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Significance of cytogenetic-risk categories and refined international prognostic scoring system for overall survival in primary myelofibrosis: A single-center experience

Značaj citogenetički rizičnih kategorija i prerađenog Međunarodnog prognoznog sistema za procenu ukupnog preživljavanja u primarnoj mijelofibrozi: iskustvo jednog centra

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Abstract

Background/Aim. Primary myelofibrosis (PMF) is a chronic, malignant hematological disease characterized by a leucoerythroblastic blood picture, anisopoikilocytosis teardrop-shaped erythrocytes, different degrees of bone marrow fibrosis and hepatosplenomegaly due to extramedullary hematopoiesis. Among genetic specificities of the disease, those that stand out are chromosomal aberrations in pathological, myeloid blood cells. The aim of this study was to examine the prognostic significance of clinical, hematologic and cytogenetic parameters in PMF. **Methods.** A retrospective study included 144 patients with PMF. Karyotypes were analyzed using conventional cytogenetic methods. **Results.** The chromosome examinations were successful in 126 (88%) patients and failed in the remainder ones (12%). Karyotype was abnormal in 36/126 (29%) subjects at presentation. The most frequent changes included +9, 13q- and 20q- (28%). Other abnormalities were: aberrations of chromosome 18 and 16, deletions (9q-, 12p-, 7q-, 5q-, 6q-, 8q-), trisomies (+1q, +8, +10, +21), monosomies (-7, -11), 3q inversion and loss of Y chromosome. We detected four novel balanced translocations in PMF: t(17;22)(q11;q13), t(15;17)(q22;q25), t(9;12)(q22;q24) and t(2;4)(q21;p16), one constitutional translocation-rob(13;14)(q10;q10) and some new karyotype anomalies - deletion of both homologues, hyperdiploidy and the coexistence of unrelated pathological clones. **Conclusion.** Chromosomal aberrations had a significant influence on overall survival of patients with PMF according to the refined cytogenetic-risk of the International Prognostic Scoring System (Refined CIPSS) ($p = 0.004$). Our patients matched the pattern of chromosome aberrations usually observed in PMF but some newly registered, balanced translocations and other rare karyotype anomalies were recorded as well.

Key words:
chromosome aberrations; cytogenetics; primary myelofibrosis; prognosis.

Apstrakt

Uvod/Cilj. Primarna mijelofibroza (PMF) je hronična, maligna hematološka bolest koja se karakteriše leukoeritroblastnom krvnom slikom, anizopoikilocitozom eritrocita u obliku suze, različitim stepenom fibroze kostne srži i hepatosplenomegalijom usled ekstramedularne hematopoeze. Od genetičkih specifičnosti bolesti, ističu se hromozomske aberacije u patološkim, mijeloidnim ćelijama krvi. Cilj rada bio je da se ispita prognostički značaj kliničkih, hematoloških i citogenetičkih parametara u PMF. **Metode.** Retrospektivnom studijom su bila obuhvaćena 144 bolesnika sa PMF. Analiza kariotipa vršena je konvencionalnom citogenetičkom metodom. **Rezultati.** Hromozomska analiza je bila uspešna kod 126 (88%) bolesnika, a neuspešna kod ostalih bolesnika (12%). Aberantan kariotip je bio registrovan kod 36/126 (29%) ispitanika na prezentaciji. Najčešće aberacije bile su: +9, 13q- i 20q- (28%). Druge abnormalnosti bile su: aberacije hromozoma 18 i 16, delecije (9q-, 12p-,7q-, 5q-, 6q-, 8q-), trizomije (+1q, +8, +10, +21), monozomije (-7, -11), inverzija 3q i gubitak Y hromozoma. Otkrili smo i četri nove balansirane translokacije u PMF: t(17;22)(q11;q13), t(15;17)(q22;q25), t(9;12)(q22;q24) i t(2;4)(q21;p16), jednu konstitucionu translokaciju - rob(13;14)(q10;q10) i neke nove anomalije kariotipa -

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delecija oba, homologa hromozoma, hiperdiploidiju i koegzistenciju nepovezanih patoloških klonova. **Zaključak.** Prema citogenetički prerađenom Međunarodnom prognoznom sistemu hromozomske aberacije su statistički značajno ($p = 0.004$) uticale na ukupno preživljavanje bolesnika sa PMF. Kod naših bolesnika nađene su hromozomske aberacije uobičajne za PMF, ali su registrovane i nove balansirane translokacije, kao i druge, retke kariotipske anomalije.

Ključne reči:
hromosomi, aberacije; citogenetika; mijelofibroza, primarna; prognoza.

Introduction

Primary myelofibrosis (PMF) is a clonal myeloproliferative neoplasm (MPN) characterized by bone marrow fibrosis and extramedullary hematopoiesis [1, 2]. Patients with PMF are heterogeneous at presentation. Adverse prognostic factors include: advanced age, presence of constitutional symptoms, anemia, decreased or elevated white blood cell count, thrombocytopenia, circulating myeloblasts and the presence of clonal chromosomal aberrations [3, 4].

Cytogenetic data in PMF are often scarce and inconclusive. Their prognostic relevance is limited by difficulties in obtaining good quality metaphases from the bone marrow aspirates [5]. However, studies reporting successful cytogenetics showed that recurrent cytogenetic abnormalities are seen in approximately one-third of patients at diagnosis and they increase in frequency over the course of disease.

The most frequent aberrations in PMF (+1q, 13q-, 20q-, +9, +8) appear in two-thirds of patients with a pathologic karyotype [5, 6]. Conversely, other abnormalities, such as balanced translocations, complex karyotypes, the coexistence of two or more unrelated pathological clones, are rare. In consequence, cytogenetics is one of the fundamental prognostic parameters in some current Prognostic Scoring Systems (PSSs) in PMF.

The aim this study was to examine the prognostic significance of clinical, hematologic and cytogenetic parameters in PMF.

Methods

We presented a retrospective analysis of 144 PMF patients who were cytogenetically evaluated. The type and frequency of chromosome abnormalities were assessed at presentation. Besides typical chromosomal abnormalities encountered in PMF, we presented a number of rather rare cytogenetic findings. In addition, we tested the prognostic impact of the chromosomal aberrations on patient survival from presentation up to the completion of the study. Due to different categorization of abnormalities in different PSSs in PMF, we examined their prognostic significance by stratifying patients in accordance with the stipulations of cytogenetic (C) PSSs [CLille, CMayo, C International PSS – (CIPSS) and Refined CIPSS] [3, 7–9].

Furthermore, the impact of clinical and hematological parameters on overall survival (OS) of our patients was examined by applying different PSSs (Lille, Cervantes, IPSS, Dynamic IPSS - DIPSS, Mayo and Mayo for younger patients) [3, 4, 10–13].

Patients

Between January 2004 and December 2010, 144 patients were diagnosed with PMF at the Clinic of Hematology, Clinical Center of Serbia, Belgrade. All patients fulfilled the WHO diagnostic criteria for PMF [14, 15]. Clinical and laboratory data along with cytogenetic results were collected retrospectively up to 2013, when 95 (66%) of the patients were alive and 49 (34%) had died.

Bone marrow aspirates and trephine biopsies were taken with the consent of the patients or their families. The study was approved by the Ethics Committee of the Clinical Center of Serbia in Belgrade.

Cytogenetic analysis

Conventional cytogenetic analyses were performed on metaphases obtained from unstimulated bone marrow aspirates or peripheral blood cultures, using a previously reported technique [16]. Karyotypes were interpreted according to the International System for Human Cytogenetic Nomenclature [17]. Whenever possible, twenty metaphases were examined.

Statistics

Statistical analysis of the prognostic significance of clinical and laboratory data, as well as cytogenetic status was performed using several PSSs and cytogenetic PSSs. Survival was measured from diagnosis until the last contact or death. The data are presented as median (minimum-maximum) or n (%). Survival was evaluated using Kaplan-Meier curves and the Log-rank test for group comparisons. All analyses were performed using SPSS 20.0 (IBM corp.). Probability (p) values ≤ 0.05 were considered statistically significant.

Results

Bone marrow aspirate or peripheral blood samples were taken from 144 patients with PMF [median age 65.5 years (range 28–80 years)] for cytogenetic analysis. Comprehensive clinical and laboratory evaluations were performed at diagnosis (Table 1). Karyotype analysis failed in 18/144 (12%) patients. A normal karyotype was seen in 91/126 (72%) patients including an individual with a Robertsonian translocation. Abnormal pathologic clones were spotted in the remaining 36/126 (28%) patients. The results of cytogenetic analysis for 37 patients are presented in Table 2. The most prevalent changes were +9, 13q- and 20q-, comprising 28% of the abnormal karyotypes and were found in 10 patients, either as a single abnormality or as part of a complex karyotype. Three patients had aberrations of chromosome 18. Aberrations of 16q, deletion of chromosomes 9q, 12p and 7q as well as loss of the Y chromosome were found in two patients each. In one patient (aged 76), -Y was part of the con-

stitutional karyotype, while in the other one (aged 59) it was a clonal chromosomal abnormality. Each of the following aberrations was seen in a single patient: +1q, inv(3), 5q-, 6q-, -7, +8, 8q-, +10, -11, +21.

Table 1

Clinical and hematological characteristics in 144 patients at presentation

Parameter	Median (minimum-maximum)	n/N*
Age, years	65.5 (28-80)	144
Age ≤ 60 years	54.5 (28-60)	50/144
Sex, F/M		55/89
Hemoglobin (g/L)	124.0 (45-181)	
Hb < 100 g/L		21/144
WBC count (x10^9/L)	11.1 (1.6-83.2)	
WBC count < 4 or > 30 x 10^9/L		19/144
Platelet count (x 10^9/L)	687.5 (28-684)	
Platelets < 100 x 10^9/L		9/144
Circulating blasts (≥ 1%)	(0-9)	21/144
Constitutional symptoms		25/144
Palpable splenomegaly		98/137
Cytogenetics		126/144
Karyotype, normal/aberrant		90/36

n – parameterized; N – total number of patients examined; Hb – hemoglobin; **WBC – white blood cell; F – female; M – male.**

Table 2

Karyotype abnormalities at presentation (n = 37)

Patient No.	Sex/age (years)	Karyotype
1	F/64	47,XX,+8[3]/48XX,+8,+10[5]/46XX[2]
2	M/77	46,XY,del(6)(p23),del(8)(q22)[20]
3	M/60	46,XY,del(13)(q12q22)[19]/46,XY[1]
4	M/68	47,XY,+mar[20]
5	M/57	46,XY,-7,+dmin[15]/46,XY[5]
6	M/62	46,XY,del(20)(q11q13)[20]
7	F/48	46,XX,rob(13;14)(q10;q10)[10]
8	F/65	47,XX,+9[1]/46,XX[19]
9	F/9	46,XX,del(13)(q12q22)[19]/46,XX[1]
10	F/64	45,XX,-18[3]/46,XX[17]
11	M/72	46,XY,del(9)(q21)[8]/46,XY[5]
12	F/62	47,XX,1qh+c,+9[5]/46,XX,1qh+c[5]
13	M/73	47,XY,+9[6]/[46,XY[9]
14	F/80	46,XX,t(17;22)(q11;q13)[20]
15	M/62	47,XY,+9[3]/46,XY[13]
16	F/45	46,XX,del(9)(q22)[3]/47,XX,idem,+del(9)(q22)[17]
17	M/58	46,XY,t(15;17)(q22;q25)[15]/46,XY,add(18)(p11)[3]
18	M/63	46,XY,del(5)(q13q31)[9]/46,XY[8]
19	F/59	46,XX,del(13)(q12q22)[1]/46,XX,idem,-11,+mar[19]
20	M/70	46,XY,t(9;12)(q22;q24)[2]/46,XY[20]
21	F/70	46,XX, add(18)(p11)[18]/50~52,XX,inc[cp2]
22	M/75	46,XY,del(12)(p11p13)[3]
23	F/54	46,XX,ins(16)(q?)[2]/46,XX[8]
24	M/79	48,XY,+2mar[8]/46,XY[12]
25	M/80	47,XY,+mar[10]
26	F/70	46,XX,der(15)t(1;15)(q12;p11)[20]
27	M/75	46,XY,del(7)(q31)[12]/46,XY[8]
28	M/70	46,XY,del(7)(q32)[18]/46,XY[2]
29	F/60	46,XX,del(20)(q11q13)[20]
30	M/69	46,XY,del(20)(q11q13)[10]
31	F/66	46,XX,add(16)(q?)[11]/46,XX[3]
32	M/68	47,XY,+21[3]/46,XY[10]
33	M/73	46,XY,del(12)(p11p13)[20]
34	F/61	46,XX,inv(3)(p13q27)[3]/46,XX[7]
35	M/50	45,X,-Y[10]
36	F/70	46,XX,t(2;4)(q21;p16)[10]
37	M/76	45,X,-Yc[10]

F - female; M - male.

Partial trisomy of 1q was detected as an unbalanced translocation with chromosome 15 [der(15)t(1;15) (q12;p11)]. We registered the Robertsonian translocation, rob(13;14) (q10;q10) (Table 2, No. 7) in the karyotype of one patient. This has not been previously described in PMF. Each of the following translocations: t(17;22)(q11;q13), t(15;17) (q22;q25), t(9;12) (q22;q24), t(2;4)(q21;p16) was detected in a single patient (Table 2, Nos.14, 17, 20, and 36). Two patients had karyotypes with two unrelated pathologic clones. One of them had one clone with balanced t(15;17)(q22;q25) (Table 2, No.17) and the other had additional material to the18p. This patient (Table 2, No. 21) had unrelated clones with add(18)(p11) and a hyperdiploid chromosome number.

Impact of clinical and hematological parameters on overall survival

The female/male ratio was 55/89 and the median age was 65 years. The median follow-up finishing in 2013 was 83 months with 49 (34%) recorded deaths. There was no difference in OS between females and males ($p = 0.353$).

The stratification of patients according to clinical and hematological data, presented in Table 1, showed statistical significance for OS prediction when using Lille, Cervantes, IPSS, DIPSS, Mayo, and Mayo PSSs for younger patients (≤ 60 years) ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.001$, and $p = 0.013$, respectively) (Figure 1). The scoring of clinical and hematological parameters and stratification of risk by categories for all PSSs are presented in Table 3.

Impact of the karyotype pattern on overall survival

The impact of chromosomal aberrations on OS was estimated independently according to the CLille, CMayo, CIPSS and Refined CIPSS recommendations (Table 4). The CLille system found no statistically significant difference ($p = 0.155$) in OS between the groups of patients with and without chromosome aberrations (Figure 2a). A similar result was obtained ($p = 0.214$) using the CMayo system (Figure 2b).

Application of the CIPSS [8] to our data also disclosed no significant differences ($p = 0.152$) in OS for patients belonging to the four distinct risk groups of this prognostic system (Figure 2c). However, the Refined CIPSS (Figure 2d) detected strong statistical significance ($p = 0.004$) for a difference in OS between just two cytogenetic categories of patients (Table 3): one with a favorable karyotype (108 patients) and the other with unfavorable chromosome aberrations (18 patients).

Table 3

Prognostic Scoring Systems (PSSs) for risk assessment in primary myelofibrosis patients (n = 144)

PSSs	Prognostic parameters	Risk stratification	Risk category	Prognostic significance for surviving, *p*-values
Lille [3]	1. Hb (< 100 g/L) 2. WBC count (< 4 or > 30 x 10^9/L)	0 1 2	low intermediate high	< 0.001
Cervantes [4]	1. age (> 64 years) 2. constitutional symptoms* 3. Hb (< 100 g/L) 4. blood blasts	0 1 2 3	low intermediate-1 intermediate-2 high	< 0.001
IPSS [10]	1. age (> 65 years) 2. constitutional symptoms* 3. Hb (< 100 g/L) 4. WBC count (> 25 x 10^9/L) 5. circulating blasts (> 1%)	0 1 2 ≥ 3	low intermediate-1 intermediate-2 high	< 0.001
DIPSS [11]	1. age (> 65 years) 2. constitutional symptoms* 3. Hb (< 100 g/L) 4. WBC count (> 25 x 10^9/L) 5. circulating blasts (≥ 1%)	0 1 or 2 3 or 4 > 4	low intermediate-1 intermediate-2 high	< 0.001
Mayo [12]	1. Hb (< 100 g/L) 2. WBC count (< 4 or > 30 x 10^9/L) 3. Pt (< 100 x 109/L) 4. monocytes (> 1 x 109/L) 5. circulating blasts	0 1 ≥ 2	low intermediate high	0.001
Mayo (≤ 60 years) [13]	1. Hb (< 100 g/L) 2. WBC count (< 4 or > 30 x 10^9/L) 3. Pt (< 100 x 109/L) 4. monocytes (> 1 x 10^9/L)	0 1 ≥ 2	low intermediate high	0.013

***Constitutional symptoms included fever, night sweats or weight loss of ≥ 10% within the last 6 months.**

Hb – hemoglobin; WBC – white blood cell; Pt – plafelet.

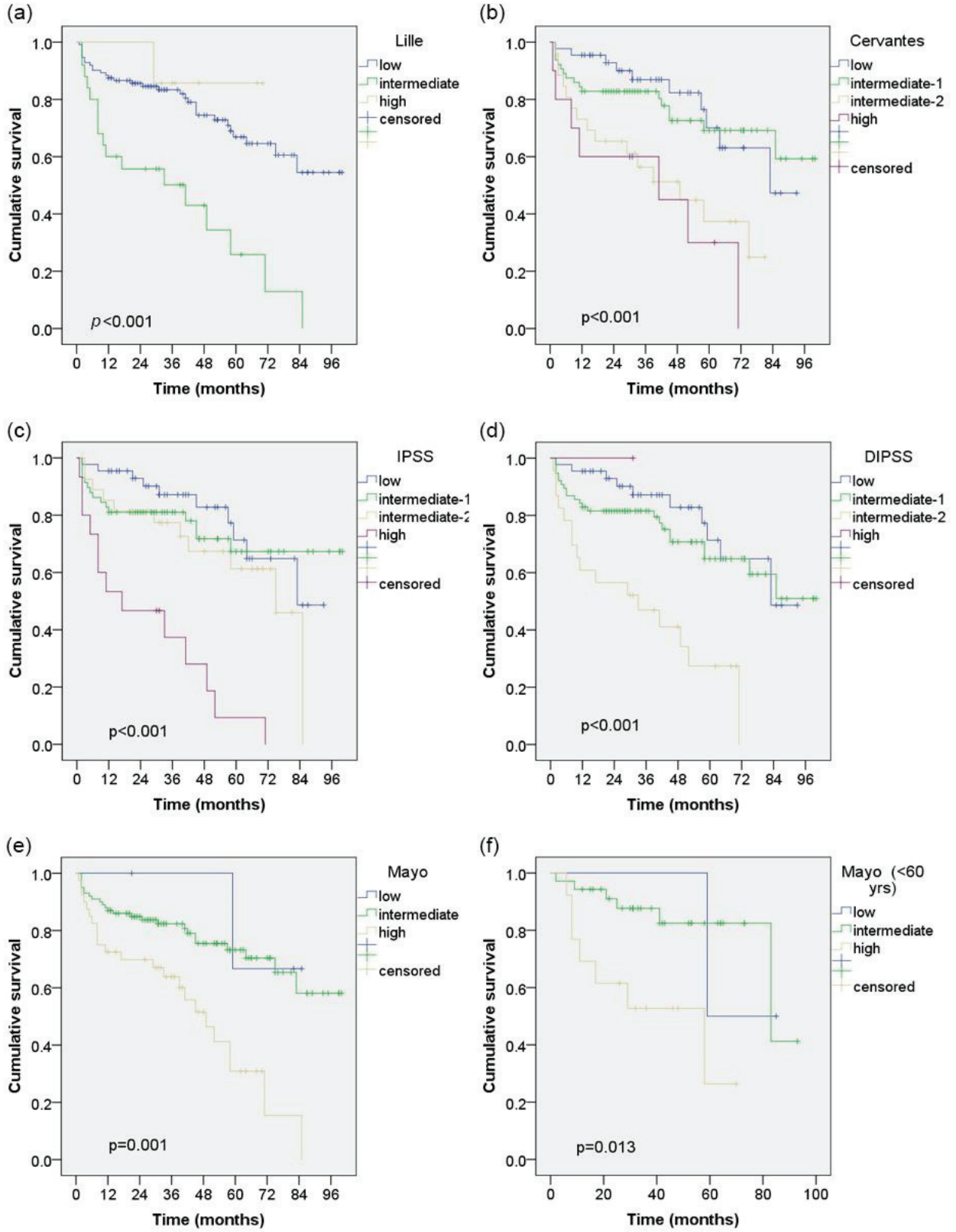

Fig. 1 – Kaplan-Meier survival curves for 144 patients with primary myelofibrosis stratified by clinical and hematological characteristics, based on the: a) Lille; b) Cervantes; c) International Prognostic Scoring System (IPPS); d) Dynamic International Prognostic Scoring System (DIPSS); e) Mayo for all patients; f) Mayo (≤ 60 year-old) patients (see Table 3 for details of these prognostic systems).

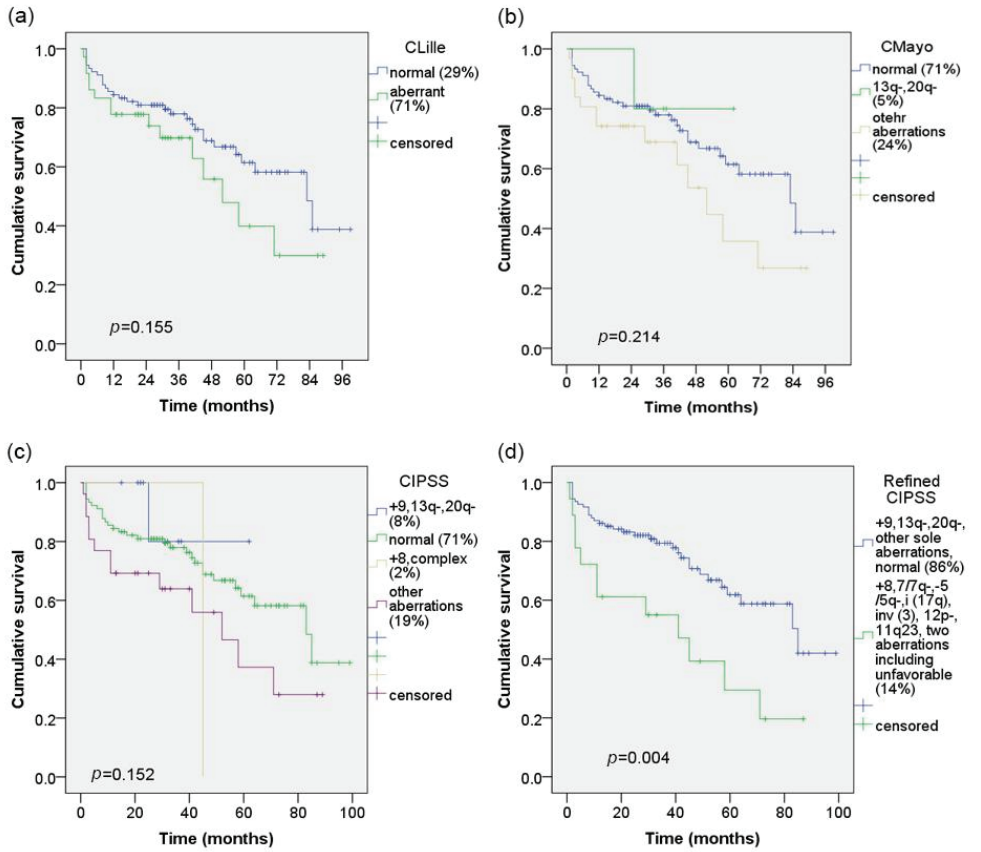

Fig. 2 – Kaplan-Meier survival curves for 126 patients stratified by cytogenetic (C) criteria alone based on the: a) CLille; b) CMayo; c) Cytogenetic International Prognostic Scoring System (CIPSS); d) Refined CIPSS (see Table 4 for details of these prognostic systems).

Table 4

Independent Cytogenetic Prognostic Scoring Systems (CPSSs) for risk assessment (n*=126)

CPSSs	Karyotype	Risk category	Prognostic significance for surviving, *p*-values
CLille [3]	1. normal 2. aberrant	favorable unfavorable	0.155
CMayo [7]	1. normal 2. 13q- or 20q- 3. other aberrations	favorable unfavorable	0.214
CIPSS [8]	1. +9 or 13q- or 20q- 2. normal 3. other aberrations 4. +8 or complex karyotype (≥ 3 aberrations)		
Refined CIPSS [9]	1. sole 13q- t/dup(1q) sole 20q- sole +9 other sole aberrations two aberrations excluding unfavorable normal karyotype 2. complex karyotype (≥ 3 aberrations) sole +8 sole -5/5q- sole -7/7q- i(17q) inv(3) 12p- 11q23 two aberrations including at least one unfavorable	favorable unfavorable	0.004

***n – total number of patients with successful cytogenetics.**

Discussion

Overall survival in PMF depends on clinical, laboratory, cytogenetic and molecular characteristics of the disease. It is affected by the patient's age, physical condition and associated morbidities. In order to opt for the most favorable therapy at the time of diagnosis, it is imperative to try to pinpoint those features with the greatest impact on survival and quality of life.

Prospective studies of the prognostic impact of cytogenetic data in PMF patients are relatively rare [18–20]. Technical difficulties in obtaining representative aspirates from the fibrotic bone marrow make estimates of the frequency of abnormal clones difficult. In consequence, reported pathologic karyotypes in PMF range between 30% and 75% [3, 5, 6, 18, 19]. Among the registered aberrations in this disease, more that 90% include 20q-, 13q-, +8, +9, -Y, +21, 11q-, 12p-, partial trisomy of 1q, and rearrangements of chromosomes 5 and 7 [20]. The aberrations 20q-, 13q- and +9 were detected in 15%-50% of cases, usually as solitary changes [8, 9, 18–21].

In our study, the most common abnormalities were +9, 13q- and 20q- (28%), which is in concordance with earlier findings [21]. The frequency of trisomy 9 in PMF is estimated to be 5%–10% [8, 20, 21], while in our group it was slightly higher – 11% (4 patients). Interstitial deletions of 13q and 20q were detected in six (17%) patients (Table 2). Molecular analyses of 13q- and 20q- identified two genes responsible for the development of myeloid disorders: the retinoblastoma gene on 13q14 and protooncogene *C-SRC1*, located distal to 20q12-q13 [5]. Deletions of 13q- and 20q- are prominent features in PMF, suggesting that gene loss underlies the pathogenesis of the disease.

Partial trisomy of 1q is a specific aberration in PMF. Its frequency varies from only 3% [3] in some studies to more than 30% in others [21], or is even not seen at all [5]. In our group, +1q was detected in a single (3%) patient [der(15)t(1;15)(q12;p11)]. It is known that rearranged 1q usually leads to gene amplification enabling proliferative advantage of the malignant clone [22]. This was confirmed in our case where +1q was registered in all analyzed cells.

Aberrations of chromosomes 5 and 7 are less frequent in PMF but have significant influence on the prognosis. Survival of patients with -5/5q- and -7/7q- rearrangements is inferior when compared with patients having a normal karyotype and similar to those with complex karyotypes [9]. We detected 5q- in one (3%) case and -7/7q- in three (8%) individuals. Those with -7 and 7q- had a lethal outcome with overall survival of 3-58 months after disease presentation, confirming published data [9] indicating that aberrations of -7/7q- are a poor predictive factor. While our patient with 5q- was alive 13 months after presentation, this monitoring period was too short to conclude about its impact on OS.

Two (6%) of our patients had 12p deletion. Since both individuals survived for only 2 to 3 months after diagnosis, we can conclude that del(12)(p11p13) is a very poor prognostic parameter in PMF. Patients with 12p- were classified in a high-risk category based on criteria of all tested PSSs. The most likely explanation for their short survival is an association of poor prognostic parameters, clinical, hematological and cytogenetical.

Pericentric inversion of chromosome 3 with p13q27 breakpoints was detected in a single (3%) patient. Paracentric inversion of chromosome 3 and translocation t(3;3) with (q21q26) breakpoints represent distinct entities in acute myeloid leukemias and are recognised as a molecular marker of poor prognosis [23]. Our patient with pericentric inversion inv(3)(p13q27), represents the first case with this abnormality to be reported in PMF so far. At the moment of completion of the study the patient was alive (49 months) without any indication of evolution of the disease to acute leukemia.

Deletions of the long arm of chromosome 9 are a rare finding in PMF. When present, they are usually associated with other abnormalities in a complex karyotype. The most commonly rearranged bands on 9q are q21-q22, representing 46% of the total rearrangements affecting bands 9q11 to 9q33 [24]. Interstitial deletions of 9q are relatively infrequent and have been found almost exclusively in MPN [24]. Terminal deletions of 9q are less common and predominantly involve the same breakpoints (q21-q22). Two (6%) of our patients had terminal 9q deletions with the above mentioned breakpoints q21 and q22. In one patient (Table 2, No. 16) we noted a clone with 9q- as a single aberration, associated with another subclone (a clone in evolution) where this aberration affected both homologues. This cytogenetic finding is rarely seen in PMF. At the moment of completion of the study, the patient was alive (73 months) without any clinical signs of disease progression. The other patient had 9q- as the sole abnormality (alive for 21 months). As the number of patients with 9q- was small, we can only speculate that 9q- aberrations do not belong to the group of poor cytogenetic parameters in PMF.

Sex chromosome aneuploidies are common numeric aberrations in hematologic diseases, including PMF. Loss of Y can be a primary or secondary event [25] reflecting disease evolution or a normal aging process [25]. Our patient with –Y, as the clonal abnormality, was alive (31 months) in 2013. We assume that clonal aberrations of the Y chromosome are not an unfavorable prognostic parameter for PMF, although the time of follow-up was short.

When compared with other studies, our results show an increased frequency of chromosomal translocations. Balanced translocations were detected in five patients (14%) (Table 2), one (3%) of whom carried the Robertsonian type. Translocations were always solitary changes in the karyotype. In one patient with t(15;17), there was another coexisting but unrelated clone with extramaterial added to the 18p (Table 2, No. 17). The mosaic karyotype of this patient represents a unique cytogenetic finding in PMF. Since the karyotype with two associated unrelated clones was present at disease presentation, it is possible that it was the first sign of leukemic transformation (after 33 months follow-up), which was not seen when analyzing other clinical and hematological parameters.

The majority of Robertsonian translocations detected in hematologic diseases are of natal origin. Welborn [26] analyzed the frequency of Robertsonian translocations in the karyo-

type of 5,633 patients with different hematological malignancies. Most were the rob(13;14) and rob(13;15) type and occurred equally in all types of hematological malignancies. These chromosome fusions can be induced *in vitro* in animal systems and are associated with the development of neoplasia [26]. In our study, rob(13;14) was a constitutional change, detected in one (3%) patient, who was alive at the moment of completion of the study and 27 months after diagnosis.

PMF is a disease that occasionally transforms into acute myeloid leukemia. It has been shown that patients with -7/7q-, -5/5q-, 12p-, aberrations of 1q, +8 and +9 transform more often (50%, 30%, 25%, 19%, 21% and 17%, respectively) than patients with 20q- or 13q- (10% and 0%, respectively) [21]. In our group, no case of transformation into acute leukemia was registered. Therefore, we can not conclude that aberrations carry leukemogenic potential themselves, but we can speculate about their prognostic potential. Our patients with single karyotype changes: der(15)t(1;15), del(7q), del(12p), der(16q), ins(16q), +21, as well as those with more than one chromosomal aberration: +8 with +10; del(6p) with del(8q); -7 with +dmin; del(9q) with +del(9q); +2mar; del(13q) with -11 and +mar; add(18p) with hyperdiploid karyotype, had a lethal outcome with OS of 2-71 months after disease presentation. In many of the CPSSs, aberrations +9, 13q-, and 20q- have been associated with a favorable prognosis, which was confirmed in our group of patients.

All subjects with single recurrent aberrations (+9, 13q-, 20q-), as well as those with -Y, and inv(3q), were alive at the time of the study realization (a survival period of 13-49 months after diagnosis). Similarly, all patients with balanced translocations and rob(13;14) were alive, with a survival time of 20 to 89 months. We can conclude that balanced translocations are not a poor prognostic parameter in PMF.

In this retrospective, single-center investigation covering a 7-year-period, pathologic karyotypes were found in 29% of patients at diagnosis. Reported estimates of the presence of chromosome aberrations in myeloproliferative neoplasm at presentation are ~35% [6]. Higher frequencies of aberrations can be expected in later phases of the disease or during the myelofibrotic transformations of essential thrombocythemia and polycythemia vera (post-essential thrombocythemia myelofibrosis and post-polycysthemia vera myelofibrosis) [27]. Our study included only PMF patients at presentation (at the beginning of the disease), which may explain the lower incidence of abnormal karyotypes compared with data in the literature.

Statistical analysis of survival based on clinical and hematologic parameters was performed for 144 patients. In all applied PSS [Lille, Cervantes, IPSS, DIPSS, Mayo, Mayo (aged ≤ 60 years)] the recorded survival of patients among different risk categories showed significant differences. We concluded that all of the PSSs are quite informative and equally efficent in risk estimation and prediction of PMF disease. In the group of younger patients aged ≤ 60 years (60 patients) we applied the Mayo PSS model.

Chromosome aberrations were treated as independent prognostic parameters and their influence on cumulative patient survival was tested by univariate analysis. More precisely, we applied various CPSSs because of their diverse definitions of benchmarks for inclusion into particular prognostic groups, i.e. the same chromosome aberrations are given disparate risk weights in different CPSSs.

Using CLille, CMayo and CIPSS, no statistical significance of karyotype profile on patient survival was documented. Normal karyotype and chromosome aberrations included in these CPSSs (+9, +8, 13q-, 20q-, complex karyotype, and all other aberrations) seemed to have no influence on patient survival, irrespective of the degree of risk. On the contrary, the Refined CIPSS showed high statistical significance regarding patient survival. However, dividing patients into two cohorts according to the karyotypic changes seems too simple for survival prediction in PMF.

Conclusion

This study confirms that karyotype analysis remains a powerful prognostic tool and its interaction with clinical, hematological and molecular risk factors is an important driver of the disease course. It should be included in future revisions of prognostic models.

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