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Research Article

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Evaluation and simplification of risk factors in FIGO 2000 scoring system for gestational trophoblastic neoplasia: a 19-year retrospective analysis

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Abstract: Objective: The International Federation of Gynecology and Obstetrics (FIGO) 2000 scoring system classifies gestational trophoblastic neoplasia (GTN) patients into low- and high-risk groups, so that single- or multi-agent chemotherapy can be administered accordingly. However, a number of FIGO-defined low-risk patients still exhibit resistance to single-agent regimens, and the risk factors currently adopted in the FIGO scoring system possess inequable values for predicting single-agent chemoresistance. The purpose of this study is therefore to evaluate the efficacy of risk factors in predicting single-agent chemoresistance and explore the feasibility of simplifying the FIGO 2000 scoring system for GTN. Methods: The clinical data of 578 GTN patients who received chemotherapy between January 2000 and December 2018 were retrospectively reviewed. Univariate and multivariate logistic regression analyses were carried out to identify risk factors associated with single-agent chemoresistance in low-risk GTN patients. Then, simplified models were built and compared with the original FIGO 2000 scoring system. Results: Among the eight FIGO risk factors, the univariate and multivariate analyses identified that pretreatment serum human chorionic gonadotropin (hCG) level and interval from antecedent pregnancy were consistently independent predictors for both first-line and subsequent single-agent chemoresistance. The simplified model with two independent factors showed a better performance in predicting single-agent chemoresistance than the model with the other four non-independent factors. However, the addition of other co-factors did improve the efficiency. Overall, simplified models can achieve favorable performance, but the original FIGO 2000 prognostic system still features the highest discrimination. Conclusions: Pretreatment serum hCG level and interval from antecedent pregnancy were independent predictors for both first-line and subsequent single-agent chemoresistance, and they had greater weight than other non-independent factors in predicting single-agent chemoresistance. The simplified model composed of certain selected factors is a promising alternative to the original FIGO 2000 prognostic system, and it shows comparable performance.

Key words: Gestational trophoblastic neoplasia (GTN); Single-agent chemotherapy; Chemoresistance; Risk factor

1 Introduction

Gestational trophoblastic neoplasia (GTN) is a sort of pregnancy-related, frequently malignant trophoblastic disease, which includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. GTN is a less common group of gynecological cancers, and it can be mostly cured by chemotherapy alone even with wide metastases, with the effective drugs introduced almost 60 years ago (Lurain, 2003).

In 2002, the Cancer Committee of International Federation of Gynecology and Obstetrics (FIGO) combined an anatomic FIGO system with the modified World Health Organization (WHO) scoring system to provide clinicians with a unified FIGO classification for reporting GTN, which allowed the valid comparison of the outcomes from different institutions (FIGO Oncology Committee, 2002). This prognostic

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scoring system, which is comprised of eight factors to calculate the risk of developing chemoresistance to single-agent therapies, stratifies GTN patients into two categories. A score of 6 or less indicates a "low risk" of resistance to single-agent chemotherapy with methotrexate or actinomycin-D, whereas a score of 7 or more signifies a "high risk" of resistance to single drug and demands combination chemotherapy (Kohorn, 2002).

Guided by the well-established FIGO 2000 system, the primary remission rates with methotrexate therapies reached 69%–93% (Smith et al., 1982; Wong et al., 1985; Gleeson et al., 1993; Abrão et al., 2008; Lertkhachonsuk et al., 2009; Kang et al., 2010b; Uberti et al., 2015), and the complete remission (CR) rates of salvage actinomycin-D therapies reached 75%–92% (Abrão et al., 2008; Chalouhi et al., 2009; Lurain et al., 2012; Prouvot et al., 2018). Other alternative single-agent options for low-risk GTN patients in Asia include fluorouracil and etoposide, and their remission rates varied from 67% to 85% based on different protocols (Sung et al., 1984; Lurain and Elfstrand, 1995; Cyriac et al., 2011; Mora et al., 2019). However, there is still a gap between the successful rate of single-agent chemotherapy predicted by the FIGO 2000 prognostic system and the actual outcomes. Furthermore, this system is quite elaborate, because several of the risk factors are relevant to tumor burden and therefore may be repetitive and interrelated with each other. In addition, a wide range of variables feature a growing variability, which may lead to inconvenience for clinical implementation and difficulties in disease management.

In this study, we retrospectively reviewed GTN patients treated in a territorial referral center of East China, and analyzed the FIGO risk factors associated with single-agent chemoresistance in low-risk patients. Our aim was to explore any potential improvements to the risk evaluation of single-agent chemoresistance, so that the accuracy of the FIGO prognostic scoring system can be enhanced and it can be made more concise.

2 Materials and methods

2.1 Patients and data

The data of patients diagnosed with GTN between January 2000 and December 2018 were retrospectively collected from the Medical Record Review System of Women's Hospital, School of Medicine, Zhejiang University, China. Patients with incomplete data of diagnosis or treatments or the presence of placental site trophoblastic tumor or epithelioid trophoblastic tumor were excluded. All patients underwent a comprehensive evaluation prior to first chemotherapy at our hospital and were classified according to the revised FIGO 2000 staging and scoring system. A score of 6 or less was considered as low risk and a score of 7 or more was ranked as high risk (Ngan et al., 2018). Considering the retrospective nature of the study, no sample size calculation was performed, and all eligible patients were included in the analysis.

The data on demographics and clinical characteristics included patient age, history of previous pregnancy and delivery, history of surgery, physical and laboratory examination, and pathological diagnosis if the patient had undergone surgery. In addition, information on primary, secondary and subsequent treatments, as well as the relevant responses was collected.

2.2 Treatment protocols

The treatments were formulated by the stage and risk score. Low-risk and high-risk patients were started with single-agent and multi-agent chemotherapy regimens, respectively. During the studied period of 19 years, several chemotherapy regimens were involved. The single-agent chemotherapy regimens included: (1) 5-d methotrexate, (2) 8-d methotrexate/folinic acid, (3) weekly methotrexate, (4) 5-d actinomycin-D, (5) 8-d 5-fluorouracil, and (6) 5-d etoposide. The multi-agent chemotherapy regimens included: (1) EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine), (2) EMA/EP (etoposide, methotrexate, actinomycin-D/etoposide, cisplatin) or EP/EMA, and (3) TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide).

Drug resistance was clinically defined as follows: after two successive chemotherapy cycles, (1) the serum human chorionic gonadotropin (hCG) level was not decreased logarithmically, or remained at a plateau above normal or increased; or (2) imaging tests indicated that the tumor size was enlarged or new lesions emerged (Song et al., 2004). Toxicity was scaled in each cycle conforming to WHO criteria (Miller et al., 1981). In cases with the presence of drug resistance or unendurable toxicity, the chemotherapy regimens would be changed. For low-risk patients, the initial single-agent regimen would be replaced with

an alternative single-agent regimen and the multi-agent chemotherapy would be administrated when secondary single-agent regimens still failed. Additional consolidation cycles were continued for at least two rounds in low-risk patients and three in high-risk patients after serum hCG normalization. A CR was defined as three consecutive weekly normal serum hCG levels (<5.3 IU/L) after completing the treatments.

2.3 Statistical analysis

The patient characteristics were summarized by descriptive statistics. Continuous data were presented as median and interquartile range (IQR), while categorical data were reported as number and proportion. Univariate and multivariate logistic regression analyses were conducted to identify the values of the risk factors for predicting single-agent chemoresistance in low-risk GTN patients, with a two-side $P \leqslant 0.05$ set as the statistical significant level. Then, modified risk models based on multivariate logistic regression were built for predicting single-agent chemoresistance, and the receiver operating characteristic (ROC) curves were used to assess the performance. Moreover, multivariate logistic regression using stepwise process was carried out in all patients based on the previous results. A number of simplified models that had excellent classification performance in accordance with the original FIGO system were established, and the ROC curves were used to evaluate the discrimination. All data management and statistical analyses were accomplished by IBM SPSS Statistics (Version 20.0, International Business Machines Corporation, Armonk, NY, USA).

3 Results

3.1 Overview of patient information

This study included a total of 578 GTN patients, among which 475 were low-risk and 103 were high-risk according to the revised FIGO 2000 staging and scoring system (Ngan et al., 2018). The median (IQR) age of enrolled patients was 28 (25, 37) years and the median (IQR) value of pretreatment serum hCG level was 5612 (1201, 23 302) IU/L. Metastases outside the uterus were found in 69.6% of patients. Fig. 1 shows the flowchart of patient inclusion. All patients were treated with chemotherapy and some of them underwent concomitant surgeries depending on their condition, among which 7.6% of low-risk patients and 18.4% of high-risk patients underwent hysterectomy. The demographic and clinical characteristics of the patients were summarized in Table 1. Among low-risk patients, 58.1% achieved CR with first-line single-agent,

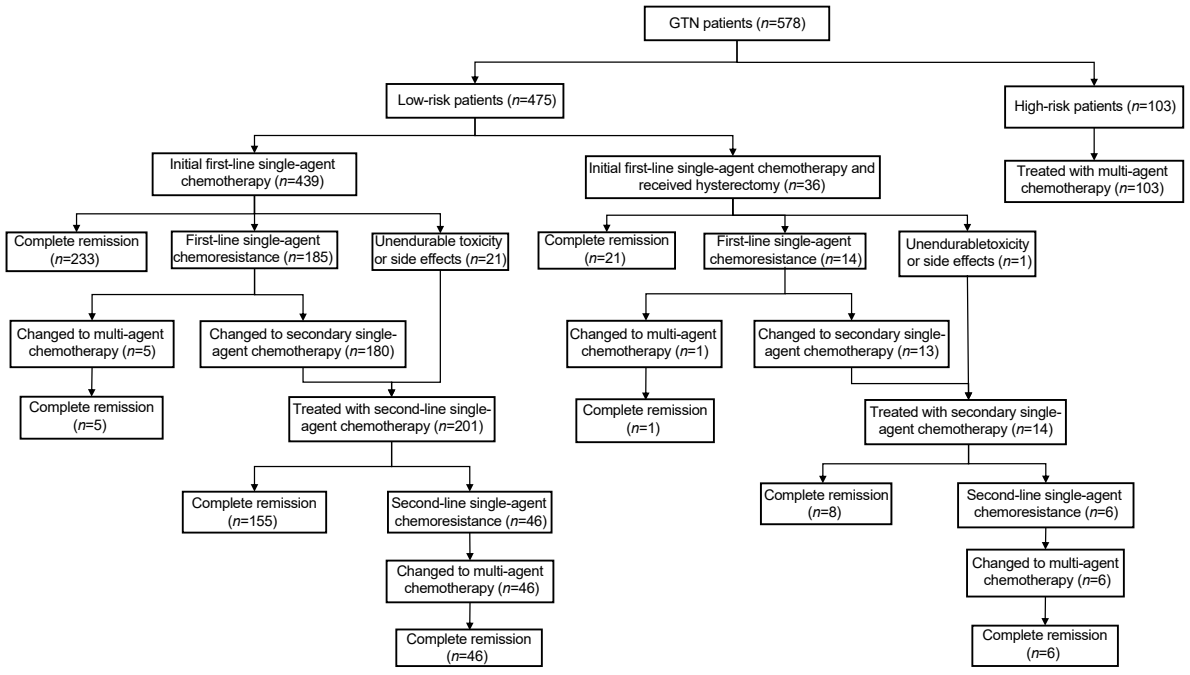

Fig. 1 Flowchart of the enrolled gestational trophoblastic neoplasia (GTN) patients treated with chemotherapy.

an additional 30.7% achieved CR with secondary single-agent, and the remaining 11.2% needed multi-agent to salvage. All of the low-risk patients eventually achieved CR.

3.2 Risk factor analysis

In order to determine the risk factors associated with single-agent chemoresistance, univariate and multivariate analyses were performed in 439 of 475 low-risk patients. The remaining 36 patients underwent hysterectomy, among which 25 received surgery as a primary therapy and 11 received it after first-line or second-line chemotherapy as a salvage treatment. These patients were excluded because advanced age was the main indication of surgery and the operation was influential to subsequent treatment, which would consequently result in a large bias. The details of the single-agent chemotherapy regimens of 439 low-risk patients were shown in Table 2. Six FIGO risk factors were taken into account, including age, antecedent pregnancy type, interval from antecedent pregnancy, pretreatment serum hCG level, largest tumor size including uterus, and number of metastases. The site of metastases was not listed because low-risk patients were confirmed as having no distant metastases other than in the lung, and previous failed chemotherapy was not shown because the included low-risk patients were all scored before first-line chemotherapy.

Table 1 Demographic and clinical characteristics of patients

Characteristics	Low-risk (*n*=475)	High-risk (*n*=103)
Age (years)	28 (25, 37)	29 (25, 38)
Obstetric history		
Gravidity	2 (1, 3)	2 (2, 3)
Parity	0 (0, 1)	1 (0, 1)
Pretreatment serum hCG (IU/L)	3996 (910, 15 719)	42 512 (10 000, 178 413)
FIGO score	2 (1, 3)	8 (7, 10)
FIGO stage		
I	151 (31.8%)	25 (24.3%)
II	6 (1.3%)	5 (4.9%)
III	318 (66.9%)	66 (64.1%)
IV	0	7 (6.8%)
Surgery		
Hysterectomy	36 (7.6%)	19 (18.4%)
Uterine lesion resection	5 (1.1%)	9 (8.7%)
Pulmonary lobectomy	2 (0.4%)	2 (1.9%)
Other	21 (4.4%)	28 (27.2%)

Data are expressed as median (IQR) or number (percentage). hCG: human chorionic gonadotropin; FIGO: International Federation of Gynecology and Obstetrics; IQR: interquartile range.

Table 2 Single-agent chemotherapy regimens used for low-risk GTN patients

Agent	Usage	Course interval* (d)	Number of patients	
			Agent used as first-line therapy	Agent used as second-line therapy
Methotrexate	0.4 mg/(kg·d) IV or IM for 5 d	14	401	2
Methotrexate/folinic acid	Methotrexate 1 mg/(kg·d) IM on Days 1, 3, 5, and 7 with folinic acid 0.1 mg/(kg·d) on Days 2, 4, 6, and 8	14	30	1
Methotrexate weekly	30–50 mg/m^2 IM weekly	7	4	0
Actinomycin-D	10–12 μg/(kg·d) IV for 5 d	14	2	193
5-Fluorouracil	28–30 mg/(kg·d) IV for 8 d	21	2	4
Etoposide	100 mg/(m^2·d) IV for 5 d	14	0	1

* The course interval usually means the interval from the first day of the last course to the first day of the next course. IV: intravenous injection; IM: intramuscular injection.

Univariate and multivariate analyses were carried out sequentially in low-risk GTN patients treated with single-agent chemotherapy. The univariate analysis revealed that the interval from antecedent pregnancy and pretreatment serum hCG level were significantly associated with the risk of resistance to first-line single-agent therapy, whereas age, antecedent pregnancy type, largest tumor size, or the number of metastases was not. In multivariate analysis, interval exceeding 12 months (odds ratio (OR)=22.37, P=0.003) and pretreatment serum hCG level between 10 000 and 100 000 IU/L (OR=2.79, P=0.001) were detected as strongly related to first-line single-agent chemoresistance. The detailed results were shown in Table 3.

When patients failed to respond to a first-line single-agent, they were referred to a second-line single-agent. Thus, the risks of chemoresistance to both first-line and second-line single agents were analyzed. The interval from antecedent pregnancy, pretreatment serum hCG level, and largest tumor size were found to be statistically significant by univariate analysis. Subsequent multivariate logistic regression analysis consistently recognized an interval exceeding 7 months (OR=9.44, P=0.027) and 12 months (OR=7.02, P=0.014), and pretreatment serum hCG level above 10 000 IU/L (OR=5.58, P=0.003) and 100 000 IU/L (OR=34.88, P=0.009) as the independent predictive factors for single-agent chemoresistance, although the numbers in some categories were relatively small. The obtained data were presented in Table 4.

3.3 Comparison between the simplified models and the FIGO 2000 scoring system

We applied ROC curves on the simplified risk models based on multivariate logistic regression results to measure their capabilities of predicting single-agent chemoresistance in low-risk patients. As shown in Fig. 2, the simplified models with selected risk factors

Table 3 Factors associated with first-line single-agent chemoresistance

Characteristics	Rate of first-line single agent resistance (%)	Univariate		Multivariate	
		OR (95% CI)	P value	OR (95% CI)	P value
Age (years)			0.303		0.506
<40	43.2 (161/373)	Reference		Reference	
≥40	36.4 (24/66)	0.75 (0.44–1.29)	0.303	0.82 (0.47–1.46)	0.506
Antecedent pregnancy			0.586		0.575
Hydatidiform mole	41.9 (163/389)	Reference		Reference	
Miscarriage	47.5 (19/40)	1.25 (0.65–2.41)	0.496	1.07 (0.51–2.25)	0.857
Term	30.0 (3/10)	0.59 (0.15–2.33)	0.456	0.48 (0.12–1.97)	0.305
Interval (months)			0.014		0.012
<4	41.4 (163/394)	Reference		Reference	
4–6	25.9 (7/27)	0.50 (0.20–1.20)	0.120	0.58 (0.22–1.54)	0.275
7–12	60.0 (3/5)	2.13 (0.35–12.87)	0.412	2.47 (0.40–15.38)	0.334
>12	92.3 (12/13)	17.01 (2.19–132.08)	0.007	22.37 (2.79–179.59)	0.003
Pretreatment serum hCG (IU/L)			0.020		0.008
$<1\times10^3$	37.4 (46/123)	Reference		Reference	
1×10^3–1×10^4	36.8 (70/190)	0.98 (0.61–1.56)	0.921	1.24 (0.74–2.08)	0.415
1×10^4–1×10^5	53.7 (66/123)	1.94 (1.17–3.22)	0.011	2.79 (1.49–5.25)	0.001
$>1\times10^5$	100.0 (3/3)		0.999		0.999
Largest tumor size including uterus (cm)			0.463		0.514
<3	41.2 (127/308)	Reference		Reference	
3–<5	41.9 (44/105)	1.03 (0.66–1.61)	0.904	0.73 (0.43–1.26)	0.259
≥5	53.8 (14/26)	1.66 (0.74–3.71)	0.215	0.95 (0.38–2.38)	0.908
Number of metastases			0.748		0.810
0	42.1 (146/347)	Reference		Reference	
1–4	43.5 (37/85)	1.06 (0.66–1.71)	0.808	1.08 (0.65–1.79)	0.770
≥5	28.6 (2/7)	0.55 (0.11–2.88)	0.479	0.62 (0.11–3.35)	0.576

hCG: human chorionic gonadotropin; OR: odds ratio; CI: confidence interval.

Table 4 Factors associated with single-agent chemoresistance

Characteristics	Rate of single-agent resistance (%)	Univariate		Multivariate	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (years)			0.100		0.208
<40	11.5 (43/373)	Reference		Reference	
⩾40	4.5 (3/66)	0.37 (0.11–1.21)	0.100	0.45 (0.13–1.56)	0.208
Antecedent pregnancy			0.555		0.875
Hydatidiform mole	10.0 (39/389)	Reference		Reference	
Miscarriage	12.5 (5/40)	1.28 (0.47–3.46)	0.624	0.86 (0.28–2.60)	0.788
Term	20.0 (2/10)	2.24 (0.46–10.94)	0.317	1.43 (0.28–7.39)	0.673
Interval (months)			0.115		0.022
<4	9.6 (38/394)	Reference		Reference	
4–6	11.1 (3/27)	1.17 (0.34–4.07)	0.804	1.70 (0.39–7.37)	0.477
7–12	40.0 (2/5)	6.25 (1.01–38.55)	0.049	9.44 (1.29–69.06)	0.027
>12	23.1 (3/13)	2.81 (0.74–10.66)	0.129	7.02 (1.48–33.30)	0.014
Pretreatment serum hCG (IU/L)			<0.001		0.002
$<1\times10^3$	6.5 (8/123)	Reference		Reference	
1×10^3–1×10^4	6.3 (12/190)	0.97 (0.38–2.44)	0.947	1.60 (0.56–4.60)	0.383
1×10^4–1×10^5	19.5 (24/123)	3.48 (1.50–8.11)	0.004	5.58 (1.81–17.26)	0.003
$>1\times10^5$	66.7 (2/3)	28.75 (2.35–352.05)	0.009	34.88 (2.41–504.51)	0.009
Largest tumor size including uterus (cm)			0.044		0.972
<3	8.1 (25/308)	Reference		Reference	
3–<5	15.2 (16/105)	2.04 (1.04–3.98)	0.038	1.06 (0.47–2.41)	0.890
⩾5	19.2 (5/26)	2.70 (0.94–7.76)	0.066	1.16 (0.33–4.00)	0.817
Number of metastases			0.919		0.978
0	11.0 (38/347)	Reference		Reference	
1–4	9.4 (8/85)	0.84 (0.38–1.88)	0.680	0.91 (0.39–2.13)	0.832
⩾5	0 (0/7)		0.999		0.999

hCG: human chorionic gonadotropin; OR: odds ratio; CI: confidence interval.

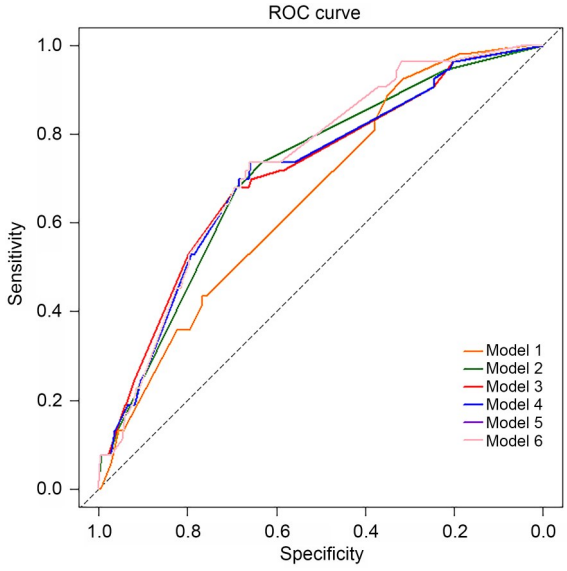

Fig. 2 Receiver operating characteristic (ROC) curves of simplified risk models for predicting single-agent chemoresistance.

revealed discrepant predicting capacities. For instance, the interval from antecedent pregnancy and pretreatment serum hCG level, as two FIGO risk factors, were identified as independent parameters for predicting first-line and sequential single-agent resistance in our series. Thus, Model 2, which contains the two independent risk factors, had a predictive accuracy of 66.3%, identical to the actual outcome. In contrast, Model 1, containing four non-independent risk factors, only had an accuracy of 36.9%, which is much lower than that of Model 2. Moreover, with the risk factors adding into the models one by one, the predictive accuracies of the models were gradually increased, but still lagged far behind the intact FIGO 2000 system. The detail results were listed in Table 5.

Then, utilizing stepwise logistic regression, we proceeded to conduct these models on all patients to investigate whether simplification of the original FIGO 2000 system for stratifying patients was feasible.

Table 5 Simplified models and their performance in predicting single-agent chemoresistance

Model	Risk factor	Number of patients		Positive predictive value	Negative predictive value	Sensitivity	Specificity	Accuracy
		Predictive positive	Predictive negative					
Model 1	Age; Antecedent pregnancy; Largest tumor size; Number of metastases	313	126	0.131	0.960	0.891	0.308	0.369
Model 2	Interval; Pretreatment serum hCG	168	271	0.196	0.952	0.717	0.656	0.663
Model 3	Interval; Pretreatment serum hCG; Largest tumor size	168	271	0.196	0.952	0.717	0.656	0.663
Model 4	Interval; Pretreatment serum hCG; Largest tumor size; Antecedent pregnancy	174	265	0.201	0.958	0.761	0.646	0.658
Model 5	Interval; Pretreatment serum hCG; Largest tumor size; Number of metastases; Antecedent pregnancy	153	286	0.216	0.955	0.717	0.695	0.697
Model 6	Age; Interval; Pretreatment serum hCG; Largest tumor size; Number of metastases; Antecedent pregnancy	152	287	0.217	0.955	0.717	0.697	0.699
Original FIGO 2000		0	439	0	0.895	0	1.000	0.895

Given that all low-risk patients had already been deemed to have single-agent success according to the FIGO 2000 system, the sensitivity, specificity, accuracy, and predictive values were calculated with the actual outcomes. Here, the single-agent resistance was set as "positive" and single-agent success was set as "negative." hCG: human chorionic gonadotropin; FIGO: International Federation of Gynecology and Obstetrics.

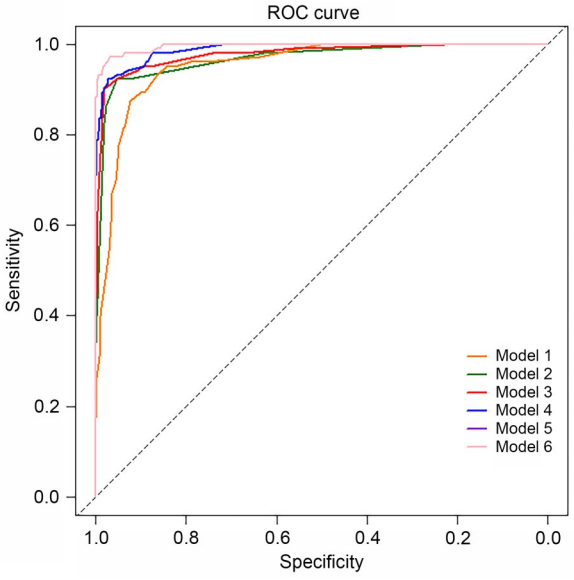

Fig. 3 Receiver operating characteristic (ROC) curves of simplified models for classifying low- and high-risk gestational trophoblastic neoplasia (GTN) patients.

Fig. 3 delineated the discriminating power of these simplified models using ROC analysis when compared with the original FIGO 2000 system. As listed in Table 6, Model 2 was able to classify 94.8% of patients in accordance with the original FIGO criteria. In contrast, Model 1 consisting of four risk factors with inadequate statistical significance was only able to classify 91.5% of patients. With the numbers of adopted risk factors growing from two to six, the accuracies of Model 2 to Model 6 rose from 94.8% to 97.9%, which gradually approached 100%, but still fell behind the integrated FIGO 2000 system. However, the prediction was not always incorrect for the cases with inconsistent classification from the original FIGO 2000 system. For example, in Model 3, with the variables of interval from antecedent pregnancy, pretreatment serum hCG level, and the largest tumor size, nine patients were changed from low-risk to high-risk, among which four turned out to be cases of actual

Table 6 Simplified models and their performance in classifying low- and high-risk patients

Model	Risk factor	Number of patients				Sensitivity	Specificity	Accuracy
		True positive	False positive	False negative	True negative			
Model 1	Age; Antecedent pregnancy; Largest tumor size; Number of metastases	90	36	13	439	0.874	0.924	0.915
Model 2	Interval; Pretreatment serum hCG	95	22	8	453	0.922	0.954	0.948
Model 3	Interval; Pretreatment serum hCG; Largest tumor size	93	9	10	466	0.903	0.981	0.967
Model 4	Interval; Pretreatment serum hCG; Largest tumor size; Antecedent pregnancy	95	13	8	462	0.922	0.973	0.964
Model 5	Interval; Pretreatment serum hCG; Largest tumor size; Number of metastases; Antecedent pregnancy	100	15	3	460	0.971	0.968	0.969
Model 6	Age; Interval; Pretreatment serum hCG; Largest tumor size; Number of metastases; Antecedent pregnancy	98	7	5	468	0.951	0.985	0.979
Original FIGO 2000		103	0	0	475	1.000	1.000	1.000

Due to the fact that the original FIGO 2000 system had already been used as "gold standard" for these particular data, the sensitivity, specificity, and accuracy were considered as 100%. Here, the high-risk patients were set as "positive" and the low-risk patients were set as "negative." hCG: human chorionic gonadotropin; FIGO: International Federation of Gynecology and Obstetrics.

single-agent chemoresistance. Similarly, in Model 6, only seven patients were classified differently, and three were finally proved to be cases of single-agent chemoresistance.

4 Discussion

Over the years, there have been a variety of staging and classifying systems to assist clinicians with judging prognosis and selecting treatments for GTN patients; however, no worldwide consensus has been reached on the optimal classification system (Hancock, 2003). Bagshawe (1976) derived a weighted scoring system with thirteen prognostic factors that influenced the response to chemotherapy, which subsequently formed the basis of the WHO prognostic scoring system. In 2000, a combination of the FIGO staging and modified WHO scoring system was proposed and later widely accepted. The main purpose of classifying patients into low- and high-risk groups is to determine at the time of diagnosis whether a given patient would respond to single-agent chemotherapy or not, so as to avoid potential undertreatment or overtreatment (Seckl et al., 2010).

Several studies have shown that the eight prognostic factors in the currently adopted FIGO scoring system possess inequable values for predicting single-agent chemoresistance. A case-control designed study in Iran reviewed 168 low-risk GTN patients treated with methotrexate- or actinomycin-D-based therapies as initial and alternative single-agent chemotherapies, and reported a resistance rate of 43% and 19% to initial and sequential single-agent chemotherapies, respectively. An interval more than 4 months from antecedent pregnancy, tumor size larger than 3 cm, serum hCG level higher than 100 000 IU/L, and presence of metastases were identified as independent risk factors

for resistance to single-agent chemotherapy (Mousavi et al., 2015). Another retrospective study of 358 low-risk GTN patients in USA indicated a response rate of 81% to an initial 5-d methotrexate regimen and a complete response rate of 94% to sequential single-agent chemotherapy with a 5-d actinomycin-D regimen as an alternative. Clinicopathologic diagnosis of choriocarcinoma, higher pretreatment hCG level, and presence of metastases were found to be significantly associated with resistance to initial methotrexate therapy, while only diagnosis of choriocarcinoma was strongly related to sequential single-agent chemoresistance (Chapman-Davis et al., 2012). In this study, we retrospectively investigated the treatments of 475 low-risk GTN patients in a Chinese population with a remission rate of 58.1% and 88.8% to first-line and sequential single-agent chemotherapies, respectively. By conducting univariate and multivariate logistic regression analyses, the pretreatment serum hCG level and interval from antecedent pregnancy were consistently identified to be significantly independent risk factors for both first-line and sequential single-agent chemoresistance.

As expected, pretreatment serum hCG level emerged as the most dominant risk factor, as hCG is an irreplaceable marker in diagnosing GTN owing to the fact that its sensitivity is GTN tumor-specific. It is also an indispensable index for monitoring treatment responses, since it quantitatively reflects the tumor burden. Our results showed that patients with a higher pretreatment serum hCG level carried an obviously higher risk of resistance to both first-line and sequential single-agent therapies, which was in accordance with several previous studies (Mcgrath et al., 2010; Chapman-Davis et al., 2012; Taylor et al., 2013), even though the precise threshold level for predicting single-agent failure was inconclusive (Growdon et al., 2010; Kang et al., 2010a; Winter et al., 2016; Hoeijmakers et al., 2020; Wu et al., 2020). Another influential element was the interval from the antecedent pregnancy. We observed a remarkably elevated risk of chemoresistance to both first-line and secondary single-agent therapies with the growing of time span between antecedent pregnancy and disease diagnosis. As a matter of fact, a long interval usually indicates that the malignancy is more advanced. Postmolar patients with a duration of less than 6 months are more likely to have invasive mole, while those with a duration of more than 12 months are more likely to have choriocarcinoma instead. The longer the interval, the higher the likelihood of choriocarcinoma (Le et al., 2007). Some researchers have indicated that GTN patients with a histological diagnosis of choriocarcinoma had a poorer response to initial methotrexate chemotherapy and alternative single-agent chemotherapy than those with a clinicopathological diagnosis of invasive mole or postmolar GTN (Lurain and Elfstrand, 1995; Osborne et al., 2011; Braga et al., 2021).

Although the aforementioned studies presented different independent risk factors for predicting single-agent chemoresistance, they concurred that some risk factors indeed influenced prognosis while others lacked significance. This may be because some factors incorporated in the FIGO scoring system are correlated with each other and are not independently prognostic (Soper et al., 1994). For instance, tumor size is always seen as a concretization of tumor burden and the number of metastases is also a reflection of tumor progression, both of which are linked to the level of serum hCG. Moreover, the duration of tumor evolution before diagnosis was usually related to the type of antecedent pregnancy to a certain extent (Le et al., 2007). Therefore, there would be a probability to simplify the FIGO scoring system. A prior study of 813 GTN patients from the Charing Cross Hospital in London (UK) provided a simplified model with five risk factors including age, antecedent pregnancy type, interval, pretreatment hCG level, and number of metastases, which achieved an accuracy of 99.9% identical to the original FIGO 2000 system in classifying low- and high-risk GTN patients (Eysbouts et al., 2017). Another study from the Peking Union Medical Hospital (China) proposed a new prognostic system, which comprised five risk factors including antecedent pregnancy type, interval, previous failed chemotherapy, site and number of metastases with weighted score for each, and it showed a significant increase in prognostic efficiency relative to the original FIGO 2000 system (Jiang et al., 2018). The discrepancies between the two studies may be associated with the differences in selection criteria for patients, treatment protocols, definitions of outcomes, and statistical methodology.

Herein, we attempted to reduce the number of existing factors and evaluate the performance of the simplified models. The simplified model with two independent factors, pretreatment serum hCG level and

interval from the antecedent pregnancy, showed a much higher prediction efficiency than the model with the other four non-independent factors. However, the addition of other co-factors did improve the predictive accuracy, and the original FIGO 2000 prognostic system showed the highest accuracy. Furthermore, as the classification of the original FIGO 2000 prognostic system was set as the reference, the simplified model with two independent factors also expressed a much higher discriminative capacity than the model with the other four non-independent factors. Likewise, the simplified models obtained extra improvement in classification accuracy through the addition of any combination of the remaining non-independent factors. Besides, certain simplified models also ameliorated misclassifications in some cases by the original FIGO 2000 system. Thus, our results overall suggested that the independent factors have greater weight in predicting single-agent chemoresistance than other non-independent risk factors. Moreover, simplified models can preserve a comparable performance in classifying patients, but whether they can completely replace the FIGO prognostic system still needs further evaluation using sufficient patient numbers.

This study has several limitations that need to be addressed. First, given the rarity of GTN and the difficulty of follow-up, it is only a single-center retrospective study with a small sample size. Second, the patient population was heterogeneous with respect to the different drug regimens, surgical interventions, and failure reasons, which might make the results unspecific or inconsistent. Last but not least, although the ROC analysis of the simplified model displayed reasonable discriminative ability, the internal validation might have potentially overestimated the performance. Therefore, more diverse and larger-scale data are needed to certify the performance of the simplified model by external validation and to determine whether this model provides better prediction of patient outcomes when compared with the currently available system.

5 Conclusions

In summary, our study evaluated the individual value of each prognostic factor and identified pretreatment serum hCG level and interval from antecedent pregnancy as independent risk factors for both first-line and sequential single-agent chemoresistance in low-risk GTN patients. These independent risk factors showed greater weight than other non-independent factors in predicting single-agent chemoresistance, but were unable to replace them completely. On the whole, a simplified system composed of partial factors is credible in classifying patients, but whether it can substitute the original FIGO 2000 prognostic system still needs further validation.

Author contributions

Yang WENG and Yuanyuan LIU contributed to data interpretation, statistical analysis, and writing the manuscript. Yuanyuan LIU and Xiaodong WU contributed to data extraction and draft preparation. Chitapa BENJOED contributed to revising the manuscript. Yang WENG and Sangsang TANG contributed to statistical analysis. Xiao LI contributed to data interpretation and supervision. Xing XIE and Weiguo LU contributed to conception, reviewing and editing the final manuscript. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data.

Compliance with ethics guidelines

Yang WENG, Yuanyuan LIU, Chitapa BENJOED, Xiaodong WU, Sangsang TANG, Xiao LI, Xing XIE, and Weiguo LU declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the Ethics Committee of Women's Hospital, School of Medicine, Zhejiang University (approval number: IRB-20190003-R) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was waived due to its nature of retrospective analysis.

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