Società Italiana di Ematologia

Convegno interregionale

Delegazioni Emilia Romagna e Toscana

Gli ematologi insieme contro le malattie rare

LA DIAGNOSI:

DISTRICARSI TRA LE TANTE FORME

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Disclosures of Elisa Lucchini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen							Honoraria
Roche							Honoraria

Epidemiology

Incidence of ITP: 1.6-3.9 per 100.000/person/year among adults

- Female predominance
- Bimodal distribution among males: higer rates among boys < 18 years of age and 75-85 years
- Incidence rate relatively constant for women up to 60 years of age.

Prevalence of chronic ITP: 12.1 per 100.000/person

Definitions

Primary ITP: isolated thrombocytopenia (<100 x10^9/L) with no other apparent causes of thrombocytopenia

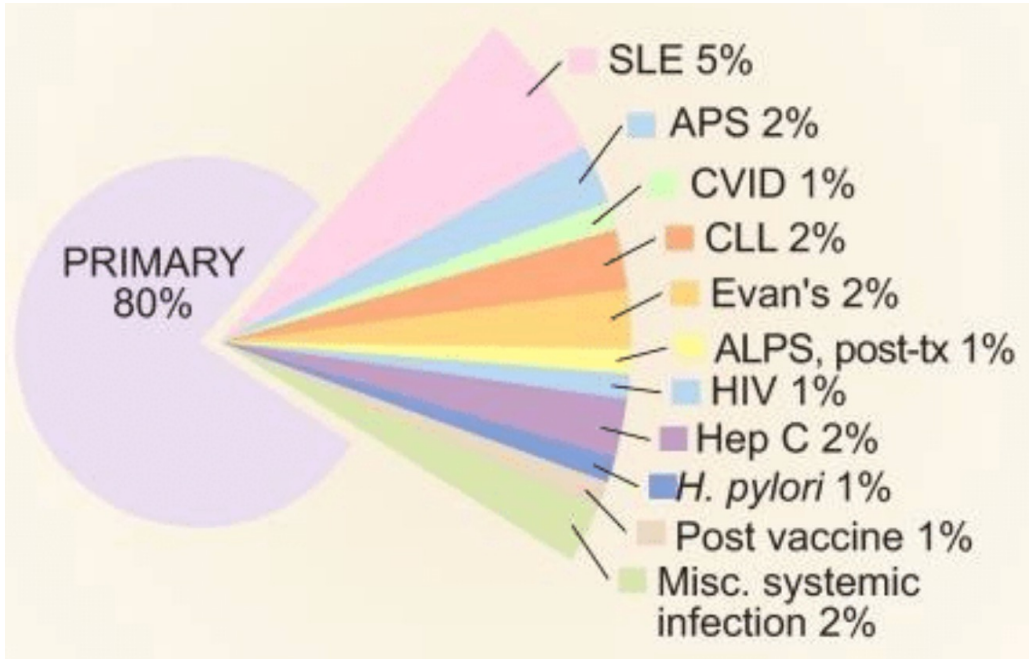
Non-specific diagnostic criterion

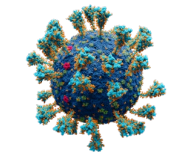
ITP is a diagnosis of **EXCLUSION**

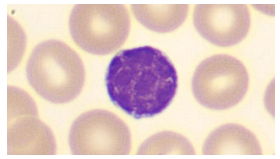
Secondary ITP: immune-mediated thrombocytopenia that is associated with other diseases, including autoimmune disorders, infections or malignancies

Isolated thrombocytopenia (**non-immune** mediated) in the context of other diseases (e.g: familial, MDS, liver disease, drug-induced …)

Secondary ITP





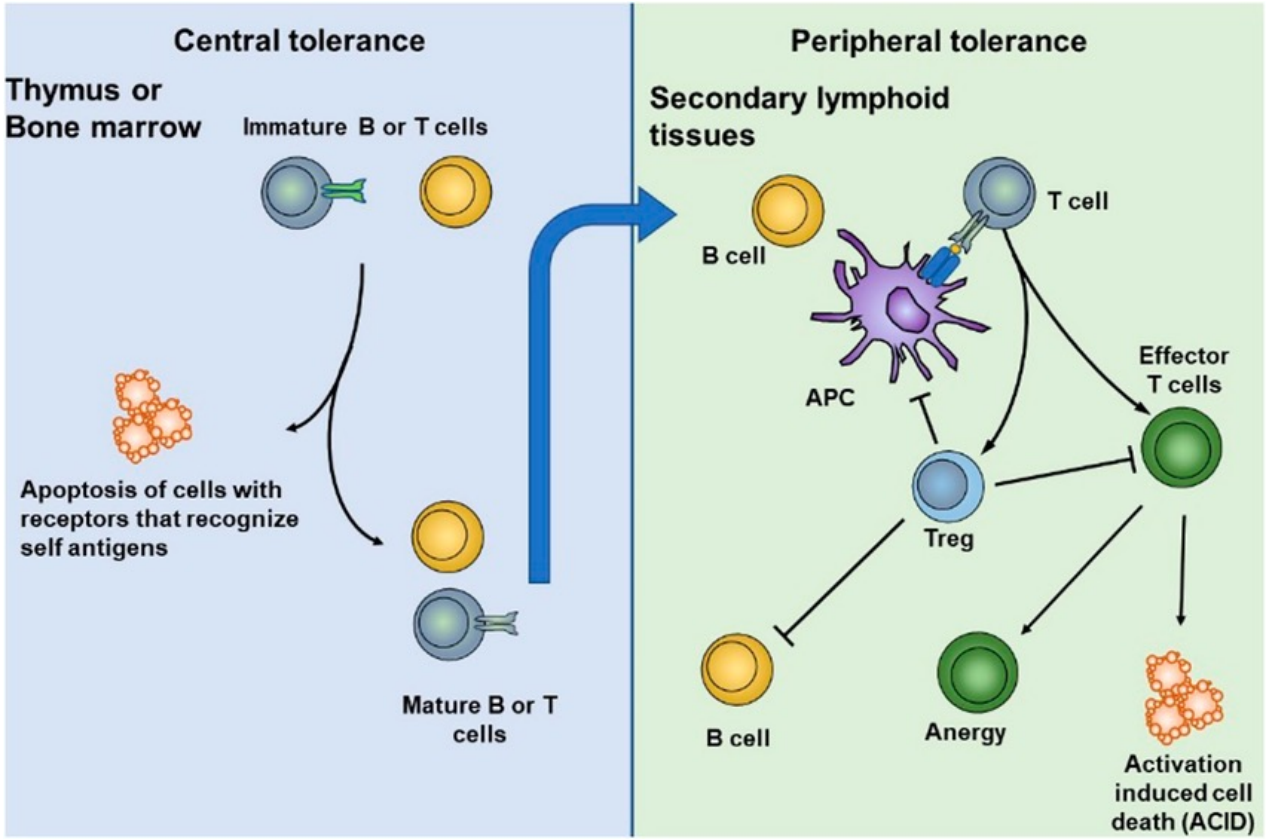


Secondary ITP

- Frequency: up to 20%
- Older age at onset
- No female predominance
- Clinical manifestations, natural history, treatments and responses tipically differ from primary ITP

Cines DB et al. Semin Hematol. 2009

Secondary ITP: pathogenesis



Central mechanisms

Disorders of differentiation

Peripheral tolerance defects

Central tolerance:

- Takes place in primary lymphoid organs (thymus and bone marrow)
- Ensures that immature lymphocytes that strongly recognize self-antigens are removed during development

Peripheral tolerance:

- Takes place in secondary lymphoid tissues
- To control self-reactive cells that escaped thymus or bone marrow
- Induction of anergy; conversion to regulatory T cells

Dendritic cells play an important role in both mechanisms

Gonzalez-Lopez et al. Blood reviews. 2023; Schifferli et al. Frontiers in Medicine 2021; Bussel JB & Garcia C, Haematologica 2022; Cines DB et al. Semin hematol 2009; Yu et al. Frontiers in Bioeng and Biotech

Secondary ITP: pathogenesis

- Secondary ITP arising from defects in central tolerance are usually more difficult to treat
- The more central the defect, the more cell lines may be affected (eg: ITP + AIHA + AIN)
- Infection-triggered ITP usually exhibits a good prognosis

Gonzalez-Lopez et al. Blood reviews. 2023; Schifferli et al. Frontiers in Medicine 2021; Bussel JB & Garcia C, Haematologica 2022; Cines DB et al. Semin hematol 2009

Secondary ITP: pathogenesis & etiology

Autoimmune diseases	Immunodeficiencies	Lymphoproliferative disorders	Infections & drugs
• ALPS • Systemic lupus erythematosus • Antiphospholipid syndrome	• CVID • Haematopoietic cell transplantation	• CLL • Other non-Hodgkin's lymphoma • Hodgkin's lymphoma	• HCV • HIV • Sars-COV-2 • Helicobacter pylori • Drug-induced

Gonzalez-Lopez et al. Blood reviews. 2023; Schifferli et al. Frontiers in Medicine 2021; Bussel JB & Garcia C, Haematologica 2022; Cines DB et al. Semin hematol 2009

Secondary ITP: pathogenesis & etiology

Autoimmune diseases

- ALPS
- **Systemic lupus erythematosus**
- Antiphospholipid syndrome

Prevalence of ANA seropositivity (≥1:160) in patients with ITP: up to 40%

- No differences in response to first-line therapy
- Higher probability of chronic ITP
- Higher response to rituximab; role of hydroxychloroquine

Cumulative incidence of SLE in patients with ITP: 2-5% at 5 years, with the highest risk in young women

Immunodeficiencies

- **CVID**
- Haematopoietic cell transplantation

The most common genetic antibody defect - incidence 1:25.000 – 50.000
Age at diagnosis: 20-45 yrs

25% of patients with CVID will develop ITP

Gonzalez-Lopez et al. Blood reviews. 2023; Schifferli et al. Frontiers in Medicine 2021; Bussel JB & Garcia C, Haematologica 2022; Cines DB et al. Semin hematol 2009; Moulis G et al. BJH 2023; Modi D et al. Thromb Haemost 2025

Secondary ITP: pathogenesis & etiology

Lymphoproliferative disorders

- CLL
- Other non-Hodgkin's lymphoma
- Hodgkin's lymphoma

- CLL (5%), other NHL (0.76%), HL (0.2-1%)

Pathogenesis:

- Polyclonal high-affinity IgG produced by non-malignant cells (90%)
- CLL-produced autoantibodies (10%)

Infections & drugs

- HCV, CMV
- HIV
- Sars-COV-2
- **Helicobacter pylori**
- Drug-induced

Molecular mimicry of the Cag-A protein with platelet glycoproteins

Prevalence in the general population varies across countries: the highest in Japan (70%). In Italy: 50%.

Gonzalez-Lopez et al. Blood reviews. 2023; Schifferli et al. Frontiers in Medicine 2021; Bussel JB & Garcia C, Haematologica 2022; Cines DB et al. Semin hematol 2009; Modi D et al. Thromb Haemost 2025

Arnold et al. Blood Advances, 2017

Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry

Canadian registry including patients >18 years with platelet count < 150 $x10^9$/L

12.2% of patients initially diagnosed as primary ITP, were re-diagnosed during follow-up.

Cause of thrombocytopenia	N° pts
Myelodisplastic syndrome	7
Familial thrombocytopenia	4
Hypersplenism	3
Liver disease	3
Pseudothrombocytopenia	2
Bernard-Soulier syndrome	1
Cancer-associated thrombocytopenia	1
Drug-induced ITP	2
Secondary to H. pylori infection	2
Secondary to other autoimmune diseases	6
Other causes	5

blood advances

Misdiagnosis of primary immune thrombocytopenia and frequency of bleeding: lessons from the McMaster ITP Registry

Arnold et al. Blood Advances, 2017

Clinical characteristics of patients misdiagnosed as having primary ITP, compared with patients who were properly analized

	All misdiagnosed patients (n = 46)	Patients correctly diagnosed as primary ITP (n = 259)
Age, median (IQR), y	59.5 (38.8-73.5)	50 (32.5-64)
Female, n (%)	25 (54.3)	163 (62.9)
Lowest platelet count ever, median (IQR)	43 (15-62.5)	14 (3.5-45.5)
Patients with platelet nadir $<20 \times 10^9$/L, n (%)	13 (28.3)	146 (56.4)
No bleeding, n (%)	9 (19.6)	39 (15.1)
Minor bleeding only, n (%)	21 (45.7)	73 (28.2)
Any grade 2 bleed, n (%)	16 (34.8)	147 (56.8)
Any nonskin grade 2 bleed, n (%)	4 (8.7)	123 (47.5)
ICH, n (%)	1 (2.2)	6 (2.3)
Number of ITP treatments until last follow-up, median (IQR)	1 (0-2)	3 (1-5)
Untreated patients, n (%)	15 (32.6)	53 (20.5)

Misdiagnosed thrombocytopenia in children and adolescents: analysis of the Pediatric and Adult Registry on Chronic ITP

Blood Advances 2020

Alexandra Schifferli,[1] Andrea Heiri,[2] Paul Imbach,[1] Susanne Holzhauer,[3] Markus G. Seidel,[4] Diane Nugent,[5] Marc Michel,[6] and Thomas Kühne[1]

113 children (3 months to 16 yrs of age) whose diagnosis of primary ITP was revised within 24 months of follow-up

Children with **infection-associated** ITP had clinical features similar to those with primary ITP

Other secondary ITP and non-immune clinically differ from primary ITP: older age, female sex, comorbidities, family history.

Those with malignancies and aplastic anemia had higher platelet counts compared to infection-associated and primary

Cause of thrombocytopenia	N° pts
Infections	53
Autoimmunity	42
Aplastic anemia	6
Malignancy	7
Immunodeficiency	4
Drug-induced	1

Recommendations for the diagnosis of ITP in children and adults

Basic evaluation in all patients	Tests of potential utility in the management of an ITP patient	Tests of unproven or uncertain benefit‡
Patient history	Glycoprotein-specific antibody (can be used in difficult cases; has poor sensitivity and is not a primary diagnostic test)	TPO level
Family history	Antiphospholipid antibodies (including anticardiolipin and lupus anticoagulant) if there are clinical features of antiphospholipid syndrome	Reticulated platelets/ immature platelet fraction
Physical examination	Antithyroid antibodies and thyroid function	Platelet survival study
Complete blood count and reticulocyte count	Pregnancy test in women of childbearing potential	Bleeding time
Peripheral blood film	Antinuclear antibodies	Serum complement
Quantitative immunoglobulin level measurement*	Viral PCR for EBV, CMV and parvovirus	
Blood group (Rh)	Bone marrow examination (in selected patients; refer to text)	
HIV†	Direct antiglobulin test	
HCV†	H. pylori†	

Provan et al Blood Advances 2019

The role of genetic sequencing in the diagnostic workup for chronic immune thrombocytopenia

80 patients with chronic ITP, 67% adults WGS or targeted sequencing of genes associated with bleeding and platelet disorders or primary immunodeficiencies	Patients more likely to have a variant were those who had CR to treatment, who require treatment, and with another autoimmune condition

	Bleeding and platelet disorders	Primary immunodeficiencies
Pathogenic/likely pathogenic	7 patients • ANKRD26 (x2) (autosomal dominant thrombocytopenia) • GP1BB (Bernard-Soulier) • TUBB1 (autosomal dominant macrothrombocytopenia) • ETV6 (x2) (thrombocytopenia and leukemia predisposition) • vWF	2 patients • NOD2 (gene associated to increase risk of inflammatory bowel disease and autoinflammation) • UNC13D (familial hemophagocytic lymphohistiocytosis)
Variants of uncertain significance	11 patients	15 patients

Joshi N et al. Blood Advances 2025

Clonal hematopoiesis in patients with autoimmune thrombocytopenia: an international multicenter study

167 adult patients with ITP who underwent myeloid panel NGS to rule out myeloid neoplasm.
Median age at NGS 64 yrs (53-75)

76% tested after >6 months from diagnosis; 83% had received at least 1 line of therapy

39% had a condition associated with thrombocytopenia, mainly autoimmune disease

Clonal hematopoiesis (CHIP) in 18.5% of patients
Most commonly mutated genes: TET2, DNMT3A, SRSF2, ASXL1. Median VAF: 29%.

Patients with CHIP were more frequently males and older (median age 77 vs 59 years)

Increased risk of thrombosis in patients with ITP and CHIP

Fattizzo B et al. Blood Advances 2024

Antiplatelet antibodies

MAIPA assay is considered the gold standard for platelet antibodies detection:

- **Direct**: platelet-rich plasma, at least $20x10^6$ plt needed, fresh sample
- **Indirect**: serum

- **Specificity > 95%** → conformational changes of the antigen; limited panel of antibodies
- **Sensitivity 80%** → too low platelets; low antigen expression; antigen not accessible

➢ Limited to be a «rule-in» test

Other options:

- PIFT: flow cytometry for platelet-associated IgG; also with low platelet counts; low specificity
- MACE: modified antigen-capture enzyme-linked immunosorbent assay
- Immunobeads

Vrbensky J et al. Journal of thrombosis and haemostasis 2019

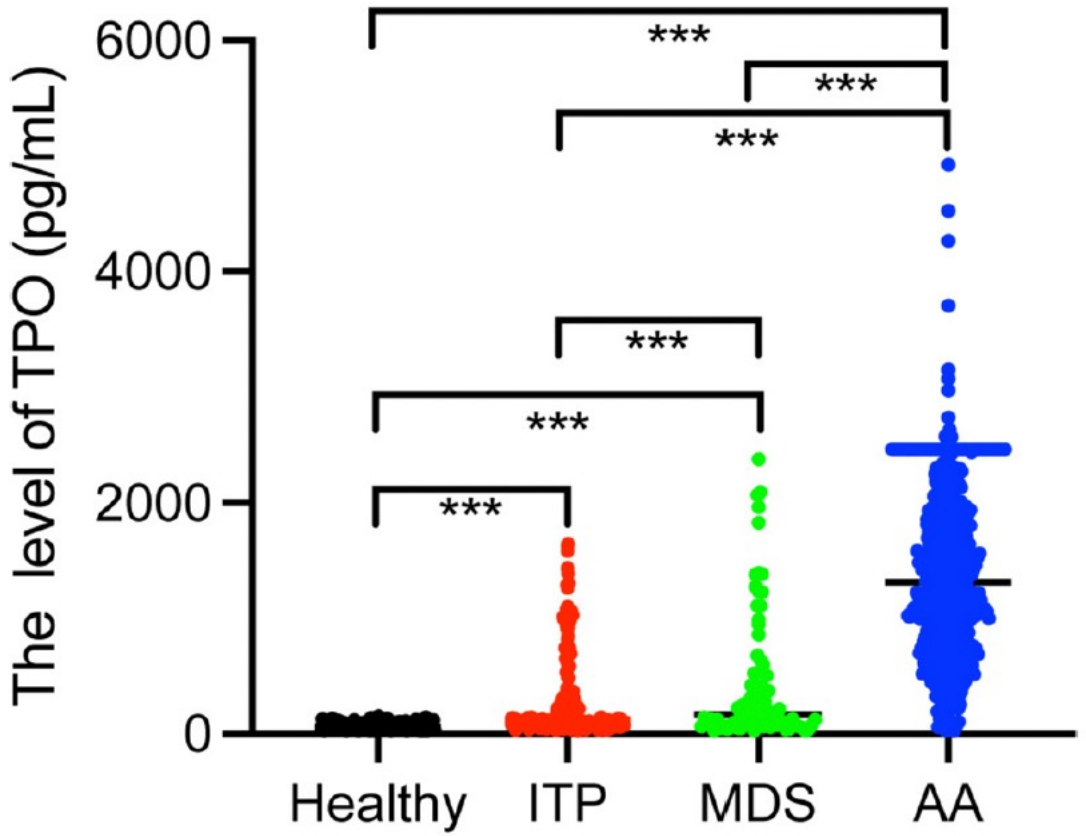
TPO serum levels

751 pts:

- 174 ITP
- 492 AA
- 85 MDS

TPO serum levels higher in patients with AA and MDS vs ITP

Cut-off value for distinguish ITP and MDS: 127 pg/mL



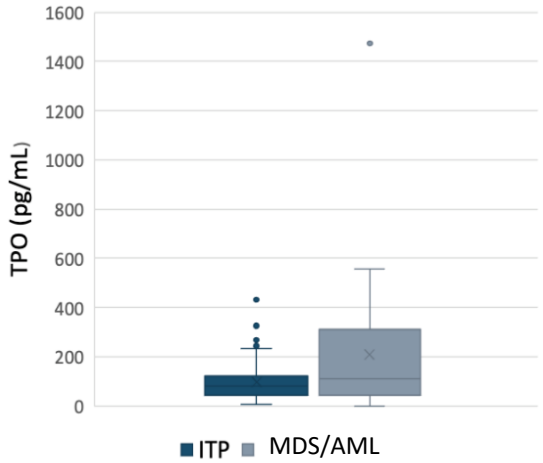
Zhu et al. Annals of hematology 2025

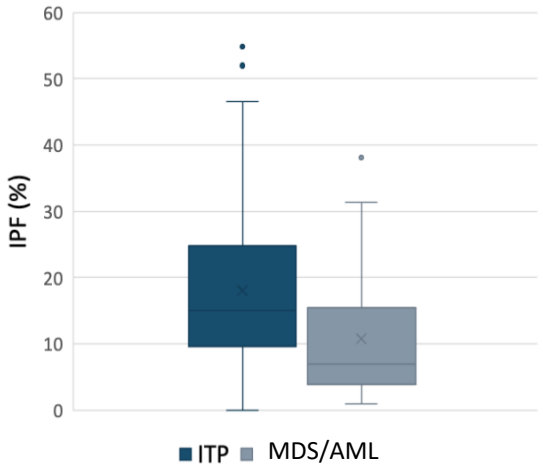
TPO serum levels and platelet indices

Monocenter study:

- 68 ITP
- 41 MDS/AML
- No significant differences in terms of platelet count and plateletcrit
- **MPV**, **PDW** and **P-LCR** were significantly higher in ITP patients

In ITP patients, **TPO** levels were significantly low and **IPF** was significantly higher





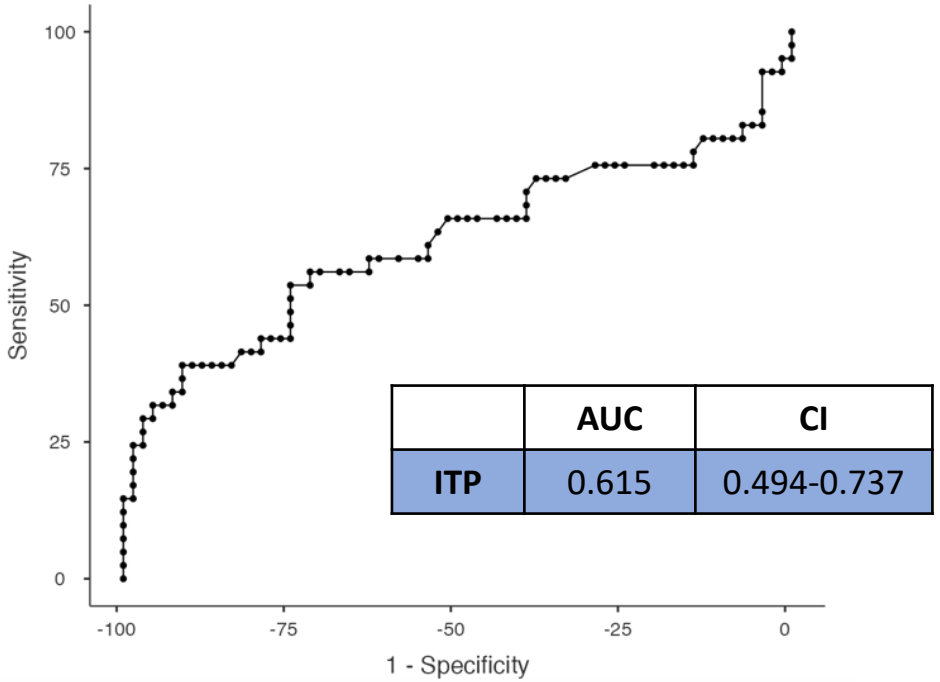
Lucchini et al. oral presentation SIE 2023

TPO serum levels and platelet indices

IPF better than TPO

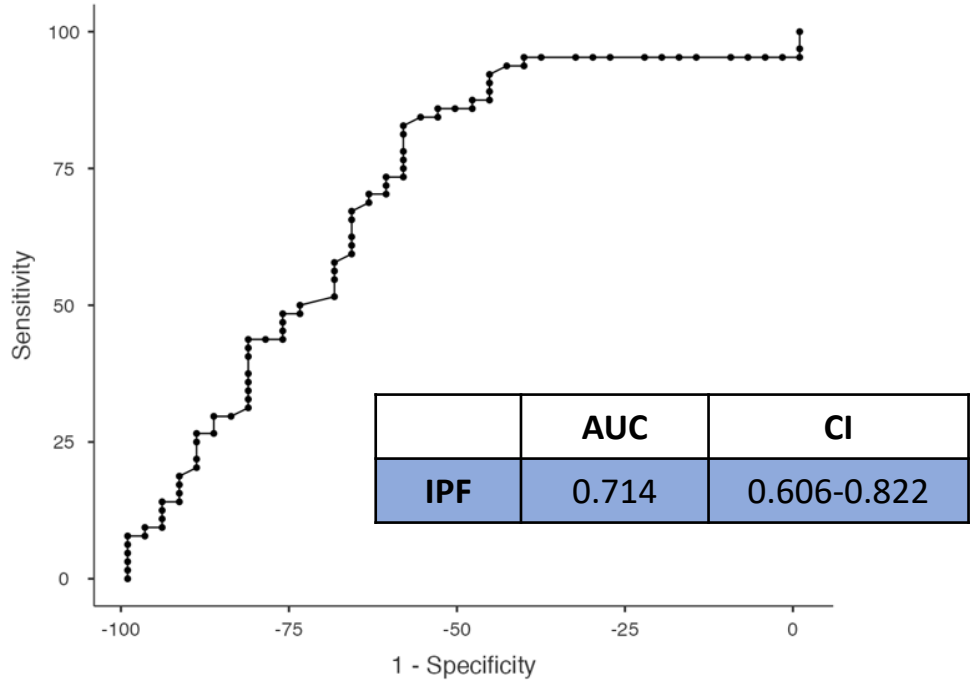
IPF > 8% separates the two groups with a sensitivity of 84% and a specificity of 56%

ROC Curve: TPO (pg/mL)



	AUC	CI
ITP	0.615	0.494-0.737

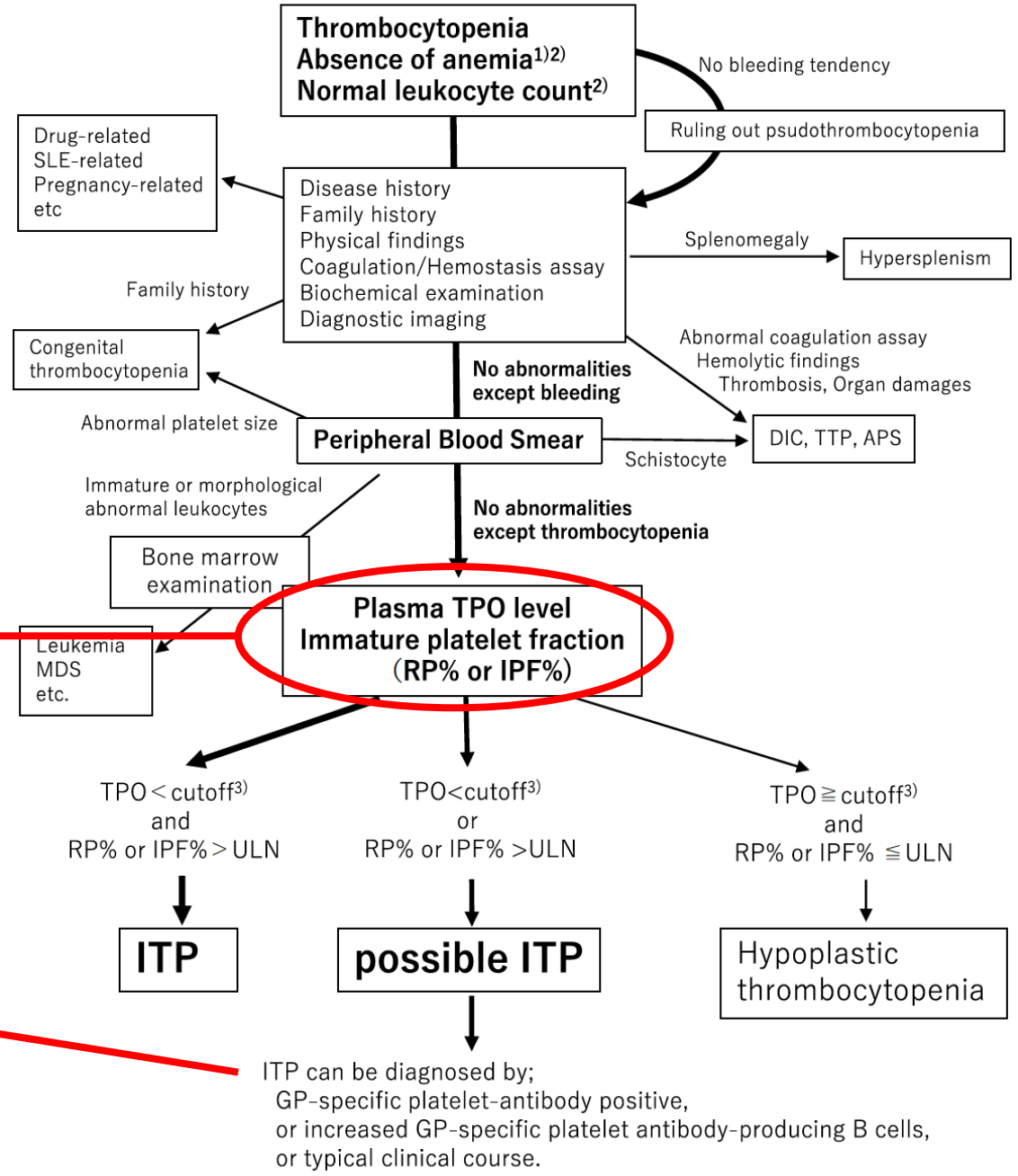
ROC curve: IPF (%)



	AUC	CI
IPF	0.714	0.606-0.822

Lucchini et al. oral presentation SIE 2023

Japanese guidelines



300 pg/mL with R&D systems kit and 70 pg/mL with TPO-CLEIA

- MAIPA/MACE assay
- ELISPOT

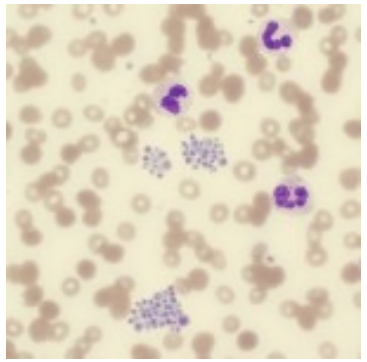
(only available in few labs)

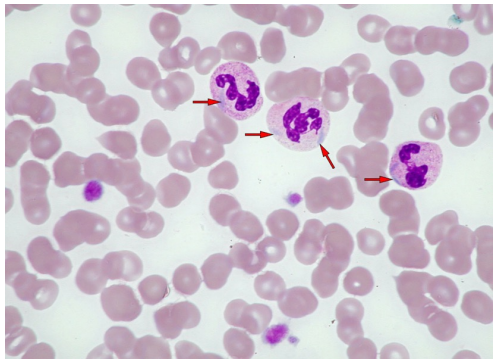
Kashiwagi H et al. Int J Hem 2024

Conclusions

ITP remains a diagnosis of exclusion

- Peripheral blood smear!
- Exclude pseudothrombocytopenia





Response to ITP-directed therapy is a reliable ex-juvantibus criterion, BUT always think about reassessing the diagnosis in refractory patients or if atypical findings

Biomarkers are still not validated tools, but promising role of TPO levels, with platelet indices and antiplatelet antibodies

More expensive diagnostics (NGS..) should be reserved to «non-typical» cases