International Journal of Medicine Research
ISSN: 2455-7404
Impact Factor: RJIF 5.42
www.medicinesjournal.com
Volume 3; Issue 4; October 2018; Page No. 88-91

Survival outcome and platelet anisometry in myelodysplastic syndromes

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Abstract
Background: Myelodysplastic syndromes (MDS) are a group of diverse clonal haematopoietic disorders manifested by morphologic dysplasia in haematopoietic cells and by peripheral cytopenia(s) and bone marrow failure. It is usually seen in the elderly. The objective of the study was to determine survival outcome and platelet anisometry in myelodysplastic syndromes.
Materials and Methods. Ten normal healthy subjects and thirty patients with MDS were recruited. Full Blood Count for haemoglobin, white blood cells red blood cells, haematocrit, platelets, mean platelet volume and platelet anisometry was investigated.
Results and Discussion: No statistical differences for age (*P*=0.06) and white blood cells *(P*=0.48) between normal subjects and MDS. Leukopenia 53.3%), leucocytosis (13.3%), low haemoglobin (76.7%), low red blood cells (100%), low haematocrit (93.3%), thrombocytopenia (80%), high mean platelet volume (81.3%) in MDS. Patients with platelets of $<10x10^9$/L (n=6) succumbed to the disease within one to twelve months. Platelet anisometry (mean 8.1 ± 3.9 %) present in all MDS patients and none in normal subjects. Seventeen patients (65.4%) succumbed to the disease within 12 months and the remainder still living past 12 months to 28 months. Patients who succumbed to the disease was significantly younger (mean 44.8 ± 19.10 years vs. mean 58.2 ± 11.6 years) (*P*=0.04).
Conclusion: Our study showed that only platelets of $<10x10^9$/L had predictive adverse outcome within twelve months and no other predictive prognostic markers seen despite the cytopenias present in those still living. Platelet anisometry present in all MDS patients suggest it is a good predictive marker for MDS with mortality of 65.4% seen in our cohorts.

Keywords: MDS, platelet anisometry, survival outcome

1. Introduction
Myelodysplastic syndromes (MDS) are a group of diverse clonal haematopoietic disorders manifested by morphologic dysplasia in haematopoietic cells and by peripheral cytopenia(s) and bone marrow failure. It is usually seen in the elderly and about 30% or one-third of MDS show progression to acute myeloid leukaemia within a few months up to several years [1, 2]. Majority of affected patients are diagnosed during blood tests and their symptoms are often secondary to the peripheral cytopenia causes by bone marrow failure [3]. MDS are diseases of the elderly of median age 70 years but in Asian patients it tends to occur at an earlier age, often with a hypocellular marrow, less often with isolate 5q deletion but trisomy 8 occurs more often than seen in Western populations [4, 5, 6]. The clinical course is variable and main clinical manifestation are related to cytopenias, anaemia, leukopenia with increased incidence of infections and thrombocytopenia with risks of bleeding. Low platelets are associated with poor prognosis and platelet mass as well as the presence of giant platelets and platelet anisometry has been reported to be associated with an adverse outcome [7] but these findings contrasted to earlier published data [8]. Thrombocytopenia is seen in about 40% to 65% of MDS and bleeding the cause of death in 10% to 20% [9, 10]. Low platelets have been considered as prognostic marker as it is believed to reflect bone marrow function and reserve [11, 12, 13]. The overall survival rate had been reported to range from 4.6 years in patients with lower-risk disease [11] to less than 2 years with higher-risk disease [14, 15]. Anisometry as defined by the Webster New World College Dictionary to mean non-isometric, unsymmetrical parts of unequal measurements having unequal axes or as we described for platelet anisometry where one of the axes either longitudinal or horizontal is greater than 3 times the length of the other axis, if less than 3 times it is considered normal isometry.
The WHO classification of MDS was last updated in 2008. The new revised classification (2016) introduced refinements in the cytopenia and morphological changes and also the influence of genetic information in MDS diagnosis and classification [16, 17]. The WHO thresholds defining cytopenia still remain; haemoglobin (Hb) <10 g/dL, platelets $<100x10^9$/L, Absolute Neutrophil Count (ANC) <1.8 x 109/L [18].
The objective of the study was to determine prognostic markers for survival outcome and platelet anisometry in myelodysplastic syndrome.

2. Materials and Methods
The study received approval from the ethical committee of the Medical Faculty, University of North Sumatera/Haj Adam Malik Hospital Medan, Indonesia (No.306/TGL/KEPK FK USU/RSUP HAM 2017).

Normal Subjects
Ten normal healthy individuals with no history of health issues (males n=2, females n=8) of mean age 40.9±10.0 years and ranged between 31 years and 58 years old were recruited after receiving their Informed Consent to participate in the study.

MDS Patients
30 patients (males n=10, females n=20) who were diagnosed to have myelodysplastic syndrome following their bone marrow aspirate examinations were recruited. Their mean age was 49.7±16.8 years and ranged between 19 years and 73 years old were recruited after receiving their Informed Consent to participate in the study. The MDS patients were classified according to the new WHO classification for MDS 2016 [16, 17].

Management
As there is no specific treatment for MDS, the goals of our MDS therapy are to control symptoms, improve quality of life and overall survival to reduce the progression to acute myeloid leukaemia. For patients with Hb < 7 g/dL either human recombinant erythropoietin or red blood cells transfusion are given to achieve a Hb of >9 g/dL besides the iron sulphate tablets and vitamin B6 given to those with Hb between 7 and 9 g/dL. Filgastrim for leukopenia and to achieve WBC level of >1500/mm^3 to avoid infection. Oral rebozet (thrombopoietin) or platelet transfusion were given to raise the platelet level to > 50 x 10^9/L or to stop bleeding symptoms.

Laboratory investigation
From a clean venepuncture of the median vein 3 mL of blood was drawn into the vacutainer tube containing EDTA anticoagulant. Full blood count for haemoglobin (Hb), white blood cells (WBC), red blood cells (RBC), platelets, mean platelet volume (MPV) were determined by Sysmex XN-1000 analyser. Haematocrit (Hct) was determined by centrifugation.

Platelet anisometry
Microscopy counts of 200 platelets was carried out and the number of platelet anisometry where platelets with more than 3 times the longitudinal or horizontal axes measurement was expressed as percentage of the count.

Statistical Analysis
The Statistical Package for Social Sciences (SPS 22 IBM Corp. NY, USA) was used to perform statistical analysis. The independent sample t-test, Mann-Whitney for differences between groups and Pearson's correlation was also determined. A *P* value of <0.05 was considered statistically significant.

3. Results

Characteristics of normal subjects and patients with myelodysplastic syndrome
Ten normal healthy individuals of mean age 40.9 ±10 years and ranged between 31 years and 58 years and the group with MDS of mean age of 49.7 ±16.8 years and ranged between 19 years and 73 years were recruited into the study. The MDS patients were classified according to the new WHO classification for MDS 2016 as shown (Table 1). Mortality outcome within 12 months was 65.4% excluding 4 patients lost to follow-up, still living past 12 months (n=3) and between 15 months to 28 months (n=6) Table 1.

Haematological parameters and platelet anisometry in normal subjects and patients with myelodysplastic syndrome
There were no statistically significant differences between age (*P*= 0.06) and WBC (*P*= 0.48) between normal and MDS patients. In WBC there is a wide variation in results especially in MDS patients, leukopenia (<4000/mm^3) were seen in 16 patients (53.3%) and leukocytosis (>11000/mm^3) in 4 patients (13.3%). Statistically significant differences were seen for haemoglobin, RBC, platelets, platelet anisometry (*P*=<0.001) and MPV (*P*=0.004). No platelet anisometry was observed in all the healthy subjects but present between 2% and 15% in MDS (mean 8.1 ±3.9%). (Table 2). Low haemoglobin (<10 g/dL) was seen in 23 (76.7%) patients and between 10 – 12 g/dL n= 6 (20%), RBC <4.5 mil/mm3 was evident in all MDS patients (100%), platelets <100 x10$^{9/}$L was seen in 24/30 (80%) patients and <10 x 10^9/L in 6 patients (20%). Hct, less than 36% concentration was seen in 28/30 (93.3%) patients and MPV greater than 9.5 fL was seen in 81.3% of MDS patients. Mortality was 65.4% seen within 12 months of diagnosis (Table 2).

Platelet anisometry
Normal platelet and platelet anisometry are shown in Figure 1 and their distribution between those who succumbed to the disease (n=17) within 12 months (mean 7.7 ±4.2%) and still living past 12 months and 28 months **(**mean 9.4±3.0%; *P*=0.22) are shown in Figure 2.

Correlation studies
Pearson's correlation showed no statistical correlation between mortality in MDS and those still living; haemoglobin (r=0.24, *P*=0.24), RBC (r=0.26, *P*=0.44), WBC (r=0.14, *P*=0.14), Platelets (r=0.25, *P*=0.22) and platelet anisometry (r=0.2, *P*=0.22).

Survival outcome in MDS
Four patients were lost to follow-up and therefore was not included in the final analysis. Seventeen patients (65.4 %) succumbed to the disease within 12 months and nine (34.6%) were still living past 12 months and 28 months (Table 1). The patients who succumbed to the disease were significantly younger (mean age 44.8 ±19.10 years) compared to those still living (mean age 58.2 ± 11.6 years; *P*=0.04). No statistically significant differences were seen for haemoglobin *(P*=0.15), RBC (*P*=0.37), WBC (*P*=0.40), platelets (*P*=0.34), Hct *(P*=0.14), MPV (*P*=0.36) and platelet anisometry (*P*=0.22) between those who succumbed to the disease and those still living. However, MDS patients with platelets <10x10^9/L (n=6, 20%) succumbed to the disease within one to 12 months.

Table 1: Characteristics of normal subjects and patients with myelodysplastic syndrome.

Normal subjects: n = 10, male n = 2, female n = 8
Age mean (SD) years: 40.9 (10.0), range 31 - 58
Myeloblastic Syndrome: n = 30, male n=10, female n=20
Age mean (SD) years 49.7 (16.8), range 19 - 73
Myelodysplastic Syndrome (MDS): (WHO classification 2016)
SLD (single lineage) n = 2
MLD (multi-lineage) n = 21
EB1 (blast cells 5-10%) n = 3
EB2 (blast cells 11- 19%) n = 1
Unclassified n = 3
Mortality outcome: ≤ 6 months n=10, 7-12 months n=7, total n=17/26 (65.4%)
Still living past 12 months n=3; 15 months to 28 months n=6
Lost to follow-up n=4

Table 2: Haematological parameters and platelet anisometry (mean±SD) in normal subjects and patients with myelodysplastic syndrome (MDS).

N	Normal	MDS	*P*
	10	30	
Age years	409 (10.0)	493 (16.8)	0.06
Haemoglobin (2) g/gIL	114 (01)	82 (2.2)	<0.001
Red Blood Cells (RBC) /mm3	439 (0A7	238 (0.84)	<0.001
White Blood Cells (WBC) /mm3	7648 (2328)	6484 (8071	0.48
Haematocrit (Ha) %	41.0 (1.8)	243 (6.8)	<0.001
Platelets x109/L	2792 (46.0)	62.6 (78.7)	<0.001
Mean Platelet Volume (MPV) L	93 (01)	10.5 (1.1)	0.004
Platelet aniumdet %	0	8.1 (3.9)	<0.001

Myelodysplastic Syndrome
Haemoglobin: <10 g/dL n=28 (76.7%)
RBC: < 4.5mil/mm^3 n=30 (100%)
WBC: <4000/mm^3 n=16 (53,3%); >11000/mm^3 n=4 (13.3%)
Hct: <36% n=28 (93.3%)
Platelets: <100 x 10^9/L n=24 (80%); <10x 10^9/L n=6 (20%)
MPV: >9.5 fL n=13/16 (81.3%)

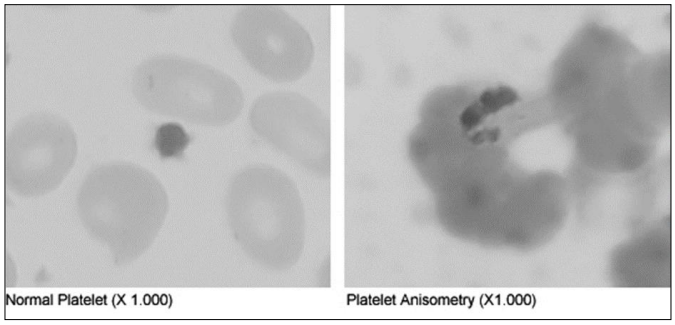

Fig 1: Microphotograph of normal platelet (left) and platelet anisometry (right).

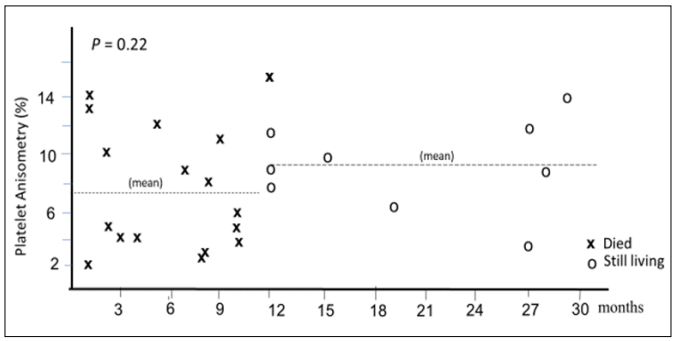

Fig 2: Platelet anisometry distribution in myelodysplastic syndrome (died n=17, still living n=9 (excluding lost to follow-up n=4).

4. Discussion

Myelodysplastic syndromes are a group of diverse clonal haematopoiesis disorders manifested by morphologic dysplasia in haematopoietic cells and by peripheral cytopenia(s) and progression to acute myeloid leukaemia in one third of patients [1]. It is usually seen in the elderly of median age 70 years but tends to occur at an earlier age in Asians [4, 5]. The clinical course is variable and main clinical manifestation are related to cytopenias, anaemia, leukopenia and thrombocytopenia. Thrombocytopenia is seen in about 40% to 65% of MDS [9, 10]. The presence of platelet anisometry in MDS has been reported to be associated with adverse outcome [7]. The overall survival rate was reported to range from 4.6 years in patients with lower-risk disease [11] to less than 2 years with higher-risk disease [14, 15].

In our study MDS occurs at a younger age group of mean 49.7 years ranging from 19 years to 73 years compared to the Western populations of median 70 years [4, 5]. Peripheral blood cytopenias are seen in MDS with haemoglobin of less than 10g/dL in 76.7%, RBC (100%), leukopenia (53.3%), low Hct (93.3%) and thrombocytopenia 80%. Thrombocytopenia in our study showed higher incidence than 40% to 65% reported earlier [9, 10]. Adverse outcome within one to twelve months for patents with platelets of less than 10 x 10^9/L. Platelet anisometry was not present in normal healthy subjects but were present in all MDS patients suggesting that platelet anisometry is a good predictive marker for the presence of MDS. No correlation or predictive prognostic markers could be shown to predict mortality outcome in our study except for platelets <10 x 10^9/L despite the cytopenias present in those still living. Survival outcome in our study showed that 65.4% of MDS patients did not survive beyond twelve months as contrasted from 2 years to 4.6 years as reported [11, 14, 15]. This may be due to the more aggressive syndrome affecting our younger patients.

In conclusion our study showed that only platelets of <10x10^9/L had predictive adverse outcome in MDS. However, 65.4% did not survive beyond 12 months and no other prognostic markers could be found despite the cytopenias present in those still living. Platelet anisometry present in all MDS patients and none in healthy subjects suggest it is a good predictive marker for the presence of myelodysplastic syndrome.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgements

We wish to express our sincere gratitude to Dr Handoko Halim for his expert statistical assistance and to Dr Tonny Wongso for the microphotographs.

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