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Original Article

Predictive values of the ratio of beta-human chorionic gonadotropin for failure of salpingostomy in ectopic pregnancy

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Abstract: Background: We evaluated the predictors of unsuccessful salpingostomy that required surgical treatment or additional medical treatment after initial removal of ectopic pregnancy (EP) by laparoscopy. Material/Methods: The study was an observational retrospective cohort study done at International Peace Maternity and Child Health Hospital in Shanghai, which included patients with ectopic pregnancy (EP). The predictors of persistent ectopic pregnancy (PEP) were measured either on serum β-hCG ratios before and after salpingostomy or demographics (age, parity, in-vitro fertilization (IVF), abortion history, EP history, mass location, appendectomy history and diameter of EP lesion). We used nomogram analyses to evaluate the significant factors consisting of serum β-hCG ratio, parity and performed IVF that predicted the failure or success of salpingostomy. Results: We retrospectively analyzed 429 patients in this study who received salpingostomy for EP from January 2013 and December 2017. Of these patients, 29 (6.76%) were diagnosed with PEP after salpingostomy and 400 (93.24%) had satisfactory treatment. The median of serum β-hCG ratio (after salpingostomy 24 h/after salpingostomy 48 h) 2.43 in PEP patients was lower than that in successful treatment patients (P<0.001). Logistic regression analyses identified several predictors for PEP, including parity, IVF and serum β-hCG (after salpingostomy 24 h/after salpingostomy 48 h), with a higher clear predictive value (area under the curve [AUC]=0.865, 95% CI: 0.812-0.919, P<0.001). Conclusions: The serum β-hCG ratio (after salpingostomy 24 h/after salpingostomy 48 h) in combination with parity and IVF are important predictors for PEP patients after surgery. These findings provide higher risk PEP patients for early interventions to improve outcome.

Keywords: Ectopic, pregnancy, persistent ectopic pregnancy, serum β-human chorionic gonadotropin, salpingostomy

Introduction

An ectopic pregnancy is any pregnancy implanted of the endometrial cavity, the incidence of ectopic pregnancy in women attending first trimester is 1.5-3.0% of pregnancies [1-3]. Implantation in the fallopian tube accounts for approximately 90% of all ectopic pregnancies [4]. The important risk factors for ectopic pregnancy include multiple ectopic pregnancy history, previous damage to the fallopian tubes, prior pelvic or fallopian tube surgery, pelvic infection and previous caesarean delivery [5]. Women with tubal factor infertility and multiple embryo transfer are also increased risk of ectopic pregnancy [6]. However, about 50% of all women do not have any known risk to diagnose the ectopic pregnancy [7]. Based on the two randomized controlled trials (RCTs) and eight cohort studies, the results indicate that for patients with a healthy contralateral tube operated for tubal pregnancy, the subsequent fertility after salpingectomy and salpingotomy are similar in the long term [8]. The choice of operating type is determined by the state of patient's health, future fertility expectation, and the extent of fallopian tube damage. Therefore, more and more young patients are required to retain the affected fallopian tubes. Because of advances in transvaginal ultrasonography and speedy quantification of serum human chorionic gonadotropin, ectopic pregnancy can be

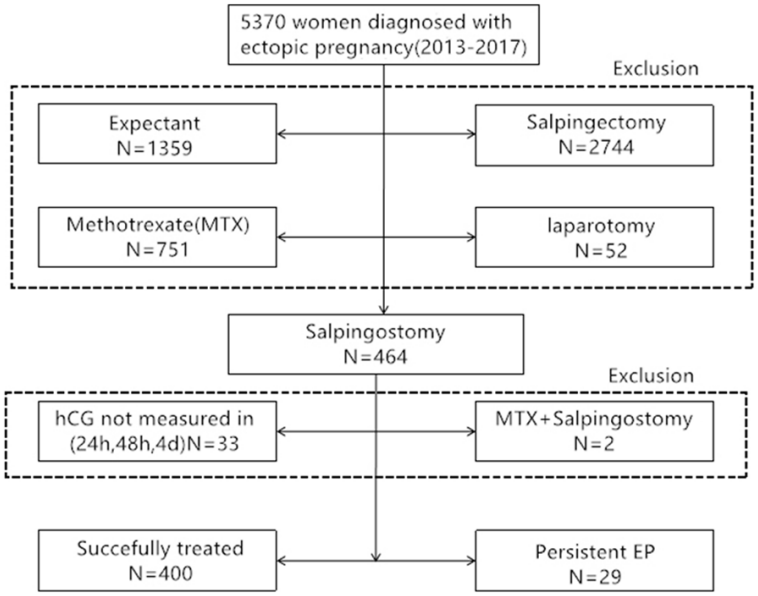

Figure 1. Study population flow chart.

identified early and therapy can be given promptly. This has enabled patients to accept conservative surgical procedures with preservation of the tube [9].

With advantages of shorter operation time, less intraoperative blood loss, shorter hospital stay, lower cost, lower analgesic requirements and less adhesion formation, laparoscopy has become the gold standard surgical treatment of ectopic pregnancy [10]. For patients who wish to preserve reproductive function, salpingostomy laparoscopic conservative surgery is the most widely used [11]. However, as its disadvantage, persistent ectopic pregnancy (PEP), can occur as a complication, conservative consideration for the fallopian tube may result in the persistence of some residual trophoblasts even after the hematoma is removed [12]. If PEP not detected at an early stage, it may result in intraperitoneal hemorrhage and shock which needs emergency surgery. These not only increase the suffering of patients but also aggravate the patient's economic burden. Therefore, a determination of the predictors of postoperative occurrence of PEP is urgently required.

The main aim of this study was to evaluate the predictors of unsuccessful salpingostomy that required surgical treatment or additional medical treatment after initial removal of the EP by laparoscopy.

Material and methods

Patient enrollment

The study was designed to identify the ratio of serum β-hCG at different times as a predictor of unsuccessful salpingostomy after EP operation by laparoscopy. Samples were collected from International Peace Maternity and Child Health Hospital (IPMCH), a large-population based ectopic pregnancy women. All patients were treated for EP between January 2013 and December 2017. Unsuccessful salpingostomy patients who required a second operation or medical treatment were evaluated for β-hCG ratio and more accurate prediction. In total 5370 EP women were enrolled in this study. Women with salpingectomy, expectant treatment, methotrexate treatment or laparotomy were excluded from the analysis (N=2,744, N=1,359, N=751, N=52, respectively). There remained 464 patients treated for salpingostomy, two of them were injected with MTX during salpingostomy surgery and thirty three of them were not systemic measured β-hCG at 24 h, 48 h and 4 day after salpingostomy surgery. The final subjects included in the analysis comprised 429 women, while 400 of these patients were treated successfully (control group), 29 of them were treated unsuccessfully (PEP group) (**Figure 1**). We collected the subjects' ages, abortion history, EP history, parity and ultrasound records.

Sample collection and measurement

Fasting blood samples were drawn from the median cubital vein, and were sent immediately to measure the concentrations (IU/L) of β-hCG after centrifuged with 2100 rpm. The β-hCG was measured in serum using a solid-phase two-site chemiluminiscent immunometric assay on an Immulite 2000 XPi system (Siemens Healthcare Diagnostics, Deerfield, IL, USA). The β-hCG levels of patients were measured at 24 h and 48 h after surgery and monitored after discharge on postoperative day 4. The diagnosis of EP was made according to clinical gold standards as the following: The minimum diagnostic

Table 1. Basic characteristics

Variables	PEP	Control	*P*
	N (%)	N (%)	
Age, n (%)			0.543
<25	7 (24.1)	79 (19.8)	
25-30	10 (34.5)	180 (45.0)	
>30	12 (41.4)	141 (35.3)	
Abortion history, n (%)			0.255
No	18 (62.1)	204 (51.1)	
Yes	11 (37.9)	195 (48.9)	
IVF, n (%)			0.001
No	23 (79.3)	379 (94.8)	
Yes	6 (20.7)	21 (5.2)	
EP history, n (%)			0.906
No	26 (89.7)	355 (88.9)	
Yes	3 (10.3)	44 (11.1)	
Parity, n (%)			0.104
Primiparous	9 (31.0)	186 (46.6)	
Multiparous	20 (69.0)	213 (53.4)	
Adnexal mass location, n (%)			0.450
Ovary	2 (6.9)	41 (11.5)	
Beside of uterine body	27 (93.1)	316 (88.5)	
Appendectomy history, n (%)			0.092
No	27 (93.1)	392 (98.0)	
Yes	2 (6.9)	8 (2.0)	
Diameter of EP lesion (mm), Median (Quartile)	21.3 (15.8-26.5)	20.3 (16.0-25.7)	0.695

evaluation of a suspected ectopic pregnancy is a transvaginal ultrasound evaluation and confirmation of pregnancy. Serial evaluation with transvaginal ultrasonography, or serum hCG level measurement, or both, often is required to confirm the diagnosis [13].

Statistical analysis

Data are presented as median and interquartile (IQR) for continuous variables with non-normal distribution, and as frequency and percentage for categorical variables. A Pearson's χ^2 test was used to analyze categorical variables. The non-parametric Wilcoxon rank test was used to comparing β-hCG level between PEP and control group. ROC curve was used to evaluate the diagnostic value of β-hCG ratios in EP patients with salpingostomy surgery. We used multiple logistic regression models to study the association of β-hCG ratios with predicted PEP risk. Nonlinearity was assessed using restricted cubic splines with 3 knots at the 10th, 50th, and 90th percentiles [14]. All the model fit and remaining model assumptions were assessed by plotting model residuals and evaluating R^2/sum of squared residuals. We adjusted for potential confounders such as age, parity and IVF, change of the effect estimates of interest, and/or reduction in the residual variability of the outcome. The nomogram was used to estimate the probability of PEP for an individual patient, for each predictor identifies the number of points associated with the score of the patient. All statistical analyses were performed using R statistical software version 3.4.1 (*package rms*) or Statistical Package of Social Sciences v20.0 for Windows (SPSS v22.0; IBM Corp, Armonk, NY).

Results

After exclusions, the final study population comprised 429 EP patients (**Figure 1**), descriptive characteristics of whom are shown in **Table 1**. The IVF performed or multiparous patients have higher incidence of PEP than those with successfully performed salpingostomy surgery (*P*=0.001, *P*=0.047). However, there was no significant difference between ages, history of

Table 2. Comparison of β-hCG levels between PEP and control group

β-hCG levels	PEP	Control	*P*
Diagnosis (<24 h before surgery)	1027.0 (549.1-2662.0)	1604.5 (694.2-3577.3)	0.218
After salpingostomy (24 h)	559.3 (237.4-1246.0)	424.8 (132.3-878.7)	0.111
After salpingostomy (48 h)	221.9 (97.0-462.5)	67.3 (22.4-214.3)	0.001
After salpingostomy (4 d)	124.0 (4.5-355.0)	9.1 (2.3-35.9)	<0.001

Data are presented as median (quartiles). PEP: persistent ectopic pregnancy after salpingostomy surgery; Control: successfully performed salpingostomy surgery; β-hCG: β-human chorionic gonadotropin.

Table 3. Comparison of hCG ratios between PEP and control group

β-hCG levels	PEP	Control	*P*
D(24 h)/As(24 h)	2.07 (1.72-3.94)	2.49 (2.09-3.22)	0.385
D(24 h)/As(48 h)	7.39 (2.59-10.19)	17.48 (9.48-59.52)	<0.001
D(24 h)/As(4 d)	11.55 (2.05-75.04)	186.68 (69.56-489.70)	<0.001
As(24 h)/As(48 h)	2.43 (1.18-3.56)	5.89 (3.55-21.25)	<0.001
As(24 h)/As(4 d)	3.35 (1.07-35.06)	66.82 (22.15-178.60)	<0.001

D(24 h): diagnosis (<24 h before surgery); As(24 h): after salpingostomy (24 h); As(48 h): after salpingostomy (48 h); As(4 d): after salpingostomy (4 d).

previous abortion, history of previous EP, history of previous appendectomy and adnexal mass location in two groups.

Serum β-hCG concentration and ratio in PEP and control groups

The β-hCG levels of patients were measured within 24 h before surgery (D 24 h), and at 24 h (As 24 h) and 48 h (As 48 h) after surgery and monitored after discharge on postoperative day 4 (As 4 d). The levels of β-hCG within 24 hours before- and after-operation both showed no statistically significant difference between PEP and control groups (P=0.218 and P=0.111, respectively), while the difference within 48 hours and 4 days after-operation was statistically significant (P=0.001 and P<0.001, respectively) (**Table 2**).

As shown in **Table 3**, the median of the ratio of D(24 h)/As(48 h), D(24 h)/As(4 d), As(24 h)/As(48 h) and As(24 h)/As(4 d) were all significantly greater in control group than in PEP group (P<0.001). However, the median of the ratio of D(24 h)/As(24 h) in control group (median, 2.49; quartile, 2.09-3.22) compared with that in PEP group (median, 2.07; quartile, 1.72-3.94) were not significant (P=0.543).

Predicted value of β-hCG ratio for PEP risk

The ROC of β-hCG ratio of the EP in predicting unsuccessful cases was calculated and cut-off β-hCG ratio of the EP was distinguished (**Figure 2**). The area under the ROC curve of D(24 h)/As(24 h) was 0.548, P=0.445, suggesting no statistical significance. The area under the ROC curve of D(24 h)/As(48 h), D(24 h)/As(4 d) and As(24 h)/As(4 d) were 0.759, 0.803 and 0.850, which were all significant (P< 0.001). The area under the ROC curve of As(24 h)/As(48 h) was maximum (AUC, 0.865, P<0.001) and the cut-off ratio of the EP was found to be 3.24 (**Table 4**). The correlating sensitivity rate was 75.9% and specificity was 81.5%. Positive and negative predictive values were 22.3% and 97.9%, respectively (**Table 3**).

As shown in **Figure 3**, the probability of PEP was more strongly related to β-hCG ratios (**Figure 3**), resulting a non-linear shape association, with the highest probability of PEP around a lower ratios. In the regression model, the procedure-selected predictors were identical to those of the model except for age, abortion history, EP history, adnexal mass location, appendectomy history and diameter of EP lesion. For primiparous and not performed IVF patients were associated with a successful salpingostomy surgery. The estimated equation was: Log[P/(1-P)]=0.4274 + 1.0022 * parity + 2.6217 * IVF ± 2.5621 * ln[(As24h/As48) + 1] A nomogram summarizes these effects (**Figure 4**).

Discussion

In the current study, we investigated the predictive value of hCG ratio with PEP during the preoperation and post-operation. Our main finding is that, while we can replicate findings from other studies showing that patients were considered PEP, whose hCG levels slightly decreased or did not decrease after being

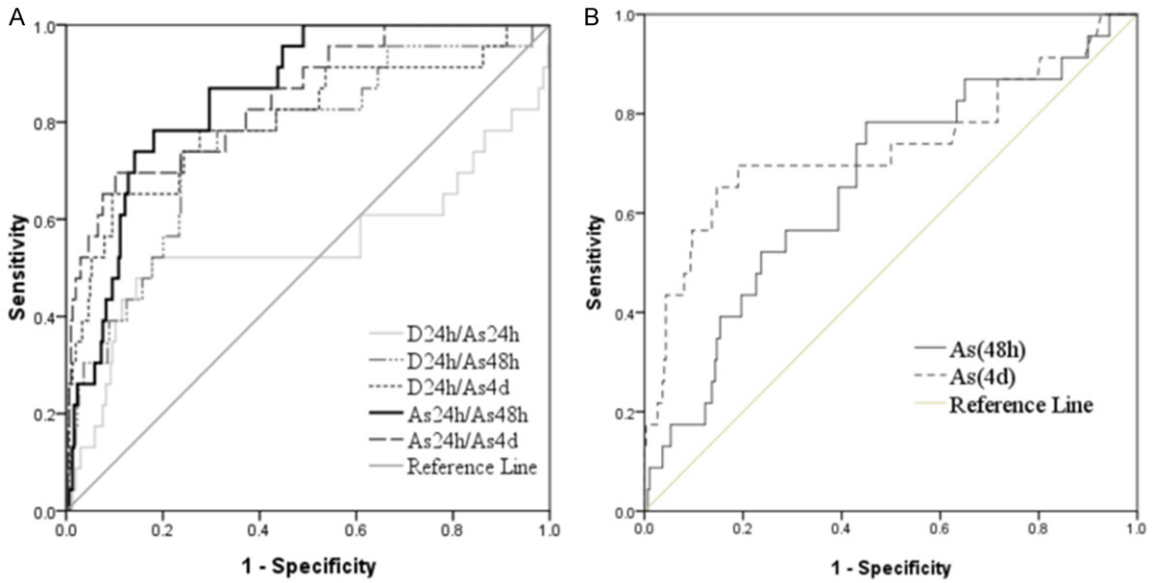

Figure 2. ROC curve to predict the PEP diagnosis value.

Table 4. Area under the curve for PEP risk

β-hCG ratios	AUC	95% CI	*P*
As(48 h)	0.660	0.542-0.778	0.011
As(4 d)	0.732	0.598-0.866	<0.001
D(24 h)/As(24 h)	0.548	0.384-0.712	0.445
D(24 h)/As(48 h)	0.759	0.653-0.866	<0.001
D(24 h)/As(4 d)	0.803	0.692-0.914	<0.001
As(24 h)/As(48 h)	0.865	0.812-0.919	<0.001
As(24 h)/As(4 d)	0.850	0.764-0.935	<0.001

D(24 h): diagnosis (<24 h before surgery); As(24 h): after salpingostomy (24 h); As(48 h): after salpingostomy (48 h); As(4 d): after salpingostomy (4 d).

treated for EP [15, 16] it is actually a ratio of hCG that is associated with PEP risk. Women with hCG ratio greater than 3.24 between postoperative 24 hours and 48 hours had a higher successful probability of salpingostomy surgery for EP, with effect estimates which are similar or even larger than previous risk factors such as gestational age, mass size, pelvic adhesions, and postoperative day 1 or day 3 serum hCG decline [17-19].

Laparoscopic surgery is the gold standard treatment of EP. In surgical strategies, salpingostomy or salpingectomy can be a choice. Salpingotomy and salpingectomy show similar rates of subsequent intrauterine pregnancy in women with ectopic pregnancy desiring future pregnancy or repeat ectopic pregnancy [20]. Salpingostomy should be considered in patients who desire future fertility but have damage to the contralateral fallopian tube and in whom removal would require assisted reproduction for future childbearing [21]. The most significant complication of each conservative treatment and the major reason for secondary intervention is persistent EP [22]. The incidence of postoperative PEP is from 1.4% to 5.4%, but the reported occurrence is inconsistent [16, 17]. In our study, the incidence of PEP was 6.25%, slightly higher than reported, possibly because our study reflects an initial stage and perhaps large baseline patients for EP. Thus the large sample size of the ectopic pregnancy receiving salpingostomy allowed us to find that PEP risk is associated with postoperative serum hCG ratio.

In our study, there was no statistically significant difference at the concentrations of preoperative 24 h or postoperative 24 h serum hCG between the PEP and control groups. However, after surgery 48 h or 4 day, hCG decline in the patients with PEP was significantly less than in the control group. So it was important to monitor the patient with serial hCG measurement to ensure resolution of ectopic trophoblastic tissue when salpingostomy was performed [21], especially after surgery 48 h and 4 day. Our findings were in concordance with other studies. One study showed that both the preopera-

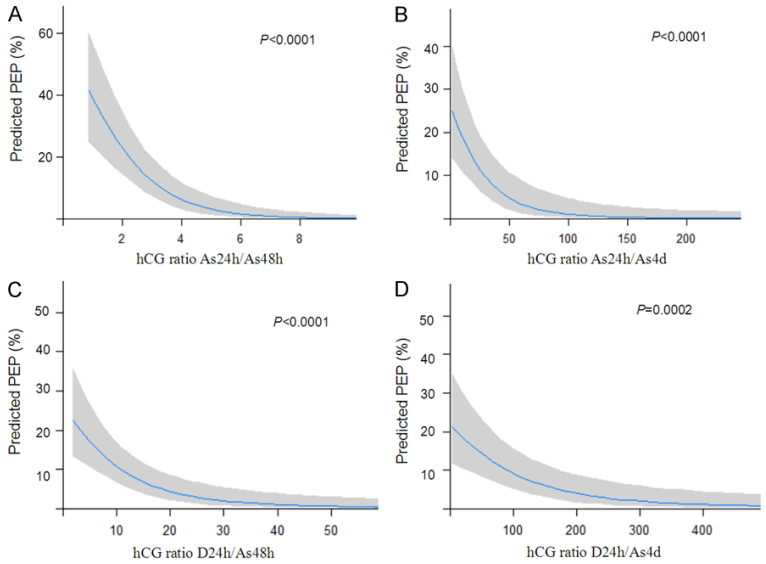

Figure 3. The association of hCG ratio with PEP risk. Plots show the logistic regression models for D(24 h)/As(48 h) (A), D(24 h)/As(4 d) (B), As(24 h)/As(48 h) (C) and As(24 h)/As(4 d) (D) with PEP risk, as predicted mean with 95% CI. The models were adjusted for age, parity, anf IVF with three knots of restricted cubic spline analysis.

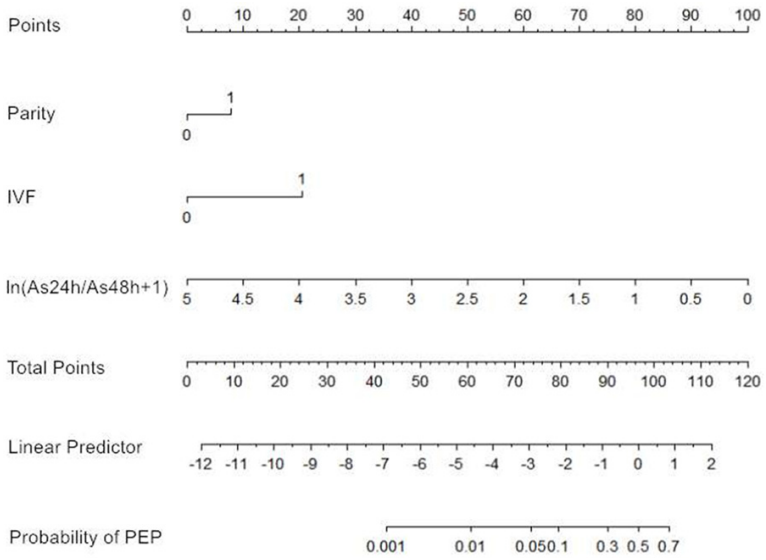

Figure 4. Nomogram to estimate probability of PEP after salpingostomy surgery. Based on the logistic regression model, the nomogram will predict the probability of PEP for an individual patient. For each predictor identify the number of points associated with the score of the patient. For example, an IVF factor would imply 20 points. Compute the sum of points for all predictors, and denote this value as the Total points. Identify the value of the Linear predictor (LP) associated with the total points by placing a vertical ruler on the nomogram. For example, a score of 96 on the Total points is associated with a value of 0 on the linear predictor. Calculate the probability of PEP (PPEP) as PPEP=1/(1 + exp(-LP)).

tive and the early postoperative hCG levels had a low diagnostic sensitivity and specificity for predicting PEP [23]. On the other hand, persistent EP can be predicted by a less than 55% decline of the hCG level at the third postoperative day [18]. The decline hCG in patients with PEP was completely outside the 95% CI of the control group during days 5 or 6, which constitute an important marker of the presence or absence of PEP [16]. The probability of PEP was 15% or less when the serum hCG level decreased by 50% or more the day after salpingotomy, and that the relative risk of PEP was 3.5 (95% CI, 1.25-6.68) in patients in whom the rate of decrease in hCG the day after surgery was <50% [19].

Therefore, it is possible that the rate of decrease in the hCG level the day after surgery may be useful for diagnosing PEP. The serum concentration of hCG decline is an important predictor for PEP risk but the hCG ratio after surgery 24 h to 48 h had a higher predicted value than before. We used a regression model to estimate probability of PEP. The covariates of parity and IVF were also included in the nomogram, which implies that multiple pregnancy or IVF is a risk factor for PEP.

The ROC curves based on the hCG data show a higher sensitivity and specificity for the serum hCG ratio (hCG 24 h/hCG 48 h) after salpingostomy but the regression models apparently have a better performance regarding predictive PEP probability. In clinical practice these models are complex and often need computer analyses. For clinical practice, our analyses might allow a new nomogram to identify patients who are at risk of PEP

that interfere with actual probability, since waiting for abdominal haemorrhage and clinical symptoms of rupturing EP puts serious health risks on these patients. At-risk patients subsequently could be contacted immediately within 48 h after surgery to determine which patient needs a second line methotrexate therapy. With this approach, the selection of those patients who have to be the next treatment can be narrowed down; also the patients can know themselves' the precise probability of PEP. Several studies have suggested that early treatment might be effective in preventing the development of PEP [24].

We believe that application of the predictive model allows for early identification of high-risk patients with possibilities for timely treatment. Although our models have yet to undergo external validation and internal validation, it would be done to construct a validation cohort to investigate the sensitivity and specificity in the future.

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Disclosure of conflict of interest

None.

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