mindray

HemaBook

Discover the latest clinical applications and technologies about Mindray hematology

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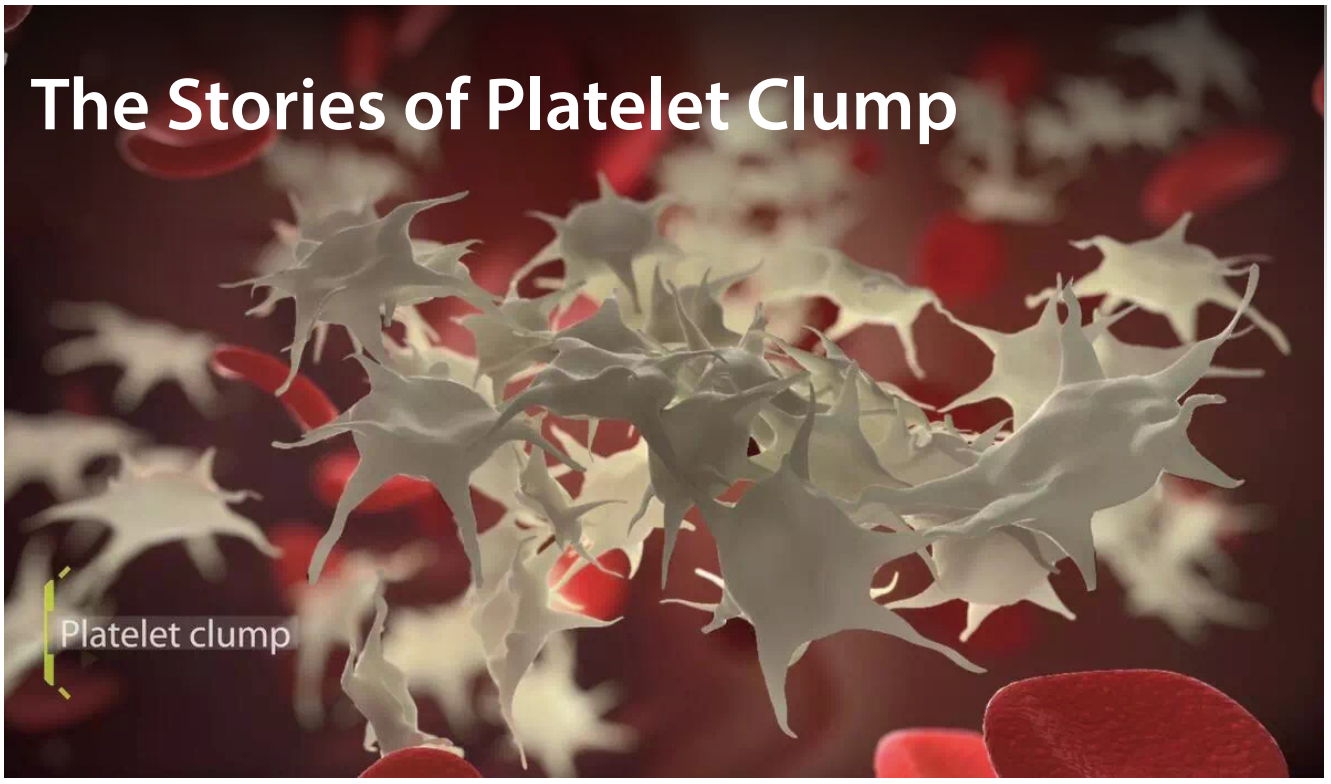


Thrombocytopenia is a condition characterized by abnormally low levels of platelets in the blood. However, falsely low platelet counts, or pseudothrombocytopenia (PTCP), though easily unrecognized, are found in clinical cases. It is an in vitro phenomenon caused by platelet clumping that results in reporting of a spuriously low platelet count by automatic hematology analyzers.

Resolving platelet clumping has been a headache for laboratory technicians. **Is there a hassle-free solution?**

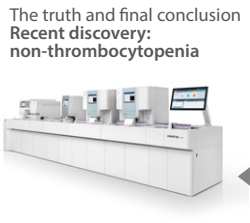
Let's look at two clinical cases that happened during the COVID-19 pandemic.

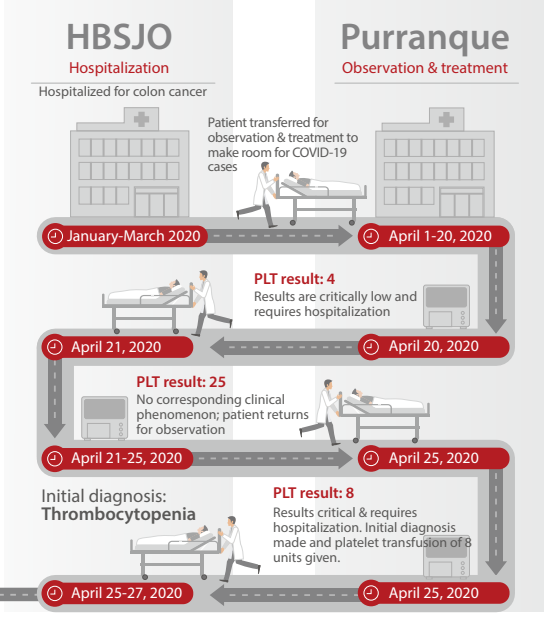
A Tale of Two Hospitals

The first case presented here was courtesy of San José Osorno Base Hospital in Chile. A patient had spent prolonged periods at the San José Osorno Base Hospital (HBSJO) between January and March 2020 without any history of thrombocytopenia. While at HBSJO, the patient needed care for an acute gastric ulcer bleed and a post-surgical infection. But as COVID-19 cases rose, so did the tensions and hospitalizations at HBSJO.

For their safety, all non-COVID-19 patients, including this patient, needed to be transferred to other hospitals. He was then moved to Purranque Hospital for continued treatment.

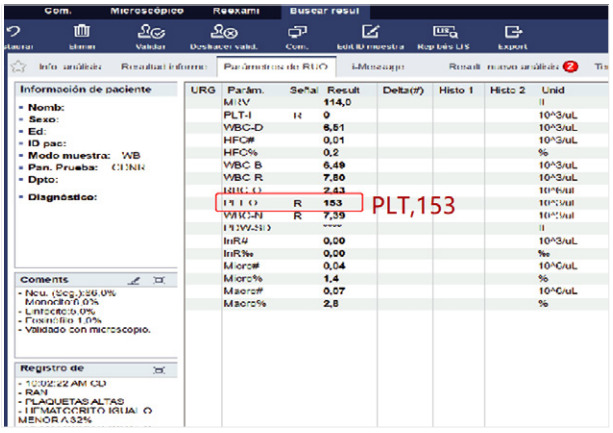
Purranque Hospital,while safely away from COVID-19, could not provide the same comprehensive services as HBSJO if an urgent clinical case were to arise. So, we go from one patient's story to the tale of two hospitals.



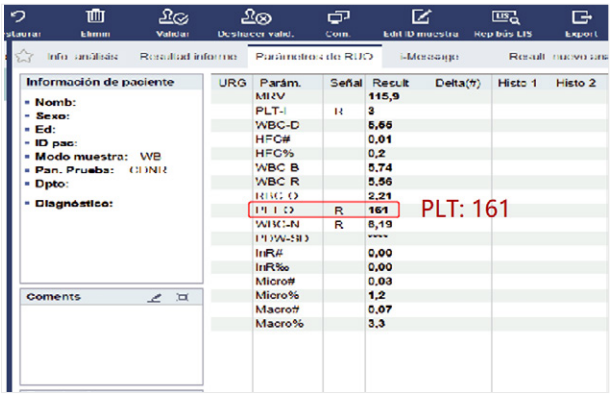


As can be seen, the patient' s clinical symptoms were not consistent with the test results that were given. In order to study the interference of anticoagulants on platelet counts, the laboratory staff from HBSJO collected two samples from the patient and conducted a study on Mindray CAL 8000 Cellular Analysis Line to test two different types of anticoagulants - EDTA and sodium citrate (3.2%). And the result was as follows:

CAL 8000 result		
Sample ID	4270198 (EDTA)	427199 (sodium citrate 3.2%)
First measurement	PLT-I: 1000/ul	3000/ul
Second measurement	PLT-I: 0 PLT-O: 153,000/ul	PLT-I: 3000/ul PLT-O: 161,000/ul



4270198(EDTA): Second measurement of PLT-I and PLT-O result



427199(sodium citrate 3.2%): Second measurement of PLT-I and PLT-O result

A PLT-I result was reported after the first measurement. After opening the RET channel, a PLT-O result was reported at the second measurement.

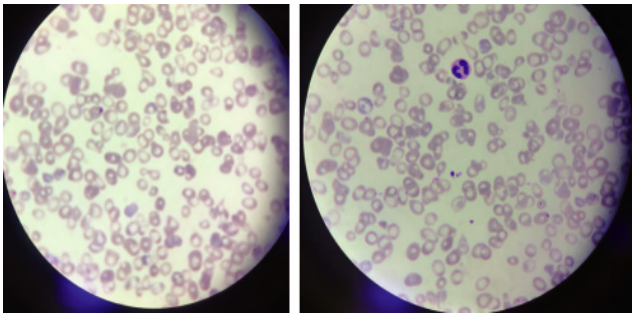
Looking at the results under a microscope, the truth was found. After an unforgettable back- and-forth between hospitals, the patient was finally given the right diagnosis and the correct medical treatment.

A Tricky but Solvable Medical Issue

PLT aggregation can lead to false diagnoses of thrombocytopenia, but it's not unsolvable.

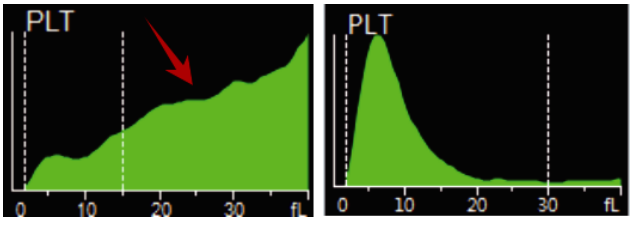
Here, on the other side of the planet, we had a case of a 23-year old male from China who was admitted to the Infectious Disease Department of a Chinese Hospital.

The patient had a CBC performed on Mindray CAL 8000 Cellular Analysis Line. According to the records, the platelet counts for this patient were usually 100+, but currently they were only at 61 which triggered a flag for "platelet clump" by CAL 8000. Under the microscope, however, no PLT aggregation was seen.



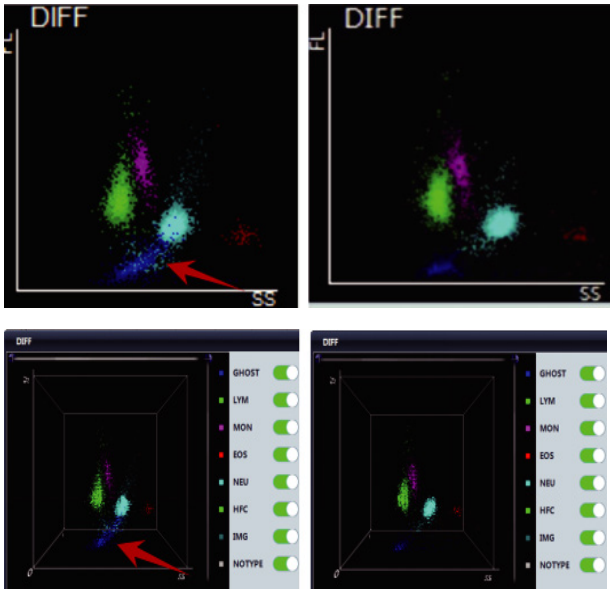
The laboratory technician did the first observation under a low-power lens, where no platelet aggregation was found.

Using an oil microscope, the number of platelets were evaluated again. And there was still no noticeable evidence of clumped PLT.

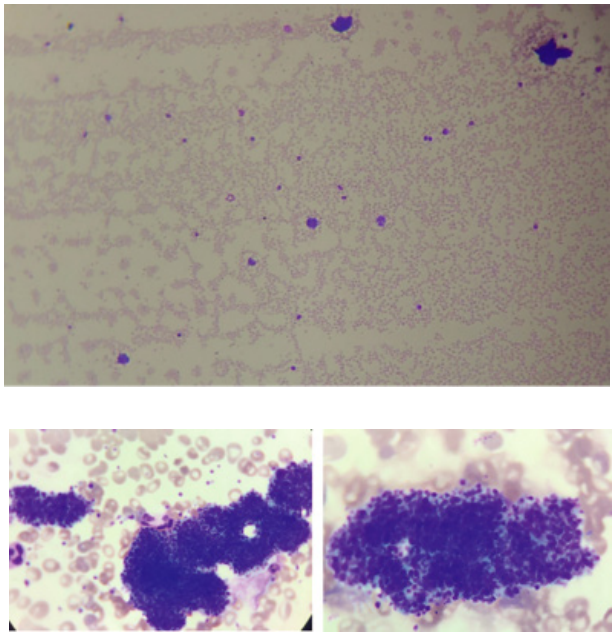


Histogram of the sample (left) and normal histogram (right)

Looking at the histogram of the sample, it should indicate there were small red blood cells or fragments. Compared to the normal scatter plot, the sample' s scatter plot had a cluster of blue particles, which indicated there was platelet aggregation.



The technicians kept looking for clues, all the way at the edge of the microscope slide.



The RET channel on CAL 8000 was opened and a PLT-O result was reported.

WBC		6.45	2.720	3.73	6.95	10^9/L
Neu#	R	3.86	1.560	2.30	5.55	10^9/L
Lym#		2.16	0.970	1.19	0.89	10^9/L
Mon#		0.31	0.120	0.19	0.46	10^9/L
Eos#	R	0.10	0.060	0.04	0.02	10^9/L
Bas#	R	0.02	0.010	0.01	0.03	10^9/L
IMG#		0.19	0.190	0.00	0.06	10^9/L
Neu%	R	59.9	-1.70	61.6	79.9	%
Lym%		33.6	1.70	31.9	12.9	%
Mon%		4.8	-0.30	5.1	6.6	%
Eos%	R	1.5	0.40	1.1	0.2	%
Bas%	R	0.2	-0.10	0.3	0.4	%
IMG%		3.0	2.90	0.1	0.9	%
RBC		3.56	0.750	2.81	3.22	10^12/L
HGB	L	90	20.0	70	80	g/L
HCT	L	30.1	7.20	22.9	26.7	%
MCV		84.5	2.90	81.6	83.0	fL
MCH	L	25.2	0.10	25.1	25.0	pg
MCHC	L	298	-9.0	307	301	g/L
RDW-CV	H	23.7	2.80	20.9	21.4	%
RDW-SD	H	71.0	10.10	60.9	63.2	fL
PLT	&R	193			178	10^9/L
MPV		****		9.2	****	fL
PDW		****		15.9	****	
PCT		****		0.172	****	%
P-LCC		****		56	****	10^9/L

PLT: 193

MRV		90.8			90.6	fL
PLT-I	R	60	-126.0	186	218	10^9/L
WBC-D		6.58	2.920	3.66	7.07	10^9/L
HFC#		0.01	0.010	0.00	0.00	10^9/L
HFC%		0.1	0.10	0.0	0.1	%
WBC-B		6.45	2.720	3.73	6.95	10^9/L
WBC-R		7.96			8.05	10^9/L
RBC-O		3.63			3.26	10^12/L
PLT-O	R	193			178	10^9/L
PDW-SD		****		17.6	****	fL
InR#		0.00	0.000	0.00	0.00	10^9/L
InR‰		0.00	0.000	0.00	0.00	‰
Micro#		0.45	0.080	0.37	0.40	10^12/L
Micro%		12.5	-0.90	13.4	12.4	%
Macro#		0.11	0.070	0.04	0.07	10^12/L
Macro%		3.0	1.50	1.5	2.1	%
RHE	L	27.1			27.1	pg

PLT-I: 60

PLT-O: 193

Based on the data, checking the PLT-O numbers can make it easy to identify a falsely low PLT reading caused by PLT aggregation - and easy to avoid a misdiagnosis.

In both clinical cases, pseudothrombocytopenia (PCTP) was caused by platelet aggregation. While platelet aggregation is caused by both in vivo and in vitro factors, these cases focused on in vitro.

platelet aggregation in vitro

- **EDTA-PTCP**
  Occurence of this in hospitals is about 0.07 - 0.21%
- **Blood sampling**
  Commonly found in capillary blood
- **Heparin-induced**
  Happens to about 4% of patients treated
- **Citrate causes**
  Occurrence percent not available

EDTA-dependent pseudothrombocytopenia (EDTA-PTCP) induced by EDTA anticoagulants is a common laboratory phenomenon. So when it does happen and isn't quickly identified, it creates misinformation which may lead to a misdiagnosis and, ultimately, the wrong medical treatment for the patient.

The good news is that, with technological advancements in laboratory medicine, more and more parameters can be added to the hematology analyzer to avoid situations like that. Currently, platelet testing can be done through PLT-I (based on DC sheath flow impedance) and PLT-O (based on nucleic acid fluorescent staining and done on the RET channel). When there is a blood sample with a high possibility of platelet aggregation, the PLT-O detection technology by the Mindray BC-6000 Series Auto Hematology Analyzer and the CAL8000/6000 Cellular Analysis Line can effectively correct PLT counts - especially when it comes to blood samples with pseudo-platelet reduction due to EDTA.

References:

[1] PLT case study. LABORATORIO HBSJO CHILE, Dra. Sandra.

[2] Can you see the "coastline"? Liuzhou Municipal Liutie Central Hospital, zhenni Lu,xiaoyong Liu, jiajia Huang.

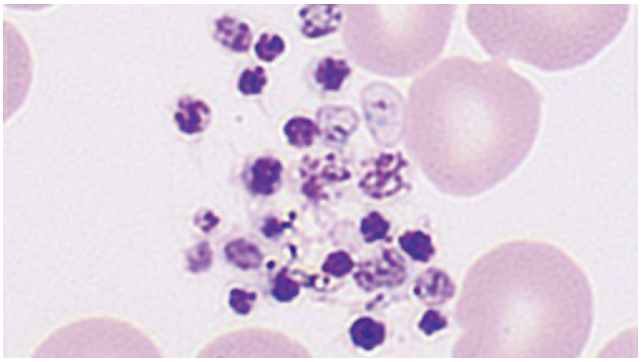
[3] PLT-O, getting a More Accurate Result for EDTA-PTCPPatients. Department of Laboratory Medicine at the Second People's Hospital inNeijiang, Sichuan Province. Zhenzhong Zhou.

One More Option to Solve EDTA-PTCP?

Ethylenediaminetetraacetic Acid - Pseudothrombocytopenia (EDTA-PTCP) is a laboratory artifact that may lead to an incorrect evaluation and unnecessary treatment of patients.

Which of the following method (or methods) would you take to correct platelet counts in case of an EDTA-induced platelet aggregation in thrombocytopenia?

- Recheck with blood smear and estimate the platelet count
- Recheck with addition of amikacin
- Recheck after warming at 37°C
- Recheck immediately dilution without any anticoagulant
- Reexamine on another hematology device
- Recheck with other anticoagulants



Professional clinical laboratory doctors pursue accuracy and truth with the highest sense of responsibility. Nowadays, some clinical studies have been conducted to explore EDTA-PTCP solutions, suggesting that Mindray hematology systems with SF Cube technology would be an option to effectively assist lab technicians in identifying correct platelet counts.

Mindray SF-Cube technology: An effective way for correcting platelet count in individuals with EDTA dependent pseudo thrombocytopenia

A Clinical Case Report

The patient here is a 32-year-old female with infertility. After the patient's EDTA-anticoagulated blood was drawn, it was analyzed within fifty-five minutes, and it showed a low platelet count (28×10^9/L). The test was done by the impedance method (PLT-I) on a popular brand's hematology system (device A). Platelet aggregation was confirmed by microscopic examination of the smear, indicating pseudothrombocytopenia (PTCP). Shortly after, a reexamination of this sample was done using the CDR (PLT-O) method on the Mindray BC-6800Plus. The results showed a markedly higher platelet count with a value of 180×10^9/L.

It's suspected that the low platelet count obtained by device A was due to EDTA-induced PTCP. So, the patient was asked to consent for an additional test using a blood sample tube with sodium citrate this time. Thirty minutes after the sample was collected it was then analyzed. The resulting platelet parameters of the blood samples run through various testing methods and devices are listed in Table 1.

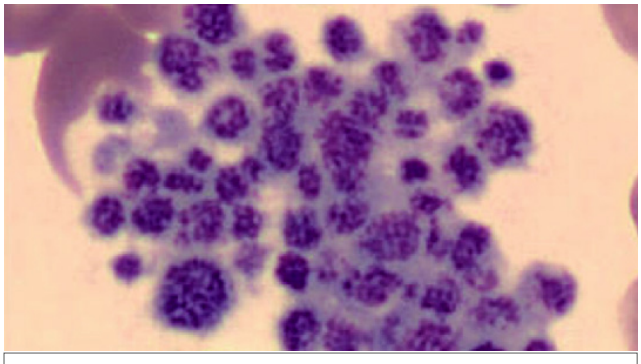


Table 1
Comparison of platelet parameters in EDTA and sodium citrate anticoagulant measured with different methods.

Platelet parameters	EDTA -anticoagulated		Sodium citrate-anticoagulated	
	PLT-I on device A	CDR (PLT-O) of Mindray BC-6800 Plus	PLT-F on device A	Neubauer chamber
Count (x 10^9/L)	28	180	166	176
MPV (fL)	10.9	12.2	11.3	-
PDW (fL)	12.8	17.6	16.0	-

-: Not detected; MPV: mean platelet volume; PDW: platelet distribution width.

Further Comparison of Other Samples

Under microscopic evaluation of the blood smear, the EDTA-anticoagulated blood showed platelet aggregation while the sodium citrate-anticoagulated blood showed none. The blood samples were analyzed within four hours from the time of collection, according to the manufacturer's instructions. In addition to that patient, the data from an additional five cases of EDTA-PTCP were collected and assessed (Table 2).

In the end, the author concludes: In patients with known or suspected EDTA-PTCP Mindray SF-Cube technology is a straightforward and effective way of determining the platelet count in EDTA-anticoagulated blood.

Table 2
Data on the different compared samples.

Cases	Platelet count (x10^9/L)			
	EDTA -anticoagulated		Sodium citrate-anticoagulated	
	PLT-I on device A	CDR (PLT-O) of Mindray BC-6800 Plus	PLT-F on device A	Neubauer chamber
1	86	322	292	300
2	12	133	195	173
3	29	345	334	326
4	14	192	179	185
5	77	227	236	260
Mean	44	244	247	249

Correction of spurious low platelet counts by optical Fluorescence platelet counting of BC-6800 hematology analyzer in EDTA-dependent pseudo thrombocytopenia patients

Identification and Characteristics of EDTA-PTCP Samples

Samples that triggered the "PLT aggregation" flag on the hematology analyzer showed a typical serrated irregularity and a zigzag tail (Figure 1) on the platelet histogram. Also, under microscopic evaluation, the presence of platelet satellitism, or giant platelets, is not seen.

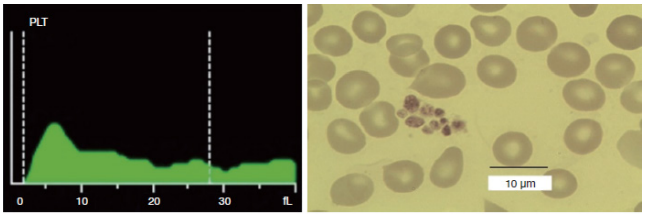


Figure 1: Typical platelet histogram and microscopic pictures of EDTA-PTCP samples. EDTA-PTCP, ethylene diamine tetraacetic acid-dependent pseudo thrombocytopenia.

Spurious Low Platelet Counts of BC-6800 by Optical Platelet Counting (PLT-O)

Twenty-three EDTA-PTCP samples in EDTA tubes (with platelet aggregation) were tested in the impedence (PLT-I (EDTA)) and reticulocyte channel of the Mindray BC-6800 (PLT-O (EDTA)). Interestingly, the PLT-O (EDTA) results were comparable to) the platelet counts of the re-collected samples in citrate tubes (PLT-I (Citrate)), which proves that the PLT-O (EDTA) method can accurately adjust for the platelet aggregation issue caused by EDTA (Figure 2).

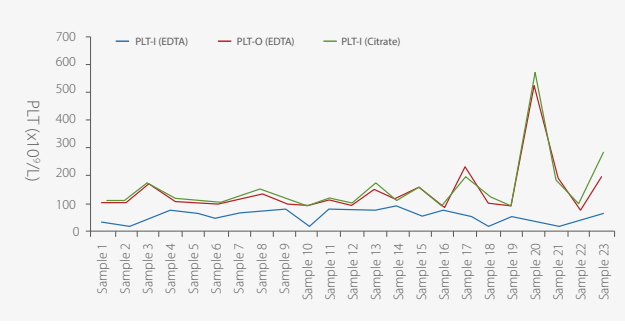


Figure 2: BC-6800's optical fluorescence platelet counts of EDTA-PTCP samples in EDTA tubes were comparable with impedance platelet counts of EDTA-PTCP samples in citrate tubes. PLT-I (EDTA), impedance platelet counts of EDTA-PTCP samples in EDTA tubes; PLT-O (EDTA), optical fluorescence platelet counts of EDTA-PTCP samples in EDTA tubes; PLT-I (citrate), impedance platelet counts of EDTA-PTCP samples in citrate tubes; EDTA-PTCP, ethylene diamine tetraacetic acid-dependent pseudo thrombocytopenia.

One Mainstream Brand's Hematology System's EDTA-PTCP Dissociation Effect: Available with Fluorescent Dye Staining?

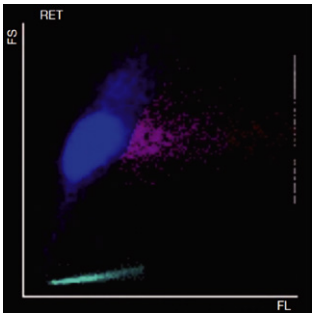
Optical fluorescence platelet counting is available in both high-end hematology analyzers (device B) and Mindray BC-6000 series hematology analyzers. In this method, a fluorescent dye is used to stain the nucleic acids in platelets, allowing the recognition of large platelets and excluding non-platelet particles such as erythrocyte debris, micro erythrocytes, or leukocyte debris.

To verify whether the dissociation effect of optical fluorescence platelet counting was dependent on fluorescent dye staining, 17 of those 23 EDTA-PTCP samples in EDTA tubes were also tested on device B' s reticulocyte channel and impedance channel., It was found that here was no significant difference between the platelet counts of reticulocyte channel and impedance channel (Figure 3). Only one of the 17 EDTA-PTCP samples showed a dissociation rate of more than 80%, with an average dissociation rate of 56% among all 17 EDTA-PTCP samples (Figure 3).

Figure 3: No dissociation effect of device B's optical fuorescence platelet counting on EDTA-PTCP patients. PLT-I (EDTA), impedanceplatelet counts of EDTA-PTCP samples in EDTA tubes; PLT-O (EDTA), optical fluorescence platelet counts of EDTA-PTCP samplesin EDTA tubes; PLT-I (citrate), impedance platelet counts of EDTA-PTCP samples in citrate tubes; EDTA-PTCP, ethylene diaminetetraacetic acid-dependent pseudo thrombocytopenia.

Conclusion

In summary, the author concludes: Optical fluorescence platelet counting of the BC-6800 hematology analyzer is effective for the correction of spurious low platelet counts in EDTA-PTCP patients, and its dissociation effect on EDTA-PTCP samples is independent of fluorescent dye staining.



SF Cube

In the busy daily work of the laboratory, PTCP is an inevitable trouble. Mindray SF Cube technology provides PLT-O (based on nucleic acid fluorescent staining and done on the RET channel) to correct PLT counts when there is pseudo-platelet reduction due to EDTA. PLT-O is available on Mindray BC-6000 Series Auto Hematology Analyzer and the CAL 8000/6000 Cellular Analysis Line.

References:

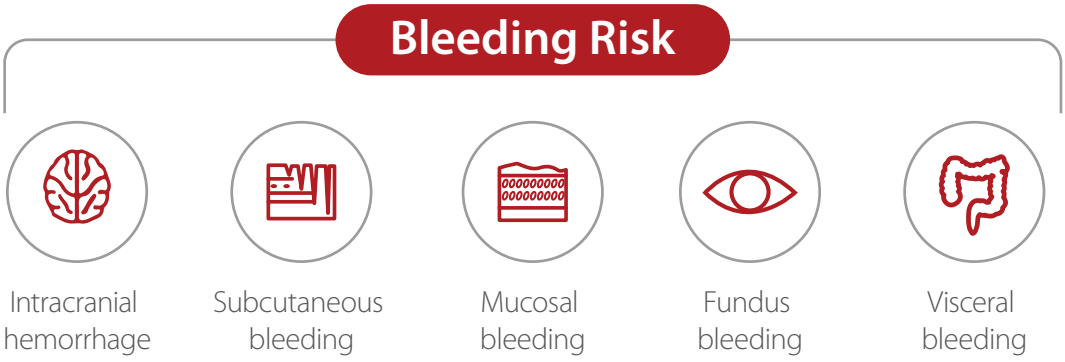
[1] J. Deng, et al. Mindray SF-Cube technology: An effective way for correcting platelet count in individuals with EDTA dependent pseudo thrombocytopenia. Clinica Chimica Acta 502 (2020) 99–101

[2] Y. Bao, et al. Correction of spurious low platelet counts by optical fluorescence platelet counting of BC-6800 hematology analyzer in EDTA-dependent pseudo thrombocytopenia patients. Transl Cancer Res 2020;9(1):166-172

Low Value? High Risk?

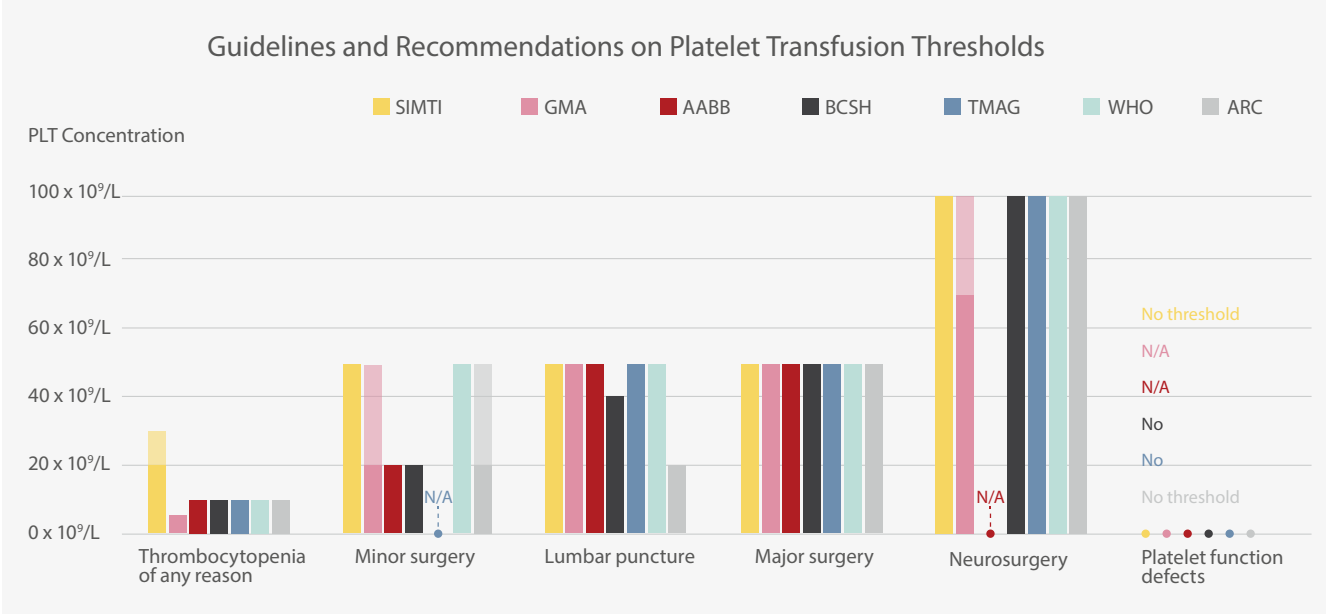
Resolve Your Concerns about the Risk of Low-value Platelet Measurements

When the platelet value is low, patients are at risk of bleeding. Bleeding in vital organs is life-threatening.



According to Giuseppe Lippi and other professors, there is no universal agreement on the definition of platelet transfusion thresholds.[1] However, the degree of accuracy and imprecision of the vast majority of fully automated hematological analyzers appears unsatisfactory, especially in the lower thrombocytopenic range, i.e.,<50× 10^9/L .

The current guidelines and recommendations show that there is no consensus on the low PLT infusion threshold in several specific clinical situations, as shown in the following table. [1]



Abbreviations: SIMTI, Italian Society of Transfusion Medicine and Immunohaematology; GMA, German Medical Association; AABB, American Association of Blood Banks; BCSH, British Committee for Standards in Haematology; TMAG, British Columbia Transfusion Medicine Advisory Group; WHO, World Health Organization; ARC, American Red Cross; N/A, not available.

*Only in case of perioperative bleeding.

Low-value platelet counts also play an important role in evaluating the effectiveness of platelet transfusion. In the most common platelet transfusion formulas, including the post-transfusion platelet increment (PPI), the percentage platelet recovery (PPR), and the corrected count increment (CCI), the absolute count of platelet is one of the key calculation factors.[2] Among them, most clinicians use an estimate of transfused platelet content and average body surface area to calculate the CCI, and an absolute platelet increment of greater than 10×10^9/L at 1 or 24 hours is considered a successful transfusion, which is consistent with the previous formula.[3]

The platelet count results are still regarded as the mainstay for driving platelet transfusion practices, but the hematology analyzers, as the method, show different analytical performance. The Italian Working Group on Diagnostic Hematology of the Italian Society of Clinical Chemistry, Clinical Molecular Biology (WGDH-SIBioC) has conducted a multicenter study based on international guidelines, to verify the analytical performance of nine different types of hematology analyzers (HAs) in the automated platelet analysis. Let's take a look at the report below.

ORIGINAL ARTICLE

WILEY

Multicenter evaluation of analytical performances of plateletcounts and platelet parameters: Carryover, precision, and stability

Four hundred and eighty-six peripheral blood samples (PB), collected in K3EDTA tubes, were analyzed by ABX Pentra, ADVIA2120i, BC-6800, BC-6800Plus, Cell-DYN Sapphire, DxH800, XE-2100, XE-5000, and XN-20 with PLT-F App.

TABLE 1 Hematology analyzers and methods of platelet counts

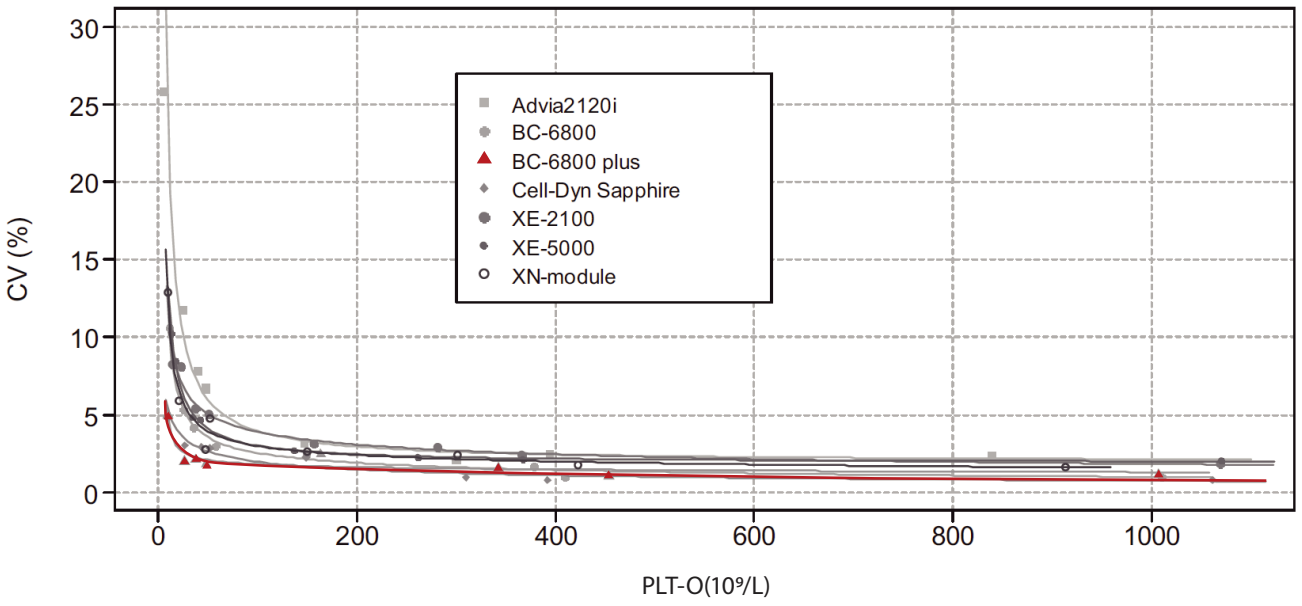
Methods of platelet counts	Hematology analyzer								
	ABX Pentra	ADVIA 2120i	BC-6800	BC- 6800 Plus	Cell-DYN Sapphire	DxH800	XE-2100	XE-5000	XN-20 module with PLT-F App
Impedance method (PLT-I)	X		X	X	X	X	X	X	X
Optical method (PLT-O)		X	X	X	X		X	X	X
Fluorescence method (PLT-F)									X

TABLE 2 Carryover (CO) and low limit of quantification (LoQ)

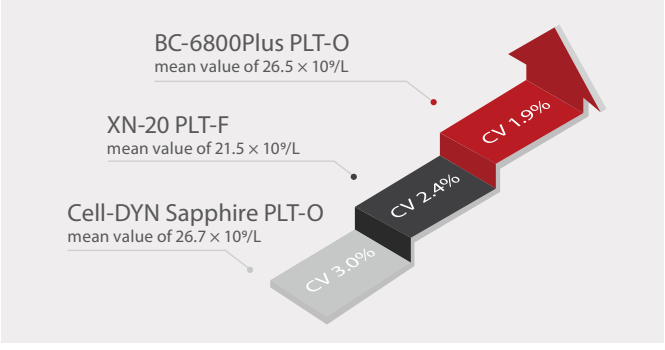
	ABX Pentra		ADVIA2120i		BC-6800		BC-6800 Plus		DxH800		Cell-DYN Sapphire		XE-2100		XE-5000		XN-20 module	
	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ	CO	LoQ
PLT-F (x10^9/L)	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	//	0.00%	4.0
PLT-I (x10^9/L)	0.00%	16.0	//	//	0.00%	19.0	0.00%	23	0.05%	8.0	0.03%	5	0.09%	18.6	0.05%	14.6	0.35%	9.0
PLT-O (x 10^9/L)	//	//	0.50%	2.50	0.00%	11.0	0.00%	4	//		0.09%	2	0.07%	11.5	0.07%	13.9	0.36%	12.0
IPF absolute value[a](x10^9/L)	//	//	//	//	//	//	//	//	//	//	//	//	0.00%	6.0	0.00%	11.8	0.00%	1.0
IPF relative value (%)	//	//	//	//	0.00%	//	0.00%	//	//	//	//	//	0.00%	//	0.00%	//	0.00%	//
PCT (%)	0.00%	//	//	//	0.00%	//	0.00%	//	0.040%	//	0.00%	//	0.05%	//	0.00%	//	0.00%	//
P-LCR or large PLT count (%)		//	0.30%	//	0.00%	//	0.00%	//	//	//	//	//	0.00%	//	0.00%	//	0.00%	//

Note: The PLT limit of acceptability for carryover is 0.5% according to Vis et al.[31]

The carry-over (CO) rates of BC-6800 and BC-6800Plus both meet the requirements, the lowest in the group. The limit of quantification (LoQ) of PLT-O of BC-6800 and BC-6800Plus is lower than that of PLT-I, and the LoQ of PLT-O of BC-6800Plus is as low as 4x10⁹/L, which is lower than PLT-O of XN-20, which is equivalent to PLT-F of XN-20. Interestingly, LoQ of PLT-I of XN-20 is lower than that of PLT-O.



Generally speaking, the imprecision (%CV) increases as the platelet count decreases. In the segment of chart B (PLT-O precision), BC-6800Plus shows the lowest CV at all concentration levels. In the abstract, it' s described as: No HAs showed desirable CVAPS for PLT counts less than 50.0 × 10⁹/L, with the exception of Cell-DYN Sapphire (CV 3.0% with PLT-O mean value of 26.7 × 10⁹/L), XN-20 (CV 2.4% with PLT-F mean value of 21.5 × 10⁹/L), and BC-6800Plus (CV 1.9% with PLT-O mean value of 26.5 × 10⁹/L).



Among the cells of peripheral blood, platelets are the smallest, but as a population, the concentration of platelets plays an important role in hemostasis. To account for the risk of bleeding caused by low platelets, Mindray has introduced multi-fold PLT-O platform (SF Cube) to provide the correct count for thrombocytopenia samples. PLT-O is available in Mindray BC-6000 Series Auto Hematology Analyzers and the CAL 8000/6000 Cellular Analysis Lines.

References:

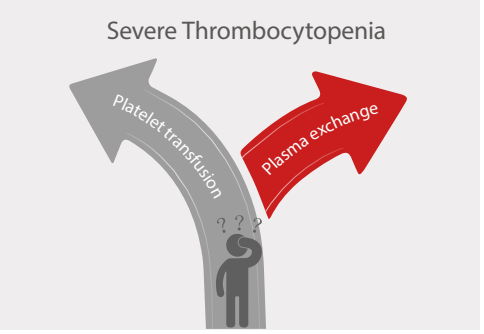
[1] Platelet Transfusion Thresholds: How Low Can We Go in Respect to Platelet Counting? Lippi G, Favaloro EJ, Buoro S. Semin Thromb Hemost. 2019 Sep 28. doi: 10.1055/s-0039-1696943. [Epub ahead of print]

[2] Rebulla P. Formulae for the definition of refractoriness to platelet transfusion. Transfus Med 1993;3(1):91–3.

[3] Hod E, Schwartz J. Platelet transfusion refractoriness. Br J Haematol 2008;142(3): 348–60.

Is Platelet Transfusion Always Required in Thrombocytopenia?

When the platelet (PLT) count is extremely low, is platelet transfusion really required? Let's analyze the following case, which tells us a different answer.



Case background

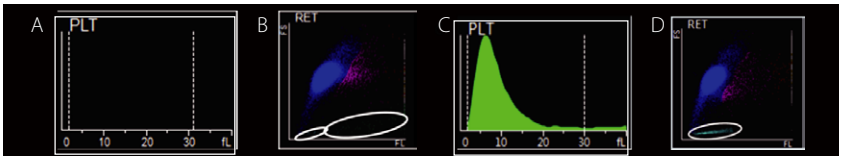
A 49-year-old woman went to the emergency department due to transient cognitive disorder. She had obvious paroxysmal headaches, with vomiting and epigastric pain. Brain CT revealed no abnormalities. The laboratory results revealed anemia and severe thrombocytopenia. What should be expected?

▸ Blood Test

Blood test (Figure 1) showed low RBC count of 3.07×10^{12}/L and low HGB concentration, which indicated anemia. PLT-O count was 15×10^{9}/L (CDR mode, Mindray BC-6200). Such a low PLT count and abnormal RBC-related parameters caught our attention: Should platelet transfusion be initiated?

Name	XXX						
Gender	Female						
Age	49-year-old						
Items	Resluts	Reference Range	Unit	Items	Resluts	Reference Range	Unit
ABO	B			HCT	25.3	35-45	%
Rh	+			MCV	82.6	82.0-100.0	fL
WBC	6.08	3.5-9.5	10^9/L	MCH	26.8	27.0-34.0	pg
NEUT%	60.30	40-75	%	MCHC	324	316-354	g/L
LYMPH%	29.50	20-50	%	RDW-CV	14.5	11.0-16.0	%
MONO	8.20	3-10	%	RDW-SD	42.2	35.0-56.0	fL
EO%	1.80	0.4-8.0	%	PLT	15	125-350	10^9/L
BASO%	0.20	0.0-1.0	%	MPV	....	6.5-12.0	fL
NEUT#	3.67	1.8-6.3	10^9/L	PDW	....	9.0-17.0	%
LYMPH#	1.79	1.1-3.2	10^9/L	PCT	....	0.108-0.282	%
MONO#	0.50	0.1-0.6	10^9/L	P-LCR	....	19.1-46.6	%
EO#	0.11	0.02-0.52	10^9/L	RET#	124.6	22.4-82.9	10^9/L
BASO#	0.01	0-0.06	10^9/L	RET#	4.6	0.67-1.92	%
RBC	3.07	3.8-5.1	10^{12}/L	IRF	14.4	2.4-17.5	%
HGB	82.00	115-150	g/L	LFR	85.6	89.4-99.5	%

Figure 1. Blood test showed low PLT count, RBC count, and increased RET%



The PLT histogram was far from the normal ones. We then checked RET scattergram, in which few PLT dots were observed and RET increased (Figure 2).

Figure 2. Comparison of PLT-I & PLT-O results (A/B: the case; C/D: normal)

These abnormal results triggered the re-exam rule, and then the peripheral blood smear was reviewed (Figure 3). The result demonstrated evidence of intravascular hemolysis, which included schistocytes, a small number of spherocytes, helmet cells, and thrombocytopenia.

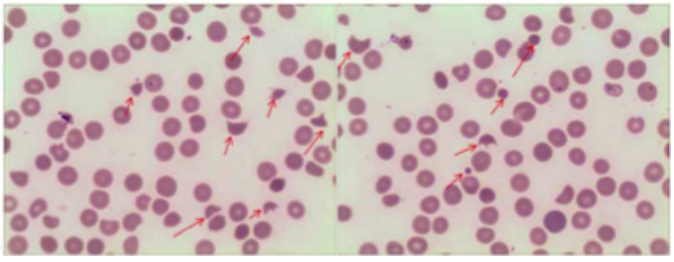


Figure 3. PLT was rarely seen, and schistocytes, small numbers of spherocytes and helmet cells were found. (100x)

▸ Bone Marrow Examination

Erythrocytic cell lines 44%, Granulocytic cell lines 40%, G/E=0.91/1.

Undifferentiated erythroblasts were common in the bone marrow smear, and Howell-Jolly body were found. A total of 257 megakaryocytes were found in the smear, and 50 were differentiated, including 3 megakaryoblasts, 44 promegakaryocytes and 3 naked nucleus megakaryocytes. PLT was rarely seen. Such bone marrow smear showed a megakaryocytic thrombocytopenia, increased function of erythroid differentiation.

▸ Chemistry Test

In the chemistry test, the result of total bilirubin (TBIL) increased, indirect bilirubin (IBIL) increased, which showed hemolytic disease.

Name	XXX		
Gender	Female		
Age	49		
Items	Resluts	Unit	Reference Range
TBIL	60.50	umol/L	2.0-20.4
DBIL	14.70	umol/L	0.0-6.80
IBIL	45.80	umol/L	3.40-14.00
AST	27 00	U/L	7-40
AST	33.00	U/L	13-35
ALT/AST	1.22		0.23-247
v-Glutamyl transferase	8.00	U/L	7-45
Alkaline Phosphatase	76.00	U/L	40-150
Total Bile Acid	8.00	umol/L	0.00-10.00
Glycocholic Acid	1.39	mg/L	0-2.7
Cholinesterase	8924.00	U/L	4500-13000
Total Protein	65.60	g/L	60.00-95.00
Albumin	39.50	g/L	35.00-55.00
Globulin	26.10	g/L	20.00 40.00
Albumin/Globulin	1.51		1.20-2.40
Glucose	9.15	mmol/L	3.61-6.11
Urine Nitrogen	8.27	mmol/L	1.79-7.14
Creatinine	99.00	umol/L	40-120

Figure 4. Chemistry testing results

Considering the cases with typical symptoms: (1) hemolytic anemia (schistocytes); (2) thrombocytopenia; (3) neurologic symptoms (transient mental disorder), thrombotic thrombocytopenia (TTP) disease is likely. The results and TTP diagnostic suggestion were transferred to doctors immediately. And Further ADAMTS13 testing confirmed TTP. Finally, plasma exchange instead of platelet transfusion was taken.

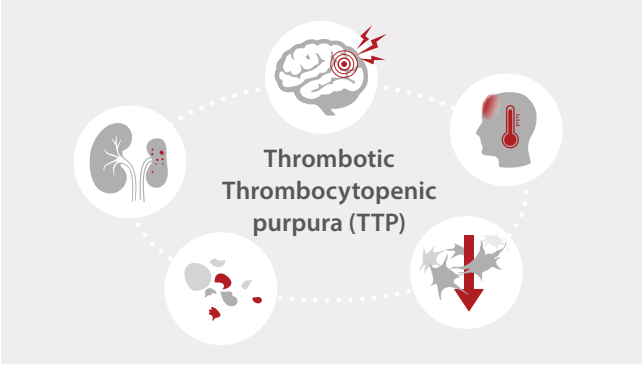


Figure 5. Clinical symptoms of TTP disease

Five medical signs[2]	In this case
Fever	No
Hemolytic Anemia	Yes
Thrombocytopenia	Yes
Transient neurologic symptoms	Yes
Reduced kidney function	No

Conclusion

If the PLT level is lower than the decision-making threshold, experienced doctors will immediately recheck whether the specimen is qualified, the histogram and scattergram are normal or not, and any other abnormal cell counting results or significant flag messages, etc. Further confirmation will be carried out by blood smear examination under the microscope. Finally, after considering the patient's symptoms and medical history information, the laboratory can report the results and provide possible diagnosis.

Mindray's automatic 8x PLT-O counting (SF Cube technology) provides accurate and stable counting for thrombocytopenia samples. Together with high quality blood smear from SC-120 Auto Slide Maker, Mindray hematology solutions support efficient management of thrombocytopenia. PLT-O is available in Mindray BC-6000 Series Auto Hematology Analyzers, and the CAL 8000/6000 Cellular Analysis Lines.

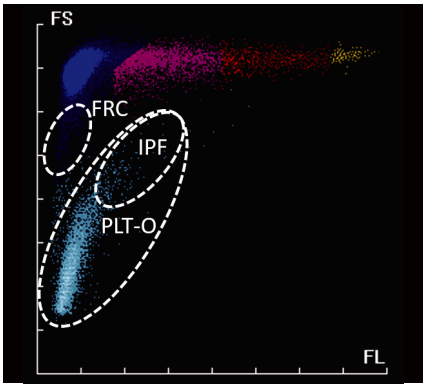


Figure 6. PLT-O scattergram

Extension: Why is platelet transfusion not recommended in thrombotic thrombocytopenia?

Common causes of thrombocytopenia include decreased production in bone marrow, increased destruction in peripheral blood, and medication induced[1].

Thrombotic thrombocytopenia, including TTP in this case, is a kind of disease caused by increased PLT destruction. Because of von Willebrand factor (VWF) cleavage protease (ADAMTS13) deficiency, VWF cannot be cut off normally, and ultra-large VWF (ULVWF) accumulate, resulting in abnormal PLT aggregation, microthrombosis and fragmented RBC[2]. Under such condition, platelet transfusion may accelerate thrombosis, leading to worsening symptoms[3]. So for thrombotic thrombocytopenia, the main treatment should be plasma exchange.

Acknowledgement

We would like to extend our thanks to Dr. Xiao Zuomiao, Dr. Chen Xianchun, Dr. Xiao Dejun and Dr. Luo Shi from Ganzhou People's Hospital, China, for providing the case information.

References:

[1] What Is Thrombocytopenia? - NHLBI, NIH". www.nhlbi.nih.gov. Retrieved 2015-05-01.

[2] Tsai, Han-Mou(2010). "Pathophysiology of thrombotic thrombocytopenic purpura." International journal of hematology vol. 91,1: 1-19. doi:10.1007/s12185-009-0476-1.

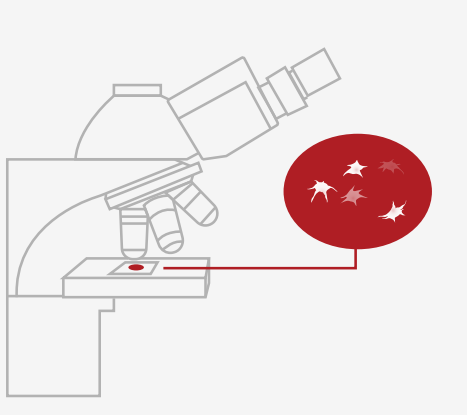
[3] Joly, BS; Coppo, P; Veyradier, A (2017). "Thrombotic thrombocytopenic purpura." Blood. 129 (21): 2836–2846. doi:10.1182/blood-2016-10-709857.

How Mindray Counts Low Platelets Correctly

Clinical Significance

Derived from megakaryocytes, platelets (PLT) are produced and matured in the bone marrow. Besides widely known thrombosis and wound repair, PLT also plays important roles in inflammation, immunity and cancer biology[1]. Normal reference intervals of PLT in peripheral blood varies in the range of 150-400×10⁹/L. When the PLT value is lower than 100×10⁹/L, a common clinical problem identified as thrombocytopenia (low PLT) may be the result[2].

There are several causes of thrombocytopenia including decreased PLT production, increased PLT destruction, increased splenic sequestration and dilution[3]. Currently, complete blood count (CBC) and blood smear reviews are essential diagnostic methods for the initial evaluation of thrombocytopenia samples[2]. Therefore, counting low PLT correctly by an auto hematology analyzer might be a prospective approach which will greatly reduce the blood smear rate, and save laborious time in the diagnostic lab, rapidly screening out thrombocytopenia samples.

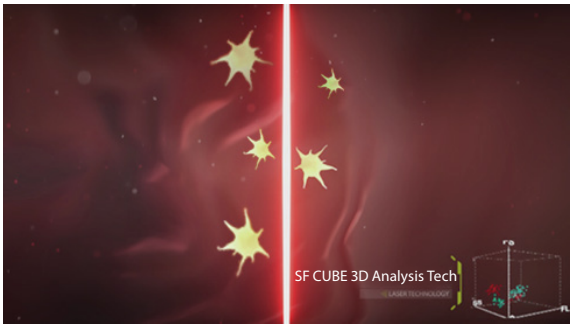


However, counting low PLT correctly is not a simple process. How does Mindray's high-end auto-hematology analyzer deal with low PLT samples?

Mindray Solution

▸ **Tech 1. Highly specific fluorescent staining**

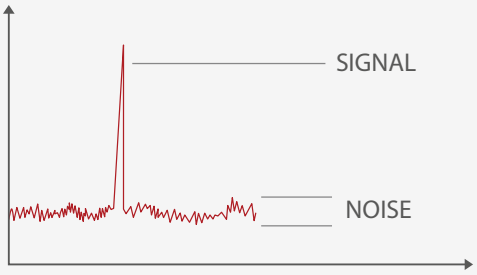
Fluorescent staining dye (FR dye) has been specially designed with the ability to identify target cells immediately. Next, the fluorescent molecule captures nucleic acid in PLT cells while avoiding interferences from small RBCs, RBC /WBC fragments and other small particles. PLT stained with specific fluorescent dye subsequently goes through the laser detector for optical measurement. The high specificity and affinity of fluorescent dye ensures that the binding inside PLT cells is stable enough for cells to flow through the laser. This ensures that even low amounts of PLT can be mapped and counted in the SF CUBE 3D scattergram accurately.



SF Cube

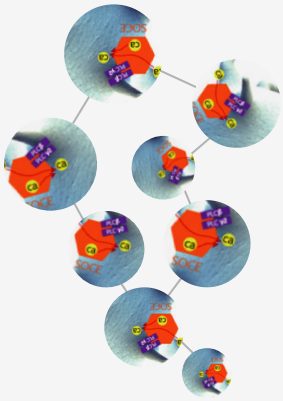
▸ Tech 2. High-resolution optical detection

Also, Mindray's high-end hematology analyzer combines reflective light suppression technology with SiPM (Silicon photomultiplier), which is highly sensitive to fluorescence signals while simultaneously minimizing the background noise during optical detection. This greatly improves the detection limit of particles, and the lower limit for small particles reaching up to 1um (a diameter of 2 um is defined as small PLT), ensuring that the sample results are not interfered by small PLT or particles.

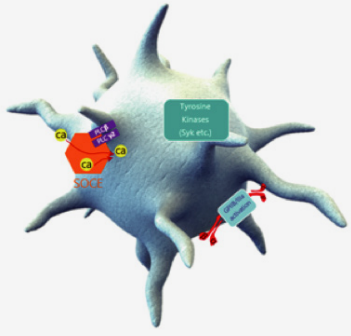


▸ Tech 3. PLT de-aggregation

Pseudothrombocytopenia is caused by in vitro platelet clumping in EDTA-anticoagulated blood tube, which may lead to a falsely low PLT count[4]. Mindray's R&D conducted preliminary studies focusing on PLT's activation mechanisms, which is mainly regulated by calcium channel, tyrosine kinase pathway and GPIIb/IIIa. And then antagonists are applied in DR dilluent to directly block the binding sites on the surface of PLT which greatly minimizes the formation of PLT clumps.More detailed PLT de-aggregation mechanism will be released in the next HemaBook Chapter.

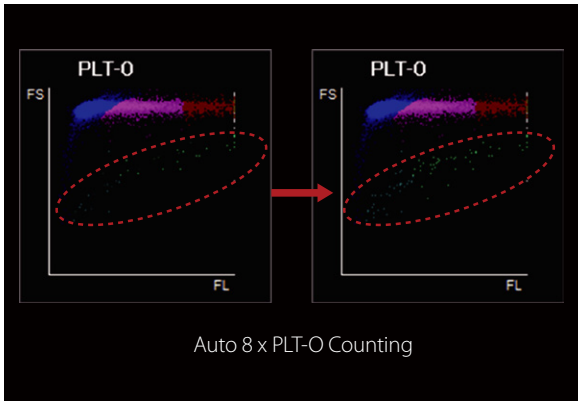


PLT Clump



▸ Tech 4. Auto 8×PLT-O counting

Mindray is in the process of a patent application (see below picture) for Auto 8×PLT-O Counting Technology. To begin with, PLT-I value obtained from impedance channel is firstly compared with a default value (50×10⁹/L). If this is lower than the cutoff value, the analyzer can automatically prolong counting time up to 8-fold in order to collect more PLT particles for further analysis. In addition, Auto 8×PLT-O Counting Tech can eliminate other interference factors (e.g. fragmented RBC/WBC) which are often easily miscounted as PLT by the impedance channel. No additional sampling, no manual intervention, no additional channels and reagents required – 8×PLT-O counting is both efficient and effective in counting low PLT correctly .



Auto 8 x PLT-O Counting

IPC No.

G01N 15/10 (2006.01) G01N 33/48 (2006.01) G01N 15/14 (2006.01)

Title: BLOOD DETECTION METHOD AND DEVICE

Prepare a first detection solution using a blood sample

↓

Control the first detection solution to pass through an impedance detection area

↓

Perform platelet detection on the first detection solution in the impedance detection area with an impedance method to obtain a first platelet detection result

↓

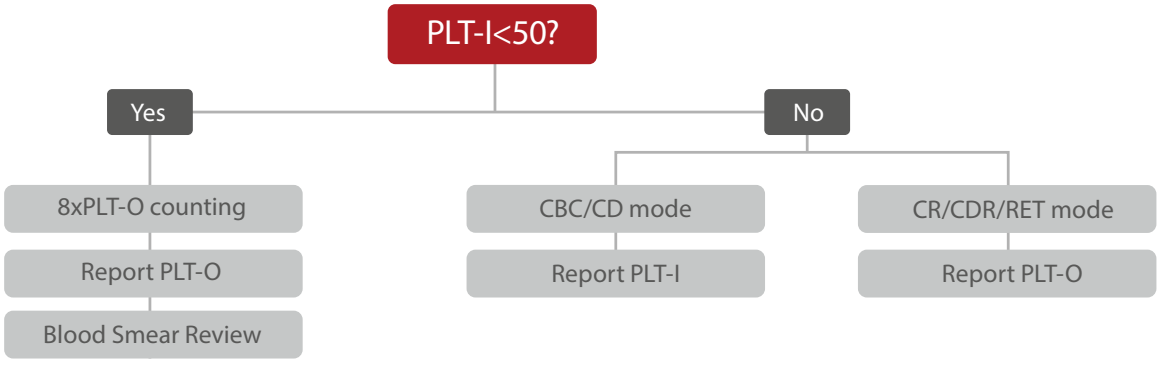
Prepare a second detection solution using the blood sample when the first platelet detection result is less than a preset platelet detection threshold

↓

Control the second detection solution to pass through the impedance detection area

↓

Perform platelet detection on the second detection solution in the impedance detection area with the impedance method to obtain a second platelet detection result



References:

[1] Thrombocytopenia, Eun-Ju Lee, et al, Prim Care Clin Office Pract 43 (2016) 543–557

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[3] Thrombocytopenia: an update, K. J. Smock, et al, Int. Jnl. Lab. Hem. 2014, 36, 269–278

[4] Pseudothrombocytopenia, M Blonska, et al, Wiad Lek. 2001;54(5-6):333-6.

Mindray's Solution for Solving In-vitro PLT Aggregation

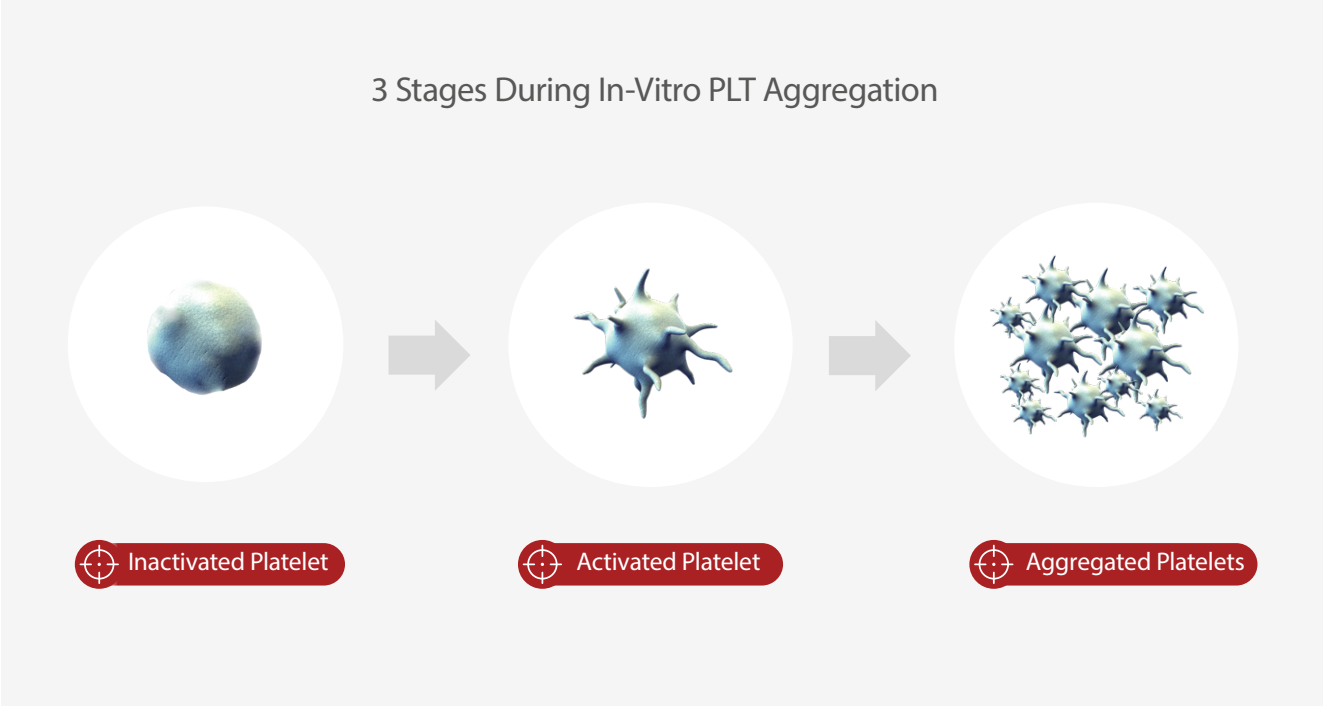
EDTA-dependent pseudothrombocytopenia (EDTA-PTCP) induced by EDTA anticoagulants is a common laboratory phenomenon. It is caused by in-vitro PLT aggregation and may lead to a low PLT result and, ultimately, misdiagnosis and wrong medical treatment for the patient.

In the previous chapter (The Stories of Platelet Clump), we looked at two clinical cases which initially had incorrect low PLT results using the traditional PLT measurement principle. After re-running the samples in the Mindray hematology analyzer using RET mode, PLT-O showed a more reliable result and finally gave the correct diagnosis.

Today, let's explore how the Mindray solution solves the in-vitro PLT aggregation problem.

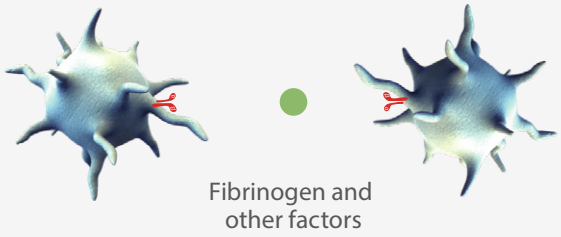
What are the critical factors of in-vitro PLT aggregation?

During PLT aggregation, PLT has three stages: inactivated PLT/activated PLT/ aggregated PLT. PLT activation is the most critical step for PLT aggregation.[1]

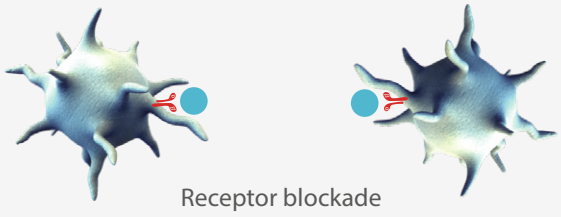


Thus, the PLT aggregation problem may be solved by blocking the PLT activation process. In order to discover the mechanism of PLT activation, we carried out a further exploration into the subcellular structure and cellular signaling pathway, and found there were three main regulatory pathways during PLT activation: the calciumion pathway, Tryosine kinases pathway, and glycoprotein GPIIb/IIIa pathway. [2]

In addition, the corresponding receptor antagonist research has been done to block the regulatory pathway to achieve the aim of PLT de-aggregation. Several different kinds of receptor antagonists have been tried and found to perform well in blocking PLT aggregation.

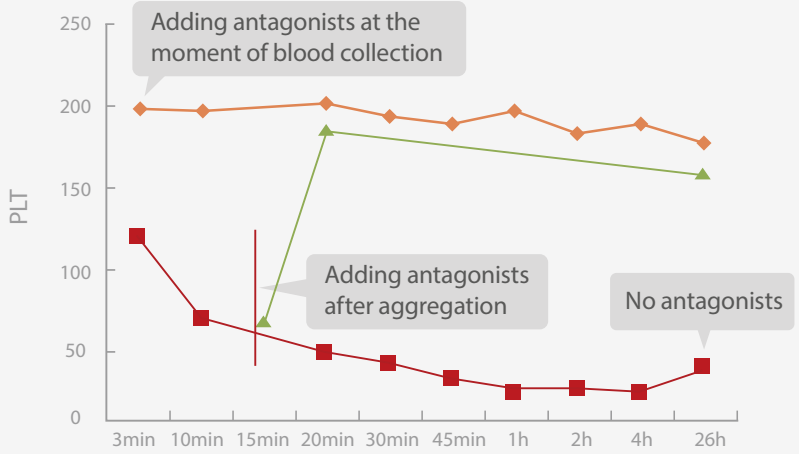


Without receptor antagonist (2 PLT gather together)



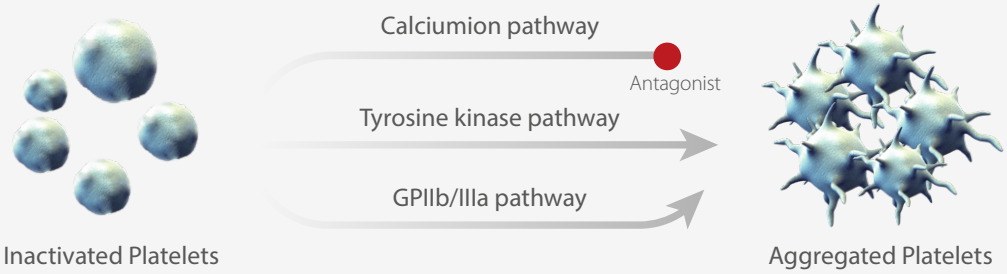
With receptor antagonist (cannot successfully aggregate)

As the data shown below, adding antagonists to samples sensitive to receptor antagonists before aggregation can prevent aggregation from happening; adding antagonists after aggregation can realize PLT de-aggregation as well.

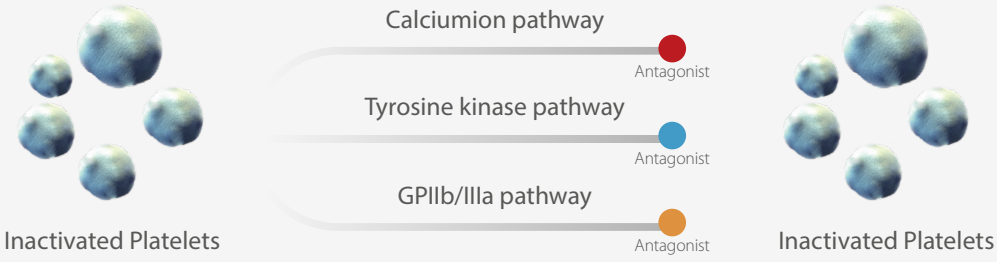


However, after testing different kinds of samples, there are still some samples that are not sensitive to these antagonists. This is because these antagonists can only target single regulatory pathway and have a limited effect on the other two pathways.

A further study was done by combining the molecular biology method to explore the molecular mechanism and different radical group characteristics. Ultimately, from thousands of potential chemical compounds, a series of optimal compounds were found which contain specific radical groups which are highly efficient at blocking the three regulatory pathways.

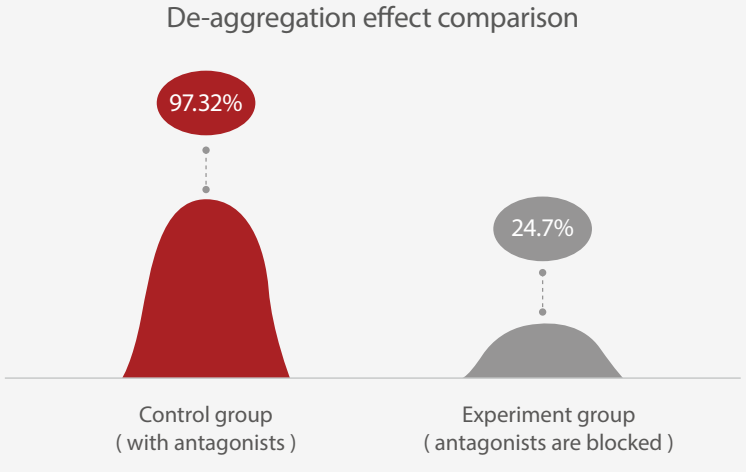


Traditional solution: single target antagonist



Mindray solution: a series of optimal compounds which can block the three pathways

In order to further prove their effects on PLT de-aggregation using those antagonists, a comparison experiment was performed between control group and the group where antagonists were blocked. The experiment results are shown below:



From the experiment, we have found that antagonists containing specific radical groups have an obvious effect on platelet de-aggregation.

Besides, there are also 3 critical factors (appropriate pH, temperature, mechanical mixing) that enhance the PLT de-aggregation. The superposition effect of these factors in de-aggregation is obvious. Thanks to the joint effects of multiple factors, the aggregation platelets are de-aggregated, and a reliable platelet value is obtained.

The PLT de-aggregation function was used in BC-6800/BC-6200/BC-6800Plus/CAL 6000/CAL 8000 in RET mode.

References :

[1] The Platelet Membrane Glycoprotein IIb/IIIa Complex, David R. Phillips, etc.,Annals of the New York Academy of Science(509), 177-187

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How D-dimer in Coagulation Correlates with COVID-19?

D-dimer in COVID-19

As COVID-19 continues to swipe around the world, rapid diagnosis as well as prognosis and treatment of the COVID-19 patients has become an equally important topic among clinicians. Recently scientists have discovered that COVID-19 has a host cell receptor, Angiotensin Converting Enzyme II [1] or ACE2. With the help of ACE2, COVID-19 invades the human body rapidly by reproducing on its own at a massive rate, destroying normal cell, tissue and microvascular system, finally causing acute lung injury, multiple organ failure [2-4], and intravascular coagulation which occurs in 71.4% of patients who died from COVID-19 [5]. It is widely known that D-dimer is a significant bio-marker which correlates with hypercoagulability. More clinical studies have also revealed the relationship between D-dimer and COVID-19.

As published on Jama by Zhi Yong's Group, in the patients' death(non-survivor) group of novel coronavirus pneumonia, the D-dimer level initially increased as the disease developed, until the 7th day when the D-dimer level broke through the normal range, and finally plateaued at a high level [Figure 1 A] [6]. In comparison, the survivor group remained within the normal range consistently. Another article published in the Lancet also claims that there is a close correlation between the D-dimer level and the mortality rate of victims [Figure 1 B] [7]. The same conclusion was also drawn in Shah' s research, which utilized a systematic meta-analysis method (including results from 18 articles and a total of 3,682 patients) to draw the forest plots [Figure 1 C, D] [8]. To sum up, whether in severe or dead COVID-19 patients, the D-dimer level was higher than that which was found in non-severe or surviving patients.

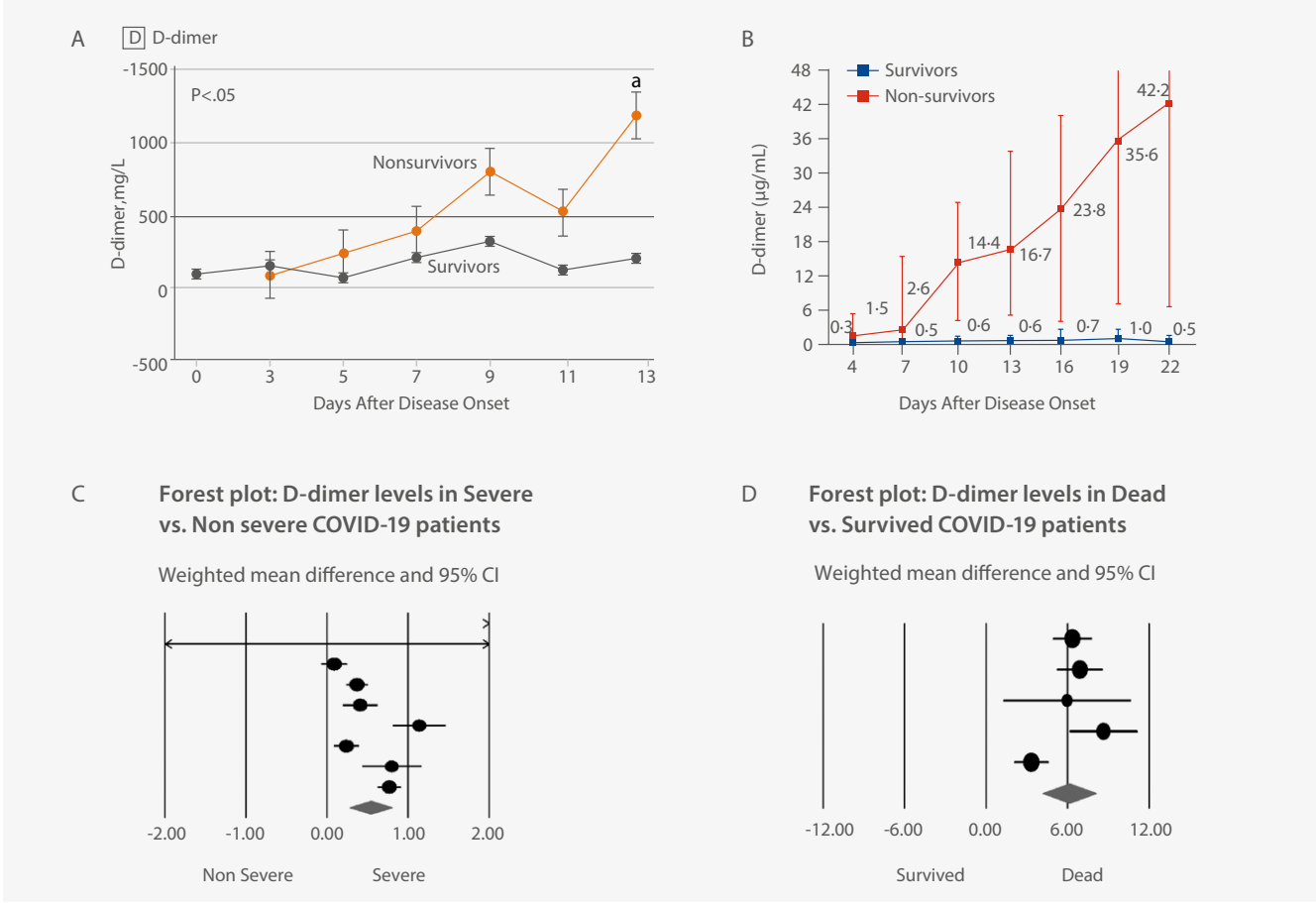


Figure 1: Correlation between D-dimer and COVID-19

Application of D-dimer in COVID-19 Prognosis

According to the study by Zhang's group, D-dimer among all parameters tested in patients with COVID-19 had the highest C-index, which indicates that it has the highest prediction coincidence rate in routine lab testing methods [Figure 3A]. In addition, they also found the 2 μg/ml of D-dimer could be the cut-off value of mortality risk of COVID-19, as DD > 2 μg/ml the survival probability will decrease dramatically [Figure 2B]. Consequently, they based the evaluation of this value and manifested that when 2 μg/ml was set as the cut-off value, 92.3% of sensitivity and 83.3% of specificity is the optimum in all groups [Figure 2C] [9].

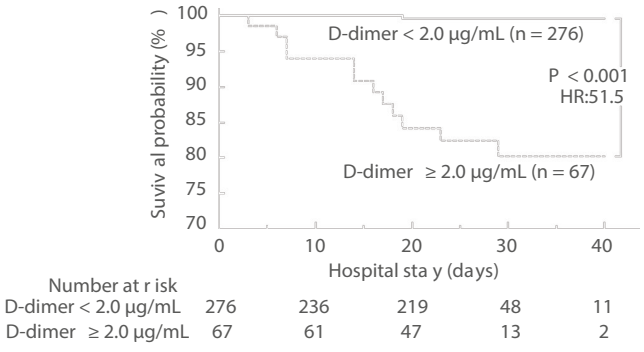
There has been evidence regarding an increased incidence of venous thromboembolic events (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients with severe COVID-19 infection [9], and D-dimer can also be used as a monitoring indicator of VTE and PE with a cut-off value of 0.55 μg/ml. Furthermore, Yao not only found that patients with over 2 μg/ml D-dimer needed intensive care and early intervention, but suggested a cut-off value of 1 μg/ml could help doctors identify patients with a poor prognosis [10].

A

Routine Laboratory Tests	C-index	95% CI
D-dimer	0.883	0.842-0.916
Lymphocyte	0.872	0.832-0.906
Prothrombin time	0.858	0.814-0.895
C-reaction protein	0.844	0.799-0.882
Platelet	0.781	0.734-0.824
Neutrophil	0.773	0.725-0.817
White blood cell	0.625	0.571-0.676
Hemoglobin	0.583	0.528-0.635
Creatinine	0.567	0.510-0.623

Abbreviation: CI, confidential interval.

B



Number at r isk					
D-dimer < 2.0 μg/mL	276	236	219	48	11
D-dimer ≥ 2.0 μg/mL	67	61	47	13	2

C

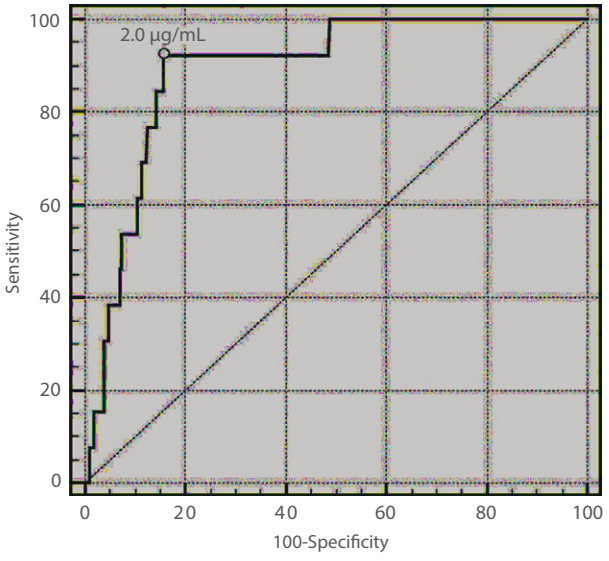


Figure 2: Numberic Results of D-Dimer by Zhang's Group

In conclusion, D-dimer has enormous clinical values in the treatment and prognosis of COVID-19 as a sensitive monitoring index. In consideration of disordered coagulation micro-environment in patients infected with COVID-19 or at high risk of VTE induced by reduced activity, increased bed time, or in people being quarantined for hospitalization, testing of D-dimer on a regular basis is necessary for rapid monitoring of disease treatment. While a cut-off value of over 2 ug/ml has been proved by many researchers monitoring patients' treatment, laboratories are still advised to set their own standard so the variation in demographics can be taken into account.

Mindray's Coagulation D-dimer Solution

Mindray' s auto-coagulation analyzers C3100 & C3510 are equipped with both classic mechanical and optical detection mechanisms. The mechanical methodology is insensitive to interference from icteric, lipemic, chylus and hemolytic samples. Moreover, the patented VRIM(VLin-Rate Integrative Method) algorithm has also been developed to combine "Two Point End Method" at a low D-dimer concentration together with "Rate Method" at a higher level [Figure 3]. This has enabled a much wider linearity range of D-dimer results compared with other models on the market [Figure 4].

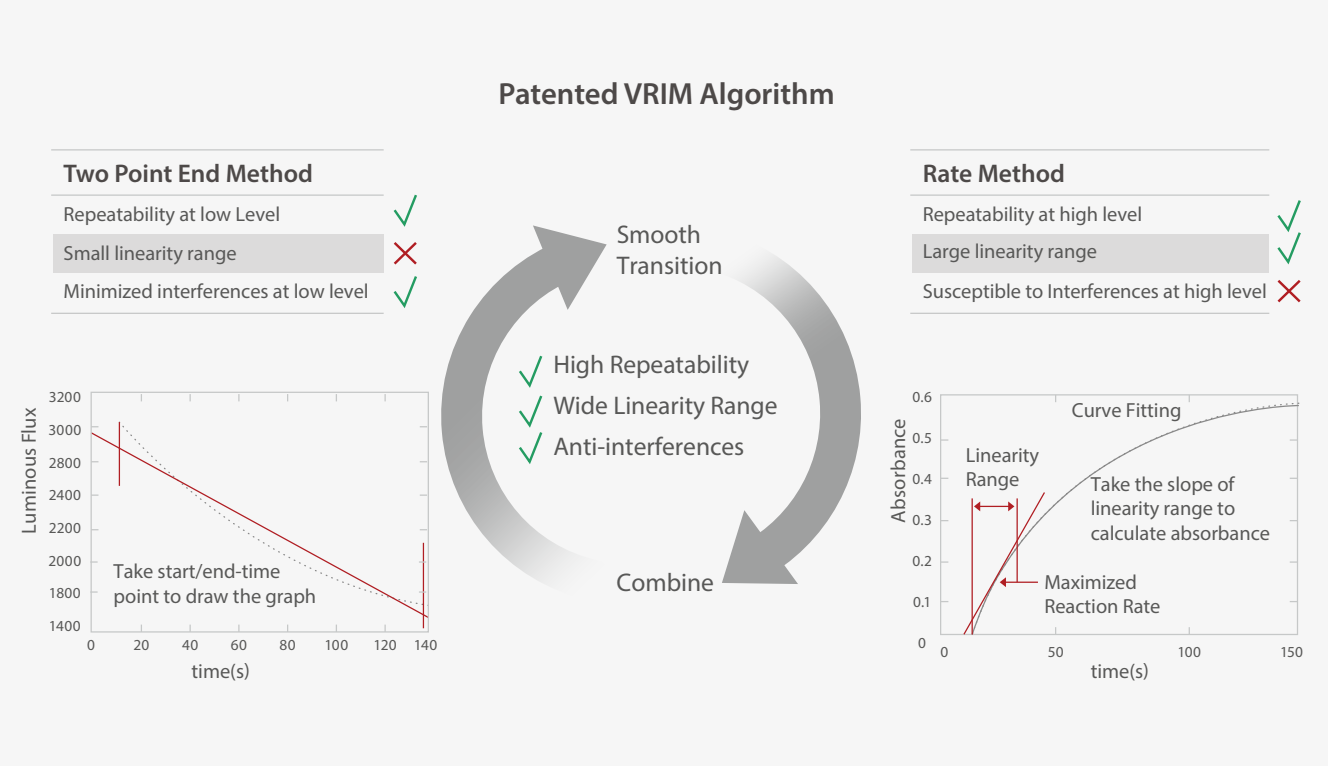


Figure 3: Mindray's patented VRIM Algorithm for D-dimer testing

Manufacturer	Algorithm	Linearity Range (μg/ml)
Mindray	VRIM	0.20~8.0
Brand A	Rate	0.17~4.4
Brand B	Two Point End	0.15~3.7
Brand C	Two Point End	0.22~3.0

Figure 4: Comparison of Linearity Range (without dilution) between Mindray and other brands

In addition, Mindray' s coagulation solution to D-dimer testing is less susceptible to common interferents. As is shown in [Figure 5], when the serum samples are added with bilirubin, hemoglobin, triglycerides and rheumatoid factors at respective concentration, D-dimer results remain at constant levels as before. The Comparison study with Sysmex CS5100 has also shown a good correlation with R2> 97% with interferents added.

Interferent (Concentration)	Before Adding	After Adding
Bilirubin (40 mg/dL)	2.43	2.38
Hemoglobin (200 mg/dL)	2.31	2.36
Triglycerides (1800 mg/dL)	2.39	2.25
Rheumatoid Factor (1300 IU/mL)	1.54	1.55

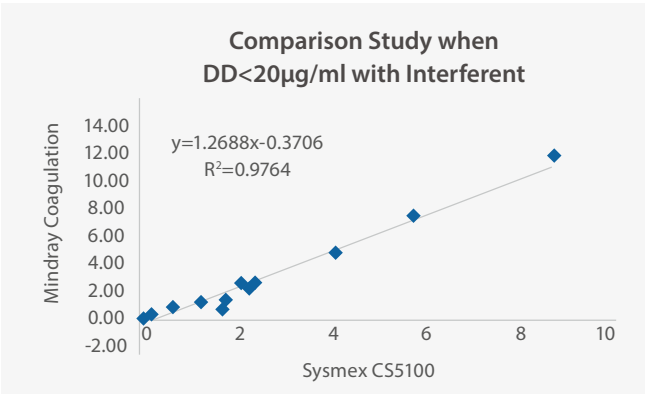


Figure 5: Comparison study with interferents

Figure 6: Mindray's D-dimer coagulation reagents

Mindray's D-dimer coagulation reagents are all manufactured in a bottled liquid state which are ready to use [Figure 6], while the majority of coagulation testing kits are made into powder. Simply by opening the cap and loading D-dimer reagents onto the analyzer, preparation can be set up rapidly with ease on Mindray' s coagulation analyzers.

C3100

- Throughput: up to **200** test/h (PT), up to **44** test/h (D-dimer)
- D-dimer tested with special optical channel
- **61** sample position, 11 reagent position
- **12** incubation channel, 4 mechanical testing channel
- Separate sample/reagent probe ensure low carry over

C3510

- Throughput: up to **300** test/h(PT), up to **91** test/h(D-dimer)
- D-dimer tested with special optical channel
- **80** sample position, 24 (cooling) + 4 reagent position
- **16** incubation channel, 4 mechanical+6 optical testing channel
- Separate sample/reagent probe ensure low carry over

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Have You Noticed the Changes of Red Blood Cells in COVID-19?

As of January 26th, 2021, the coronavirus disease 2019 (COVID-19) pandemic has affected over 100 million people worldwide. Vaccination would help improve the situation in future. However, at this time, identifying patients at highest risk for severe disease is important. In order to facilitate early intervention and to manage local hospital resources to mitigate the critical care crises, our smart doctors conduct research in routine, low-cost, and suggestive parameters to assist with COVID-19 prognosis and the identification of severe cases[1] [2] [3].

Figure 1. Applications of routine blood tests.

Inflammatory parameters, such as white blood cell count (WBC), neutrophil count, neutrophil-to-lymphocyte ratio (NLR) could support COVID-19 diagnosis and prognosis. How about red blood cells?

Observed erythrocytes changes in critically ill patients

Dr. Wang compared hematological results from the good and poor outcome groups and found the best single parameter for predicting the prognosis of severe patients is RDW-SD[4,7]. What's more, combined parameters Lym# & RDW-CV as well as Lym# & RDW-SD are better for predicting the prognosis of severe COVID-19 (Figure 2)[7].

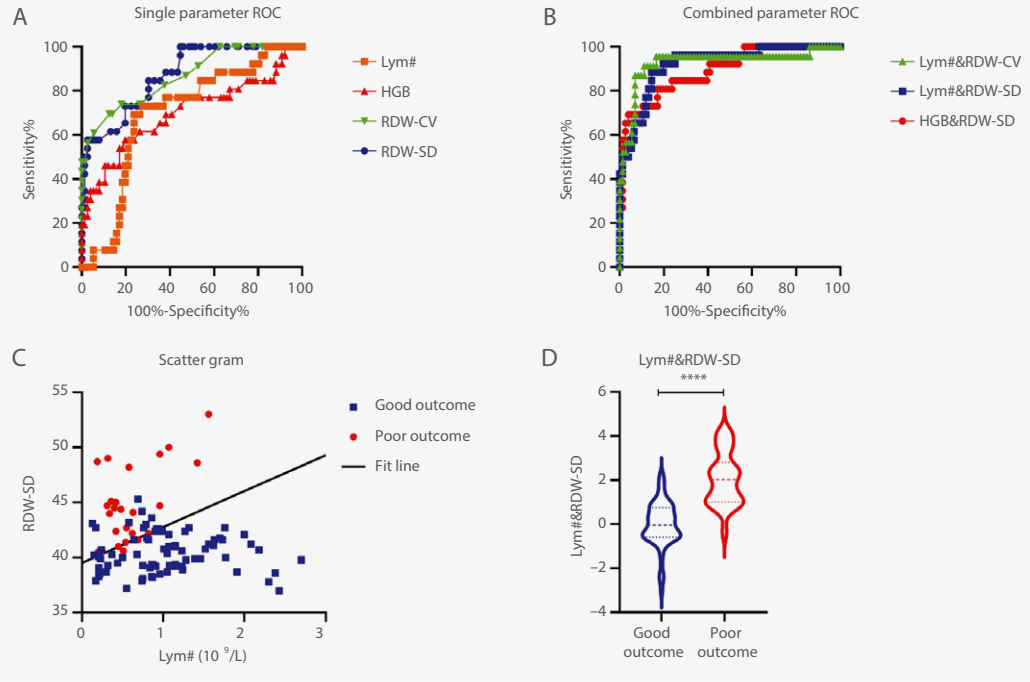


Figure 2. Prediction analysis of hematology parameters and the outcomes of patients with severe COVID-19.
(A) ROC curve, the single parameter for predicting the prognosis of ill patients; (B) ROC curve, joint parameters for predicting the prognosis of ill patients; (C) the linearly fitted schematic scatter plot for Lym# & RDW-SD; (D) comparison of Lym# & RDW-SD in ill patients with different prognoses. Lym# & RDW-SD: joint parameter generated after linear fitting of Lym# and RDW-SD. ****, P<0.0001.

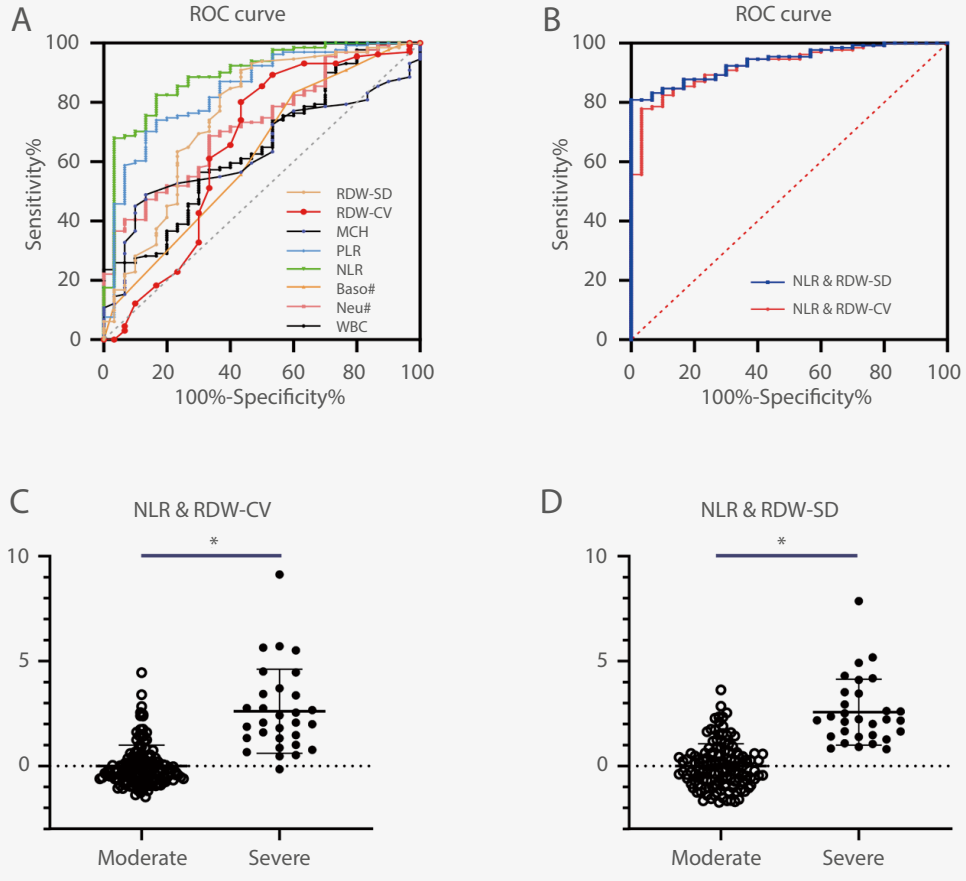
Dr. Zhang has found that HGB is lower in the severe group than in the moderate group[5]. New joint parameters Lym% & HGB have the best sensitivity and specificity (Table1). So Lym% & HGB can be used as indicators of disease prognosis..

Table 1. Receiver operating characteristic analysis results for the three parameters

Parameter	AUC	95% CI	Cutoff	Sensitivity	Specificity	Predict value (+)	Predict value (-)
Lym (%)	0.89	0.88-0.91	18.8	85.6%	77.5%	0.83	0.81
HGB (g/L)	0.79	0.76-0.81	116	71.1%	77.2%	0.80	0.68
Lym% & HGB	0.92	0.91-0.94	0.481	88.9%	79.8%	0.85	0.85

AUC, area under the ROC; Lym%, percentage of lymphocytes; HGB, hemoglobin.

Another article from Dr. Wang[6] described that many hematological parameters changed as the disease progressed, including NLR, RDW-CV, RDW-SD. The combined parameters of NLR & RDW-SD, as generated by linear fitting, had the better diagnostic efficiency (AUC =0.938), which was the best one among single parameters (Figure 3). When the cut-off value was 1.046, the sensitivity for distinguishing the severe cases from the moderate cases of COVID-19 was 90.0% while the specificity was 84.7%.



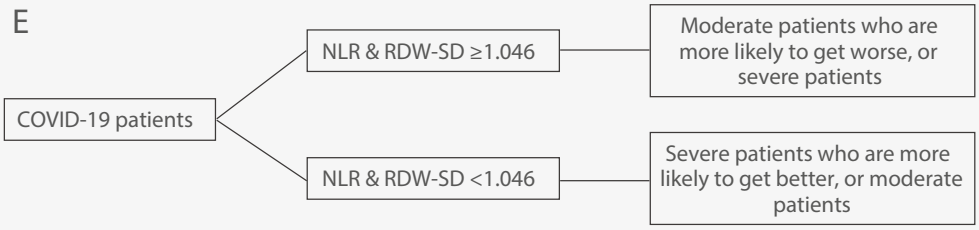


Figure 3. ROC analysis using single and combined parameters in the diagnosis of severe cases of COVID-19. Differentiated diagnosis of moderate and severe COVID-19 patients using different parameters. The positive sample is the blood routine result of the severe patient, and the negative sample is the blood routine result of the moderate patient. Panel A is an ROC plot that uses a single parameter to identify severe from moderate patients. Panel B is an ROC plot that uses the combined parameters of NLR and RDW-SD and NLR and RDW-CV to identify patients; Panels C and D are scatter plots that use the combined parameters for comparison between the two groups; Panel E is a recommendation management strategy for COVID-19 patients. "*" standing for significant deviation.

Why did these erythrocyte changes happen in critically ill patients?

It's been found that the increase in RET may contribute to elevated RDW (Figure 4). As the disease progressed, MFR and HFR increased, so did RDW-SD. The increased RET in peripheral blood may cause an increase in anisocytosis.

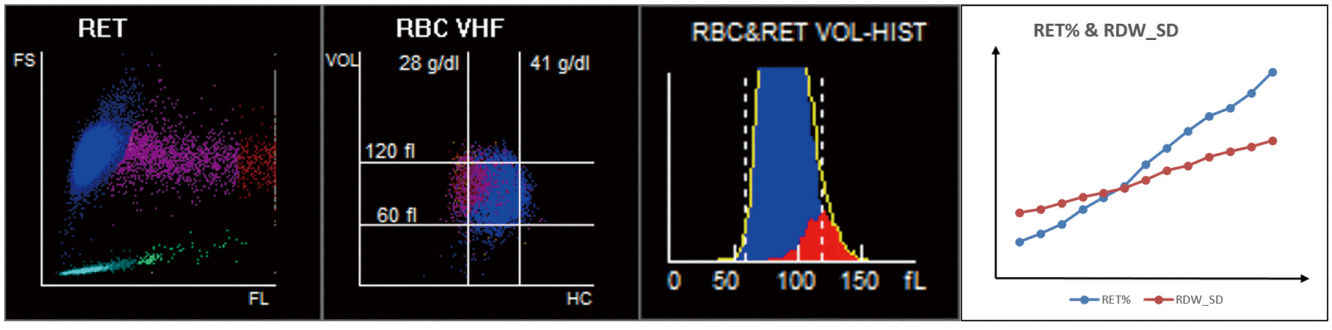


Figure 4. Dynamic monitoring of RET scattergram in critical COVID-19 cases. RET scattergram is from Mindray BC-6800Plus.

Increased RDW-SD

1. As the disease progressed, MFR and HFR increased, RDW-SD increased.

2. As the infection symptoms worsen, the level of oxidative stress in the body increases, oxygen free radicals increase. Insufficient circulating nutrients in patients may also lead to an increase in RBC membrane instability, followed by increased RDW.

Decreased HGB

1. Long-term hypoxia leads to increased synthesis of erythropoietin and active erythropoietin hyperplasia.

2. On the contrary, HGB synthesis is prevented in critically ill patients due to malnutrition or iron deficiency, resulting in low HGB and low-HC (hemoglobin concentration) RETs.

Figure 5. Mechanism of RDW-SD and HGB change in COVID-19[6].

How can we observe these erythrocyte changes in the hematology analyzer?

When we look at the 9-square scattergram, the RBC volume/hemoglobin concentration (V/HC) scattergram showed that the magenta scatters of critical patients were significantly left-skewed, indicating that RETs with a low HC (hemoglobin concentration) increased significantly, which may represent a unique pattern of erythroid hyperplasia in critical COVID-19 patients (Figure 6A)[7]. However, whether such low-HC RETs could be a diagnostic marker of critical COVID-19 still requires further investigation[7].

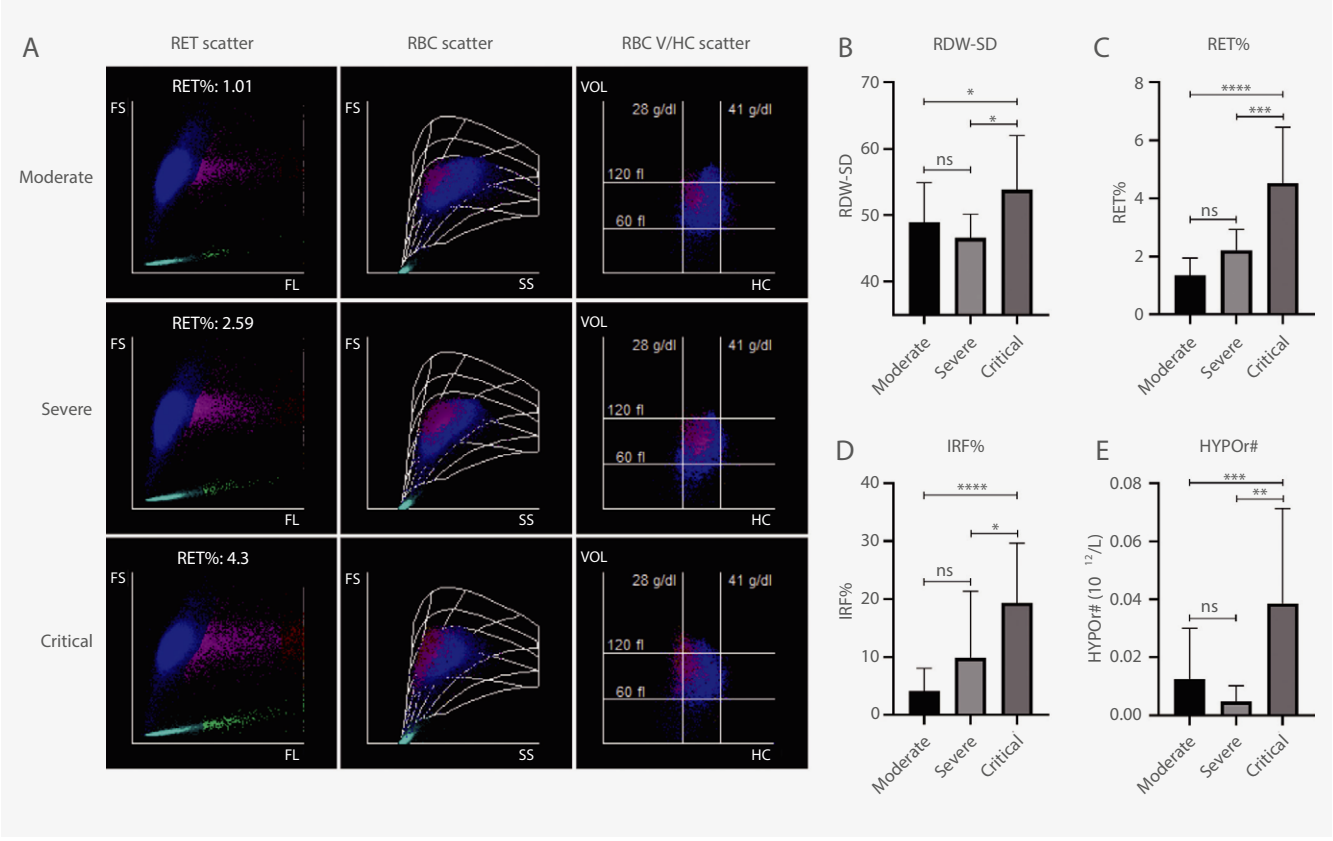


Figure 6. Differences of RET scattergram results in patients with different severity of COVID-19. (A) Scattergram of RET channel data from Mindray BC-6800 hematology analyzer. Blue scatters are RBCs, magenta, and the red scatter is the RETs, and cyan scatters are PLTs. (B,C,D,E) Comparison of parameters obtained from the RET channel for patients with different severities of COVID-19. Data are shown as the mean ± SD. ****, P<0.0001; ***, P<0.001; **, P<0.01; *, P<0.05. FS, forward scatter; SS, side scatter; FL, fluorescence; HC, hemoglobin concentration; VOL, volume; ns, nonsignificant.

With advanced technologies, the newly combined hematological parameters, such as Lym% & RDW-SD, Lym# & HGB and NLR & RDW-SD, have been found as supportive predictors during COVID-19 prognostics. More and more covariates can be studied and developed on the Mindray BC-6000 series analyzers. Especially on BC-6800Plus, the RET channel can detect the number, size, and hemoglobin concentration of RBCs and RETs highly sensitive laser scattering technology. Thus, it's recommended to start using self-defined parameters for COVID-19 prognosis now.

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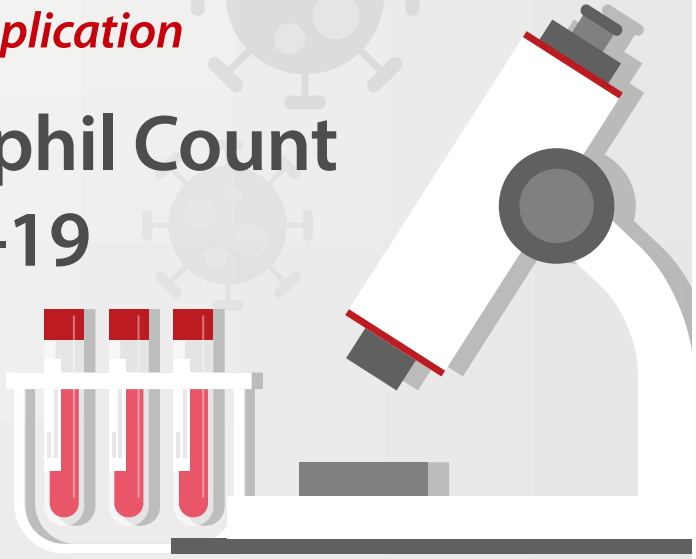
Common parameter, new application

How Does Eosinophil Count Change in COVID-19 Patients?



Is prophylactic anticoagulant therapy a common treatment for clinicians to deal with thrombotic events in COVID-19?

Is there a connection between the eosinophil count and anticoagulation monitoring in COVID-19 patients?

Thrombotic events in COVID-19 patients

Thrombosis has emerged as an important complication among hospitalized patients with COVID-19. A prothrombotic state induced by SARS-Cov-2 can manifest in venous thromboembolism (VTE), arterial thrombosis and disseminated intravenous coagulation (DIC). [1]

In 28 studies including 2928 patients, thrombotic complications occurred in 34% of ICU patients, deep venous thrombosis (DVT) reported in 16.1% and pulmonary embolism in 12.6% of patients, and were associated with high mortality. [2]

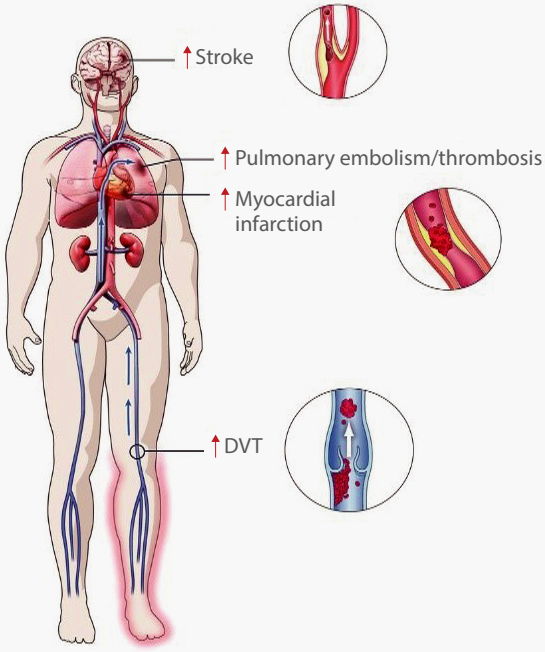


Figure 1. Possible venous and arterial thrombotic complications associated with COVID-19. [1]

Antithrombotic treatment of low molecular weight heparin in COVID-19 patients

Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are recommended by the international society for thrombosis on hemostasis (ISTH), American Society of Hematology (ASH) for the treatment of thrombotic events associated with SARS-CoV-2 infection. Particularly, LMWH has a stronger antithrombotic effect than UFH.

LMWH dose monitoring

LMWH predominantly acts on factor Xa. For this reason, LMWH activity is monitored using serum anti-factor Xa activity (AFXa) levels instead of activated Partial Thromboplastin Time (aPTT) (Figure 2). [3]

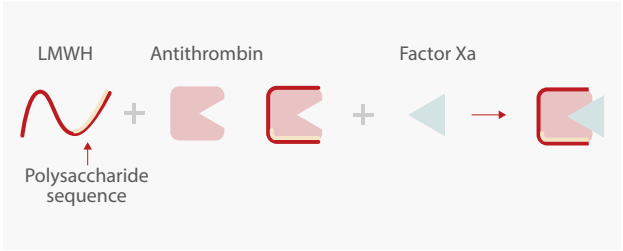


Figure 2. The antithrombotic mechanism of LMWH. [3]

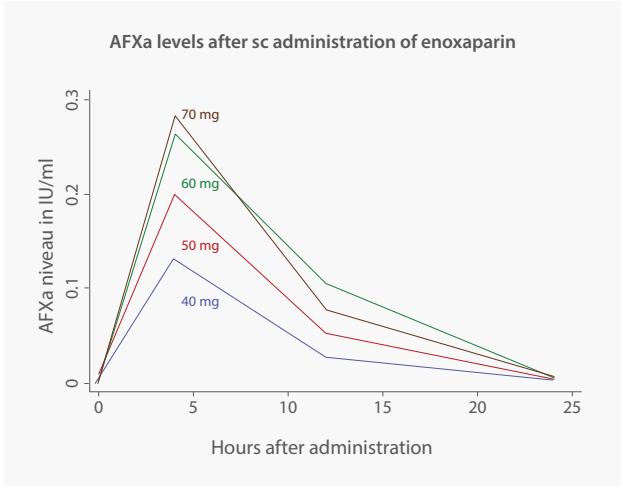


Figure 3. Variation in AFXa over time for each dose of enoxaparin. [4]

Enoxaparin is one of the most important LMWH. The AFXa level reached peak 3-5 hours after administration. The AFXa levels below 0.2 IU/mL may increase the risk of VTE in COVID-19 patients, due to the hypercoagulability. [4]

Eosinophil counts in antithrombotic treatment to COVID-19 patients

Dr. Selma Ari has found the increased eosinophil count is associated with the level of subprophylactic anticoagulation in COVID-19 patients. [5]

Table 1 Results of laboratory parameters at admission

Variable	Subprophylactic anticoagulation group (13 patients) anti-factor Xa < 0.2 IU/mL	Prophylactic anticoagulation group (67 patients) anti-factor Xa > 0.2 IU/mL	*p* value
WBC X10³ /mL	5.91 ± 1.31	5.54 ± 1.89	0.51
Neutrophil	3.57 ± 1.27	3.51 ± 1.71	0.91
Lymphocyte	1.76 ± 0.60	1.54 ± 0.66	0.25
Eosinophil (%)	2.96 ± 2.55	0.90 ± 1.28	*0.001*
Eosinophil count	168.42 ± 147.25	50.32 ± 73.42	*0.001*
Platelet X10³ /mL	232.00 ± 62.21	197.57 ± 57.87	0.06
CRP (mg/L)	12.18 ± 16.66	25.12 ± 31.04	0.08
Fibrinogen (mg/dl)	367.08 ± 134.97	410.00 ± 117.34	0.24
D-dimer (µgr/mL)	0.57 ± 0.38	1.21 ± 3.35	0.50
PT	11.55 ± 0.91	11.82 ± 1.92	0.62
aPTT (s)	23.25 ± 3.24	25.62 ± 8.45	0.32
INR	0.95 ± 0.06	0.96 ± 0.19	0.89
Baseline anti-factor Xa level (IU/mL)	0.18 ± 0.06	0.43 ± 0.23	*<0.001*

Parameters whose p<0.05 are written in italics

In the laboratory results, only eosinophil counts and AFXa are significantly different between subprophylactic anticoagulation group and prophylactic anticoagulation group when the patients are admitted to hospital (Table 1). [5]

Table 2 Results of laboratory parameters before discharge

Variable	Subprophylactic anticoagulation group (13 patients) anti-factor Xa < 0.2 IU/mL	Prophylactic anticoagulation group (67 patients) anti-factor Xa > 0.2 IU/mL	*p* value
WBC X10³ /mL	6.25 ± 0.82	5.55 ± 1.95	0.08
Neutrophil	3.81 ± 1.14	3.26 ± 1.58	0.08
Lymphocyte	1.81 ± 0.69	1.79 ± 0.78	0.52
Eosinophil (%)	3.06 ± 1.49	2.07 ± 1.92	*0.001*
Eosinophil count	182.49 ± 95.81	112.18 ± 102.54	*0.009*
Platelet X10³ /mL	264.42 ± 117.14	226.94 ± 89.08	0.25
CRP (mg/L)	8.54 ± 11.47	19.45 ± 35.44	0.19
Fibrinogen (mg/dl)	377.33 ± 145.03	416.98 ± 148.71	0.31
D-dimer (µgr/mL)	0.72 ± 0.77	0.78 ± 1.08	0.91
PT	11.72 ± 0.59	11.93 ± 1.28	0.65
aPTT (s)	22.34 ± 1.38	24.38 ± 3.58	0.01
INR	0.96 ± 0.05	0.98 ± 0.11	0.46
Control anti-factor Xa level (IU/mL)	0.16 ± 0.04	0.53 ± 0.26	*<0.001*

Parameters whose p<0.05 are written in italics

Laboratory analysis collected before the discharge of patients revealed that eosinophil counts in subprophylactic anticoagulation group were higher than in prophylactic anticoagulation group , whereas AFXa were lower in subprophylactic anticoagulation group (Table 2). [5]

Eosinophils and thrombosis

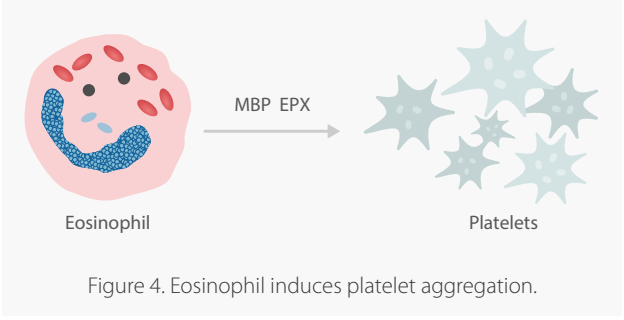


Figure 4. Eosinophil induces platelet aggregation.

Eosinophil induces platelet aggregation and thrombus formation through the production of major basic protein (MBP) and eosinophil peroxidase (EPX). [6]

Enzymes released from eosinophils (peroxidases, cationic proteins, and neurotoxins) may decrease the anticoagulant activity of heparin. [7]

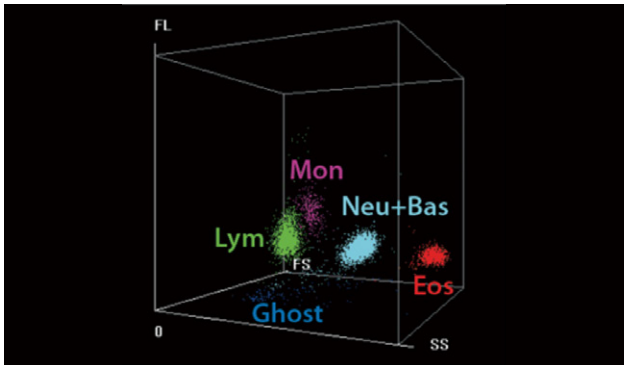


Figure 5. SF Cube on Mindray BC-6800.

In this study, in subprophylactic anticoagulation group, high eosinophil levels had lower anticoagulant activity in COVID-19 patients. Eosinophil counts were examined with Mindray BC- 6800 auto hematology analyzer. Its SF Cube analysis technology can produce three-dimensional scattergram which can help doctors better identify and differentiate blood cell populations, especially to reveal abnormal cell population undetected by other techniques.

Nowadays a large number of parameters on BC-6800 can be used in clinical diagnosis and scientific research. There fore, clinicians are welcome to do more research on COVID-19 on Mindray BC-6200/BC-6800/BC-6800Plus/ CAL 6000/CAL 8000.

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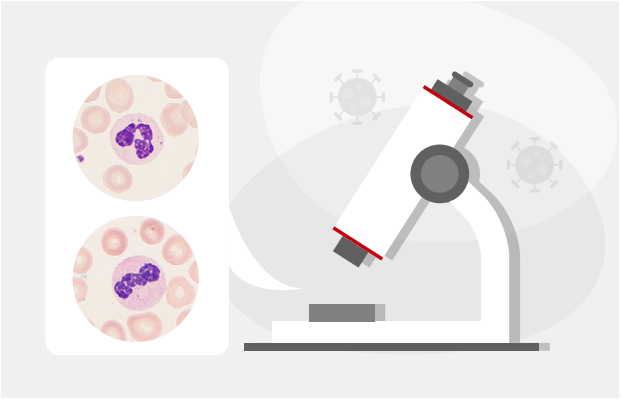
How Does a Digital Morphology System Help Labs to Optimize Their Workflow?

Nowadays, hematology analyzers are used widely in laboratories to automatically count and differentiate blood cells. Nevertheless, blood morphology examination for the presence of abnormal cells is still the 'gold standard' in the routine blood count. Microscopic examination is the most valuable procedure in the laboratory, which can suggest some disorders previously identified by the analyzer.



However, a skillful examination requires an experienced technician, can take a long time, and is very labor intensive. As a result, there is an increasing demand for digital morphology systems which help to optimize the labs' workflow by:

Providing a reliable cell pre-classification result using intelligent algorithms

- A digital morphology analyzer can automatically locate, capture, and identify cells, which helps technicians to check cell morphology easily on a big screen.

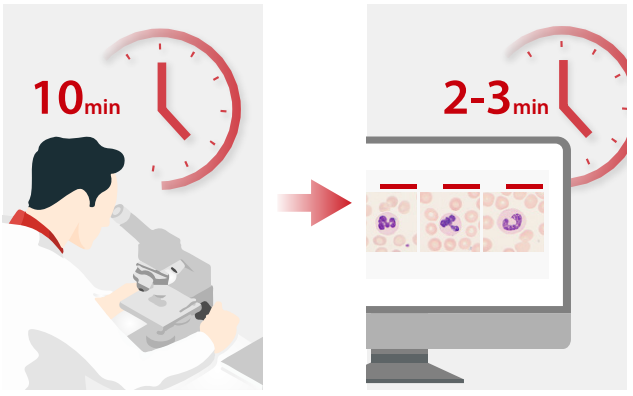
· With the help of intelligent algorithms, a digital morphology system can help to pre-classify different cells in different groups and give a reliable pre-classification result.

· A digital morphology system avoids inter-observer variability and retains the same standard when pre-classifying cells.

Improving the efficiency of the morphology examination

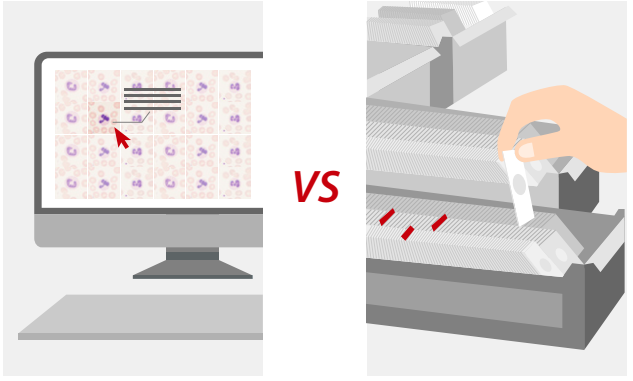
· Generally, a manual morphology examination takes around 10 mins, and more time is needed for abnormal samples.

· By using digital morphology systems, the average examination only takes 2-3 minutes, which improves lab efficiency dramatically.



Enabling convenient data management and remote consultation

· With the help of cell digitalization, laboratories can store slides and morphology results in a single PC instead of storing a lot of conventional glass slides.



· By using the remote review function, senior technicians in satellite labs or even from home can easily review the slide results sent from the core labs.

Today, an increasing number of advanced automated digital morphology systems have been developed and introduced to the laboratory. These digital morphology systems optimize the labs' workflow by improving lab quality assurance, reducing labor costs, providing the availability of morphology digitalization and enabling remote consultations.

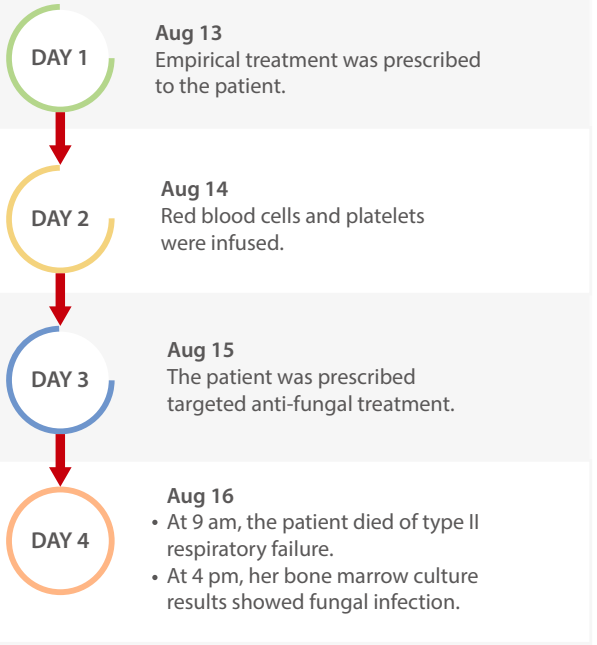
Mindray is soon going to launch a brand new digital morphology system. Stay tuned as we bring you more updates!

A 'Sherlock Holmes' Helps You to Capture the Culprit of Diseases

A 43-year-old woman presented with persistent fever for two months. She had visited different hospitals more than three times, but there was no significant improvement in her symptoms. After being admitted to a top-tier hospital in China, she underwent a series of examinations. Her serology test was positive for human immunodeficiency virus (HIV) infection. Her chest computed tomography (CT) scan showed diffuse small nodules in both lungs. Disseminated *Talaromyces marneffei* infection was considered, based on the patient's symptom of fever, laboratory test and CT scan results. She was prescribed targeted anti-fungal treatment.

Unfortunately, she died four days after admission to the hospital as the infection worsened and her condition rapidly deteriorated. Seven hours after she died, hyphae-like structures were spotted on the gram stain of the positive bone marrow culture.

Figure 1. Brief medical history



What is Talaromyces marneffei?

Talaromyces marneffei is a fungus that causes opportunistic systemic mycoses in patients with AIDS or other immunodeficiency syndromes. The fungus was first isolated from the hepatic lesions of a bamboo rats (Rhizomys sinensis) in 1956 (Figure 2). It has been suggested that these animals serve as a reservoir for the fungus. It is not clear whether the rats are infected by *Talaromyces marneffei* or are merely carriers of the fungus.

Figure 2. Bamboo rat [1].

(A) Rat's cave and stool of the rat; (B) bamboo root in the burrow; (C) the soil and debris of food; (D) petiole; (E) bamboo leaves; (F) bamboo rat

Talaromyces marneffei is usually diagnosed by microscopic identification of the fungus in various clinical specimens and by standard microbiological culture, based on its morphological characteristics and thermally dimorphic properties between 25°C (mycelium form) and 37°C (yeast form) (Figure 3).

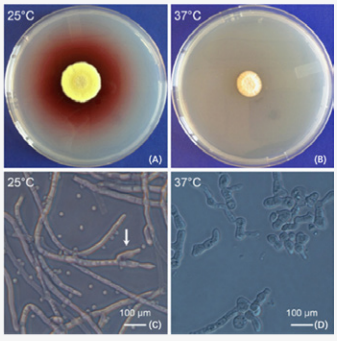


Figure 3 . Temperature-dependent dimorphism in *Talaromyces marneffei* [2].

(A) Soluble red pigments were produced and diffused into the agar at 25°C; (B) a yeast-type colony formed with decreased production of pigments at 37°C; (C) x400 microscopic views of long mycelia, conidia, and conidiophore (white arrow) at 25°C; (D) x400 microscopic views of fission yeast-like cells (arthroconidia) at 37°C.

Epidemiology

Talaromyces marneffei is endemic in Myanmar, Cambodia, Southern China, Indonesia, Laos, Malaysia, Thailand and Vietnam. Patients spread the AIDS and Talaromycosis all over the world through travel.

Figure 4 . Map showing regions where *Talaromyces marneffei* is endemic (red shading) [3].

Clinical presentation

Talaromycosis is a potentially fatal infection causing rapid deterioration[4]. The main manifestations of *Talaromyces marneffei* infection are fever, cough, lymphadenectasis, hepatosplenomegaly, skin lesion, dyspnea, and weight loss, but they are nonspecific and have no significance for differential diagnosis[5].

Since its clinical manifestations lack specificity, it is easy to be dismissed as a diagnosis or misdiagnosed, leading to high mortality and poor prognosis.

Laboratory diagnosis

Microbiological culture is a 'gold standard' diagnostic method. However, it lacks sensitivity and is time-consuming, which affects clinical decisions and delays the initiation of appropriate treatment. Although metagenomic next-generation sequencing (mNGS), polymerase chain reaction (PCR) and Tzanck cytology smear tests can detect *Talaromyces marneffei*, they are relatively expensive and they require sophisticated instruments and skilled laboratory personnel[6-8].

In the previous clinical case, using peripheral blood smears, Mindray's brand new Automatic Digital Cell Morphology Analyzer detected *Talaromyces marneffei* yeast cells (black arrow) that had been phagocytized by neutrophils (Figure 5). The yeast cells were round to oval and measured 2-5μm in diameter. Occasional clear cross wall septa were seen.

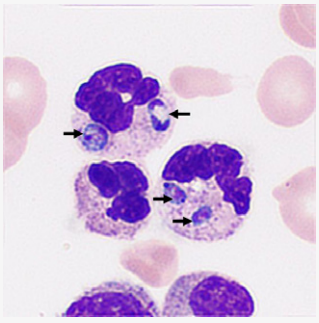


Figure 5 . Neutrophils having phagocytized *Talaromyces marneffei* yeast cells.

In adults, Talaromyces marneffei infects patients with AIDS. Nevertheless, recent studies showed most pediatric patients were HIV negative, yet still had severe systemic complications and poor prognosis.

Therefore, simpler and faster tests with higher sensitivity and specificity are required. A digital morphology system can help to establish a rapid clinical diagnosis of talaromycosis before results from cultures are reported. In particular, Mindray's brand-new digital morphology system can provide a convenient and high-performance method to aid diagnosis of Talaromyces marneffei infection. Please stay tuned for more details on this new system.

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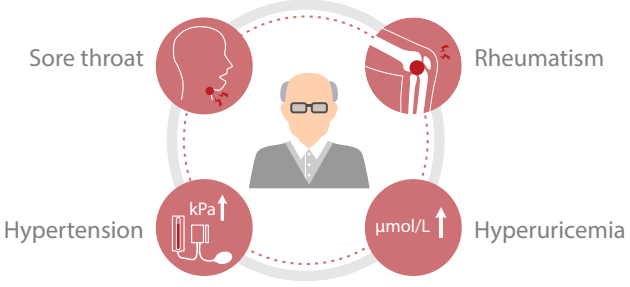
In the laboratory, what is the most common reason for you to gather with colleagues to look at and discuss samples or patient results on the screen or in a report?

The answers may vary. One of the reasons may be to discuss the special cell cases you find in a morphological examination. The routine hematology analysis is one of the most important screening tools among in-vitro diagnostics methods. The professionalism of the pathologist guarantees fast and accurate diagnosis based on the results from hematology analysis. Experienced and skilled cell morphology experts, in particular, play a vital role in it.

A Clinical Case

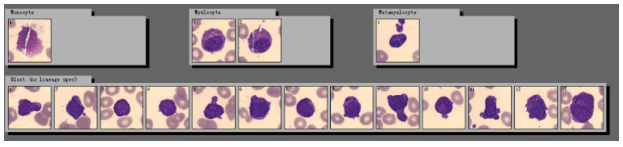
According to the IDF, there are approximately 232 million people with undiagnosed DM worldwide. Many guidelines tend to suggest DM screening in the population with or without specific medical conditions, and HbA1c is a convenient test to meet this objective. [2] Unlike glucose tests, HbA1c is not affected by recent food intake, so patients do not have to fast or intake certain quantities of glucose before the test. Accompanied with medical history and some auxiliary evidence, doctors can make the DM diagnosis if the patient's HbA1c matches the criteria.

The hematology results showed pancytopenia and flagged many causes for concern, including anemia, thrombocytopenia, white blood cell abnormal scattergram, and immature granulocytes.



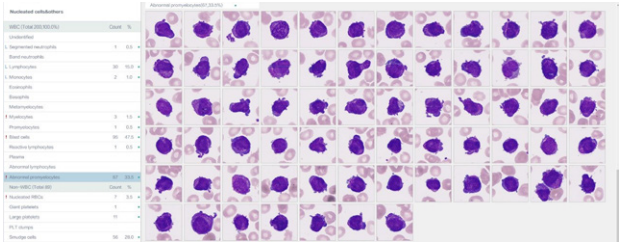
The re-exam rule was triggered, so the doctor carried out the smear and stained it in the slide marker. The current digital cell morphology system read the blood smear automatically, and a high percentage of blasts and a few immature granulocytes were found.

White blood cell	Cell count	Percentage %
• Unidentified	19	9.5
• Band neutrophil	-	-
• Segmented neutrophil	4	2.0
• Eosinophil	-	-
• Basophil	30	15.0
• Lymphocyte	127	63.5
• Monocyte	1	0.5
• Promyelocyte	-	-
• Myelocyte	2	1.0
• Metamyelocyte	1	0.5
Immature eosinophil	-	-
Immature basophil	-	-
Promonocyte	-	-
Prolymphocyte	-	-
• Blast(no lineage spec)	13	6.5
• Lymphocyte,variant form	-	-
• Plasma cell	3	1.5
Large granular lymphocyte	-	-



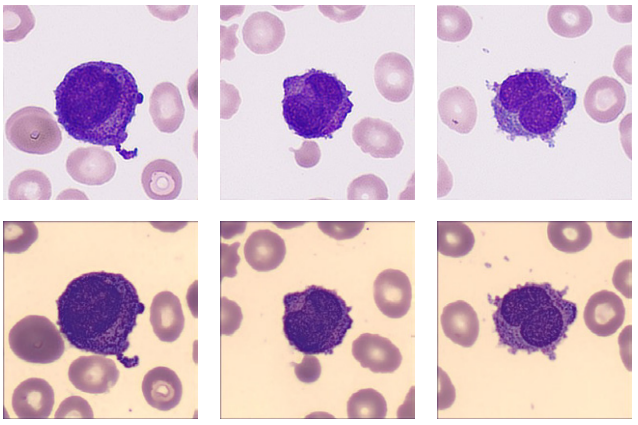
The pre-classification result by the current digital cell morphology system

"My god! Look at this!" One technician exclaimed. He read the same slide on the hospital's trial digital cell morphology system from Mindray, where he found a more critical signal. In addition to high numbers of blast cells, a new cell type "Abnormal promyelocyte" appeared on the screen, with a percentage as high as 33.5%!



The abnormal promyelocytes on the trial digital cell morphology system from Mindray.

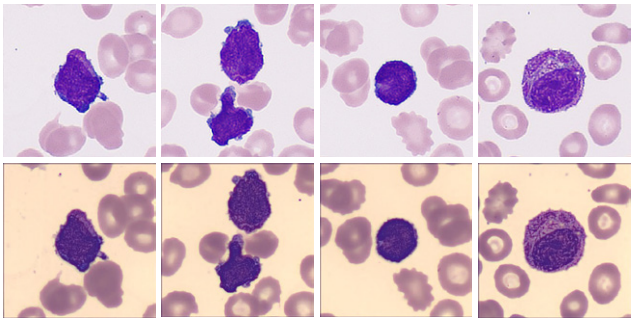
Many typical characteristics had been found in these cells, such as the abondent purple-red auer rods, the orange-red cytoplasm particles like sunset clouds, and two leaf-like nuclei. The laboratory immediately decided to report the cirital values to the clinical department.



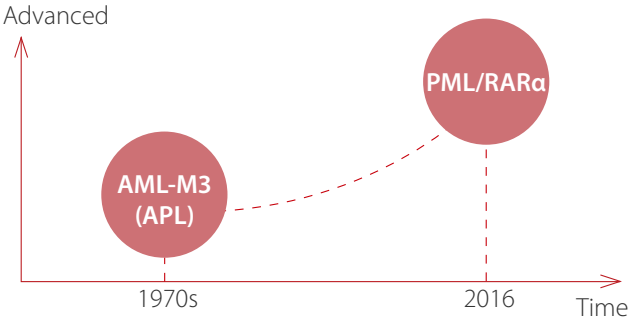
The typical abnormal promyelocytes on both digital cell morphology systems

The patient was quickly treated with all-trans retinoic acid (ATRA) + arsenic program, and then fluorescence in situ hybridization (FISH) confirmed a chromosome translocation of t(15;17) (q22;q12) forming the fusion gene PML/RARα.

More pairs on both systems (from the same slide):



About PML/RARα



In the 1970s, a group of French, American, and British leukemia experts divided AML into subtypes, M0 through M7, based on the type of cell where the leukemia develops and how mature those cells are.Acute promyelocytic

leukemia (APL) is the subtype AML-M3 using the French-American-British (FAB) classification.By taking into account many of the factors that are now known to affect prognosis, the World Health Organization (WHO) system updated the classification of AML in 2016. APL with the PML- RARα fusion gene was independently listed, as PML/RARα is the central leukemia-inducing lesion in APL. It is directly targeted by all trans retinoic acid (ATRA) and by arsenic, with both compounds able to induce complete remissions (CRs).

Clinically, it is critical that APL is distinguished from other AML subtypes quickly, because of:

- Its life-threatening bleeding disorders in case of delay in the proper treatment
- Its achievement of CRs in about 90% of APL patients upon ATRA treatment
- Its induction of CRs in 75–90% of APL patients upon exposure to low-dose arsenic trioxide

However, the low incidence of PML/RARα and the rapid deterioration of the disease mean that rapid diagnosis and the timely and successful treatment of patients are still huge challenges facing medical professionals today.

Conclusion

Although there are a variety of digital cell morphology systems with automatic cell classification on the market, there are still problems with insufficient recognition ability and low levels of efficiency. It takes a lot of manpower to check and confirm abnormalities on the cell image, and even check the smear under the microscope again.

Mindray provides reliable hematology solutions that can deliver efficient, accurate information about the true conditions of patients, helping health professionals, especially morphology experts, to find abnormalities, identify emergencies, as well as treat and cure patients fast.

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Capture the truth about cell morphology

Many laboratories are troubled by problems such as lengthy analysis processes and less efficient microscopic examinations due to lacking of experts in cell morphology and inadequate equipment. This makes them hard to reach a 30% overall re-exam rate, a target recommended by the international consensus group for hematology review. Furthermore, the abilities of the laboratory staff are varied, leading to inconsistency in lab standards and results.

Mindray's MC-80 Automated Digital Cell Morphology Analyzer is designed to provide "More Clarity, More Intelligence, and More Productivity" for cell morphology analysis, with intelligent tools to help discover the truth about cells.

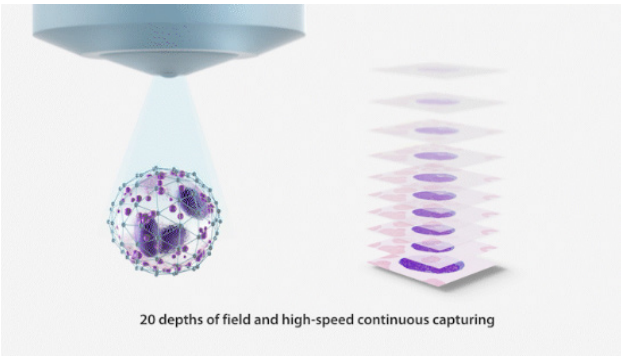
Committed to improving the efficiency and accuracy of laboratories, Mindray has been collaborating with experts and scholars in hospitals around the world since 2014. Based on intensive research, Mindray has come up with the innovative solutions in cell imaging such as Multi-layer fusion technology, "Solid Rock" Hyper-stable Anti-shake System, Fly-mode Technology, and many more.

More Clarity: more details beyond appearances

Cells are the basic units of life, and cell morphology test is one of the prime tools for detecting malignant diseases. Pathologists study the internal structure and details of the cells for various needs.

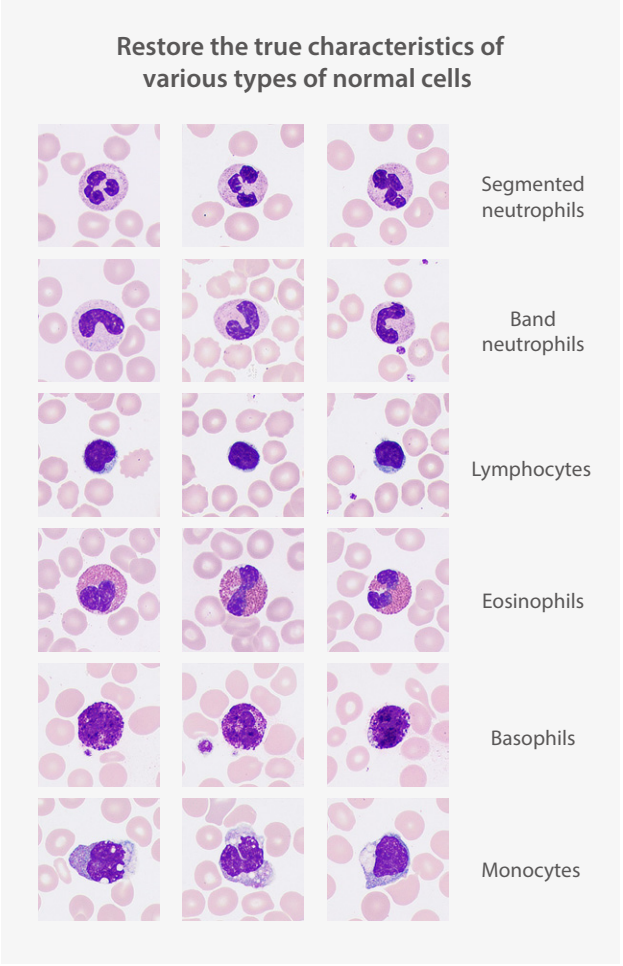
Currently in most laboratories, morphology experts observe the cell images of each re-examination sample manually with a microscope, making it a prolonged process when the test volume is large.

In order to effectively alleviate the workload of manual analysis with a microscope, cell morphology analyzers need to simulate the details captured by manual microscopy as clearly as possible. How can planar imaging of cells achieve this?



The MC-80 innovatively captures 20 images of each cell at different depths of field.

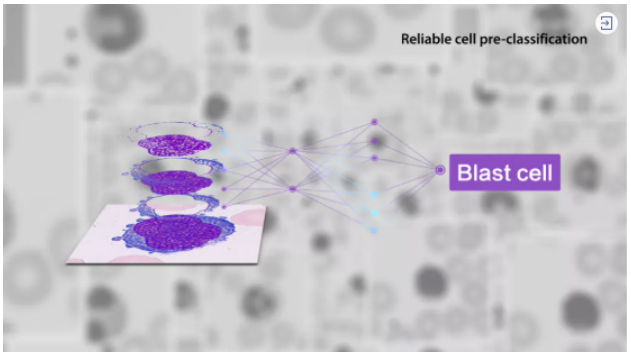
The essence of the multi-depth fusion technology is to recreate manual focusing normally performed by the doctor by superimposing the clear parts of the 20 images. In the cell imaging from the MC-80, the features and internal details of normal and abnormal cells can be clearly presented.



Therefore, doctors can gain insight into the pathological features of cells for more accurate early screening of blood disorders and infectious diseases, avoiding misdetection.

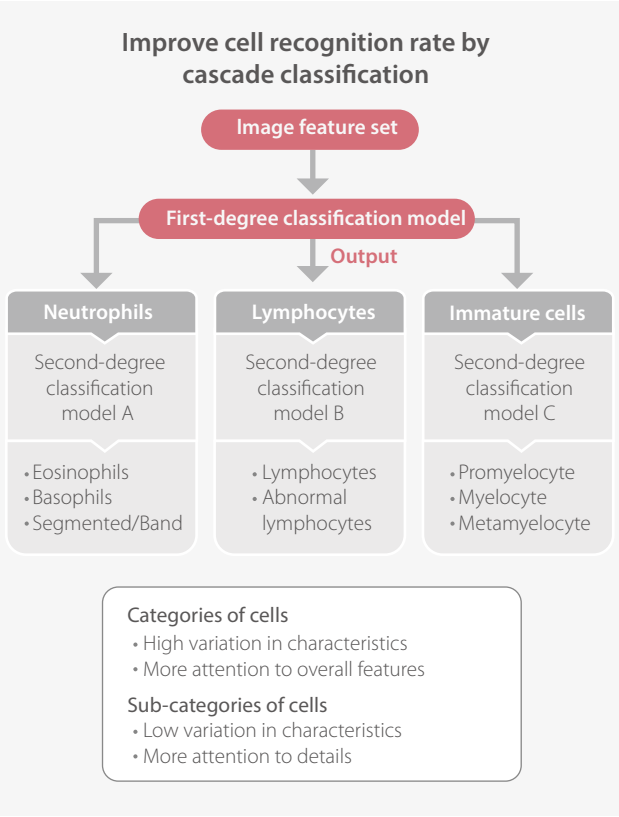
More Intelligence: delivering an all-round view of samples

Collecting cell images is just the beginning. It is then necessary to classify each cell correctly to reflect the all-around view of the sample. When analyzing manually, the classification process is often recorded once at a time by the doctor. However, as the various types of cells are similar, doctors can only classify them based on their details. Over time, errors occur, affecting the accuracy and efficiency.

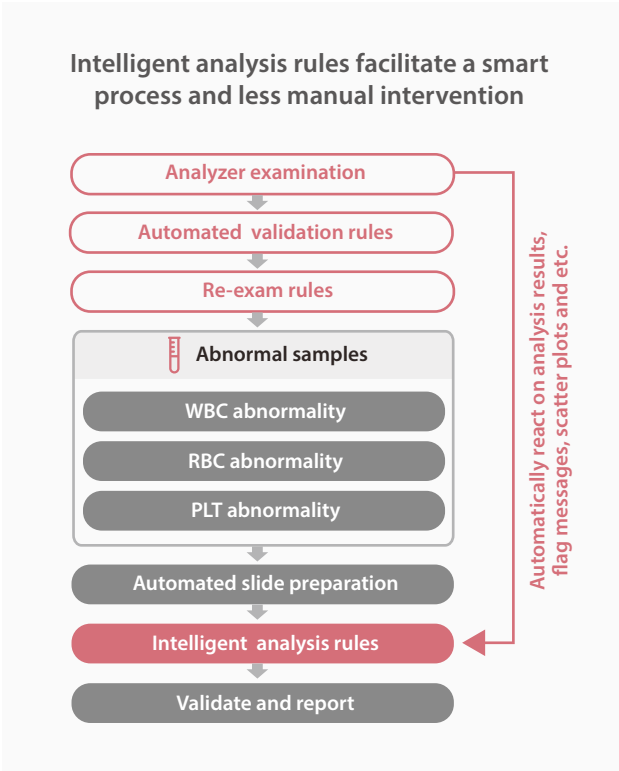


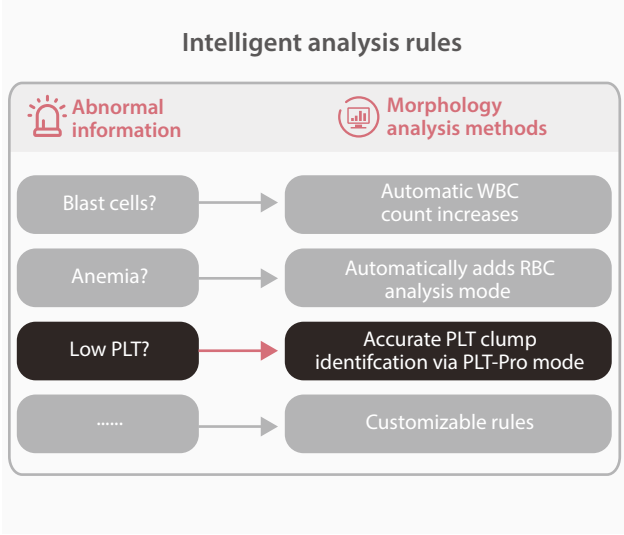
Through reliable identification and pre-classification of different types of cells, the MC-80 can accurately reflect the all-around view of the sample, helping doctors to understand the patient's true status.

Accurate recognition is based on the accurate extraction of features from the digital images of cells. With the guidance of morphology and pathology experts in the early stage, Mindray team extracts the information regarding cell color, texture, and geometric characteristics on different scales. By improving the recognition rate of cells using cascade classification, pathologists can accurately confirm the types of cells through comparison within categories and subcategories.

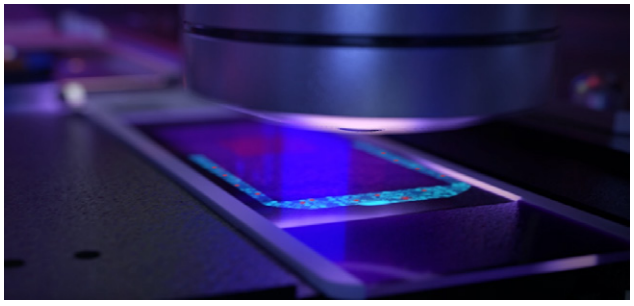


The MC-80 can intelligently adjust the analysis mode before and during the process according to the information from the cellular analysis line to improve diagnostic efficiency.





For the falsely decreased platelet counts due to clumping, the MC-80, with its unique high-speed FLY-MODE, can scan the body, both sides, and tail of the smear within one minute, accurately identifying platelet clumping, avoiding time-consuming manual confirmation.



More Productivity: improving the efficiency of morphology analysis

Until now, under stable lighting, capturing a clear image requires long exposure time and almost no camera movement. It seems that speed and clarity can't be achieved at the same time.

The same goes for cell morphology analysis. In addition to clarity, efficiency is also important for finding the truth faster. Traditional manual analysis takes 5-8 minutes for each sample. In large laboratories, the huge workload requires specialized personnel, resulting in high labor costs.

5~8 mins
Microscopic review of each sample

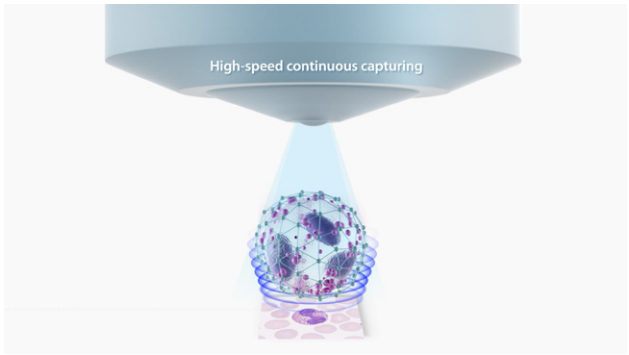
100+
Daily sample size for microscopic review

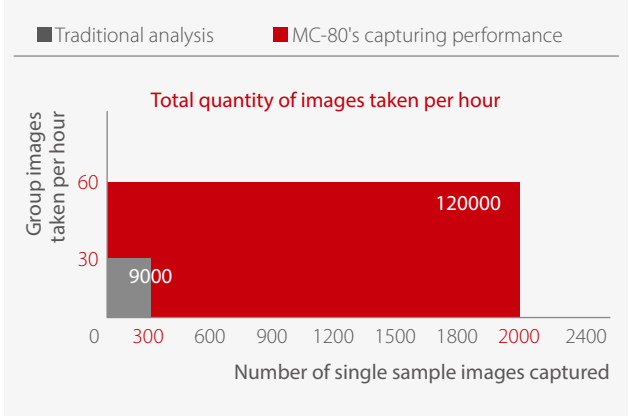
8~13 hours
Total analysis time of one microscopic expert

VS

1.5 hours
Total analysis time for MC-80

Only by completing the test faster can the microscopic examination be further popularized. Increasing cell morphology testing efficiency is a major goal in the pursuit of truth.





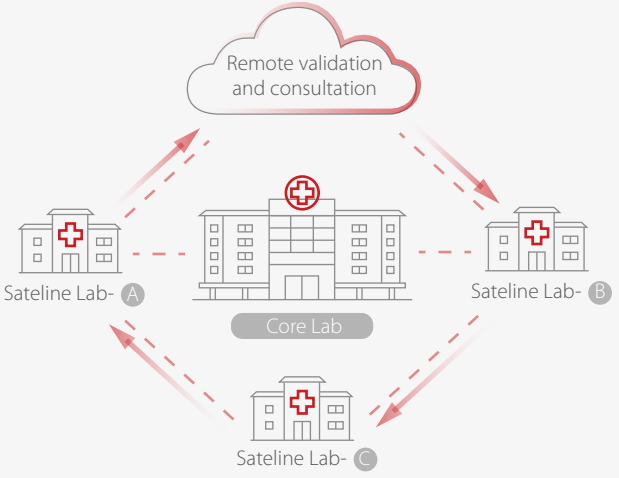
The MC-80 consistently captures cell images at a high speed, processing one sample per minute. Through flexible single-slide sampling, it can quickly generate results for urgent cases.

Compared with traditional cell analyzers, the MC-80 has many breakthrough features.

MC-80 is equipped with a built-in SOLID ROCK hyper-stable anti-shake system. After repeated verifications, the new aerospace material can provide the stiffness required by the MC-80 during high-speed motion. The stable structure and advanced high-frequency exposure algorithm can address the small horizontal and vertical perturbation to ensure fast, accurate, and reliable cell analysis.

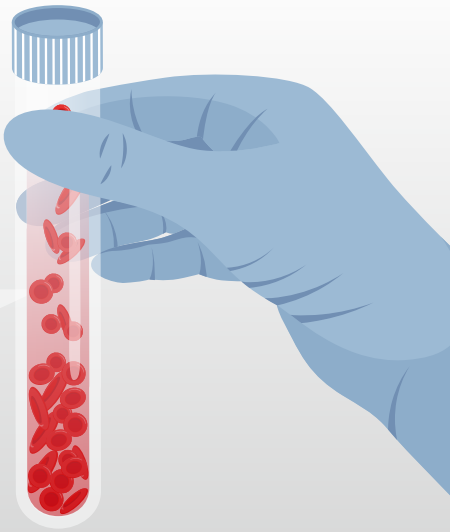
In case of technical problems during the examination, the MC-80 supports multi-terminal remote validation, allowing consultation to be immediately available.

Remote review and consultation in multiple locations



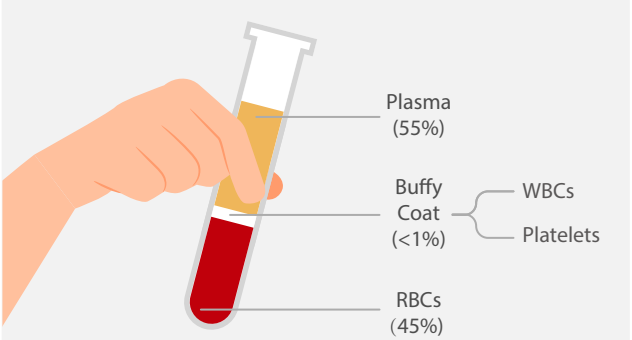
Mindray's MC-80 Automated Cell Morphology Analyzer provides more accurate and reliable morphology analysis with its industry-leading technology in the field. By addressing the key challenges in morphology analysis, Mindray provides an comprehensive auto hematology analysis solution to empower trust, delivering accurate results while meeting laboratories' demands on efficiency worldwide.

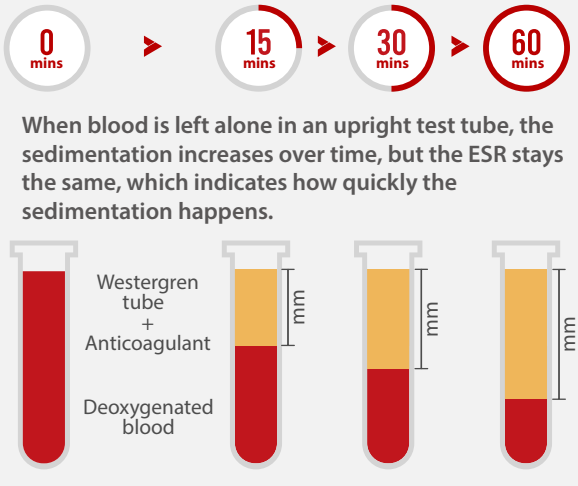
Quick Facts About Erythrocyte Sedimentation Rate (ESR) Part A

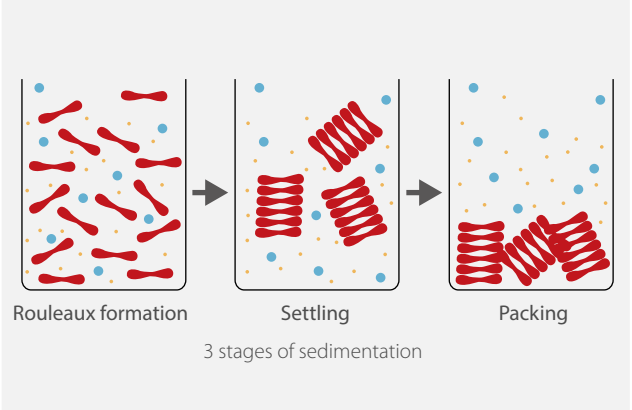


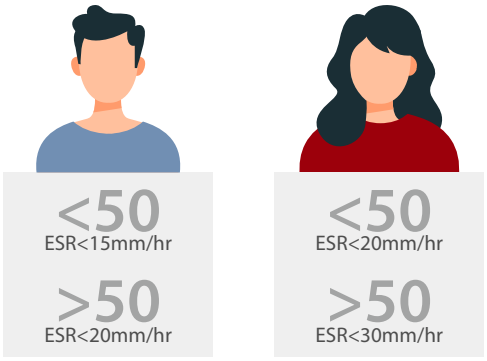
What is erythrocyte sedimentation rate

The erythrocyte sedimentation rate (ESR), which is determined by the Westergren method, measures how quickly red blood cells (RBCs) settle at the bottom of a blood sample tube in millimeters (mm) in one hour.





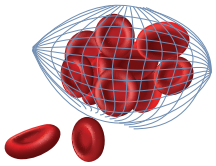




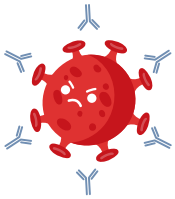
ESR increases as one gets older

Factors that affect sedimentation

Any factor that increases rouleaux formation raises the ESR



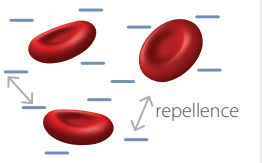
Increase in plasma fibrinogen levels → Sedimentation↑ → ESR↑

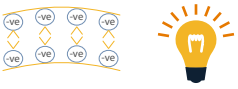


Increase in immunoglobulin levels → Sedimentation↑ → ESR↑

e.g., Increase in fibrinogen/immunoglobulin levels

Any factor that resists sedimentation decreases the ESR



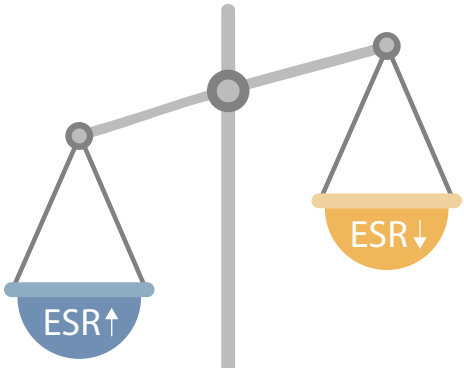


Why are there negative charges on RBCs? This is because RBCs have a cell membrane (a lipid bilayer), and the negative charges come primarily from the carbohydrates of the cell membrane.

Rouleaux formation decreases due to the negative charges on the surface of RBCs → Sedimentation↓ → ESR↓

e.g. Negative charges on the surface of RBCs

Conditions affecting the ESR

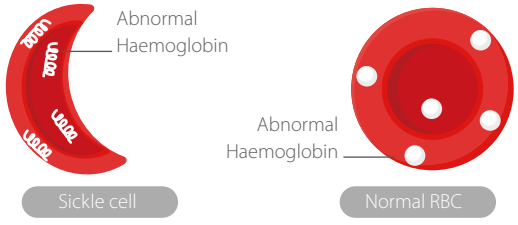


Rheumatoid arthritis → Fbg, IgG↑	Hyperviscosity syndrome → -ve or RBC↑
Infection e.g., tuberculosis → Fbg, IgG↑	Polycythemia → -ve or RBC↑
Anemia → -ve charge on RBC↓	Sickle cell → Rouleaux↓
Multiple myeloma → Rouleaux, IgG↑	Microcytosis → Rouleaux↓
Waldenstrom macroglobulinemia → IgM↑	Spherocytosis → Rouleaux↓

Before we move onto the next lesson, here are some take-home messages for you.

In general, ESR has higher sensitivity and negative predictive value (NPV) but lower specificity and positive predictive value (PPV).

- ESR is a very important means to rule out giant cell arteritis.
- In sickle cell disease → asymptomatic → ESR↓
  painful crises → inflammation → Fibrinogen↑ → ESR↑
- In sickle cell frait → no sickle cells → normal ESR



- Both ESR and CRP will be detected to elevate in the case of any inflammation.
- ESR starts to rise 24-48 hours after onset of inflammation.
- ESR elevation is one of the minor criteria for diagnosis of rheumatic fever.

Mindray is soon going to launch a new hematology series that incorporates both CBC and ESR analysis. Stay tuned for its global launch lunch event on March 1st!

References

[1] Aldo F.F.R, Luiz J.S. Alteration in the Erythrocyte Sedimentation Rate in Dengue Patients: Analysis of 1,398 Cases The Brazilian journal of infectious diseases: an official publication of the Brazilian Society of Infectious Diseases Med 2009;12(6):472-5.

[2]. https://labtestsonline.org.uk/tests/erythrocyte- sedimentation-rate-esr

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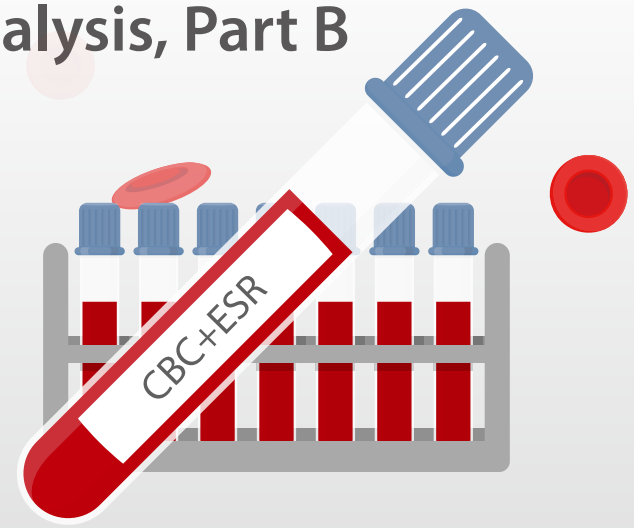
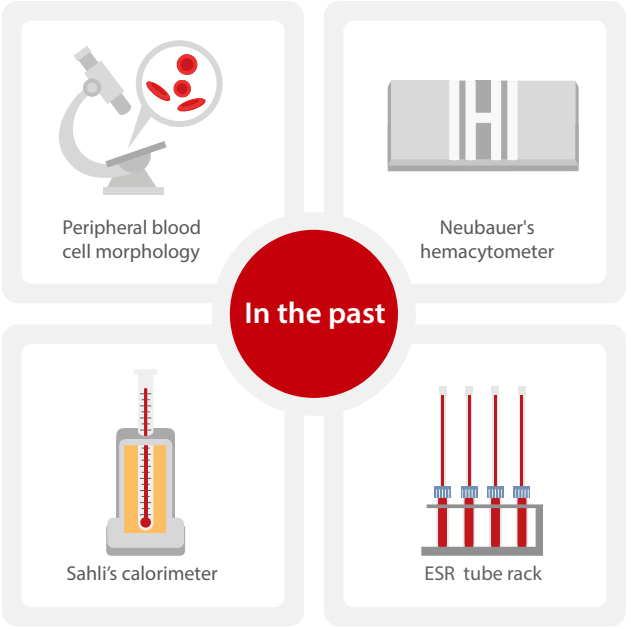
Applications of CBC, ESR and CRP Analysis, Part B



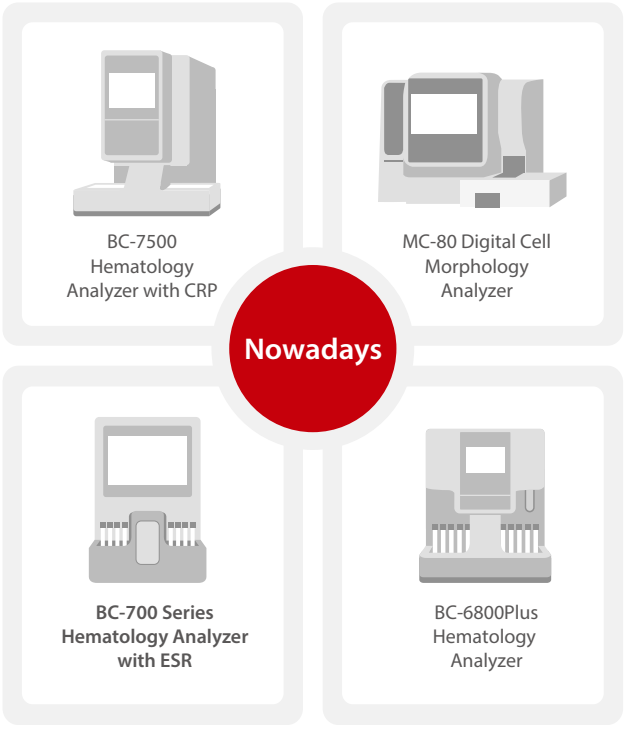
Three routine laboratory tests

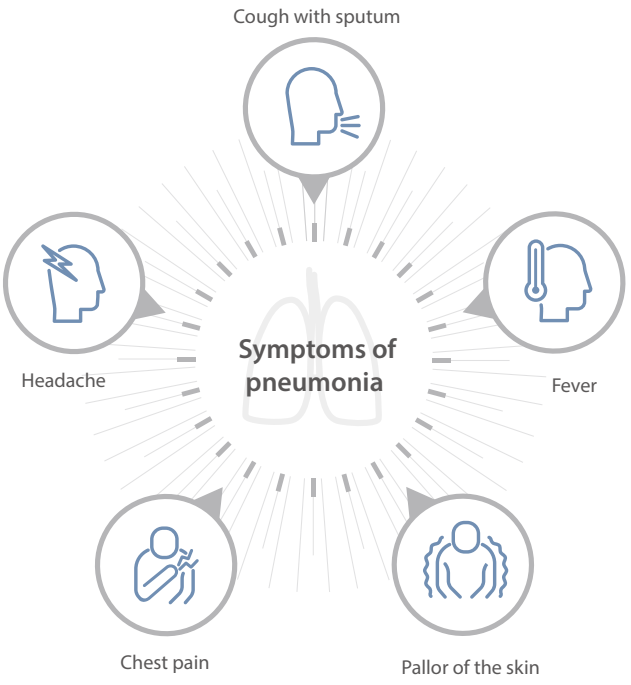
Blood, urine and feces analysis are the three common tests in clinical laboratories. Among them, blood testing is the most important way to keep track of one's overall physical well-being.

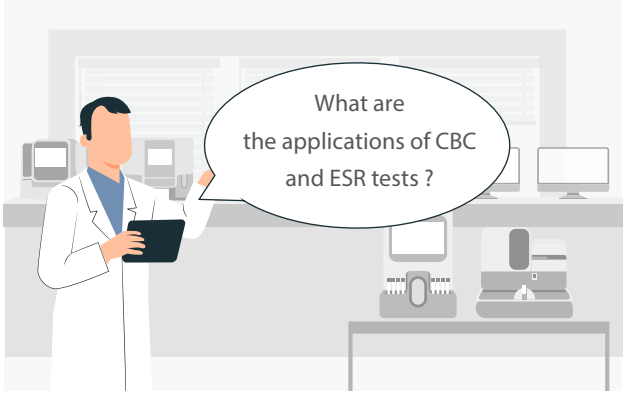
In the past, routine blood tests were performed manually on a microscope, Neubauer's hemacytometer, Sahli's colorimeter and ESR tube rack.



In addition to complete blood count (CBC) and white blood cell differential (DIFF) count which have become fully automated, other simple but time-consuming blood tests like ESR and CRP also transform from manual methods to automated analysis. Integrated systems have been developed for easier operation.

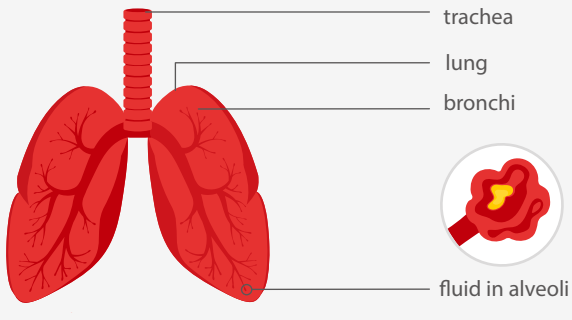






Diagnosis of pulmonary diseases

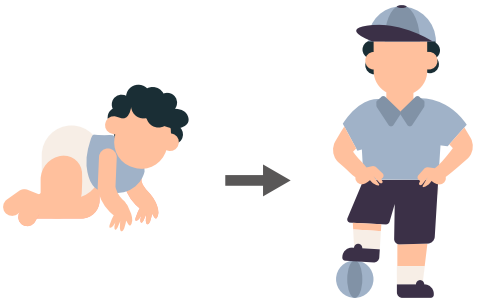
Pneumonia of the lungs



Study A

A comparison of different investigations in their sensitivities for the diagnosis of Community Acquired Pneumonia (CAP)

Age group

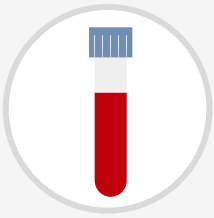


One-month to 5-year old

Diagnostic methods

Chest radiographs

Blood culture



serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total leucocyte count (TLC)

Results

Diagnostic method	Positive +ve	N=? (Total n= 66)
Chest radiographs	93.9%	62
Blood culture	6.1%	4
CRP	90.9%	60
ESR	72.7%	42
TLC	48.5%	38

Conclusion

Both CRP and ESR analysis can be used as an alternative test to the chest radiographs at peripheral centres, where X-ray machines are not available.

Study B

Elevated Erythrocyte Sedimentation Rate Is Predictive of Interstitial Lung Disease and Mortality in Dermatomyositis: A Korean Retrospective Cohort Study

Age group

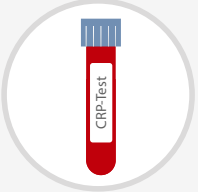
Interstitial lung disease (ILD) is a major cause of death in patients with dermatomyositis (DM). This study was aimed to examine the utility of the erythrocyte sedimentation rate (ESR) as a predictor of ILD and prognostic marker of mortality in patients with DM.

Target group

144 patients with DM, including 28 with clinically amyopathic DM (CADM).

Methods

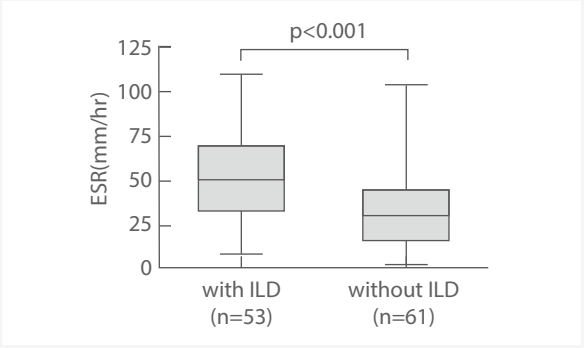
Diagnosis of ILD: High resolution computed tomography (HRCT) scans



Examination of the association between elevated ESR and pulmonary impairment and mortality

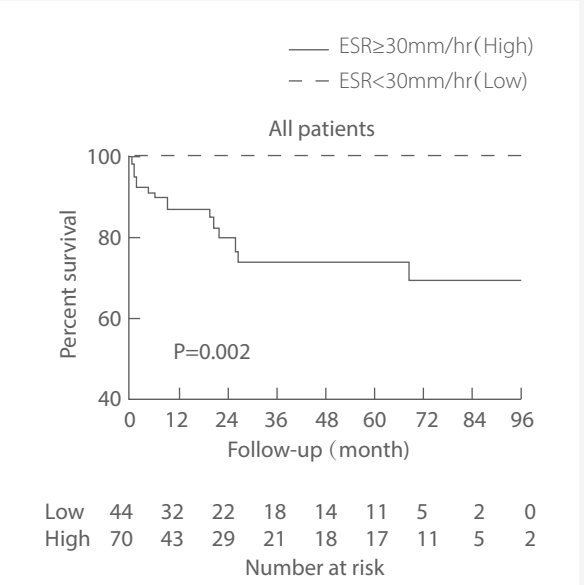
Results

Association between elevation of the baseline ESR and pulmonary impairment in patients with DM.



ESR levels at the time of DM diagnosis were higher in patients with ILD than in those without.

Elevated ESR was predictive of mortality.



All-cause mortality for patients with a baseline ESR ≥ 30 mm/hour was higher than that for patients with a baseline ESR < 30 mm/hour. No deaths were observed in DM patients with a normal baseline ESR, even after 8 years of follow-up.

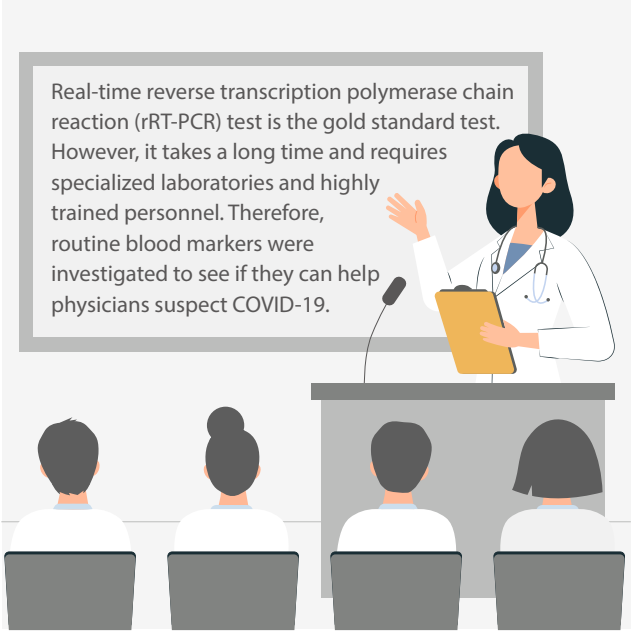
Conclusion

Elevated ESR is associated with increased mortality in patients with DM due to respiratory failure. Thus, monitoring ESR should be an integral part of the clinical care of DM patients.

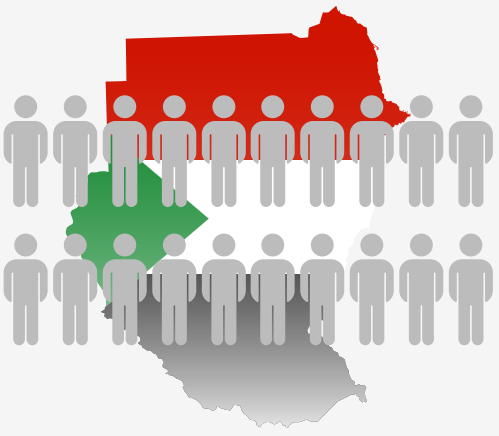
Applications in covid-19

Study C

Blood markers (percentage of lymophocytes, neutrophils, CRP and ESR can help prioritize RT-PCR testing in patients suspected of Covid-19 in countries with limited health resources

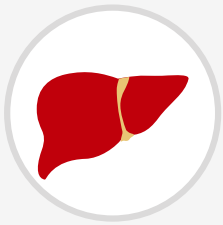


Target group

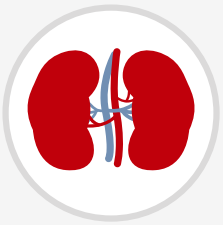


56 COVID-19 patients from Sudan

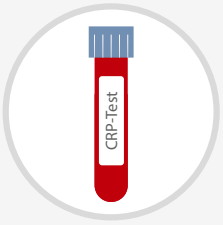
Methods



liver function tests (LFT)



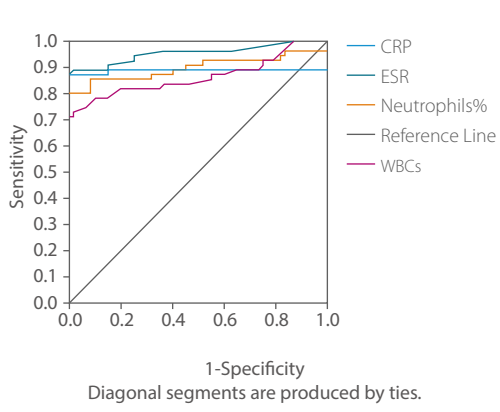
renal function tests (RFT)



complete blood count (CBC), CRP, ESR

Results

Lymphocytes % showed decrease to 9.2 (P-value=0.000) and significant increase in neutrophils to 83.05 (P-value=0.005), ESR to 65.54 (P-value=0.000) and CRP to 91.07 (P-value=0.000).



Diagonal segments are produced by ties.

The receiver operating characteristic curve (ROC)/area under the curve (AUC) ensured the expellant result of lymphocytes % as a predictor with 92% area under the curve, neutrophils were 90% and ESR 95.8%.

The percent of detecting COVID-19 positive RT-PCR (98%) for suspected individuals using ROC showed best cutoff of ≤21.8 for lymphocytes %, ≥ 67.7 for neutrophils, ≥37.5 for ESR, ≥6.2 for CRP and ≥7.15 for WBCs.

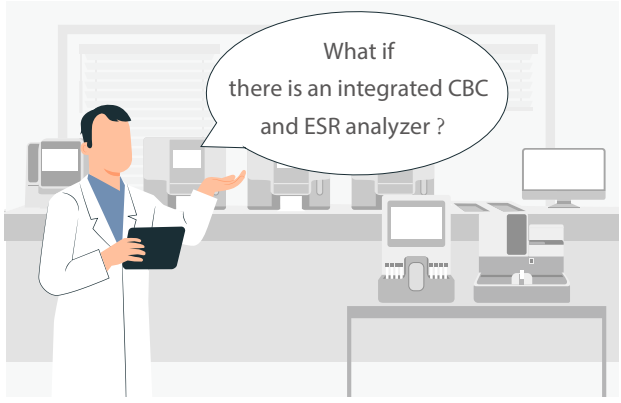
Conclusion

Lymphocyte percentages, neutrophils, CRP and ESR can be used as markers for COVID-19, helping in prioritizing individuals for rRT-PCR tests.

Diagnostic value of combined ESR and WBC tests for inflammation

- ESR and CRP are traditional biomarkers of inflammation.
- Elevated levels only indicate that there is a focus of inflammation somewhere in the body, but the tests cannot pinpoint the exact location of inflammation.
- ESR and CRP can be used as routine aides to detect inflammation and monitor treatment effectiveness.
- After high levels are detected, the patient should undergo reexamination every 1 to 3 months to help determine whether the treatment is successful in reducing inflammation.

Relationship between the change of inflammatory markers (WBC, ESR and CRP) and the use of antibiotics during hospitalization.



Mindray is going to launch a new hematology series that incorporates both CBC and ESR analysis. Stay tuned for our global launch lunch event on March 2 !

Registration link to the BC-700 Series Hematology Analyzer Virtual Launch Event:
https://www.mindray.com/en/events/bc-700-launch

References

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HemaBook
Chapter 16

World Malaria Day April 25

Quick Facts about Malaria

According to the World Health Organization (WHO), there were an estimated 241 million cases of malaria worldwide in 2020, and the estimated number of malaria deaths stood at 627,000 in that year. The African Region was home to 95% of malaria cases and 96% of malaria deaths. Children under 5 accounted for an estimated 80% of all malaria deaths in the Region.1

Source: World Health Organization

Diagnostic Gold Standard

In the guidelines of the Centers for Disease Control and Prevention (CDC), malaria can be diagnosed using three common methods: microscopy, rapid diagnostic test (RDTs), and serology. Microscopic examination remains the "gold standard" for laboratory confirmation of malaria. Species determination is based on the morphological characteristics of the four species of human malaria parasites and the infected red blood cells. In addition, all positive RDTs should be followed by microscopy.

Three common methods for malaria detection

These tests should be performed immediately without delay when ordered by a health-care provider. It is vital that health-care providers receive results from these tests within hours in order to appropriately treat their patients infected with malaria.2

However, many factors can influence a laboratory's choice of microscopy as a diagnostic tool for malaria, including the skills of laboratory staff, patient sample testing load, and epidemiology of malaria and possible use of microscopy for other diseases.3

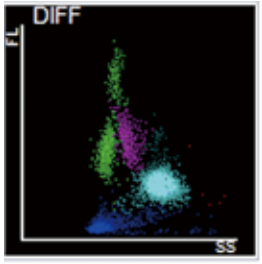
Quick, easy and clear visualization of parasites in blood cells through microscopy is key.

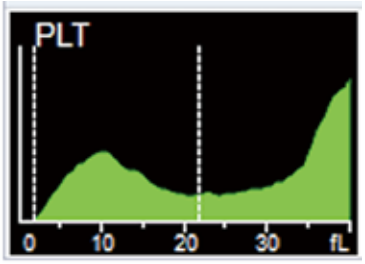
A Clinical Case Study

In Europe, around 8,000 cases of imported malaria are reported every year, the majority due to Plasmodium falciparum (P. falciparum).4 The rise in malaria infections has become a concern of Spain.5 6 It is important to get diagnosis clues through the microscopic results from front-line checks, so doctors can act quickly and provide effective treatment for the infected immigrants and summer travelers.

Dr. Anna Merino from the Core Laboratory, Hospital Clinic, in Barcelona, Spain, shared a recent case in her laboratory.

A 48-year-old man was admitted to the hospital with a high fever. A blood cell check was done on the Mindray BC-6800Plus hematology analyzer. The low platelet count result (66 x 109/L) and flags on immature granulocytes, atypical lymphocytes, and an abnormal PLT histogram triggered the re-exam rules.

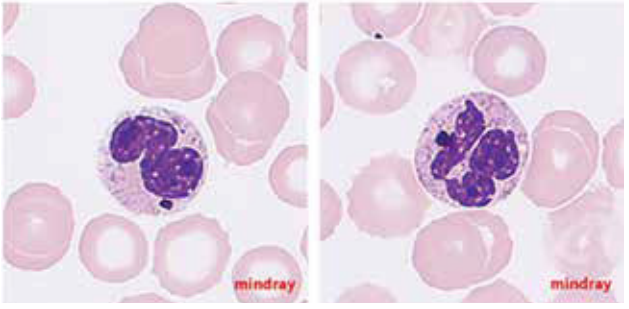




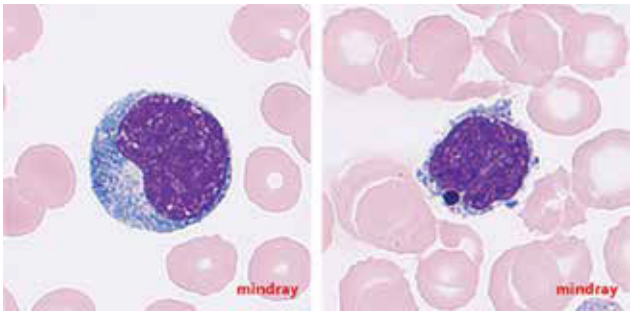
Therefore, a blood smear test was performed on the Mindray SC-120 Auto Slide Marker and Stainer. Then, the smear was loaded onto the MC-80 automatic digital morphology system. A couple of minutes later, the scanning was completed.

Mindray MC-80 Digital Cell Morphology Analyzer

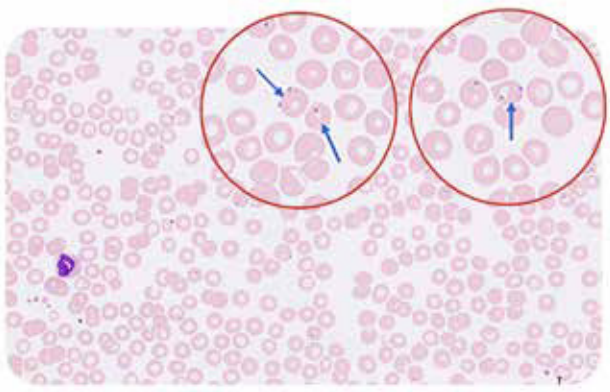
Several important morphological findings were revealed in validating the cells. The presence of inclusions within red blood cells (RBCs) was the first and most important finding, which corresponded to malaria-derived parasites. Another important finding was the malaria-derived pigments inside of neutrophils (Maurer pigments).



Atypical lymphocytes, as flagged by the hematology analyzer, were found in the smear. Some lymphocytes also contained malaria-derived pigments.



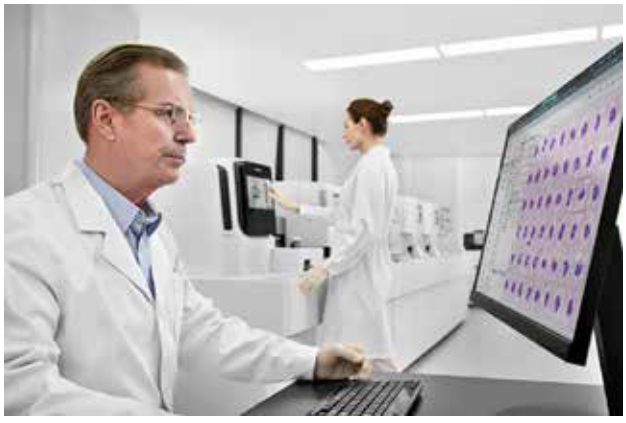
With a careful look at the RBC scanning screen, several infected RBCs could be found (indicated by the arrows).



RBC scanning screen with arrow marks

From Dr. Anna Merino's experience: "The image clearly shows a blood sample corresponding to a patient infected by malaria (P. falciparum species) as we can observe two or more parasites inside RBCs and two dots of chromatin." A quick report was made and handed to the clinicians. The anaylysis of a thick drop in the microbiology laboratory confirmed the diagnosis. During the following medical consulation, the patient admitted that he once travelled to the Ivory coast in western Africa. The patient received treatment with Artesunate (Eurartesim(R) 320/40 mg) immediately and recovered quickly as expected.

As a new digital morphology system, the Mindray MC-80 provides faster scanning and clearer visualization of the conditions to facilitate the traditional microscopic examination, enabling accurate diagnosis and effective treatment through modern clinical testing procedures.



References:

[1] https://www.who.int/news-room/fact-sheets/detail/malaria

[2] https://www.cdc.gov/malaria/diagnosis_treatment/diagnostic_tools.html

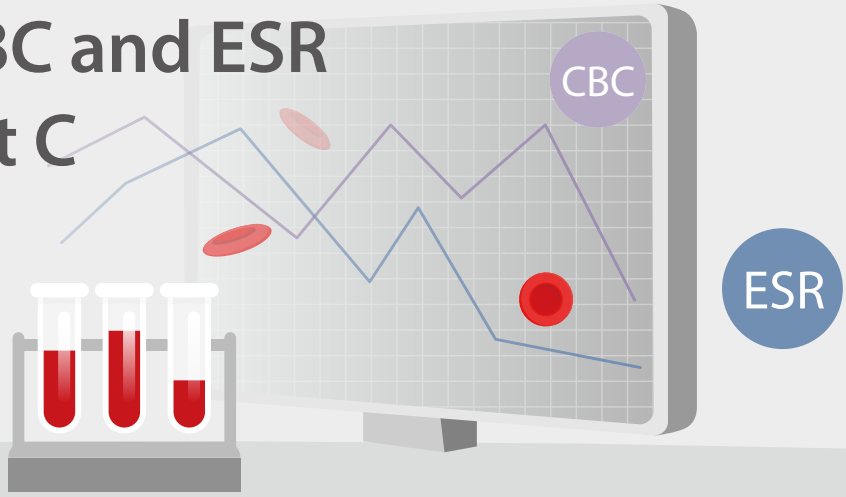
[3] Ngasala, B., Bushukatale, S. Evaluation of malaria microscopy diagnostic performance at private health facilities in Tanzania. Malar J 18, 375 (2019).

[4] European Centre for Disease Prevention and Control. Malaria. In: ECDC. Annual epidemiological report for 2018. Stockholm: ECDC; 2020.

[5] Pousibet-Puerto, J., Lozano-Serrano, A.B., Soriano-Pérez, M.J. et al. Migration-associated malaria from Africa in southern Spain. Parasites Vectors 14, 240 (2021).

[6] Domínguez García, M., Feja Solana, C., Vergara Ugarriza, A. et al. Imported malaria cases: the connection with the European ex-colonies. Malar J 18, 397 (2019).

The clinical significance of all-in-one CBC and ESR analysis, Part C



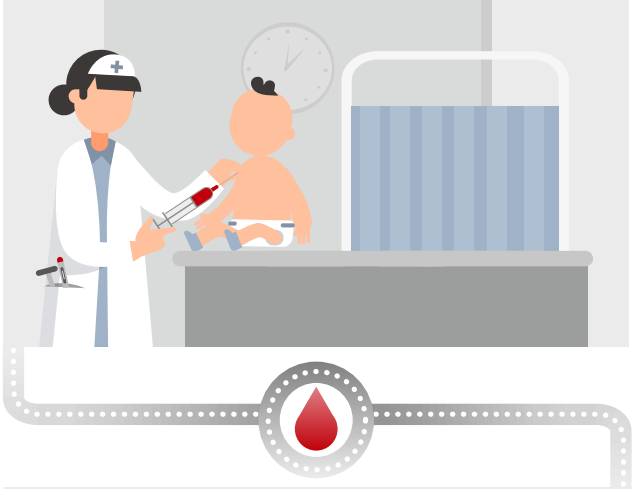
In the last two chapters, we talked about what ESR is and the applications of ESR, CRP and CBC analysis. ESR is an acute phase reactant and serves as a marker for inflammation. It correlates with disease activity and response to therapy. We understand that single tests are not adequate to confirm any diagnosis, but they do give us important clues.

Today, all these tests can be performed via an automated analyzer. You do not have to do this by yourself anymore. This helps to streamline the workflow of the laboratory and allows patients to get the diagnosis in the earliest time possible.

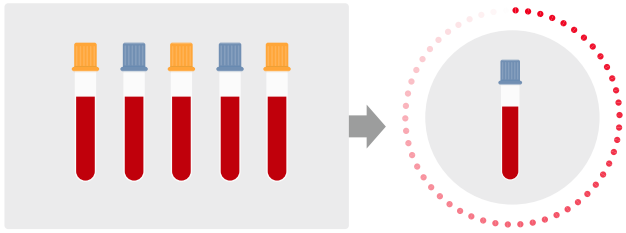
So, what are the advantages of automated measurement of ESR with CBC in one analysis from clinical laboratory perspectives?

Advantages from clinical laboratory perspectives

Reducing the volume of blood to draw from patients, especially for children and the elderly



Only one tube of blood is required for ESR and CBC tests, reducing the workload of blood drawing and labor & consumables costs



Simplified workflow

Integrated ERS machine Vs. manual ERS method in workflow

CBC analysis first

Followed by ESR (instrument method)		Followed by ESR (manual method)	
Registration of the samples	01		
	02	Code scanning/ number input	
Sample loading	03		
	04	Analysis	
Identifying the samples to undergo ESR test	05		
	06	RCBC review and reporting	
	07		Acceptance
Code scanning/ number input	07		
	08		Code scanning/ number input
Mixing well	08		
	09		Mixing well
Cap opening	09		
	11		Cap opening
Sample loading	10		
	12		Aspiration
Test	11		
	13		Fixation
Cap covering	12		
	14		Letting stand for 1 hour
Sorting and back into plate	13		
	15		ESR review and reporting
	16		Back into plate
ESR review and reporting	14		
	17		Manual report input

For manual method

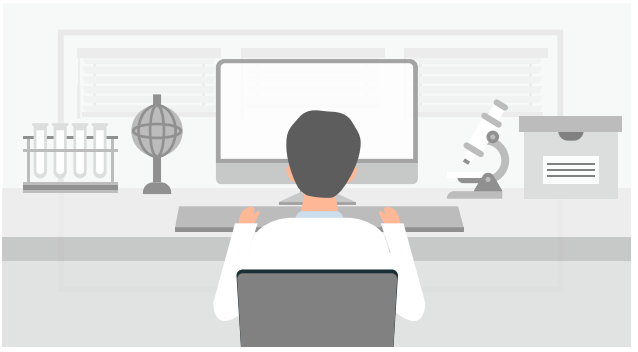
- Additional tubes
- Additional manpower
- Time consuming
- Potential biosafety hazards due to the blood exposure during the whole process

For instrument method

- Additional instrument cost
- Additional maintenance cost

Shortening the turnaround time (TAT)

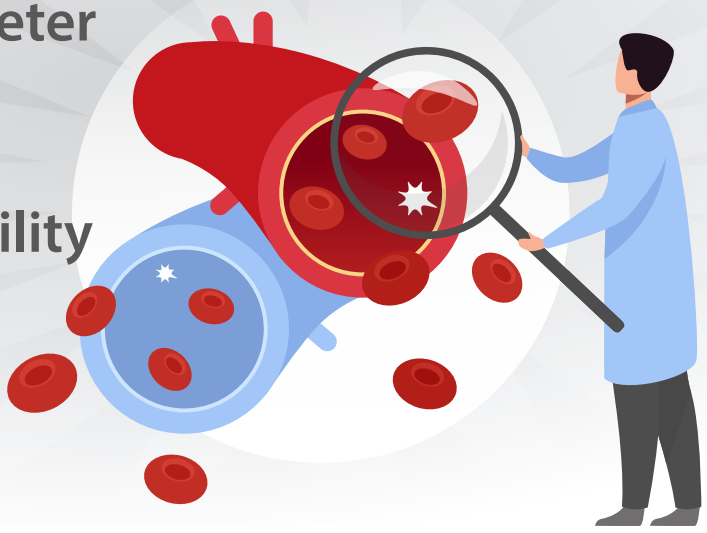
Avoiding manual input of incorrect results



CBC and other parameters as well as ESR results will be combined, and true negative samples will be automatically validated and then transmitted to the LIS. Lab technicians only need to verify the abnormal results.

Mindray has launched the new BC-700 Series, a revolutionary hematology analyzer series that incorporates both CBC and ESR tests. This series, including two open vial models BC-700/BC-720 and two autoloader models BC-760/BC-780, is designed to empower medium-volume laboratories with advanced diagnostics technologies that are applied in the premium products.

PLT-H: A new parameter for accurate platelet counting with anti-interference ability



Hemostasis and coagulation are the main functions of platelets (PLTs). Thrombocytopenia is a common cause of bleeding. A PLT count from 20 to 50×10^9/L may indicate mild or surgical bleeding. If it is lower than 20×10^9/L, this may indicate severe bleeding. If it reduces to 5×10^9/L or lower, the patient may be experiencing a life-threatening condition.

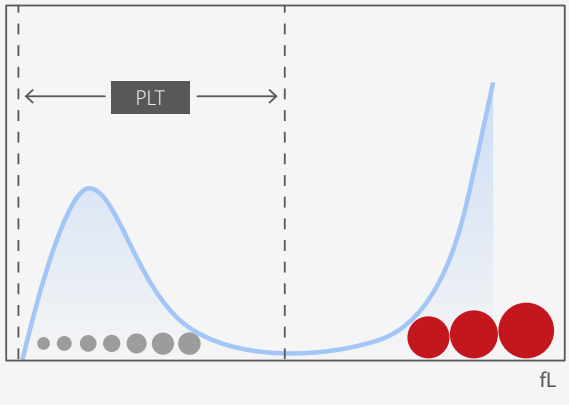
Nowadays, laboratories usually count PLTs by using automatic hematology analyzers, which work based on various methods with different characteristics.

Conventional impedance methods (PLT-I)

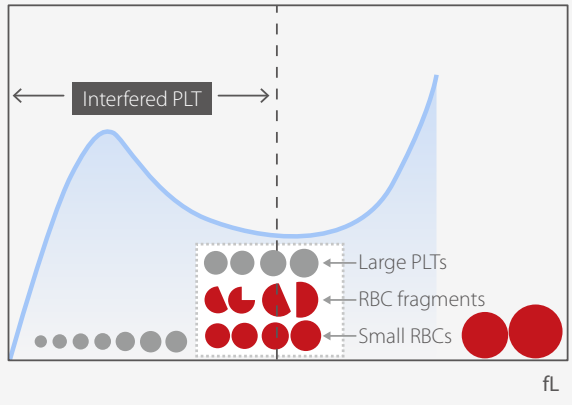
PLTs and red blood cells (RBCs) can be distinguished by the magnitude of the electrical impedance signal in normal samples. However, PLT-I is subject to the interference of microcytic RBCs, fragments, and large PLTs when it is used to differentiate PLTs by cell volume.

When microcytic RBCs and fragments are present in the blood, the result of PLT-I will be falsely high due to the interference of RBCs; when large PLTs or PLT aggregations are present in the blood, the PLT measurement result will be falsely low.

Histogram of PLT counts by the impedance method in normal samples



Histogram of PLT counts by the impedance method with interferences of small RBCs, RBC fragments and large PLTs

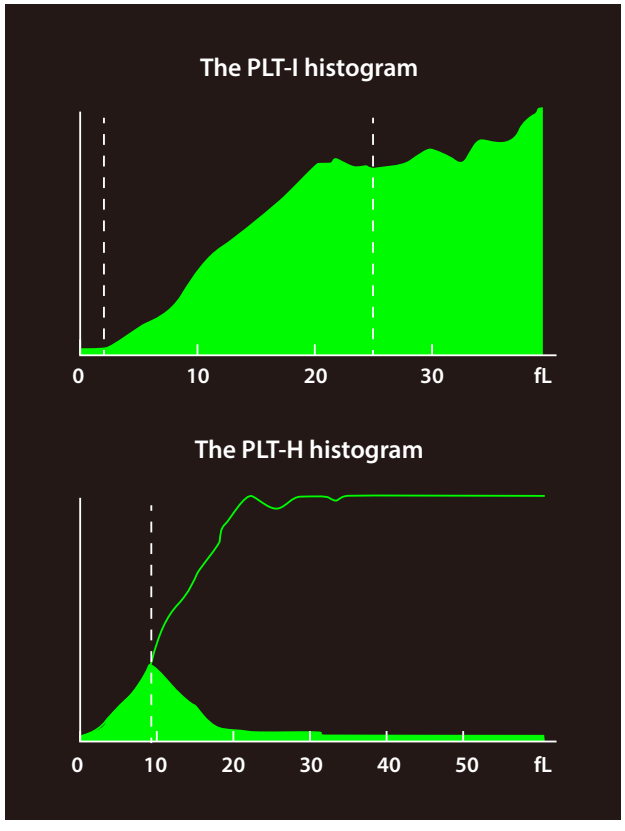


Although the PLT-O (optical platelet) method can be used to avoid the above inferences, it requires additional reagents for the analysis. PLT-H is a new parameter provided by Mindray BC-700 Series that can resist interferences in conventional PLT detection and requires no extra reagents in every CBC and DIFF analysis. Let's take a look at how PLT-H provides accurate PLT measurement results.

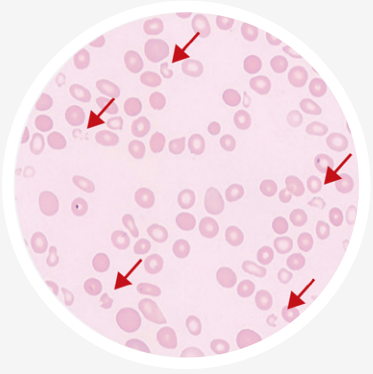
Clinical case study 1

A patient with acute lymphoblastic leukemia, hospitalized for 11 months, was undergoing chemotherapy and preparing for bone marrow transplantation.

CBC results from BC-700 Series	
RBC	3.23x10^{12}/L
HGB	87g/L
MCV	76.7fL
RFC%	7.5%
PLT-I	77×10^{9}/L
PLT-H	29×10^{9}/L



Microscopic examination revealed evident RBC fragments (arrows) in multiple high-power lens.



Method	PLT-I	PLT-H	Flow cytometry (FCM)
PLT(x10^{9}/L)	77	29	27

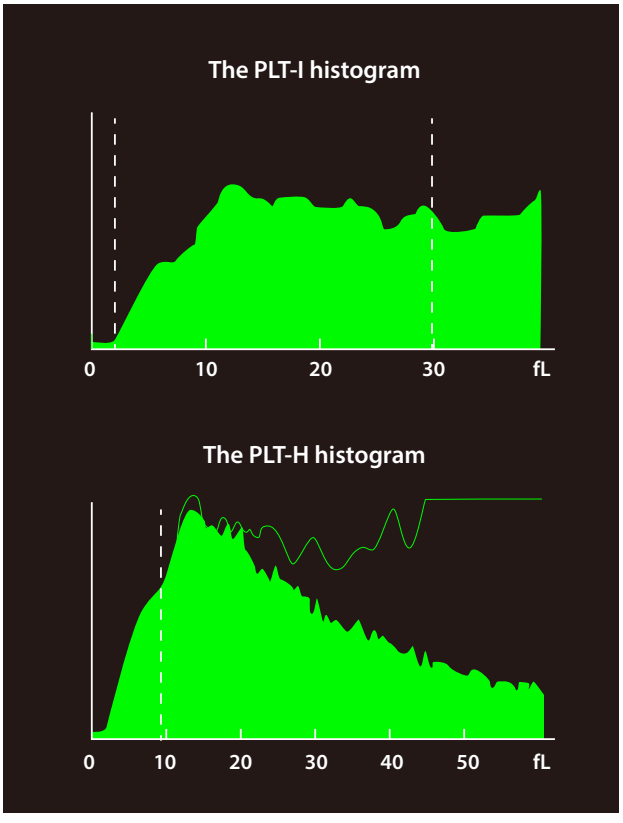
The PLT count measured by flow cytometry was 27X10^{9}/L, which was consistent with that by PLT-H.

In this case, an RBC fragments alarm was triggered in the instrument, and the FRC value was 7.5%. The tail of the PLT histogram was elevated, suggesting that RBC fragments may be present in this sample, which would cause a false high value in PLT. During chemotherapy, patients usually exhibit a decrease in whole blood cells and an increase in cell fragility. Despite the presence of RBC fragments, PLT-H can accurately measure the PLT count and monitor the risk of bleeding in a timely manner.

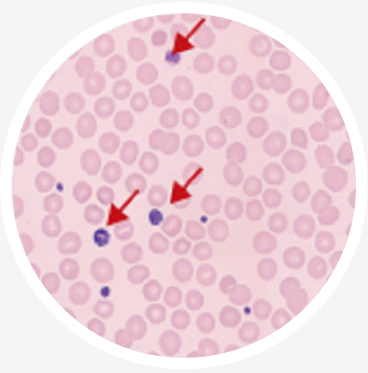
Clinical case study 2

A patient with systematic lupus erythematosus revisited the hospital and got checked by Mindray BC-700 Series hematology analyzer.

CBC results from BC-700 Series	
MCV	98.8fL
MPV	17.0fL
P-LCR	75.2%
PLT-I	52×10^9/L
PLT-H	89×10^9/L



Microscopic examination revealed evident large PLTs (arrows) having a similar size to the RBCs in multiple high-power lens.



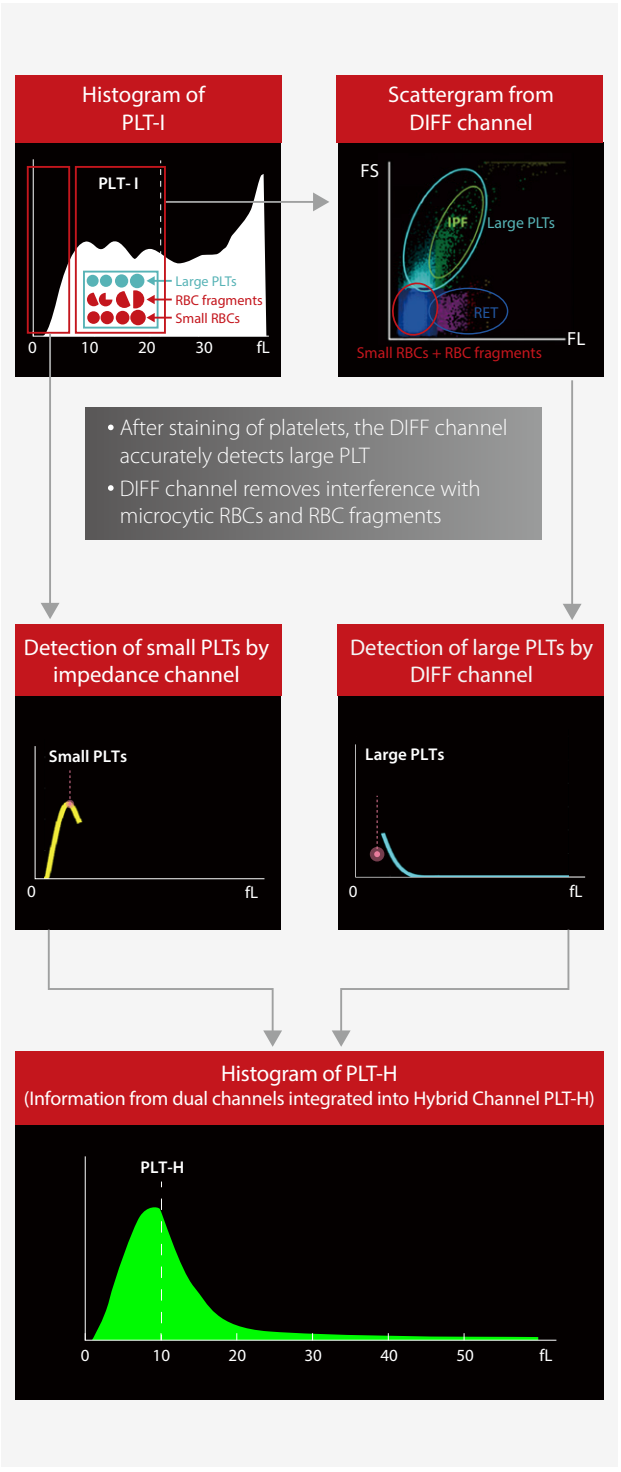
Method	PLT-I	PLT-H	Flow cytometry (FCM)
PLT(x10^9/L)	52	89	90

The PLT count measured by flow cytometry was 90X10^9/L, which was consistent with that by PLT-H.

In this case, the MPV and P-LCR values increased significantly. The tail of the PLT histogram was elevated, suggesting that large PLTs may be present in this sample, which would cause a pseudo-thrombocytopenia. The information obtained from the DIFF channel can ensure the accurate detection of large PLTs, avoiding unnecessary blood transfusion.

Principle of brand-new parameter - PLT-H

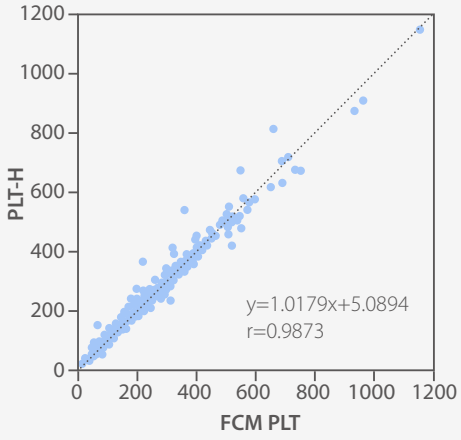
From the impedance channel, the large PLTs are interfered by microcytic RBCs and fragments, but the small ones are not. From the DIFF channel, the RBCs are dissolved by specific reagents, the PLT structure remains intact, and large PLTs are detected by the precise optical methodology. By combining the small PLTs from the conventional impedance method and the large ones from the optical method, an accurate PLT count will be obtained.



In Thailand, 405 PLT samples were collected(excluding aggregation samples). As revealed by microscopic examination, 200 samples contained interfering factors, including large PLTs, microcytic RBCs and RBC fragments. The PLTs were detected by Mindray BC-760 and BD flow cytometers, respectively. BC-760 PLT-H had a good correlation with flow cytometry (r=0.9873, y=1.0179x+5.0894).

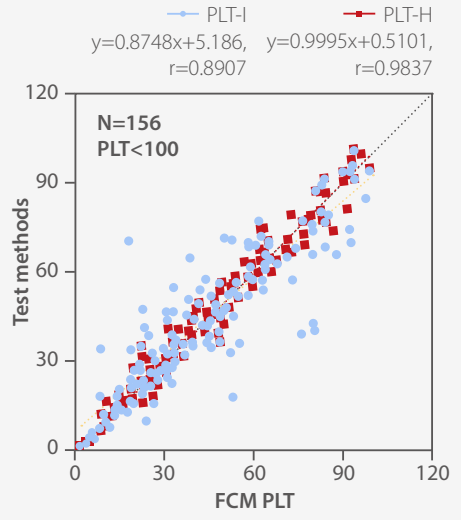
Correlation between PLT-H and flow cytometry (reference method)

Flow cytometry is the reference method recommended by ICSH.



156 low PLT count [Please confrm the correct term.] samples were selected. Using flow detection (CD41+CD61) as the reference method, the correlation between PLT-H and PLT-I in the low-count [Please confirm the correct term.] segment of Mindray's hematology analyzer was analyzed, as shown in the figure. It can be seen from that PLT-H has a strong correlation with flow cytometry (r=0.9837, y=0.9995x+0.5101).

Comparison of low PLT count [Please confirm the term.] samples and flow correlation



In conclusion, the use of PLT-H technology can significantly reduce the inaccurate counts caused by the interferences of RBC fragments, large PLTs, and small RBCs, helping greatly in generating accurate and reliable PLT detection reports for clinical purposes.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BC-6200
CAL 6000


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SC-120
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BC-6200
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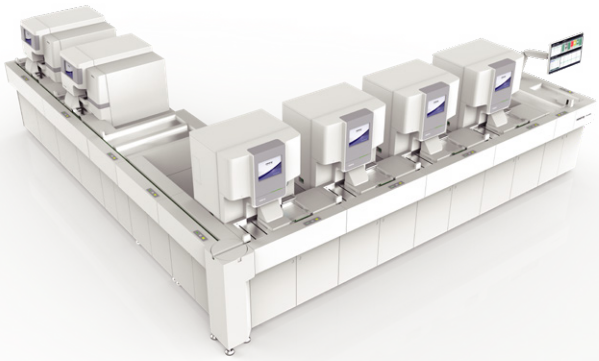
CAL 6000



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