Jodi Mones, MD
Associate Professor
Associate Fellowship Program Director

Thrombocytopenia (other than ITP, HITT and TTP…LOL….)

Memorial Sloan Kettering Cancer Center

Disclosures:

- Janssen
- Dova Advisory Boards

What We'll Cover

- Bleeding risk
  - General population
  - Chemotherapy – induced
- Inherited causes of thrombocytopenia
  - MYH9
  - Mediterranean thrombocytopenia
  - Pseudothrombocytopenia
- Acquired thrombocytopenia
  - Drug induced
  - PTP
  - Thrombocytopenia in critically ill (MICU/SICU)
  - Pregnancy

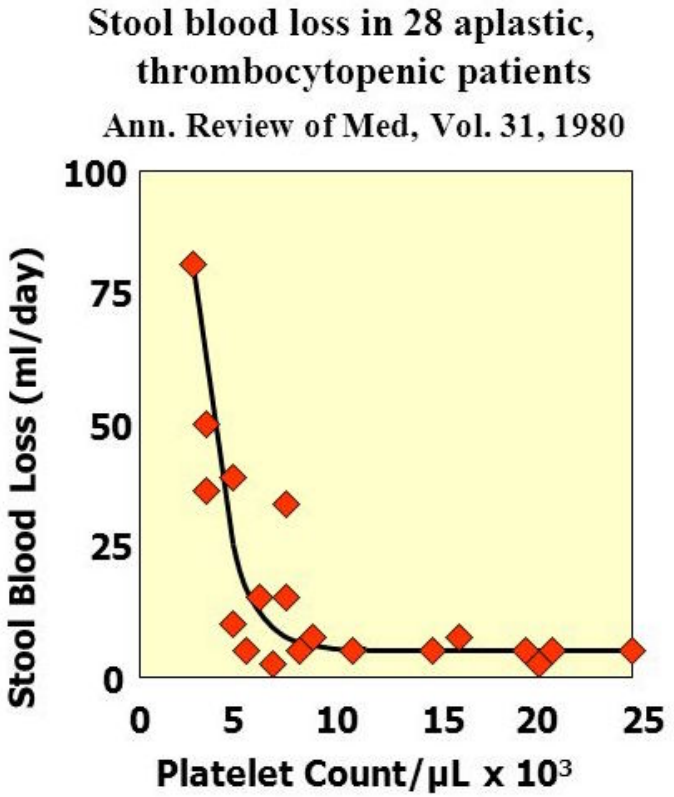
Thrombocytopenia

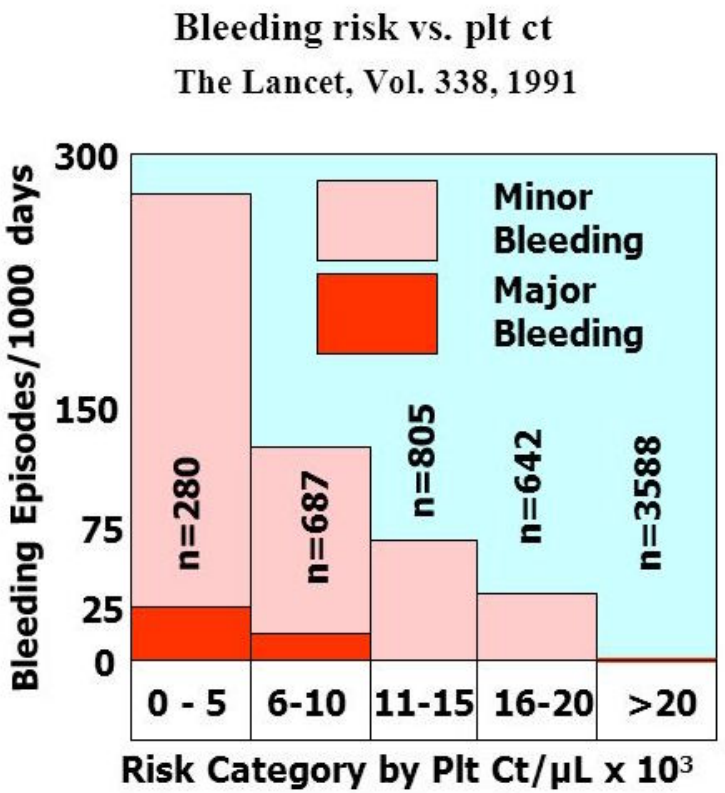
- Why do we care?
  - Quantifying the risk of bleeding…….
  - Utilization of resources
    - 30% of hematology inpatient consults
    - 5-10% of hospitalized general medicine patients are thrombocytopenic
    - 35% of ICU patient have thrombocytopenia
- Normal reference range at MSK:
  - 160 – 400 K/mcL

Hui P. Chest 2011 Feb; 139 (2): 271

Risk of Bleeding & Platelet Count

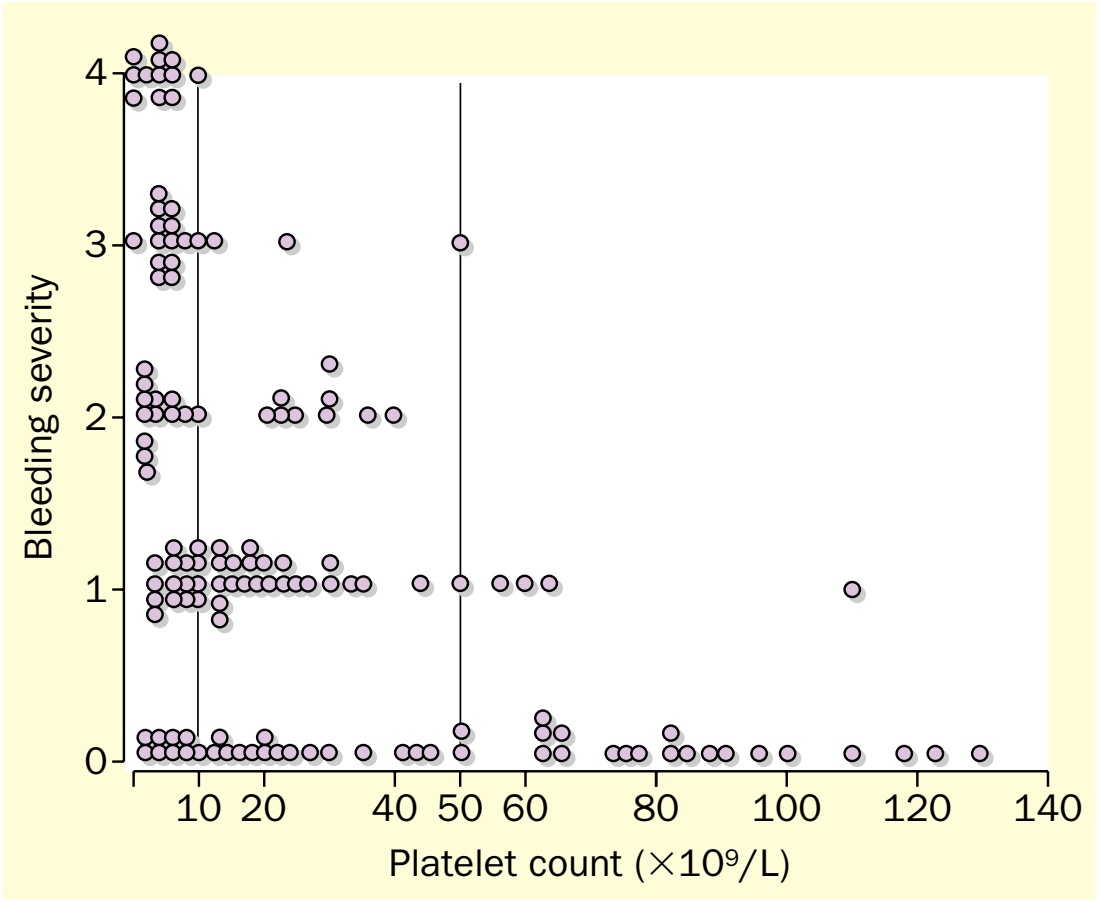
Clinically significant spontaneous bleeding: less than 10-20 × 10^9/L





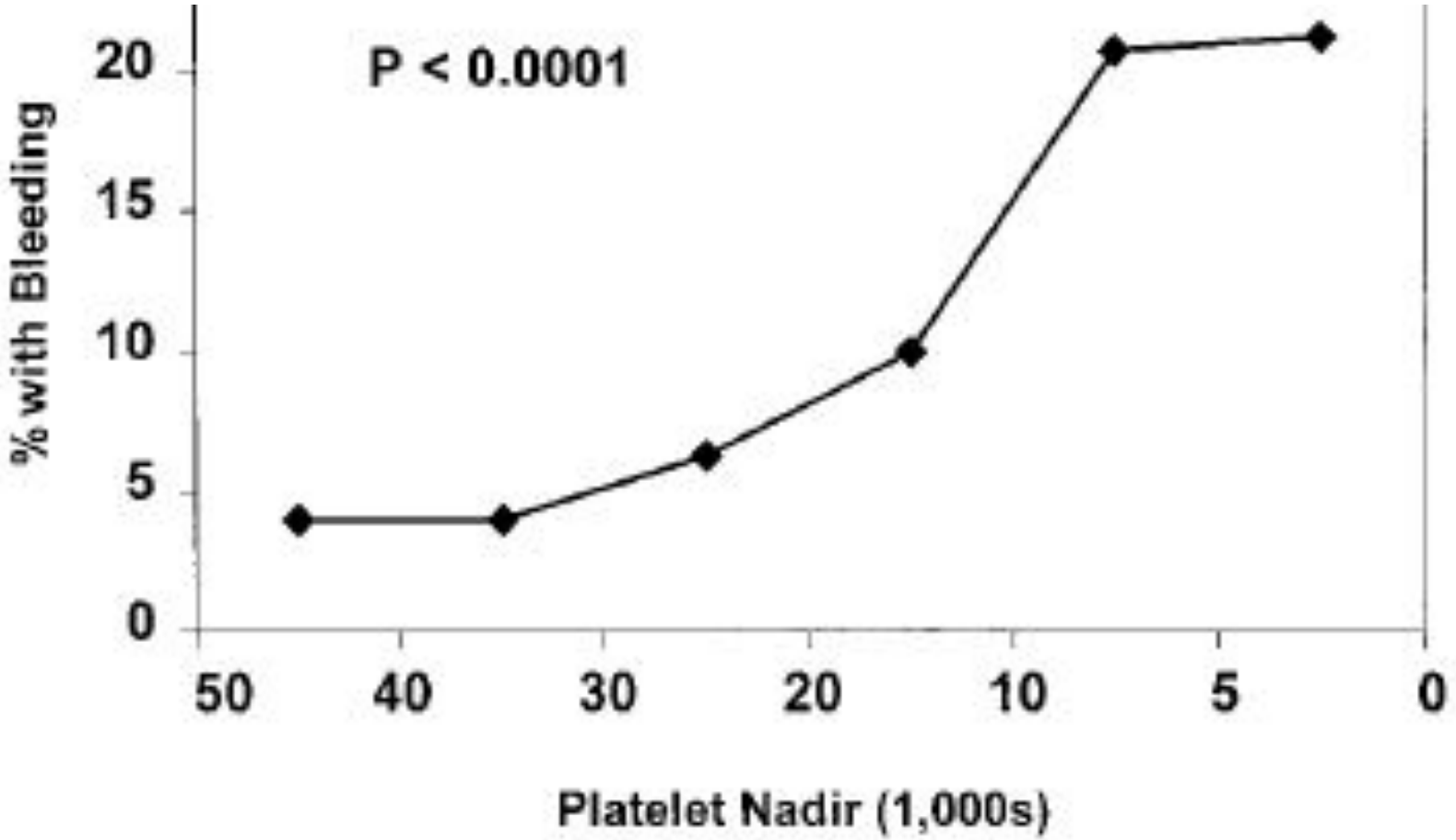
http://images.slideplayer.com/14/4494169/slides/slide_13.jpg

Bleeding Severity in Relation to Platelet Count



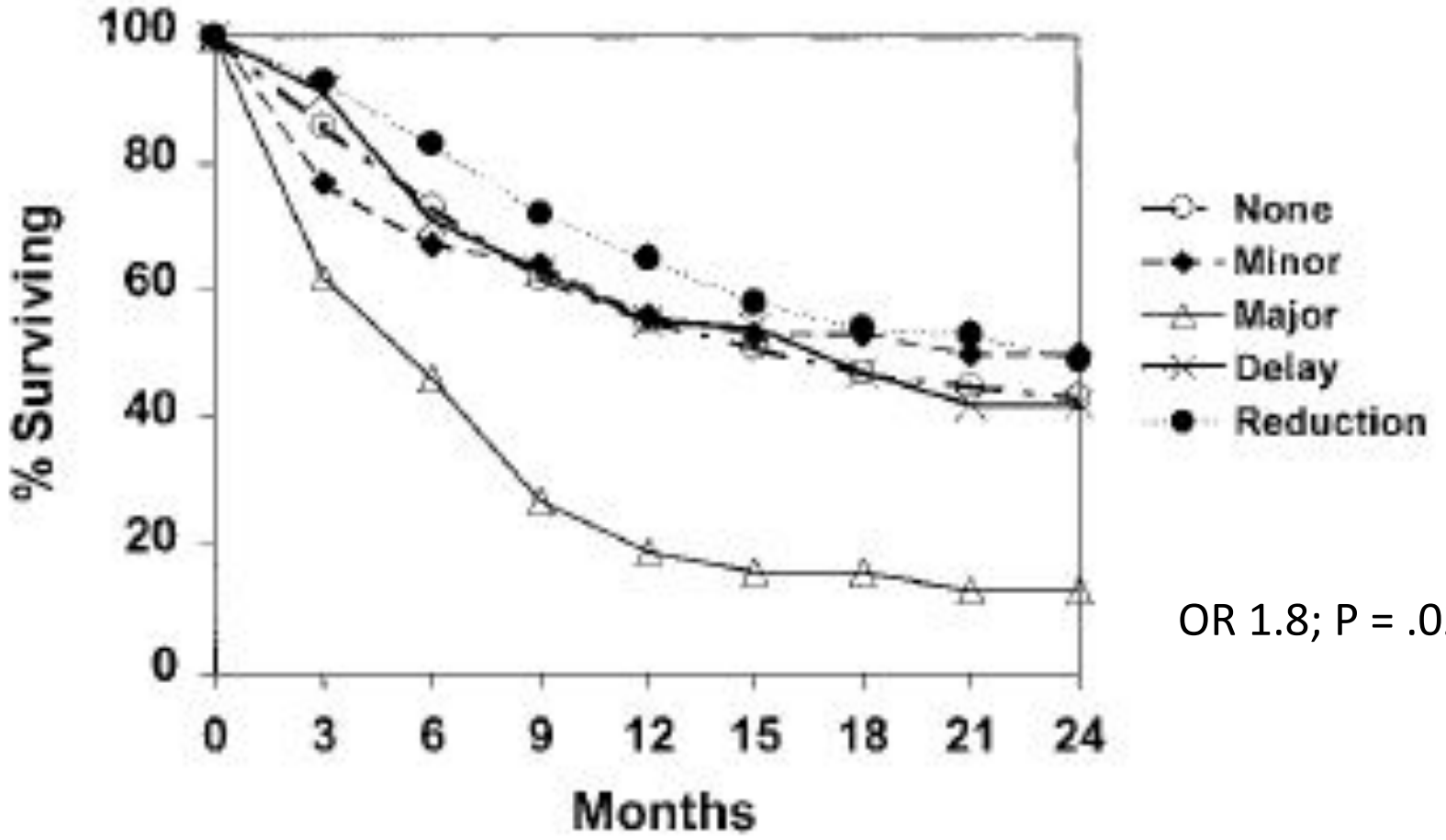
Lacey and Penner, Seminars in Thrombosis and Hemostasis 1977; 3: 3

Bleeding Severity in Relation to Platelet Count – CIT (chemotherapy induced thromboctyopenia)



L. Etling et al JCO Vol 19; No 4 (Feb 15 2001) pp 1137-1146

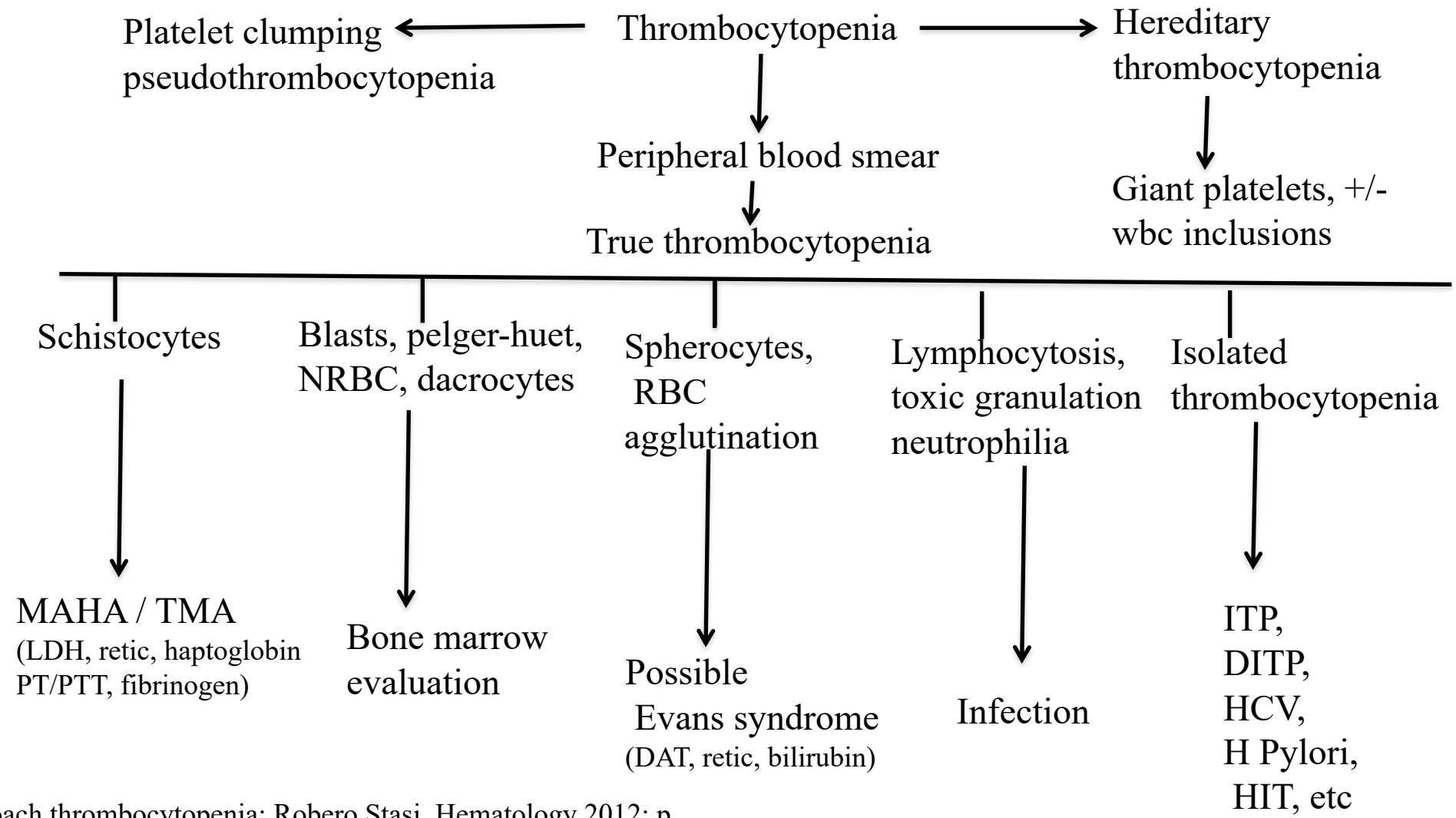
Bleeding Severity in Relation to Platelet Count – CIT (chemotherapy induced thromboctyopenia)



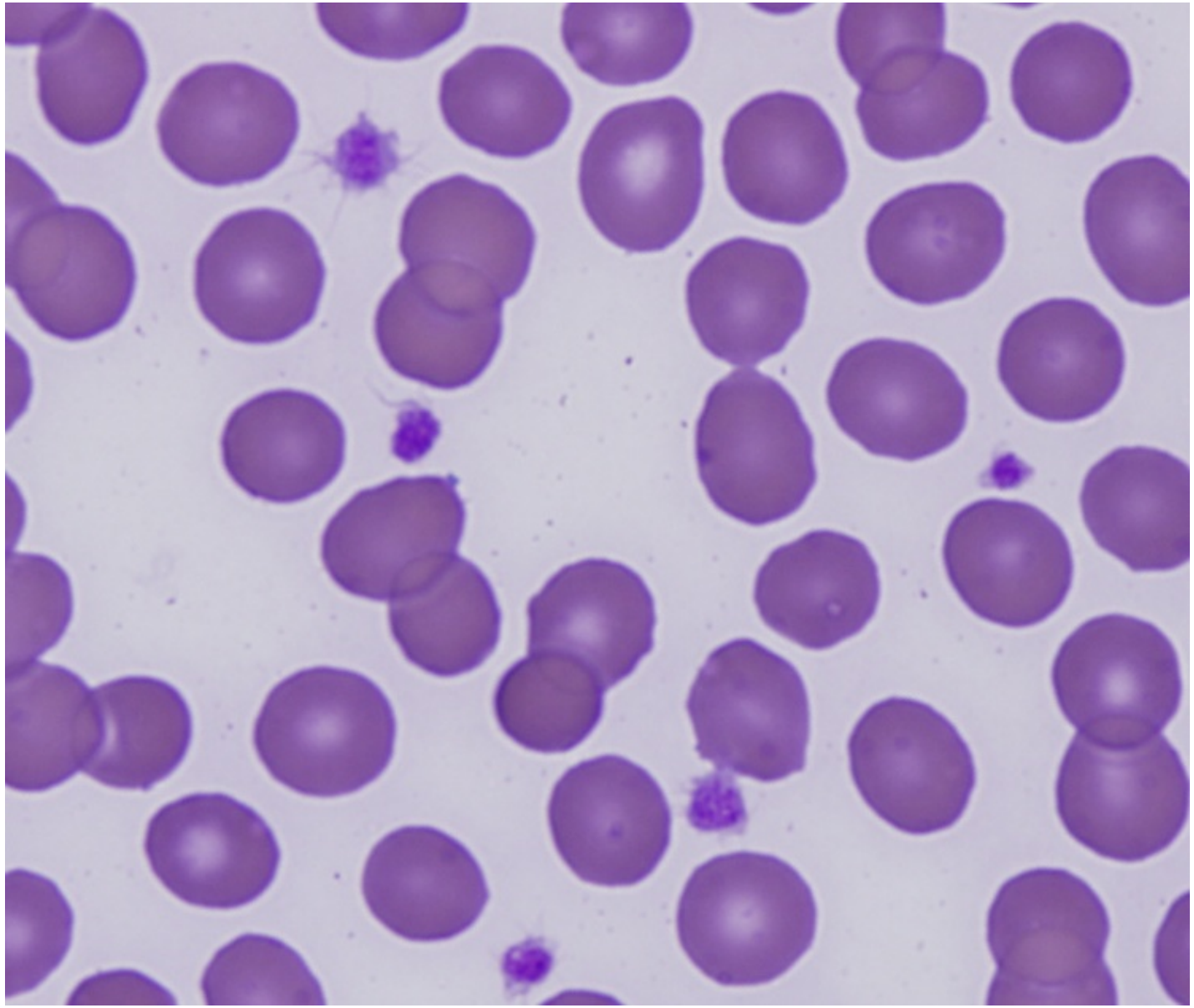
OR 1.8; P = .02

L. Etling et al JCO Vol 19; No 4 (Feb 15 2001) pp 1137-1146

Algorithm for thrombocytopenia evaluation

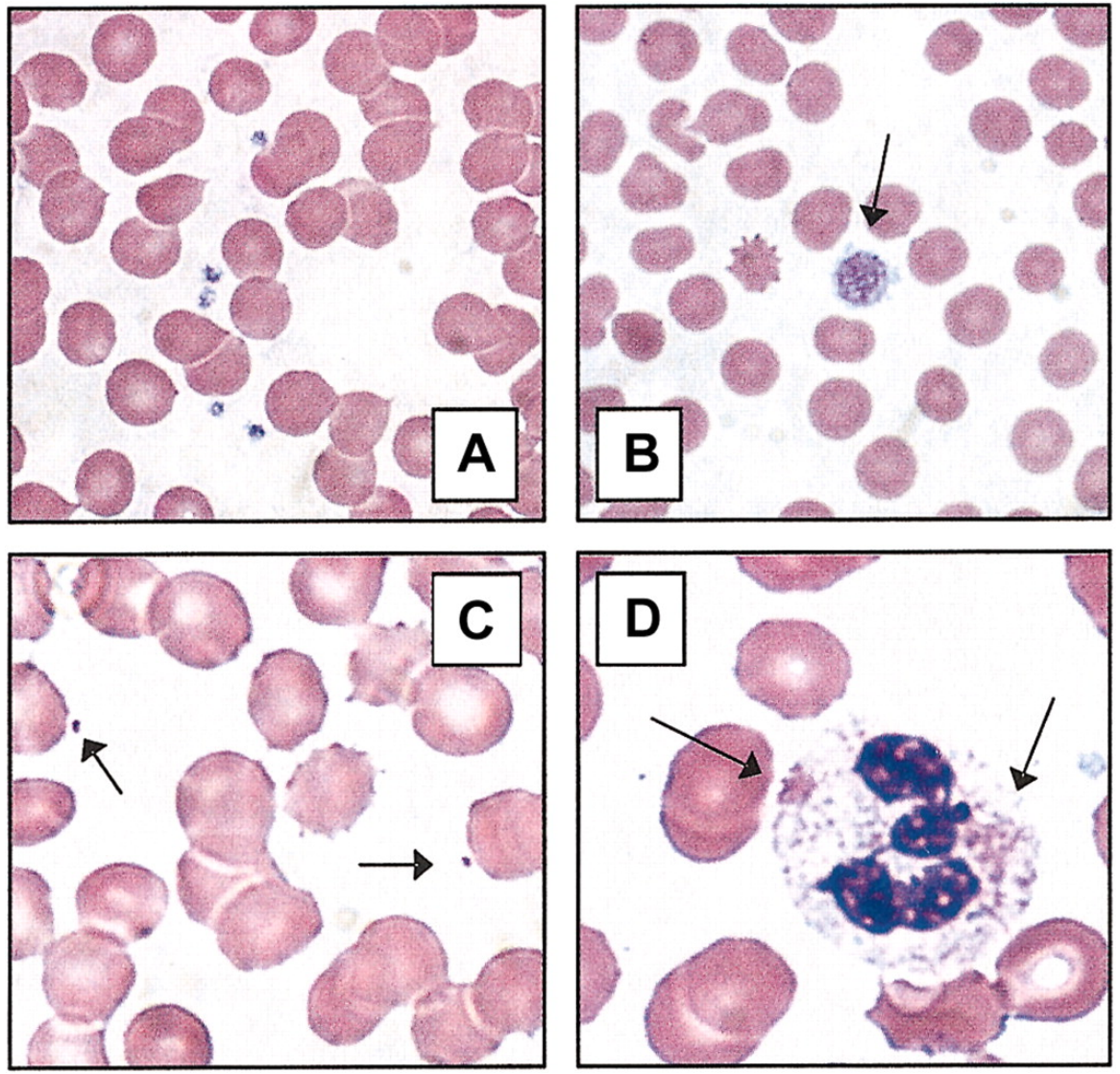


How to approach thrombocytopenia; Robero Stasi, Hematology 2012; p. 191-197



(A) Normal blood smear

(B) Macrothrombocyte



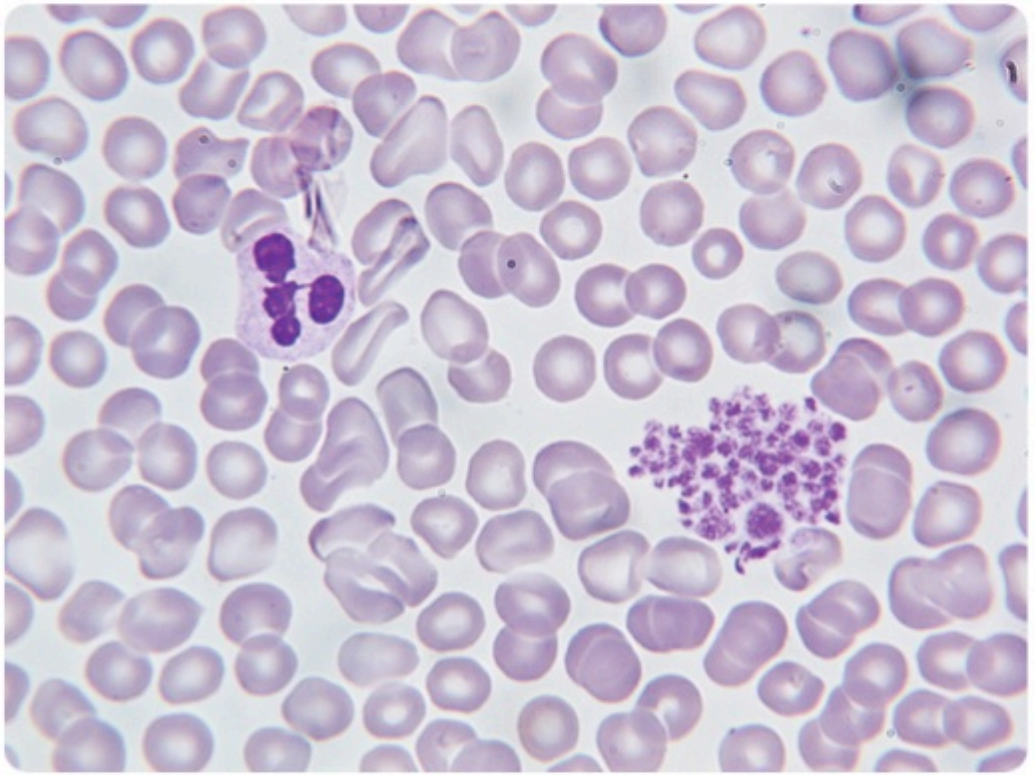
(C) Microthrombocyte

(D) Döhle-like bodies

Jonathan G. Drachman Blood 2004; 103:390-398

Pseudothrombocytopenia

- EDTA-Dependent Antiplatelet Antibody against GPIIB/IIIA epitope
- On evaluation of peripheral smear, see "clumps" platelets or satellitism
- Redraw blood in "blue-top" sodium citrate or "green-top" heparin



American Society of Hematology et al. Blood 2011;117:4168-4168

Inherited Thrombocytopenia (when a low platelet count does not mean ITP)

Small platelets, MPV less than 7 fL	Normal platelets, MPV 7-11 fL	Large/giant platelets, MPV greater than 11 fL
Wiskott-Aldrich syndrome	Familial platelet disorder/acute myeloid leukemia	May-Hegglin anomaly
		Fechtner syndrome
X-linked thrombocytopenia		Epstein syndrome
	Chromosome 10/THC2	Sebastian syndrome
		Mediterranean thrombocytopenia
	Congenital amegakaryocytic thrombocytopenia	Bernard-Soulier syndrome
		Velocardiofacial/DiGeorge syndrome
		GATA1 mutation
	Thrombocytopenia and absent radii	Gray platelet syndrome
		Paris-Trousseau thrombocytopenia/Jacobsen syndrome

Drachman JG. Blood. 2004;103: 390-398

Inherited Thrombocytopenia (when a low platelet count does not mean ITP)

Syndrome	Gene mutation	Chromosomal location	Associated findings
***MYH9*-related thrombocytopenia**			
May-Hegglin anomaly	*MYH9*	22q11	Neutrophil inclusions, sensorineural hearing loss, nephritis, cataracts (Table 6)
Fechtner syndrome	*MYH9*	22q11	
Epstein syndrome	*MYH9*	22q11	
Sebastian syndrome	*MYH9*	22q11	
Mediterranean thrombocytopenia/Bernard-Soulier carrier	*GP1BB*, possibly others	17pter-p12	None
Bernard-Soulier syndrome	*GP1BA, GP1BB*	17pter-p12	None
Velocardiofacial/DiGeorge syndrome (CATCH22)	*?GP1BB*	22q11	Cardiac, facial, parathyroid, and thymus anomalies, cognitive/learning impairment
Familial platelet disorder/acute myeloid leukemia	*AML1*	21q22.2	Myelodysplasia, acute myeloid leukemia
Chromosome 10/THC2	*?FLJ14813*	10p12-11.2	None
Paris-Trousseau thrombocytopenia/Jacobsen syndrome	*?FLI1*	11q23	Psychomotor retardation, facial anomalies (Jacobsen syndrome)
Gray platelet syndrome	Unknown	Unknown	None
Congenital amegakaryocytic thrombocytopenia	*MPL*	1p34	Marrow failure during 2nd decade
Thrombocytopenia and absent radii	Unknown	Unknown	Shortened/absent radii bilaterally
Thrombocytopenia and radial synostosus	*HOXA11*	7p15-p14.2	Fused radius, incomplete range of motion
Wiskott-Aldrich syndrome	*WAS*	Xp11.23-p11.22	Immunodeficiency, eczema, lymphoma
X-linked thrombocytopenia	*WAS*	Xp11.23-p11.22	None
GATA-1 mutation	*GATA1*	Xp11.23	Anemia, dyserythropoiesis, thalassemia

Drachman JG. Blood. 2004;103: 390-398

Mediterranean Macrothrombocytopenia

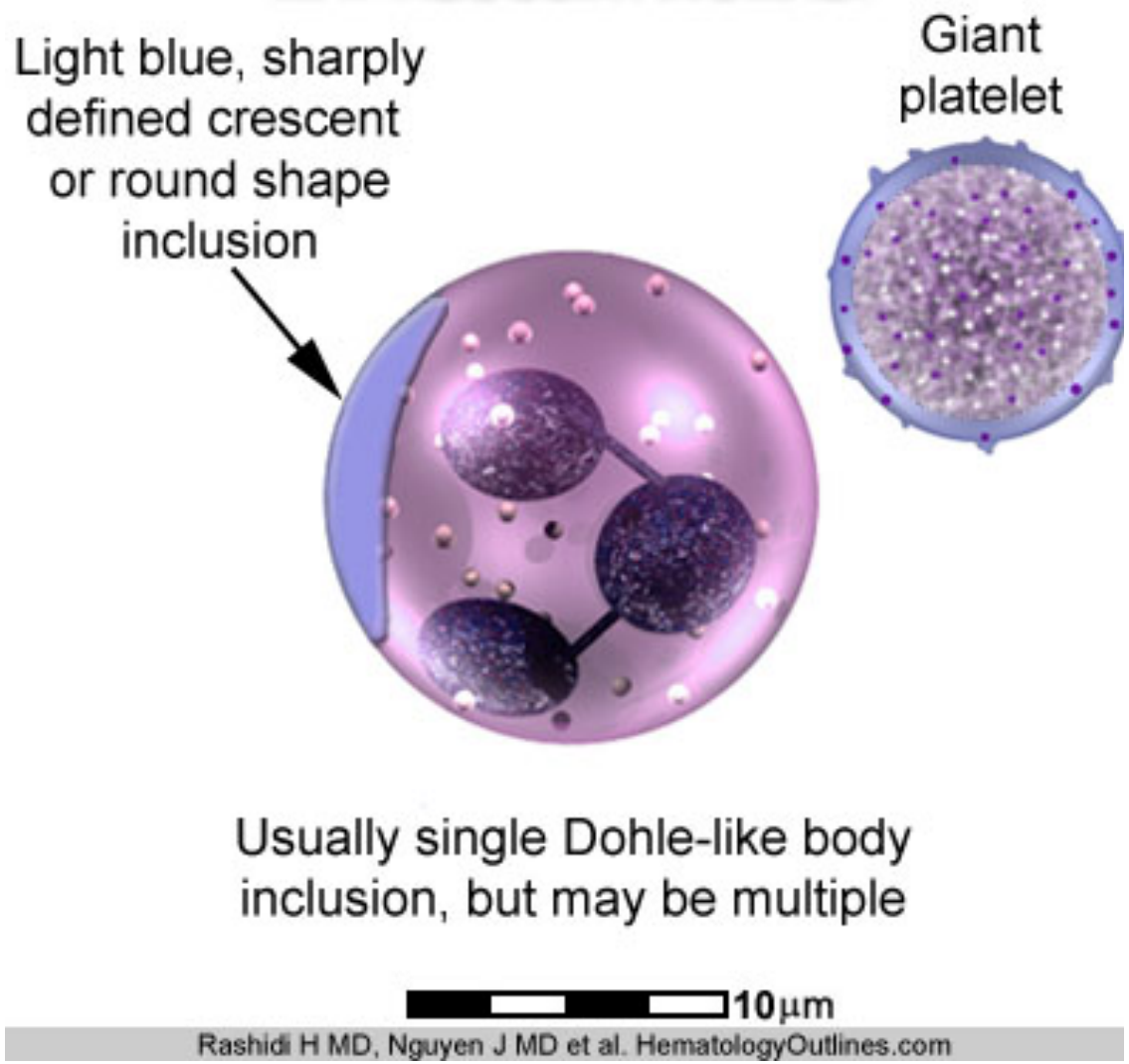
- Southern Europe
- Chromosome 17 – impaired expression of GP1b/IX/V (VWF receptor)
- Relatively common and mild
- Absence of significant bleeding or bruising,
- Usually identified incidentally during routine blood analysis
- Range 70 000-150 000 platelets/L

Drachman JG. Blood. 2004;103: 390-398 Behrens WE. Blood. 1975;46:199-208

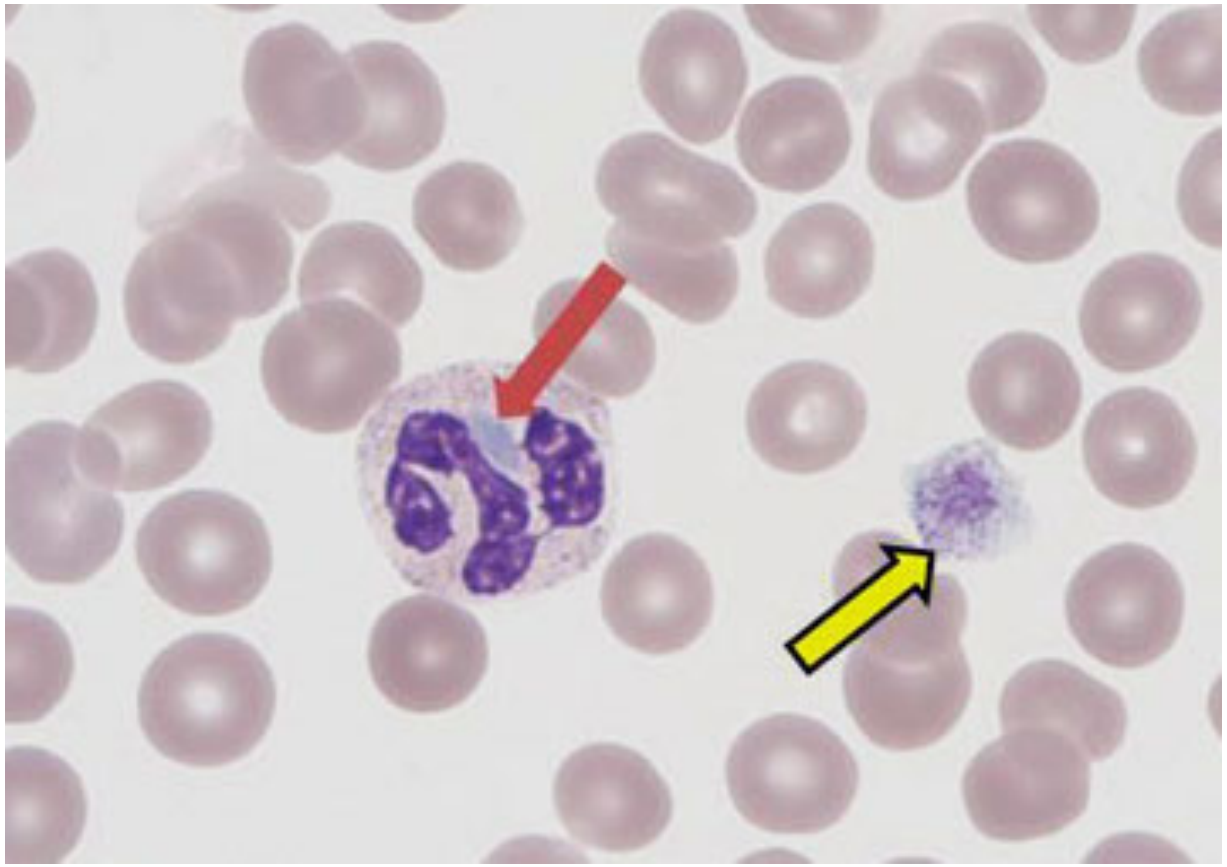
MYH9-Related Disorders:

- Autosomal-Dominant Diseases
- Mild thrombocytopenia; cell automators may underestimate platelet count – misdiagnosed with ITP
- Mildly increased risk bleeding
- Dohle bodies: Inclusion bodies in neutrophils and thrombocytopenia with giant- sized platelets
- Renal problems , Hearing loss

MYH9-Related Disorders: May-Hegglin Anomaly



MYH9-Related Disorders: May-Hegglin Anomaly



http://hematologyoutlines.com/atlas_topics/136.html

Post-Transfusion Purpura

- 50 yo G1P0 with metastatic clear cell ovarian cancer
- On carbo / gem – third line therapy
- 5/5/17: Symptomatic anemia required one unit packed red blood cells
- 5/18/17: UCC with thrombocytopenia and GI bleed

Post-Transfusion Purpura

PRBC's

	0/16 22	05/04/16 12:47	05/06/16 18:17	05/11/16 13:45	05/18/16 14:54	05/18/16 16:26	05/19/16 12:08	
elocytes					0.0		↑ 0.1	
myelocytes							0.0	
	3.6	4.7	8.0	5.5	↓ 1.5	↓ 1.7	↓ 1.9	↓
	3.10	↓ 2.49	↓ 2.94	↓ 3.50	↓ 2.49	↓ 2.33	↓ 2.16	↓
	9.3	↓ 7.6	↓ 8.8	↓ 10.5	↓ 7.6	↓ 7.1	↓ 6.5	↓
	27.3	↓ 23.0	↓ 26.4	↓ 30.9	↓ 23.0	↓ 20.4	↓ 18.6	↓
.	171	247	245	↓ 146	↓↓ 4	↓↓ 4	↓↓ 5	↓
hil	72.8	71.1	↑ 94.6	↑ 87.0	70.0		65.0	
	0.0	4.0	0.0	0.5	0.0		0.0	
	0.3	0.6	0.0	0.5	0.0		1.0	

Post-Transfusion Purpura

See Comments

Antibody Identification performed by New York Blood Center, 4501 Vernon Blvd, LIC, NY 11101
Platelet antibody screen is POSITIVE for BOTH platelet and HLA antibodies. Patient reacted with 11/13 cells which have both HLA and PLT antigens. The antibody screen remained positive with some cells and reduced in strength or became completely negative in others. Some of the antibody reactivity is HLA related and some is platelet specific. Recommend crossmatched platelets for future transfusion. Please contact the Blood Bank at least 2-3 days prior to initiating platelet transfusion therapy. Dr. David L. Wuest, MD.

Positive reactivity detected in patient's serum against intact platelets indicating the presence of platelet-reactive antibodies and/or immune complexes.

Positive reactions detected in patient's serum against Class I HLA.

Positive reactions detected in patient's serum against HPA-1b positive platelets only. The platelet typing, together with the serological results, indicate the presence of HPA-1b antibodies. These results would support a diagnosis of Post Transfusion Purpura (PTP).

Testing performed at:
Blood Center of Wisconsin, Inc.
638 N 18 Street
Milwaukee, WI 53233-2121

Post-Transfusion Purpura

- Caused by reexposure to foreign platelet antigen via blood product transfusion
- Almost all cases in multiparous women
- HPA-1a (formerly PLA1) antigen most commonly involved (present in 98% of population)
- Antibodies cause destruction of patient's own platelets by uncertain mechanism.

Post-Transfusion Purpura

- IVIG – mainstay of treatment
- Steroids, plasma exchange in patients unable/unwilling to receive IVIG
- Future transfusions with HPA-1a negative products OR products that have been washed

Post-Transfusion Purpura

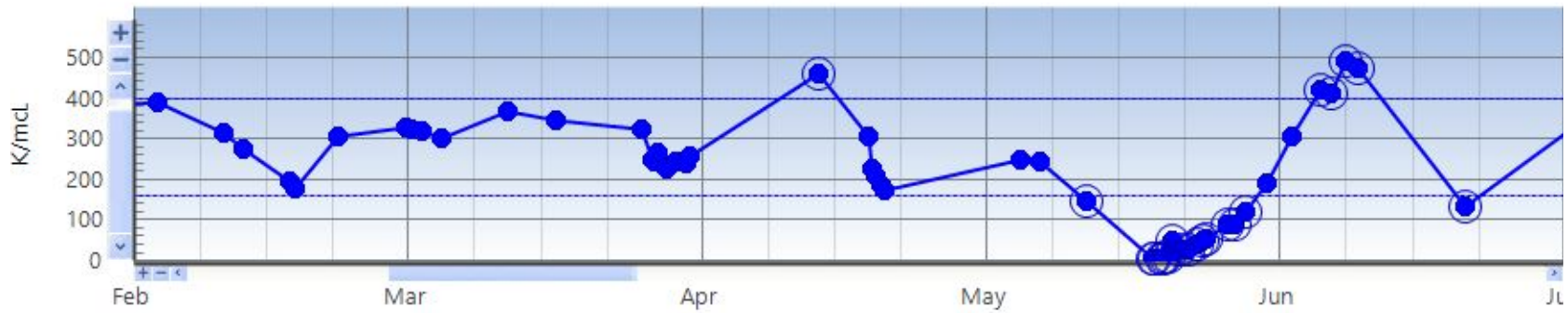
IVIG

Display Format | Display View | Reset | Order Details | Order Set Details | View | Annotation Details | Modify Time Scale | Reorder | Print Results for Order | for Order | Release to Patient | Annotations | Graph Options | Item Info

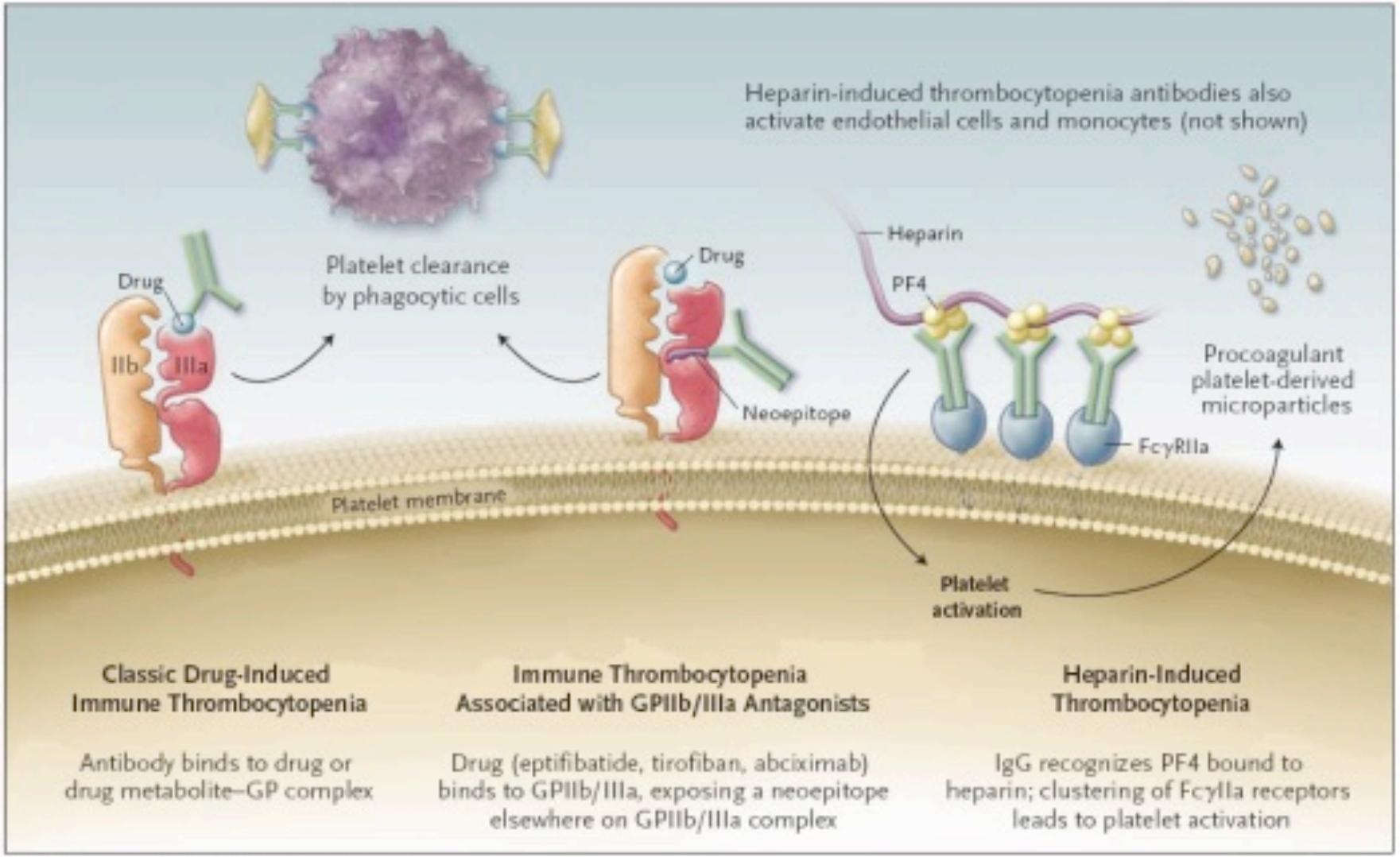
Tracking new results. Some results may not be shown for **all available charts** for **performed dates** from 01/17/2016; Result Selection: **CBC**

	16	05/19/16 13:17	05/20/16 06:55	05/20/16 16:57	05/21/16 10:05	05/22/16 09:32	05/23/16 07:35	05/23/16 18:45
RBC	.36	↓ 2.56	↓ 2.72	↓ 2.53	↓ 3.63	↓ 3.36	↓ 3.56	↓ 3.91
HGB	7.1	↓ 7.7	↓ 8.0	↓ 7.6	↓ 10.6	↓ 10.0	↓ 10.6	11.5
HCT	0.1							
Platelets.	6	↓↓ 7	↓↓ 10	↓ 50	↓ 28	↓ 26	↓ 38	↓ 50
Neutrophil		67.0	↑ 85.0		↑ 87.0	↑ 85.9	↑ 88.8	72.0
Eos		0.0	0.0		0.0	0.3	0.0	0.0
Baso		0.0	0.0		0.0	0.1	0.0	0.0
Lymph		17.0	↓ 3.0		↓ 6.0	↓ 3.5	↓ 3.8	↓ 7.0
Mono		↑ 14.0	9.0		4.0	10.2	7.4	8.0
Abs Neut		2.6	5.2		↑ 10.9	↑ 15.5	↑ 18.6	↑ 17.9

Platelets.



Immune Drug-Induced Thrombocytopenia



Shah RA, Musthaq A, Khardori N - J Med Case Rep (2009)

Drug-Induced Thrombocytopenia – *immune* mediated mechanisms (

Antibody type	Mechanism	Examples
Quinine type	Drug binds to DDabs ** and platelet integrin (eg GPIIB/IIa)	Quinine, sulfonamides, NSAIDS
Hapten dependent	Drug links to membrane protein and induces binding by DDabs	penicillins and cephalosporins
Fiban type	Drug reacts with GPIIb/IIIa and induces neoepitope for the DDabs	Tirofiban, eptifibatide
Drug Specific	DDabs recognize murine component of chimeric Fab fragment for specific GPIIIa	Abciximab
Autoantibody	Drug induces antibody that reacts with autologous platelets in the absence of drug	Gold salts, procainamide
Immune complexes	Antibodies form immune complexes with their target antigens	Heparin, protamine

** drug-dependent antibodies

Tanam Bakchoul and Irene Marini; Drug – associated thrombocytopenia ASH Education Program 2018; pp 576 - 583

Drug-Induced Thrombocytopenia – *nonimmune* mechanisms

Impaired thrombopoiesis	Proapoptosis effect
Chemotherapy	Tamoxifen
Interferon - α	Navitoclax
Linezolid	Methotrexate
Bortezomib	NFkB inhibitors
Thiazide diuretics	Lovastatin
Ethanol	Doxorubicin
Tolbutamide	Bexarotene
Ganciclovir	Arsenic trioxide
	Aspirin
	Vancomycin
	Carmustine
	Cisplatin

Tanam Bakchoul and Irene Marini; Drug – associated thrombocytopenia ASH Education Program 2018; pp 576 - 583

Thrombocytopenia in the ICU

- 20-30% patients upon admission have thrombocytopenia (pre-covid data)
- Inverse correlation between platelet count at ICU admission and survival
- Thrombocytopenic patients admitted to the ICU have higher MODS and APACHE scores
- Inverse correlation between ICU platelet count and mortality (mortality rate 31%– 46% in thrombocytopenic patients vs 16%–20% nonthrombocytopenic patients)

Greinacher Thrombocytopenia in the ICU ASH Ed Book 2010

Thrombocytopenia in the ICU

Pseudo-thrombocytopenia	Clotting in the blood sample EDTA-induced *ex vivo* platelet clumping Platelet satellitism/rosetting with leukocytes GPIIb/IIIa inhibitor induced pseudothrombocytopenia Macrothrombocytes (rare, patients with hereditary giant platelet disorders)
Hemodilution	Infusion of fluids Transfusion of red blood cell concentrates and plasma
Increased platelet consumption	Major bleeding Sepsis, septic shock (bacteremia, fungemia) Malaria (in endemic regions) Acute disseminated intravascular coagulopathy (trauma, burns, shock, infection, promyelocytic leukemia, obstetrical complications [HELLP syndrome, eclampsia, amniotic fluid embolism]) Chronic disseminated intravascular coagulopathy (malignancy, large aortic aneurysm, large hemangioma) Hyperfibrinolysis (liver cirrhosis, metastatic prostate/ovarial cancer) Hemophagocytosis Thrombotic microvascular disorders (thrombotic thrombocytopenic purpura; hemolytic uremic syndrome) Extracorporeal circulation with large surface exposure (hemofiltration, extracorporeal lung assist) Intravascular devices (intra-aortic ballon pump, cardiac assist devices) Severe pulmonary embolism/severe thrombosis
Increased platelet destruction	Severe infections (sepsis, hemorrhagic fever [Dengue virus], cross-reacting antibodies) Heparin-induced thrombocytopenia Auto-immune thrombocytopenia (platelet autoantibodies) Passive and active posttransfusion purpura (platelet alloantibodies) Drug-dependent thrombocytopenia
Decreased platelet production	Toxic effects on bone marrow (drugs, intoxications) Severe infection (bacterial toxins) Myelodysplasia and leukemia Cancer bone marrow infiltration Chronic liver disease Chronic alcohol abuse with folate deficiency Radiation Delayed engraftment after stem cells transplantation
Increased platelet sequestration	Hypersplenism Hypothermia

A. Greinacher Thrombocytopenia in the ICU ASH Ed Book 2010

Thrombocytopenia and pregnancy

- Physiologic changes during pregnancy contributing to
  - gestational thrombocytopenia

- Increased plasma volume resulting in dilution of platelets

- 50% increase in spleen size during pregnancy –
  - physiologic pooling of 1/3 of platelets
  - in slow-flow splenic sinusoids

- Platelet pooling in placental circulation

Thrombocytopenia and pregnancy

- Gestational Thrombocytopenia/Benign thrombocytopenia of pregnancy.
  - Occurs in up to 5% of term pregnancies
  - Asymptomatic, mild, occurs late in gestation
  - No need for intervention

- Microangiopathy
  - Preeclampsia/ecclampsia, HELLP, TTP

- ITP

Original Article

Platelet Counts during Pregnancy

Jessica A. Reese, Ph.D., Jennifer D. Peck, Ph.D., David R. Deschamps, M.D., Jennifer J. McIntosh, D.O., Eric J. Knudtson, M.D., Deirdra R. Terrell, Ph.D., Sara K. Vesely, Ph.D., and James N. George, M.D.

N Engl J Med
Volume 379(1):32-43
July 5, 2018

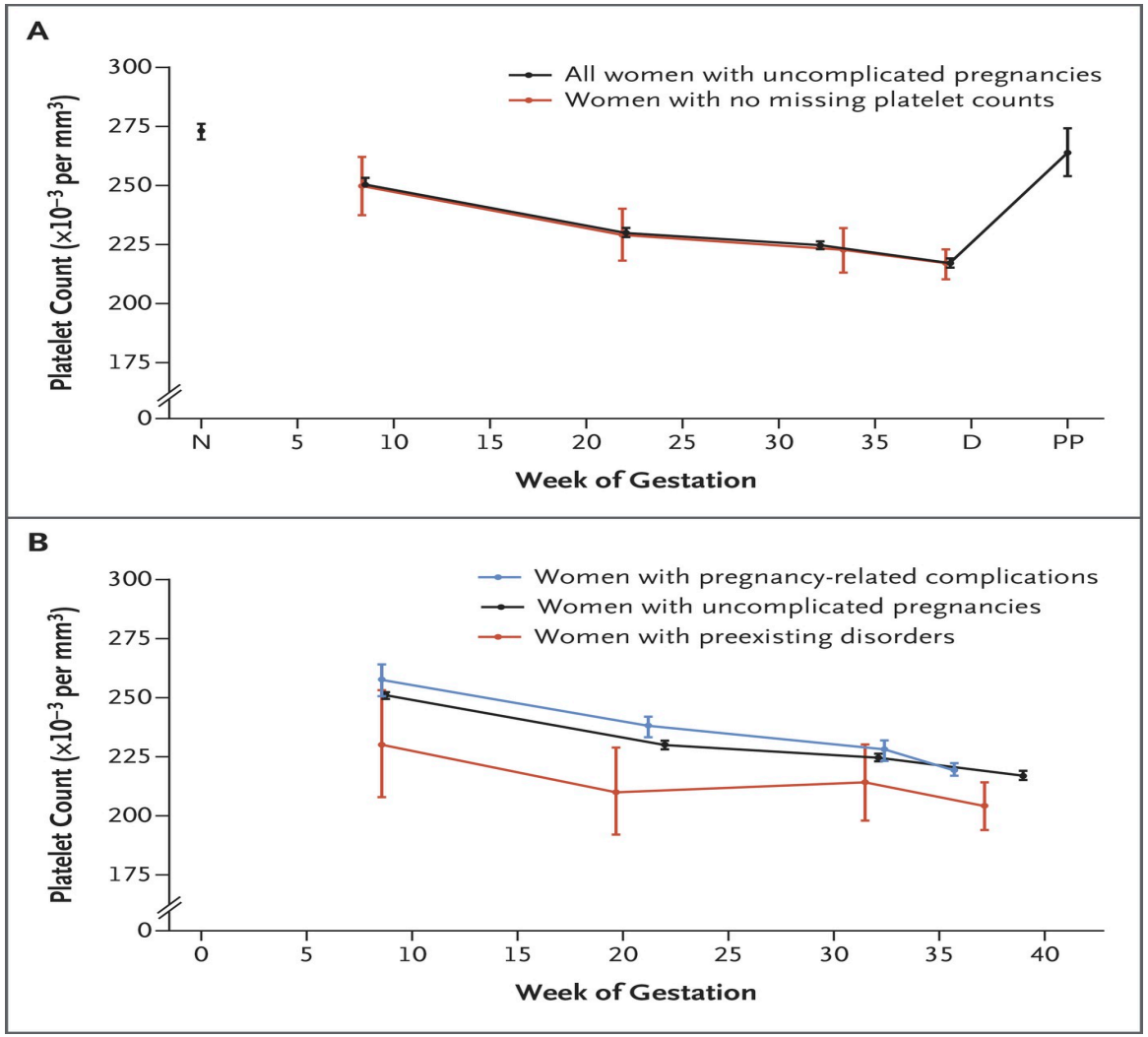
Study Objectives

- Uncomplicated pregnancies
  - Define normal course of thrombocytopenia
  - Define the potential severity of gestational thrombocytopenia
  - Define the risk of recurrence with subsequent pregnancies
- Complicated pregnancies
  - Determine a relationship between identified complications and platelet counts
- Preexisting thrombocytopenia
  - Determine if and how much thrombocytopenia worsens during pregnancy

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med
Volume 379(1):32-43
July 5, 2018

Mean Platelet Counts over Time.



The NEW ENGLAND JOURNAL of MEDICINE

Reese JA et al. N Engl J Med 2018;379:32-43

Platelet Counts during Pregnancy and at the Time of Delivery.

< 150K= 9.9%

< 100K= 1.0%

< 150K= 11.9%
P = 0.01

Table 2. Platelet Counts during Pregnancy and at the Time of Delivery.*

Platelet count (per mm³), According to Type of Pregnancy	First Trimester	Second Trimester	Third Trimester	Delivery
	number of women (percent)			
Women with uncomplicated pregnancies†				
≥150,000	2264 (98.2)	2430 (95.2)	2062 (91.5)	4115 (90.1)
125,000–149,000	36 (1.6)	89 (3.5)	128 (5.7)	293 (6.4)
100,000–124,000	5 (0.2)	29 (1.1)	48 (2.1)	126 (2.7)
80,000–99,000	1 (<0.1)	2 (0.1)	12 (0.5)	27 (0.6)
60,000–79,000	0	0	2 (0.1)	4 (0.1)
<60,000	0	0	0	0
Women with uncomplicated pregnancies, platelet counts <80,000 per cubic millimeter, and an alternative cause for thrombocytopenia†				
60,000–79,000	0	2 (0.1)	1 (<0.1)	3 (0.1)
<60,000	0	1 (<0.1)	1 (<0.1)	0
Women with pregnancy-related complications‡				
≥150,000	1060 (97.9)	1264 (95.5)	1506 (90.5)	2279 (88.1)
125,000–149,000	18 (1.7)	47 (3.5)	99 (5.9)	178 (6.9)
100,000–124,000	1 (0.1)	10 (0.7)	39 (2.3)	82 (3.2)
80,000–99,000	1 (0.1)	1 (0.1)	13 (0.8)	22 (0.9)
60,000–79,000	0	1 (0.1)	6 (0.4)	16 (0.6)
<60,000	2 (0.2)	1 (0.1)	1 (0.1)	9 (0.3)
Women with preexisting disorders associated with thrombocytopenia§				
≥150,000	73 (85.8)	95 (79.2)	105 (75.0)	158 (80.2)
125,000–149,000	5 (5.9)	3 (2.5)	10 (7.1)	12 (6.1)
100,000–124,000	2 (2.4)	10 (8.3)	6 (4.3)	12 (6.1)
80,000–99,000	2 (2.4)	4 (3.3)	8 (5.7)	7 (3.6)
60,000–79,000	0	3 (2.5)	5 (3.6)	2 (1.0)
<60,000	3 (3.5)	5 (4.2)	6 (4.3)	6 (3.0)

The NEW ENGLAND JOURNAL of MEDICINE

Reese JA et al. N Engl J Med 2018;379:32-43

Conclusions

- Mean platelet counts decreased during pregnancy in all the women, beginning in the first trimester.
- In women who have a platelet count of less than 100,000 per cubic millimetre, a cause other than pregnancy or its complications should be considered.

Thrombocytopenia and COVID-19

- COVID-19 patient develop a unique coagulopathy with very elevated d-dimers and increased rates of VTE
- Patient's with COVID-19 pneumonia develop hypoxia which induces hypoxia-inducible transcription factors (affects PAI-1 and TF) --- > prothrombotic state
- Acute lung injury leads to cytokine storm with ↑ IL6 leading to endothelial damage and thrombin generation stimulating tPA release
- Tentative "conclusion" = Thrombosis due to hypoxia and inflammation

ISTH Webinar; Prof Beverly Hunt OBE; London, UK. April 9, 2020

Thrombocytopenia and COVID-19

- Significant percent of COVID patients have thrombocytopenia; may have prognostic implications ??
- Platelet count negatively correlated with 28-day mortality

Adapted. Ning Tang, Ziyong Sun et al. JTH. April 2020. doi:10.1111/JTH.14817

Thrombocytopenia and COVID-19 – characteristics associated with severe infection

Parameter	COVID Survivor	COVID non-survivor	P value
Age (years)	63.7 +/- 12.2	68.7 +/- 11.4	<0.001
Meet SIC criteria	13.3% (42)	41.0% (55)	<0.001
PT (sec)	14.6 +/- 2.1	16.5 +/- 8.4	<0.001
Platelet (x10^9 /L)	231 +/- 99	178 +/- 92	<0.001
D – dimer (ug/mL); normal <0.5	1.47 (0.78-4.16)	4.70 (1.42 – 21)	0.001

Adapted. Ning Tang, Ziyong Sun et al. JTH. April 2020. doi:10.1111/JTH.14817

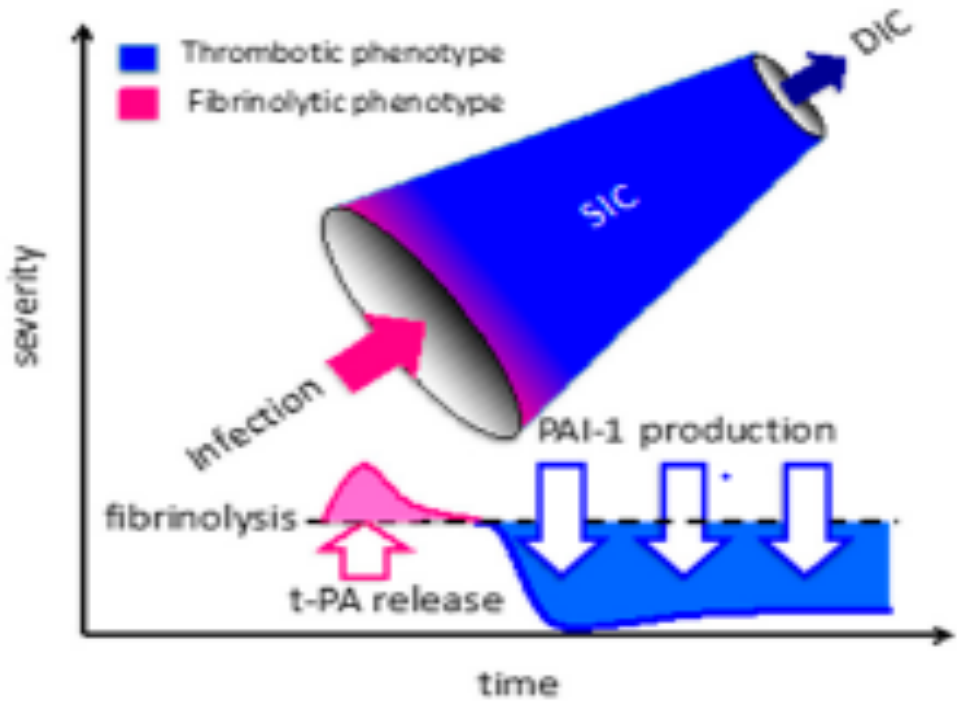
Thrombocytopenia and COVID-19

SIC (sepsis induced coagulopathy) score.

Item	Score	Range
Platelet count (x10^9 /L)	1	100-150
	2	< 100
PT/INR	1	1.2-1.4
	2	>1.4
SOFA	1	1
	2	≥2
Total score	≥ 4	

Adapted. Iba T, Warkentin TE et al. JTH 2019; 17(11): 1989-94

Thrombocytopenia and COVID-19



Iba T, Warkentin TE et al. *J. Clin. Med.* **2019**, *8*(5), 728; https://doi.org/10.3390/jcm8050728

Thrombocytopenia and COVID-19

Correlative factors of 28-day mortality in severe infection

	Odds Ratio (95% CI)	P value
Age	1.033 (1.01-1.05)	0.002
Prothrombin time	1.107 (1.008-1.215)	0.033
Platelet count	0.996 (0.993-0.998)	0.001
D-dimer	1.058 (1.028-1.090)	< 0.001

Adapted. Ning Tang, Ziyong Sun et al. JTH. April 2020. doi:10.1111/JTH.14817

Stay safe and healthy
Thank you