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Original Article

Thyroid-stimulating hormone and total bile acids can predict adverse pregnancy outcome among patients with gestational hypertension

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Abstract: Objective: To investigate the correlation between serum thyroid-stimulating hormone (TSH) and total bile acid (TBA) levels in gestational hypertension and their combined predictive value for pregnancy outcome. Methods: A total of 194 patients with gestational hypertension (GH), treated from June 2020 to May 2022, were included in this study. The patients were divided into two subgroups based on pregnancy outcome: an adverse pregnancy outcome group (77 cases) and a normal pregnancy outcome group (117 cases). Additionally, 50 healthy pregnant women undergoing routine prenatal checkups during the same period served as the control group. In this study, serum TBA and TSH levels were measured and compared between the control and GH groups as well as between adverse pregnancy outcome and normal pregnancy outcome groups. The independent risk factors for adverse pregnancy outcome were screened using logistic regression, and their predictive value for pregnancy outcome in patients with GH was analyzed using receiver operating characteristic (ROC) curves. Results: Serum TSH and TBA levels were significantly higher in the GH group compared to the normal group (both $P < 0.001$). Logistic regression analysis revealed that age, body mass index (BMI), TSH, and TBA were independent risk factors for adverse pregnancy outcome. ROC curve analysis showed that combined TSH and TBA for predicting adverse pregnancy outcome had an Area Under the Curve (AUC) of 0.896, surpassing the AUCs of each individual index (0.843 for TSH and 0.765 for TBA), which indicates a stronger predictive value ($P < 0.001$). Conclusion: The combined measurement of serum TBA and TSH can serve as a valuable predictive tool for pregnancy outcome in patients with gestational hypertension.

Keywords: Thyroid-stimulating hormone, total bile acids, prediction, gestation, hypertension, adverse outcome

Introduction

Gestational hypertension (GH) is a condition of elevated blood pressure during pregnancy, often presenting after 20 weeks of gestational age and resolving immediately after delivery [1]. Statistically, the incidence of GH is about 5% to 12% [2]. GH poses significant risks, including temporary hypertension, proteinuria, and edema during pregnancy, resulting in intrauterine growth restriction, preterm labor, and other problems [3]. In severe cases, GH can escalate to convulsions, coma, and even death of the mother and fetus [4], representing a critical factor for of increased maternal and perinatal mortality. The pathophysiology of GH involves systemic minor vessel spasms, vascular endothelial damage, and localized ischemia and hypoxia, resulting in inadequate blood perfusion to vital organs [5]. Such impairment in placental function can lead to inadequate oxygen and nutrient supply to the fetus, potentially causing serious complications like poor intrauterine growth and fetal distress [6]. In severe cases, the condition may escalate to eclampsia, circulatory disorders, or multiple organ damage, posing significant risks to both mother and fetus [7]. Given these risks, it is imperative for obstetricians to deepen their understanding of the etiology, screening markers, and maternal-infant outcomes associated with GH. This will to enhance preventive and therapeutic strategies.

Total bile acids (TBAs), produced by the liver, play a crucial role in digestion and absorption of

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fats [8]. During pregnancy, TBA levels may fluctuate due to physiologic changes. A study [9] has shown that in patients with GH, elevated TBA may be indicative of impaired hepatic function. Thyroid-stimulating hormone (TSH), a hormone secreted by the pituitary gland, regulates the activity of the thyroid gland and influences the production of thyroid hormones [10]. During pregnancy, changes in thyroid hormone levels may affect maternal and fetal health. Recent evidence suggests a link between TSH and GH [11]. Abnormal TSH levels may be associated with the development of hypertension during pregnancy. For example, hypothyroidism, i.e., elevated TSH levels, may increase the risk of during pregnancy [12]. In the study of Zeng et al. [13], serum TSH was found to be significantly higher in GH patients with preeclampsia than in healthy pregnant women. Also, Deng et al. [14] found that TBA was considerably higher in the preeclampsia and gestational hypertension groups than in the non-hypertension group. However, the studies on the association of TSH and TBA with adverse outcomes in GH patients are scarce.

Although previous studies have revealed changes in TSH and TBA levels in GH, their association with adverse pregnancy outcome in GH patients has not been fully explored. The present study aimed to bridge this gap and assess the predictive accuracy of TSH and TBA for adverse pregnancy outcome in a GH population.

Materials and methods

Sample size

According to the literature, the prevalence of GH is about 5~12% [15, 16]. We take the highest prevalence rate for sample size calculation according to the function: $\frac{Z^2 \times P \times (1 - P)}{d^2}$, where Z value is 95%, the *P* value is the prevalence rate of 12%, d is the allowable error range of 5%. Substituting into the formula, we need a total of 162 samples, and in calculating 10% data loss or deletion of models, we need a total of 179 cases.

Sample sources

A retrospective analysis was conducted on the clinical data of patients with GH who were treated in Northwest Women's and Children's Hospital and Baoji Maternal and Child Health Hospital from June 2020 to May 2022. The clinical data of 50 healthy pregnant women who underwent routine prenatal checkups within the same timeframe at both institutions were collected for reference (Note: The healthy pregnant women group was included primarily as a control to establish baseline levels of TSH and TBA. However, it's important to note that pregnancy outcomes for this group were not measured. This decision was made to maintain the study's focus on hypertensive disorders during pregnancy). This study was approved by the Ethics Committee of Baoji Maternal and Child Health Hospital.

Inclusion and exclusion criteria

Inclusion criteria: (1) meeting the relevant diagnostic criteria of pregnancy-induced hypertension according to the Expert Consensus on Blood Pressure Management of Hypertensive Diseases in Pregnancy (2019) [3]; (2) no mental disorders or cognitive impairment; and (3) complete clinical data.

Exclusion criteria: (1) intrahepatic cholestasis during pregnancy; (2) gestational diabetes mellitus; (3) comorbid hyperthyroidism during pregnancy; (4) a history of pre-existing thyroid disease; and (5) cardiorespiratory dysfunction.

According to the inclusion-exclusion criteria, we collected 194 samples that met the requirements. According to adverse pregnancy outcome, the patients were divided into an adverse pregnancy outcome group (n=77) and a normal pregnancy outcome group (n=117). The adverse pregnancy outcomes include: preterm labor, low birth weight, intrauterine growth restriction, fetal distress, and intrauterine fetal death [7].

Clinical data collection

Clinical data of the patients were extracted from the electronic medical record system of Northwest Women's and Children's Hospital and Baoji Maternal and Child Health Hospital. The data included age, gestational week, pre-pregnancy BMI (Body Mass Index), number of pregnancies, number of deliveries, educational level, per capita monthly family income, and adverse pregnancy outcome (**Figure 1**).

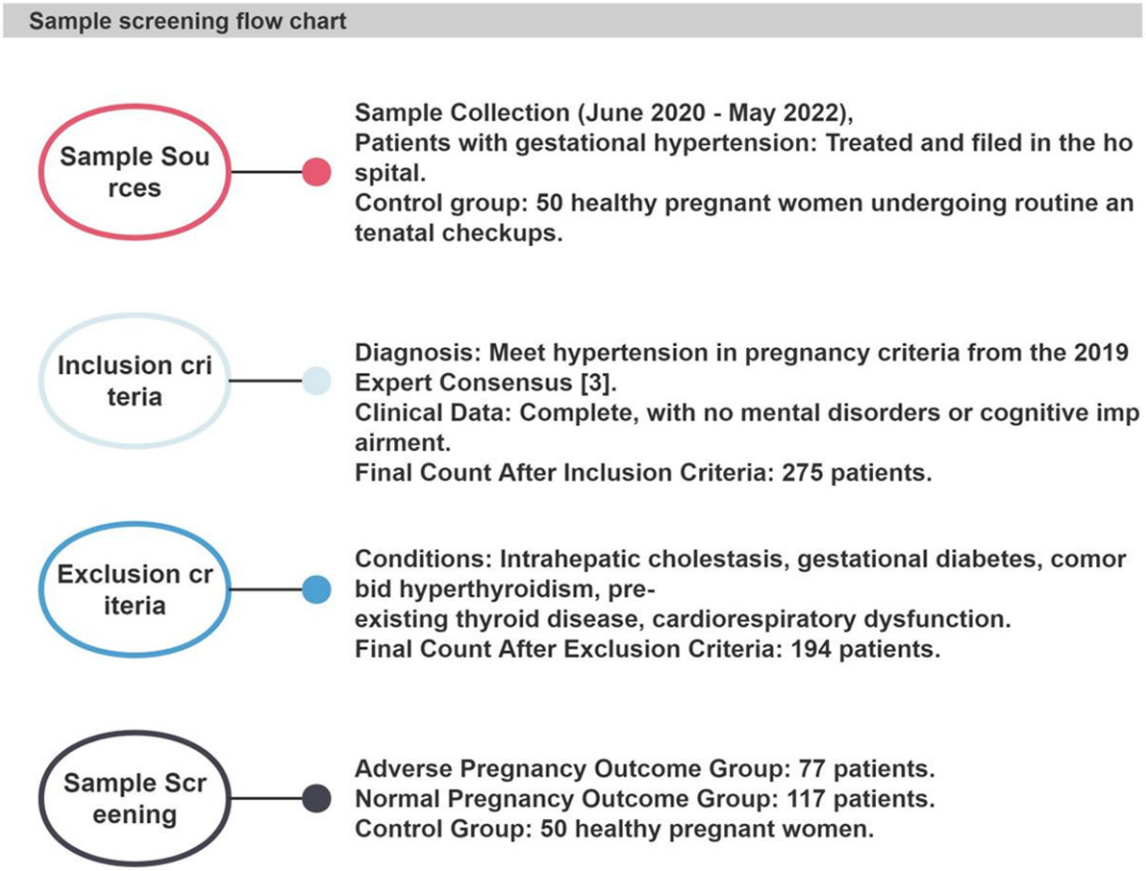

Figure 1. Flow diagram of sample screening.

Laboratory data included TSH and TBA at 24 weeks gestation. TSH level was detected by automatic electrochemiluminescence immunoanalyzer (Roche, Switzerland, E170), and TBA level was analyzed by automatic biochemical analyzer (USA, AU2700).

Outcome measurement

The primary measurements included TSH and TBA levels at 24 weeks of gestation, and the prognostic value of the screened risk factors for the pregnancy outcome. The serum TSH and TBA levels were compared between the control group (n=50) and the GH group (n=194), as well as between the adverse pregnancy outcome group (n=77) and normal pregnancy outcome group (n=117). Risk factors for adverse pregnancy outcome were screened by logistic regression analysis, and their predictive performances were analyzed by receiver operating characteristic (ROC) curve. The secondary measurements included clinical data comparison between groups.

Statistical analysis

Data were processed using SPSS 20.0 software. Data distribution was analyzed using the Kolmogorov-Smirnov test. Normally distributed data were expressed as Mean ± SD, and the inter-group and intra-group comparisons were conducted using the independent samples t-test and paired t-test respectively, described as t. Non-normally distributed data were tested using a nonparametric test, described as Z. Comparison of counted data (n, %) was performed using the χ^2 test. Logistic regression was used to screen independent risk factors for adverse pregnancy outcome. ROC curve was used to analyze the predictive value of various risk factors for adverse pregnancy outcome, and the results were compared using the Delong test. $P < 0.05$ was considered a significant difference.

Table 1. Comparison of clinical data between control group and GH group

Item	Control group (n=50)	GH group (n=194)	χ^2-value	*P*-value
Age				
≥ 30	23	78	0.55	0.458
< 30	27	116		
Gestational week of enrollment				
≥ 24 weeks	20	97	1.593	0.207
< 24 weeks	30	97		
Pre-pregnancy BMI				
≥ 23 kg/m^2	12	35	0.908	0.341
< 23 kg/m^2	38	159		
Number of pregnancies				
≥ 2 times	20	70	0.262	0.609
< 2 times	30	124		
Number of births				
Multipara	13	52	0.013	0.909
Primipara	37	142		
Education attainment				
University or above	28	116	0.237	0.627
High school or blow	22	78		
Monthly per capita household income (¥)				
≥ 5000	20	87	0.379	0.538
< 5000	30	107		

BMI: Body Mass Index.

Results

Comparison of clinical data between control group and GH group

We first compared the clinical data of the patients between the control group and the GH group. It was found that there was no statistical difference between the two groups in terms of age, gestational weeks, pre-pregnancy BMI, number of pregnancies, number of deliveries, educational level, and per capita monthly family income (all P > 0.05, **Table 1**).

Comparison of clinical data between GH patients with different pregnancy outcome

In this study, we further analyzed the clinical data of patients with normal and adverse pregnancy outcome. The results showed that the proportions of patients with age ≥ 30 years and pre-pregnancy BMI ≥ 23 kg/m^2 in the adverse pregnancy outcome group were significantly higher than those of the patients in normal pregnancy outcome group (both P < 0.001, **Table 2**).

Comparison of TSH and TBA levels between control group and GH group

We compared the serum TSH and TBA levels between the control group and GH group, and found that both TSH and TBA levels were higher in the GH group than in the control group (both P < 0.001, **Figure 2A**, **2B**).

Comparison of TSH and TBA levels compared between GH patients with different pregnancy outcome

We further compared TSH and TBA levels in patients with normal and adverse pregnancy outcome, and the results showed that patients in the adverse pregnancy outcome group had significantly higher TSH and TBA levels than patients in the normal pregnancy outcome group (both P < 0.001, **Figure 3A**, **3B**).

Screening of risk factors for adverse pregnancy outcome and their efficacy assessment

Subsequently, we collected data related to adverse pregnancy outcome, and found that

Table 2. Comparison of clinical data of patients with adverse pregnancy outcomes

Consideration	Adverse pregnancy outcome group (n=77)	Normal pregnancy outcome subgroup (n=117)	χ^2-value	*P*-value
Age				
≥ 30	41	37	10.92	< 0.001
< 30	36	80		
Gestational week of enrollment				
≥ 24 weeks	35	62	1.593	0.207
< 24 weeks	42	55		
Pre-pregnancy BMI				
≥ 23 kg/m^2	23	12	17.97	< 0.001
< 23 kg/m^2	54	105		
Number of pregnancies				
≥ 2 times	31	39	0.262	0.609
< 2 times	46	78		
Number of births				
Multipara	23	29	0.013	0.909
Primipara	54	88		
Education attainment				
University or above	42	74	0.237	0.627
High school or below	35	43		
Monthly per capita household income (¥)				
≥ 5000	32	55	0.379	0.538
< 5000	45	62		

BMI: body mass index.

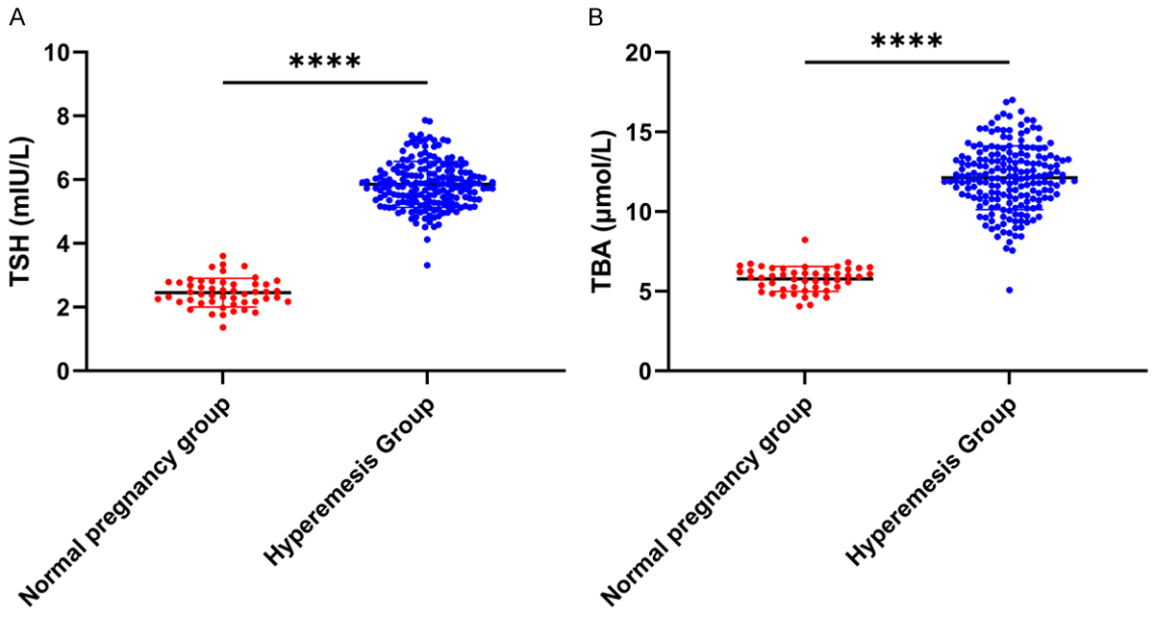

Figure 2. Serum levels of TSH (A) and TBA (B) at 24 weeks of gestation in control group and GH group. TSH: thyroid stimulating hormone; TBA: total bile acids; GH: gestational hypertension. ****P < 0.0001.

age, BMI, TSH, and TBA were independent risk factors affecting outcome by logistic regression analysis (all P < 0.05, **Table 4**). Then, the efficacy of each indicator in predicting adverse

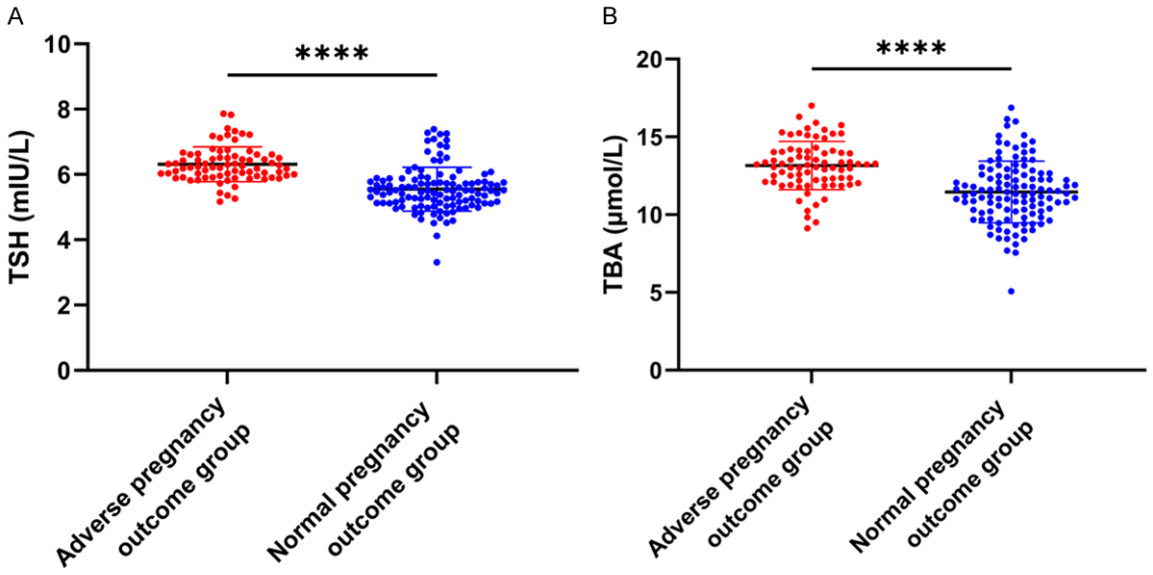

Figure 3. Serum levels of TSH (A) and TBA (B) at 24 weeks of gestation in normal and adverse pregnancy outcome groups. TSH: thyroid stimulating hormone; TBA: total bile acids. ****P < 0.0001.

Table 3. Parameters of ROC analysis for predicting adverse pregnancy outcome

	AUC	95% CI	Specificity	Sensitivity	Youden index	Cut off
TSH	0.843	0.785-0.900	76.07%	92.21%	68.28%	5.805
TBA	0.765	0.697-0.832	62.39%	88.31%	50.70%	11.845
Age	0.616	0.532-0.699	82.91%	40.26%	23.17%	33.5
BMI	0.602	0.518-0.686	90.60%	29.87%	20.47%	23.05
Join	0.896	0.846-0.945	79.49%	97.40%	76.89%	0.869

TSH: thyroid stimulating hormone; TBA: total bile acids; BMI: body mass index; AUC: area under the curve.

Table 4. Multivariate logistic regression analysis

	β	Standard error	χ^2	*P* value	OR value	95% CI	
						Lower	Upper
TSH	-4.02	0.615	42.728	< 0.001	0.018	0.005	0.060
TBA	-2.689	0.551	23.802	< 0.001	0.068	0.023	0.200
Age	-1.111	0.501	4.922	0.027	0.329	0.123	0.879
BMI	-1.606	0.631	6.47	0.011	0.201	0.058	0.692

pregnancy outcome was assessed by ROC curve. The results showed that the area under the curve (AUC) for TSH, TBA, age, and BMI in predicting poor pregnancy outcome was 0.843, 0.765, 0.616, and 0.602, respectively (**Table 3**). We further analyzed the ROC curve of their combined detection (risk score calculation: 15.896 + TSH * -4.390 + TBA * 0.848) and found that the AUC for the joint detection was 0.896 (**Figure 4**). Further analysis by Delong's test revealed that the AUC for joint detection was significantly higher than the other individual metrics (all P < 0.001, **Table 5**).

Discussion

Gestational hypertension (GH) can induce spasms in small arteries, impairing the function of essential organs like the eyes, brain, heart, kidneys, and liver in pregnant women [17]. This condition is characterized by its complexity and rapid progression, increasing the risk of de-

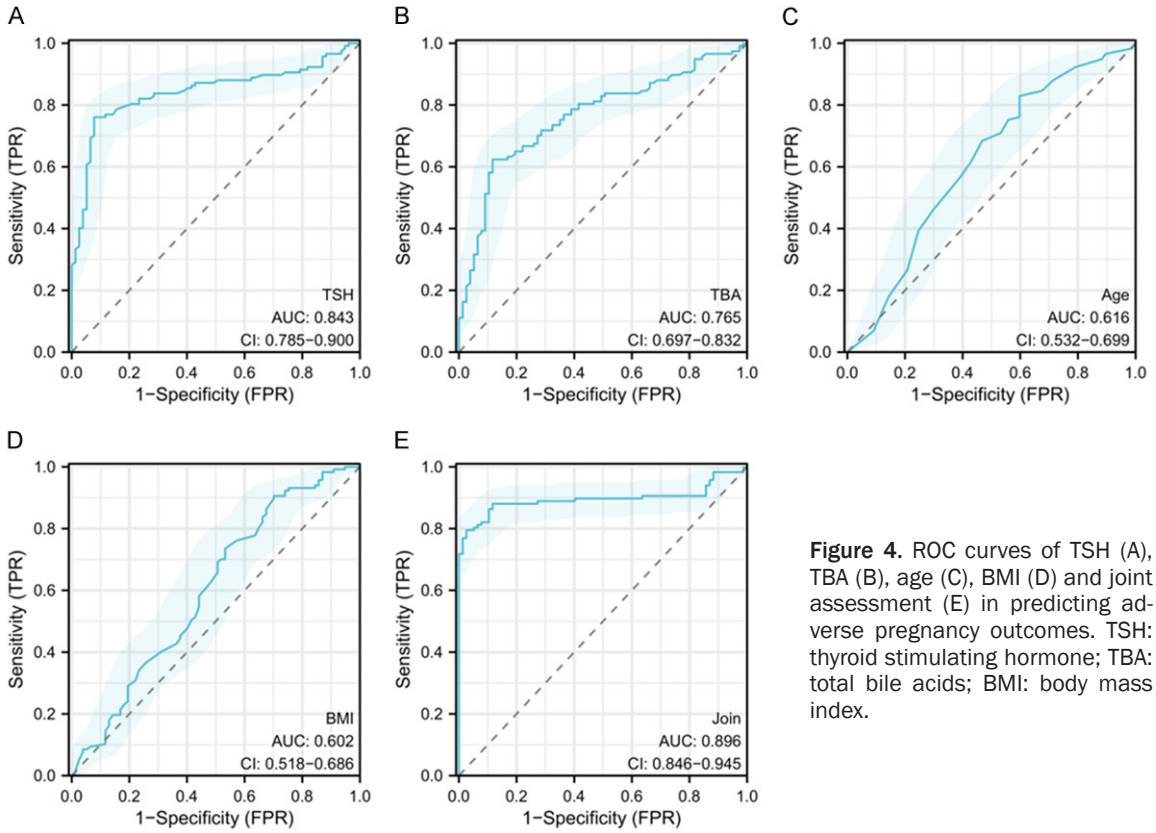

Figure 4. ROC curves of TSH (A), TBA (B), age (C), BMI (D) and joint assessment (E) in predicting adverse pregnancy outcomes. TSH: thyroid stimulating hormone; TBA: total bile acids; BMI: body mass index.

Table 5. Comparison of AUC of each index

	Z value	*P* value	AUC difference	95% CI
TSH-TBA	4.633	< 0.001	0.078	0.045~0.111
TSH-Age	4.527	< 0.001	0.227	0.129~0.326
TSH-BMI	5.078	< 0.001	0.241	0.148~0.334
TSH-Join	-3.494	< 0.001	-0.053	-0.082~-0.023
TBA-Age	2.695	0.007	0.149	0.041~0.257
TBA-BMI	3.056	0.002	0.163	0.058~0.267
TBA-Join	-4.492	< 0.001	-0.131	-0.188~-0.074
Age-BMI	0.318	0.751	0.014	-0.071~0.098
Age-Join	-5.947	< 0.001	-0.28	-0.372~-0.188
BMI-Join	-6.456	< 0.001	-0.294	-0.383~-0.205

TSH: thyroid stimulating hormone; TBA: total bile acids; BMI: body mass index; AUC: area under the curve.

veloping preeclampsia. Pregnancy presents a unique physiological interaction between mother and fetus, marked by intricate and complex processes [18, 19].

With advances in medical care, there has been an increase in pregnancies among women of childbearing age who have chronic conditions [20]. This trend has heightened the risk of developing GH, which is associated with adverse pregnancy outcome and may even contribute to perinatal and maternal mortality [21]. In this context, early prediction of adverse outcome of hypertensive pregnancies and implementing timely clinical interventions have become crucial. A recent study indicated that a combination of serum biomarkers, pregnancy-associated plasma protein A, free β human chorionic gonadotropin, and maternal serum alpha-fetoprotein, effectively predicts risks such as preterm labor, low birth weight, and preeclampsia [22].

Furthermore, GH has been linked to maternal serum levels of TSH and TBA. A study showed that thyroid function impairment is more prevalent in preeclampsia than in gestational hypertension alone [10]. It was also found that maternal serum TBA level was significantly elevated in preeclampsia and gestational hypertension groups compared to the non-hypertension group, correlating with an increased risk of severe preeclampsia [14]. Our research has pinpointed distinct patterns of TSH and TBA

expression in normal versus gestationally hypertensive mothers, with the latter group exhibiting higher levels of both markers. This is attributed to significant changes in the female endocrine system during pregnancy, affecting thyroid hormones and bile acid levels [23]. Such changes are particularly pronounced in gestational hypertension. Additionally, gestational hypertension may induce liver stress or injury, altering bile acid metabolism and excretion, hence elevating serum TBA levels [24]. Additionally, GH is also linked to placental dysfunction, indirectly influencing maternal thyroid hormone and bile acid levels [25]. These physiologic changes and stress responses, more pronounced in mothers, result in elevated TSH and TBA levels, underscoring the impact of GH on maternal systemic metabolism and endocrine function [26].

Predicting adverse pregnancy outcome in expectant mothers is crucial in clinical practice, facilitating the early identification of high-risk patients and the implementation of appropriate interventions [27, 28]. This approach not only improves maternal and neonatal health but also optimizes the use of healthcare resources. In our study, age, BMI, TSH, and TBA were identified as independent risk factors contributing to poor pregnancy outcome in GH. It is noteworthy that the AUC for the joint detection was significantly higher than for age or BMI. Furthermore, the Delong test demonstrated that the AUC for the joint detection surpassed the AUCs of each indicator alone. This indicates that combined detection is more effective in predicting adverse pregnancy outcome in expectant mothers. Comparatively, in the study by Sun et al. [29], insulin-like growth factor-1 and soluble Fms-like tyrosine kinase-1 individually showed AUCs of 0.880 and 0.805 for predicting adverse pregnancy outcome. Zheng et al. [30] also developed a prediction model using a column-line graph, achieving AUCs of 0.781 and 0.777. These findings underscore the value of the joint assessment of various risk factors in the early detection for high-risk patients with gestational hypertension, aiding in clinical decision-making and formulating personalized treatment plans.

However, there were some limitations in this study. First, the sample size was small, with only 194 GH patients included, which could not fully represent the whole population. Second, the study was a single-center retrospective study with certain degree of selective bias. Finally, other relevant biochemical indicators that may affect pregnancy outcome, such as blood uric acid and placental growth factor, were not included in this study for comparison. These indicators may also be associated with poor pregnancy outcome. In the future, we will adopt a prospective multicenter study design to expand the sample size and collect more clinical indicators to improve the representativeness and statistical robustness of our findings.

In conclusion, serum TBA and TSH levels of patients with gestational hypertension are abnormal, showing a specific correlation with the pregnancy outcome. The combined detection of serum TBA, TSH, age and BMI has a high predictive value for these pregnancy outcomes.

Disclosure of conflict of interest

None.

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