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# Serum β-hCG as an Indicator for Persistence in Gestational Trophoblastic Neoplasia

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***ABSTRACT***

***Background****: Gestational trophoblastic neoplasia (GTN) is a potentially aggressive trophoblastic disorder in which persistent elevation or abnormal regression of serum beta-human chorionic gonadotropin (β-hCG) after molar evacuation may indicate persistent disease. Early identification of persistent GTN is essential to reduce morbidity and improve treatment outcomes. Aim of the study: To evaluate the role of serial serum β-hCG levels as an indicator for predicting persistence in gestational trophoblastic neoplasia during post-evacuation follow-up.* ***Methods & Materials****: This prospective observational study was conducted in the Department of Gynecological Oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh, from January 2021 to December 2021. Fifty patients with histopathologically confirmed hydatidiform mole who underwent suction evacuation were enrolled consecutively. Serial serum β-hCG levels were measured 48 hours after evacuation and monitored weekly for at least 8 weeks. Patients were categorized into persistent GTN (Group A, n=7) and spontaneous remission (Group B, n=43). Statistical analyses included chi-square test, unpaired t-test, ROC curve analysis, and multivariate logistic regression.* ***Result****: Persistent GTN developed in 14.0% of patients. Younger age, low socioeconomic status, low BMI, previous molar pregnancy, thyrotoxic features, uterine enlargement, expulsion of grape-like vesicles, large theca lutein cysts, and vesicular uterine appearance on ultrasonography were significantly associated with persistent GTN. All patients with persistent GTN had 48-hour post-evacuation β-hCG levels >100,000 mIU/mL (p=0.011). Mean log β-hCG values became significantly higher in persistent GTN cases from the 5th week onward (p=0.001). Diagnostic performance improved progressively over time, with the highest predictive accuracy observed at the 8th week (cutoff 1.59; sensitivity 97.7%, specificity 100%, AUC 0.997). Multivariate logistic regression identified younger age and elevated 48-hour β-hCG levels as independent predictors of persistent GTN.* ***Conclusion****: Serial serum β-hCG monitoring is a highly effective tool for early detection of persistent GTN following molar evacuation. Elevated 48-hour β-hCG levels and delayed decline of β-hCG after the 5th post-evacuation week are strong predictors of persistence. Regular β-hCG surveillance may facilitate timely intervention and improve clinical outcomes in patients with gestational trophoblastic disease.*

***Keywords:*** *Gestational trophoblastic neoplasia, β-hCG, persistent GTN, hydatidiform mole, post-evacuation monitoring.*

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## INTRODUCTION

Gestational trophoblastic neoplasia (GTN) is a rare but potentially aggressive group of pregnancy-related tumors that develop from abnormal proliferation of placental trophoblastic tissue after conception [1]. Serum beta-human chorionic gonadotropin (β-hCG) is a glycoprotein hormone produced by trophoblastic cells of the placenta during pregnancy, and its serum level is used as a sensitive biochemical marker for the diagnosis, monitoring, and detection of persistence or recurrence in gestational trophoblastic neoplasia [2]. Worldwide, GTN develops in approximately 1-3 per 1000 pregnancies, although the frequency varies among geographic regions and ethnic populations [3]. In Bangladesh and other South Asian countries, the burden appears relatively higher, with persistent GTN reported in nearly 10-15% of complete molar pregnancies [4]. The disease process begins with abnormal fertilization, leading to uncontrolled trophoblastic proliferation and excessive production of β-hCG [5]. After the evacuation of a molar pregnancy, serum β-hCG levels are expected to decline gradually until normalization. Persistent elevation, plateauing, or re-elevation of β-hCG may indicate residual trophoblastic tissue or malignant transformation into GTN [6]. Because β-hCG is secreted directly from trophoblastic cells, serial serum measurement provides a sensitive biochemical marker for monitoring disease activity and treatment response. This monitoring strategy has significantly improved early diagnosis and survival outcomes in affected women [7]. GTN can produce serious maternal complications if persistent disease is not identified early. Delayed diagnosis may lead to uterine invasion, metastatic spread, hemorrhage, infertility, or even death [8]. However, with timely monitoring and chemotherapy, cure rates now exceed 90-95%, even in metastatic disease [9]. Regular β-hCG surveillance has major importance as it allows clinicians to detect persistence before severe complications occur. In addition, early intervention helps preserve reproductive potential and reduces psychological distress associated with prolonged illness [10].

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The use of serum β-hCG as an indicator for persistence has several advantages. It is minimally invasive, cost-effective, highly sensitive, and suitable for repeated follow-up assessments [11]. Serum measurement also enables risk stratification and guides therapeutic decisions during chemotherapy and remission monitoring. Despite these benefits, certain disadvantages remain. False-positive fluctuations, laboratory variability, and inconsistent follow-up schedules may occasionally affect interpretation [12]. Furthermore, many existing studies have focused mainly on diagnosis and treatment outcomes rather than evaluating the predictive value of serial β-hCG trends for persistent GTN in resource-limited settings. Another important limitation in current research is the scarcity of updated regional data from Bangladesh regarding post-evacuation β-hCG monitoring and persistence patterns [4,11]. Differences in socioeconomic conditions, delayed hospital presentation, and irregular follow-up may influence disease progression locally. Consequently, findings from Western populations cannot always be generalized to Bangladeshi women [12]. So, there is a growing need for context-specific evidence to improve monitoring strategies and optimize patient outcomes. The objective of this study was to evaluate the role of serial serum β-hCG levels as an indicator for predicting persistence in gestational trophoblastic neoplasia during post-treatment follow-up.

## METHODS & MATERIALS

This prospective observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Bangladesh. The study period was between January 2021 and December 2021. A total of 50 patients diagnosed with hydatidiform mole and undergoing uterine evacuation were enrolled consecutively in the study. Participants were followed after evacuation with serial serum β-hCG measurements to determine the development of persistent gestational trophoblastic neoplasia (PGTN). Participants were categorized into two groups:

**Group A (n=7):** Patients who developed persistent GTN

**Group B (n=43):** Patients who achieved spontaneous remission without persistence

**Inclusion Criteria:**

- Histopathologically confirmed hydatidiform mole
- Patients who underwent suction evacuation
- Availability of serial serum β-hCG follow-up data

**Exclusion Criteria:**

- Patients with previously diagnosed malignant GTN before evacuation
- Diagnosed cases of abortion, including missed or incomplete abortion
- Patients with severe medical illness interfering with follow-up

### Ethical Considerations

Ethical clearance for the study was obtained from the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University prior to data collection. All participants were informed about the purpose, procedures, benefits, and possible risks of the study, and written informed consent was obtained before enrollment. Participation was voluntary, and confidentiality of all patient information and records was strictly maintained throughout the study.

### Data Collection

Molar pregnancy was diagnosed initially by history of amenorrhoea, P/V bleeding, expulsion of mole. Then on clinical examination, USG report, β-hCG level and finally confirmed by histopathology. Detailed demographic and clinical information were collected using a structured questionnaire and hospital records. Variables included age, monthly family income, body mass index (BMI), parity, gestational age, previous history of molar pregnancy, family history of molar pregnancy, and history of thyrotoxic features. Clinical examination findings such as uterine size and expulsion of grape-like vesicles were recorded. Ultrasonographic findings including vesicular uterine appearance, necrotic uterine tissue, and presence and size of theca lutein cysts were also documented.

Serum β-hCG levels were measured 48 hours after molar evacuation and subsequently monitored weekly. Serial β-hCG monitoring was continued for at least 8 weeks or until normalization of β-hCG levels. Persistent GTN was diagnosed according to the FIGO 2000 criteria, including:

- Plateau of serum β-hCG levels over at least 3 consecutive weeks
- Rise in serum β-hCG levels over at least 2 consecutive weeks

The serial β-hCG levels from the 1st to 8th post-evacuation weeks were analyzed using log-transformed values to assess their predictive ability for persistent GTN. Due to the markedly skewed distribution of serum β-hCG values, logarithmic transformation of β-hCG values was performed before statistical analysis. Patients diagnosed with persistent GTN were further categorized into low-risk and high-risk groups according to the FIGO scoring system.

### Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 20. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as frequency and percentage. Comparisons between groups were performed using unpaired student's t-test for continuous variables and chi-square test for categorical variables. Repeated measures of log-transformed β-hCG concentrations from the 1st to 8th week after evacuation were analyzed to evaluate their association with development of PGTN. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal β-hCG cutoff values, sensitivity, specificity, area under the curve (AUC). Multivariate logistic regression analysis was conducted to identify independent predictors of persistent GTN. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value less than 0.05 was considered statistically significant.

## RESULTS

Group A patients were significantly younger than Group B patients, with 71.43% aged <20 years compared with 16.28% in Group B (p=0.024), and a lower mean age (25±11.28 and 34.28±9.59 years). Low monthly income (<6000 Tk) was more frequent in Group A (85.71%, p=0.038). All patients in Group A had a BMI <18.5 kg/m$^2$ compared with 48.84% in Group B (p=0.040). Higher parity was more common in Group A (p=0.049), while gestational age showed no significant difference between groups (p=0.268). History of thyrotoxic features (85.71% and 74.42%) and previous molar pregnancy (71.43% and 79.07%) were significantly associated between groups. Positive family history of molar pregnancy or choriocarcinoma was observed only in Group A (p<0.001) (*Table I*).

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**Table I: Baseline characteristics of study participants (*n*=50).**

| Variables | Group A (n=7) | | Group B (n=43) | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Age (Years) | | | | | |
| <20 | 5 | 71.43 | 7 | 16.28 | 0.024 |
| 20-40 | 0 | 0.00 | 16 | 37.21 | |
| >40 | 2 | 28.57 | 20 | 46.51 | |
| Mean±SD | 25±11.28 | | 34.28±9.59 | | |
| Monthly income (Tk) | | | | | |
| <6000 | 6 | 85.71 | 13 | 30.23 | 0.038 |
| 6001-15000 | 1 | 14.29 | 9 | 20.93 | |
| 15001-30000 | 0 | 0.00 | 13 | 30.23 | |
| >30000 | 0 | 0.00 | 8 | 18.60 | |
| BMI (kg/m2) | | | | | |
| <18.5 | 7 | 100.00 | 21 | 48.84 | 0.04 |
| 18.5-24.5 | 0 | 0.00 | 18 | 41.86 | |
| 25-29.9 | 0 | 0.00 | 4 | 9.30 | |
| Parity | | | | | |
| 0 | 3 | 42.86 | 8 | 18.60 | 0.049 |
| 1-3 | 0 | 0.00 | 21 | 48.84 | |
| >3 | 4 | 57.14 | 14 | 32.56 | |
| Gestational age (weeks) | | | | | |
| 0-8 | 2 | 28.57 | 20 | 46.51 | 0.268 |
| 9-12 | 4 | 57.14 | 22 | 51.16 | |
| >12 | 1 | 14.29 | 1 | 2.33 | |
| History of thyrotoxic feature | | | | | |
| Present | 6 | 85.71 | 11 | 25.58 | 0.001 |
| Absent | 1 | 14.29 | 32 | 74.42 | |
| History of mole in previous pregnancy | | | | | |
| Present | 5 | 71.43 | 9 | 20.93 | 0.005 |
| Absent | 2 | 28.57 | 34 | 79.07 | |
| Family history of molar pregnancy | | | | | |
| Molar pregnancy | 4 | 57.14 | 0 | 0.00 | 0.00 |
| Choriocarcinoma | 1 | 14.29 | 0 | 0.00 | |
| No | 2 | 28.57 | 43 | 100.00 | |

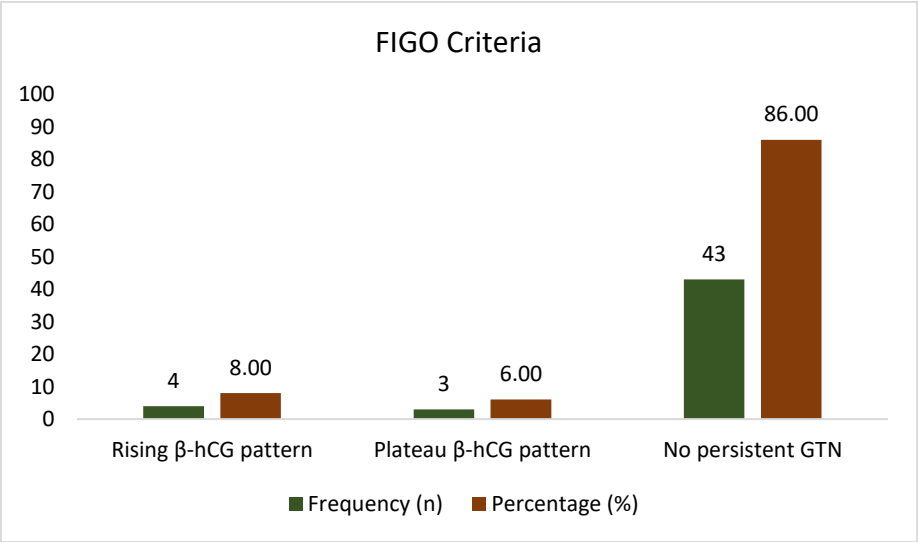


**Figure 1: FIGO criteria pattern among participants (*n*=50).**

No persistent GTN was identified in 86.00%, while 8.00% and 6.00% had a rising β-hCG pattern and a plateau β-hCG pattern (*Figure 1*).

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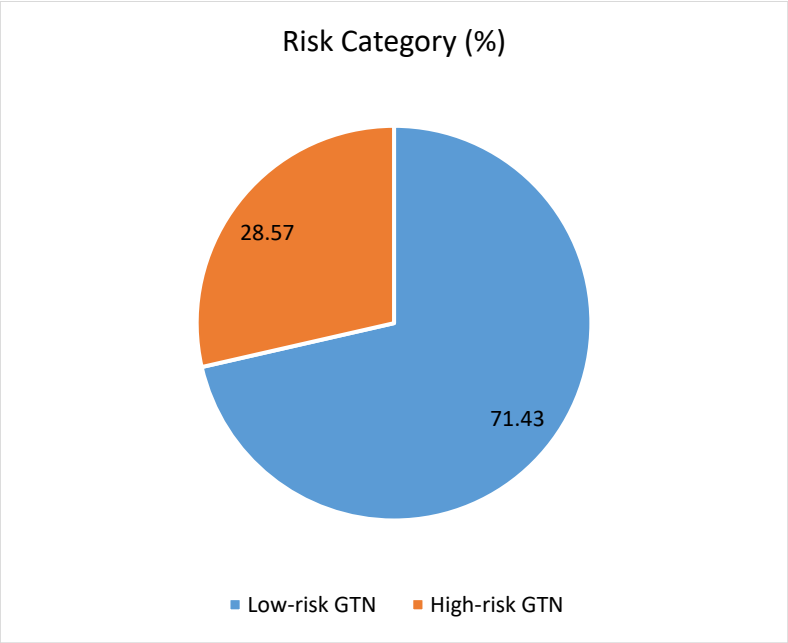


**Figure 2: Risk category among PGTN positive patients (*n*=7).**

71.43% were categorized as low-risk GTN and 28.57% as high-risk GTN (*Figure 2*).

Expulsion of grape-like vesicles was observed in all patients of Group A compared with 60.47% in Group B (p=0.041). Uterine size > period of gestation was significantly higher in Group A (85.71%, p=0.043). Theca lutein cysts >6 cm were more frequent in Group A (57.14%, p=0.029), while vesicular/cystic uterine appearance on ultrasonography was also significantly associated with Group A (71.43%). Necrotic uterine tissue on USG was found only in Group A patients (28.57%; p=0.012). Although the presence of theca lutein cysts was higher in Group A (71.43%), the association was not statistically significant (p=0.088) (*Table II*).

**Table II: Clinical and ultrasonographic predictors of persistent GTN (*n*=50)**

| Variables | Group A (n=7) | | Group B (n=43) | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| Expulsion of grape-like vesicles | 7 | 100.00 | 26 | 60.47 | 0.041 |
| Uterine size > period of gestation | 6 | 85.71 | 13 | 30.23 | 0.043 |
| Theca lutein cyst present | 5 | 71.43 | 16 | 37.21 | 0.088 |
| Theca lutein cyst >6 cm | 4 | 57.14 | 6 | 13.95 | 0.029 |
| Vesicular/cystic uterine appearance on USG | 5 | 71.43 | 18 | 41.86 | 0.005 |
| Necrotic uterine tissue on USG | 2 | 28.57 | 0 | 0.00 | 0.012 |

All PGTN-positive patients had 48-hour serum β-hCG levels >100,000, compared with 48.84% of PGTN-negative patients (p=0.011) (*Table III*).

**Table III: Correlation of PGTN status with 48 hours post evacuation β-hCG level (*n*=50).**

| 48 hours post evacuation β-hCG | Group A (n=7) | | Group B (n=43) | | p-value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| <100000 | 0 | 0.00 | 22 | 51.16 | 0.011 |
| >100000 | 7 | 100.00 | 21 | 48.84 | |

During the first 4 weeks, mean log β-hCG levels were comparable between Group A and Group B, with no statistically significant differences. From the 5th week onward, Group A showed persistently higher β-hCG levels compared to Group B, with significant differences (p=0.001), indicating a slower decline of β-hCG in persistent GTN cases (*Table IV*).

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**Table IV: Serial post-evacuation serum β-hCG trend according to PGTN status.**

| Follow-up Week | Group A, Mean log β-hCG ± SD | Group B, Mean log β-hCG ± SD | p-value |
|---|---|---|---|
| 1st week | 4.68 ± 0.49 | 4.69 ± 0.42 | 0.954 |
| 2nd week | 4.32 ± 0.54 | 4.37 ± 0.59 | 0.834 |
| 3rd week | 4.12 ± 0.51 | 3.88 ± 0.71 | 0.396 |
| 4th week | 4.04 ± 0.74 | 3.47 ± 0.78 | 0.077 |
| 5th week | 4.15 ± 0.68 | 3.01 ± 0.85 | 0.001 |
| 6th week | 4.09 ± 0.76 | 2.41 ± 0.91 | 0.001 |
| 7th week | 4.34 ± 0.94 | 1.82 ± 0.70 | 0.001 |
| 8th week | 3.99 ± 1.18 | −1.31 ± 0.77 | 0.001 |

Diagnostic accuracy was modest during the early weeks but increased substantially after the 5th week. The highest predictive value was observed at the 8th week with a cutoff value of 1.59, showing 97.7% sensitivity, 100% specificity, and an AUC of 0.997 (*Table V*).

**Table V: Diagnostic performance of serum β-hCG for predicting persistent GTN**

| Weeks | Cut off value | Sensitivity (%) | Specificity (%) | AUC |
|---|---|---|---|---|
| 1st week | 4.6 | 71.4 | 27.9 | 0.513 |
| 2nd week | 4.61 | 71.4 | 37.2 | 0.505 |
| 3rd week | 4.45 | 74.4 | 42.9 | 0.601 |
| 4th week | 4.06 | 79.1 | 57.1 | 0.698 |
| 5th week | 3.7 | 83.7 | 71.4 | 0.852 |
| 6th week | 3.63 | 86 | 75.1 | 0.907 |
| 7th week | 2.62 | 86 | 85.7 | 0.977 |
| 8th week | 1.59 | 97.7 | 100 | 0.997 |

Younger age was significantly associated with persistent disease (adjusted OR 1.17). A 48-hour β-hCG level >100,000 mIU/mL showed a strong independent association with persistent GTN (adjusted OR 3.82). Previous molar pregnancy, thyrotoxic features, and enlarged uterine size showed no statistically significant associations with persistent GTN (*Table VI*).

**Table VI: Multivariate logistic regression analysis for predictors of persistent GTN**

| Variables | Adjusted OR | 95% CI | p value |
|---|---|---|---|
| Younger age | 1.17 | 1.02–16.35 | 0.03 |
| Previous molar pregnancy | 0.48 | 0.35–1.93 | 0.199 |
| Thyrotoxic features | 0.03 | 0.20–1.05 | 0.363 |
| Enlarged uterine size | 0.88 | 0.52–2.94 | 0.119 |
| 48-hour β-hCG >100,000 mIU/mL | 3.82 | 1.41–10.32 | 0.008 |

## DISCUSSION

Gestational trophoblastic neoplasia (GTN) remains a highly curable malignancy when identified early, and serial serum β-hCG monitoring has emerged as the cornerstone for detecting persistent trophoblastic activity following molar evacuation [13]. In our study, younger age (<20 years), low socioeconomic status, low BMI, nulliparity, and prior molar pregnancy were significantly associated with persistent GTN. Kang et al. demonstrated that extremes of maternal age and previous molar pregnancy significantly increase the risk of GTN development, consistent with our finding that younger patients had higher persistence rates [14]. Similarly, Khoo (2003) identified prior molar pregnancy as a strong independent predictor of persistent trophoblastic disease, reinforcing our observation of a 71.4% recurrence history in Group A [15]. Mousavi et al. reported that delayed follow-up and poor socioeconomic status significantly increase persistent disease likelihood, aligning with our findings of significantly higher GTN in low-income groups [16]. Our observation of a strong association between thyrotoxic features and persistent GTN (85.7%) is biologically plausible, as elevated β-hCG can stimulate TSH receptors. This has been well documented in GTD literature, where hyperthyroidism is considered a marker of high tumor burden [17]. Among our pGTN cases, 8.00% presented with a rising β-hCG pattern, while 6.00% showed a plateau. This distribution matches the findings of Wolfberg et al., who noted that while a plateauing pattern is more frequent in larger groups, a rising trend indicates highly aggressive, actively proliferating trophoblastic tissue [18]. In our study, 71.43% were classified as low-risk GTN and 28.57% as high-risk GTN using the FIGO scoring system. This finding aligns closely with Niemann et al., who found that the vast majority of post-molar persistence cases present as low-risk disease that responds well to single-agent chemotherapy [19]. We found that uterine size larger than gestational age, grape-like vesicles, cystic uterine appearance, and large theca lutein cysts were significantly associated with persistent GTN. These findings are strongly supported by Lurain (2010), who emphasized that uterine enlargement and theca lutein cysts reflect excessive trophoblastic stimulation and high β-hCG levels, correlating with malignant potential [1]. Furthermore, Kang et al. showed that uterine size disproportion is a strong predictor of post-molar malignancy progression, reinforcing our findings of 85.7% uterine enlargement in Group A [14]. Another study by Robson & Waugh (2012) confirms that excessive uterine enlargement caused by rapid trophoblastic overgrowth is an independent warning sign for post-molar persistence [20]. Large theca lutein cysts >6 cm (p=0.029) and a classic vesicular/cystic uterine appearance (p=0.005) were highly prevalent in the persistent group. These findings are consistent with Ghorani & Seckl (2025), who reported that

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prominent hyperstimulation of the ovaries (theca lutein cysts) driven by massive endogenous β-hCG production directly correlates with an increased risk of persistence [21]. A 48-hour post-evacuation β-hCG level >100,000 mIU/mL was significantly associated with persistent GTN (100% in Group A and 48.8% in Group B, p=0.011). This is consistent with Mousavi et al., who demonstrated that early post-evacuation β-hCG levels are strong predictors of persistent disease, with higher baseline and early post-evacuation levels strongly correlating with GTN development [16]. This sharp contrast confirms the findings of Neelakanthi, who proposed that a 48-hour post-evacuation threshold of 100,000 mIU/mL serves as an excellent early screening tool to flag patients requiring closer surveillance [22]. Our longitudinal analysis demonstrated a progressive divergence in β-hCG trends after the 4th week, with statistically significant differences from week 5 onward ($p<0.001$), and markedly elevated levels persisting in Group A. Lybol et al. demonstrated that log-linear β-hCG regression over time accurately differentiates spontaneous remission from GTN progression, with persistent plateau or slow decline indicating malignancy [23]. Similarly, Kohorn (2001) emphasized that failure of β-hCG to decline exponentially after evacuation is the earliest biochemical marker of persistent GTN, which mirrors our finding of sustained elevated log β-hCG in Group A through week 8 [24]. Similarly, Yarandi et al. found that early β-hCG decline patterns within the first week are significantly different between GTN and non-GTN cases, reinforcing the prognostic value of early post-evacuation levels [25]. During the first three weeks, the mean log values between Group A and Group B were statistically indistinguishable, showing that early downward trends can mimic normal regression. This kinetic pattern mirrors research by Cole (2009), who explained that early post-evacuation β-hCG measurements often fluctuate due to the clearance of degenerating, non-viable villi. True clinical persistence becomes apparent only after 4 to 6 weeks, as autonomous, viable trophoblastic tissue continues to secrete the hormone [26]. We observed increasing diagnostic accuracy over time, with AUC rising from 0.513 (week 1) to 0.997 (week 8), indicating excellent predictive performance of late β-hCG levels. At this final point, a log cut-off value of 1.59 provides a sensitivity of 97.7% and a specificity of 100%. These results are comparable with those of Kang et al., who reported that 2-week β-hCG levels had an AUC ~0.80 for predicting GTN [14]. Another study by Mousavi et al., who found that β-hCG at 2-3 weeks provides the highest diagnostic accuracy (AUC up to 0.80) [16]. More advanced modeling studies by Trommel et al. demonstrated that β-hCG slope analysis can achieve an AUC >0.90 in predicting persistent disease, closely matching our late-week performance [27]. Our regression analysis identified younger age and elevated 48-hour β-hCG (>100,000 mIU/mL) as independent predictors of persistent GTN. Additionally, Jin-Kai et al., noted that while clinical signs like uterine enlargement and thyrotoxicosis are valuable during initial exams, early biochemical markers exert the strongest independent impact when predicting true clinical persistence [28].

## LIMITATIONS

- The sample size was relatively small, particularly the number of patients with persistent GTN (n=7), which may have reduced the statistical power of subgroup analyses.
- Serial β-hCG measurements were performed in a single institutional laboratory; therefore, inter-laboratory variability could not be evaluated.
- The study did not compare serum β-hCG monitoring with other potential biomarkers or imaging modalities for prediction of persistent GTN.

## CONCLUSION & RECOMMENDATIONS

This study demonstrated that serial serum β-hCG measurement is a reliable and sensitive method for predicting persistent gestational trophoblastic neoplasia after molar evacuation. Patients with elevated 48-hour post-evacuation β-hCG levels and delayed regression of β-hCG during follow-up were at significantly higher risk of developing persistent disease. Significant divergence in β-hCG trends became evident from the 5th post-evacuation week onward, with excellent diagnostic accuracy observed by the 8th week. Younger age and markedly elevated early β-hCG levels were identified as independent predictors of persistence. Regular and structured β-hCG surveillance following evacuation of molar pregnancy can facilitate early diagnosis, prompt treatment initiation, and improved patient outcomes, particularly in resource-limited settings such as Bangladesh.

## FUNDING

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## CONFLICT OF INTEREST

None declared

## ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee.

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