Original Article

Screening for malignant tumor cells in serous effusions with an automatic hematology analyzer using a novel diagnostic algorithm

Dehua Sun[1#], Xinru Mao[1#], Taixue An[1#], Xiaojing He[1], Kai Qiu[1], Yuhong Luo[1], Zheyuan Qin[2], Yongjian He[1], Tie Xiong[1], Houmei Feng[1], Jin Li[2], Lei Zheng[1]

[1]Department of Laboratory Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Department of Hematology Research and Development, Shenzhen Mindray Bio-Medical Electronic Co., Ltd., Shenzhen, China

Contributions: (I) Conception and design: L Zheng; (II) Administrative support: L Zheng, D Sun; (III) Provision of study materials or patients: D Sun, X Mao, T An; (IV) Collection and assembly of data: X He, K Qiu; (V) Data analysis and interpretation: Y Luo, Y He; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lei Zheng. Department of Laboratory Medicine, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Email: nfyyzhenglei@smu.edu.cn.

Background: Due to the high false-positive rate of the high-fluorescence body fluid (HF-BF) cell parameter of the hematology analyzer in BF mode, a novel algorithm based on the Mindray BC-6800 Plus hematology analyzer (BC-6800Plus), with higher diagnostic accuracy compared to that of the traditional HF-BF algorithm, was used to screen for malignant tumor cells in clinical BF samples. In this study, the body fluid mode of BC-6800Plus was applied to investigate the ability of its available parameters and characteristic regional particles in tumor cells screening.

Methods: A total of 220 BF samples (including pleural effusion and ascites) were randomly classified into a training cohort (154 samples) and a validation cohort (66 samples), and detected on the BC-6800Plus in BF mode. Based on the scatter plot analysis of the instrument, a novel gating algorithm, malignant cell algorithm-body fluid (MA-BF), was designed to detect the aggregated cells expressing highest fluorescence (FL) signals and side-scatter (SS) signals than other cells. BF collection and analyses were performed in compliance with the CLSI H56-A guideline. tumor cell-positive samples were defined as greater than or equal to confirIIIb (Papanicolaou class system) by the pathological examination. The diagnostic accuracy of HF-BF and MA-BF were determined by the receiver operating characteristic (ROC) curve analysis.

Results: When the cutoff values of the absolute count (HF-BF#) and relative count (HF-BF%) were set as 0.022×10^9/L and 3.0%, respectively, the area under curve (AUC), sensitivity, and specificity were 0.76, 0.85 and 0.55 for HF-BF#, and were 0.70, 0.85, and 0.49 for HF-BF%, respectively. The new parameters, the absolute tumor cell count (MA-BF#) and relative count (MA-BF%), were established in the training cohort using the novel algorithm. We confirmed the cutoff values of MA-HF# and MA-HF% in BF were set as 0.006×10^9/L and 0.2% in the training cohort, respectively. In the validation cohort, the AUC, sensitivity, and specificity were 0.89, 0.93, and 0.78 for MA-BF#, and were 0.89, 0.87 and 0.75 for MA-BF%, respectively.

Conclusions: The MA-BF parameters of the novel algorithm output had better diagnostic accuracy for BF tumor cells than the traditional HF-BF parameters.

Keywords: Hematology analyzer; body fluid (BF); malignant cells; high-fluorescent; novel algorithm

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Introduction

Cytomorphological examination of body fluids (BF) is one of the routine tools for tumor screening and diagnosis. Due to its manual nature, it has low sensitivity, is time-consuming, and requires high professional competence of the operators. The exfoliative cytological examination of BF has difficulty meeting the needs of tumor screening in medical institutions at all levels (1,2). Recently, significant advances in automated hematology analyzer of BF analysis have been developed over the past 20 years. BC-6800 Plus hematology analyzer (Mindray, Shenzhen, China) that works on flow cytometry principles were equipped with a novel BF mode. The BF mode on this type of instrument uses laser scattering to detect cells and can output three signal parameters, in which the forward-scatter (FS) light reflects the size of the cells, the side-scatter (SS) light reflects the intracellular particle content and the complexity of the nucleus, and the lateral fluorescence (FL) reflects the concentration of nucleic acid material in the nucleus (3,4). A number of parameters can be obtained from the calculation of these signals, such as white blood cells in BF (WBC-BF), polymorphonuclear (PMN) cells, mononuclear (MN) cells, and high-fluorescence body fluid (HF-BF) cells. These parameters can be used to help clinicians determine the properties of BF. Compared to the manual exfoliative cytological examination in BF, the hematology analyzer is a convenient, fast, low-cost, and non-empirical detection method, and is especially suitable for the screening of tumor cells in BF (5). Tumor cells have more nucleic acid than leukocytes in BF. Therefore, HF-BF is a commonly used measure for detecting the presence of tumor cells in BF.

HF-BF has a high false-positive rate in the detection of tumor cells (6-8), which is the main reason for the limited clinical application of hematology analyzers in the detection of tumor cells. The HF cells produced by the hematology analyzer not only include tumor cells, but also include normal cells such as mesothelial cells and macrophages. Mesothelial cells have the greatest influence on the detection of tumor cells (9,10). There are many studies on how to distinguish mesothelial cells from tumor cells, with methods including acid phosphatase staining (11) and carcinoembryonic antigen markers (12). However, these methods require the addition of new detection procedures, and the process is cumbersome and time consuming. Therefore, how to improve the accuracy of hematology analyzers in screening for tumor cells in BF is an urgent problem to be solved in clinical laboratories.

In this study, the body fluid mode of Mindray BC-6800 Plus hematology analyzer was applied to investigate the ability of its available parameters and characteristic regional particles in tumor cells screening. The novel algorithm will lay the foundation for clinical application of this automated BF analysis. We present the following article in accordance with the STARD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-411/rc).

Methods

Samples

This study collected a total of 220 BF samples from inpatients of the Department of Oncology, Department of Hepatology, Department of Respiratory Diseases, and Department of Critical Care Medicine of the Nanfang Hospital of Southern Medical University, China, between February 2019 and July 2019. These included 127 samples of pleural effusion, 86 samples of ascites, and seven samples of other BF types (one cerebrospinal fluid, three puncture fluid, and three drainage fluid) by dating back to the BF results. All BF samples were treated with the di-potassium ethylene di-amine tetra-acetic acid (K2-EDTA) anticoagulant, except for cerebrospinal fluid. Using the results of pathology examination of BF as the gold standard, all BF samples were divided into a tumor cell-positive group (61 samples) and a tumor cell-negative group (159 samples). In the first group, adenocarcinoma predominated, and squamous carcinoma was less common. Thirty-eight samples were from males and 23 were from females. The age range of the patients was 30–78 years (median age: 62). The tumor cell-negative samples were mainly mesothelial cells and lymphocytes. A few were epithelial cells, phagocytes, and neutrophils. No heterotypic cells were observed. There were 111 samples from males and 48 from females, whose age range was 17–92 years (median age: 55). All BF sample were randomly classified into a training cohort and a validation cohort. The training cohort consisted of 46 tumor cell-positive samples and 108 tumor cell-negative samples. Meanwhile, the validation cohort included cohort 15 tumor cell-positive samples and 51 tumor cell-negative samples. All the specimens enrolled in this study were specimens left over after the laboratory issued its test reports. We have no contact with patients, and the privacy and interests of patients were not infringed. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University, Guangzhou, China (No.

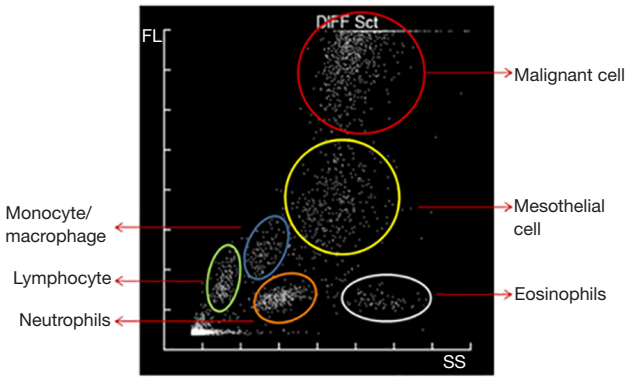

Figure 1 Grayscale image of the novel tumor cell algorithm in BF. Green circles indicate lymphocytes; blue circles indicate monocytes/macrophages; orange circles indicate neutrophils; gray circles indicate eosinophils; yellow circles indicate mesothelial cells; and red circles indicate tumor cells. FL, fluorescence; SS, side scatter; DIFF, differential; BF, body fluid.

NFEC-2018-071) and informed consent was exempted by the Medical Ethics Committee of Nanfang Hospital.

Pathology and cytological examinations

For cell differentiation, cytospin slides were prepared by centrifugation at 1,500 rpm/min for 5 min. The Slides were stained by Wright-Giemsa (BASO, China) staining and examined by an experienced medical technologist. BF collection and analyses were performed in compliance with the CLSI H56-A guideline (13). Concurrent pathological examinations were performed with Papanicolaou (PAP) stained slides and confirmed by a senior clinical pathologist. Malignant cells were defined as greater than or equal to confirIIIb (Papanicolaou class system) by the pathological examination. All assessors were blinded to the clinical results of the whole sample.

Hematology analyzer examination

A BC-6800 Plus hematology analyzer (Mindray, Shenzhen, China) was used to perform one test on another tube of sample, which was completed within 2 h of specimen collection. The results of the parameters of interest, including WBC-BF, total nucleated cells in body fluid (TC-BF), relative MN cell count (MN#/%), relative PMN cell count (PMN#/%), and the parameter (HF-BF#/%) of the samples under BF mode were recorded, and the differential (DIFF) scatter plots of the BF samples were saved. The novel tumor cell recognition algorithm was used to quantify the number and percentage of particles in the characteristic regions of tumor cells in the scatter plot to obtain the novel parameter, malignant cell algorithm-body fluid (MA-BF#/%). All performers were blinded to the clinical results of all samples.

Novel algorithm for tumor cell detection

Based on the scatter plot analysis of the instrument, we found that the FL intensities of lymphocytes, monocyte/macrophages, neutrophils, and eosinophils were all relatively low, and the FL intensity of mesothelial cells was higher than that of monocyte/macrophages. Also, the fluorescence intensity of tumor cells was the highest, and the SS intensity of tumor cells was also slightly higher than that of mesothelial cells (as indicated in red circle area, *Figure 1*). Therefore, a novel gating algorithm was designed to detect the aggregated cells expressing highest FL signals and SS signals than other cells. BF samples that meet the criterion were detected as malignant cells.

Statistical analysis

Statistical analysis was performed using Analyse-it v4.92 statistical software (Analyse-it, Leeds, UK) and the results are presented as percentiles. From 220 samples, no outlier was detected, and the data of BF parameters between the tumor cell-positive group and the tumor cell-negative group were compared using the Wilcoxon rank sum test because a normal data distribution could not be demonstrated. Receiver operating characteristic (ROC) curves were produced to evaluate the diagnostic accuracy of HF-BF and MA-BF. Combined with statistical analysis (the smallest sum of squares of false negatives and false positives) and the intended clinical use (relative high sensitivity for screening), the optimal cut-off values for screening and diagnosis were defined. The rates of the two groups were compared using the χ^2 test or Fisher's exact probability method. Two sided P value<0.05 were considered statistically significant.

Results

Diagnostic accuracy of HF-BF for the detection of tumor cells

Firstly, we identified the BF parameters of interest to distinguish tumor cell-positive samples from tumor cell-

Table 1 Comparison of the results of the two groups of samples run in the Mindray BC-6800Plus

Parameters	Malignant cell group (n=61) median (P_{25}-P_{75})	Nonmalignant cell group (n=159) median (P_{25}-P_{75})	P value
WBC-BF (×10^9/L)	1.16 (0.52–1.85)	0.74 (0.23–2.04)	0.097
TC-BF (×10^9/L)	1.28 (0.61–2.11)	0.86(0.26–2.48)	0.078
MN# (×10^9/L)	0.57 (0.34–1.17)	0.46 (0.12–1.21)	0.053
MN% (%)	71.50 (53.85–88.17)	80.60 (47.10–91.67)	0.889
PMN# (×10^9/L)	0.32 (0.13–0.58)	0.14 (0.03–0.39)	0.077
PMN% (%)	28.50 (11.83–46.15)	19.40 (8.33–52.90)	0.889
HF-BF# (×10^9/L)	0.08 (0.03–0.19)	0.02 (0.005–0.06)	<0.001
HF-BF% (%)	7.20 (3.52–17.20)	3.25 (0.74–8.16)	<0.001

P_{25}–P_{75}, 25th and 75th percentiles; WBC-BF, white blood cells in body fluid; TC-BF, total nucleated cells in body fluid; MN#, absolute mononuclear cell count; MN%, relative mononuclear cell count; PMN#, absolute polymorphonuclear cell count; PMN%, relative polymorphonuclear cell count; HF-BF#, absolute high fluorescent cell count in body fluid; HF-BF%, relatively high-fluorescence cell count in body fluid.

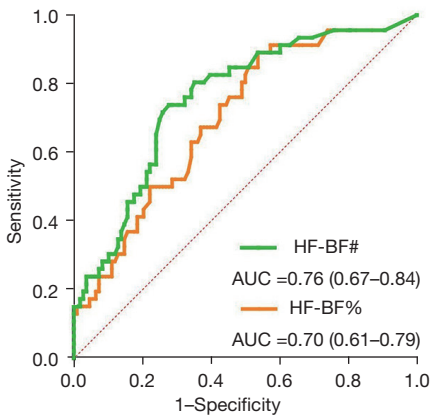

Figure 2 ROC curves of HF-BF for predicting malignant cells in body fluid. HF-BF#, absolute high fluorescent cell count in body fluid; HF-BF%, relatively high-fluorescence cell count in body fluid; AUC, area under the curve; ROC, receiver operating characteristic.

negative samples in the training cohort. The comparison of the hematology analyzer results between the two groups is shown in *Table 1*. Except for HF-BF# and HF-BF%, which showed significant differences between the two groups (P<0.05), the differences in other parameters, including WBC-BF, TC-BF, MN#, MN%, PMN#, and PMN%, were not statistically significant (P>0.05). The ROC analysis results of HF-BF# and HF-BF% are shown in *Figure 2*. The area under the curve (AUC), used for screening and diagnosis of malignant BF, with its 95% confidence interval (CI) was 0.76 (0.67–0.84) and 0.70 (0.61–0.79) in the two groups, respectively. When the cutoff value of HF-BF# was set as 0.022×10^9/L, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.85, 0.55, 0.44, and 0.89, respectively. When the cutoff value of HF-BF% was set as of 3.0%, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.85, 0.49, 0.41, and 0.88, respectively.

Factors affecting the HF-BF diagnosis of tumor cells

To investigate the reasons for the low specificity of the HF-BF diagnosis of tumor cells, we analyzed samples that were false positive for diagnosis of tumor cells by HF-BF# and HF-BF%. Most of the HF-BF scattered points of false-positive samples had moderately or highly intense FL and SS signals (*Figure 3A*), and the scattered points were slightly larger than those of monocyte/macrophages. Most HF-BF scattered points of the true positive samples had extremely high-intensity FL signals and scattered points of relatively high-intensity SS signals (*Figure 3B*), including a small to large number of scattered points of mesothelial cells. We compared the samples above by the cytomorphological examination. HF-BF scattered points of the false positive samples showed many mesothelial cells with round or ovoid shape, abundant cytoplasm, regular central nucleus, fine and uniform chromatin, and no heterotypic cells or tumor cells. Therefore, false-positive HF-BF in these samples seemed to be due to mesothelial cells (*Figure 3C*). HF-BF scattered points of the true positive samples showed heterotypic cells. Most were

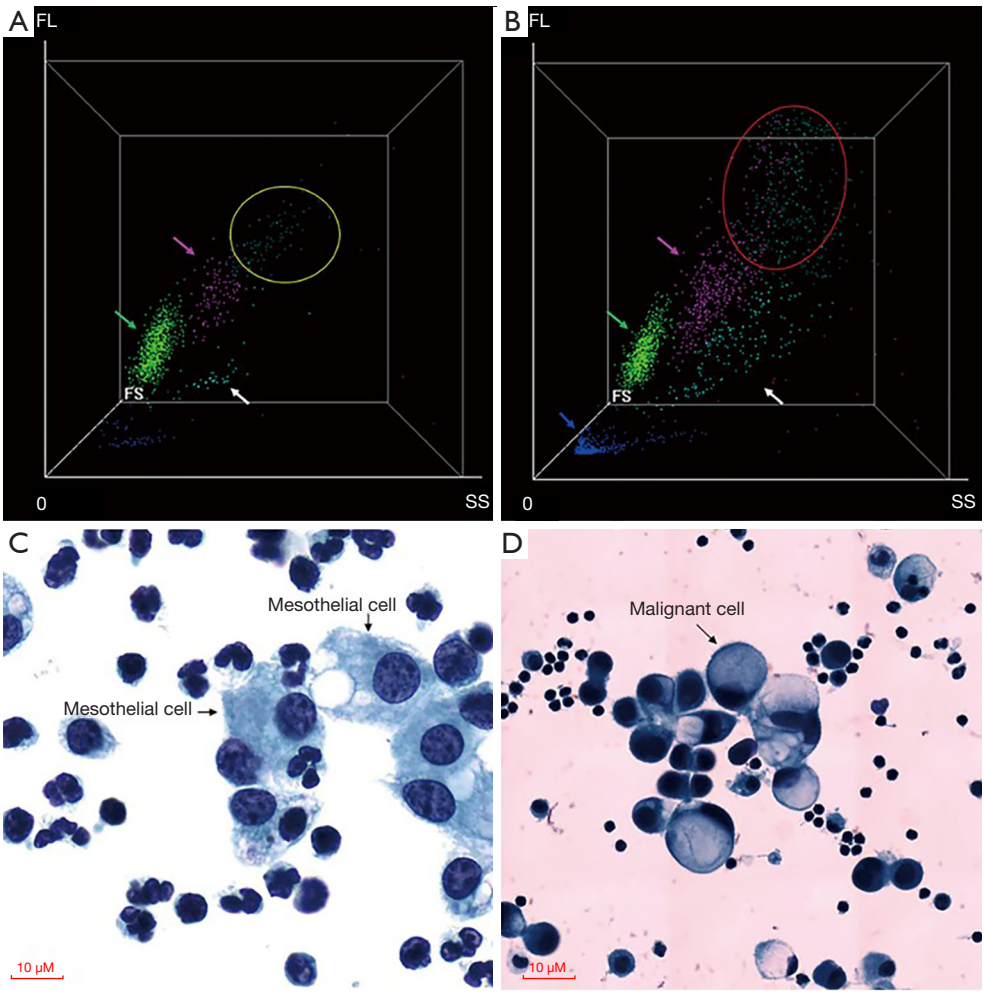

Figure 3 HF-BF influencing factor analysis. (A) Three-dimensional DIFF scatter plot of the mesothelial cell samples. (B) Three-dimensional DIFF scatter plot of the malignant tumor samples. (C) Cytological examination of the mesothelial cells in BF (Papanicolaou staining). (D) Cytological examination of the malignant tumor cells in BF (Papanicolaou staining). Blue arrow points to a blood shadow; green arrow points to lymphocytes; magenta arrow points to monocyte/macrophages; white arrow points to neutrophils; yellow circle represents mesothelial cells; red circle represents tumor cells in BF. FL, fluorescence; FS, forward scatter; SS, side scatter; HF-BF, high-fluorescence body fluid; DIFF, differential.

adenocarcinoma cells, with larger cell volumes, irregular cell bodies, rich cytoplasm, irregular karyotype, and coarse chromatin, often forming glandular luminal structures (*Figure 3D*). In addition, such thoracoabdominal fluid samples all contained more or fewer mesothelial cells.

Diagnostic accuracy of the novel algorithm

To improve the accuracy with which the hematology analyzer detects tumor cells in BF, we improved the algorithm for scatter plot classification of BF detection by the Mindray BC-6800 Plus hematology analyzer. The new parameters for the detection of tumor cells in BF, MA-BF#, and MA-BF% were established in the training cohort using the novel algorithm. The training cohort results are shown in *Figure 4A*. The AUCs of MA-BF# and MA-BF% were 0.90 and 0.89, respectively (*Table 2*). According to the criteria of the optimal cut-off value, when the cutoff value of MA-BF# was set as 0.006×10^9/L, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.85, 0.80, 0.64, and 0.92, respectively. When the cutoff value of MA-BF% was set as 0.2%, the sensitivity,

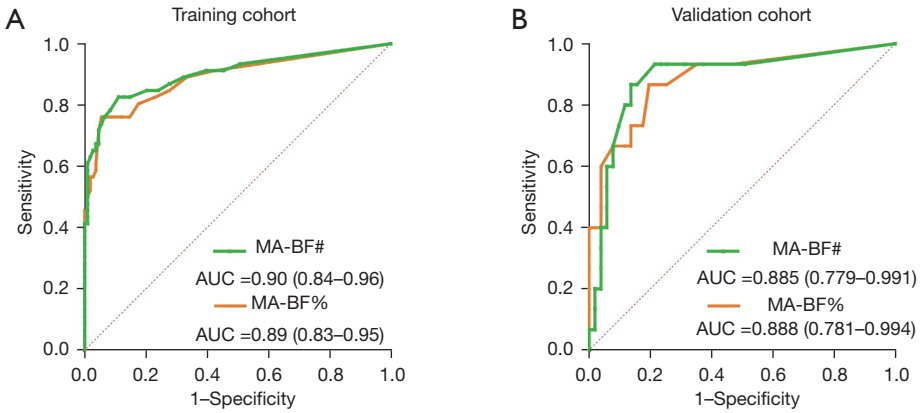

Figure 4 ROC curves of MA-BF for predicting malignant cells in the training cohort (A) and the validation cohort (B). MA-BF#, absolute count of malignant cells in body fluid; MA-BF%, relative percentage of malignant cells in body fluid; ROC, receiver operating characteristic; AUC, area under the curve.

Table 2 Performance of the MA-BF# and MA-BF% in the detection of tumor cells

Cohort	Cutoff value	AUC, 95% CI	Sensitivity	Specificity	PPV	NPV
Training cohort						
MA-BF#	0.006×10^9/L	0.90(0.84–0.96)	0.85	0.80	0.64	0.92
MA-BF%	0.2%	0.89 (0.83–0.95)	0.85	0.72	0.57	0.92
Validation cohort						
MA-BF#	0.006×10^9/L	0.89 (0.78–0.99)	0.93	0.78	0.56	0.98
MA-BF%	0.2%	0.89 (0.78–0.99)	0.87	0.75	0.50	0.95

MA-BF#, absolute count of malignant cells in body fluid; MA-BF%, relative percentage of malignant cells in body fluid; AUC, area under the receiver operating characteristic curve; PPV, positive predicative value; NPV, negative predicative value.

specificity, positive predictive value, and negative predictive value were 0.85, 0.72, 0.57 and 0.92, respectively. Moreover, we confirmed the diagnostic accuracy of MA-BF# and MA-BF% in the validation cohort (*Figure 4B*). In this cohort, the diagnostic accuracy of MA-BF# and MA-BF% was similar to that of the training cohort, respectively (*Table 2*). At a threshold of 0.006×10^9/L, the sensitivity, specificity, positive predictive value, and negative predictive value of MA-BF# were 0.93, 0.78, 0.56, and 0.98, respectively. With regard to a MA-BF% of 0.2%, the sensitivity, specificity, positive predictive value, and negative predictive value were 0.87, 0.75, 0.50, and 0.95, respectively.

Table 3 compares the performance of the traditional parameter, HF-BF#, and the new parameter, MA-BF#, in the detection of tumor cells in the validation cohort. The sensitivity of MA-BF# to tumor cells was not significantly different from that of HF-BF# (P>0.05). However, the specificity was significantly increased from 0.51 to 0.78 (P<0.05), indicating that the new parameter MA-BF# could better avoid interference from mesothelial cells and monocytes/macrophages, and considerably improved the accuracy of tumor cell detection (P<0.05).

Discussion

Cytomorphological examination is still the critical measurement for the detection of tumor cells in BF (13). However, to determine whether the cytomorphological examination of BF samples is necessary relies on the experience of clinicians. Lack of experience often leads to a failure of early diagnosis and missed optimal treatment window in tumor patients. A hematology analyzer uses flow cytometry technology to quickly sort and count BF cells, which is well suited to the screening and detection of tumor

Table 3 Comparison of the detection parameters between HF-BF# and MA-BF# in the validation cohort

Diagnostic accuracy	HF-BF#	MA-BF#	P value
Cutoff value	0.022×10^9/L	0.006×10^9/L	–
Sensitivity	0.80	0.93	0.280
Specificity	0.51	0.78	0.002
PPV	0.32	0.56	0.065
NPV	0.90	0.98	0.160
Efficiency	0.58	0.82	0.002

HF-BF#, absolute high fluorescent cell count in body fluid; MA-BF#, absolute count of malignant cells in body fluid; PPV, positive predicative value; NPV, negative predicative value.

cells in BF. When the highly fluorescent cell parameter HF-BF is higher than the threshold value, cytomorphological examination can be initiated (14,15). However, since the false-positive rate of BF-BF diagnosis of tumor cells is too high, it is difficult to meet the requirements of clinical screening (16). Therefore, this study aimed to optimize the parameters for diagnosing tumor cells from the perspective of the tumor cell characterization algorithm of the scatter plot of a hematology analyzer, in order to significantly improve the specificity of tumor cell detection without reducing the sensitivity, so that the hematology analyzer can be more successfully used for the screening and auxiliary diagnosis of tumor cells in BF.

Pleural effusion and ascites are the BFs with the highest detection rates of tumor cells in clinical practice. Therefore, the BF samples collected in this study were mainly composed of these two types. With a training cohort of 47 tumor cell-positives samples and 108 tumor cell-negative samples, we analyzed the diagnostic accuracy of the traditional parameters, HF-BF# and HF-BF%, in the Mindray BC-6800 Plus hematology analyzer BF mode. The results showed that HF-BF# and HF-BF% in the tumor cell-positive group were significantly higher than those in the tumor cell-negative group (respectively, 0.08 *vs.* 0.02, 7.20 *vs.* 3.25, both $P<0.05$). However, they both showed low specificity for diagnosing tumor cells (0.55 and 0.51, respectively). These results suggest that there is a relatively high false-positive rate when using these two parameters to diagnose tumor cells, which greatly hinders laboratory efficiency.

This study found that mesothelial cells were the main reason for the high false-positive rate of the tumor cell detection in pleural effusion and ascites by the hematology analyzer. The cytomorphological examination results showed that HF-BF# and HF-BF% false-positive samples all had more mesothelial cells. Mesothelial cells form the serous membrane of the human body cavity, and will fall off into the serous cavity in large numbers after being stimulated by inflammation or a tumor environment. Mesothelial cells have larger volumes than white blood cells, with a diameter of approximately 25 μm, and they also have relatively high nucleic acid content. Therefore, in the scatter plot of the hematology analyzer, mesothelial cells are classified as highly fluorescent cells (17).

Distinguishing mesothelial cells from tumor cells remains a difficult problem for clinicians. Compared with mesothelial cells, malignant tumor cells usually have a different morphology and size. Therefore, it is unreasonable to distinguish two types of cells only based on cell volume. We noticed that although tumor cells are heteromorphic and their cellular/nuclear morphology and sizes can vary, the nucleus/cytoplasm ratio is almost always high, the nucleic acid content in the nucleus is high, and their nuclear chromatin is rough (18). These features manifest as stronger FL and SS signals on the hematology analyzer. Thus, using the intensity of FL and SS signals may be able to help differentiate tumor cells from mesothelial cells in BF.

This study improved the scatter plot classification algorithm of the Mindray BC-6800 Plus hematology analyzer and identified the main particle distribution areas of mesothelial cells and tumor cells in the training cohort. In addition, we found that some tumor cell-negative BF samples showed strong FL and SS signals in the mesothelial cells. The scatter plot showed the continuously scattered points from the mesothelial cell area to the tumor cell area. After comparison of these results with the cytomorphological results, we found that the cytomorphological examination results of such samples showed increased heterogeneity of mesothelial cells, enlarged nuclei, thickened nuclear chromatin, and vacuoles in the cytoplasms of some cells. When the serosal cavity of the human body is under long-term stimulation by stimuli such as inflammation, tumors, or peritoneal dialysis, mesothelial cells can undergo epithelial-mesenchymal transition (EMT). The cells transform from epithelial-like cells to fibroblast-like cells, showing increased pseudopodial protrusions, enlarged nuclei, and increased invasiveness (19,20). Therefore, we hypothesized that this kind of reactive mesothelial cell is the source of the FL signal and the increased SS points on the scatter plot of

the hematology analyzer. EMT is a continuous process; the newly exfoliated mesothelial cells in the serosal cavity coexist with mesothelial cells that are still in the process of transformation. This may be related to the fact that the scattered points of mesothelial cells in such samples are present in a continuous form from the mesothelial cell region to the tumor cell region.

A novel algorithm for tumor cells in BF was established and tested in an independent cohort. In the validation cohort, the sensitivity and specificity of the new parameter, MA-BF#, were 0.93 and 0.78, respectively. Compared with the sensitivity (0.80) and specificity (0.51) of HF-BF#, there was no significant difference in the sensitivity ($P>0.05$), but markedly higher specificity ($P<0.05$) of the new parameter for detecting tumor cells in BF, indicating that MA-BF# can provide accurate and efficient screening of tumor cells in BF. For the false-negative samples of the MA-BF#, from the scatter plot and microscopic image analysis in cytological examination, the scatter plots showed diffuse particles in the mesothelial cell region, while there were almost no particle spots in the tumor cell region. The microscopic images showed that there were indeed a few small adenocarcinoma cells in the samples, but their cell body was small, the cytoplasm was mildly basophilic, small vacuoles were visible, the nucleus/cytoplasm ratio was relatively large, the nucleus was atypical with a round or irregular shape, the chromatin was in the form of coarse granules, and the nucleolus was visible. The location of tumor cells in this type of BF specimen overlapped with the mesothelial cell area on the scatter plot of the hematology analyzer, and there are no good means for distinguishing them at present. In future studies, we will continue to explore new methods or conduct more studies from new perspectives, in order to further improve the screening ability for malignant tumor cells in BF specimens.

In summary, the novel algorithm of the Mindray BC-6800 Plus hematology analyzer can accurately and efficiently screen malignant tumor cells in a BF specimen. As a general screening method, the hematology analyzer can achieve rapid screening of many BF specimens in the laboratory (21). It provides more accurate supporting diagnostic information for the laboratory and clinic. Thus, many patients who go undiagnosed due to a lack of cytomorphological examinations can now be diagnosed. Changes in the quantitative results of tumor cells in BF specimens may provide valuable information on condition monitoring, clinical efficacy evaluation, and prognosis.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-411/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-411/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-411/coif). ZQ and JL report that they are from Shenzhen Mindray Bio-Medical Electronic Co. The other 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). The study was approved by the Medical Ethics Committee of Nanfang Hospital, Southern Medical University, Guangzhou, China (No. NFEC-2018-071) and informed consent was exempted by the Medical Ethics Committee of Nanfang Hospital.

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