

Original Article

IMPORTANCE OF TOTAL GALACTOSE AND GALT ACTIVITY FOR THE DIAGNOSIS OF CLASSICAL GALACTOSEMIA

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ABSTRACT

Classical galactosaemia (CG) is an autosomal recessive inherited disorder caused by deficiency of galactose-1-phosphate uridyl transferase (GALT) enzyme, resulting in accumulation of galactose and galactose-1-phosphate. Common clinical presentations are jaundice, lethargy, poor feeding, vomiting, septicaemia and may progress to death within a few weeks of life. It is crucial to detect affected newborns before symptoms appear to prevent complications. Therefore, we aimed to determine the analytical and diagnostic efficiency for total galactose measurement and GALT activity quantitation for the diagnosis of CG in Malaysia. A total of 5313 dried blood spots (DBS) from infants aged less than 1 year, including one DBS from a known case of CG were collected from various hospitals in Malaysia. These DBS were subjected to total galactose analysis and GALT activity. The diagnostic performance of total galactose, GALT analysis, and the combination of both methods was calculated and evaluated using receiver operating characteristic (ROC) curve analysis. Total galactose assay as a single screening method for CG showed 0.32% in sensitivity and 98.9 % for specificity. The sensitivity and specificity for the isolated GALT assay were 5.7% and 82.3%, respectively. High sensitivity and specificity of 100% and 99.9% respectively, were achieved

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when using both methods as a screening method for CG. CG can be confidently diagnosed using both total galactose and GALT assay in DBS.

KEYWORDS: Classical Galactosaemia, Total Galactose, Galactose-1-phosphate Uridyl Transferase, Newborn Screening, Dried Blood Spot

INTRODUCTION

Classical galactosaemia (CG) (OMIM 230400) is an autosomal recessively inherited inborn errors of metabolism (IEM) in galactose metabolism due to a defect of galactose-1-phosphate uridylyltransferase (GALT) enzyme (GALT; EC 2.7.7.12) (1). The incidence of classical galactosemia varies; quite common in Western Europe (between 1:23,000 and 1:89,000) (2) and Singapore (1:3,656) (3) but rare in Korea (1:52,700) (4); Japan (1:73,700) (5) and Taiwan (1:419,286) (6).

Affected infants typically look healthy upon birth, but once they have been introduced to breast milk or milk formulae which contain galactose, they gradually become ill and deteriorate. Infants with galactosaemia may present with prolonged jaundice, vomiting, organomegaly, either hepatomegaly or splenomegaly and eventually septicaemia, which leads to death during the neonatal period (7).

Therefore, detecting affected newborns as early as possible before presenting symptoms is essential. The newborn screening (NBS) program began in the early 1960s to detect IEM disorders. Currently, NBS for galactosaemia is conducted by either quantifying GALT activity (8) or targeted metabolite (total galactose), where these analytes are in an abnormal range within the affected infants (9). GALT mutational analysis is still the gold standard for confirmation testing of CG (10). Nevertheless, comparing NBS with confirmation testing can be complicated as it involves the deficient activity of any of the three enzymes in the galactose pathway, with clinical presentation that may overlap between the subtypes of galactosaemia disorder (11). Positive CG patients may continue to receive lifelong galactose restriction treatment, whereas presumptive newborns whose results were positive during screening but later proved to be negative through confirmation testing by mutational analysis may resume their normal diet (11). Changing the diet from milk to lactose-free milk (e.g., soy milk or galactose-free formula) is implemented once the patient has been identified positive through NBS result, until follow-up testing or confirmation is completed (12).

In Malaysia, laboratory diagnosis of CG was conducted in the Institute for Medical Research (IMR) using a quantitative commercial kit for GALT activity since 2000. However, due to the high cost, the GALT testing was only performed in high-risk infants strongly presumed to have CG. Since the introduction of the total galactose measurement assay in 2006 (13), there is an increasing demand for the test, including screening of non-symptomatic newborns which has allowed for more detection of CG in Malaysia. However, there is a need to emphasise the importance of this combination of total galactose measurement and GALT activity as the first-line screening tier for CG. To our knowledge, this is the first study that assessed the total galactose assay and GALT activity performance as CG screening methods in high-risk infants in Malaysia. As such, we intend to determine its analytical and diagnostic efficacy in order to improve CG diagnosis among high-risk infants in Malaysia.

MATERIALS AND METHODS

Study Population

A total of 5313 babies aged from three days to 1 year in various hospitals in Malaysia were included in this study. The mean and median age were 2.3 ± 3.03 months and 1.0 month, respectively. Majority of the samples were taken from central region consists of Federal Territory of Kuala Lumpur and Putrajaya, State of Selangor and Negeri Sembilan (39.5%), followed by northern region (State of Pulau Pinang, Kedah, Perak and Perlis-23.7%), East Coast region (State of Kelantan, Terengganu and Pahang-17.2%), East Malaysia region (Region of Sabah, Sarawak and Federal Territory of Labuan-14.1%), and Southern region (State of Johor and Melaka-5.5%).

Samples

This retrospective study was conducted at the Biochemistry laboratory, IMR, Malaysia. Dried blood spot samples (DBS) were selected based on the following inclusion criteria: (i) prolonged jaundice, and/or (ii) hepatomegaly/splenomegaly/hepatosplenomegaly, and/or (iii) neonatal cataract, and/or (iv) liver failure. Patients with glucose-6-phosphate dehydrogenase deficiency (G6PD) or hereditary fructose intolerance were excluded.

To prevent deterioration of GALT enzyme activity and minimise false-positive results, all DBS samples were stored at -30°C until analysis. In cases where initial screening total galactose (TG) and/or GALT activity assay suggested possible CG, confirmatory testing was carried out. This included reanalysis of TG and GALT activity assays on a fresh DBS (when available) and molecular analysis targeting the GALT gene to confirm or rule out CG. False positives were defined as cases with abnormal initial TG or GALT results not supported by follow-up biochemical or genetic testing. Due to the low prevalence of CG in Malaysia, we were only able to obtain a sample from one patient diagnosed with CG (intron 4, c. 377+2dup) for the validation study and diagnostic test analysis.

Total Galactose & GALT Assay

The DBS was subjected to total galactose analysis as described by Yamaguchi et al. (9) before being modified and validated by Omar et al. (13). This method measured both blood galactose and red blood cell Galactose-1-Phosphate. Briefly, 3 mm blood spots were punched into a 96-well plate and fixed with a methanol/acetone mixture to inactivate endogenous enzyme activity and prevent protein elution. The spots were incubated with a reaction mixture containing alkaline phosphatase (ALP), galactose dehydrogenase (GDH) and β -nicotinamide adenine dinucleotide (NAD). The ALP enzyme converted the galactose-1-phosphate to galactose. All galactose was then converted to galactonolactone with the reduced form of β -nicotinamide adenine dinucleotide (NADH) by GDH. The production of NADH was quantified by measuring fluorescence with reference to dried blood spot standards using a Victor2 D fluorometer (PerkinElmer, United States).

Activity of GALT enzyme was measured using a commercial kit as described in the kit insert by the manufacturer (GSP Neonatal GALT Kit, Perkin Elmer, Turku, Finland). In short, a 3 mm disk from DBS was punched into a 96-well microplate, followed by the addition of 100 μL of substrate reagent containing galactose-1-phosphate (Gal-1-P) and uridine diphosphoglucose (UDPG). GALT in the sample catalyses the formation of Gal-1-P and UDPG, with subsequent reactions leading to the reduction of β -nicotinamide adenine dinucleotide phosphate (NADP^+) to β -nicotinamide adenine dinucleotide phosphate (NADPH) by glucose-6-phosphate dehydrogenase (G6PD). The microplate was incubated for 3 hours at 37°C in the incubator before the GALT activity was terminated by adding 200 μL of

ethanol. The generated NADPH exhibits fluorescence measured at an excitation wavelength of 355 nm and emission at 460 nm.

The cut-off for total galactose assay was $>528 \mu\text{mol/L}$ (99th percentiles), and GALT activity was $<2.4 \text{ U/g Hb}$ (99th percentiles). The DBS was also subjected to IEM screening using a Micromass Quattro Micro Mass Spectrometer (Micromass Limited, Manchester, United Kingdom) coupled to a Waters Alliance 2975 HPLC (Waters, Milford, MA, USA), to exclude any IEM abnormalities.

Data Analysis

Statistical analysis was performed using IBM SPSS Statistics version 20 (IBM Corporation, Armonk, NY) and clinical research calculator on the Vassar University statistics web interface (<http://vassarstats.net/>). 2-sided p-values with a significance level of 0.05 and 95% confidence intervals (CI) for all statistical analyses were used in this study.

Different approaches were used to evaluate the effectiveness of the screening method: (i) Approach A: Number of positive results using screening by total galactose only; (ii) Approach B: Number of positive results using screening by GALT activity only; and (iii) Approach C: Number of positive results using screening by total galactose and GALT activity.

The diagnostic test parameters, such as sensitivity, specificity, positive and negative predictive values (with 95% CI) for each approach, were calculated and assessed. Receiver operating characteristics (ROC) curves were plotted using sensitivity versus 100-specificity on a continuous scale and the area under the curve (AUC) was used to determine the relative diagnostic validity.

RESULTS

Diagnostic Test Analysis

Figure 1 shows the median concentration (min-max value) of total galactose and GALT activity among the study population was $72 \mu\text{mol/L}$ ($1\text{--}9667 \mu\text{mol/L}$) and 8.0 U/g Hb ($1.5\text{--}43.0 \text{ U/g Hb}$), respectively.

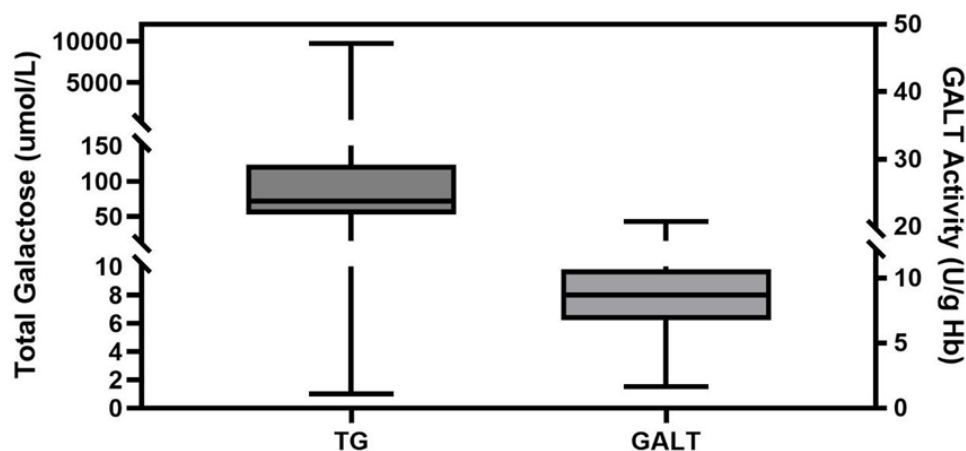


Figure 1. Distribution of total galactose and GALT activity among study population

A 2x2 contingency table for each approach were shown in Table 1. Table 2 showed diagnostic test parameters between the three approaches. Low sensitivity yet satisfactory specificity (0.32% & 98.9% respectively) was observed when using only the total galactose assay as a screening method for CG (approach A). The sensitivity rate for approach B (5.7%) improved when using the GALT assay as the first line of CG screening; however, the specificity declined compared to approach A (82.3%). Combining total galactose assay and GALT activity (approach C), higher sensitivity and specificity of 100% and 99.9% were achieved.

Table 1. 2x2 contingency table for each approach

	Approach A		Approach B		Approach C	
	Healthy	Disease	Healthy	Disease	Healthy	Disease
Test Negative	4330 (True Negative)	930 (False Negative)	4330 (True Negative)	50 (False Negative)	5311 (True Negative)	0 (False Negative)
Test Positive	50 (False Positive)	3 (True Positive)	930 (False Positive)	3 (True Positive)	1 (False Positive)	1 (True Positive)

Table 2. Diagnostic test analysis

Diagnostic Test Parameters	Calculation Formula	Approach		
		A	B	C
Sensitivity	$(\text{True Positive})/[\text{True Positive} + \text{False Negative}]$	0.32%	5.66%	100.00%
Specificity	$(\text{True Negative})/[\text{True Positive} + \text{False Negative}]$	98.86%	82.32%	99.98%
Positive Predictive Value	$(\text{True Positive})/[\text{True Positive} + \text{False Positive}]$	5.66%	0.32%	50.00%
Negative Predictive Value	$(\text{True Negative})/[\text{True Negative} + \text{False Negative}]$	82.32%	98.86%	100.00%

ROC analysis in DBS samples from patients yielded different AUC for different approaches (Figure 2). The yielded AUC for approach A was only 0.549 (95% CI: 0.535-0.564) at the cut-off value of 528 $\mu\text{mol/L}$ while for approach B, the AUC was 0.63 (95% CI: 0.615-0.644) at the cut-off value of 2.4 U/g Hb. Approach C gave the highest AUC among all approaches where AUC was 0.997 (95% CI: 0.995-0.999).

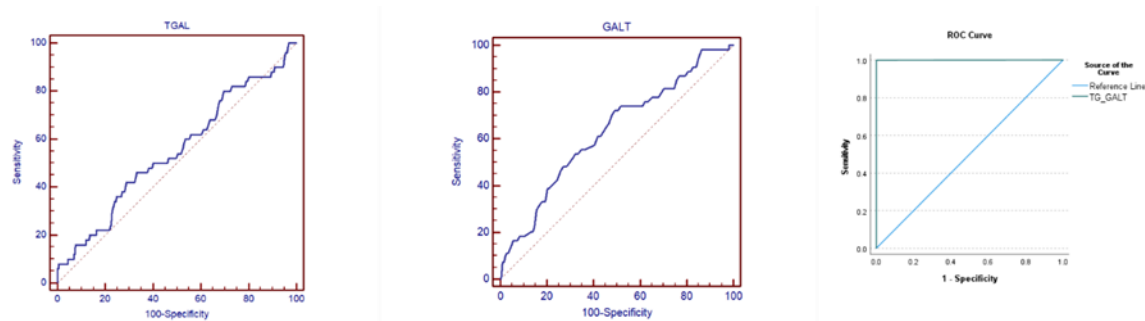


Figure 2. Receiver Operating Characteristics (ROC) Curve according to different approaches (A: Approach A, B: Approach B and C: Approach C)

DISCUSSION

Early diagnosis of classical galactosemia (CG) remains a clinical priority due to its significant implications for treatment and genetic counselling. However, timely detection is often hindered by logistical, clinical, and diagnostic challenges that vary across regions. In this study, we reported the results of different approaches on CG screening among infants with a high risk of CG, especially those with prolonged jaundice in Malaysia. We demonstrated that a combination of total galactose assay and GALT activity as a screening method for CG yielded higher sensitivity and specificity, with better AUC performance.

The sample population consisted of infants who met the inclusion criteria, particularly those with prolonged jaundice (hyperbilirubinaemia). Due to the uncertainty of prevalence and incidence of CG in Asia, there was a significant association between CG and early indirect hyperbilirubinaemia, which may indicate a strong justification in choosing babies with prolonged jaundice as the sample population in this study (14).

Approach A, which used total galactose (TG) assay alone, demonstrated high specificity but poor sensitivity (AUC = 0.549), indicating a low probability of correctly identifying true CG cases. This result aligns with studies showing TG alone lacks sufficient discriminatory power due to its susceptibility to non-specific elevations in conditions like citrin deficiency, liver immaturity, or sepsis (15,16). In our cohort, several false positives in approach A were later diagnosed as citrin deficiency, which also presents with hypergalactosaemia due to impaired galactose metabolism (17). These findings highlight the limitation of relying solely on TG for CG screening.

In Approach B, GALT activity was used as the first-line marker. While sensitivity improved, specificity dropped, partly due to known confounders. Notably, patients with G6PD deficiency produced false-positive GALT results due to interference with the enzyme assay (18), and those who had undergone blood transfusions before screening yielded false negatives, as the transfused donor erythrocytes can mask the recipient's actual GALT activity (16). These practical issues significantly affect diagnostic accuracy and highlight the limitations of single-marker approaches.

Approach C, which combined GALT activity and TG levels, showed the highest diagnostic performance (AUC close to 1), confirming its superior discriminative power. The higher value of AUC seen in approach C suggested that this approach would be more ideal, and the risk of false positive results in non-CG could be alleviated when using this approach (19). Combining both assays enables more stringent case classification, particularly when other differential diagnoses, such as G6PD deficiency and citrin deficiency, have been excluded and when pre-analytical confounders, like transfusion status, are controlled. This aligns with screening strategies adopted in countries like the UK and Australia, where dual-parameter approaches have been shown to enhance diagnostic accuracy and reduce false outcomes (20). As such, Approach C strengthens the reliability of presumptive CG diagnoses, contributing to better early clinical decisions and long-term patient management.

The diagnostic performance of Approach C was further supported by ROC analysis which yielded an AUC close to 1, indicating excellent discriminative ability between CG and non-CG cases. This near-perfect AUC suggests that the combined use of GALT activity and TG assay is highly reliable in distinguishing true positives from false positives in the studied cohort (21–23).

Given the variability in TG and GALT levels across populations and pre-analytical conditions, the current use of the 99th percentile as a cut-off may not be optimal. Based on our ROC analysis, a slightly lower cut-off for TG (e.g., 95th–97th percentile) or the inclusion of a grey zone with reflex GALT testing could improve sensitivity without sacrificing specificity. Similarly, adjusting GALT activity thresholds based on transfusion history or using age-specific reference ranges may reduce false negatives. However, these suggestions would require larger prospective studies for validation.

CONCLUSION

The present study shows that combining total galactose assay and GALT activity to detect CG could increase its sensitivity and specificity, with a better diagnostic performance to discriminate between healthy and diseased CG individuals. It also provides useful information on deciding to proceed with other confirmatory tests and offers a guide for treating and managing disease-positive individuals.

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