool (EGCRISC) to assess HCV risk in the general population in Egypt and demonstrated its diagnostic value. EGCRISC can taper the need for mass serologic screening in those at apparently very low or no risk. Widespread use of electronic and self- or interviewer-administered risk-based screening strategy may facilitate and promote HCV screening and detection in diverse populations. Targeted HCV screening in high risk individuals is more cost-effective and can be beneficial in early identification of individuals at risk for progressive liver disease who may benefit from counseling and prompt treatment to reduce HCV-related liver injury. An impact analysis or randomized control trial of this model is warranted to evaluate both the clinical value and cost-effectiveness.

**Supporting Information**

S1 Table. Stratified analysis of HCV risk factors by age and gender. (DOCX)

S2 Table. Limits for risk of having HCV based on the scoring system of the selected risk factors. (DOCX)

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References

1. Bialek SR, Terrault NA. The changing epidemiology and natural history of hepatitis C virus infection. Clin Liver Dis. 2006; 10(4):697–715. Epub 2006/12/14. S1089-3261(06)00018-3 [pii]. doi: 10.1016/j.cld.2006.08.005 PMID: 17164113

2. National Committee for the Control of Viral Hepatitis. Egyptian national control strategy for viral hepatitis 2008–2012 Ministry of Health and Population Available at: www.eipr.org/sites/default/files/pdf/hcv_treatment_in_egypt.pdf. 2008.

3. Zuure FR, Bouman J, Martens M, Vanhommerig JW, Urbanus AT, Davidovich U, et al. Screening for hepatitis B and C in first-generation Egyptian migrants living in the Netherlands. Liver Int. 2013; 33 (5):727–38. Epub 2013/03/02. doi: 10.1111/liv.12131 PMID: 23448397

4. Edlin BR, Kresina TF, Raymond DB, Carden MR, Gourevitch MN, Rich JD, et al. Overcoming barriers to prevention, care, and treatment of hepatitis C in illicit drug users. Clin Infect Dis. 2005; 40 Suppl 5: S276–85. Epub 2005/03/16. CID34646 [pii]. PubMed Central PMCID: PMC1510897.

5. Wand H, Iversen J, Wilson D, Topp L, Maher L. Developing and validating a scoring tool for identifying people who inject drugs at increased risk of hepatitis C virus infection. BMJ Open. 2012; 2(1):e000387. Epub 2012/01/06. bmjopen-2011-000387 [pii]. PubMed Central PMCID: PMC3253425. doi: 10.1136/bmjopen-2011-000387 PMID: 22218720

6. Vickers AJ, Basch E, Kattan MW. Against diagnosis. Ann Intern Med. 2008; 140(3):200–3. Epub 2008/08/06. 140/3/200 [pii]. PubMed Central PMCID: PMC2677291. PMID: 18678847

7. Anonymous. Screening for hepatitis C virus infection in adults: recommendation statement. Ann Intern Med. 2004; 140(6):462–4. Epub 2004/03/17. 140/6/462 [pii]. PMID: 15023712

8. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003; 125 (1):80–8. Epub 2003/07/10. S0016508503006681 [pii]. PMID: 12851873

9. Kamal SM, Fouly AE, Kamel RR, Hockenjos B, Al Tawil A, Khalifa KE, et al. Peginterferon alfa-2b therapy in acute hepatitis C: impact of onset of therapy on sustained virologic response. Gastroenterology. 2006; 130(3):632–8. Epub 2006/03/15. S0016-5085(06)00061-8 [pii]. doi: 10.1053/j.gastro.2006.01.034 PMID: 16530993

10. Dore GJ, Hellard M, Matthews GV, Grebely J, Haber PS, Petoumenos K, et al. Effective treatment of injecting drug users with recently acquired hepatitis C virus infection. Gastroenterology. 2010; 138...
11. Arumainayagam J, Grimshaw R, Acharya S, Chandramani S, Morrall IA, Pugh RN. Value of targeting at-risk populations at outreach venues: findings from a local sauna. Int J STD AIDS. 2009; 20(9):642–3. Epub 2009/08/28. doi: 10.1258/jisda.2008.008424 PMID: 19710339

12. Boyce DE, Tice AD, Ona FV, Akinaka KT, Lusk H. Viral hepatitis in a homeless shelter in Hawai'i. Hawaii Med J. 2009; 68(5):113–6. Epub 2009/07/09. PMID: 19583106

13. El-Ghitan y EM, Farghaly AG, Abdel Wahab MM, Farag S, Abd El-Wahab EW. Toward a simple risk assessment screening tool for HCV infection in Egypt, J Med Virol. 2016; 88(10):1767–75. Epub 2016/03/13. doi: 10.1002/jmv.24520 PMID: 26970264

14. El-Zanaty F. Egypt Health Issue Survey. Ministry of Health and Population, Cairo, Egypt. 2015.

15. Mohamoud YA, Mumtaz GR, Riome S, Miller D, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Egypt: a systematic review and data synthesis. BMC Infect Dis. 2013; 13:288. Epub 2013/06/27. 1471-2334-13-288 [pii]. PubMed Central PMCID: PMC3702438. doi: 10.1186/1471-2334-13-288 PMID: 23799878

16. Gower E, Estes C, Blach S, Razavi-Shearer K, Razavi H. Global epidemiology and genotype distribution of the hepatitis C virus infection. J Hepatol. 2014; 61(1 Suppl):S45–57. Epub 2014/08/03. S0168-8278(14)00526-1 [pii]. doi: 10.1016/j.jhep.2014.07.027 PMID: 25086286

17. Shehab TM, Orrego M, Chunduri R, Lok AS. Identification and management of hepatitis C patients in primary care clinics. Am J Gastroenterol. 2003; 98(3):639–44. Epub 2003/03/26. S0002-927002060537 [pii]. PMID: 12650800

18. Lapane KL, Jakiche AF, Sugano D, Weng CS, Carey WD. Hepatitis C infection risk analysis: who should be screened? Comparison of multiple screening strategies based on the National Hepatitis Surveillance Program. Am J Gastroenterol. 1998; 93(4):591–6. Epub 1998/05/12. S0002-9270(98)00047-1 [pii]. doi: 10.1111/j.15720241.1998.170b.x PMID: 9576453

19. Nguyen MT, Herrine SK, Laine CA, Ruth K, Weinberg DS. Description of a new hepatitis C risk assessment tool. Arch Intern Med. 2005; 165(17):2013–8. Epub 2005/09/28. 165/17/2013 [pii]. doi: 10.1001/archinte.165.17.2013

20. Mallette C, Flynn MA, Promrat K. Outcome of screening for hepatitis C virus infection based on risk factors. Am J Gastroenterol. 2008; 103(1):131–7. Epub 2007/09/27. AJG1522 [pii]. doi: 10.1111/j.1572-0241.2007.01522.x PMID: 17894850

21. McGinn T, O’Connor-Moore N, Alfandre D, Gardenier D, Wisnivesky J. Validation of a hepatitis C screening tool in primary care. Arch Intern Med. 2008; 168(18):2009–13. Epub 2008/10/15. doi: 10.1001/archinte.168.18.2009 PMID: 18852403

22. Zuurfe F, Davidovich U, Kok G, Depla AC, Hoebe C, van den Hoek A, et al. Evaluation of a risk assessment questionnaire to assist hepatitis C screening in the general population. Euro Surveill. 2010; 15 (15):19539. Epub 2010/05/01. 19539 [pii]. PMID: 20429995

23. Park S, Park SE, Kim MJ, Jung HY, Choi JS, Park KH, et al. Development and validation of the Pictorial Cognitive Screening Inventory for illiterate people with dementia. Neuropsychiatr Dis Treat. 2014; 10:1837–45. Epub 2014/10/07. ndt-10-1837 [pii]. PubMed Central PMCID: PMC4181741. doi: 10.2147/NDT.S64151 PMID: 25285007

24. Vandersmissen GJ, Godderis L. Evaluation of the Finnish Diabetes Risk Score (FINDRISC) for diabetes screening in occupational health care. Int J Occup Med Environ Health. 2015; 28(3):587–91. Epub 2015/07/21. doi: 10.13075/ijomeh.1896.00407 PMID: 26190733

25. Oh SM, Song BM, Nam BH, Rhee Y, Moon SH, Kim DY, et al. Development and Validation of Osteoporosis Risk-Assessment Model for Korean Men. Yonsei Med J. 2016; 57(1):187–96. Epub 2015/12/04. PubMed Central PMCID: PMC4696952. doi: 10.3349/ymj.2016.57.1.187 PMID: 26632400

26. Alssema M, Newson RS, Bakker SJ, Stehouwer CD, Heymans MW, Nijpels G, et al. One risk assessment tool for cardiovascular disease, type 2 diabetes, and chronic kidney disease. Diabetes Care. 2012; 35(4):741–8. Epub 2012/02/18. PubMed Central PMCID: PMC3308277. doi: 10.2337/dc11-1417 PMID: 22338109