TABLE 131-4 THREE CURRENT SCORING SYSTEMS FOR ESTIMATING PROGNOSIS IN PMF PATIENTS

Risk Factor	IPSS (2009)[a]	DIPSS (2010)[b]	DIPSS Plus (2011)[c]
Anemia (<10 g/dL)	X	X	X
Leukocytosis (>25,000/μL)	X	X	X
Peripheral blood blasts (≥1%)	X	X	X
Constitutional symptoms	X	X	X
Age (>65 years)	X	X	X
Unfavorable karyotype			X
Platelet count (<100,000/μL)			X
Transfusion dependence			X

[a]Blood 113:2895, 2009. [b]Blood 115:1703, 2010. [c]J Clin Oncol 29:392, 2011.

Note: The Dynamic International Prognostic Scoring System (DIPSS) was developed to determine if the International Prognostic Scoring System (IPSS) risk factors identified as important for survival at the time of primary myelofibrosis (PMF) diagnosis could also be used for risk stratification following their acquisition during the course of the disease. One point is assigned to each risk factor for IPSS scoring. For DIPSS, the same is true, but age >65 years, anemia, blood blasts, and constitutional symptoms are assigned 2 points each. The DIPSS Plus scoring system represents recognition that the addition of unfavorable karyotype, thrombocytopenia, and transfusion dependence improved the DIPSS risk stratification system for which additional points are assigned (Table 131-5). More recent studies suggest that mutational analysis of the *ASXL1*, *EZH2*, *SRSF2*, and *IDH1/2* genes further improves risk stratification for survival and leukemic transformation (Leukemia 27:1861, 2013).

factors for disease acceleration during the course of PMF include the presence of complex cytogenetic abnormalities, thrombocytopenia, and transfusion-dependent anemia. Most recently, mutations in the *ASXL1*, *EZH2*, *SRSF2*, and *IDH1/2* genes have been identified as risk factors for early death or transformation to acute leukemia and may prove to be more useful for PMF risk assessment than any clinical scoring system.

TREATMENT PRIMARY MYELOFIBROSIS

No specific therapy exists for PMF. The causes for anemia are multifarious and include ineffective erythropoiesis uncompensated by splenic extramedullary hematopoiesis, hemodilution due to splenomegaly, splenic sequestration, blood loss secondary to thrombocytopenia or portal hypertension, folic acid deficiency, systemic inflammation, and autoimmune hemolysis. Neither recombinant erythropoietin nor androgens such as danazol have proven to be consistently effective as therapy for anemia. Erythropoietin may worsen splenomegaly and will be ineffective if the serum erythropoietin level is >125 mU/L. Given the inflammatory milieu that characterizes PMF, corticosteroids can ameliorate anemia as well as constitutional symptoms such as fever, chills, night sweats, anorexia, and weight loss, and low-dose thalidomide together with prednisone has proved effective as well. Thrombocytopenia can be due to impaired marrow function, splenic sequestration, or autoimmune destruction and may also respond to low-dose thalidomide together with prednisone. Splenomegaly is by far the most distressing and intractable problem for PMF patients, causing abdominal pain, portal hypertension, easy satiety, and cachexia, whereas surgical removal of a massive spleen is associated with significant postoperative complications including mesenteric venous thrombosis, hemorrhage, rebound leukocytosis and thrombocytosis, and hepatic extramedullary hematopoiesis with no amelioration of either anemia or thrombocytopenia when present. For unexplained reasons, splenectomy also increases the risk of blastic transformation. Splenic irradiation is, at best, temporarily palliative and associated with a significant risk of neutropenia, infection, and subsequent operative hemorrhage if splenectomy is attempted. Allopurinol can control significant hyperuricemia, and bone pain can be alleviated by local irradiation. The role of IFN-α is still undefined; its side effects are more pronounced in the older individuals, and it may exacerbate the bone marrow failure. The JAK2 inhibitor, ruxolitinib, has proved effective in reducing splenomegaly and alleviating constitutional symptoms in a majority of advanced PMF patients while also prolonging survival, although it does not significantly influence the *JAK2* V617F allele burden. Allogeneic bone marrow transplantation is the only curative treatment for PMF and should be considered in younger patients; nonmyeloablative conditioning regimens may permit hematopoietic cell transplantation to be extended to older individuals, but this approach is currently under investigation.

TABLE 131-5 IPSS AND DIPSS RISK STRATIFICATION SYSTEMS

	Number of Risk Factors		
Risk Categories[a]	IPSS	DIPSS	DIPSS PLUS
Low	0	0	0
Intermediate-1	1	1–2	1
Intermediate-2	2	3–4	2–3
High	≥3	>4	4–6

[a]The corresponding survival curves for each risk category can be found in the references cited in the footnotes of Table 131-4.

Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System.

ESSENTIAL THROMBOCYTOSIS

Essential thrombocytosis (other designations include *essential thrombocythemia*, *idiopathic thrombocytosis*, *primary thrombocytosis*, and *hemorrhagic thrombocythemia*) is a clonal disorder of unknown etiology involving a multipotent hematopoietic progenitor cell manifested clinically by overproduction of platelets without a definable cause. ET is an uncommon disorder, with an incidence of 1–2/100,000 and a distinct female predominance. No clonal marker is available to consistently distinguish ET from the more common nonclonal, reactive forms of thrombocytosis (Table 131-6), making its diagnosis difficult. Once considered a disease of the elderly and responsible for significant morbidity due to hemorrhage or thrombosis, with the widespread use of electronic cell counters, it is now clear that ET can occur at any age in adults and often without symptoms or disturbances of hemostasis. There is an unexplained female predominance in contrast to PMF or the reactive forms of thrombocytosis where no sex difference exists. Because no specific clonal marker is available, clinical criteria have been proposed to distinguish ET from the other chronic MPNs, which may also present with thrombocytosis but have differing prognoses and therapies (Table 131-6). These criteria do not establish clonality; therefore, they are truly useful only in identifying disorders such as CML, PV, or myelodysplasia, which can masquerade as ET, as opposed to actually establishing the presence of ET. Furthermore, as with "idiopathic" erythrocytosis, nonclonal benign forms of thrombocytosis

TABLE 131-6 CAUSES OF THROMBOCYTOSIS

Tissue inflammation: collagen vascular disease, inflammatory bowel disease	Hemorrhage
Malignancy	Iron-deficiency anemia
Infection	Surgery
Myeloproliferative disorders: polycythemia vera, primary myelofibrosis, essential thrombocytosis, chronic myelogenous leukemia	Rebound: Correction of vitamin B_{12} or folate deficiency, post-ethanol abuse
Myelodysplastic disorders: 5q− syndrome, idiopathic refractory sideroblastic anemia	Hemolysis
Postsplenectomy or hyposplenism	Familial: Thrombopoietin overproduction, *MPL* mutations