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Comparison of beta-human chorionic gonadotropin-based prognostic models on the clinical outcomes of gestational trophoblastic disease patients in the Philippines

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Abstract:

OBJECTIVE: Despite the widespread use and measurement of beta-human chorionic gonadotropin (β-HCG) among hydatidiform mole (HM) patients, models derived from this biomarker to predict the remission or postmolar gestational trophoblastic neoplasia (GTN) rarely perform well. The study aimed to generate cutoff points for postevacuation β-HCG levels and evaluate their performance among women with complete molar pregnancies.

METHODS: A retrospective cohort study composed of women with complete HM underwent bivariate procedures comparing characteristics between the comparison groups. Cut points using Liu's and Youden's indices were estimated, and their performance was evaluated using receiver operating characteristic curve analysis. Cox regression to compare time-to-progression across these proposed β-HCG cutoffs was also performed.

RESULTS: The incidence of postmolar GTN among the 155 women in the study was 15.5% (95% confidence interval: 10.2%–22.2%). Postevacuation HCG levels had a better prediction of disease status than preevacuation and HCG ratio models (χ^2: 163.07, $P < 0.01$). A cutoff at 508 mIU/mL the 3rd-week postevacuation (area under the curve [AUC]: 0.89, sensitivity: 87.5%, specificity: 90.1%) was comparable with the 185 mIU/mL cutoff at the 5th-week postevacuation (AUC: 0.89, sensitivity: 91.7%, specificity: 87%). The hazards ratio of postmolar GTN was 29.74 (8.53–103.71) and 39.89 (8.82–180.38) for the 3rd and 5th weeks HCG after evacuation adjusting for clinically relevant variables.

CONCLUSION: The first 3rd- and 5th-week postevacuation levels of β-HCG demonstrated potential in predicting postmolar GTN. However, further refinement and adjustment for clinically relevant risk factors are still needed.

Keywords:

Beta-human chorionic gonadotropin, choriocarcinoma, gestational trophoblastic disease, gestational trophoblastic neoplasia, prognostic factors

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Introduction

The potential clinical use of routinely collected patient information in improving the diagnosis and management of select disease conditions, particularly for rare diseases, has been considered in the current healthcare landscape. In the Philippines, the beta-human chorionic gonadotropin (β-HCG) levels are an example of patient information that is repeatedly collected, kept recorded, and examined among women with gestational trophoblastic disease.

The incidence of GTD tends to vary from a rare status in North America and Europe

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to a more frequent occurrence among Asians and Latin Americans. However, it was mentioned that its incidence in the latter group has decreased.[1] However, in the Philippines, there is a notably high incidence of HM, with a national prevalence estimated at 2.4/1000 pregnancies and reaching up to 13–14/1000 pregnancies in GTD specialty institutions.[2,3]

GTD refers to a group of conditions characterized by abnormal changes in the uterus stemming from the placental tissue,[4] and has a unique pathogenesis in that tumors arise from tissue associated with pregnancy that can eventually range from benign conditions to malignant ones. Its most common form is the hydatidiform mole (HM), or molar pregnancy, and considered to be a benign or premalignant disease.[5] This means that not all GTD patients will demonstrate regression of their β-HCG levels and proceed to a spontaneous recovery.

With this, the reason why some molar pregnancies spontaneously regress after molar evacuation while others progress to postmolar gestational trophoblastic neoplasia (GTN), and eventually would require chemotherapy and advanced treatment regimens, remains unclear despite efforts to identify clinical characteristics that might predict postmolar status.[6]

Mathematical and clinical prediction models have been created to provide answers to the previously posed question. However, the commonly identified characteristics (e.g., advanced maternal age, history of HM) appeared to be weak predictors of GTN, and further refinement is still needed in the use of risk-scoring systems.[7,8]

As mentioned before, the repeated measurement of the β-HCG is one of the useful tools in managing this condition. This glycoprotein is a sensitive indicator used for continuous and complete postevacuation surveillance among GTD patients up to 6 months after the initial intervention. The serum levels of HCG are assessed if it does not decrease or increase again after reaching normal levels, after which the clinician evaluates the woman for possibly persistent trophoblastic disease or GTN.[9]

Local experts have recommended this serial measurement of the serum titer 1 week after molar evacuation followed by every 2 weeks until it reaches normal levels, with normal defined as <5 mIU/mL.[10] However, there remains to be varying perspectives on the monitoring and the prognostic utility of β-HCG after molar evacuation.

Mousavi *et al*.[9] mentioned that preevacuation did not demonstrate a significant relationship with determining if a women will have progression to persistent GTN as opposed to what was accepted in practice. Several studies have recommended that early postevacuation levels of β-HCG such as two measurements,[11] or within 5 weeks[12] postevacuation are more clinically precise and useful in estimating the ensuing outcomes of GTD patients. Recent trends focused on examining changes in the levels of HCG after evacuation across different time points, and subsequently identifying patients who would proceed into remission or develop GTN,[13,14] but none of these models generated demonstrated sufficient external validity and precision to guide in the management of these patients.

Moreover, despite the relatively large number of GTD cases in the Philippines, there remains a dearth of studies examining the regression of HCG levels, its role as an indicator of postmolar GTN, or even generating Philippine-specific cut points for HCG monitoring.

Hence, the current study aimed to generate cutoff points for postevacuation β-HCG levels and evaluate their performance among women with complete molar pregnancies. The study will refine and titrate the β-HCG-based prognostic models currently implemented in practice, and proposed by researchers to generate local cutoffs, and compare different decision values of the biomarker (in mIU/ml) during the various periods of HCG monitoring vis-à-vis disease status of the patients.

The findings from the study do not only result to the creation of β-HCG-based prognostic models for Filipino women but can also contribute to the early identification of women likely to have progression during the surveillance period, as well as improve risk stratification and prediction among GTD patients and be later reflected in the practice and training of clinicians.

Methods

Research design and sampling

A dataset derived from a retrospective cohort of women with complete HM seen between 2009 and 2018 in a tertiary level institution with trophoblastic disease specialty for better identification of the clinical characteristics, and ascertainment of the outcomes.

The owners of the dataset originally examined 799 cases of molar pregnancy admitted between 2009 and 2018, but only 155 of them had complete and consecutive information until the 5th-week postevacuation.[12] As a result of the limited number of available patients, all patient data available was gathered by the researchers. Patients were de-identified and anonymized before any data processing or analysis procedure. Ethical clearance from the institutional review board was sought before the conduct of the study (UPMREB 2019-173-01).

Variables in the dataset

Characteristics known to be associated with progression to GTN were collected specifically age in years, obstetric history (i.e., gravidity, parity, history of abortion), gestational age, uterine size, mode of evacuation (i.e., suction curettage, total hysterectomy), and chemoprophylaxis. The event of interest is progression to GTN or remission in the study population, which was based on the latest clinical diagnosis of the trophoblastic disease specialist who has managed the patient in the said institution.

The levels of the β-HCG at baseline, 1st, 3rd, and 5th weeks after molar evacuation were also collected. Duration of monitoring and losses to follow-up were also noted.

Missing information was not imputed to avoid introducing bias or other sources of validity concerns in a relatively limited number and quality of observations.

Data analysis

Data were manually entered into an electronic spreadsheet file and subsequent data processing, and analysis was carried out using JASP (version 0.12.2. Amsterdam, The Netherlands: JASP Team).[15] Descriptive statistics such as mean, standard deviation, median, and interquartile range were used for numerical variables. Frequency and percentage were used for the categorical data variables. Bivariate procedures such as Wilcoxon rank sum and Chi-square tests were performed to determine differences between the comparison groups in terms of clinicodemographic variables.

The proportion of patients identified to remain at risk for developing GTN across various prognostic factors and time points of beta HCG measurement will also be presented. Point and 95% interval estimates of diagnostic characteristics such as the sensitivity, specificity, positive and negative predictive values, and the area under the curve (AUC) were also computed, considering the most recent regression or progression as the endpoint.

Cutoff points were generated using Youden's and Liu's indices, and their diagnostic performance was compared using modified Chi-square tests. Hazard ratios for disease progression were estimated using Cox regression models using the 3rd and 5th post-evacuation β-HCG values accounting for select clinically relevant data such as age, gravidity, uterine size, mode of evacuation, and chemoprophylaxis. Kaplan–Meier survival plots, stratifying across classifiers, were generated as well.

The level of significance for all sets of analysis was set at a $P < 0.05$ using two-tailed comparisons.

Results

The current study involved a secondary analysis of a dataset that contained relevant information from 155 women who had the complete type of molar pregnancy and were managed in the institution. Table 1 compared known clinico-demographic characteristics of women in the study across disease status (i.e., remission, progression).

The incidence of progression from complete HM to GTN in the study cohort was 15.5% (95% confidence interval [CI]: 10.2%–22.2%). The mean age of the sample population was 31 years old, and there was no noted variability in age between disease status. Similarly, there was no noted difference in known clinical predictors of progression such as obstetric history (i.e., gravidity, parity, abortion), mode of evacuation, and chemoprophylaxis between the women in the comparison groups.

However, even if there was no difference between the groups in terms of gestational age. It can be noted that the mean uterine size and the median difference between gestational age and uterine size were significantly larger among women who developed postmolar GTN, than otherwise.

In terms of β-HCG related variables, it can be noted that the median levels of the glycoprotein across all different time points (i.e., preevacuation; 1st-, 3rd-, and 5th-week levels postevacuation) varied significantly between the comparison groups, as shown in Table 2.

It can be noted that using the cutoff implemented in the country for GTD monitoring at 5 mIU/mL does not appear to significantly discern remission or progression in these patients. All women had β-HCG levels greater than the cutoff a week after evacuation, and these proportions did not significantly vary in the 3rd week postprocedure. The proportion of women with β-HCG levels beyond the cutoff was notably higher among those who progressed to GTN than otherwise. However, majority of the women in the remission group still had levels beyond the implemented cutoff.

In addition, proposed β-HCG-based prognostic models that are believed to discriminate against women who would have remission or progression of disease were also evaluated using the current sample. It can be noted that the preevacuation β-HCG levels used in most Asian countries; and the β-HCG ratios, specifically the preevacuation to 1-week postevacuation and preevacuation to 3-weeks postevacuation, proposed by various authors did not appear to discern well the disease status of women in the current study.

Table 1: Association of known predictors across disease status of gestational trophoblastic disease patients (*n*=155)

Characteristics	Overall, *n* (%)	GTD status		*P*
		Remission, *n* (%)	Progression, *n* (%)	
Frequency (%)	155 (100)	131 (84.52)	24 (15.48)	-
Age (years)				
Mean±SD	30.50±9.61	30.31±9.49	31.54±10.37	0.59
≤21 years old	20 (12.90)	77 (58.78)	3 (12.50)	0.99
21–35 years old	91 (58.71)	17 (12.98)	14 (58.33)	
>35 years old	44 (28.3)	37 (28.24)	7 (29.17)	
Gravidity				
≤1	37 (23.87)	33 (25.19)	4 (16.67)	0.37
>1	118 (76.13)	98 (74.81)	20 (83.33)	
Parity				
Nulliparous	41 (26.45)	36 (27.48)	5 (20.83)	0.78
Primiparous	40 (25.81)	33 (25.19)	7 (29.17)	
Multiparous	74 (47.74)	62 (47.33)	12 (50)	
History of abortion	25 (16.13)	21 (16.03)	4 (16.67)	0.94
Gestational age (weeks)	14.56±3.90	14.60±4.06	14.33±2.92	0.70
Uterine size (weeks)	16.99±3.67	16.60±3.56	19.08±3.59	<0.01**
Difference	3 (0–5)	2 (0–4)	4 (3–6)	<0.01**
Mode of evacuation				
Suction curettage	127 (81.94)	106 (80.92)	21 (87.50)	0.44
Hysterectomy	28 (18.06)	25 (19.08)	3 (12.50)	
Chemoprophylaxis				
Not done	31 (20)	25 (19.08)	6 (25)	0.51
Done	124 (80)	106 (80.92)	18 (75)	

SD: Standard deviation, GTD: Gestational trophoblastic disease. * :p<0.05, ** :p<0.01

Table 2: Association of beta-human chorionic gonadotropin values across disease status of gestational trophoblastic disease patients (*n*=155)

Characteristics	Overall	GTD status		*P*
		Remission	Progression	
Median β-HCG levels				
Preevacuation	358,000	311,331	1,030,519	<0.01**
1st week	1784	1557	5977.43	<0.01**
3rd week	146.10	118.10	1079.36	<0.01**
>5 (mIU/mL)	152 (98.06)	128 (97.71)	24 (100)	0.45
5th week	30.98	21.87	920.52	<0.01**
>5 (mIU/mL)	133 (85.81)	109 (83.21)	24 (100)	0.03*
Preevacuation (mIU/mL)				
≤100,000	14 (9.03)	13 (9.92)	1 (4.17)	0.37
>100,000	141 (90.97)	118 (90.08)	23 (95.83)	
β-HCG ratio				
Preevacuation to 1 week				
<10	3 (1.94)	2 (1.53)	1 (4.17)	0.39
≥10	152 (98.06)	129 (98.47)	23 (95.83)	
Preevacuation to 3 weeks				
<30	1 (0.65)	1 (0.76)	-	0.85
≥30	154 (99.35)	130 (99.24)	24 (100)	
1–3 weeks				
<4	35 (22.58)	23 (17.56)	12 (50)	<0.01**
≥4	120 (77.42)	108 (82.44)	12 (50)	
β-HCG at 5 weeks (mIU/mL)				
<20,000	153 (98.71)	131 (100)	22 (91.67)	0.02*
≥20,000	2 (1.29)	-	2 (8.33)	

GTD: Gestational trophoblastic disease, β-HCG: Beta-human chorionic gonadotropin. * :p<0.05, ** :p<0.01

It can be noted that despite the statistical significance, the predicted outcomes for the women in the study using the ratio of β-HCG from 1-and 3-weeks postevacuation, and the cutoff at 20,000 mIU/mL at least 4 weeks after evacuation did not appear to be aligned with the actual disease status observed among women in the sample.

With these findings, the predictive performance of the four β-HCG-based prognostic variables that appeared to have potential in predicting disease status was compared and presented in Figure 1. It can be noted both graphically and statistically that the HCG at 3-and 5-weeks postmolar evacuation had a better prediction of disease progression (χ^2: 163.07, $P < 0.01$) than preevacuation β-HCG (AUC: 0.75, 95% CI: 0.64–0.86), and the β-HCG ratio of the 1st- and 3rd-week measurements (AUC: 0.22, 95% CI: 0.12–0.33).

However, the AUC between the 3-week (AUC: 0.94, 95% CI: 0.90–0.98), and 5-week postevacuation β-HCG levels (AUC: 0.96, 95% CI: 0.93–0.99) did not significantly differ (χ^2: 1.35, $P = 0.25$). The receiver operating characteristic (ROC) curve suggested that the use of the β-HCG ratios as the prognostic model does not appear to be helpful in predicting subsequent outcomes among women in the study. On the hand, the potential for use as a prognostic model is noted for the three remaining β-HCG level measurements.

Various cut points were generated using the three measurements of the glycoprotein, and considering the methods of Liu and Youden, which amplifies the product and sum of the sensitivity and specificity, respectively.[16] The best cutoff for the β-HCG levels preevacuation was <703,000 mIU/mL as of lower risk, and a higher risk if the levels were ≥703,000 mIU/mL. Similar approaches to determining the cutoffs were employed for the 3rd-week and 5th-week postevacuation β-HCG levels, except that the cutoff levels decrease as the period from evacuation increases.

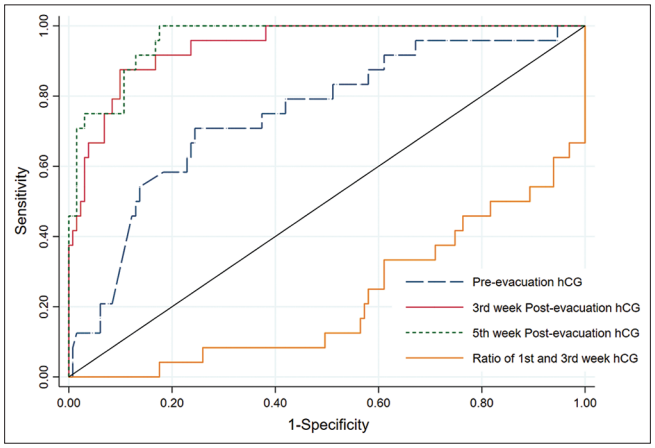

Figure 1: Comparative ROC Curves of β-HCG-based prognostic models and progression. β-HCG: Beta-human chorionic gonadotropin, ROC: Receiver operating characteristic

The diagnostic characteristics of the three β-HCG-based prognostic models are presented in Table 3. It appeared that the predictive performance of the post-evacuation β-HCG levels performed better than the levels before molar evacuation (χ^2: 8.36, $P = 0.02$). Despite having a higher detection rate, its sensitivity, specificity, and predictive values were significantly lower.

Again, no significant difference in the performance between 3rd- and 5th-week postevacuation levels was noted (χ^2: 0.02, $P = 0.89$). The ≥508 mIU/mL cutoff on the 3rd week postevacuation monitoring demonstrated higher specificity, while the ≥185 mIU/mL cutoff on the 5th-week postevacuation demonstrated higher sensitivity.

Both measures had a similar overall classification rate, as exhibited by the area under the receiver operating characteristic curve (AUROC), and negative predictive value. This finding suggests that patients who exhibited remission are more likely to be regarded as low-risk using either classification. However, the proportion of women who had progression and were classified as high risk was higher using the 3rd-week postevacuation β-HCG levels.

Time-to-event analysis using these postevacuation β-HCG-based models was performed to account for relevant factors associated with progression to GTN and shown in Table 4. It can also be said that the rate of progression for every unit increase in uterine size was 1.16 times and 1.20 times higher adjusting for the 3rd-week and 5th-week postevacuation β-HCG, respectively, as well as age in years, gravidity, mode of evacuation, and chemoprophylaxis.

In addition, it can be said that for every one woman who developed progression among those with <508 mIU/mL during the 3rd-week β-HCG surveillance, there will be around 30 women with 3rd-week β-HCG levels ≥508 mIU/mL who had progression. Similarly, that for every one woman who developed progression among those with <185 mIU/mL during the 5th week β-HCG surveillance, there will be around 40 women with 5th-week β-HCG levels ≥185 mIU/mL who had progression.

The said patterns were observed in the survival plots presented in Figure 2, the steeper slopes among those women with β-HCG levels ≥3rd and 5th-week postevacuation cutoffs suggest that these patients developed progression more frequently and at an earlier follow-up period, than otherwise. This further supported the clinical utility of using these cutoffs for β-HCG levels in monitoring patients at the 3rd and 5th after uterine evacuation.

Table 3: Association of beta-human chorionic gonadotropin values across disease status of gestational trophoblastic disease patients (*n*=155)

Characteristics	Preevacuation β-HCG	β-HCG 3rd-week postevacuation	β-HCG 5th-week postevacuation
Cutoff point (mIU/mL)	703,000	508	185
Sensitivity (%)	70.8	87.5	91.7
n/N	17/24	21/24	22/24
95% CI	48.9–87.4	67.6–97.3	73–99
Specificity (%)	75.6	90.1	87
n/N	99/131	118/131	114/131
95% CI	67.3–82.7	83.6–94.6	80–92.3
Positive predictive value (%)	34.7	61.8	56.4
n/N	17/49	21/34	22/39
95% CI	21.7–49.6	43.6–77.8	39.6–72.2
Negative predictive value (%)	93.4	97.5	98.3
n/N	99/106	118/121	114/116
95% CI	86.9–97.3	92.9–99.5	93.9–99.8
AUROC	0.73	0.89	0.89
95% CI	0.63–0.83	0.82–0.96	0.83–0.96
Detection proportion (%)	31.61	21.94	25.16

β-HCG: Beta-human chorionic gonadotropin, CI: Confidence interval, AUROC: Area under the receiver operating characteristic

Table 4: Multivariable Cox regression analysis of disease progression

Covariates	3rd week β-HCG, HR (95% CI)	*P*	5th week β-HCG, HR (95% CI)	*P*
Age (years)	1.06 (0.99–1.13)	0.07	1.04 (0.97–1.11)	0.27
Gravidity	0.97 (0.74–1.25)	0.80	0.95 (0.71–1.25)	0.70
Uterine size (weeks)	1.16 (1.03–1.30)	0.01*	1.20 (1.07–1.33)	<0.01**
Mode of evacuation				
Suction curettage	1.00		1.00	0.12
Total hysterectomy	0.24 (0.05–1.09)	0.07	0.29 (0.06–1.39)	
Chemoprophylaxis				
Not done	1.00		1.00	0.83
Done	1.62 (0.41–6.38)	0.49	1.13 (0.37–3.52)	
β-HCG postevacuation				
Below cutoff	1.00		1.00	<0.01**
Above or equal to cutoff	29.74 (8.53–103.71)	<0.01**	39.89 (8.82–180.38)	

HR: Hazard ratio, β-HCG: Beta human chorionic gonadotropin, CI: Confidence interval. * :p<0.05, ** :p<0.01

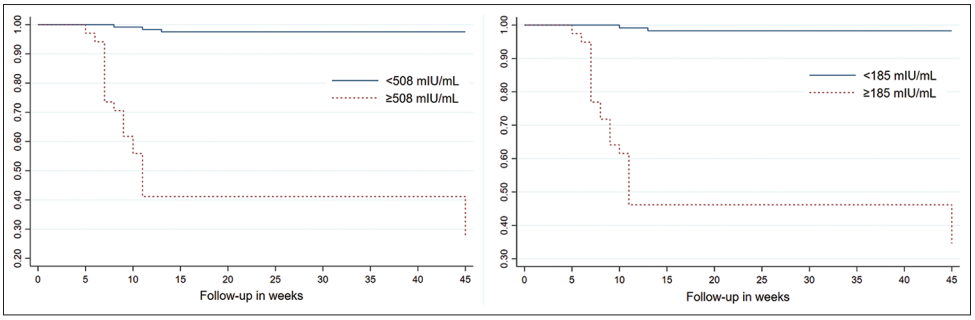

Figure 2: Kaplan–Meier plots for disease progression across 3rd- and 5th-week postevacuation

Furthermore, log-rank test for equality of the plots was performed, suggesting that the time-to-progression curves between <508 and ≥508 mIU/mL levels at the 3rd week of monitoring was indeed not the same (χ^2: 80.71, P = 0.25). The same observation can be said for the 5th-week β-HCG levels, with the survival curves between <185 and ≥185 mIU/mL not being equal (χ^2: 72.17, P = 0.25).

Discussion

The current study was undertaken to improve the early monitoring of β-HCG levels among women with molar pregnancy and refine β-HCG-based prognostic models of GTN.

The incidence of GTN in the sample was not entirely different from previous findings suggesting that

around 15%–20% of women with complete HM eventually develop the said outcome.[17] In contrast, this rate is lower than the 20.5% rate of progression identified in the same institution[18] which can be attributed to the decreasing rates of the condition in Korea and Japan;[19] and a shorter duration of follow-up in the current study.

The findings also showed that the currently implemented -HCG cutoffs used to predict the likelihood of disease progression in the Philippines did not appear to be as discerning. This is further exemplified by the use of a preevacuation HCG level >100,000 mIU/mL previously considered as cut-point suggestive of a higher risk for progression to GTN did not appear to predict the outcomes in the study population.[10,20] A study showed that the majority of Filipino women had preintervention β-HCG levels higher than the cut-point regardless of the disease status.[21] This was the rationale for a higher calculated cutoff at >700,000 mIU/mL to improve the prediction of the outcome, yet the performance of preevacuation HCG levels was still less accurate than postevacuation models.

The categorical classification of an HCG level >5 mIU/mL that would suggest an additional increase in monitoring was not found to be useful in the current sample as well. As such, it can be suggested that reevaluation of prolonged follow-up among women who had molar pregnancy not only to curb the cost of repeated diagnostic testing and visits to the clinician but also to provide prompt intervention to those at a higher risk, and relief to those at a lower probability of developing postmolar GTN.

In addition, the study findings contrasted the reported utility of using ratios of β-HCG of the current over the previous monitoring period.[9,22] In the study, chance appeared to have a better predictive capability than the β-HCG ratio cutoffs, which might be attributed to the more pronounced in HCG levels among Filipino women as compared to the slow and steady change in the glycoprotein levels among European women.[22] The relatively dismal performance of these β-HCG ratio models can be attributed to discrepancies and discordant patterns between the preevacuation and the subsequent HCG levels.[23]

Moreover, the previous observation was supported by a lower cutoff to discriminate disease progression at the 3rd- and 5th-week postevacuation monitoring than the 20,000 mIU/mL cutoff at the 4th week of monitoring that was proposed in other studies.[24] However, the findings concurred with the suggestion of some studies for a shorter surveillance of the β-HCG levels due to early monitoring levels, within 5 weeks after evacuation, can predict precisely the likelihood of disease progression among GTN patients.[9,11]

Multivariable models to account for known risk factors for developing progression were also created. The findings agreed with what was found in literature that the age of the patient, and obstetric history and baseline levels of the serum HCG did not exhibit a strong association with persistent disease.[25] Only uterine size appeared to be another significant predictor of the hazard of postmolar GTN in the sample, which contrasted with what was found in the literature, suggesting that maternal age[26] and antecedent pregnancy[27] are significant predictors of possible GTN.

ROC curve analysis was performed to identify optimum cut-off β-HCG levels in the sample. It can be noted that the cut point for pre-evacuation HCG was higher, while the cut point for HCG levels after the evacuation was notably lower than the ones identified in previous studies.[9,11,22] Other studies preferred a higher cutoff due to a false-negative result more prone to using the β-hCG as a monitoring tool, thus avoiding delayed disease identification or premature withdrawal of therapy.[28]

However, the use of such approaches in estimating the likelihood of disease status do not consider the role of demographic, clinical, and therapeutic characteristics of the women, but rather concentrates on the serum levels of the glycoprotein.

Nevertheless, the survival plots exemplified the utility and potential of using these different postevacuation cutoffs as guidance to the clinician. Given the lack of a statistically significant difference in the performance of the 3rd- and 5th-week biomarker levels, one might question the utility of these cut points, but the concepts of public health surveillance may be applied in this matter.[29] The estimated cutoffs do not suggest curtailing the duration of post-evacuation β-HCG level surveillance rather, the findings suggest a more active approach to risk stratification among these patients. The higher specificity conferred during the 3rd week of monitoring increases the proportion of women considered less likely to develop GTN, but the results of the 5th-week monitoring, which has a higher sensitivity, will eventually help the clinician focus on the women at risk for progression, and might need more invasive procedures or therapy. At the same time, the clinician may opt to reduce the frequency of follow-up among women less likely to develop postmolar GTN.

An important limitation of the study is the limited number of observations to generate externally valid cut points of the β-HCG monitoring as compared to other studies that performed similar methodologies.[9,11,18] The initial cohort included a larger number of women with

a molar pregnancy, but there was a significant loss to follow-up due to various reasons such as limited funds to perform the laboratory procedures, typically costing about 1000 Philippine pesos (PHP 1000), or access to specialty institutions, especially since these patients reside in remote or geographically isolated areas.[12]

Related to this, calibration of prediction using β-HCG-based prognostic models cannot be accommodated due to the small sample size, incomplete and irregular assessment of postevacuation of β-HCG levels, and difficulty to ascertain the disease status of the women in the cohort. Thus, the suggestion of using standardized regression curves from weekly HCG follow-up values to improve the precision and applicability of the measure to all observations cannot be accommodated due to these limitations.[30]

Another important limitation is that the estimated cutoffs did not consider other relevant covariates and maximized the findings based on the serum levels alone. Complex methodologies such as penalized logistic regression and Bayesian approaches have been suggested to improve the discriminant capability and validity of serum level cutoffs in repeated diagnostic measurements. However, the dataset used in the study was quite limited and assumptions to perform the aforementioned procedure might be violated.[31,32]

Lastly, the retrospective nature of the study is an important source of potential bias in the ascertainment of outcomes and covariates, as well as the limited generalizability of the study findings.

Conclusion

The primary interest of the research is to compare the performance of β-HCG based prognostic models in predicting progression to GTN among women who had a complete molar pregnancy. The findings suggest that re-evaluation of the currently implemented practice guidelines in terms of monitoring and surveillance of women with the gestational trophoblastic disease might be needed, given the changing patient landscape of the said disease.[6]

The study can also conclude that the use of β-HCG levels as a first-line preventive measure, considering it was shown to be a significant independent risk factor along with the uterine size and other relevant clinicodemographic characteristics, can facilitate early diagnosis and timely intervention among these women. Moreover, this study demonstrated that the β-HCG levels within the first 3 and 5 weeks after molar evacuation appear to discern subsequent disease outcomes among these patients. The proposed optimum cutoff level of 508 mIU/ml and 185 mIU/mL correctly classified 90% and 88% of the cases, respectively.

The use of these cutoff levels for post-evacuation β-HCG has important implications in terms of clinical practice and education. Practitioners can provide more appropriate and targeted counseling for women with complete HM, specifically on the importance of strictly complying with follow-up consults and adhering to recommended regimens (e.g., avoiding pregnancy after molar evacuation). The additional utility of the corresponding sensitivity and specificity of these cutoff HCG levels allows the classification of these women into high risk and low risk for post-molar GTN, with identification of the former resulting in early and prompt management for potential treatment resistance and neoplasia.

However, before implementing these cutoffs to a wider scale, follow-up research and preferably validation using a larger number of observations, both in cases and in the number of measurements, are highly recommended. Collaborative relationships with local and international institutions with trophoblastic disease specialization can also provide large numbers of patients eligible for inclusion in the study, leading to an even more accurate and diagnostically useful cut-offs for HCG for risk prediction of postmolar GTN, and potentially chemotherapeutic resistance.

Moreover, optimal management and health care planning for rare conditions like gestational trophoblastic disease can be achieved through centralization, as recommended by experts.[33] A national surveillance or disease registry system that will actively collect data on the pretreatment and treatment characteristics of these patients as well as other relevant variables, will demand considerable time and dedication, and resources. However, its yield may provide not only improvements in the care for patients who had molar pregnancy but similar rare or overlooked conditions.

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Authorship contributions

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Maria Stephanie Fay S. Cagayan - Conceptualization, Methodology, Investigation, Validation, Resources, Writing - review & editing, Supervision, Project administration.

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Conflicts of interest
There are no conflicts of interest.

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