烏日林新醫院
Wuri Lin Shin Hospital

新冠肺炎疫情下Ret-He & IPF在貧血與血小板低下的臨床應用

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(Aug. 01, 2021)

Outline

- Introduction
  - Why we need Ret-He & IPF tests?
- Ret-He for anemia patients
  - DDx and Application
- IPF% for thrombocytopenia and COVID-19
  - DDx, Monitoring, and Application
  - IPF marker in COVID-19
- Summary

Why we need Ret-He & IPF tests?

- ★ Anemia: Ret-He (Reticulocyte Hemoglobin)
  - Diagnosis- 不耐久候、即刻確診
  - Treatment- 不願回診、要求慢簽
- ★ Thrombocytopenia: IPF (Immature Platelet Fract.)
  - Diagnosis- 打疫苗怕血栓、不打又怕重症
  - Treatment- 需要吃類固醇嗎？可不可以停藥
  - Monitoring-定期追蹤血小板、出血風險？
- ★ 結論：需要簡單判讀、快速報告的Marker

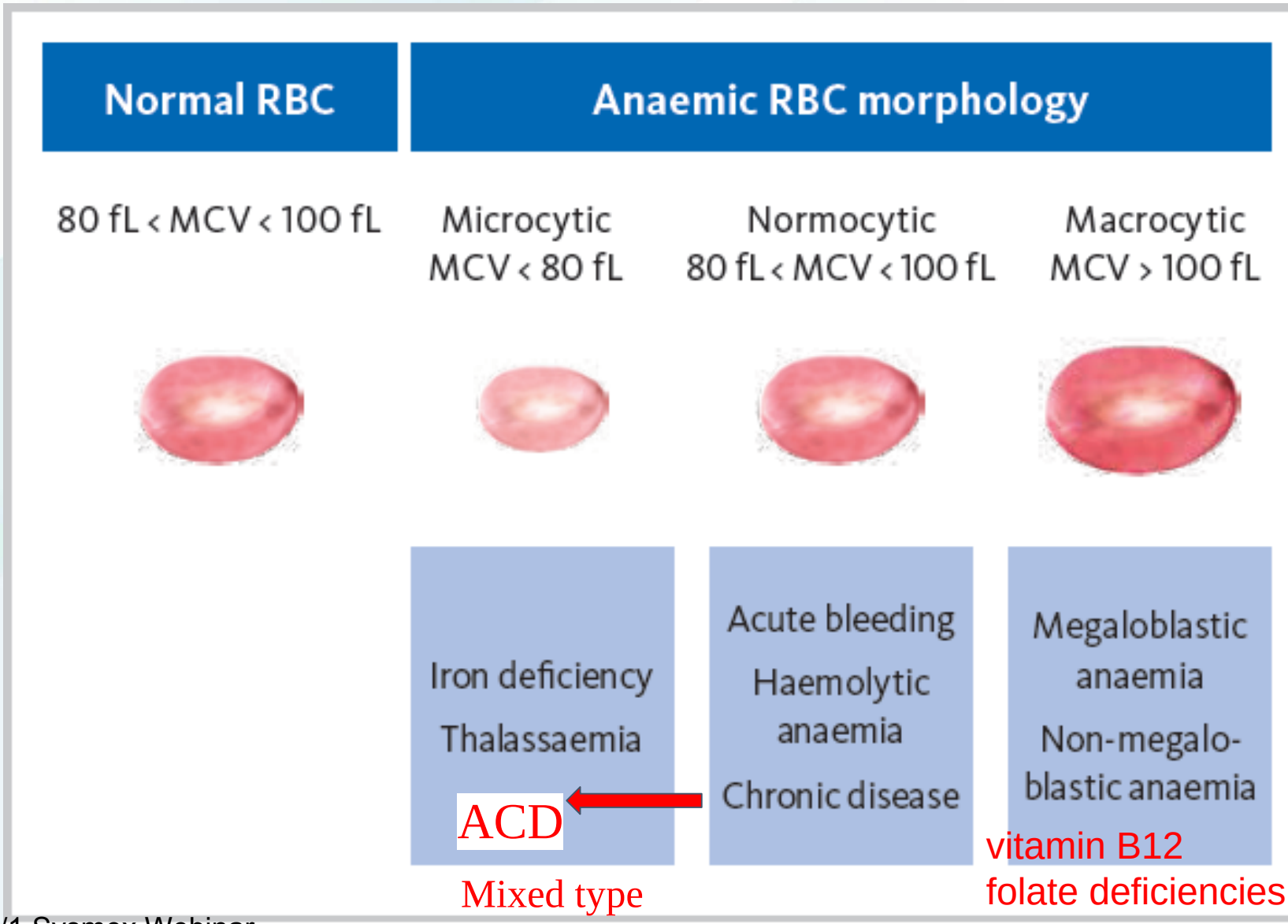
Anemia- WHO criteria

Population	Non -Anaemia*	Anaemia*		
		Mild[a]	Moderate	Severe
Children 6 - 59 months of age	110 or higher	100-109	70-99	lower than 70
Children 5 - 11 years of age	115 or higher	110-114	80-109	lower than 80
Children 12 - 14 years of age	120 or higher	110-119	80-109	lower than 80
Non-pregnant women (15 years of age and above)	120 or higher	110-119	80-109	lower than 80
Pregnant women	110 or higher	100-109	70-99	lower than 70
Men (15 years of age and above)	130 or higher	110-129	80-109	lower than 80

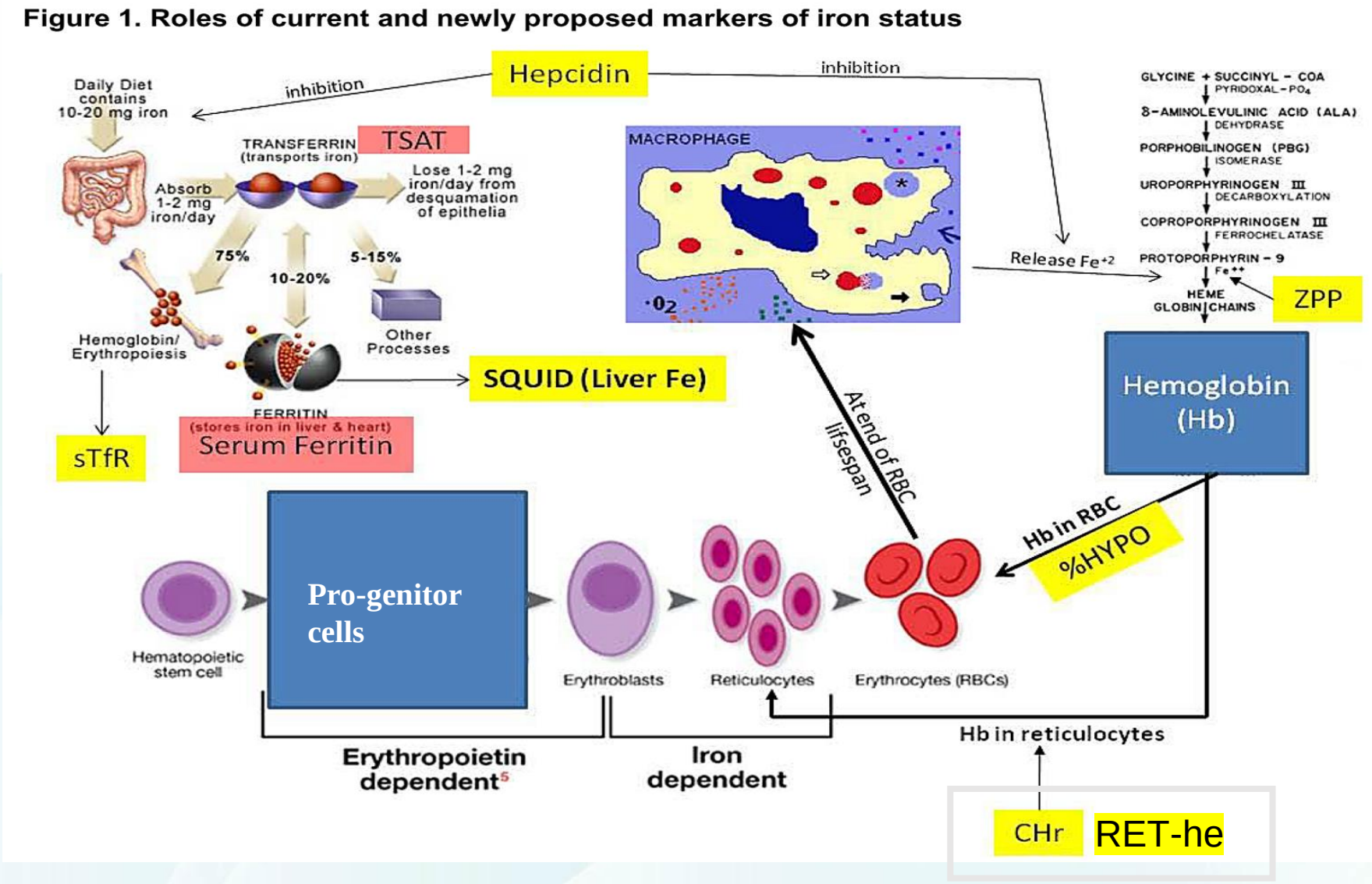
± Adapted from references 5 and 6
* Haemoglobin in grams per litre
a "Mild" is a misnomer: iron deficiency is already advanced by the time anaemia is detected. The deficiency has consequences even when no anaemia is clinically apparent.

Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity WHO/NMH/NHD/MNM/11.1

Anemia classification



Iron metabolism



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55/F, Dizziness, Arthragia, Insomnia; Thalassemia? (2020-04) => MCV/RBC < 13; RI < 2%, No TIBC, ferritin data ， => Fe supplement? Benefit? AE? Duration?

WBC	4.510	4.5~10	*10^3/ul	正常
RBC	5.310	4~5.5	*10^6/ul	正常
Hemoglobin	8.500	12~16	g/dl	偏低
Data had rechecked				
Ht	28.800	34~44	%	偏低
MCV	54.200	80~100	Fl	偏低
MCH	16.000	27~33	Pg	偏低
MCHC	29.500	32~36	g/dl	偏低
Platelet	238.000	120~350	*10^3/ul	正常
WBC Classification			%	
Neutrophil_Seg%	57.100	55~71	%	正常
Lymphocytes%	32.900	20~56	%	正常
Monocytes%	7.400	0~12	%	正常
Eosinophlis%	1.400	0~5	%	正常
Basophlis%	1.200	0~1	%	偏高
Reticulocyte	1.500	0.5~1.5	%	正常

Follow up 6 Months Later….. Hb, ferritin increased, but MCV, Ret-He, highly suspicious Thalassemia (Hb EP-)

RET-He	W.B.C	RBC	Hemoglobin (Hb)	HCT	MCV	MCH	MCHC	PLT	RDW-SD
23.3	5.79	6.54	13.6	43.0	65.7	20.8	31.6	216	34.1
23.7	7.62	6.36	13.2	41.8	65.7	20.8	31.6	263	39.4
22.4	5.67	5.18	10.9	34.9	67.4	21.0	31.2	254	36.4
	6.94	5.06	10.9	34.3	67.8	21.5	31.8	278	
21.1	6.09	4.58	9.9	31.3	68.3	21.6	31.6	269	
23.4	4.81	5.11	10.7	33.9	66.3	20.9	31.6	209	

報到日期	CRP(定量)	ALT (GPT)	Creatinine (Blood)	eGFR
1091128				
1091128	<0.1	13	0.80	79.45

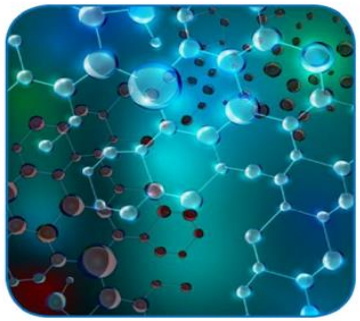
報到日期	Ferritin
1100728	114.24
1100407	29.21
1100113	16.86
1091117	9.84
1091020	21.87

Laboratory test

sysmex

DIAGNOSIS OF IRON DEFICIENCY

Biochemical Parameters



- Transferrin, Transferrin saturation (TSAT) Fe/TIBC
- Ferritin
- Serum iron
- Hepcidin

Hematological Parameters

- Based on RBC:
  - Hgb, MCV, RDW
- Based on Reticulocytes
  - Retic # and %
  - IRF
  - RET-He

More stability

Source of Variation	Coefficient of Variation (%)				
	Hb	Hct	CHr/RET-H*e*	TSAT	Ferritin
Analytical	2.0	2.2	2.4	2.7	6.9
Biological	4.0	4.0	4.8	38.0	15.1
Total	6.0	6.2	7.2	40.7	22.0

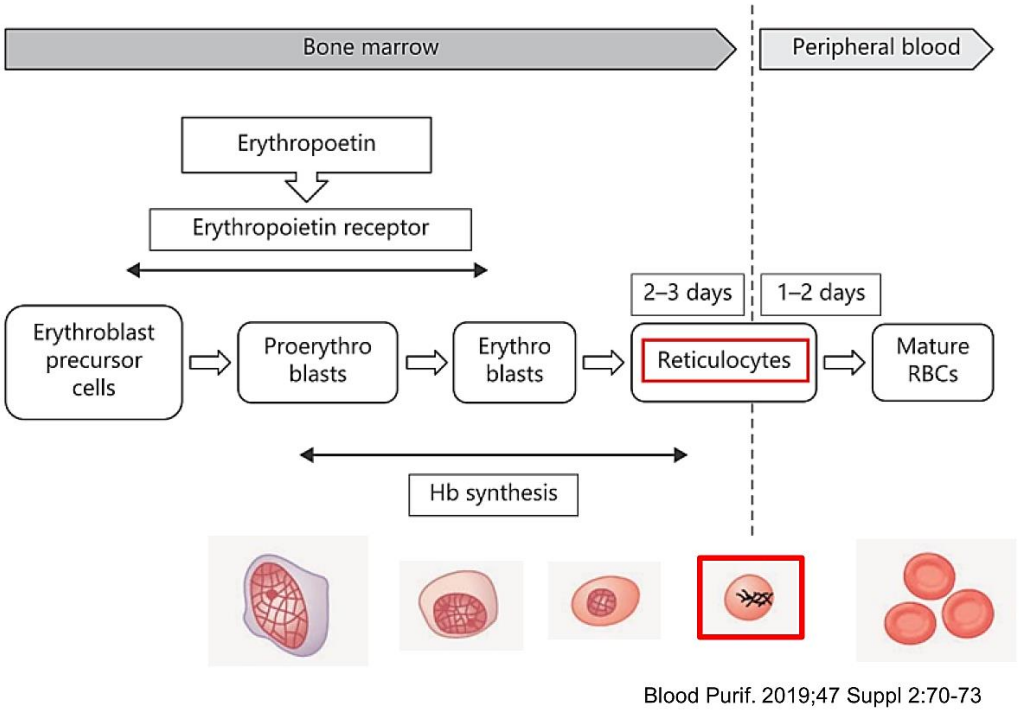
Abbreviations: CHr/RET-H*e*, reticulocyte hemoglobin; Hb, hemoglobin; Hct, hematocrit; TSAT, transferrin saturation.

Table 1: Hb, Hct and RET-H*e* show low biological and total variation, making them valuable tests for physician use. From Van Wyck.[5]

Early predictor

Ret-He : Reticulocyte hemoglobin equivalent

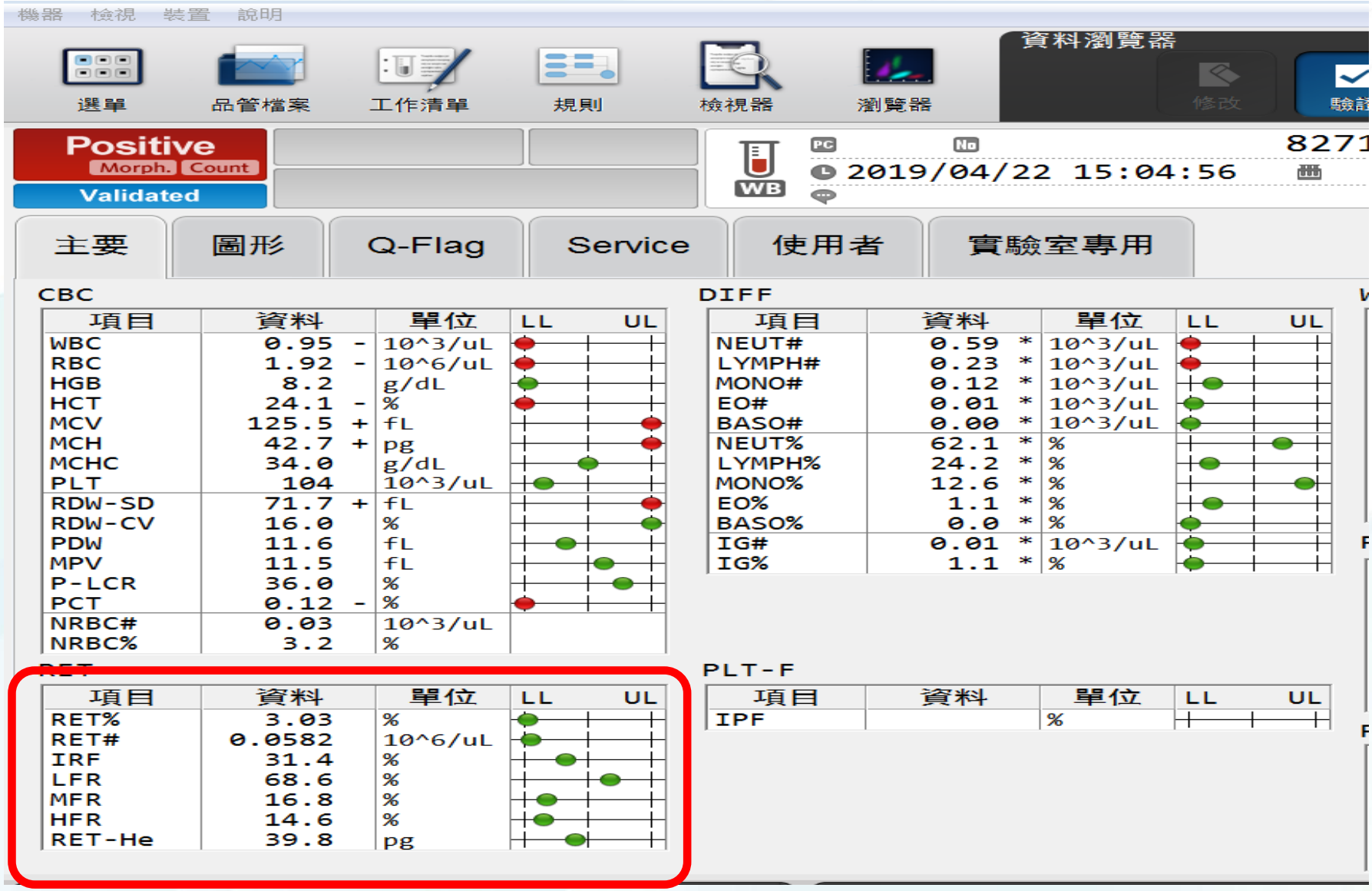
Measure hemoglobin content in newest erythrocyte (reticulocytes)
Indicates functional iron available over the previous 3-4 days



Blood Purif. 2019;47 Suppl 2:70-73

- ✔ Direct access the iron used for biosynthesis of Hb
- ✔ Indicate **available iron** for **erythropoiesis**
- ✔ Snapshot of the **quality** of **erythropoiesis**

XN IPU Screen



RET-He : 鑑別 IDA vs ACD

- Investigate **RET-He** in differentiating between iron deficiency anemia (IDA) and anemia of chronic diseases (ACD)

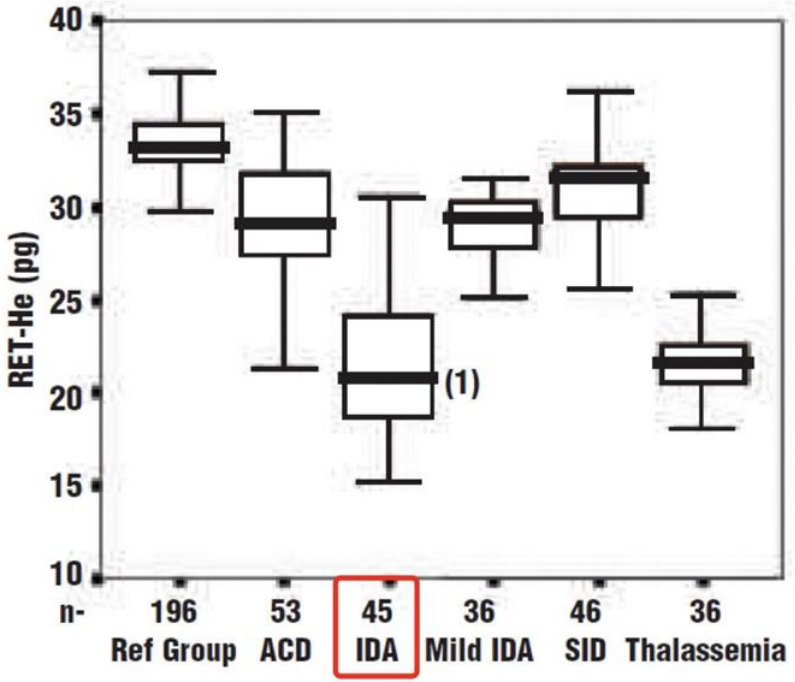


Fig. Distribution of RET-He in the different groups.

Groups	RET-He (pg)
Reference group	33.4 (29.8 - 37.7)
Anemia of chronic disorders (ACD)	**29.2 (21.4 - 35.1)**
Iron deficiency anemia (IDA)	**21.8 (15.2 - 30.6)**
Mild-IDA	28.9 (23.7 - 315)
Storage iron deficiency (SID)	30.9 (22.8 - 36.3)
Thalassemia train	21.8 (18.0–26.7)

鑑別 IDA 與 ACD

RET-He *(AUC=0.90)*

Cut-off : ***25.0 pg***

(Se.=76% , Sp.=81%)

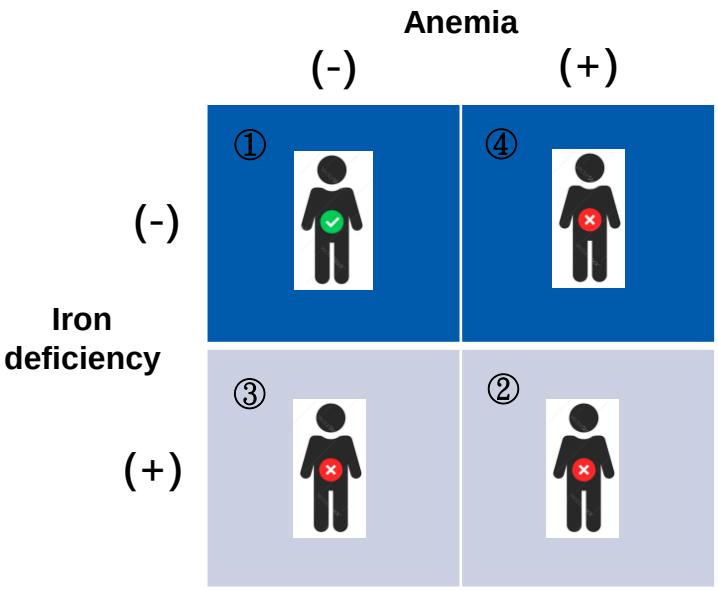
資料來源： Haematologica. 2005 Aug;90(8):1133-4

Sysmex Corporation

Mauro Buttarello*, Rachele Pajola, Enrica Novello, Giacomo Mezzapelle and Mario Plebani

Evaluation of the hypochromic erythrocyte and reticulocyte hemoglobin content provided by the Sysmex XE-5000 analyzer in diagnosis of iron deficiency erythropoiesis

- Assess the performance of **RET-He** and **%Hypo-He** in the diagnosis of iron deficiency conditions with or without anemia



- **Anemia**

  Hb<12 g/dL in women, <13 g/dL in men

- **Iron deficiency**

  Sfr <12 ng/mL in women, <15 ng/mL in men + TSAT<16%

① Healthy : N=164

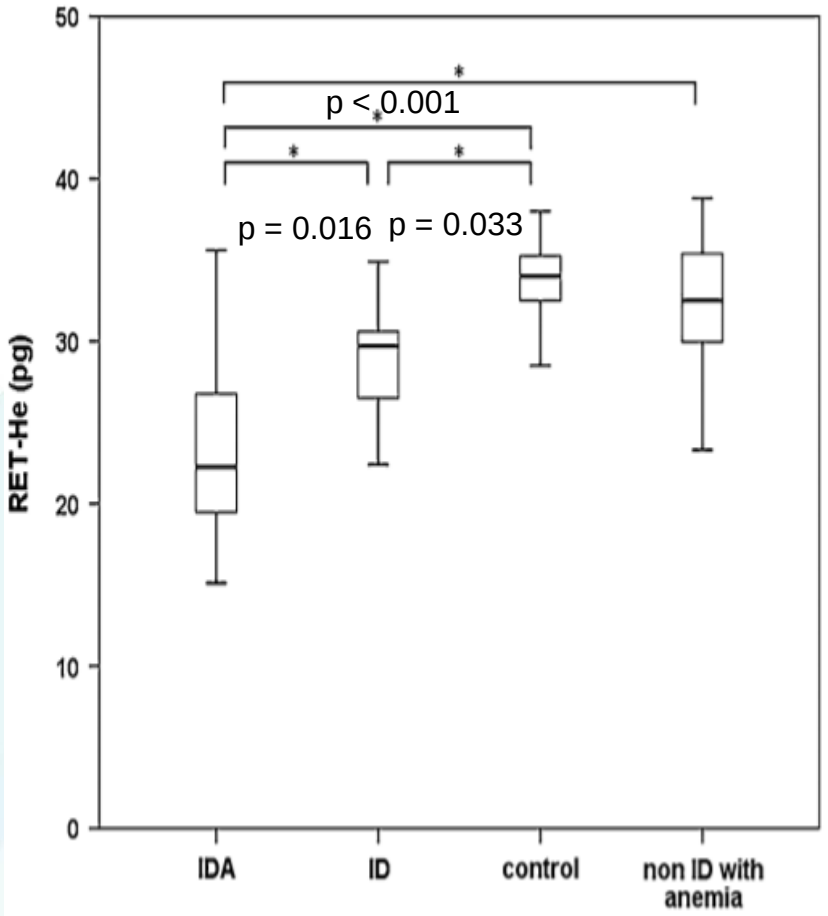
② Iron deficiency anemia : N=58

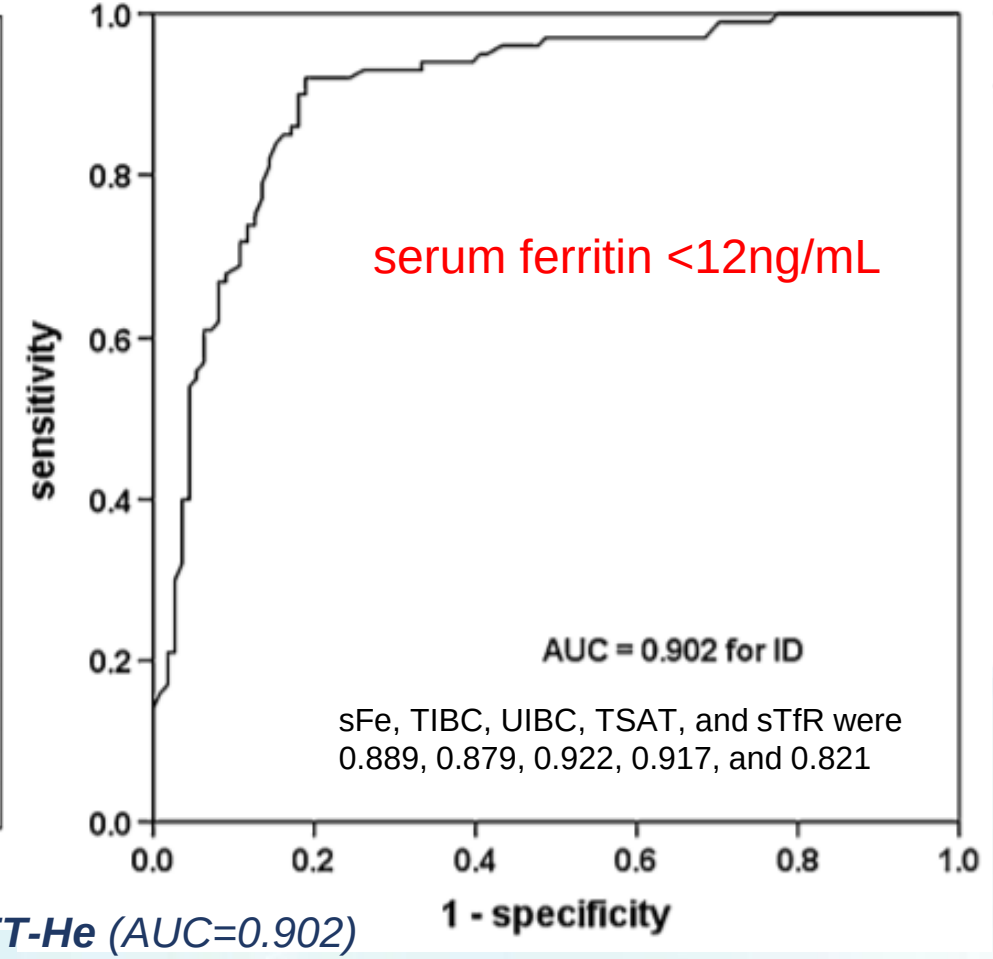
③ Iron deficiency w/o anemia : N=21

④ Trait β-thalassemia : N=23
Non-ID anemia : N=24

Clin Chem Lab Med. 2016 Dec 1;54(12):1939-1945

Reticulocyte hemoglobin equivalent as a potential marker for diagnosis of iron deficiency





RET-He *(AUC=0.902)*

Cut-off : ***28.4 pg***

(Se.=68% , Sp.=91%)

Cut-off : ***30.9 pg***

(Se.=92% , Sp.=81%)

Toki Y, et al. Int J Hematol. 2017 Sep;106(3):384-392. doi: 10.1007/s12185-017-2233-3.

Applying newer parameter Ret-He (reticulocyte haemoglobin equivalent) to assess latent iron deficiency (LID) in blood donors-study at a tertiary care hospital in India

	sTfR		
Ret-He	≥3 µg/ml	<3 µg/ml	Total
<28 pg	**135** (26.9%) [True positive]	**10** (2%) [False positive]	**145** (28.9%)
≥28 pg	**13** (2.6%) [False negative]	**343** (68.5%) [True Negative]	**356** (71.1%)
Total	**148** (29.5%)	**353** (70.5%)	**501** (100%)

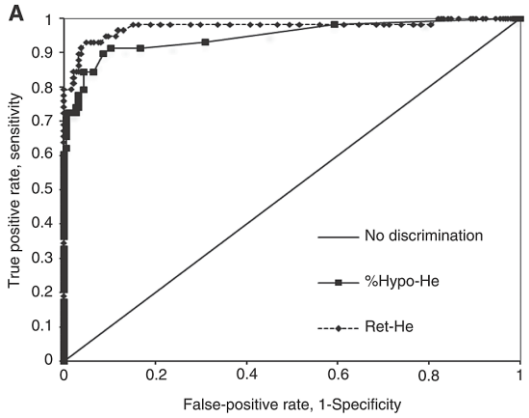
Investigations	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Classical				
MCV	6.1	100	100	71.8
MCH	12.8	98.9	82.6	73.0
MCHC	8.1	100	100	72.2
Conventional				
Serum iron	77.7	100	100	91.5
Total iron binding capacity	79.7	100	100	92.2
Transferrin saturation	79.7	100	100	92.2
Serum ferritin	87.2	99.2	97.7	95.0
Newer				
Ret-He	91.2	97.2	93.1	96.3

Vox Sang . 2018 Oct;113(7):639-646

Mauro Buttarello*, Rachele Pajola, Enrica Novello, Giacomo Mezzapelle and Mario Plebani

Evaluation of the hypochromic erythrocyte and reticulocyte hemoglobin content provided by the Sysmex XE-5000 analyzer in diagnosis of iron deficiency erythropoiesis

② Iron deficiency anemia



③ Iron deficiency w/o anemia

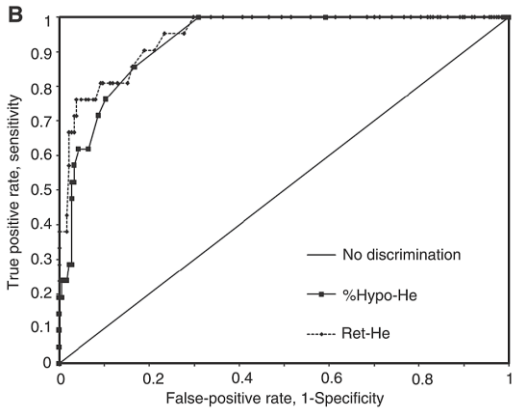


Table 2: Diagnostic characteristics of Ret-He and %Hypo-He for predicting iron deficiency in IDA and ID.

	AUC		Cutoff		Sensitivity %		p-Value	Specificity %		p-Value
	IDA	ID	IDA	ID	IDA	ID		IDA	ID	
Ret-He, pg	0.98	0.95	30.6	30.6	93.1	76.2	<0.001	95.1	95.1	NS
%Hypo-He	0.96	0.93	00.9	00.9	84.5	62.0	0.006	95.7	94.5	NS

AUC, area under the curve; NS, not significant.

Ability to identify iron deficiency are remarkable when there is anemia

Iron deficiency anemia

RET-He *(AUC=0.98)*

Cut-off : ***30.6 pg***

(Se.=93.1% , Sp.=95.1%)

%Hypo-He *(AUC=0.96)*

Cut-off : 0.9%

(Se.=84.5% , Sp.=95.7%)

Iron deficiency

RET-He *(AUC=0.95)*

Cut-off : ***30.6 pg***

(Se.=76.2% , Sp.=95.1%)

%Hypo-He *(AUC=0.93)*

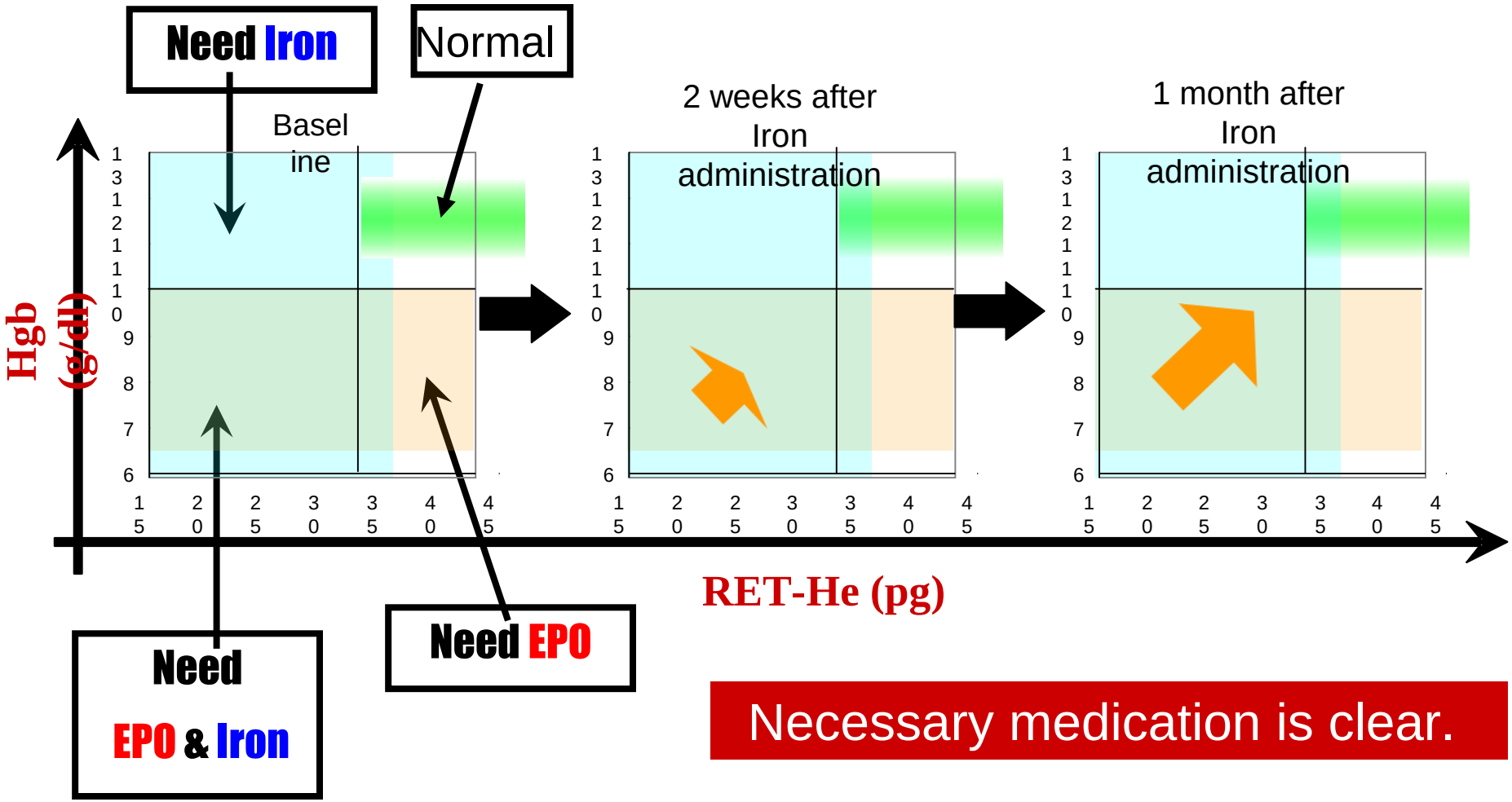
Cut-off : 0.9%

(Se.=62.0% , Sp.=94.5%)

資料來源：Clin Chem Lab Med. 2016 Dec 1;54(12):1939-1945

Support for best medication in renal anemia

Changes in RET-He and Hb after iron or EPO administration in renal anemia.



Necessary medication is clear.

N.Miwa, et al. Int. Jnl. Lab. Hem. 2010, 32, 248-255

Diagnosis of Iron Deficiency in Patients Undergoing Hemodialysis

Mauro Buttarello, MD,[1] Rachele Pajola, MD,[1] Enrica Novello, MD,[1] Mirca Rebeschini, MD,[2] Salvatore Cantaro, MD,[2] Fausto Oliosi, MD,[3] Agostino Naso, MD,[2] and Mario Plebani, MD[1,4]*

Key Words: Hypochromic erythrocytes; Reticulocyte hemoglobin content; XE-5000; ADVIA 120; Iron deficiency; Hemodialysis

Table 2

Baseline Characteristics of Patients Classified as Responders and Nonresponders to Intravenous Iron Administration*

	Responders	Nonresponders	*P*
Hemoglobin (g/L)	107.1 ± 9.1	113.3 ± 5.4	.0063
HYPO%	6.4 ± 4.9	3.8 ± 5	.0580
%Hypo-He	2.3 ± 2.2	1.6 ± 2.3	.2809
CHret (pg)	31.3 ± 1.9	33.0 ± 2.9	.0077
Ret-He (pg)	30.6 ± 2.9	32.9 ± 4.1	.0129
Ferritin (ng/mL)	255 ± 296	220 ± 181	.6247
Transferrin saturation (%)	16 ± 9	19 ± 9	.3328
CRP (mg/L)	13.6 ± 18.3	7.3 ± 6.3	.1334

CHret, mean reticulocyte hemoglobin content; CRP, C-reactive protein; HYPO%, percentage of erythrocytes with cellular hemoglobin concentration lower than 280 g/L; %Hypo-He, percentage of erythrocytes with cellular hemoglobin content lower than 17 pg; Ret-He, equivalent of the mean reticulocyte hemoglobin content.

Responders

IV鐵劑三周後任一時間 Hb上升大於1.0 g/dL

Non-responders

有顯著差異：

Hb, CHr, **RET-He**

無顯著差異：

Ferritin, TSAT(%)

資料來源：Am J Clin Pathol. 2010 Jun;133(6):949-54.

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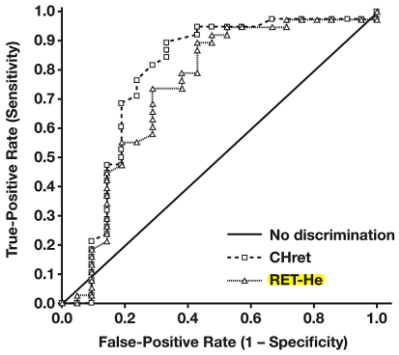
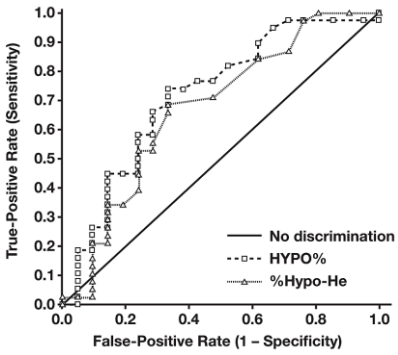
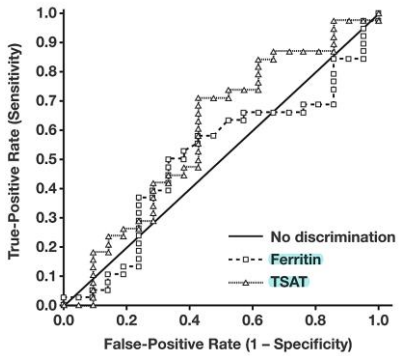






RET-He *(AUC=0.72)*

Cut-off : ***30.6 pg***

(Se.=45% , Sp.=83%)

Table 3
Diagnostic Characteristics of Tests for Predicting Iron Deficiency

Test	AUC	95% CI	*P**	Cutoff	Sensitivity (%)	Specificity (%)
CHret (pg)	0.74	0.60-0.89	<.001	31.2	47	83
Ret-He (pg)	0.72	0.58-0.86	<.003	30.6	45	83
HYPO%	0.72	0.58-0.86	<.001	5.8	45	87
%Hypo-He	0.68	0.54-0.82	<.014	2.7	34	87
Ferritin (ng/mL)	0.53	0.38-0.69	.470	—	—	—
Transferrin saturation (%)	0.56	0.40-0.72	.130	—	—	—

AUC, area under the curve; CHret, mean reticulocyte hemoglobin content; CI, confidence interval; HYPO%, percentage of erythrocytes with cellular hemoglobin concentration lower than 280 g/L; %Hypo-He, percentage of erythrocytes with cellular hemoglobin content lower than 17 pg; Ret-He, equivalent of the mean reticulocyte hemoglobin content.

* Significance of the difference from .5 (equivalent to no predictive ability).

資料來源：Am J Clin Pathol. 2010 Jun;133(6):949-54.

Limitation of RET-He

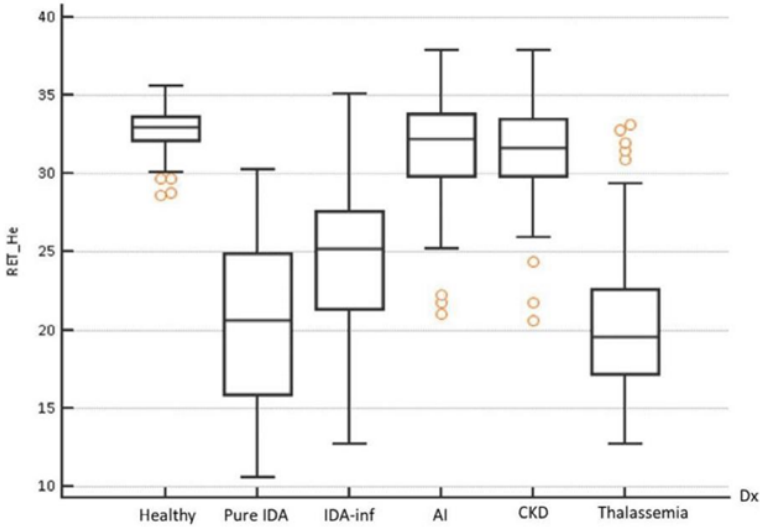
- thalassemia syndromes (海洋性貧血) – 降低
- Confounding megaloblastic anemia – 上升
- Drugs inducing transient or permanent macrocytosis (ex. chronic hydroxyurea treatment in sickle cell disease) – 上升

Interpreted with patients overall erythrocyte physiology - recent blood transfusion, iron therapy, vitamin B12 or folate deficiency, chemotherapy, and the results of Hb analysis

Diagnostic performance of reticulocyte hemoglobin equivalent in assessing the iron status

Pawadee Chinudomwong | Aleeyas Binyasing | Rangsiri Trongsakul | Karan Paisooksantivatana

- Evaluate RET-He diagnostic performance assessing the **iron status** in various conditions (including inflammation-related states)
- Proposed a **diagnostic algorithm**



	Groups	Medium	IQR	Q1	Q3
	Healthy Control	33.0	1.45	32.3	33.7
IDA	Pure IDA	20.6	9.00	16.1	25.1
	IDA-inf	25.2	6.15	22.1	28.3
Non-ID Anemia	AI	32.2	3.9	30.3	34.2
	CKD	31.8	3.53	30.0	33.6
	Thalassemia	19.6	5.33	16.9	22.3

* Anemia of inflammation (AI)

* IDA with concomitant inflammation (IDA-inf)

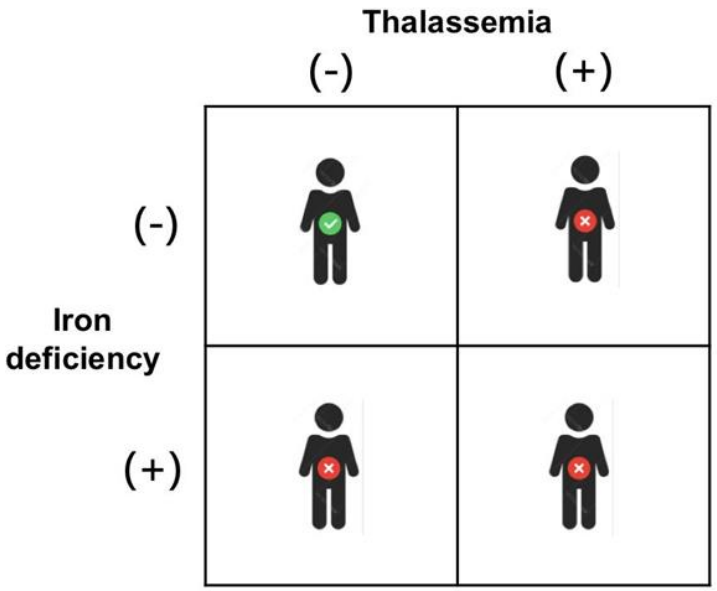
J Clin Lab Anal. 2020;34:e23225.

A New Indicator Derived From Reticulocyte Hemoglobin Content for Screening Iron Deficiency in an Area Prevalent for Thalassemia

Jutatip Jamnok, BSc,[1] Kanokwan Sanchaisuriya, PhD,[2] Chaninthorn Chaitriphop, MSc,[2] Pattara Sanchaisuriya, PhD,[3] Goonnapa Fucharoen, MSc,[2] Supan Fucharoen, DSc[2]*

- Establish a new indicator derived from RET-He & RBC indices for screening for IDA in area where thalassemia is prevalent

建立由RET-He及RBC相關參數衍生之指標,用於海洋性貧血盛行區篩檢IDA之用途



- **Inclusion** : female university students, age = 18-30 yrs. (N = 304)
- **Exclusion** : infection or inflammation, currently taking iron tablet, chronic disease

- ***Thalassemia***
  MCV, Hb profile, HbA2, PCR
- ***Iron deficiency / Iron deficiency anemia***
  ID : Sfr <15 ng/mL
  IDA : Hb < 12 g/dL in women + ID

ID 盛行率 : 25.7 %
Thalassemia 盛行率 : 49.7 %

資料來源：Lab Med. 2020 Feb 13. pii: lmz099.

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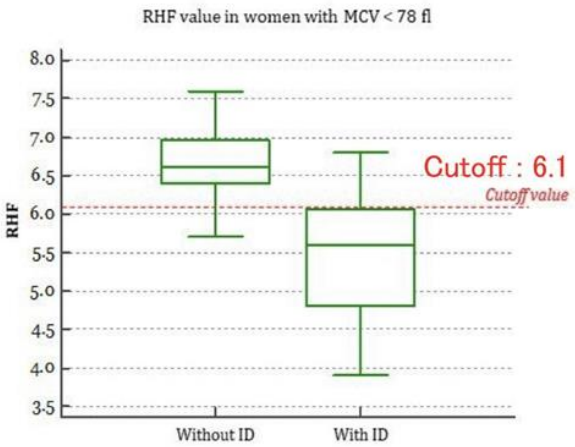
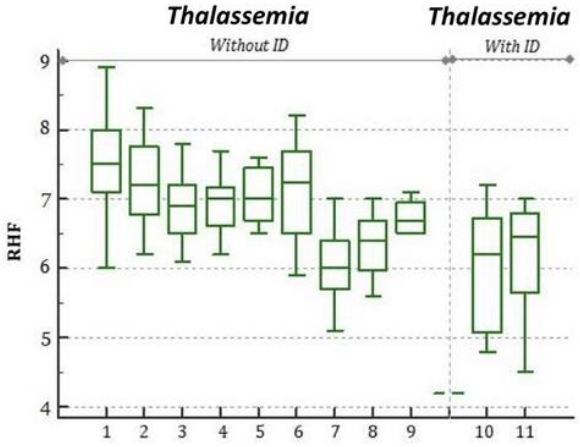
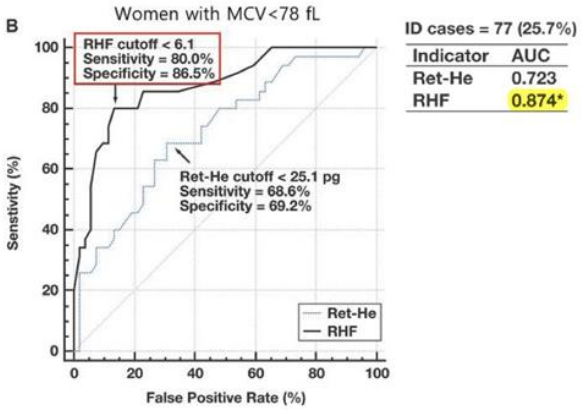
Ret-He factor (RHF)
[Ret-He / RDW-SD] × 10





1 : Non-thal/non-ID
2 : α^{+}-thal
3 : HbE trait
4 : HbE & α^{+}-thal
5 : HbCS trait
6 : HbE trait & HbCS trait
7 : α^{0}-thal trait
8 : HbE trait & α^{0}--thal
9 : Homozygous HbE & α^{+}-thal
2i : ID & α^{+}-thal
3i : ID & HbE trait



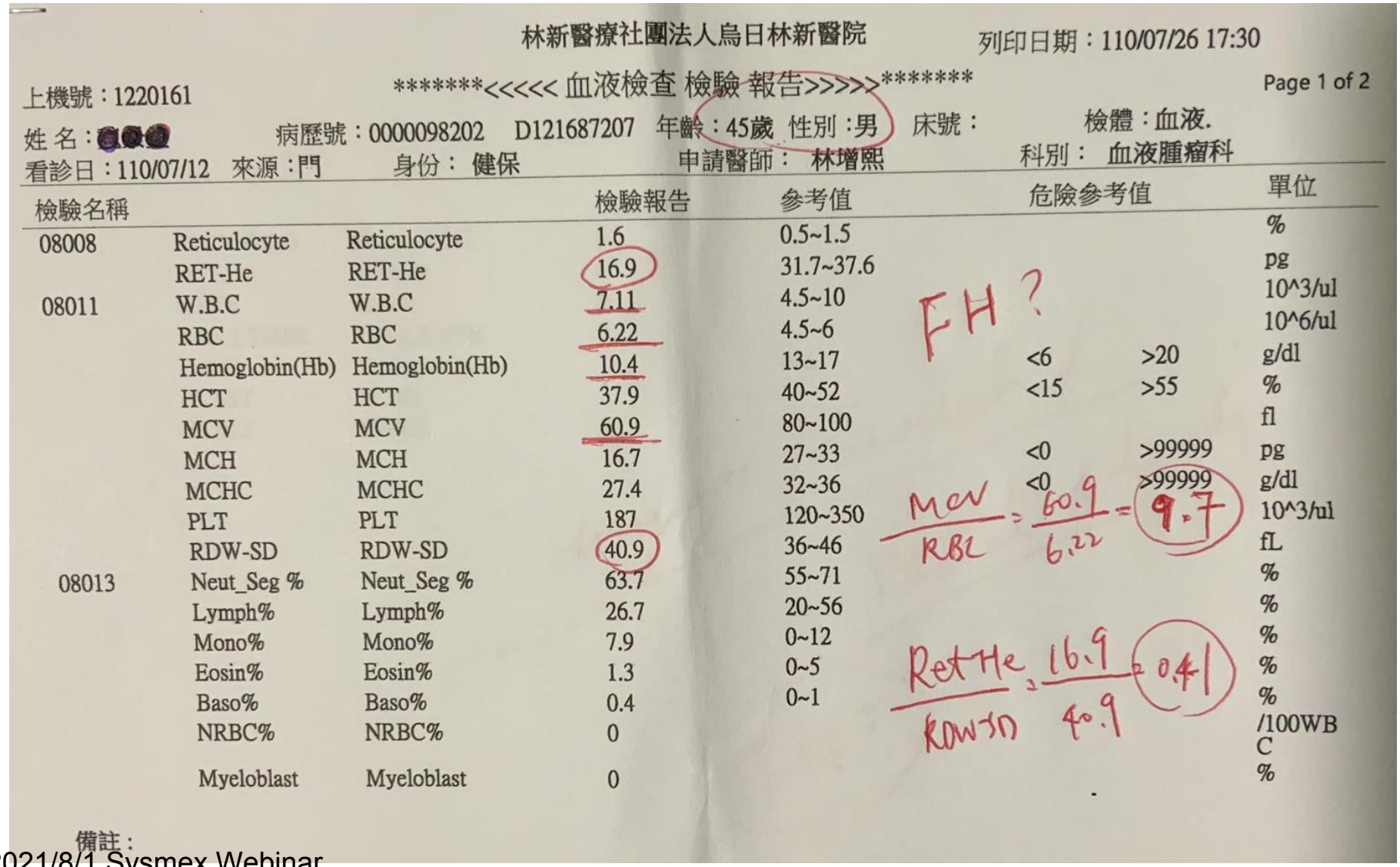
ID cases = 77 (25.7%)

Indicator	AUC
Ret-He	0.723
RHF	0.874*

In conclusion, we suggest that a prescription for iron supplement be given to women
(1) test positive for thalassemia (ie, **MCV <78 fL**) &
(2) RHF < 6.1

資料來源：Lab Med. 2020 Feb 13. pii: lmz099.

45/M, dizziness, headache, IDA? Thalassemia?



林新醫療社團法人烏日林新醫院　列印日期：110/07/26 17:30

上機號：1220161　*******<<<<< 血液檢查 檢驗 報告>>>>>*******　Page 1 of 2

姓 名：[redacted]　病歷號：0000098202　D121687207　年齡：45歲　性別：男　床號：　檢體：血液.

看診日：110/07/12　來源：門　身份： 健保　申請醫師： 林增熙　科別： 血液腫瘤科

檢驗名稱			檢驗報告	參考值	危險參考值		單位
08008	Reticulocyte	Reticulocyte	1.6	0.5~1.5			%
	RET-He	RET-He	16.9	31.7~37.6			pg
08011	W.B.C	W.B.C	7.11	4.5~10			10^3/ul
	RBC	RBC	6.22	4.5~6			10^6/ul
	Hemoglobin(Hb)	Hemoglobin(Hb)	10.4	13~17	<6	>20	g/dl
	HCT	HCT	37.9	40~52	<15	>55	%
	MCV	MCV	60.9	80~100			fl
	MCH	MCH	16.7	27~33	<0	>99999	pg
	MCHC	MCHC	27.4	32~36	<0	>99999	g/dl
	PLT	PLT	187	120~350			10^3/ul
	RDW-SD	RDW-SD	40.9	36~46			fL
08013	Neut_Seg %	Neut_Seg %	63.7	55~71			%
	Lymph%	Lymph%	26.7	20~56			%
	Mono%	Mono%	7.9	0~12			%
	Eosin%	Eosin%	1.3	0~5			%
	Baso%	Baso%	0.4	0~1			%
	NRBC%	NRBC%	0				/100WBC
	Myeloblast	Myeloblast	0				%

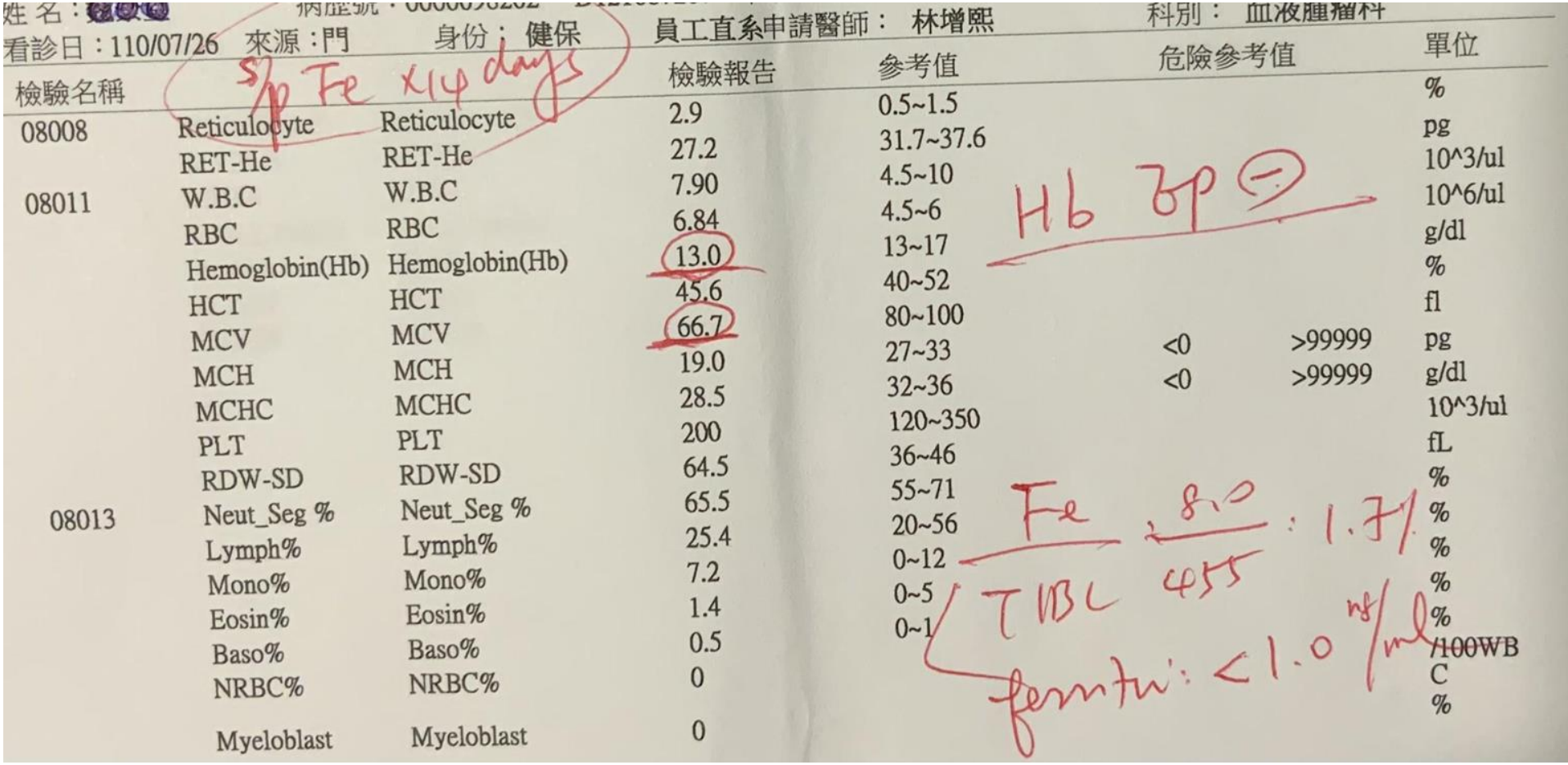
FH?

MCV / RBC = 60.9 / 6.22 = 9.7

Ret-He / RDW-SD = 16.9 / 40.9 = 0.41

備註：

After Fe supplement x 14 days Hb: 10.4 => 13.0



姓名：[redacted]　病歷號：[redacted]

看診日：110/07/26　來源：門　身份：健保　員工直系申請醫師：林增熙　科別：血液腫瘤科

S/p Fe x14 days

檢驗名稱		檢驗報告	參考值	危險參考值		單位
08008	Reticulocyte	2.9	0.5~1.5			%
	RET-He	27.2	31.7~37.6			pg
08011	W.B.C	7.90	4.5~10			10^3/ul
	RBC	6.84	4.5~6			10^6/ul
	Hemoglobin(Hb)	13.0	13~17			g/dl
	HCT	45.6	40~52			%
	MCV	66.7	80~100			fl
	MCH	19.0	27~33	<0	>99999	pg
	MCHC	28.5	32~36	<0	>99999	g/dl
	PLT	200	120~350			10^3/ul
	RDW-SD	64.5	36~46			fL
08013	Neut_Seg %	65.5	55~71			%
	Lymph%	25.4	20~56			%
	Mono%	7.2	0~12			%
	Eosin%	1.4	0~5			%
	Baso%	0.5	0~1			%
	NRBC%	0				/100WBC
	Myeloblast	0				%

Hb 改善

Fe 8.2 : 1.7%

TIBC 455

ferritin: <1.0 ng/ml

RDW for COVID-19 patients

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Original Article

Association between red blood cell distribution width and mortality of COVID-19 patients

Aim – To determine whether there is an association between ***RDW*** at ICU admission and ***mortality***

(評估 RDW 與 COVID-19 ICU病人 mortality 之關聯性)

Table 2
Laboratory data at ICU admission of non-surviving and surviving patients.

存活 死亡

	Survivors (n = 118)	Non-survivors (n = 25)	*p* Value
Lactic acid (mmol/L) – median (p 25–75)	1.33 (1.06–1.80)	1.60 (1.20–2.05)	0.20
Glucose (g/dL) – median (p 25–75)	140 (108–189)	158 (127–249)	0.14
Sodium (mEq/L)- median (p 25–75)	138 (135–141)	139 (135–143)	0.60
Creatinine (mg/dl) – median (p 25–75)	0.86 (0.66–1.09)	1.07 (0.77–1.21)	0.02
Urea (mg/dl) – median (p 25–75)	39 (27–54)	65 (52–85)	< 0.001
Protein (g/L) – median (p 25–75)	6.4 (5.9–7.0)	6.2 (5.9–6.7)	0.49
Albumin (g/L) – median (p 25–75)	3.2 (2.8–3.5)	3.4 (3.1–3.9)	0.25
Creatine kinase (U/L) – median (p 25–75)	121 (44–258)	209 (39–316)	0.63
Total bilirubin (mg/dl) – median (p 25–75)	0.60 (0.40–1.00)	0.72 (0.50–1.20)	0.16
Aspartate transaminase (U/L) – median (p 25–75)	40 (30–71)	45 (23–123)	0.74
Alanine transaminase (U/L) – median (p 25–75)	38 (27–66)	31 (19–68)	0.22
Gamma-glutamyl transpeptidase (U/L) – median (p 25–75)	55 (35–108)	102 (39–176)	0.11
Lactate dehydrogenase (U/L) – median (p 25–75)	397 (309–475)	461 (287–561)	0.19
Alkaline phosphatase (U/L) – median (p 25–75)	57 (49–79)	88 (52–117)	0.04
C-reactive protein (mg/gl) – median (p 25–75)	26 (13–102)	24 (14–59)	0.75
Procalcitonin (ng/ml) – median (p 25–75)	0.21 (0.09–0.59)	0.58 (0.16–0.84)	0.18
Ferritin (ng/ml) – median (p 25–75)	906 (593–1593)	1391 (977–1843)	0.18
NTproBNP (pg/ml) – median (p 25–75)	288 (130–1195)	3480 (468–6162)	0.07
Interleukin-6 (pg/ml) – median (p 25–75)	55 (6–237)	65 (35–249)	0.62
Haemoglobin (g/dL) – median (p 25–75)	13.0 (11.7–14.4)	12.7 (10.9–14.3)	0.50
Haematocrit (%) – median (p 25–75)	39 (35–43)	38 (34–43)	0.59
RDW (%) – median (p 25–75)	13.3 (12.5–14.5)	14.1 (13.3–16.1)	0.001
White blood cell – median*10^3 mm^{-3} (p 25–75)	8.3 (6.0–11.8)	9.4 (5.6–12.8)	0.64
Neutrophils – median*10^3 mm^{-3} (p 25–75)	7.2 (4.9–10.2)	7.6 (4.0–10.2)	0.99
Lymphocytes – median*10^3 mm^{-3} (p 25–75)	0.72 (0.52–1.04)	0.70 (0.50–1.21)	0.78
Monocytes – median*10^3 mm^{-3} (p 25–75)	0.42 (0.30–0.63)	0.40 (0.23–0.52)	0.24
Eosinophils – median*10^3 mm^{-3} (p 25–75)	0.00 (0.00–0.03)	0.01 (0.00–0.03)	0.37
Basophils – median*10^3 mm^{-3} (p 25–75)	0.01 (0.00–0.03)	0.01 (0.00–0.03)	0.91
Platelets – median*10^3 mm^{-3} (p 25–75)	243 (173–312)	198 (121–266)	0.007
INR – median (p 25–75)	1.18 (1.08–1.32)	1.25 (1.16–1.41)	0.13
aPTT (seconds) – median (p 25–75)	28 (24–32)	32 (29–36)	0.009
Fibrinogen (mg/dl) – median (p 25–75)	698 (524–810)	726 (548–894)	0.47
D-dimer (ng/mL) – median (p 25–75)	1154 (664–2663)	1758 (595–11365)	0.17
$PaO2/FIO_2$ ratio – median (p 25–75)	176 (104–234)	112 (100–174)	0.07
Arterial pH – median (p 25–75)	7.41 (7.34–7.46)	7.36 (7.29–7.42)	0.008

NTproBNP = N-terminal prohormone of Brain Natriuretic Peptide; RDW = Red blood cell Distribution Width (RDW); INR = International Normalized Ratio; aPTT = Activated Partial Thromboplastin Time; PaO_2 = Pressure of arterial Oxygen; FIO_2 = Fraction Inspired Oxygen

- Higher ***Creatinine*** (p=0.02)
- Higher ***Urea*** (p<0.001)
- Higher ***Alkaline phosphatase*** (p=0.04)
- Higher ***RDW*** (p=0.001)
- Lower ***Platelet*** (p=0.007)
- Higher ***aPTT*** (p=0.009)
- Higher ***arterial pH*** (p=0.008)

資料來源：Anaesth Crit Care Pain Med. 2021 Feb;40(1):100777.

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Original Article

Association between red blood cell distribution width and mortality of COVID-19 patients

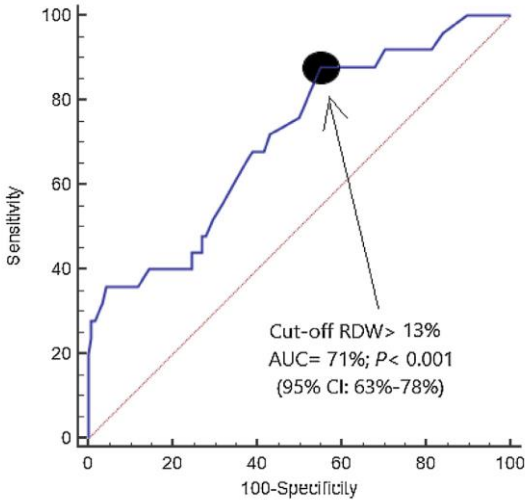


Fig. 1. Receiver operating characteristic analysis using RDW for prediction of mortality at 30 days.

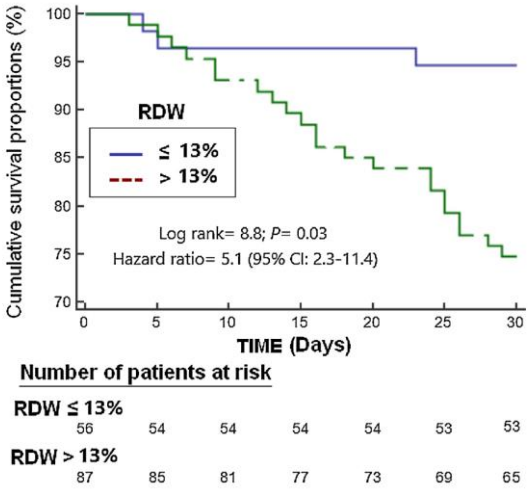


Fig. 2. Survival curves at 30 days using red blood cell distribution width (RDW) higher or lower than 13.0%.

RDW(%) 預測30天死亡率

- AUC : 0.71
- Cut-off : ***RDW > 13%***
- **敏感度** : ***88%,*** 特異性 : 45%
- **陰性預測率** : ***95%,*** 陽性預測率 : 25%

存活分析

- Group : ***RDW > 13%*** vs RDW ≤ 13%
- **Hazard ratio** = ***5.1*** (2.4 – 11.4)

資料來源：Anaesth Crit Care Pain Med. 2021 Feb;40(1):100777.

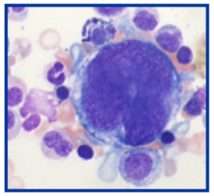
Outline

- Introduction
  - Why we need Ret-He & IPF tests?
- Ret-He for anemia patients
  - DDx and Application
- IPF% for thrombocytopenia and COVID-19
  - DDx, Monitoring, and Application
- Summary

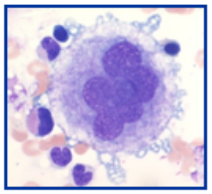
Reticulated (Immature) Platelets

- Immature Platelet Fraction (IPF) is a measure of thrombopoietic activity.
- Measured by flow cytometry using RNA binding dyes.
- Useful for the differential diagnosis of thrombocytopenia and for monitoring bone marrow recovery after chemotherapy or stem cell transplantation.

Immature platelets Fraction= IPF
Reticulated platelets



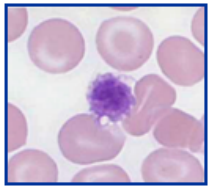
Megakaryoblast (Bone marrow 25%)
first morphological stage, no thrombocytes in cytoplasm



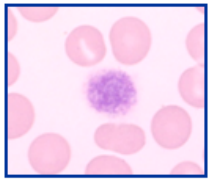
Megakaryocyte (Bone marrow 75%)
thrombocytes production in cytoplasm

4-5 days

IPF

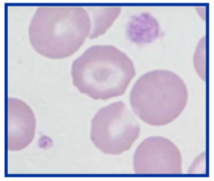


Reticulated platelet (strangulated cytoplasm of Megakaryocyte)
Young thrombocyte in peripheral blood with a lot of RNA.
Produktion of different proteins: Glycoproteine Ib, IIb (CD41) /IIIa (CD61), Cyclooxygenase, Thromboxan-Synthetase, Phospholipase, PF4.



Reticulated platelet
Young giant thrombocyte in peripheral blood

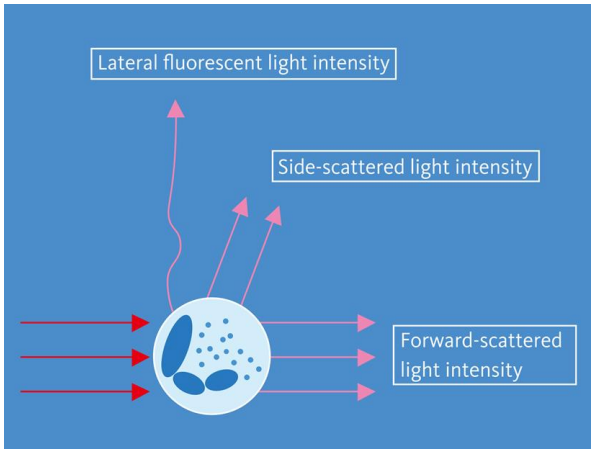
1-2 days



Mature platelets
Mature thrombocytes with different volume 2-20 fL.
Lifespan +/- 10 days.
Platelets turn over 7000/µL per day

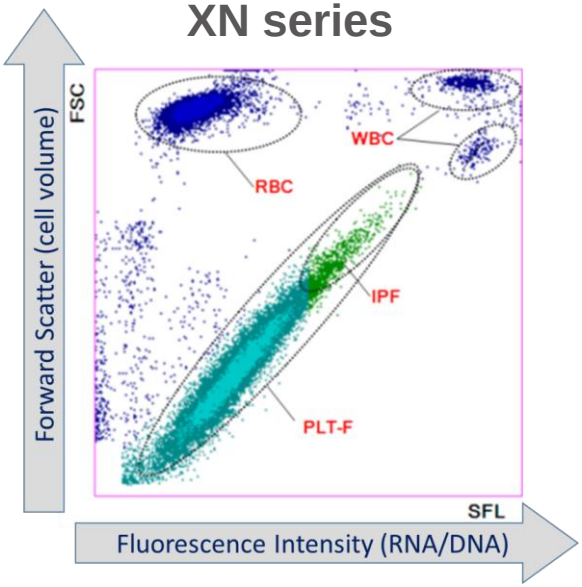
10 days

IPF Measurement on Sysmex hematology analyzer



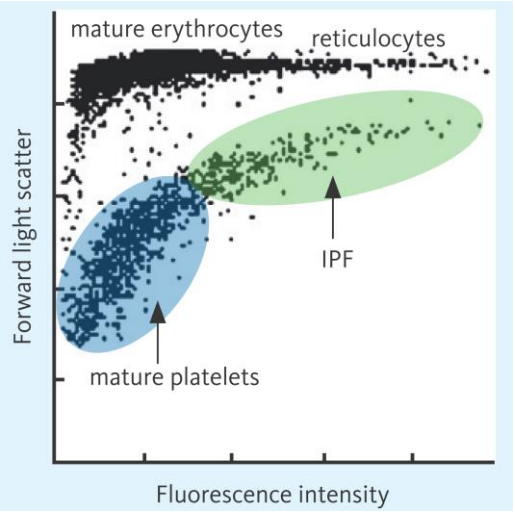
Lateral fluorescent light intensity	Information on RNA and DNA amounts
Side-scattered light intensity	Information concerning the internal structure of cells (nucleus shape, presence of cell granules, etc.)
Forward-scattered light intensity	Information on cell size

XN series



PLT-F Channel

XE series



RET Channel

IPF Normal Ranges

Sysmex XN series

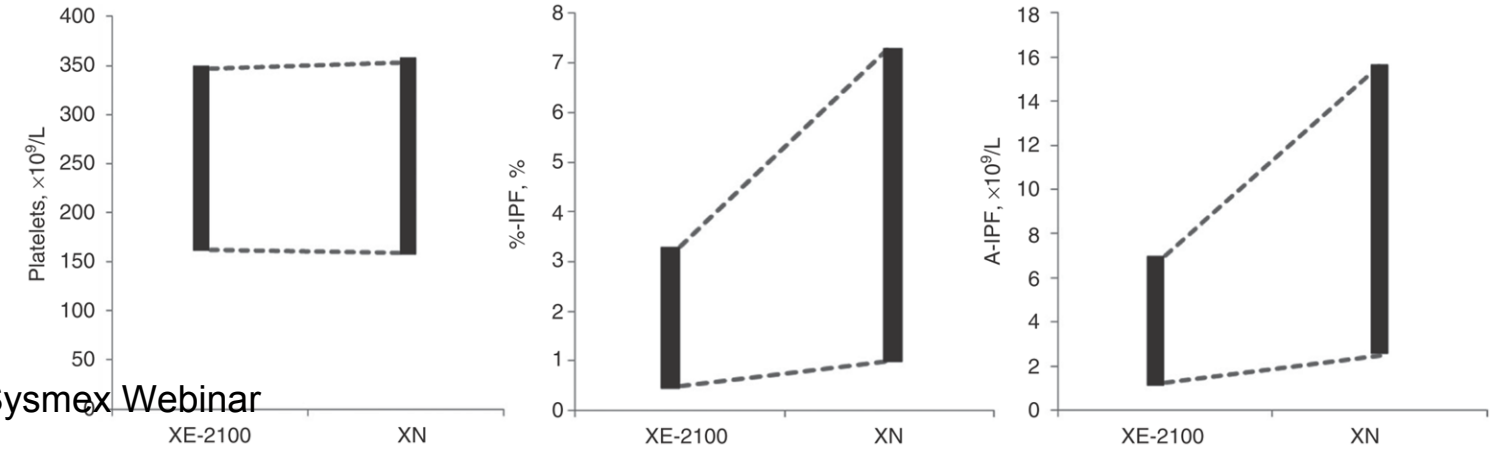
	Healthy individuals (n=2104)	Umbilical cord blood (n=140)
Platelet counts, $\times 10^9$/L		
Reference interval	159–353	174–405[a]
Lower limit (95% CI)	156–162	160–187
Upper limit (95% CI)	348–358	383–422
%-IPF, %		
Reference interval	1.0–7.3	1.0–4.4
Lower limit (95% CI)	0.9–1.0	0.9–1.1
Upper limit (95% CI)	6.9–7.6	4.1–5.8
A-IPF, $\times 10^9$/L		
Reference interval	2.5–15.6	2.9–12.8
Lower limit (95% CI)	2.3–2.6	2.5–3.4
Upper limit (95% CI)	15.0–16.3	10.7–17.8

Clin Chem Lab Med. 2015 Jun;53(7):1091-7

Sysmex XE series

	Healthy individuals			Umbilical cord blood
	Total (n = 2152)	Men (n = 1252)	Women (n = 900)	(n = 133)
Platelet counts ($\times 10^9$/L)				
Reference interval	162–347	161–338	164–360	191–392
Lower limit (95% CI)	160–164	158–164	160–169	168–208
Upper limit (95% CI)	340–353	326–344	351–372	364–447
%-IPF (%)				
Reference interval	0.5–3.3	0.5–3.1	0.5–3.4	0.7–3.8
Lower limit (95% CI)	0.5–0.5	0.5–0.6	0.5–0.5	0.7–0.9
Upper limit (95% CI)	3.2–3.4	3.0–3.3	3.3–3.5	3.0–3.8
A-IPF ($\times 10^9$/L)				
Reference interval	1.25–7.02	1.30–6.80	1.21–7.15	1.94–9.69
Lower limit (95% CI)	1.19–1.30	1.20–1.41	1.10–1.27	1.66–2.58
Upper limit (95% CI)	6.75–7.24	6.49–7.16	6.9–7.48	7.96–10.57

Int J Lab Hematol. 2013 Oct;35(5):528-33



Clin. Lab. 2018;64:XXX-XXX

ORIGINAL ARTICLE

Effects of Analyzer Detection Method, Ethnicity, and Reference Individuals on Reference Interval of Immature Platelet Fraction

Ming-Feng Wu [1, 2, *], Hsien-Hsu Hsieh [3, 6, *], Wei-Chang Huang [1, 6], Kun-Mu Lu [3], Jun-Hong Lin [3], Yi-Ching Lin [3], Jiunn-Min Wang [3], Tseng-Hsi Lin [3, 4, 5]

Background: **Immature platelet fraction (IPF) is a new biomarker for thrombopoiesis and inflammation. However, the reference interval (RI) is wildly discrepant among published reports. This study aimed to establish the RI of IPF for a population in Taiwan and evaluate the effects the detection method of the analyzer, ethnicity, and reference individuals have on the RI of IPF.**

Methods: **The RI of absolute IPF (A-IPF) and IPF% were established with healthy subjects from the outpatient services of the Health Management Department of Taichung Veterans General Hospital between January 1, 2015 and March 1, 2016. These values were used along with published reports for meta-analysis.**

Results: **A-IPF (10^9/L) and IPF% of Taiwanese were 6.9 - 7.6 and 3.1 - 3.4, respectively. Significant differences were found when performing paired comparisons of the RI of A-IPF and IPF% published in reports. For A-IPF, there was only one paired comparison with a significant difference ($Z > 1.96$) across 6 reports. Thus, the contribution of the factors examined on the RI of IPF cannot be determined. For IPF%, there were 8 paired comparisons with significant differences across 10 reports. The discrepancy rates of RI for IPF% were 41.2%, 50.0%, and 25.0% with the difference of reference individuals, the analyzer method, and ethnicity, respectively.**

Conclusions: **The RIs of Taiwanese for A-IPF and IPF% were established. Furthermore, the analyzer detection method and the reference individuals contribute to the discrepancy of the RI for IPF% and should be considered cautiously when the value of IPF is interpreted.**

(Clin. Lab. 2018;64:xx-xx. DOI: 10.7754/Clin.Lab.2018.171025)

Biological Reference Interval in Taiwan

Table 1

The demography characteristic of included subjects

	All (n= 478)	Male (n=257, 53.8%)	Female (n=221,46.2%)	Age≧45 (n=281, 58.8%)	Age< 45 (n=197, 41.2%)
Year-old⊕	47.7± 12.5	46.3± 13.2	49.2± 11.5	56.5± 7.2	35.0± 5.5
RBC#	4.8± 0.5	5.1± 0.3	4.6± 0.3	4.7± 0.4	5.0± 0.5
WBC#	6.1± 1.5	6.4± 1.5	5.7± 1.4	5.9± 1.5	6.4± 1.5
PLT#	253.2± 47.5	250.6± 45.4	256.2± 49.7	249.7± 47.0	258.2± 47.8
HGB⊕	14.5± 1.4	15.5± 0.9	13.3± 0.8	14.3± 1.4	14.7± 1.5
GOT⊕	21.6± 4.9	22.7± 5.1	20.3± 4.4	22.2± 44.9	20.6± 4.8
GPT⊕	21.6± 8.6	25.0± 9.1	17.8± 6.0	21.4± 7.7	22.0± 9.8
A-IPF⊕	7.9± 3.8	8.2± 3.9	7.6± 3.6	7.5± 3.5	8.5± 4.0
IPF(%)⊕	3.3± 1.8	3.4± 1.8	3.1± 1.7	3.1± 1.7	3.4± 1.8

Data was presented as mean± standard deviation (SD)

⊕: non- parametric with Kolmogorov-Smimov test (p> 0.05) in all subjects.

#: normal-distribution with Kolmogorov-Smimov test (p< 0.05) in all subjects.

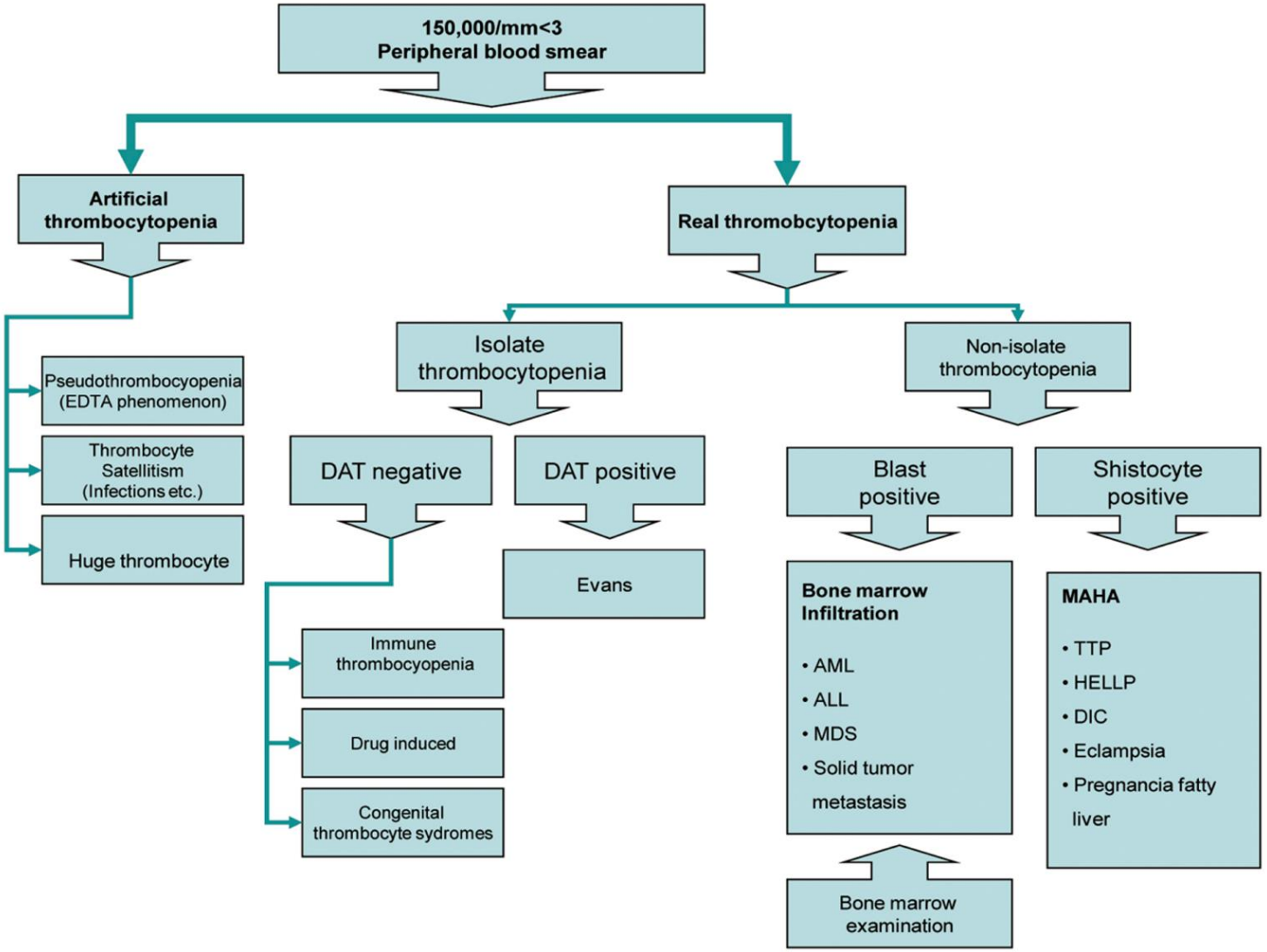
Clinical Utility of IPF

- Diagnosis of Thrombocytopenia
- Monitor of Hematopoietic Recovery
- Reduce Prophylactic Transfusion

Causes of Thrombocytopenia

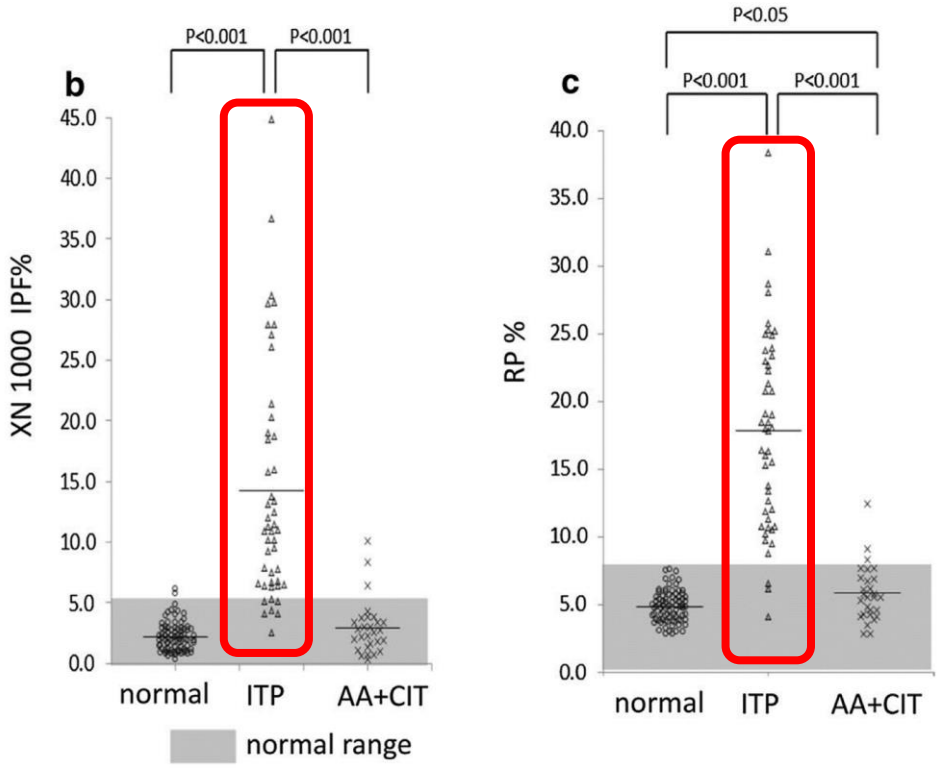
- Increased destruction/consumption
  - Idiopathic thrombocytopenic purpura (ITP)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Hemolytic uremic syndrome(HUS)
  - Hemophagocytic syndrome
- Decreased production
  - Aplastic anemia (AA)
  - Myelodysplastic syndrome (MDS)
- Infection or Medication-induced
- Other causes: pseudothrombocytopenia

Algorithm for management of thrombocytopenia



J Hematol • 2012;1(2-3):44-53

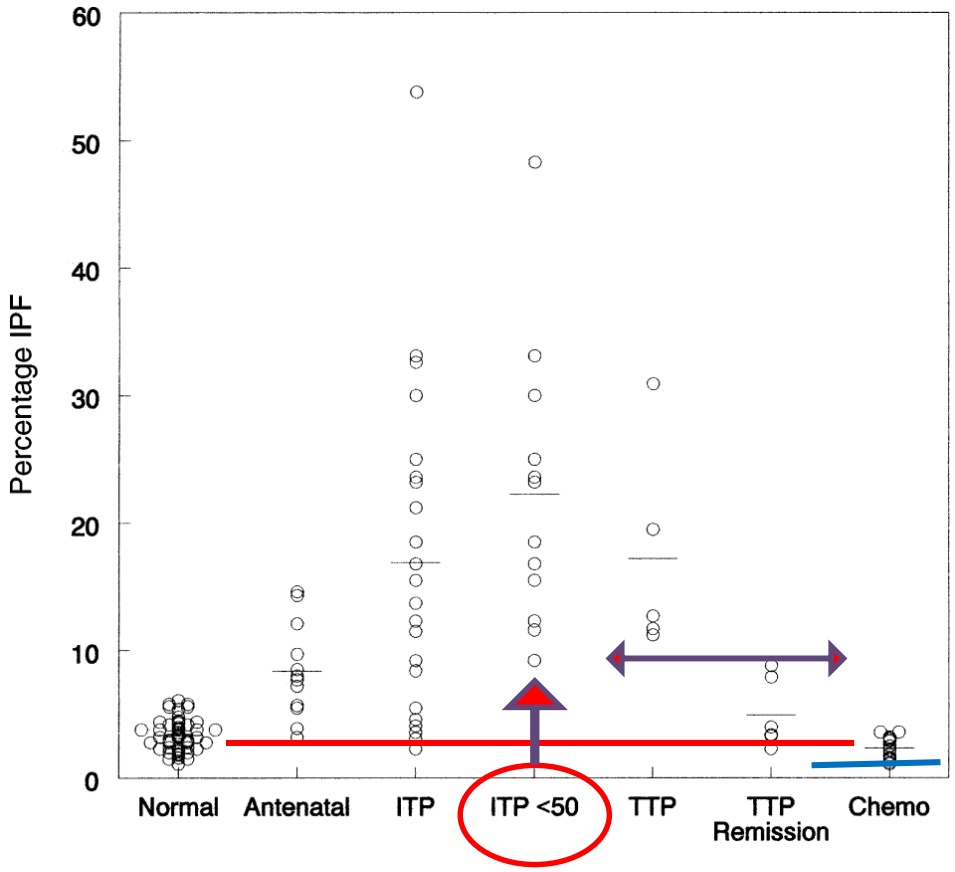
Distinguish ITP from Thrombocytopenic disorders



※ primary immune thrombocytopenia(ITP) , aplastic anemia(AA) , chemotherapy-induced thrombocytopenia(CIT)

Int J Hematol. 2015 Apr;101(4):369-75.

IPF values in thrombocytopenia – diagnosis



- 孕婦IPF較正常人高
  第三孕期 6名
  PIH□ 10.8%
  6名健康□ 6%
- ITP(PLT<5萬)及TTP100%出現IPF上升
- ITP、TTP緩解時IPF數值正常
- 化療後IPF%.A-IPF皆低於normal

Group	IPF% Mean	IPF% Minimum	IPF% Maximum	Percentage of patients with a high IPF	IPF ($\times 10^9$/l) Mean	IPF ($\times 10^9$/l) Minimum	IPF ($\times 10^9$/l) Maximum
Normal	3·4	1·1	6·1		8·6	3·1	16·4
Antenatal	8·4	3·2	14·6	75	15·0	8·6	27·7
AITP	16·8	2·3	52·1	73	8·4	1·6	38·6
AITP < (50 × 10^9/l)	22·3	9·2	48·3	100	7·8	1·6	34·3
TTP	17·2	11·2	30·9	100	5·4	1·2	9·1
TTP (remission)	5·0	2·3	8·8	33	10·4	5·4	16·5
Chemotherapy	2·4	1·1	3·8	0	0·7	0·2	1·4

Br J Haematol. 2004 Jul;126(1):93-9.

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

SOCIÉTÉ INTERNATIONALE D'ONCOLOGIE PÉDIATRIQUE SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

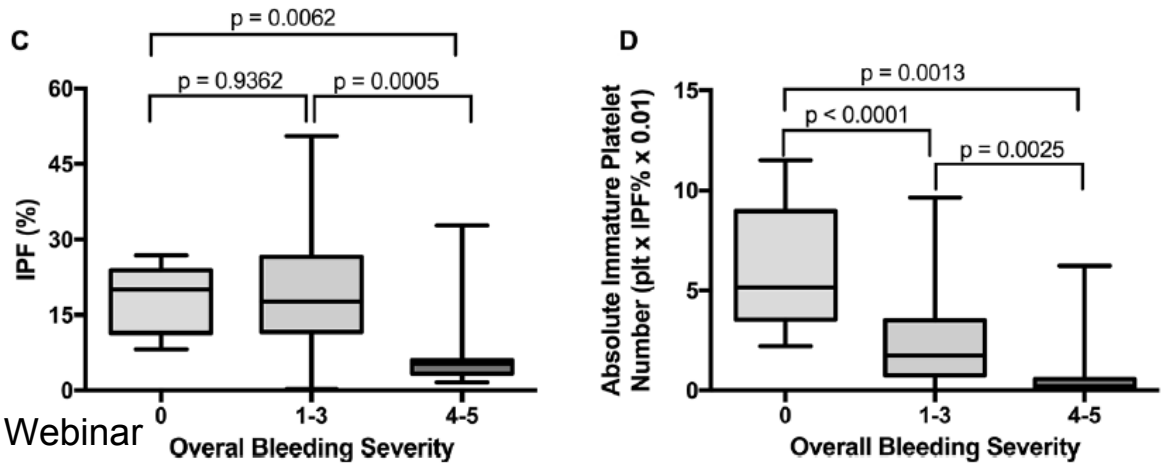
aspho The American Society of Pediatric Hematology/Oncology

Utility of the immature platelet fraction in pediatric immune thrombocytopenia: Differentiating from bone marrow failure and predicting bleeding risk

TABLE 1 Summary of cohort demographics and laboratory data

	ITP	Bone marrow failure	Malignancy	Other	All
Number of patients	97 (36%)	11 (4%)	126 (46%)	38 (14%)	272 (100%)
Age (years)	5 (0.3–20)	9 (7–14)	8 (0.3–21)	4 (0.2–19)	7 (0.2–21)
Sex					
Female	46 (47%)	7 (64%)	59 (47%)	23 (61%)	135 (49.6%)
Platelet count	11 (1–48)	12 (5–42)	20 (1–49)	31 (3–49)	16.5 (1–49)
IPF	17.5 (0.2–50.5)	2.8 (1.5–7.7)	3.2 (0.2–37.5)	8.7 (0.5–49.8)	6.7 (0.2–50.5)

Data presented as median (range) or count (% of total).



Bone Marrow Biopsy: To do or NOT to do?

Original article

Immature platelet fraction (IPF): A reliable tool to predict peripheral thrombocytopenia

Z. Van De Wyngaert[a], E. Fournier[b,c], E. Bera[d], M. Carrette[d], V. Soenen[b], J. Gauthier[a], C. Preudhomme[b], T. Boyer[b,*]

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Table 3
IPF% values and platelet counts according to mechanism of thrombocytopenia.

	Patients, n	Platelet count, 10^9/L	IPF, %
Overall	117	31 [1 – 147]	10.1 [1.1 – 41.3]
Peripheral thrombocytopenia	68 (58)	28.5 [1 – 147]	15.8 [2.9 – 41.3]
ITP	34 (29)	22 [1 – 120]	16.4 [4.3 – 41.3]
Central thrombocytopenia	49 (42)	38 [1 – 119]	6.2 [1.1 – 12.7]
MDS/AL	18 (14)	26.5 [1 – 90]	6.6 [1.2 – 12.3]

Datas are given as total numbers (percentage of 117 patients) and median [range].
ITP: Idiopathic Thrombocytopenic Purpura, MDS: MyeloDysplastic Syndrome, AL: Acute Leukaemia.

Current Research in Translational medicine, 2019

IPF > 13% on Sysmex XN predict PT, and could avoid BM test if isolated thrombocytopenia

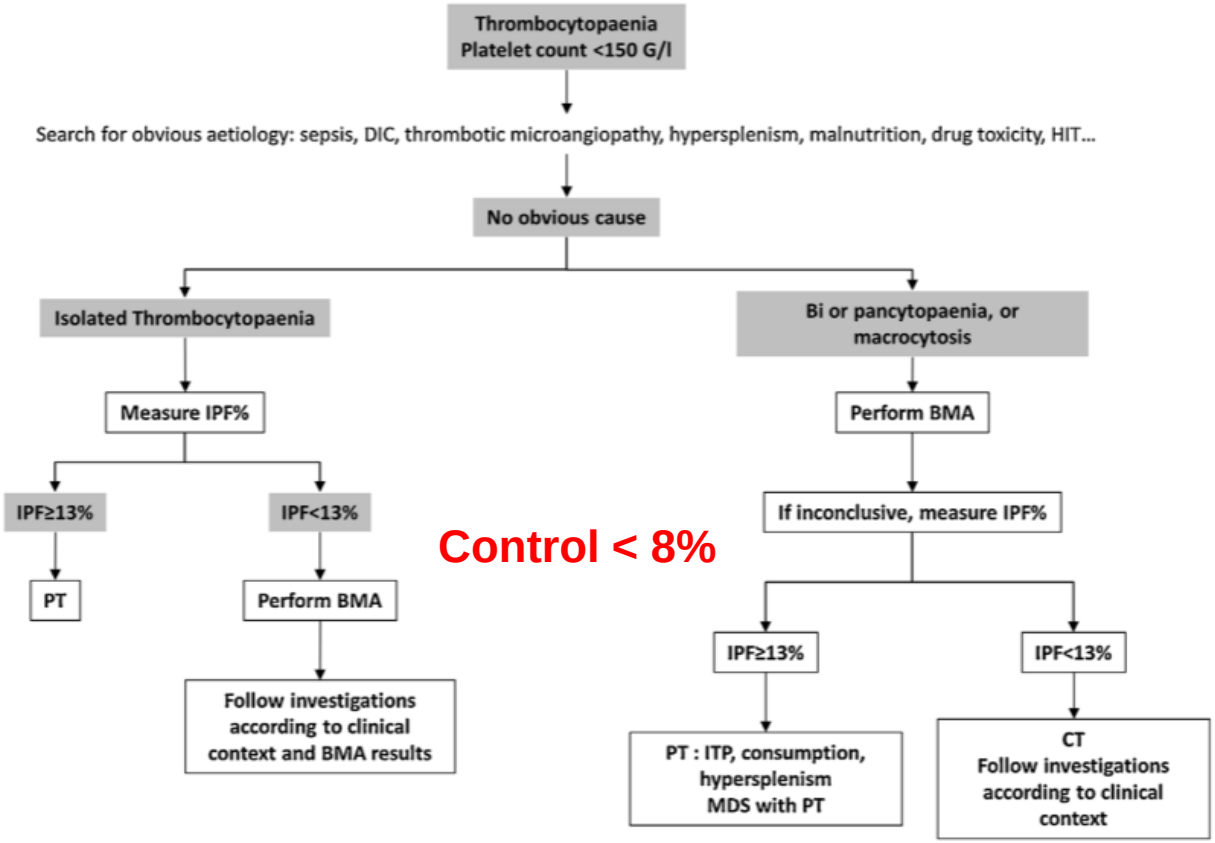


Fig. 2. Decisional flow-chart to investigate thrombocytopenia.
DIC: Disseminated Intravascular Coagulation; HIT: Heparin-Induced Thrombocytopenia; IPF: Immature Platelet Fraction; PT: peripheral thrombocytopenia; BMA: bone marrow aspiration; CT: central thrombocytopenia; MDS: myelodysplastic syndrome; ITP: Immune Thrombocytopenic Purpura

Current Research in Translational medicine, 2019

26/M, purpura, s/p transfusion at CHCH, Hx of CMV, Hiccup after steroid, Dx? Tx?

代碼	細項名稱	結果值	正常值	上限值	下限值
08006-1	Immature Platelet	23.3		7.3	1
08008	Reticulocyte	1.6	0.5~1.5	1.5	0.5
	RET-He	31.2	31.7~37.6	37.6	31.7
08011	W.B.C	6.62	4.5~10	10	4.5
	RBC	5.28	4.5~6	6	4.5
	Hemoglobin(Hb)	15.3	13~17	17	13
	HCT	45.5	40~52	52	40
	MCV	86.2	80~100	100	80
	MCH	29.0	27~33	33	27
	MCHC	33.6	32~36	36	32
	PLT	31	120~350	350	120
	RDW-SD	39.9	36~46	46	36
08013	Neut_Seg %	57.7	55~71	71	55
	Lymph%	35.1	20~56	56	20
	Mono%	4.7	0~12	12	0
	Eosin%	2.0	0~5	5	0
	Baso%	0.5	0~1	1	0

F/U CMV+, DIC- HBV- HCV- Hp-HIV-

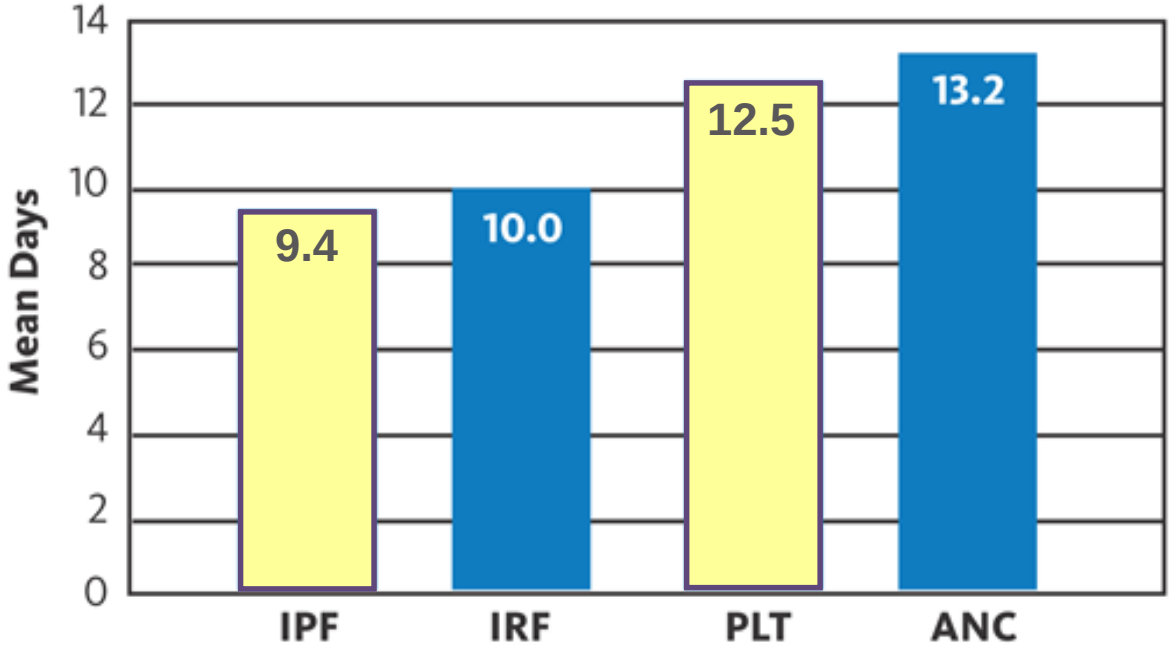
W.B.C	RBC	Hemoglobin (Hb)	HCT	MCV	MCH	MCHC	PLT
11.98	5.24	15.0	45.6	87.0	28.6	32.9	105
11.44	5.15	14.6	44.5	86.4	28.3	32.8	57
10.72	5.32	15.2	45.7	85.9	28.6	33.3	70
13.04	5.20	14.9	43.7	84.0	28.7	34.1	138
6.62	5.28	15.3	45.5	86.2	29.0	33.6	31

Clinical Utility of IPF

- Diagnosis of Thrombocytopenia
- Monitor of Hematopoietic Recovery
- Reduce Prophylactic Transfusion

Mean days to recovery after transplantation

50 patients undergoing peripheral hematopoietic cell transplants



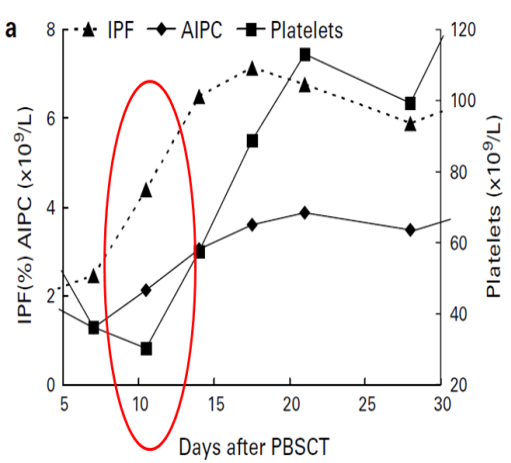
IPF recovered on average 3.1 days prior to platelet count recovery

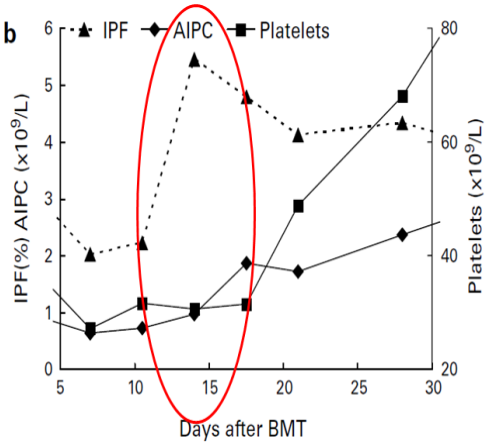
Lab Hematol. 2006;12(3):125-30.

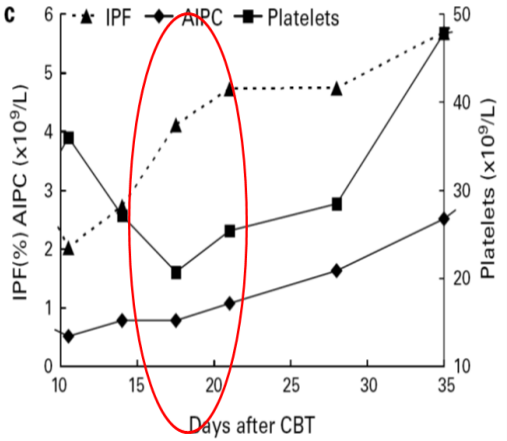
Predict hematologic recovery after transplantation

Bone Marrow Transplant. 2007 Apr;39(8):501-7

※peripheral blood stem cell transplantation(PBSCT),bone marrow transplantation(BMT), cord blood transplantation(CBT),absolute immature platelet count(AIPC),immature platelet fraction(IPF)







	PBSCT	P	*BMT*	P	*CBT*	P
			Median % (range)			
IPF, minimum	1.8 (0.4–2.5)		1.0 (0.4–2.1)		0.8 (0.4–1.2)	
IPF, maximum	8.2 (5.1–34.0)		6.3 (4.2–12.9)		11.7 (4.2–19.4)	
			Mean days post transplantation (range)			
IPF⩾3.0%	11 (7–13)	[a]	18 (6–22)	[a]	19 (15–29)	[a]
IPF⩾3.5%	11 (7–13)		21 (15–22)		23 (15–29)	
IPF⩾4.0%	12 (7–14)		21 (15–28)		24 (15–29)	
Platelet engraftment	12 (8–15)	0.3	22 (12–40)	0.01	32 (25–41)	0.01
RBC engraftment	14 (11–15)	0.2	25 (18–40)	0.02	36 (25–56)	0.01
Neutrophil engraftment	12 (10–18)	0.5	15 (11–20)	0.7	20 (12–28)	0.9
IRF⩾10%	14 (10–15)	0.7	16 (13–20)	0.9	21 (15–29)	0.4

- PBSCT restored hematopoiesis the fastest, followed by BMT.
- When IPF rise more than 3% represented the of hematologic recovery

IPF predicts PLT recovery after marrow suppression

P't with Chemotherapy

Platelet recovery after the day of peak IPF% (days)	Number of cases: Group 1 (>10%*)	Group 2 (≤10%*)
1	4	0
2	9	7
3	6	6
4	2	4
5	1	5
6	0	3
7	1	7
Range (days)	1~7	2~7
Median (days)	2	5

The median days of platelet recovery: Group 1 *vs.* Group 2, $P < 0.05$.
(>30x10⁹/L)
IPF, immature platelet fraction.
*IPF% peak value.

P't with stem cell transplantation

IPF peak

Diseases	Age/sex	HSCT	Platelet recovery after the day of peak IPF% (days): Group 1 (>10%*)	Group 2 (≤10%*)
AML	36/m	allo-BMT	2	7
AML	49/f	allo-PBSCT		4, 11
ALL	41/f	allo-PBSCT		7
RAEB-II	46/f	allo-BMT		3, 6
RAEB-II	58/m	allo-BMT	2	
NHL	40/m	allo-BMT		6
NHL	59/f	allo-BMT		4
NHL	48/m	auto-PBSCT	2	
		Range (days)	2	3~11
		Median (days)	2	6

IPF >10%, 2 days PLT recovery
IPF <10%, 5~6 days PLT recovery

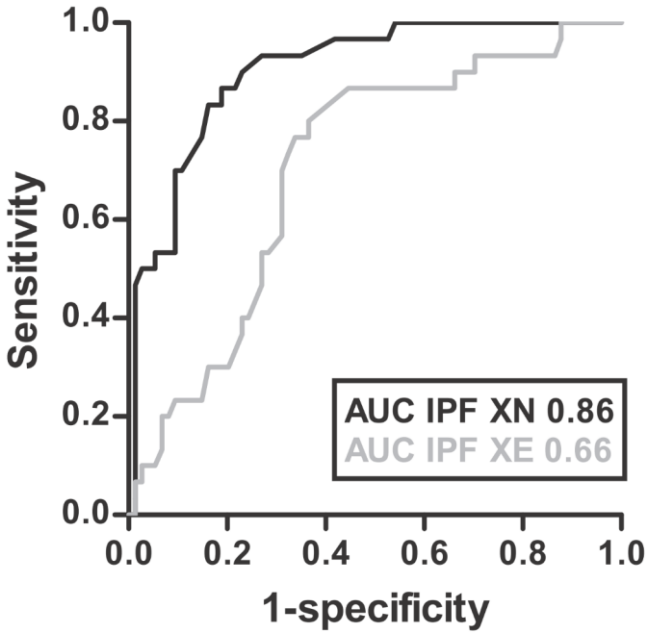
Int J Lab Hematol. 2010 Dec;32(6 Pt 1):e208-16

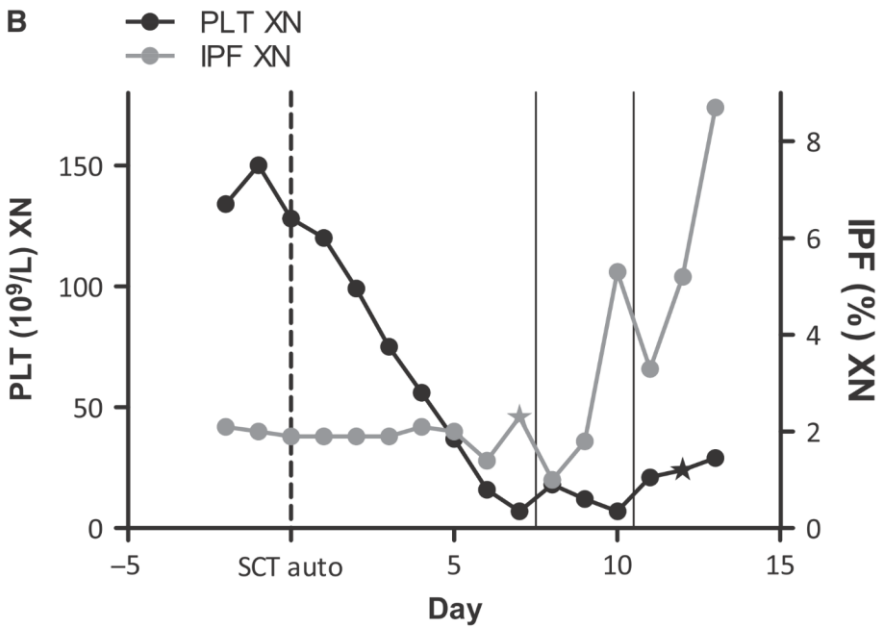
Cut-off value of using IPF on hemocytometer

EUROPEAN JOURNAL OF Haematology

European Journal of Haematology 93 (150–156)

Immature platelet fraction measured on the Sysmex XN hemocytometer predicts thrombopoietic recovery after autologous stem cell transplantation





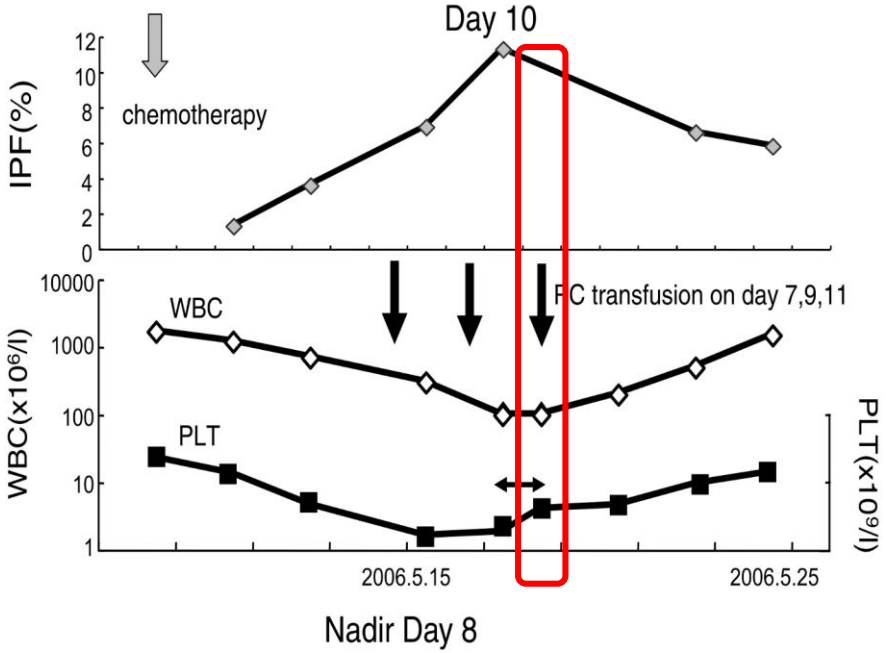
Optimal cutoff IPF was found to be 5.3% for platelet recovery within 2 days (specificity 0.98, sensitivity 0.47, PPV 0.93).

Eur J Haematol. 2014 Aug;93(2):150-6.

Clinical Utility of IPF

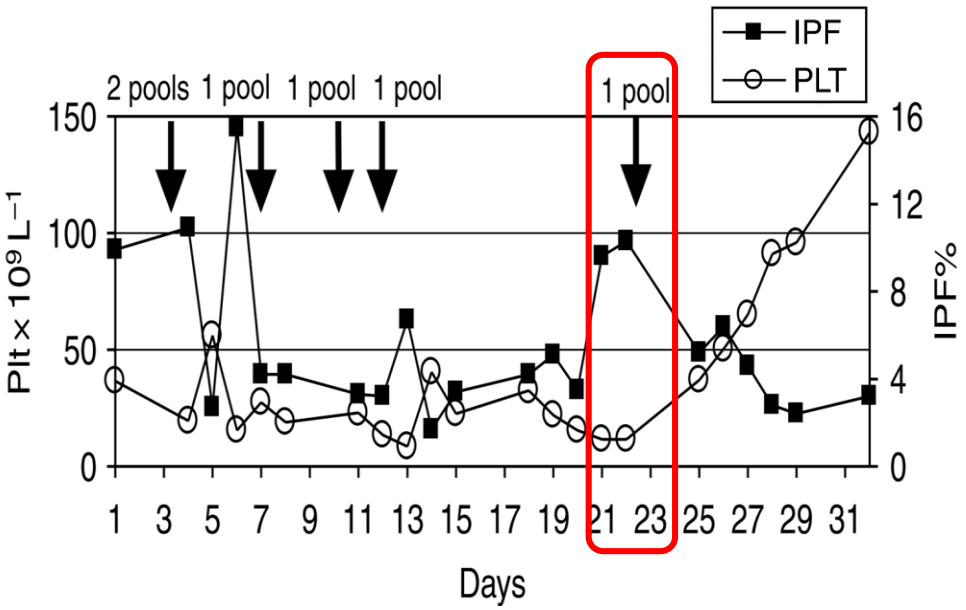
- Diagnosis of Thrombocytopenia
- Monitor of Hematopoietic Recovery
- Reduce Prophylactic Transfusion

Avoid unnecessary prophylactic platelet transfusion



Platelet recovery was defined as either PLT > 30x10^9/L or PLT increase 10x10^9/L over PLT nadir without transfusion

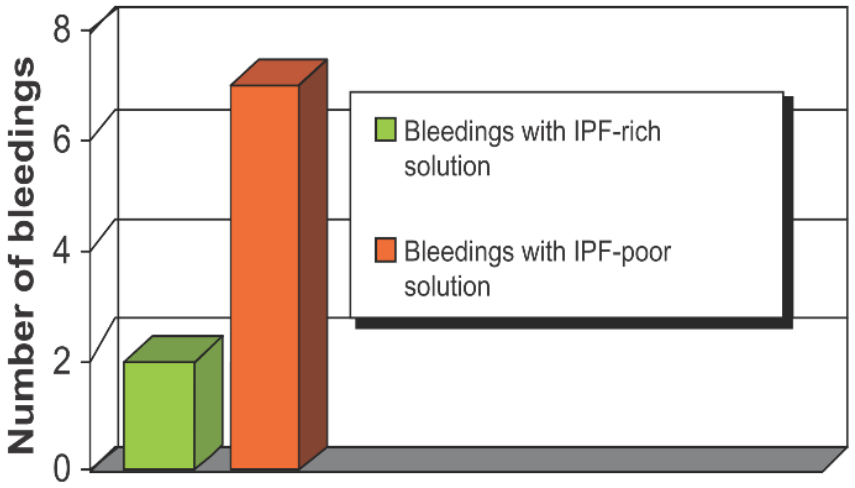
Transfus Apher Sci. 2008 Apr;38(2):127-32

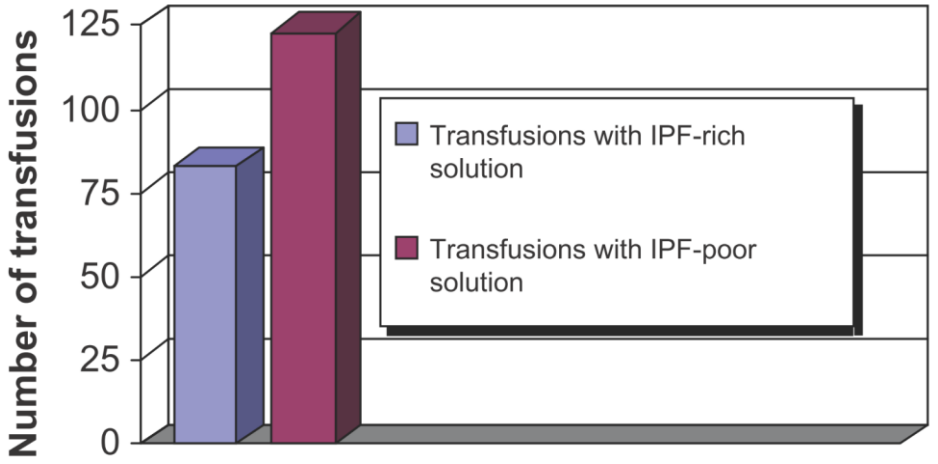


On day 21 (PLT 0.9x10^9/L; IPF 11.5%), patient was absence of bleeding or clinical evidence of sepsis. Thus, PLT transfusion on day 22 was unnecessary

Transfus Med. 2006 Apr;16(2):101-9.

Transfusion management during transplantation





Mean of the number of transfusions

Group	Mean	N	SD	Median	Minimum	Maximum
Poor IPF	6.45	20	0.759	6	6	8
Rich IPF	4.15	20	0.489	4	4	6
Total	5.30	40	1324	6	4	8

Note: The Mann–Whitney test shows a significant difference ($P < 0.001$).
Abbreviation: IPF, immature platelet fraction.

Rich IPF: 3.6%–7.0%
Poor IPF: 0.3%–3.5%

IPF reduces the number of transfusions and bleedings after peripheral blood stem cell transplantation in pediatric patients

OncoTargets and Therapy 2012:5 1–

Summary of IPF analysis on hematology analyzer

- Automated, easy to perform, standardized results.
  - Eliminate variation between operators.
  - Receive rapid report during clinic visit.
- IPF helps to distinguish thrombocytopenic disorders.
- Reduce unnecessary prophylactic platelet transfusion.
  - Monitoring of bone marrow thrombopoiesis
- New biomarkers…

IPF for COVID-19 patients

bjh research paper

Immature platelets as a biomarker for disease severity and mortality in COVID-19 patients

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Summary

COVID-19, caused by SARS-CoV-2, is a contagious life-threatening viral disease that has killed more than three million people worldwide to date. Attempts have been made to identify biomarker(s) to stratify disease severity and improve treatment and resource allocation. Patients with SARS-COV-2 infection manifest with a higher inflammatory response and platelet hyperreactivity; this raises the question of the role of thrombopoiesis in COVID-19 infection. Immature platelet fraction (IPF, %) and immature platelet counts (IPC, $\times 10^9$/l) can be used to assess thrombopoiesis. This study investigates whether the level of thrombopoiesis correlates with COVID-19 severity. A large cohort of 678 well-characterized COVID-19 patients was analyzed, including 658 (97%) hospitalized and 139 (21%) admitted to the intensive care unit (ICU). Elevated percentage IPF at presentation was predictive of length of hospitalization ($P < 0{\cdot}01$) and ICU admission ($P < 0{\cdot}05$). Additionally, percentage IPF at the peak was significantly higher among ICU patients than non-ICU patients ($6{\cdot}9 \pm 5{\cdot}1$ vs $5{\cdot}3 \pm 8{\cdot}4$, $P < 0{\cdot}01$) and among deceased patients than recovered patients ($7{\cdot}9 \pm 6{\cdot}3$ vs $5{\cdot}4 \pm 7{\cdot}8$, $P < 0{\cdot}01$). Furthermore, IPC at the peak was significantly higher among ICU patients than non-ICU patients ($18{\cdot}5 \pm 16{\cdot}2$ vs. $13{\cdot}2 \pm 8{\cdot}3$, $P < 0{\cdot}05$) and among patients on a ventilator than those not ($22{\cdot}1 \pm 20{\cdot}1$ vs.$13{\cdot}4 \pm 8{\cdot}4$, $P < 0{\cdot}05$). Our study demonstrated that elevated initial and peak values of percentage IPF and IPC might serve as prognostic biomarkers for COVID-19 progression to severe conditions.

Keywords: immature platelet, IPF, reticulated platelets, COVID-19,

Table II. IPF (%,) IPC and platelet count by severity outcomes.

Characteristics		All	In house mortality			Admitted to ICU among hospitalized			Ventilator use among hospitalized		
			Yes (n = 56)	No (n = 622)	P*	Yes (n = 139)	No (n = 519)	P*	Yes (n = 79)	No (n = 579)	P*
IPF (%) Initial presentation	Mean±SD	4·9 ± 3·2	6·4 ± 5·7	4·8 ± 2·8	0·09	5·8 ± 4·6	4·7 ± 2·6	0·03	5·8 ± 4·3	4·8 ± 3·0	0·06
IPF (%) Peak	Mean±SD	5·3 ± 3·5	7·9 ± 6·3	5·4 ± 7·8	<0·01	6·9 ± 5·1	5·3 ± 8·4	<0·01	7·5 ± 5·0	5·4 ± 8·1	<0·01
High IPF at Initial presentation (>6·1%)	High (n, %)	164 (24·2%)	17 (30·4%)	147 (23·6%)	0·2608	44 (31·7%)	113 (21·8%)	0·02	57 (34·2%)	137 (22·9%)	0·04
High IPF at peak (>6·1%)	High (n, %)	191 (28·2%)	27 (48·2%)	164 (26·4%)	<0·01	59 (42·4%)	125 (24·1%)	<0·01	40 (50·6%)	151 (25·2%)	<0·01
IPC (x10^9/l) at initial presentation	Mean±SD	10·0 ± 6·1	11·0 ± 10·6	10·6 ± 6·2	0·31	12·1 ± 9·1	10·2 ± 5·6	0·41	12·5 ± 9·7	10·4 ± 6·0	0·50
IPC (×10^9/l) at peak	Mean±SD	13·4 ± 9·7	15·9 ± 16·8	14·0 ± 10·0	0·56	18·5 ± 16·2	13·2 ± 8·3	0·045	22·1 ± 20·1	13·4 ± 8·4	0·03
Platelet count (×10^9/l) at initial presentation	Mean±SD	222·2 ± 98·9	180·9 ± 97·4	226·0 ± 98·3	<0·01	219·7 ± 104·5	224·0 ± 98·5	0·60	221·5 ± 111·9	223·3 ± 98·0	0·07
Platelet count (×10^9/l) at peak	Mean±SD	269·1 ± 127·3	223·1 ± 119·2	273·3 ± 127·3	0·01	278·9 ± 136·1	268·8 ± 126·0	0·30	292·4 ± 137·6	268·0 ± 126·7	0·80
Platelet count (×10^9/l), minimum	Mean±SD	213·8 ± 98·7	158·4 ± 107·1	218·8 ± 96·7	<0·01	193·4 ± 101·8	220·0 ± 98·2	<0·01	185·6 ± 110·4	218·3 ± 97·4	<0·01

ICU, intensive care unit; IPC, immature platelet counts; IPF, immature platelet fraction.
*Two-sided Wilcoxon rank-sum test.

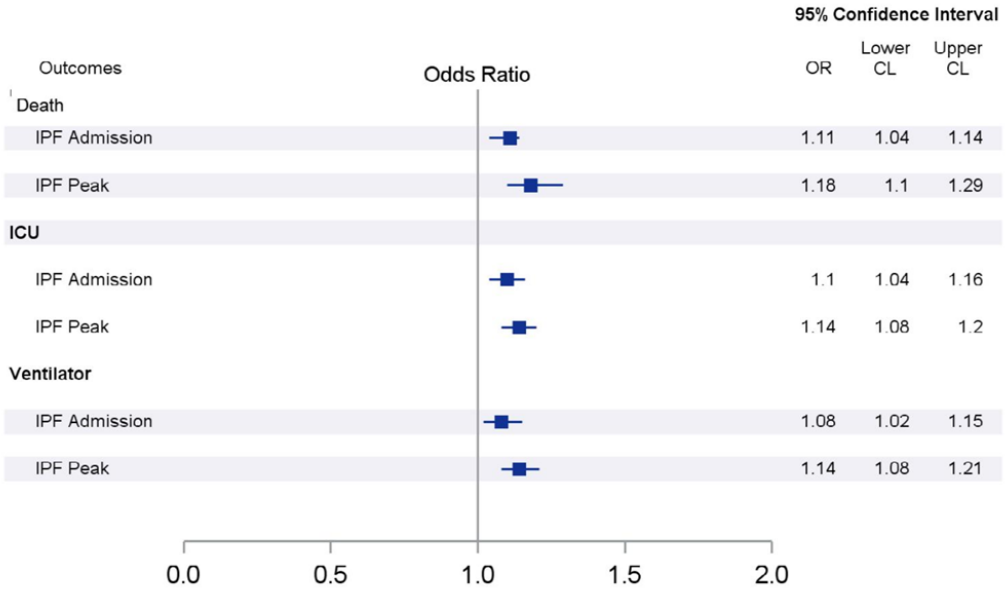

Fig 1. Logistic regression results of immature platelet fraction (IPF, %) on death, intensive care unit (ICU) and mechanical ventilation requirement. The 95% confidence interval [lower confidence limit (CL)–upper CL] of odds ratios (OR) does not include '1' and is statistically significant under α = 0·05. [Colour figure can be viewed at wileyonlinelibrary.com]

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Immature platelet fraction: is a novel early predictive marker for disease severity in patients with Covid-19 pneumonia?

[İmmatür Platelet Fraksiyonu: Covid-19 Pnömonisi Olan Hastalarda Hastalık Şiddeti İçin Yeni Bir Erken Prediktif Belirteç olabilir mi?]

Said Incir, Zeynep Komesli, Arzu Baygul, Zeynep Atam Tasdemir, Kerim Erhan Palaoglu, Hatice Kant, Mahir Kapmaz, Suda Tekin, Alparslan Kilic, Tuncay Dagel, Ayse Okan, Kayra Somay and Timur Selcuk Akpinar

From the journal Turkish Journal of Biochemistry
https://doi.org/10.1515/tjb-2021-0070

Cite this

Abstract

Objectives

In many diseases, immature platelet fraction (IPF%) is related to coagulopathy and poor outcome. This study aimed to investigate the predictive value of IPF% for the severity of pneumonia in patients with Coronavirus Disease 2019 (COVID-19).

Methods

A total of 154 patients with COVID-19 infections were included. The patients were divided into two groups according to the severity of pneumonia (severe and non-severe) regarding their oxygen demand.

Results

Given laboratory parameters, the median IPF% was significantly higher in the severe group (11.9 vs. 3.9%, $p<0.001$). Mean platelet volume ($p<0.001$), platelet-large cell ratio ($p=0.001$), platelet distribution width ($p=0.001$), D-Dimer ($p<0.001$), INR ($p=0.003$), and aPTT ($p=0.007$) were also found to be significantly higher in the severe group. Moreover, IPF ($p=0.014$, Odds ratio = 2.000, 95%CI: 1.149-3.482) was an independent predictor for the severity. The curve value from receiver operating characteristics was 0.879 ($p<0.001$, 95%CI: 0.784-0.943) for determining the severity of pneumonia. IPF% had a sensitivity and specificity value of 69.5 and 92.4% to detect the disease's severity.

Conclusions

IPF% is an independent predictor for the severity of COVID-19 pneumonia. Assessment of IPF% may both help to early determine high-risk patients with COVID-19 and to alert the physicians.

Table 1: Baseline hospital admission demographic, clinical and laboratory features of all, severe and non-severe Covid-19 patients.

	All patients (n=154)	Severe (n=44)	Non-severe (n=110)	p* value
Male/Female, n	87/67	27/17	60/50	0.607[3]
Age, years	55 (18–91)	63 (20–91)	45 (18–89)	**0.003**[1]
BMI	26 (19–31)	29 (20–31)	25 (19–31)	0.628[1]
Current smoker	6 (4%)	1 (2%)	5 (5%)	0.466[4]
Comorbid conditions				
Hypertension (n,%)	45 (29%)	21 (48%)	24 (22%)	**0.043**[3]
Diabetes (n,%)	35 (23%)	8 (19%)	27 (25%)	0.781[4]
Cardiovascular disease (n,%)	21 (14%)	8 (19%)	13 (12%)	0.650[4]
Chronic obstructive pulmonary disease (n,%)	6 (4%)	4 (9%)	2 (2%)	0.424[4]
Chronic kidney disease (n,%)	2 (1%)	2 (5%)	0	0.522[4]
Other (n,%)	37 (24%)	19 (43%)	18 (16%)	**0.024**[4]
Symptoms				
Fever (n,%)	144 (93%)	42 (95%)	102 (93%)	0,859[3]
Cough (n,%)	110 (71%)	31 (71%)	79 (72%)	0.852[3]
Sputum (n,%)	30 (19%)	17 (38%)	13 (12%)	**0.020**[4]
Dyspnea (n,%)	79 (51%)	44 (100%)	35 (32%)	**<0.001**[3]
Fatigue or myalgia (n,%)	63 (41%)	19 (43%)	44 (40%)	0.995[4]
Nausea or vomiting (n,%)	15 (10%)	4 (9%)	11 (10%)	0.777[4]
Diarrhea (n,%)	12 (8%)	2 (4%)	10 (9%)	0.770[4]
Anosmia (n,%)	75 (49%)	29 (67%)	46 (42%)	0.077[3]
Laboratory findings				
Immature platelet fraction, %	4.75 (0.70–31.1)	11.9 (3.4–31.1)	3.9 (0.70–15.2)	**<0.001**[1]
Platelet count (10^9/L)	232 (150–636)	196 (150–636)	244 (155–460)	0.065[1]
Mean platelet volume, fL	11.2 ± 1.29	12.1 ± 1.22	10.8 ± 1.10	**<0.001**[2]
Platelet-large cell ratio, %	34 ± 9.87	40.5 ± 9.30	31.4 ± 8.84	**0.001**[2]
Platelet distribution width, fL	13.1 (7.50–24.5)	15.6 (10.3–21.9)	12.4 (7.50–24.5)	**0.001**[1]
Hemoglobin, g/dL	12.1 ± 2.38	10.7 ± 2.92	12.7 ± 1.83	**0.001**[2]
Immature granulocyte ratio, %	0.60 (0.10–13.6)	1.20 (0.30–4.50)	0.50 (0.10–13.6)	**0.001**[1]
Leukocyte count (10^9/L)	7.51 (3.01–28.0)	10.0 (3.23–28.0)	7.19 (3.01–19.6)	**0.001**[1]
Neutrophil count (10^9/L)	4.77 (1.06–17.6)	7.92 (1.92–17.5)	4.36 (1.06–17.6)	**<0.001**[1]
Lymphocyte count (10^9/L)	1.28 ± 0.59	0.97 (0.19–2.05)	1.41 (0.45–9.50)	**0.002**[1]
Neutrophil-to-lymphocyte ratio	3.52 (0.26–85.2)	10.7 (1.83–85.2)	3.27 (0.26–16.7)	**<0.001**[1]
Monocyte count (10^9/L)	0.56 (0.03–9.34)	0.54 (0.11–9.34)	0.58 (0.03–2.33)	0.768[1]
C-reactive protein, mg/L	42.6 (0.60–308)	52.9 (0.80–308)	34.9 (0.60–192)	**0.024**[1]
Ferritin, ng/mL	311 (20.0–4,427)	458 (66.0–4,427)	274 (20.0–2,306)	**0.016**[1]
Lactate dehydrogenase, U/L	233 (94.0–1,015)	279 (177–1,010)	220 (94.0–1,015)	0.081[1]
Lactate, mmol/L	2.15 (0.80–8.30)	2.85 (1.20–8.30)	2.05 (0.80–4.0)	0.090[1]
D-dimer, ug/L	1,400 (190–8,650)	2,800 (340–8,650)	975 (190–6,600)	**<0.001**[1]
Prothrombin time, %	103 (19.1–165)	103 (73.9–132)	103 (19.1–165)	0.972[1]
International normalized ratio (INR)	1.02 (0.88–8.17)	1.07 (0.96–8.17)	1 (0.88–2.96)	**0.003**[1]
Activated partial thromboplastin time (s)	29.0 (15.0–73.0)	34.0 (15.0–73.0)	27.5 (17.0–52.0)	**0.007**[1]
Fibrinogen, g/L	4.47 ± 1.14	5.02 ± 1.37	4.25 ± 1.01	0.064[2]
Interleukin-6, ng/L	44.6 (1.50–2,494)	94.2 (4.70–2,494)	17.4 (1.50–216)	**0.002**[1]

*p comparison between severe and non-severe cases.[1]Mann Whitney u test, [2]Student's t-test, [3]Chi Square test, [4]Fisher Exact test.Non-normally distributed data were expressed as med (min-max), normally distributed data were expressed mean ± *SD*.

Table 2: The multivariate logistic regression analyses to detect the independent variables for the disease severity.

Dependent variable	Predictors	OR*	95% CI (lower-upper bound)	p-Value
Severity	Age	1.039	0.947–1.141	0.419
	Gender	0.074	0.001–6.645	0.257
	IPF	2.000	1.149–3.482	**0.014**
	Hemoglobin	0.690	0.180–2.646	0.589
	IG	1.382	0.811–2.353	0.234
	Leukocyte count	1.497	0.835–2.684	0.176
	NLR	1.489	0.857–2.589	0.158
	CRP	0.996	0.970–1.021	0.731
	Ferritin	1.002	0.997–1.007	0.383
	D-dimer	1.001	1.000–1.003	0.061

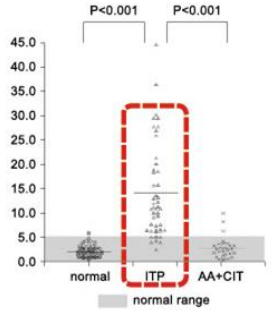
The model was statistically significant ($p<0.05$). The Nagelkerke R^2 was 0.888 and significance for model fit Hosmer Lemeshow was, $p=1.00$. IPF: Immature Platelet Fraction, IG: Immature Granulocytes, NLR: Neutrophil-to-Lymphocyte Ratio, CRP: C-reactive Protein, OR* Odds ratio.

IPF Immature Platelet Fraction臨床應用
骨髓製造血小板功能參考指標

Sysmex 血液分析儀可同時提供IPF未成熟血小板及PLT相關資訊，專一性媲美CD61/CD41單株抗體染色，提供臨床快速可靠、經濟實惠的決策輔助。

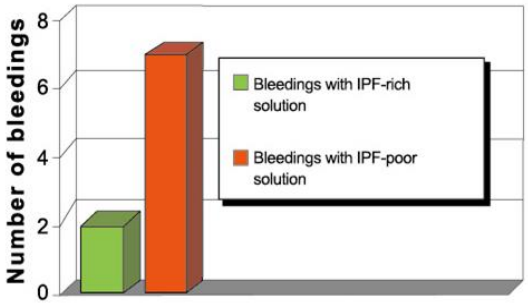
臨床應用 血小板低下症區分診斷

IPF區分診斷血小板消耗增加(ITP)或骨髓生成不足(AA)



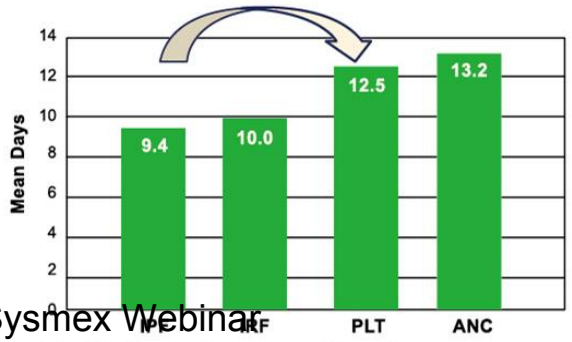
臨床應用 輸血風險管理

IPF-rich的血小板造成的出血風險較低



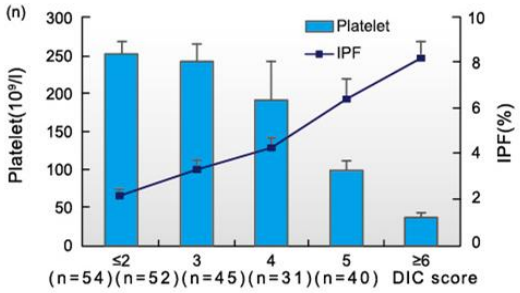
臨床應用 移植後骨髓造血指標

IPF相較PLT, 提前3-4天開始上升



臨床應用 DIC患者預後指標

IPF與DIC嚴重程度有正相關



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謝謝聆聽




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