Original Article

Performance verification of a biochemical detection system for hydrothorax and ascites and clinical diagnostic accuracy evaluation of exudate and tuberculous effusion

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Background: Lactate dehydrogenase (LDH), total protein (TP) and glucose (Glu) in pleural hydrothorax and ascites can be used in the diagnosis of exudate, and adenosine deaminase (ADA) can be used in the diagnosis of tuberculous effusion. However, the manufacturers do not claim that their biochemical reagents can be used to detect hydrothorax and ascites samples. Therefore, medical laboratories must conduct suitability studies on biochemical reagents for hydrothorax and ascites samples to comply with regulatory requirements for humor detection. This study aimed to verify the analytical performance and clinical diagnostic accuracy of the Mindray biochemical reagents, including LDH, TP, Glu and ADA, for hydrothorax and ascites.

Methods: The repeatability, detection limits and reference intervals of Mindray biochemical reagents (LDH, TP, Glu, ADA) in detecting hydrothorax and ascites were determined. The comparison of different measurement procedures was performed. Meanwhile, the diagnostic accuracy of LDH, TP, Glu and ADA were assessed.

Results: The quality control results of LDH, TP, Glu, and ADA were all under control. The repeatability coefficient of variation (%) of LDH, TP, Glu, and ADA were all less than 1%. The limits of blank of LDH, TP, Glu, and ADA were 0.33 U/L, 0.45 g/L, 0.00 mmol/L, and 0.04 U/L, respectively; the limits of detection were 1.57 U/L, 1.85 g/L, 0.05 mmol/L, and 0.12 U/L, respectively. Compared with the reference measurement program, the correlation coefficients of LDH, TP, Glu and ADA were 0.9931, 0.9983, 0.9996 and 0.9966, respectively; the regression equations were y=1.0082x–10.06, y=0.9965x–0.4732, y=0.9903x+0.0522 and y=1.0051x–0.0232, respectively. The reference intervals of LDH, TP, Glu, and ADA in hydrothorax and ascites were ≤198.39 U/L, ≤32.97 g/L, ≥5.03 mmol/L. and ≤11.00 U/L respectively. For differentiating between exudates and transudates, the area under the curve (AUC) of LDH, TP, and Glu were 0.913, 0.875, and 0.767, respectively; the AUC of ADA for the differential diagnosis of tuberculous and nontuberculous effusions was 0.876.

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Conclusions: The LDH, TP, Glu, and ADA assays were validated for use with the Mindray BS-2800 analyzer for hydrothorax and ascites evaluation. LDH, TP, and Glu in hydrothorax and ascites are applicable to the differential diagnosis of exudates and transudates; ADA in hydrothorax and ascites can be employed to differentiate and diagnose tuberculous and nontuberculous effusions.

Keywords: Hydrothorax and ascites biochemical detection system; performance verification; clinical diagnostic accuracy

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Introduction

The chemical analysis of hydrothorax and ascites is contributory to clinical diagnosis (1-5) and is thus a test frequently requested by physicians. However, reagent manufacturers rarely evaluate hydrothorax and ascites as a routine part of the biochemical reagent development process, resulting in few biochemical reagents on the market being overtly designated as suitable for hydrothorax and ascites sample detection. When biochemical reagents are used to detect hydrothorax and ascites samples in the absence of applicability statements, the test results are nonstandard and dubious. This makes it the responsibility of clinical laboratories to verify the analytical performance and characteristics of hydrothorax and ascites detection systems when providing clinical testing.

The "C49-A Analysis of Body Fluids in Clinical Chemistry; Approved Guideline", published by the Clinical and Laboratory Standards Institute (CLSI), and the Laboratory Certification Program, issued by the American Association of Pathologists, both suggest that the interference caused by the hydrothorax and ascites matrix effects should be evaluated when adopting biochemical reagents without applicability statements for hydrothorax and ascites sample detection (6,7). In 2018, Owen *et al.* conduct a matrix evaluation for pericardial, peritoneal (ascites), and pleural fluids using the Beckman Access alpha-fetoprotein (AFP) assay on the UniCel DxI 800 immunoassay system. Through recovery experiments and linearity and precision studies, it was demonstrated that matrix interference with AFP testing was not observed for pericardial, peritoneal, or pleural fluids on the Beckman UniCel DxI 800 system (8). In 2022, Allison *et al.* evaluated the performance characteristics of the Diazyme adenosine deaminase (ADA) assay for serum, pleural, pericardial, peritoneal, and cerebrospinal fluids using the Roche cobas c501 analyzer. Accuracy, linearity, recovery, precision, sensitivity, specificity, reference interval, and stability studies were conducted. Potential interference of hyaluronidase and ultracentrifugation pretreatment for viscosity on ADA concentrations were further evaluated. The Diazyme ADA assay was validated for use in Roche cobas c501 analyzer for all fluid types evaluated (9). Therefore, in order to provide accurate hydrothorax and ascites sample detection results clinically, we employed a Mindray fully automatic biochemical analyzer (BS-2800M) and Mindray biochemical reagents as the detection system for lactate dehydrogenase (LDH), total protein (TP), glucose (Glu), and ADA in hydrothorax and ascites. Performance verification and reliability evaluation of the results of the biochemical detection system for hydrothorax and ascites were conducted. Additionally, the diagnostic accuracy of LDH, TP, and Glu in distinguishing between exudates and transudates (10) and that of ADA in the auxiliary evaluation

Highlight box

Key findings

- Lactate dehydrogenase (LDH), total protein (TP), glucose (Glu), and adenosine deaminase (ADA) assays were validated for use in the Mindray BS-2800 analyzer for hydrothorax and ascites evaluation.

What is known and what is new?

- The repeatability, detection limit, and methodological comparison of LDH, TP, Glu, and ADA assays were excellent.
- The reference interval of LDH, TP, Glu, and ADA of hydrothorax and ascites was established.

What is the implication, and what should change now?

- Clinical laboratories should evaluate the performance characteristics of biochemical assays for hydrothorax and ascites.

of tuberculous effusions were evaluated (11,12). We present this article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-345/rc).

Methods

Detection system

The biochemical hydrothorax and ascites detection system in this study consisted of a BS-2800M fully automatic biochemical analyzer (Mindray Biomedical Electronics Co., Ltd., Shenzhen, China) and biochemical reagent kits for LDH, TP, Glu, and ADA (Mindray Biomedical Electronics Co., Ltd.). The system was placed in the Laboratory of The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine, and instrument parameters were set according to the manufacturer's instructions. The comparison system consisted of an ultraviolet spectrophotometer and Beijing Strong Biotechnologies, Inc. (BSBE) ADA biochemical reagent kits.

Hydrothorax and ascites samples

The hydrothorax and ascites samples used in this study were the leftover samples from the Laboratory Department of The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine and the Laboratory Department of the First Affiliated Hospital of Sun Yat-sen University. Each sample was 1.5 mL, without apparent precipitation or flocculent substances. The samples were collected after tested by Laboratory Department and stored at –20 ℃, and then these samples were tested in Mindray BS-2800M fully automatic biochemical analyzer. A total of 439 hydrothorax and ascites samples were collected, including 143 cases of exudates, 88 cases of transudates, 47 cases of tuberculous effusions, and 161 cases of nontuberculous effusions. The exudates are determined by following criteria: (I) confirmed by the physician's clinical diagnosis as exudate; (II) inflammatory effusion; (III) carcinomatous effusion; (IV) tuberculous effusions; (V) ruptured esophageal effusions; and (VI) rheumatic effusion. The transudates are determined by following criteria: (I) confirmed by the physician's clinical diagnosis as transudate; (II) venous return obstruction; (III) congestive heart failure; (IV) nephrotic syndrome; (V) severe liver diseases (such as cirrhosis and primary liver cancer); and (VI) various disease samples with significantly declined plasma albumin concentration. These criteria were verified through clinical information. Tuberculous and nontuberculous effusions were confirmed by the physician's clinical diagnosis. This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine (No. GCP-2023-013). The First Affiliated Hospital of Sun Yat-sen University was informed and agreed the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all participants involved in the study.

Internal quality control

After daily powering on and before testing, the biochemical reagent kits for the detection of LDH, TP, Glu, and ADA levels in serum or plasma samples were used to identify the quality control of two concentration levels. The test lasted for 30 days. The daily z-score were calculated to draw an internal quality control graph of the z-score.

Repeatability

A total of 35 hydrothorax and ascites samples were collected for repeated experiments. Each sample was detected 10 times in the same analytical run to calculate the average concentration and coefficient of variation (CV) (%). A scatter graph was plotted with the average concentration as the horizontal ordinate and the CV (%) as the vertical ordinate.

Limits of blank (LoB)

Five tubes of physiological saline were prepared daily as test samples, and each tube was tested four times for three consecutive days. A total of 60 data sets were obtained. The nonparametric method was adopted for data statistics. After ranking all results from small to large, the one at 95% was taken as LoB (α=0.05; P=95%), represented as follows: LoB = 0.5 (X_{58} + X_{57}).

Limits of detection (LoD)

On the first day, 2 low-value samples were selected and tested 12 times, respectively; on the second day, the same operation was repeated; on the third day, only 1 sample was taken and tested 12 times. Finally, 60 test results were obtained in total. If the results conform to a normal

distribution, the LoD is calculated by the following formula:

$$LoD = LoB + C_p SD_L \quad [1]$$

$$C_p = \frac{1.645}{1-4(L-J)} \quad [2]$$

$$SD_L = \sqrt{\frac{\sum_{i=1}^{J}(n_i-1)SD_i^2}{\sum_{i=1}^{J}(n_i-1)}} \quad [3]$$

where L is the total number of tests (L=60), and J is the total number of low-value samples (J=5).

If the detection results are abnormally distributed, and the proportion of the results less than the LoB is less than or equal to 5%, then the LoD is regarded as the median of the 60 detection results.

Methodology comparison

Exudates and transudate samples were collected, and each sample was tested twice using the hydrothorax and ascites biochemical detection system of the Mindray fully automatic biochemical analyzer (BS-2800M) and a reference measurement program (ultraviolet spectrophotometer), respectively. The mean between two replicates was calculated. A scatter plot was drawn with the test results of the reference measurement program as the x-axis (x) and the Mindray BS-2800M test results as the y-axis (y). Passing-Bablok linear regression was adopted to solve the regression equation (y = kx + b). The correlation coefficient (CC) is calculated. The Bland-Altman analysis was used to determine the consistency of the two systems.

Reference intervals

Transudate was included to establish reference intervals of LDH, TP, and Glu in hydrothorax and ascites.

Nontuberculous effusion was included to establish reference intervals of ADA in hydrothorax and ascites. Based on the CLSI EP28-A3c "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline—Third Edition" (13), the analytical data are non-normally distributed so the non-parametric method was used to calculate unilateral reference intervals.

Analysis of clinical diagnostic accuracy

Hydrothorax and ascites were divided into exudates (infectious/inflammatory, cancerous, tuberculous, esophageal rupture, and rheumatic) and transudates (venous return obstruction, congestive heart failure, nephrotic syndrome, and various diseases with significantly declined plasma albumin concentration). Receiver operating characteristic (ROC) curve analysis was performed for LDH, TP, and Glu. The effusions were classified into tuberculous effusion and nontuberculous effusion for the ROC curve analysis of ADA.

Statistical analysis

All statistical analyses in this study were conducted using MedCalc v. 15.2.2.0 (Ostend, Belgium) and Excel 2019 (Microsoft Corp., Redmond, WA, USA). Passing-Bablok regression and Bland-Altman analysis were employed for method comparison. $P<0.05$ indicated a significant difference.

Results

Internal quality control

After daily startup, LDH, TP, Glu, and ADA dual quality control products were used for internal quality control. The quality control results of LDH (*Figure 1A*), TP (*Figure 1B*), Glu (*Figure 1C*), and ADA (*Figure 1D*) for 30 consecutive days were are all under control.

Repeatability

Repeat results show that the CV values of LDH (*Figure 2A*), TP (*Figure 2B*), Glu (*Figure 2C*), and ADA (*Figure 2D*) in hydrothorax and ascites were all less than 1%.

Detection limits

According to the Mindray BS-2800M fully automatic biochemical analyzer, the LoB values of LDH, TP, Glu, and ADA in hydrothorax and ascites were 0.33 U/L, 0.45 g/L, 0.00 mmol/L, and 0.04 U/L, respectively; meanwhile, the LoD values were 1.57 U/L, 1.85 g/L, 0.05 mmol/L, and 0.12 U/L, respectively.

Methodology comparison

LDH, TP, Glu, and ADA in hydrothorax and ascites samples were detected using the biochemical detection system of the Mindray fully automatic biochemical analyzer

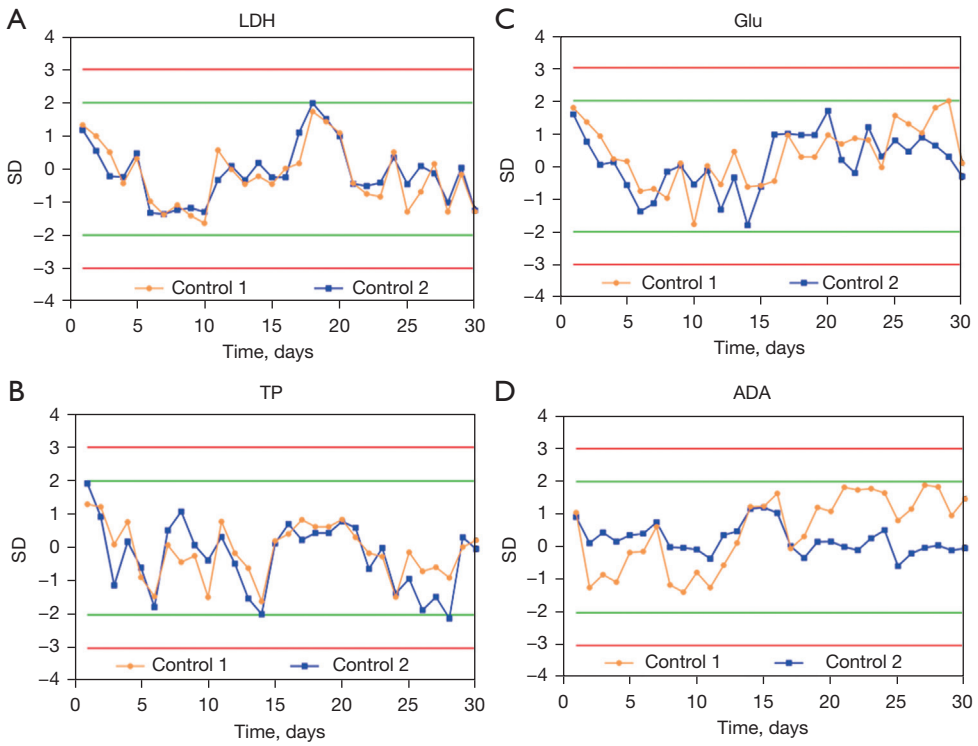

Figure 1 Quality control diagram of the Mindray fully automatic biochemical analyzer (BS-2800M). LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase; SD, standard deviation.

(BS-2800M). The detection results were compared with the reference measurement program (ultraviolet spectrophotometer). As shown in *Figure 3*, the expected acceptable slope was 0.9–1.1, and the acceptable R was ≥0.975; compared with the reference measurement program (ultraviolet spectrophotometry), the CCs (R) of LDH, TP, and Glu were 0.9931, 0.9983, and 0.9996, respectively; meanwhile, the regression equations were y=1.0082x–10.06, y=0.9965x–0.4732, and y=0.9903x+0.0522, respectively; in contrast with the comparative reagent (ADA Biochemical Kit, BSBE), the CC of ADA was 0.9966, and the regression equation was 1.0051x–0.0232.

Reference interval

The reference intervals of LDH, TP, Glu, and ADA in hydrothorax and ascites were ≤198.39 U/L (*Figure 4A*), ≤32.97 g/L (*Figure 4B*), ≥5.03 mmol/L (*Figure 4C*), and ≤11.00 U/L (*Figure 4D*), respectively.

Clinical diagnostic accuracy

A total of 231 hydrothorax and ascites samples were used to determine the efficacy of LDH, TP, and Glu in hydrothorax and ascites in the differential diagnosis of exudates and transudates, of which 38.10% (88/231) were transudates and 61.90% (143/231) were exudates. The mean values of LDH, TP, and Glu in transudates were 99.45±92.78, 16.18±11.49, and 9.86±8.90, respectively, and those in exudates were 1,043.27±1,643.93, 36.47±12.77, and 5.23±3.65, respectively. For the exudates caused by various diseases, LDH (*Figure 5A*) and TP (*Figure 5B*) markedly increased, while Glu markedly decreased (*Figure 5C*).

The diagnostic accuracy of ADA in distinguishing between tuberculous and nontuberculous effusions was investigated using 208 hydrothorax and ascites samples.

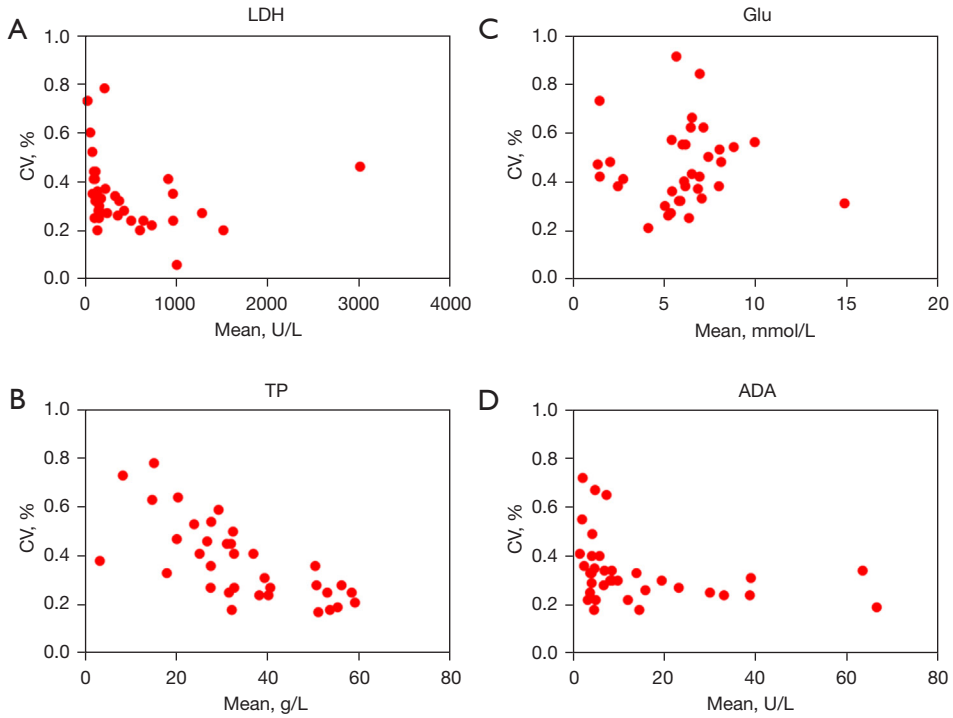

Figure 2 Repeatability of the biochemical detection system for hydrothorax and ascites. LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase; CV, coefficient of variation.

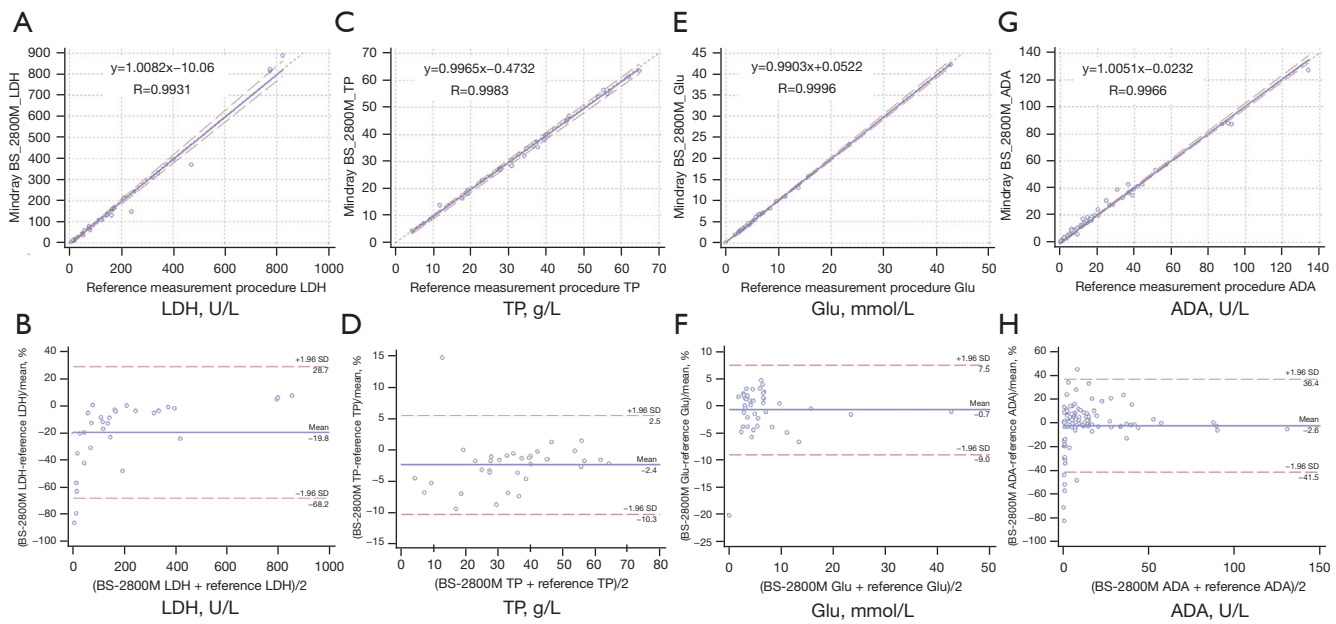

Figure 3 Methodology comparison of the hydrothorax and ascites biochemical detection system. (A-F) Comparison to the reference measurement program (ultraviolet spectrophotometer). (G,H) Comparison to the Beijing Strong Biotechnologies, Inc. Biological ADA Reagent Kit. LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase.

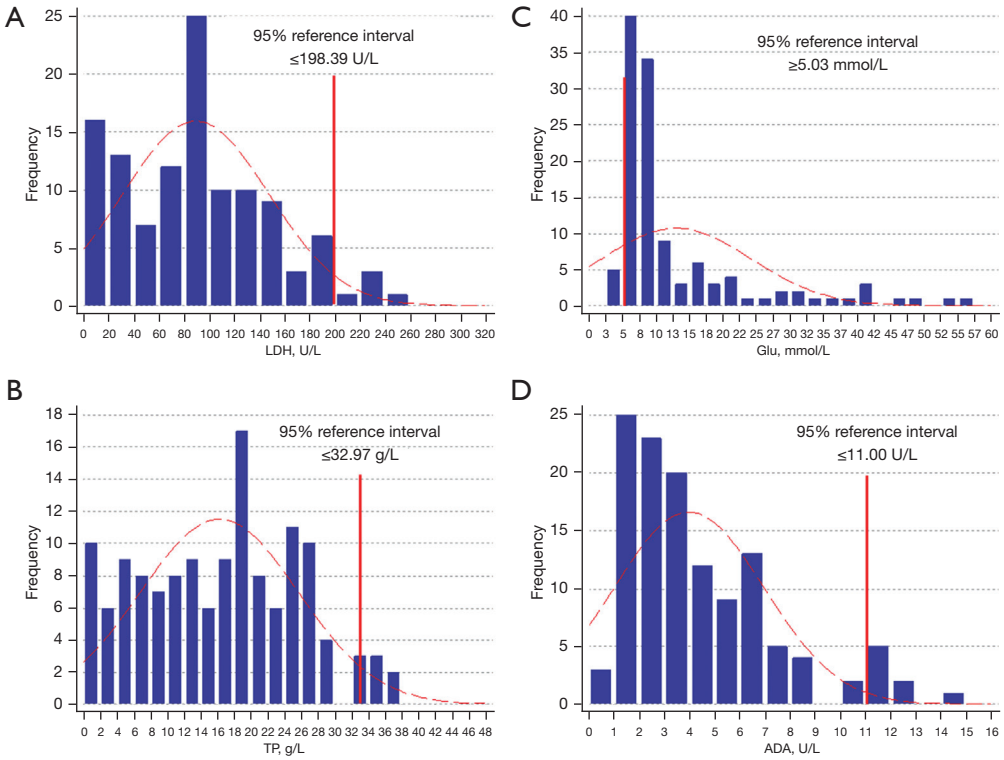

Figure 4 Reference intervals of LDH, TP, Glu, and ADA in hydrothorax and ascites. LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase.

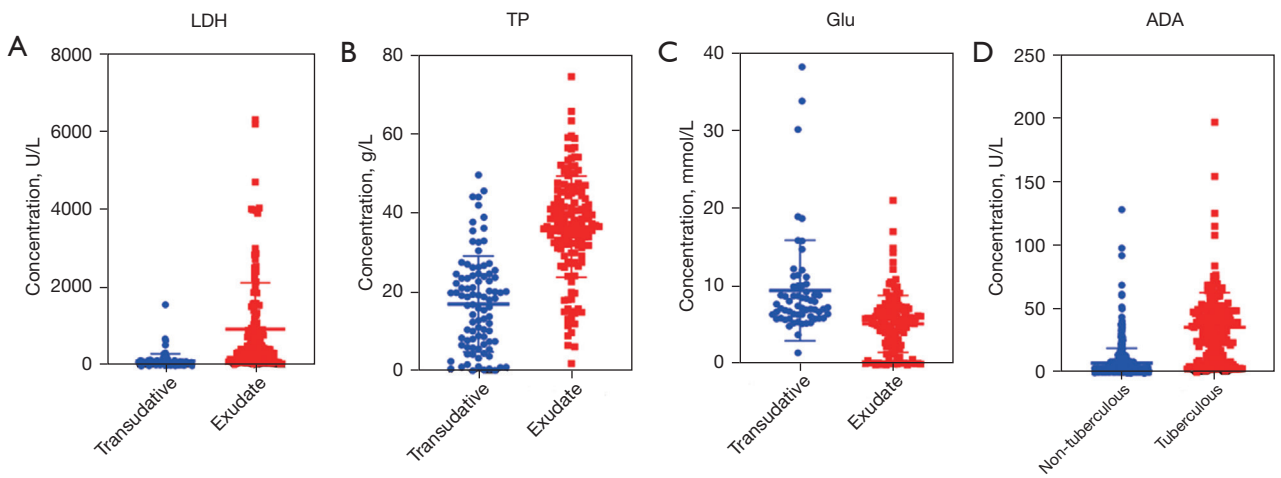

Figure 5 In the exudates caused by various diseases, LDH and TP were significantly increased while Glu was significantly decreased (P<0.05). In tuberculous effusion, ADA was significantly increased (P<0.05). LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase.

Table 1 Etiological distribution of serous cavity effusions (clinical diagnosis)

Clinical diagnosis	N	LDH (U/L)	TP (g/L)	Glu (mmol/L)	ADA (U/L)
Exudate	88	99.45±92.78	16.18±11.49	9.86±8.90	
Nephrotic syndrome	25	59.38±38.77	11.25±13.84	13.75±15.41	
Hepatoma	14	114.85±68.80	18.28±6.48	7.40±1.62	
Hepatic cirrhosis	12	126.27±172.68	12.09±7.72	8.62±3.85	
Congestive heart failure	11	115.04±49.17	22.14±11.54	10.71±4.88	
Diseases with albumin reduced	3	282.05±220.37	31.90±1.29	5.27±3.69	
Others	23	88.36±44.87	17.51±26.70	7.96±1.98	
Transudate	143	1,043.27±1,643.93	36.47±12.77	5.23±3.65	
Cancerous effusion	76	1,103.04±1,329.63	39.83±10.57	4.88±3.16	
Inflammatory hydrops	64	981.79±1991.57	32.40±14.17	5.76±4.16	
Esophageal rupture effusion	1	929.34	41.32	0.03	
Rheumatic effusion	2	796.42±796.189	36.67±13.45	3.82±0.85	
Tuberculous effusion	47				36.12±27.21
Nontuberculous effusion	161				7.96±11.65

Data are presented as mean ± standard deviation. LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase.

Table 2 ROC analytical parameters

Chemistry	Cutoff	AUC	95% CI	TP proportion (sensitivity)	TN proportion (specificity)	FP proportion	FN proportion	Youden index
Lactate dehydrogenase	>153.44 U/L	0.913	0.869–0.946	0.811	0.909	0.091	0.189	0.7203
Total protein	>27.05 g/L	0.875	0.826–0.915	0.818	0.875	0.125	0.182	0.6932
Glucose	<5.30 mmol/L	0.767	0.707–0.820	0.490	0.966	0.034	0.510	0.4554
Adenosine deaminase	>13 U/L	0.876	0.851–0.897	0.773	0.862	0.138	0.227	0.6345

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; TP, true positive; TN, true negative; FP, false positive; FN, false negative.

Among them, 22.60% (47/208) were tuberculous effusions, and 77.40% (161/208) were nontuberculous effusions (*Table 1*). The mean ADA of tuberculous effusions was 36.12±27.21, and that of nontuberculous effusions was 7.96±11.65. Compared with that in nontuberculous effusions, the ADA level in tuberculous effusions was significantly elevated (*Figure 5D*). We adopted ROC curves to further evaluate the diagnostic accuracy of LDH, TP, Glu for distinguishing between exudates and transudates. Moreover, the diagnostic accuracy of ADA in differentiating between tuberculous and nontuberculous effusions was assessed. The detailed parameters of the ROC analysis are listed in *Table 2*. The area under the curve (AUC) value of LDH was 0.913. When the cutoff value was set to >153.44 U/L, the sensitivity and the specificity were 81.10% and 90.90%, respectively (*Figure 6A*); the AUC value of TP was 0.875. When the cutoff value was set to >27.05 g/L, the sensitivity and specificity were 81.80% and 87.50%, respectively (*Figure 6B*); the AUC value of Glu was 0.767. When the cutoff value was set to <5.30 mmol/L, the sensitivity and the specificity were 49.00% and 96.60%, respectively (*Figure 6C*); the AUC value of ADA was 0.876. When the cutoff value was set to >13 U/L, the sensitivity and specificity were 77.30% and 86.20%, respectively

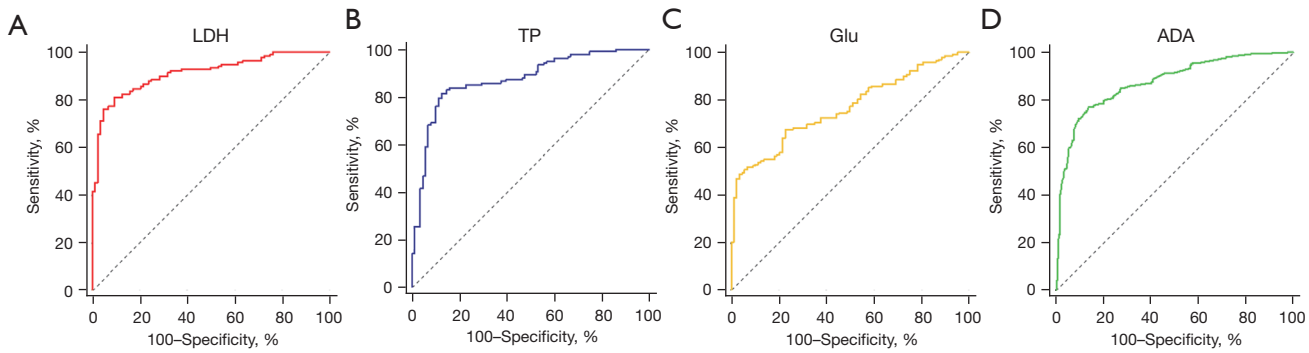

Figure 6 ROC curves of LDH, TP, Glu for the differential diagnosis of exudates and transudates. The ROC curve of ADA used in the auxiliary evaluation of tuberculous effusions. LDH, lactate dehydrogenase; TP, total protein; Glu, glucose; ADA, adenosine deaminase; ROC, receiver operating characteristic.

(*Figure 6D*).

Discussion

Pleural and peritoneal effusions (collectively referred to as hydrothorax and ascites) are common clinical signs, which can be caused by cardiovascular diseases, tuberculosis, peritoneal diseases, liver diseases, nutritional disorders, and ovarian cysts (14-16). The presence of hydrothorax and ascites is one of the manifestations of pathological changes in the body. According to their characteristics, they can be divided into exudates (inflammatory) and transudates (noninflammatory) (17) or tuberculous and nontuberculous effusions (18). At present, the differential diagnosis of exudates versus transudates and of tuberculous versus nontuberculous effusions mainly relies on laboratory biochemical tests (19,20). The differential diagnosis of exudates and transudates is achieved by quantitatively detecting the content of LDH, TP, and Glu in hydrothorax and ascites (21,22) while that of tuberculous and nontuberculous effusions is realized by the quantitative assay of ADA in hydrothorax and ascites (23,24). However, the currently available LDH, TP, Glu, and ADA biochemical reagents produced by companies such as Mindray Medical, Roche Diagnostics, and Beckmann Coulter are only claimed to be suitable for serum or plasma samples, with no statements concerning the applicability to hydrothorax and ascites samples. Since the matrices of hydrothorax and ascites differ from those of serum or plasma, biochemical reagents appropriate for serum or plasma may not necessarily be suitable for hydrothorax and ascites. When using biochemical reagents without applicability statements for detecting hydrothorax and ascites samples, inadequate relevant regulations make it the responsibility of clinical laboratories to confirm the analytical performance and characteristics of hydrothorax and ascites samples to provide clinical hydrothorax and ascites testing. Therefore, in order to obtain accurate detection results of LDH, TP, Glu, and ADA in hydrothorax and ascites, it is critical to evaluate whether the relevant biochemical detection system is suitable for hydrothorax and ascites samples. Consequently, this study evaluated the clinical performance of the hydrothorax and ascites detection system of the Mindray fully automatic biochemical analyzer (BS-2800M) to determine its applicability for detecting hydrothorax and ascites samples.

After the detection system (Mindray BS-2800M biochemical analyzer and related biochemical reagent kits) was proven to be under control using an internal quality control, we employed the relevant serum biochemical reagent kits to identify hydrothorax and ascites samples with the BS-2800M fully automatic biochemical analyzer. Repeat experiments demonstrated that the CV values of LDH, TP, Glu, and ADA in hydrothorax and ascites detected using the serum biochemical reagent kits were within the allowable testing range (1%) and clinically acceptable. The detection limit experiments verified that the LoB values of LDH, TP, Glu, and ADA in hydrothorax and ascites using serum biochemical reagent kits were 0.33 U/L, 0.45 g/L, 0.00 mmol/L, and 0.04 U/L, respectively, while the LoD values were 1.57 U/L, 1.85 g/L, 0.05 mmol/L, and 0.12 U/L, respectively. The methodological comparison confirms that the use of serum biochemical reagent kits for detecting

LDH, TP, Glu, and ADA in hydrothorax and ascites is comparable to the reference measurement program. The reference intervals of LDH, TP, Glu, and ADA in hydrothorax and ascites were ≤198.39 U/L, ≤32.97 g/L, ≥5.03 mmol/L, and ≤11.00 U/L, respectively. The diagnostic accuracy analysis verifies that the levels of LDH, TP, and ADA significantly increase in exudates, while that of Glu clearly decreases. Moreover, LDH and TP have high diagnostic accuracy in distinguishing between exudates and transudates, and the diagnostic accuracy of ADA can satisfactorily differentiate between tuberculous and nontuberculous effusions.

Conclusions

The analytical performance of the method established using Mindray biochemical reagents on the Mindray BS-2800M fully automatic biochemical analyzer for detecting LDH, TP, Glu, and ADA in hydrothorax and ascites is acceptable. The method can be applied to daily clinical testing to provide accurate hydrothorax and ascites detection results for clinical use.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-345/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-345/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-345/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-345/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of The First Affiliated Hospital of Guangzhou University of Traditional Chinese Medicine as a study involving humans (No. GCP-2023-013). The First Affiliated Hospital of Sun Yat-sen University was informed and agreed the study. Informed consent was obtained from all participants involved in the study.

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