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Algorithms for Predicting the Probability of Azoospermia from Follicle Stimulating Hormone: Design and Multi-Institutional External Validation

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Purpose: To predict the probability of azoospermia without a semen analysis in men presenting with infertility by developing an azoospermia prediction model.

Materials and Methods: Two predictive algorithms were generated, one with follicle stimulating hormone (FSH) as the only input and another logistic regression (LR) model with additional clinical inputs of age, luteinizing hormone, total testosterone, and bilateral testis volume. Men presenting between 01/2016 and 03/2020 with semen analyses, testicular ochiodemetry, and serum gonadotropin measurements collected within 120 days were included. An azoospermia prediction model was developed with multi-institutional two-fold external validation from tertiary urologic infertility clinics in Chicago, Miami, and Milan.

Results: Total 3,497 participants were included (n=Miami 946, Milan 1,955, Chicago 596). Incidence of azoospermia in Miami, Milan, and Chicago was 13.8%, 23.8%, and 32.0%, respectively. Predictive algorithms were generated with Miami data. On Milan external validation, the LR and quadratic FSH models both demonstrated good discrimination with areas under the receiver-operating-characteristic (ROC) curve (AUC) of 0.79 and 0.78, respectively. Data from Chicago performed with AUCs of 0.71 for the FSH only model and 0.72 for LR. Correlation between the quadratic FSH model and LR model was 0.95 with Milan and 0.92 with Chicago data.

Conclusions: We present and validate algorithms to predict the probability of azoospermia. The ability to predict the probability of azoospermia without a semen analysis is useful when there are logistical hurdles in obtaining a semen analysis or for reevaluation prior to surgical sperm extraction.

Keywords: Azoospermia; Follicle stimulating hormone; Inftertility; Models, statistical; Semen analysis

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INTRODUCTION

Accurate prediction of azoospermia risk without semen analysis would be a useful clinical tool, especially when barriers in obtaining a traditional semen analysis exist or for reevaluation prior to surgical sperm extraction. Semen testing can carry significant personal, social, and cultural stigma [1,2]. There has been rapid adoption of at-home sperm test kits. The utility of these at home kits will likely continue to increase with the expansion of telemedicine in the post-COVID-19 era. There are limitations to these tests. Presently, they cannot replace a World Health Organization (WHO)-quality semen analysis [3]. When an at home analyses shows oligospermia or other subfertile findings, a repeated traditional semen analysis is warranted. However, in the era of at-home semen analysis, there may be an expanded role of other relevant clinical factors such as age, gonadotropin levels, and orchidometry to validate when an at-home test shows azoospermia.

Other times, patients may be subjected to too frequent analyses. Young adolescents with Klinefelter syndrome provide yearly semen analyses for potential fertility preservation regardless of clinical characteristics. Similarly, in men actively seeking fertility, even after two semen analyses have confirmed azoospermia infertility specialists may be compelled to complete an extended semen analysis prior to testicular sperm extraction (TESE) to find rare sperm in the ejaculate [4]. The time and the manpower involved to do a comprehensive sperm search in the ejaculate can be arduous. There may be an expanded role of other relevant clinical factors to inform when to forgo extended semen analysis and proceed directly to micro-TESE.

While the relationships between relevant clinical factors of age, gonadotropin levels, and orchidometry with semen parameters are well described [5,6], the ability to determine the probability of azoospermia irrespective of semen analysis is not yet part of the infertility specialist's tool-box [7]. We sought to develop and validate models to predict the probability of azoospermia based on clinical parameters and serum follicle stimulating hormone (FSH) alone in the male infertility population.

MATERIALS AND METHODS

1. Ethics statement

This study's protocol and methodology was reviewed and approved by the Institutional Review Board of the University of Miami (approval number: 20170849). Informed consent waived by the board.

2. Study population and data collection

We reviewed data from three prospectively maintained semen analysis databases from male infertility clinics in Chicago (IL), Miami (FL), USA, and Milan, Italy, between January 2016 and March 2020. Age at semen collection, sperm concentration, FSH, luteinizing hormone (LH), total testosterone (TT), and bilateral testis volume (Miami and Milan data were estimated using a Prader orchidometer and Chicago data by testicular ultrasound) were extracted from the database. Hormone levels were measured by validated chromatography, chemiluminescence and spectrometry assays with variation coefficients below 5%. Measured hormonal and volume values were compared to reference limits of 1.8 to 8.6 IU/L for LH, 1.5 to 7.6 IU/L for FSH, 264 and 916 ng/dL for TT, and 12.5 to 19 cm^3 for bilateral testis volume [8,9]. Azoospermia was confirmed on at least two semen analyses in every case. When men had more than one semen analysis, means were used to calculate sperm parameters. Only paired sperm concentration and clinical data collected within 120 days of semen analysis were included. Men with a surgical history of vasectomy, Y chromosome microdeletion, and men with solitary testis (any reason) were excluded. Additionally, data from men who used testosterone therapy or anabolic steroids in the 120 days prior to semen analysis were excluded. Sperm and hormone data from men with diagnoses of Klinefelter syndrome and from men using medications such as clomiphene, anastrozole, and human chorionic gonadotropin were included. Missing LH, TT, and testis volume data never accounted for greater than 15% of occurrences of each variable. Missing data were imputed through the median. Multiple semen analysis and hormone data sets were included from the same individual if all data points were collected greater than 120 days apart. All data was collected under the University of Miami IRB, with the appropriate multi-institutional data sharing agreements.

3. Data analysis

After the determination of data distribution between men with sperm in the ejaculate and those with azoospermia, medians, and interquartile ranges (IQR;

25%–75%) of independent variables were reported based on relevant clinical ranges by site. Multivariable-adjusted logistic regression analysis was performed from Miami data to determine the risk of azoospermia. Stastistical analysis was perfomed using R program (R Core Team, 2020, Auckland, New Zealand). A p-value <0.05 was considered statistically significant.

4. Probabilistic modeling

Prediction models were built using data from Miami and two-fold externally validated with Chicago and Milan data sets. To determine the probability of azoospermia given FSH alone, data was binned by FSH values. FSH intervals were set to ensure greater than 20 samples per data bin. Probability was determined from the quotient of binned FSH data (number of azoospermic samples divided by the total number of samples). A second order polynomial regression, quadratic model, was set to these data to predict the probability of azoospermia given serum FSH.

For comparison, we developed a logistic regression model with continuous clinical data: age, FSH, LH, TT, and mean testis volume. Logistic regression coefficients were used to generate probabilities of azoospermia where probability=$1/\exp[-(b_0 + b_i*X_i)]$.

To validate and assess the performance of each prediction model the Pearson correlation coefficient, Receiver-operating characteristic (ROC) curves, and calibration plots were calculated. The Pearson correlation coefficient determines how similar each model prediction is and the area under the ROC curve (AUC) quantifies the ability of each model to correctly identify azoospermia from clinical data. Calibration plots, using 200 k-fold cross-validation, define how well the predicted probabilities match the actual probability of azoospermia. All analysis was performed in R version 4.0.0.

RESULTS

A total of 3,497 paired semen and hormonal evaluation samples were included in the analysis (n=Miami 946, Milan 1,955, Chicago 596). The median age at time of semen analysis was 36 years (IQR, 32–40 y). Median sperm concentration was 7.6 mil/mL (IQR, 0.2–23.8 mil/mL). The incidence of azoospermia in Miami, Milan,

Table 1. Data distribution between three clinical sites

Variable	Miami	Milan	Chicago	Total
Number of samples	946	1,955	596	3,497
Age (y)	35 (30–40)	37 (33–41)	35 (32–39)	36 (32–40)
Sperm concentration (mil/mL)	13.0 (1.3–22.0)	6.0 (0.1–25.0)	4.0 (0.0–25.3)	7.6 (0.2–23.8)
Azoospermic	131 (13.8)	465 (23.8)	191 (32.0)	787 (22.5)
FSH (IU/L)	5.1 (3.3–8.7)	5.7 (3.4–11.3)	6.4 (3.9–12.2)	5.7 (3.4–10.6)
Normal (1.5–7.6)	608 (64.3)	1,453 (74.3)	334 (56.0)	2,395 (68.5)
Low (<1.5)	51 (5.4)	54 (2.8)	16 (2.7)	121 (3.5)
High (>7.6)	287 (30.3)	448 (22.9)	246 (41.3)	981 (28.1)
LH (IU/L)	4.6 (3.3–6.1)	4.3 (3.1–6.1)	4.6 (3.4–6.8)	4.5 (3.1–6.2)
Normal (1.7–8.6)	794 (83.9)	1,648 (84.3)	486 (81.5)	2,938 (83.7)
Low (<1.7)	58 (6.1)	96 (4.9)	23 (3.9)	177 (5.1)
High (>8.6)	94 (9.9)	211 (10.8)	87 (14.6)	392 (11.2)
TT (ng/dL)	401 (301–529)	457 (351–578)	362 (263–487)	429 (320–547)
Normal (300–1,000)	694 (73.4)	1,642 (84.0)	385 (64.6)	2,721 (77.8)
Low (<300)	234 (24.7)	292 (14.9)	205 (34.4)	731 (20.9)
High (>1,000)	18 (1.9)	21 (1.1)	6 (1.0)	45 (1.3)
Mean testis size (cm^3)	14 (12–16)	15 (12–20)	14.8 (10.1–17.4)	15 (12–18)
Normal (12.5–19)	534 (56.4)	885 (45.3)	253 (42.4)	1,672 (47.8)
Small (<12.5)	321 (33.9)	505 (25.8)	233 (39.1)	1,059 (30.3)
Large (>19)	91 (9.6)	565 (28.9)	110 (18.5)	766 (21.9)

Values are presented as number only, median (interquartile range), or number (%).
FSH: follicle stimulating hormone, LH: luteinizing hormone, TT: total testosterone.

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and Chicago was 13.8%, 23.8%, and 32.0%, respectively. Due to reported differing international referral patterns, the incidences were considered similar, making comparison reliable (Table 1). To inform azoospermia predictive models, multivariate analysis was completed using data from Miami. Multivariate analysis showed men with high FSH, high LH, low TT, and small testis size were statistically more likely to have azoospermia. High FSH, >7.6 IU/L, conferred a 4.0 (95% confidence interval, 2.5–6.4; p<0.001) greater odds of being azoospermic compared to those with an FSH in the normal range (Table 2).

1. Model development

As elevated FSH conferred the highest risk of azoospermia on multivariate analysis, we set out to predict the probability of azoospermia given FSH alone. Miami data was binned data by serum FSH levels. In men with an FSH <1 IU/L, there were n=22 observations and 3 (13.6%) were azoospermic. The probability of azoospermia nadir was at an FSH between 3 and 4 IU/L, with n=144 observations and 7 (4.9%) men with azoospermia. After an FSH >25 IU/L, there were n=25 observations, all these men (100%) were azoospermic. Fig. 1 shows a "U" shaped relationship between FSH and probability of azoospermia. After removing outlier FSH values, those greater than three standard deviations above the mean, a quadratic (second degree polynomial) regression model was fit to the binned probability data. This quadratic model performed with an R^2 value of 0.95 (probability of azoospermia=0.133[FSH]^2-0.965[FSH]+10.1). Further analysis of this quadratic equation shows at undetectable FSH there is a 10.1% chance of being azoospermic and the probability of azoospermia is lowest in men with FSH values of 3.6 IU/L.

A logistic regression model with additional clinically relevant continuous inputs of age, FSH, LH, TT, and mean testis volume was developed from Miami data. Table 3 shows the logistic regression equation coefficients.

Table 2. Miami data multivariate adjusted risk analysis for azoospermia

Variable	Odds ratio	95% confidence interval	p-value
Age (1 year increase)	1.00	0.99–1.00	0.13
FSH (IU/L)			
Normal (1.5–7.6)	1.00	-	
Low (<1.5)	1.50	0.51–4.60	0.44
High (>7.6)	4.00	2.50–6.40	<0.001
LH (IU/L)			
Normal (1.7–8.6)	1.00	-	
Low (<1.7)	0.95	0.32–2.80	0.93
High (>8.6)	3.30	1.90–5.50	<0.001
TT (ng/dL)			
Normal (300–1,000)	1.00	-	
Low (<300)	2.00	1.30–3.20	0.002
High (>1,000)	0.44	0.05–3.80	0.45
Testis size (cm^3)			
Normal (12.5–19)	1.00	-	
Small (<12.5)	2.20	1.40–3.50	<0.001
Large (>19)	2.00	0.91–4.30	0.08

FSH: follicle stimulating hormone, LH: luteinizing hormone, TT: total testosterone.

2. Model validation

External validation of the FSH and logistic regres-

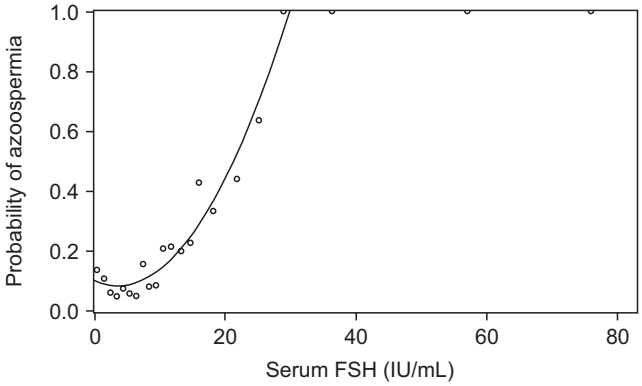

Fig. 1. Probability of azoospermia given serum FSH. Probability of azoospermia given FSH, calculated from binned FSH data (dots). Fitting a second degree-polynomial, quadratic model, to these data yields: probability of azoospermia=0.133[FSH]^2-0.965[FSH]+10.1 (line). This model preforms with a coefficient of determination R^2=0.95. FSH: follicle stimulating hormone.

Table 3. Logistic regression model coefficients

Coefficients	Value
Intercept	-1.9
Age (y)	0.02
FSH (IU/L)	0.13
LH (IU/L)	0.03
Testosterone (ng/dL)	-0.002
Mean testis volume (cm^3)	-0.08

FSH: follicle stimulating hormone, LH: luteinizing hormone, TT: total testosterone.
Probability of azoospermia=1/exp[-(b_0+b_i*X_i)].
b_0=FSH_1, b_i=0.95, X_i=independent variable.

sion models was performed two-fold with the Milan and Chicago data sets. Fig. 2 plots the probability of azoospermia by FSH at each site and the pooled probability. The highest FSH with sperm still present in ejaculated semen was 61.8 IU/L.

The Pearson correlation coefficient between the quadratic FSH model and the logistic regression model was 0.95 with the Milan validation set and 0.92 with Chicago data, demonstrating high agreement. Fig. 3 shows each the overlaid probability of azoospermia predicted by each model. ROC curves and AUC were calculated to define each model's ability accurately discern men with azoospermia from those with semen in the ejaculate. Applying each model to the Milan database yielded AUCs of 0.78 for FSH only and 0.79 for logistic regression. Chicago's database for FSH only *vs.* logistic regression had AUCs of 0.71 and 0.72 respectively. Cross-validation calibration plots were generated for each model. Each model performs with similar calibration and demonstrates good agreement between the actual and predicted incidence of azoospermia in each validation data set (Fig. 4).

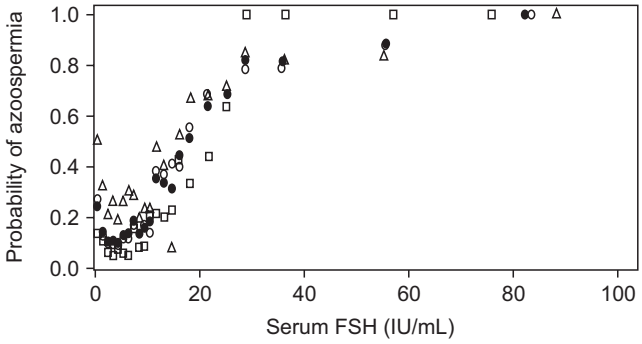

Fig. 2. Probability of azoospermia by FSH at each site and pooled probability. Predicted probability of azoospermia given FSH at each clinical site: Miami (Square), Milan (Circle), Chicago (Tringle) and the pooled probability (solid dot). Each site demonstrates a similar "U" shaped data trend. In the Miami training data set, no men with an FSH >25 IU/L had sperm in the ejaculate. However, both Milan and Chicago datasets showed sperm in the ejaculate in men with FSH as high as 61.8 IU/L. FSH: follicle stimulating hormone.

DISCUSSION

It is well known to providers in infertility clinics that elevated FSH levels, even in the upper range of normal, is suggestive of abnormal spermatogenesis. In this analysis, we present a quadratic model that predicts probability of azoospermia from serum FSH levels. The model is well calibrated to clinical data, has good discriminatory ability, and performs nearly indistinguishably from an increasingly complex logistic regression model with additional inputs of age, LH, TT, and testis volume. An individual's FSH level can be entered into the equation to give a personalized probability of azoospermia and useful clinical information arises from assessing the extremes of the equation: a patient with an undetectable FSH has a 10% chance of being azoospermic, the probability of azoospermia is

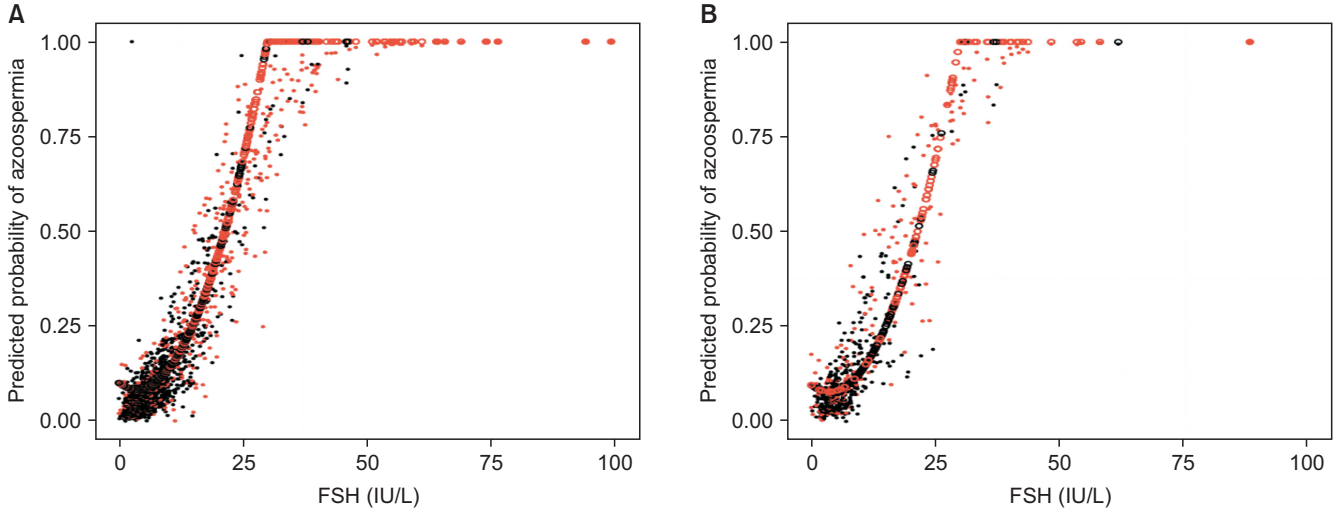

Fig. 3. Overlaid probability of azoospermia predicted by FSH and logistic regression models. Predicted probability of azoospermia for the FSH quadratic model (dots with central holes) and the logistic regression model (solid dots). Data from (A) Milan and (B) Chicago. Data are color coded based on ground truth: black dots are data from men with semen in the ejaculate and red from azoospermic men. FSH: follicle stimulating hormone.

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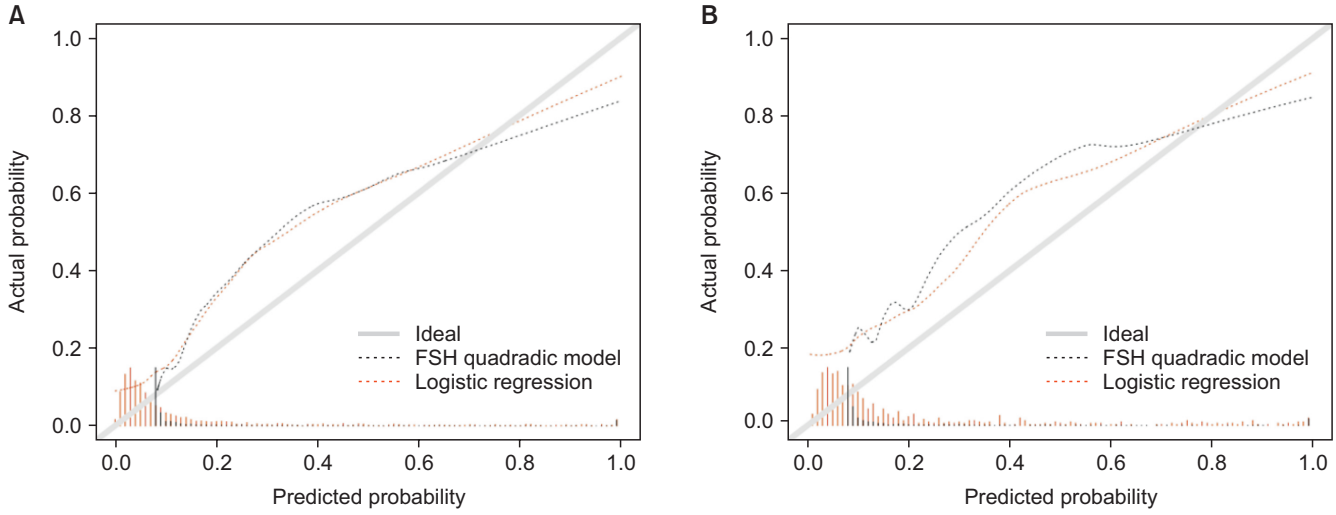

Fig. 4. Cross-validation calibration plots. Cross-validation calibration plots for the FSH quadratic model (black) and the logistic regression (red). Data from (A) Milan and (B) Chicago. Each model performs with similar calibration and demonstrates good agreement between the actual and predicted incidence of azoospermia in each external validation data set. Bottom bars are a histogram of each model's predicted probabilities. FSH: follicle stimulating hormone.

least in patients with an FSH of 3.6 IU/L, and after an FSH of 30 IU/L the majority of men will be azoospermic. When comparing our model to published studies assessing serum hormones and semen parameters, it meets or exceeds current standards.

Few studies have modeled clinical outcome predictions in men with azoospermia. Schoor et al [5] described the ability to accurately discriminate between men with azoospermia due to a production defect (non-obstructive azoospermia, NOA) and those with OA based on testis biopsy data from 153 azoospermic men, models including serum FSH and testicular long axis performed with strong discriminatory values with AUCs of 0.87 and 0.83, respectively. Additionally, they found combining the two inputs allowed for the accurate diagnosis in 96% of patients with OA and 89% with NOA [5]. However, the ability to predict successful sperm retrieval in men with NOA remains elusive. Ramasamy et al [10] showed neural network, logistic regression, and nomogram models using clinical data from 1,026 men with diagnosed NOA who underwent microdissection TESE performed with an AUC of 0.64 when predicting successful sperm retrieval. Nonetheless, this model with moderate discrimination ability might be useful in cases where a patient is equivocal on making the decision to undergo micro-TESE and the model may provide enough information to inform a clinical decision one way or the other. These data reflect the value and challenges of creating accurate predictive models for evaluating azoospermia.

Meeker et al [11] characterized the relationship between serum hormone levels and semen quality among 388 infertile men. They defined abnormal semen concentration as <20 millions/mL and found an adjusted odds ratio of 1.0 comparing men with low and normal serum FSH levels and a 4.6 increased odds of semen concentration <20 millions/mL in men with elevated FSH levels compared to those with low FSH levels [11]. Our adjusted multivariate analysis found a similar odds ratio for men with elevated FSH having 4.0 increased odds of azoospermia compared to men with normal range FSH.

Gordetsky et al [6] proposed redefining an elevated FSH level to ≥4.5 IU/L. In their analysis of 457 infertility patients without OA they calculated an ROC curve of a logistic regression model using FSH as the only independent variable and found FSH alone to be a fair predictor of having abnormal semen concentration (defined as <20 millions/mL), with an AUC of 0.75. Our model performed with AUCs of 0.71 to 0.79 on external validation datasets, and it does not exclude men with OA. Internal validation suggests removing these men would increase the discernibility of our models. However, we included data from men with OA to make the model applicable to all men presenting for initial infertility evaluation.

Strengths of the study include the large sample size with analysis being performed on nearly three thou-

sand five hundred paired hormone concentration and semen analysis data sets. This allows for data binning to be robust as each data set has a large enough denominator to limit significant variability in the probability calculations. Another strength of the study is the relatively minimum exclusionary criteria making data applicable to all men in an infertile couple presenting for initial evaluation. The simplicity of the model and ubiquity of FSH serum testing make the probability prediction accessible to any infertility specialist. Finally, we have confirmed the generalizability of our models using two large databases from international fertility centers. The primary limitation is the inability of the model to discriminate between men with OA and men with semen in the ejaculate. While the ability of the model to predict accurately the etiology is an attractive prospect, this is not the purpose of our analysis nor the intended use of the model.

When generating the model, clinical applicability and simplicity were prioritized [12]. The few exclusion criteria of testosterone or steroid use, history of vasectomy, Y chromosome microdeletion, and presence of solitary testis was intentionally designed to improve model accuracy while maintaining broad application of the model to patients presenting in the infertility clinic. While including additional information of age, LH, TT, and testis volume calculations may narrowly increase the accuracy of the predicted probability, a comparison of the FSH quadratic and logistic regression models showed FSH alone is sufficient to accurately predict azoospermia.

The utility of this study presents itself during the initial infertility encounter with a male who is apprehensive about performing a semen analysis or performing repeat semen analyses to confirm azoospermia in men with FSH >61.8. Additionally, in terms of costs, infertility workup semen analysis by WHO 2010 criteria ranges from $140.00 to $300.00 compared to FSH at an eighth of the price [13]. In the era of at-home semen analysis, there will be an expanded role of other relevant clinical factors such as FSH to validate when an at-home test shows azoospermia. Future efforts will be to assess the utility of using these predictive algorithms in conjunction with semen analysis, as discordance between predicted and observed results may warrant further evaluation into the etiology of azoospermia, and inclusion of other relevant inputs such as 17-OHP and lifestyle factors.

CONCLUSIONS

The ability to predict the probability of azoospermia without a semen analysis first would be useful to urologists when counseling patients, especially when there are logistical hurdles in obtaining a formal semen analysis or for reevaluation prior to surgical sperm extraction. While the ability to predict the probability of azoospermia from serum hormones will not replace a semen analysis, the role of hormonal may expand with the rise of at-home diagnostics. Robust external validation demonstrates FSH levels can be used alone to accurately predict chances of azoospermia with similar performance to more complex models considering multiple parameters. This analysis broadens our understanding of the relationship between FSH and azoospermia and provides a useful clinical tool to accurately counsel patients on their reproductive potential even without a semen analysis.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: MBT, WC, RLP, EI, EK, ReddyR, RamasamyR. Data curation: MBT, LAM, ReddyR, AS, CN, WC. Formal analysis: MBT, RLP, LAM. Methodology: MBT, WC, RLP, LB, RamasamyR. Project administration: MBT, WC, RLP, RamasamyR, EK, EI, CN. Resources: RamasamyR. Supervision: WC, RLP, RamasamyR, EI. Visualization: MBT, RLP, WC, ReddyR. Writing – original draft: WBT, WC, EK, ReddyR, RamasamyR. Writing – review & editing: WBT, EI, CN, ReddyR, RamasamyR.

Data Sharing Statement

The data analyzed for this study have been deposited in HARVARD Dataverse and are available at https://doi.org/10.7910/DVN/EQFMCM.

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