Liver fibrosis (LF) is a kind of chronic damage of the liver and can lead to cirrhosis. LF occurs in response to almost all causes of chronic liver injury. An accurate assessment of the degree of fibrosis or presence of cirrhosis is critical both for the appropriate management of, and to provide prognosis for, patients with chronic hepatitis C infection (CHC). Hepatic biopsy has traditionally been considered the standard procedure to define the stage of fibrosis, although sampling errors and interobserver variability are problems with the technique. The limitations and the invasive nature of liver biopsy has encouraged extensive interest in the development of noninvasive tests to measure LF in patients with CHC. Several noninvasive methods, ranging from serum marker assays to advanced imaging techniques, have been proved to be excellent tools for the evaluation of LF in patients with CHC. Many blood tests have been proposed as alternatives to liver biopsy for identifying fibrosis or cirrhosis. These blood tests are generally classified into direct and indirect markers for hepatic fibrosis. Direct markers are molecules derived from extracellular matrix turnover reflecting the activity of the fibrotic process. Indirect markers reflect alterations in hepatic functions and satisfy the request for a simple and easy to perform markers. Most direct markers are not routinely requested for assessment of liver disease, whereas most indirect markers are routinely used and readily available. Examples of indirect markers include Prothrombin index, platelet count, and aspartate aminotransferase (AST)/alanine transaminase (ALT) ratios.

Egy-Score as a Noninvasive Score for the Assessment of Hepatic Fibrosis in Chronic Hepatitis C: A Preliminary Approach

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ABSTRACT

Background and Aims: Egy-Score is a new noninvasive score for prediction of severe hepatic fibrosis in patients with chronic liver diseases. The aim of this study was to validate Egy-Score as a noninvasive score for predicting stage of hepatic fibrosis in a group of Egyptian chronic hepatitis C patients.

Patients and Methods: One hundred Egyptian patients with chronic hepatitis C were enrolled. Mean age was 40.25 ± 9.39 years. They were subjected to CA19-9, alpha-2-macroglobulin, total bilirubin, platelet count and albumin, liver biopsy, and histopathological staging of hepatic fibrosis according to METAVIR scoring system as part of their assessment for treatment. Egy-Score was calculated according to the following formula: Egy-Score = 3.52 + 0.0063 × CA19-9 + 0.0203 × age + 0.4485 × alpha-2-macroglobulin + 0.0303 × bilirubin – 0.0048 × platelet – 0.0462 × albumin. Egy-Score results were correlated to the stage of hepatic fibrosis.

Results: Egy-Score correlates positively with the stage of hepatic fibrosis (F0–F4). Egy-Score was able to differentiate significant hepatic fibrosis, severe hepatic fibrosis, and cirrhosis accurately. Cutoff values of Egy-Score were 2.91850 (for significant fibrosis), 3.28624 (for severe fibrosis), and 3.67570 (for cirrhosis). Sensitivity, specificity, and areas-under-ROC curve (AUROCs) were 75.8%, 68.42%, and 0.776 (for significant fibrosis “≥F2”), 91.67%, 77.63%, and 0.875 (for severe fibrosis “≥F3”), and 81.82%, 86.52%, and 0.874 (for cirrhosis “F4”), respectively. Conclusion: Egy-Score is a useful noninvasive panel of surrogate biomarkers that could accurately predict different stages of hepatic fibrosis in patients with chronic hepatitis C.

Key words: Biomarkers, cirrhosis, fibrosis, HCV, noninvasive

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aminotransferase (ALT) ratio. Examples of direct markers include collagens (e.g., procollagen I C-peptide, procollagen III N-peptide, type IV collagen and its fragments), glycoproteins and polysaccharides (e.g., hyaluronic acid, laminin, tenascin, YKL-40), collagens and their inhibitors (e.g., metalloproteinases, tissue inhibitors of metalloproteinases), and cytokines (e.g., transforming growth factor-β and platelet-derived growth factor).

Due to poor accuracy of individual markers to assess LF, algorithms, or indices combining panels of markers have been developed. Most commonly used panels include FibroTest, AST-to-platelet ratio index (APRI), FIB-4, FORNS’ index, HepaScore, FibroMeters, FibroIndex, FibroSpect II, and European liver fibrosis index (ELF). These markers are initially developed and validated in CHC patients and are now being applied to other chronic liver diseases. Noninvasive diagnostic approaches are not reliable to discriminate between the intermediate stages of fibrosis. Therefore, we are still in need of new and more accurate biomarkers for assessing hepatic fibrosis. Egy-Score is a relatively new panel of biomarkers used for the assessment of the stage of hepatic fibrosis in patients with chronic liver diseases. It was initially studied in a heterogeneous group of patients (chronic hepatitis C, chronic hepatitis B, and autoimmune hepatitis). Egy-Score is a result of a regression equation based on six parameters (CA19-9, age, alpha-2-macroglobulin, total bilirubin, platelet count, and albumin). Aim of the present study was to assess the performance of Egy-Score in staging hepatic fibrosis in a prospective cohort of Egyptian patients with CHC.

PATIENTS AND METHODS

Patient selection
Hundred treatment-naïve Egyptian patients with CHC were included in our observational study. They were prospectively recruited from Kasr Al-Aini Viral Hepatitis Center, Faculty of Medicine, Cairo University, between May 2011 and December 2012.

Investigations
All patients had positive hepatitis C virus antibody, positive HCV-RNA by PCR, negative ANA, negative HBsAg and HBcAb. Abdominal ultrasound was done for all subjects to assess liver disease and rule out any hepatic or pancreatic lesions.

Liver biopsy
As part of the assessment for treatment eligibility, percutaneous liver biopsies were taken from the right lobe of the liver of all patients using modified Menghini needle under ultrasound guidance. Liver biopsy specimens were fixed with formalin, embedded in paraffin, and stained with hematoxylin and eosin. Liver biopsies were examined by a single pathologist experienced in liver tissue, who was blinded to clinical and biochemical data of patients. All liver biopsy specimens were ≥20 mm in length and containing at least 11 portal tracts. Staging of hepatic fibrosis and grading of necroinflammatory activity was done according to METAVIR scoring system. Fibrosis score was staged on a five-point scale (F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = few septa, F3 = numerous septa without cirrhosis, and F4 = cirrhosis). The activity score was graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, and A3 = severe activity). Significant hepatic fibrosis, severe hepatic fibrosis, and cirrhosis were defined as a fibrosis stage ≥F2, ≥F3, and F4, respectively.

Egy-Score calculation
Patients’ sera were analyzed for (CA19-9, age, alpha-2-macroglobulin, total bilirubin, platelet count, and albumin) in the same day of performing liver biopsy. Egy-Score was calculated according to the original formula [1]: Egy-Score = 3.52 + 0.0063 × CA19-9 (U/mL) + 0.0203 × age (year) + 0.4485 × alpha-2-macroglobulin (g/L) + 0.0303 × bilirubin (µmol/L) - 0.0048 × platelet (K/µL) - 0.0462 × albumin (g/L).

Consent and ethical aspects
Informed written consent from each patient and local ethical committee approval were available before starting data collection. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis
Analysis of data was performed using SPSS 17 (Statistical Package for Scientific Studies) for Windows. Description of categorical variables was summarized by frequency counts and percentages. Continuous variables were summarized by means, medians, and standard deviations. Binary correlation was carried out by Spearman correlation test. Results were expressed in the form of correlation coefficient (r) and P values. Receiver-operating characteristic (ROC) curves were graphed to determine appropriate Egy-Score levels in predicting significant hepatic fibrosis (≥F2 METAVIR), severe hepatic fibrosis (≥F3 METAVIR), and cirrhosis (F4 METAVIR) that give optimal sensitivity, specificity, and positive and negative predictive values. All the hypotheses tested were two-sided and statistical significance was accepted at the 5% level.

RESULTS
Our study included 100 treatment-naïve patients with chronic hepatitis C; 67 males and 33 females; their mean age ± SD was 40.25 ± 9.39. The mean values ± SD of the studied parameters were albumin, 41.89 ± 4.95 g/L; total bilirubin,
Noninvasive methods for assessment of hepatic fibrosis in CHC are growing and becoming more popular, especially with the development of more effective oral interferon-free regimens. The most important stages of hepatic fibrosis on which clinicians base their decisions for management of CHC patients are significant fibrosis and cirrhosis. In this study, we validated a relatively new panel of biomarkers which clinicians base their decisions for management of CHC patients are significant fibrosis and cirrhosis. In this study, we validated a relatively new panel of biomarkers study population. 

### Table 1: General characteristics of the study population

| Variable          | Mean±SD       | Median |
|-------------------|---------------|--------|
| Age (year)        | 40.25±9.39    | 42     |
| Gender n,% (%)    |               |        |
| Males             | 67 (67)       | -      |
| Females           | 33 (33)       | -      |
| Albumin (g/L)     | 41.89±4.95    | 41.50  |
| Total Bilirubin (μmol/l) | 13.89±3.60 | 13.68  |
| Platelets count (10^9/L) | 201.58±59.02 | 196.50 |
| Alpha-2-macroglobulin (g/L) | 2.57±0.54 | 2.61   |
| CA 19.9 (U/mL)    | 15.07±16.64   | 11.45  |

SD: Standard deviation, CA: Cancer antigen

### Table 2: Cutoff values of Egy-Score for detection of significant hepatic fibrosis (≥F2)

| Cutoff value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|--------------|-----------------|-----------------|---------|---------|
| 2.71045      | 80.60           | 50.00           | 72.46   | 61.29   |
| 2.91850      | 75.80           | 68.42           | 79.66   | 63.41   |
| 3.03698      | 72.60           | 68.42           | 78.96   | 60.47   |

PPV: Positive predictive value, NPV: Negative predictive value

### Table 3: Cutoff values of Egy-Score for detection of severe hepatic fibrosis (≥F3)

| Cutoff value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|--------------|-----------------|-----------------|---------|---------|
| 3.28624      | 91.67           | 77.63           | 56.41   | 96.72   |
| 3.31874      | 87.50           | 77.63           | 55.26   | 95.16   |
| 3.03698      | 100.00          | 56.58           | 42.11   | 100.00  |
| 3.07885      | 95.83           | 59.21           | 42.59   | 97.83   |

PPV: Positive predictive value, NPV: Negative predictive value

### Table 4: Cutoff values of Egy-Score for detection of cirrhosis (F4)

| Cutoff value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|--------------|-----------------|-----------------|---------|---------|
| 3.51298      | 81.82           | 79.78           | 33.33   | 97.26   |
| 3.67570      | 81.82           | 86.52           | 42.86   | 97.47   |

PPV: Positive predictive value, NPV: Negative predictive value
CONCLUSION

Egy-Score showed good sensitivity, specificity, positive and negative predictive values, and over all accuracy for detecting different stages of hepatic fibrosis and cirrhosis in patients with chronic hepatitis C.

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Figure 1: Receiver–operating curve for Egy-Score for detection of significant hepatic fibrosis (≥F2)

Figure 2: Receiver–operating curve for Egy-Score for detection of severe hepatic fibrosis (≥F3)

Figure 3: Receiver–operating curve for Egy-Score for detection of severe hepatic fibrosis (F4)
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