Validation of the Endometriosis Fertility Index (EFI) in Infertile Filipino Women with Laparoscopically-diagnosed Endometriosis: a Preliminary Study

Ma. Isidora Margarita Yap-Garcia, MD and Delfin A. Tan, MD, FPSREI
Department of Obstetrics and Gynecology, St. Luke's Medical Center

Objective: To validate the EFI, a clinical tool that predicts the possibility of pregnancy in Filipino women with laparoscopically-diagnosed endometriosis-associated infertility.
Design: Retrospective cohort
Setting: St. Luke's Medical Center
Patients: One hundred twenty-two infertile women with laparoscopically-diagnosed endometriosis.
Methodology: Subjects were scored using the Endometriosis Fertility Index (EFI). Pregnancy rates were determined separately. Discriminative capacity of the EFI was assessed by Receiver Operator Characteristic (ROC) analysis. Sensitivity, specificity, positive and negative predictive values of the test at different thresholds were determined. Correlation of EFI scores and pregnancy rates was determined by logistic regression analysis.
Main outcome measures: EFI scores, pregnancy rates, ROC curve, Area under the curve (AUC), sensitivity, specificity, positive and negative predictive values, Logistic fit of pregnancy vs. EFI scores.
Results: Twenty-two pregnancies occurred during the 12-month period with 13 pregnancies occurring within the first six months. Over-all pregnancy rate was 18.3%. The ROC curve straddled the line and showed an AUC of 67%. The sensitivity and specificity of the EFI for each threshold showed increasing sensitivity with lower scores and higher specificity with higher scores. Positive predictive values (PPV) were low, but Negative predictive values (NPVs) were high. Logistic regression analysis showed a good correlation between EFI scores and pregnancy ($P < 0.05$).
Conclusions: The individual scores correlate well with the chances of pregnancy and the negative predictive value of the test is high. This index is a newly validated, simple clinical tool that can predict pregnancy in infertile women with endometriosis. The discrimination capability of the EFI needs further analysis.

Key words: Endometriosis Fertility Index (EFI), endometriosis, infertility, laparoscopy, pregnancy rates

Introduction

Endometriosis is a benign disease defined by the presence of endometrial glands and stroma outside of the uterus.[1] Patients with endometriosis typically present with either pain or infertility.[2,18] Local statistics on the incidence and prevalence of endometriosis are limited. However, according to US data, endometriosis affects 6 to 10 percent of women of reproductive age, 50 to 60 percent of women and teenage girls with pelvic pain, and up to 50 percent of women with infertility.[3] It is estimated that about 30 -50 percent of patients with endometriosis have some degree of infertility[6,4] and the pregnancy rate (within 3 years) for untreated patients diagnosed with endometriosis is very low (17.7%)[5,6]

In post-laparoscopy patients with endometriosis, a large proportion of pregnancies (69%) occur within 6 months of operation. Within 12 months, another significant proportion of patients (23%) is expected to get pregnant.[7] This period represents a window of opportunity where treatment of infertility may be most beneficial. This emphasizes the urgency to detect patients with poor prognosis so that treatment will be instituted as soon as possible.

In a large series of 2,080 women with infertility, a significant proportion of women (60.7%) were diagnosed with endometriosis by laparoscopy.[8,9] At face value, this suggests a relationship between endometriosis and infertility. However, more in-depth analysis reveals that there may be higher than actual reporting of endometriosis in infertility patients because of increased laparoscopic surveillance in this subset.[10] As a result, the true incidence of endometriosis-related infertility is difficult to assess. These issues underscore the difficulty of accurate and adequate reporting.

Aside from difficulty in determining the true burden of disease, a more pressing issue in the study of endometriosis is prognostication of fertility[23]. There have been numerous attempts to correlate surgical findings with fertility outcomes but not one scoring system has proven to be an accurate gauge of the fertility potential of an individual.[11,12,13,14] Inadequate prediction of subsequent pregnancy and poor reproducibility have been the major points against the usefulness of current classification systems.[12,15]

In 1979, the American Fertility Society (AFS) (now the American Society for Reproductive Medicine, or ASRM) devised a classification system for surgically managed endometriosis.[16] Concern regarding the inability of this classification to discriminate between mild, moderate and severe disease in terms of pregnancy outcome is related to arbitrary assignment of scores for each pathologic observation and its nominal assignment of severity categories.[11] The last revision in 1996 aimed to correct this by evaluating the dose-response relationship of the scoring system and pregnancy after treatment.[17] The ASRM classification system proved to be inadequate for prognostication purposes but has considerable value in terms of standardizing documentation of disease extent and morphologic findings.[10,11,16] For lack of any other recognized classification scheme, this is still the most widely used staging system for endometriosis. However, other than providing a uniform system of reporting, the ASRM classification has limited clinical application.

Aside from its impact on fertility and quality of life, the economic burden of endometriosis with respect to infertility is considerable, albeit underestimated.[18] Like any other disease, a universal language in reporting the diagnosis, clinical presentation and severity is necessary to generate data for research application, with the intent to ameliorate the consequences of the disease. Furthermore, it allows the physician and the couple to make timely, well-informed decisions. This is the driving force behind continuing efforts to develop a scoring system that has both descriptive and prognostic power. Its use may provide reassurance for patients with good prognoses and avoids wasted time and resources for those with poor prognoses.[4,18]

In 2010, a clinical tool was developed that endeavored to predict pregnancy rates (PR) in patients with surgically documented endometriosis who attempt non-IVF (in-vitro fertilization) conception. Scores were derived from historical and surgical data while incorporating the existing ASRM classification system. Another innovative aspect of this scoring system is the Least Function Score (LFS) which was found to have predictive power even after controlling for the ASRM score and the number of years of infertility (Figure 1).[18] The EFI has been validated by the same group that created it. It is their recommendation that the scoring system be validated by other clinical investigators. Since predictive models always perform better on data on which they were generated than on new data, external validation is essential before implementing predictive models in clinical practice. External validation will determine the veracity of results if the tool proves to be reproducible and reliable despite differences in race and nuances in clinical practice. Successful validation will in turn encourage widespread use to the benefit of our patients.

Objectives

General

To validate among Filipino women the Endometriosis Fertility Index (EFI), a clinical tool that predicts the possibility of pregnancy in women with endometriosis-associated infertility.

Specific

To determine the capacity of the EFI to discriminating patients with a good chance of pregnancy with those with a poor probability of pregnancy (after laparoscopic surgery for endometriosis) using Receiver Operation Characteristic (ROC) analysis.

To interpret the EFI score using sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV).

To determine if a correlation exists between the EFI score and possibility of pregnancy in Filipino women with endometriosis-related infertility.

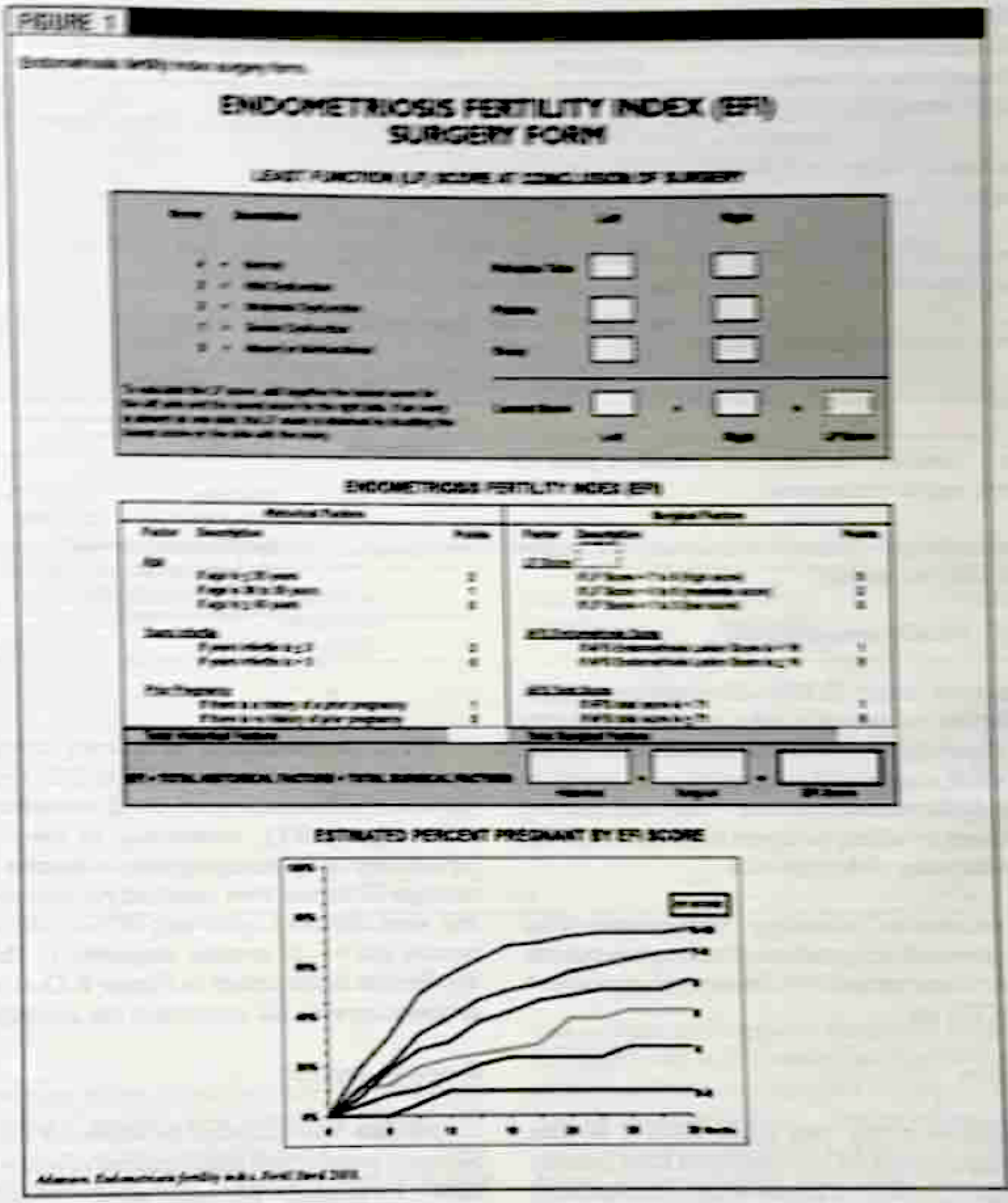

Figure 1. Endometriosis fertility index surgery form.

Materials and Methods

Study design: Retrospective cohort

Subjects:

Inclusion criteria:

1. Reproductive-age women less than 43 years old
2. Patients who underwent laparoscopic surgery at SLMC, Q.C. from January 1, 2008 to April 30, 2011
3. Patients with surgically documented endometriosis
4. Patients diagnosed with infertility

Exclusion criteria:

1. Patients with other untreated pelvic pathologies known to impair fertility:

a. Pelvic inflammatory disease
b. Submucous myoma
c. Intrauterine adhesions
d. Endometrial polyps > 1 cm

2. Patients with ambiguous or incomplete intra-operative findings

3. Patients who used any form of contraception post-operatively

4. Patients who were lost to follow-up.

Definitions

Infertility – Inability to conceive despite 1 year of unprotected, regular intercourse.

Pelvic Endometriosis – Presence of endometriotic lesions visualized laparoscopically.

Pregnancy – Positive pregnancy test

Least function score (LFS) –Parameters include functionality of the fallopian tube or fimbria or ovary (Figure 2, Figure 3). A score of 4 is assigned for a normal structure while a score of 0 is assigned to an absent or completely dysfunctional structure.[18] The least function score is obtained by adding the lowest score for the left side and the lowest score of the right side.

Assisted Reproductive Technology – Manipulation of the ovum and sperm cell and products of conception outside of the uterus. These include IVF, Intracytoplasmic sperm injection (ICSI), etc.[1]

Data Collection

One hundred ninety two (192) infertile women underwent laparoscopy for endometriosis from January 1, 2008 to April 30, 2011. Patients were excluded based on the criteria stated above and total of 122 patients were included in the study. Data were collected using items patterned after the Endometriosis Fertility Index (EFI) surgery form[19] which include 3 historical and 3 surgical items (Figure 1). The patients' obstetrical score was noted. Demographic characteristics and pregnancy rates were tabulated (Table 1). Surgical assessment was carried out by viewing available videos and scoring was done by a single individual, experienced in laparoscopic surgery. Pregnancies occurring postoperatively were not known to the scorer. For patients whose videos were not available, surgical score was gathered from the detailed operative records. Those with incomplete or ambiguous findings were excluded from the study.

Table 1. Demographic characterstics of the study population.

Total patients = 122			
Mean Age	33.7 ± 0.4		
	> 35 years	64%	
	≤34 years	36%	
Years Infertility	5.1 ± 0.31		
Nulligravid	90 (74%)		
Primigravid/ multigravid	32 (26%)		
Pregnancy rate	6 months	13 (10.7%)	
	12 months	22 (18%)	
	Spontaneous pregnancies		13 (59%)
	Via Intrauterine insemination		4 (27%)
	Via ART (IVF-ICSI)		5 (22.7%%)

Data on subsequent pregnancy were retrieved separately, after determination of the EFI. Data included the patient's obstetrical score, use of assisted reproductive technology (ART), occurrence of pregnancy after laparoscopy, and time to pregnancy in months. Pregnancy rates per EFI score were stratified per time to pregnancy and were classified under one of two categories: 0 - 6 months and >6 - 12 months, respectively. The graphical distribution is illustrated in Figure 2. Outcomes of the pregnancies were not included in the analysis.

Statistical Analysis

All data were encoded in Microsoft Excel format. Means of populations were reported as mean ± standard error. Pregnancies per score were reported in actual numbers and proportions were tabulated (Table 2). Pregnancy rates were plotted against the time to pregnancy (0, 6 and 12 months) per EFI score (Figure 2)

The Receiver Operation Characteristic (ROC) curve analysis was done to determine the discriminative value of the EFI. From this curve, the sensitivities, specificities, PPV and NPV were determined for each score (Table 3). Logistic regression analysis was performed to determine the statistical relationship between the EFI score and occurrence of pregnancy. Statistical Package for the Social Sciences (SPSS) ver. 17.0 software was used for statistical analysis.

   a. Pelvic inflammatory disease
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Descriptions of least function terms.

Structure	Dysfunction	Description
Tube	Mild	Slight injury to serosa of the fallopian tube
	Moderate	Moderate injury to serosa or muscularis of the fallopian tube; moderate limitation in mobility
	Severe	Fallopian tube fibrosis or mild/moderate salpingitis isthmica nodosa; severe limitation in mobility
	Nonfunctional	Complete tubal obstruction, extensive fibrosis or salpingitis isthmica nodosa
Fimbria	Mild	Slight injury to fimbria with minimal scarring
	Moderate	Moderate injury to fimbria, with moderate scarring, moderate loss of fimbrial architecture and minimal intrafimbrial fibrosis
	Severe	Severe injury to fimbria, with severe scarring, severe loss of fimbrial architecture and moderate intrafimbrial fibrosis
	Nonfunctional	Severe injury to fimbria, with extensive scarring, complete loss of fimbrial architecture, complete tubal occlusion or hydrosalpinx
Ovary	Mild	Normal or almost normal ovarian size; minimal or mild injury to ovarian serosa
	Moderate	Ovarian size reduced by one-third or more; moderate injury to ovarian surface
	Severe	Ovarian size reduced by two-thirds or more; severe injury to ovarian surface
	Nonfunctional	Ovary absent or completely encased in adhesions

Adamson. Endometriosis fertility index. Fertil Steril 2010.

Figure 2. Description of the components of the least function score (LFS).

Table 2. Distribution of patients and frequency of pregnancy per EFI score.

EFI score	Distribution of patients	Number of pregnancies at 6 months	% pregnant at 6 months	Number of pregnancies at 12 months	% pregnant at 12 months
0-3	28	1	3.571429	1	3.571429
4	18	1	5.555556	2	11.11111
5	16	2	12.5	4	25
6	23	5	21.73913	6	26.08696
7	20	3	15	4	20
8	9	0	0	2	22.22222
9-10	8	1	12.5	3	37.5
TOTAL	122	13	n/a	22	n/a

Results

The mean age of the 122 subjects was 33.7 ± 0.4 years. Majority (64%) of patients were older than 35 years old. The mean number of years infertile was 5.1 ± 0.31. Most patients (66.4%) underwent surgery within this time period. Thirty-two patients (26%) had prior pregnancies. Pregnancies occurred spontaneously in 59% of patients, via intrauterine insemination in 27% and via ART in 22.7% (Table 1).

Majority of the pregnancies occurred within 6 months of the operation. No additional pregnancies were observed after 12 months (Table 2). The least pregnancies occurred with an EFI score of 0 to 3, similarly the largest overall pregnancy rates were noted with a score of 9-10.

To determine the ability of the EFI tool to predict pregnancy, the ROC curve was generated for the study population (Figure 3). Model sensitivity, specificity, and positive and negative likelihood ratios were also calculated, and the best model cut-off point was considered to be one that corresponded to the highest sum of specificity and sensitivity. The cut-off value for the EFI score was determined to be 4. This is the statistical value where few pregnancies were observed. EFI scores ≤ 4 were designated as a "negative" test. Consequently, values >4 were designated as a "positive" test. Sensitivity was 87.5%, specificity was 43.9%, PPV was 27.6 and NPV was 7.0. Individual analysis of the different scores generated varying degrees of sensitivity, specificity, PPVs and NPVs (Table 3). Sensitivities were highest with low EFI scores. Conversely, the specificity increased with increasing scores. Positive predictive values were generally low but very high negative predictive values were observed.

Logistic regression analysis showed a statistically significant ($P < 0.05$, $P = 0.0103$) correlation between EFI scores and pregnancy rates up to 12 months post-operatively. The pregnancy rates generated from the data were tabulated per EFI score (Table 4).

Table 3. Accuracy of EFI in predicting pregnancy.

EFI score threshold	Sensitivity	Specificity	PPV	NPV
0-3	95%	27%	22.3%	96.4%
4	86.4%	43%	25%	93.4%
5	68%	55%	25%	88.7%
6	45.5%	72%	26.3%	85.7%
7	22.7%	88%	29.4%	83.8%
8	13.6%	95%	37.5%	83.3%

Table 4. Predicted pregnancy rates derived from the ROC curve.

EFI score	Prob pregnancy
0	4.490%
1	5.931%
2	7.798%
3	10.188%
4	13.207%
5	16.950%
6	21.492%
7	26.858%
8	33.000%
9	39.783%
10	46.982%

Discussion

Endometriosis appears as prevalent among Asian women as Caucasians, and may even be more common.[20] Some data even go as far as showing that an Asian ethnicity may increase the likelihood of endometriosis by more than eight-fold.[21] This underscores the need to accurately diagnose and predict outcomes in our patients. These data must be derived from regionally derived studies, such as this, that endeavor to provide clinical guidelines relevant to the particular needs of Asian women. This will enable us to transcend race and culture differences when using available tools generated from Western data.

To simplify the validity analysis, the EFI was treated much like a diagnostic test of pregnancy. Sensitivity, specificity and predictive values were determined using the ROC curve that was generated from the study population which concurred with the published estimates of pregnancy from the original population (Figure 3). The ROC is a graphical plot which illustrates the performance of a binary classifier system as its discrimination threshold is varied.[22] In this case, the ROC curve displays the relationship between sensitivity and specificity and the area under the ROC curve (AUC) depicts how well the model distinguishes women with and without pregnancy, a model with a greater AUC has a better-performing distinguishing function. In this population, the most discriminating score (meaning the highest combination of sensitivity and specificity) corresponds with the EFI score of 4 which confers an estimated percent pregnant of 27.7% while scores above 4 showed an estimated percent pregnant of 42.2 % (Table 4). Clinically, however, knowledge of this cut-off value has little application.

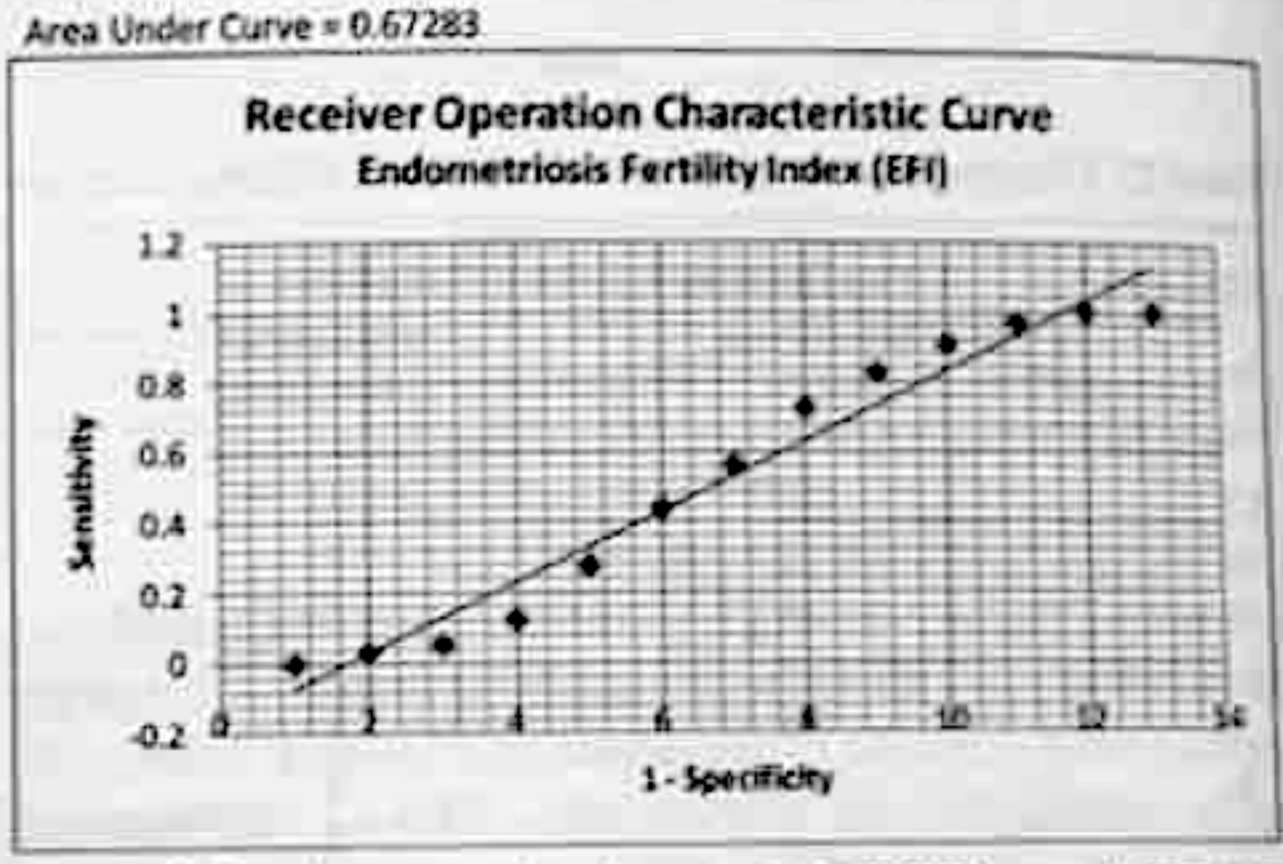


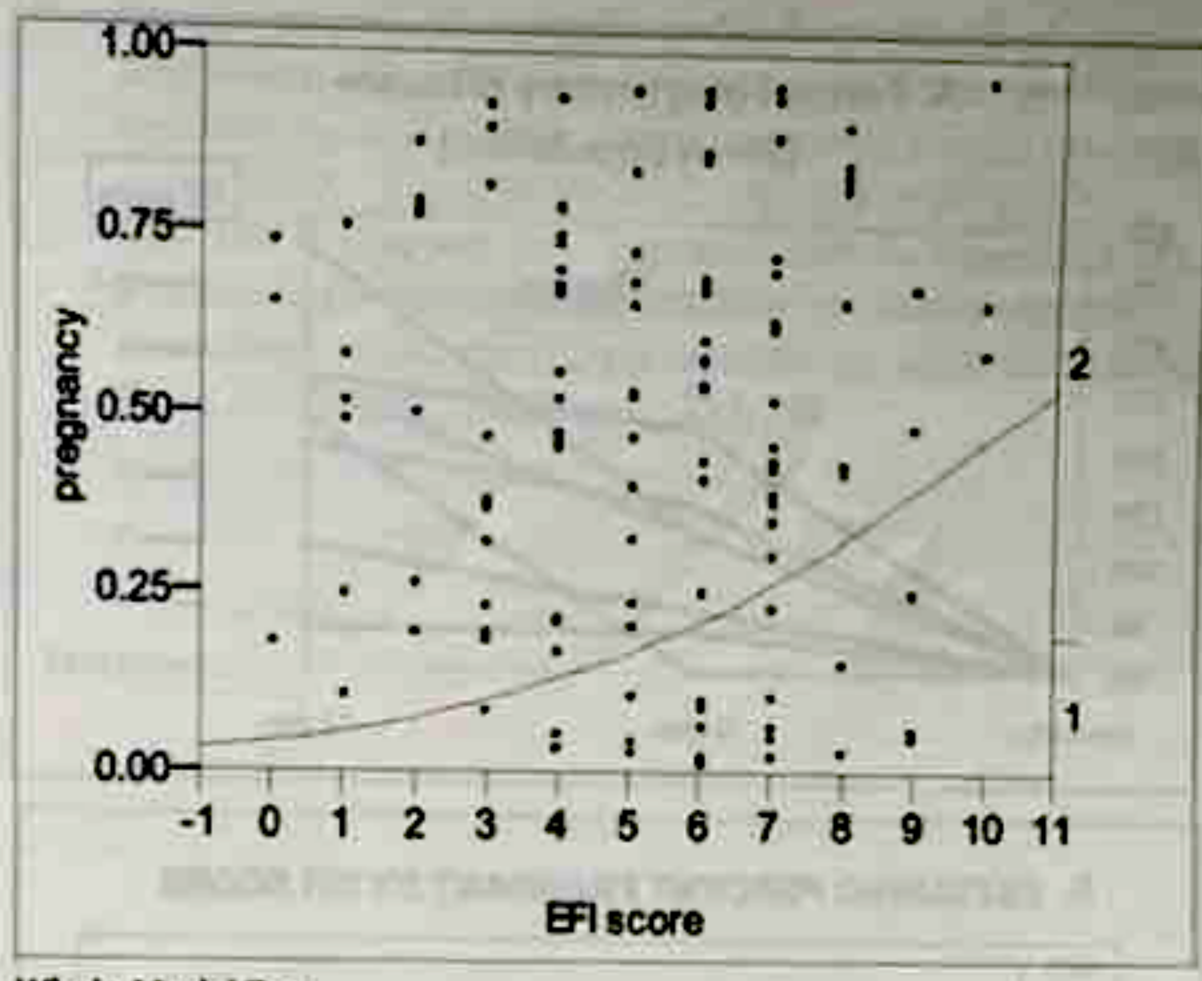
Figure 3. Receiver operating characteristic (ROC) curve, Pregnancy = '1' as positive level.

Instead, the analysis focuses on the characteristics of the curve. ROC curve in this population straddles the diagonal line (Figure 3) and the AUC (0.672), at face value, seems low. ROC analysis presumes to express the capacity to distinguish between pregnancy and non-pregnancy. However, even the couples with a very good prognosis (for example, pregnancy chance 30%) have a large chance of not getting pregnant. So even if the model could distinguish perfectly between couples with a 5% pregnancy chance and couples with a 30% pregnancy chance, the area under the ROC curve would maximally be 0.71.[23] This could explain the low value of the AUC in this case. Moreover, in the original study, patients were followed up for a total of 36 months. In this preliminary study, data were collected up to only 12 months post-operatively. Data collected for 36 months will be included in subsequent analysis and the ultimate discriminatory power of the test has yet to be analyzed. Perhaps factoring in these data will derive a more meaningful ROC analysis.

In the meantime, validity of the tool can be analyzed by looking at the predictive value of the test. Since the predictive values were derived from the ROC curve, it follows that the positive predictive values may turn out to be low. This was demonstrated in this study (Table 3). High negative predictive values were demonstrated across all thresholds. The implication of these results is that a high EFI score does not categorically mean that a patient has a high probability of pregnancy; but it can tell you that for low EFI values, the probability of pregnancy is indeed low. This can be interpreted by the clinician as a reason to be more aggressive in infertility treatment despite high scores.

However, the occurrence of low PPVs, much like the low AUC, is subject to further analysis. An inherent limitation in the PPV is that its value is subject to the over-all prevalence of the "disease" [21] – in this case pregnancy. Since the over-all prevalence is low, the PPV will also be low. This should temper the clinician when he or she advises a couple of poor prognosis.

Another means to determine the validity of the EFI is to find out if increasing scores correlate well with pregnancy rates. Logistic regression analysis showed a good, statistically significant, correlation between the EFI score and pregnancy rate ($P = 0.0105$, $P<0.05$) (Figure 4). The pregnancy rate for each given score, derived from this graph, is shown in Table 4. Clinically, this is a useful tool because it gives us concrete values for pregnancy rates post-operatively. This allows the clinician and the couple to make better decisions regarding their fertility treatment.



Whole Model Test

Model	-LogLikelihood	DF	ChiSquare	Prob>ChiSq
Difference	3.731999	1	7.463998	0.0063
Full	56.758463			
Reduced	60.490463			

RSquare (U)	0.0617
Observations (or Sum Wgts)	122

Converged by Gradient

Parameter Estimates

Term	Estimate	Std Error	ChiSquare	Prob>ChiSq
Intercept	-3.0574472	0.7277404	17.65	<.0001
EFI score	0.29358705	0.1144251	6.58	0.0103

For log odds of 1/2

Figure 4. Logistic fit of pregnancy by EFI score.

Conclusion

This index is a newly validated, simple clinical tool that can predict pregnancy in infertile women with laparoscopically diagnosed endometriosis. Through logistic regression analysis, it was demonstrated that the individual scores correlate well with the chances of pregnancy. In general, the PPVs are low but when, taken into perspective, may be useful clinically. The negative predictive value of the test is high hence patients with low scores have low probability of achieving pregnancy.

The ability of the EFI to discriminate between those with a good chance of pregnancy and those who have a poor chance after laparoscopy for endometriosis needs further prospective analysis.

Recommendations

The lowest overall pregnancy rates were found for scores ranging from 0 – 3. Similarly, the highest pregnancy rates were noted in the subset with a score of 9 – 10. In this study, higher pregnancy rates were observed for EFI scores of 5 and 6 than a score of 7 and 8 (Figure 5). This difference may be reflective of the smaller sample size of the test population compared to the original study. To illustrate the distribution of the scores, a graphical picture was interposed upon the original study distribution (Figure 6) – this was likewise done in the original validation study.

Visually, there seems to be a correlation between the results of the original population and this study's population. Correlation and goodness of fit may be used to determine if the EFI is subject to inter-observer variability. Confirmation of this correlation entails further analysis of the characteristics of both patient populations. Since the investigators of this study were not privy to the data generated from the original population, analysis of goodness of fit or homogeneity between the two models, while useful, was not possible and was deemed beyond the scope of this study.

The EFI is a new scoring system that may prove to be a very useful tool for clinicians. The proponents of the EFI recommend further prospective validation. Since the EFI was only introduced in October 2010, a serious

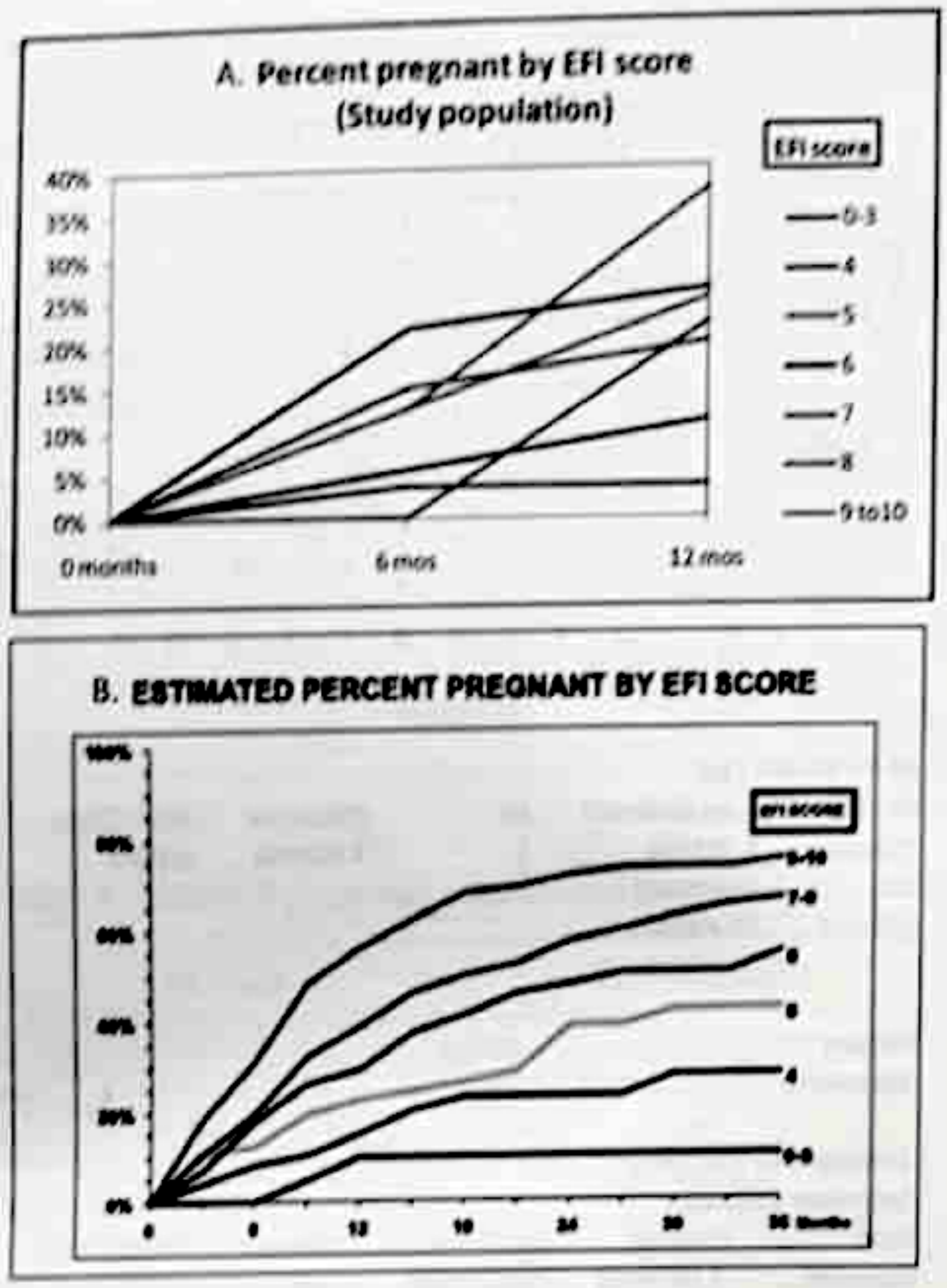


Figure 5. Distribution of pregnancy rates vs EFI score (A. Study population, B. Original population).

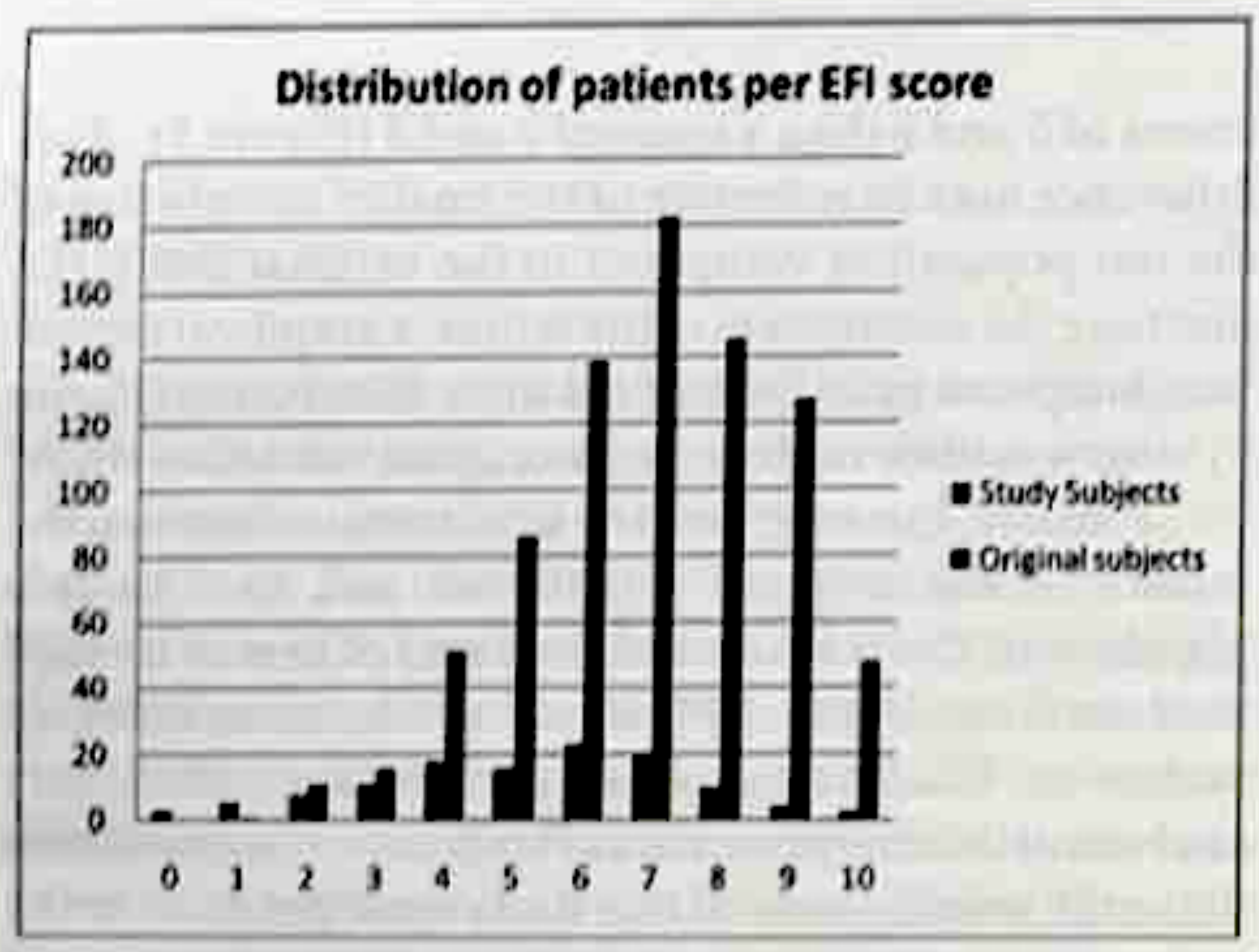


Figure 6. Comparison of distribution of subjects per EFI score.

limitation for validation is that prospective validation may take years to complete. This will render the EFI useless for the time being. Circumventing this limitation was the impetus for doing a retrospective analysis which rewarded us with significant results. However, some subjects need to be followed up to complete the 36 month period observation prescribed by the original study. Once the data are complete, the true discriminative power and prognostic capacity of the tool will be elucidated.

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