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**Original Article**

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# Platelet counts and hemorrhagic diathesis in patients with myelodysplastic syndromes (MDS)

**Running title: Bleeding in MDS**

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**Abstract**

**Objectives:** Most patients with myelodysplastic syndromes present with single or multiple lineage cytopenias in peripheral blood despite a hypercellular bone marrow. Thrombocytopenia, attributable to ineffective platelet production by dysfunctional megakaryocytes, has been estimated to occur in 40-65% of patients. However, there are hardly any studies on the clinical relevance of low platelet counts in MDS. **Methods:** We retrospectively analysed data from 2900 patients in the Duesseldorf MDS Registry who where diagnosed at our laboratory between 1982 and 2007.

**Results:** At the time of diagnosis, 43% of the patients had a platelet count lower than 100,000/µl. Platelets were lower than 20,000/µl in 7% of the patients, especially in those with advanced stages of MDS, who showed a higher frequency of thrombocytopenia and platelet transfusion dependency. On multivariate analysis, platelet anisometry, hypocellularity of megakaryopoiesis, maturational defects of megakaryocytes and platelets <20,000/µl were independent variables showing a statistically significant correlation ($p<0.05$) with clinical signs of bleeding. Platelets lower than 100,000/µl were associated with significantly shortened survival ($p<0.00005$), due to

an increased risk of progression to AML (30% vs. 21%) ($p<0.02$) and bleeding (16% vs. 8%) ($p=0.0005$).

**Conclusions:** Thrombocytopenia is a strong predictor of short survival, with or without haemorrhagic complications.

**Key words:** Myelodysplastic syndromes, MDS, platelets, thrombocytopenia, dysmegakaryopoiesis, haemorrhagic complications, bleeding

## Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired clonal stem cell disorders, characterized by ineffective haematopoiesis, morphologic and functional abnormalities of haematopoietic cells, and an increased risk of transformation into acute myeloid leukemia (AML). Most patients with MDS present with single or multiple lineage cytopenias in peripheral blood despite a hypercellular bone marrow. Platelet counts and haemoglobin values at diagnosis appear to be in inverse proportion to the length of survival (1, 2). Rough estimates of the frequency of thrombocytopenia in MDS range between 40% and 65% (3) but exact data have not yet been reported. Isolated thrombocytopenia is the presenting manifestation in 5-10% of MDS patients, and may be mistaken for ITP (4). Thrombocytopenia in MDS is mainly caused by ineffective platelet production due to disturbed proliferation and maturation of megakaryocytes or their precursors. Morphological studies showed dysplastic features including micromegakaryocytes, large mononuclear forms, multiple separated nuclei, dissociation between cytoplasmic and nuclear maturation, and megakaryocytic hypogranulation (5). Cytogenetic studies revealed that even in case of a normal appearance on light microscopy, the majority of megakaryocytes

are part of the MDS clone (6). Besides thrombocytopenia, platelet dysfunction may contribute to haemorrhagic complications in MDS (3). In the present study, we evaluated the clinical impact of platelet count at diagnosis, platelet and megakaryocyte morphology, signs of bleeding, and platelet transfusion dependency.

**Design and Methods**

Between 1982 and 2007, 3259 patients with MDS were diagnosed in our haematological cytology laboratory and included in the Duesseldorf MDS Registry with their informed consent. The median duration of observation was 18 months. The diagnostic procedures were the same as reported in our previous studies (7, 8). All blood and bone marrow smears were examined by the same two investigators C. A. and/or U. G. at our haematologic laboratory. The morphological diagnosis was made according to the proposals of the FAB (9) as well as on the basis of the WHO classification (10). Patients with CMML I or II and patients with RAEB-T were also included in the analysis. A peripheral blood smear was examined to determine the differential white blood count, recognize circulating blast cells, and assess platelet morphology. In the marrow, a differential count of 500 nucleated cells was performed to determine the proportion of medullary blasts. Megakaryopoiesis was analyzed with regard to dysmaturity and dysplastic features of megakaryocytes. Dysmegakaryopoiesis was diagnosed if at least 10 out of 25 megakaryocytes were micromegakaryocytes, mononuclear megakaryocytes, or had multiple widely separated nuclei. Dysmaturity included all other features representing disturbed maturation without clear dysmegakaryopoietic criteria. In particular, dysmaturity included small megakaryocytes but not micromegakaryocytes; hypolobated but not mononuclear megakaryocytes, bizarre megakaryocytes but not hyperlobated megakaryocytes.

Cytogenetic analysis by metaphase karyotyping was performed in the Institute of Human Genetics, Heinrich-Heine University, Duesseldorf. If possible, patients were assessed according to the International Prognostic Scoring System (IPSS) (11) and followed for platelet transfusion requirement (due to bleeding or thrombocytopenia <10,000/µl), signs of bleeding, and cause of death. Patients were considered platelet transfusion dependent if platelets had to be administered at least once per month. Petechiae, haematomas and gastrointestinal or intracerebral bleeding were taken as evidence of haemorrhagic diathesis. Patients who received induction chemotherapy or allogeneic stem cell transplantation were excluded from the survival analysis. Clinical and haematological data at the time of diagnosis were compared using the $\chi$-square and Wilcoxon rank sum test. A two-sided p-value of less than 0.05 was considered statistically significant.

**Results**

Our analysis included 2900 patients whose platelet count at diagnosis was available in the MDS Registry. Information on bleeding at diagnosis and platelet transfusions during the course of disease was available for 1373 and 1250 patients, respectively. Blood and bone marrow smears of 2475 patients were evaluable for platelet and megakaryocyte morphology. The IPSS was applicable to 1064 patients. The male:female ratio was 53:47. The median age was 71 years (range: 16-96 years). Since the majority of patients was older than 65, we did not try to adjust bone marrow cellularity for age.

*Platelet count*

At the time of diagnosis, the median leukocyte count was 4,300/µl, the median granulocytes were 2,000/µl, and the median haemoglobin was 9.5 g/dl. Median platelet count was 116,000 (range: 1-1,600,000). Platelet counts were >100,000/µl in 57% of patients, between 100,000/µl and 50,000/µl in 23%, between 50,000/µl and 20,000/µl in 13%, and below 20,000/µl in 7% of patients. Distribution of patients among WHO types of MDS was as follows: 5.5% RA, 8.3% RARS, 11.6% RCMD-RS, 18.3% RCMD, 1.7% 5q- syndrome, 11.7% RAEB-I, 15.4% RAEB-II, 11% CMML-I, 3% CMML-II, and 13% RAEB-T.

Tables 1a and 1b show the mean platelet count and the percentage of patients with thrombocytopenia <50,000/µl and <20,000/µl, respectively, according to the FAB and WHO classification. In general, patients with advanced stage MDS had lower platelet counts than patients with early stage MDS. Although 0% and 1% of patients with RARS had platelet counts of <20,000/µl and <50,000/µl, respectively, at the time of diagnosis, 4% of RARS patients presented with hemorrhagic diathesis, suggesting platelet dysfunction in a proportion of MDS patients. Risk assessment according to the International Prognostic Scoring System (IPSS) showed that at the time of diagnosis, 20% of patients scored as low-risk, 31% as intermediate-1, 21% as intermediate-2, and 28% as high-risk. The median platelet count was 240,000/µl in the IPSS low-risk group and clearly decreased in accordance with more unfavourable IPSS scores (Table 1c). In the high-risk group, 17% of patients had a platelet count lower 20,000/µl.

*Bleeding complications*

Signs of bleeding at the time of diagnosis were present in 19% of all patients. The frequency of haemorrhagic diathesis at diagnosis is shown in table 1a and 1b according to FAB and WHO type of MDS, respectively, and in table 1c according to

IPSS score. Patients with advanced WHO types or unfavourable IPSS scores showed more frequent bleeding, lower platelet counts, and higher platelet transfusion requirements**.**

Platelet transfusion dependency developed during the course of disease in 20% of patients. In the majority (63%), a bleeding tendency manifested itself as petechiae. Gastrointestinal haemorrhages occurred in 16% and epistaxis or oral mucosal bleedings in 13% of patients. Haematuria and haemorrhagic retinopathy occurred as initial signs of bleeding in 7% and 1%, respectively.

As expected, haemorrhagic diathesis already correlated with platelet counts at the time of diagnosis. In patients with platelets lower than 20,000/µl or lower than 50,000/µl, signs of bleeding were significantly more frequent (50.6% and 45.5%, respectively; $p<0.0005$) than in patients showing higher platelet counts. In patients with platelets >50,000/µl, we found signs of bleeding in 19% (data not shown). This may be attributable to platelet dysfunction.

Splenomegaly was present at diagnosis in 17.8% of all patients, with an even distribution among WHO types and IPSS risk groups. Interestingly, signs of bleeding were significantly more frequent at the time of diagnosis in patients with splenomegaly ($p<0.0001$), irrespective of platelet count or features of dysmega-karyopoiesis (data not shown). The frequency of marrow fibrosis was similar in patients with or without splenomegaly (20% vs. 17%).

*Signs of dysmegakaryopoiesis*

Anisometry of platelets and “giant platelets” were found in 35% and 17% of the blood smears, respectively. In the bone marrow, signs of dysmaturity were found in 41%, mononuclear megakaryocytes in 28%, micromegakaryocytes in 22%, and mega-karyocytes with separated nuclei in 24% of the cases. The marrow was hypocellular

in 13%, normocellular in 34%, and hypercellular in 53% of patients according to bone marrow biopsy. Megakaryopoiesis was hypocellular in 24.4%, normocellular in 45%, and hypercellular in 21% of cases. Table 2 gives the frequency of dysmegakaryopoietic features in MDS subgroups according to WHO classification and IPSS score.

A significant correlation was found between the presence of platelet anisometry and the occurrence of bleeding (62.2% vs. 46.5%; $p<0.0005$). Hypocellularity of megakaryopoiesis, found in 37.9% of patients with haemorrhagic diathesis, and maturational defects of megakaryocytes, found in 23%, were also significantly correlated with bleeding ($p<0.0005$, data not shown). On multivariate analysis, platelet anisometry, hypoplastic megakaryopoiesis, maturation defects of megakaryocytes, and platelet counts <20,000/µl were independent variables significantly predicting the risk of bleeding ($p<0.05$, Table 3). Micromegakaryocytes, mononuclear megakaryocytes, and megakaryocytes with separated nuclei were not identified as independent risk factors.

*Survival*

Patients with platelet counts lower than 20,000/µl at the time of diagnosis had the shortest survival (median: 7 months). Chances of survival increased with the number of platelets at diagnosis. The longest survival (median: 41 months) was seen in patients with a normal platelet count. Patients with a platelet count of <50,000/µl at the time of diagnosis had a statistically significantly shorter survival ($p<0.00005$, Figure 1a). On multivariate analysis, platelets <100,000/µl and hemoglobin <10 g/dl were associated with significantly shortened survival ($p<0.00005$), whereas an absolute neutrophil count <1,800/µl had no significant influence on survival ($p=0.599$). The risk of progression to AML also increased with lower platelet counts at diagnosis. Patients with initial platelet counts <100,000/µl, <50,000/µl, and <20,000/µl

showed a progressively increasing risk of AML transformation. Development of AML was significantly more frequent in patients with a platelet count <50,000/µl at the time of diagnosis (p=0.00005, Figure 1b).

*Causes of death*

The cause of death was known in 1077 patients and was disease-related in 89%. Infections and progression to AML were the most frequent causes of death (32% and 30%, respectively), followed by haemorrhagic complications (14%). Causes of death according to IPSS score are shown in table 4. Platelets lower than 100,000/µl were associated with significantly shortened survival (p<0.00005), due to an increased risk of progression to AML (30% vs. 21%) (p<0.02) and bleeding (16% vs. 8%) (p=0.0005). Patients who later died of bleeding complications had a significantly lower median platelet count at diagnosis (72,000/µl) than patients who died from other causes (median 113,000/µl) (p=0.005).

**Discussion**

In this retrospective study, we tried to determine the magnitude of the problem of thrombocytopenic bleeding in patients with MDS. First, we found that 41% of all patients showed platelet counts lower than 100,000/µl at the time of diagnosis. This is in line with previous estimates ranging between 40% and 65%. Kantarjian *et al* (3) found that 66% of patients with MDS develop thrombocytopenia during the course of disease. As expected, our data showed that frequencies of thrombocytopenia and platelet transfusion dependency correlated with advanced stages of MDS according to WHO and unfavourable risk profile according to IPSS.

How often do we see clinical manifestations of thrombocytopenia? Signs of haemorrhagic diathesis, mostly petechiae, were found in 18% of patients at the time of diagnosis. A more severe clinical manifestation, namely gastrointestinal bleeding,

was encountered during the course of disease in 16% of the patients. Twenty percent of patients became dependent on platelet transfusions during the course of their disease.

Is haemorrhagic diathesis predictable from morphological features? On multivariate analysis, we found that hypocellularity of megakaryopoiesis, microscopically discernible defects of megakaryocyte maturation, and platelet anisometry were independent prognostic markers significantly associated with bleeding complications, whereas other features of dysmegakaryopoiesis, namely mononuclear megakaryocytes, micromegakaryocytes, and megakaryocytes with multiple separated nuclei, showed no significant correlation with the frequency of haemorrhagic symptoms. Of interest, splenomegaly was observed with a frequency of 17.8% in MDS patients, with a consistent distribution among all WHO types and IPSS risk groups. Patients with splenomegaly had significantly more frequent signs of bleeding, irrespective of platelet count, dysplastic features of megakaryopoiesis, or bone marrow fibrosis. Therefore, the pathophysiological explanation of this finding remains elusive, and one can only speculate whether splenectomy may be beneficial in selected patients.

Is thrombocytopenia and haemorrhagic diathesis associated with shortened survival? This is clearly the case. Patients with platelet counts lower than 20,000/µl at the time of diagnosis had the shortest survival (median: 7 months). This is taken into account by the IPSS and also by a new risk score recently proposed by Kantarjian *et al* (12). Although it is tempting to speculate that the shortened survival was attributable to fatal haemorrhagic complications, platelet counts were also significantly associated with an increased risk of AML transformation. Among the most frequent causes of death, haemorrhagic complications (14%) were third, behind infections (32%) and leukaemic transformation (30%). In our survival analysis, we excluded established variables like age, cytogenetics, medullary blast count and performance status since

they are powerful independent variables for disease progression and survival but not for bleeding.

Our finding that the frequency of fatal bleeding was evenly distributed among all IPSS risk groups, even though patients with higher IPSS scores presented more often with thrombocytopenic bleeding at diagnosis, may be attributable to widespread platelet dysfunction in patients with MDS.

The prognostic value of platelet mass has not yet been clearly defined. Bowles *et al* suggested that a low platelet mass is associated with shorter survival (13). As previously reported, platelet volume does not seem to influence the risk of bleeding at the time of diagnosis or the risk of fatal haemorrhagic complications (14).

All in all, thrombocytopenia is a significant clinical problem in patients with MDS, partly due to haemorrhagic complications and partly owing to the fact that thrombocytopenia reflects an unfavourable biology of the underlying bone marrow disease, thereby predicting additional clinical complications not directly related to the risk of bleeding. In order to determine more precisely the clinical significance of dysmegakaryopoiesis and thrombocytopenia in MDS, prospective studies are required, with meticulous documentation of hemorrhagic features and platelet counts, as well as tests of platelet function.

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**Table 1**

1a. Platelet count and frequency of bleeding according to FAB type at diagnosis, n=1373

| FAB | n (%) | Platelets median x $10^9$/l (range) | < 20,000/µl | < 50,000/µl | Bleeding at diagnosis | Platelet transfusion in course of disease* | Bleeding as cause of death |
|---|---|---|---|---|---|---|---|
| RA | 347 (25,3%) | 120 (5-975) | 6% | 16% | 19% | 22% | 10% |
| RARS | 278 (20,2%) | 225 (8-999) | 2% | 6% | 8% | 4% | 6% |
| RAEB | 324 (23,6%) | 90 (1-809) | 11% | 25% | 21% | 29% | 14% |
| RAEB-T | 229 (16,7%) | 77 (3-777) | 14% | 33% | 27% | 35% | 10% |
| CMML | 195 (14,2%) | 101 (1-744) | 6% | 16% | 22% | 12% | 12% |

* n=1250, only patients with platelet transfusion dependency included

1b. Platelet count and frequency of bleeding according to WHO type at diagnosis, n=998

| WHO | n (%) | Platelets median x $10^9$/l (range) | < 20,000/µl | < 50,000/µl | Bleeding at diagnosis | Platelet transfusion in course of disease | Bleeding as cause of death |
|---|---|---|---|---|---|---|---|
| All types | 998 (100%) | 116 (1-975) | 7% | 19% | 18% | 20% | 24% |
| RA | 76 (5,5%) | 129 (8-975) | 5% | 19% | 15% | 20% | 11% |
| RCMD | 251 (18,0%) | 118 (5-823) | 8% | 15% | 22% | 24% | 4% |
| RARS | 114 (8,3%) | 300 (43-456) | 0% | 1% | 4% | 2% | 2% |
| RCMD-RS | 160 (11,6%) | 197 (7-450) | 6% | 9% | 13% | 9% | 8% |
| del(5q) | 24 (1,7%) | 283 (28-676) | 0% | 5% | 0% | 5% | 5% |
| RAEB I | 161 (11,7%) | 92 (1-778) | 10% | 21% | 23% | 27% | 12% |
| RAEB II | 212 (15,4%) | 80 (3-809) | 12% | 29% | 20% | 35% | 15% |

1c. Platelet count and frequency of bleeding according to IPSS at diagnosis, n=529

| IPSS | % | Platelets median x $10^9$/l (range) | < 20,000/µl | < 50,000/µl | Bleeding at diagnosis | Platelet transfusion in course of disease | Bleeding as cause of death |
|---|---|---|---|---|---|---|---|
| **Low** | 20% | 240 (10-1500) | 2% | 7% | 5% | 12% | 14% |
| **Int 1** | 31% | 100 (2-999) | 8% | 21% | 26% | 29% | 14% |
| **Int 2** | 21% | 77 (2-701) | 8% | 28% | 27% | 35% | 12% |
| **High** | 28% | 60 (3-809) | 17% | 40% | 43% | 32% | 13% |

**Table 2**

Features of dysmegakaryopoiesis according to MDS types

2a. WHO classification

| WHO | Hypocellularity of mega-karyocytes | Giant platelets | Platelet anisometry |
|---|---|---|---|
| **All Types** | 24.4 % | 17.0 % | 35.0 % |
| **RA** | 26.5 % | 6.1 % | 19.2 % |
| **RCMD** | 19.9 % | 10.9 % | 24.0 % |
| **RARS** | 7.2 % | 7.5 % | 29.1 % |
| **RCMD-RS** | 11.4 % | 16.3 % | 35.4 % |
| **5q-syndrome** | 4.5 % | 24.4 % | 51.2 % |
| **RAEB-I** | 32.1 % | 17.3 % | 33.9 % |
| **RAEB-II** | 35.9 % | 20.6 % | 41.8 % |
| **CMML-I** | 23.2 % | 29.1 % | 43.8 % |
| **CMML-II** | 33.3 % | 25.5 % | 52.9 % |

2b. IPSS score; n=957

| IPSS | Hypocellularity of megakaryocytes | Giant platelets | Platelet anisometry |
|---|---|---|---|
| **low** | 7% | 15% | 16% |
| **Int-1** | 28% | 17% | 22% |
| **Int-2** | 23% | 30% | 23% |
| **high** | 42% | 39% | 39% |

**Table 3**

Multivariate analysis for the risk of hemorrhagic diathesis in patients with MDS

| Parameter | $\chi^2$ | Significance |
|---|---|---|
| Platelet anisometry | 9,395 | 0.002 |
| Hypocellularity of megakaryocytes | 5,136 | 0.023 |
| Impaired maturation of megakaryocytes | 8,828 | 0.003 |
| Platelet count < 20,000/µl | 32,735 | 0.0005 |

**Table 4**

Causes of death according to IPSS risk category; n=427

| initial IPSS | Infection | Bleeding | Heart failure | AML | Other disease related | Not disease related |
|---|---|---|---|---|---|---|
| **low** | 37.2 % | 14.0 % | 9.3 % | 18.6 % | 9.3 % | 11.6 % |
| **Int-1** | 40.5 % | 14.0 % | 4.1 % | 28.1 % | 4.1 % | 9.1 % |
| **Int-2** | 33.0 % | 12.2 % | 2.2 % | 46.2 % | 3.3 % | 3.3 % |
| **high** | 27.3 % | 13.4 % | n.a. | 52.3 % | 4.7 % | 2.3 % |
| **Total** | 33.3 % | 13.3 % | 2.6 % | 40.7 % | 4.7 % | 5.4 % |

**Figure 1a**

Cumulative survival of MDS patients according to platelet count

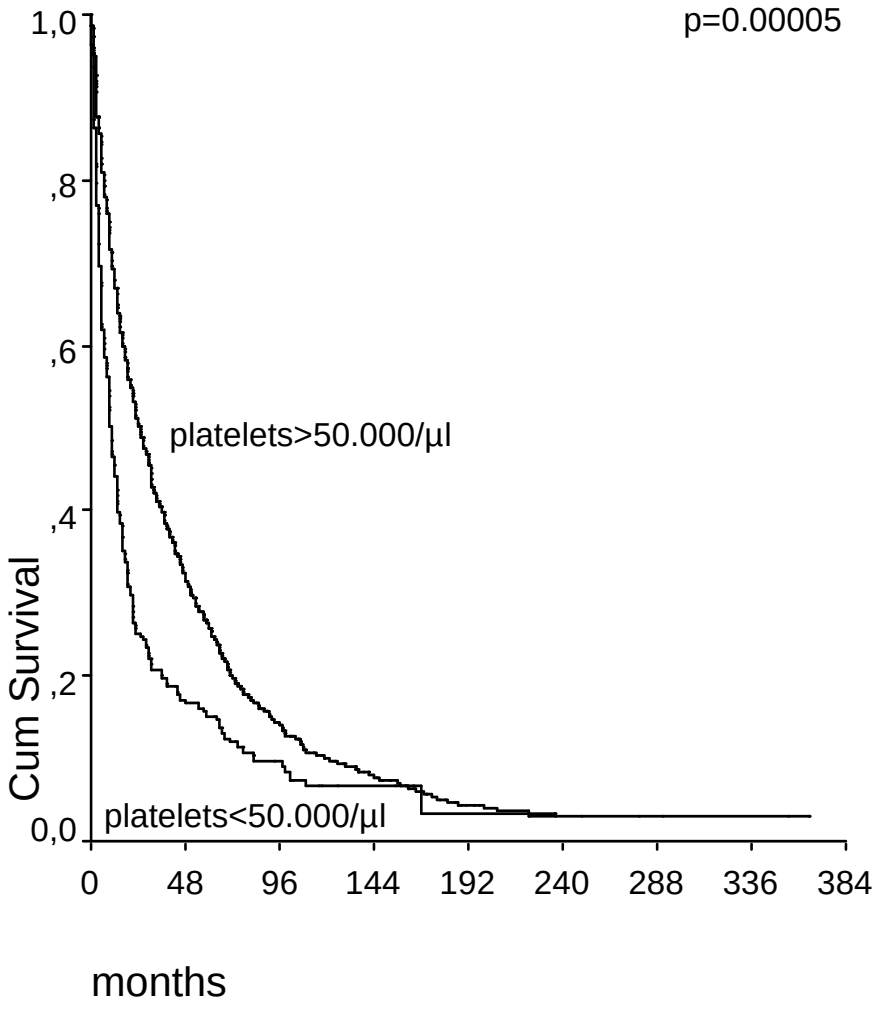

**Figure 1b**

Cumulative risk of AML evolution according to platelet count