Noninvasive Diagnosis of Myelodysplastic Syndromes (MDS)

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Myelodysplastic Syndromes (MDS)

- Clonal hematopoietic stem cell disease
- Abnormal
  - differentiation, maturation, apoptosis
- Anemia – common
  - often treated with EPO
- Cytopenias:
  - WBC and Platelets
- Transformation
  - Acute Leukemia (20%-60%)
MDS Diagnosis – gold standard

Bone marrow examination

But...

- Invasive
- Painful
- Possible bleeding (thrombocytopenia)
- Difficult for the older patients
Aim of this study

Can we diagnose MDS noninvasively in at least a portion of the patients?
Stage I: Logistic regression (LoR)

MDS patients: 48
Control patients: 63
Stage I: Logistic regression (LoR)

MDS patients: 48
Control patients: 63

\[
Y = \frac{e^{(B_1X_1+B_2X_2+...+B_6X_6+C)}}{1 + e^{(B_1X_1+B_2X_2+...+B_6X_6+C)}}
\]

- Gender (X_1)
- Age (X_2)
- Hb (X_3)
- MCV (X_4)
- WBC (X_5)
- Platelets (X_6)
Stage I: Logistic regression (LoR)

\[
Y = \frac{e^{(B_1X_1 + B_2X_2 + \ldots + B_6X_6 + C)}}{1 + e^{(B_1X_1 + B_2X_2 + \ldots + B_6X_6 + C)}}
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- Hb \((X_3)\)
- MCV \((X_4)\)
- WBC \((X_5)\)
- Platelets \((X_6)\)

MDS patients: 48
Control patients: 63

Probably not MDS (pnMDS)  
Probable MDS (pMDS)
Stage I: Logistic regression (LoR)

- Area under ROC curve (AUC) = 0.748
- Two cutoffs:

Approximately 50% could benefit from noninvasive diagnosis

(Oster et al. *Leuk & Lymph* 2018: 59; 2222)
Model improvement

Improve the AUC  →  Narrow the undetermined region

More patients could benefit from noninvasive diagnosis of MDS
Improved model (Stages II and III)

• More patients
  – MDS:
    • Israel MDS registry (>260)
    • European MDS registry (>2600)
  – Controls: Ichilov pathology data base

• More variables

• Better model
  – Gradient Boosted Model (GBM)
  – Much more complex than LoR
  – Takes into account the interactions among variables

• Collaboration with York University
Improved model

• Stage II (ASH 2017)
  – Patients:
    • MDS: 178
    • Controls: 178
  – Gradient Boosted Model (GBM)
  – Number of variables: 6 variables

• Stage III (ASH 2018)
  – Patients:
    • MDS: 502
    • Controls: 502
  – Gradient Boosted Model (GBM)
  – Number of variables: 10 variables
A

Age →
Gender →
Hb →
WBC →
PLT →
MCV →

$Y = \frac{e^{(B_1X_1 + B_2X_2 + \cdots + B_6X_6 + C)}}{1 + e^{(B_1X_1 + B_2X_2 + \cdots + B_6X_6 + C)}}$

$X_i$ (i=1…6) – Each variable
$B_i$ (i=1…6) – Relative weights of $X_i$
C – A constant

B

Age →
Gender →
Hb →
WBC →
PLT →
MCV →
Neutrophils →
Monocytes →
Glucose →
Creatinine →

GBM algorithm computation

→ Y

→ GBM Score
New GBM (Stage III)

LoR Model (Stage I)

Previous GBM (Stage II)

AUC = 0.97 (95% CI 0.96-0.98)
Noninvasive MDS diagnosis, in practice

shiny.york.ac.uk/mds
Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

Disclaimer
This web application is experimental, and should not be used in the diagnosis of any medical condition.

What is the age of the patient? (In years)
75

Sex (M/F)
- Male
- Female

Haemoglobin Count?
10.5

White Blood Count?
3.1

Platelet Count?
125

Mean Corpuscular Volume?
101

Neutrophil Count?
0.9

Monocyte Count?
0.2

Blood Glucose Concentration?
100

Creatinine?
1.1

shiny.york.ac.uk/mds
### Noninvasive MDS diagnosis, in practice

#### MDS Predictive Modelling

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>75</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>10.5</td>
</tr>
<tr>
<td>Platelets</td>
<td>125</td>
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</table>

[shiny.york.ac.uk/mds](shiny.york.ac.uk/mds)
Noninvasive MDS diagnosis, in practice

Probable MDS (pMDS)

shiny.york.ac.uk/mds
Model Quality

• One cut-off (AUC = 0.97): improved!
  – Sensitivity = 88%
  – Specificity = 95%

• Two cut-offs
  – 90% PPV (above upper cut-off)
  – 95% NPV (below lower cut-off)
  – Indeterminate region: improved!
    • 14% of the patients
    • (50% in our earlier model)
Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

Disclaimer
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What is the age of the patient? (In years)
60
Sex (M/F)
Male
Haemoglobin Count?
13
White Blood Count?
7
Mean Corpuscular Volume?
101
Platelet Count?
220
Neutrophil Count?
190
Monocyte Count?
2.0
Blood Glucose Concentration?
100
Creatinine?
0.5

Calculate

Distribution of Scores when MDS is Present
Distribution of Scores when MDS is Absent

0.0 0.2 0.4 0.6 0.8 1.0
Predicted Probability of MDS

Probability Density

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Noninvasive MDS diagnosis, in practice

MDS Predictive Modelling

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What is the age of the patient? (in years)
70

Sex (M/F)
☐ Male
☐ Female

Haemoglobin Count?
12

White Blood Count?
8

Platelet Count?
220

Mean Corpuscular Volume?
80

Neutrophil Count?
6

Monocyte Count?

0.7

Blood Glucose Concentration?
130

Creatinine?

1.4

Calculate

Probably not MDS (pnMDS)

MDS Predictive Modelling

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What is the age of the patient? (in years)
60

Sex (M/F)
☐ Male
☐ Female

Haemoglobin Count?
13

White Blood Count?

7

Platelet Count?
190

Mean Corpuscular Volume?

101

Neutrophil Count?

2.0

Monocyte Count?

0.5

Blood Glucose Concentration?

100

Creatinine?

1.1

Calculate

Indeterminate

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Future Work

• Complete/improve (internet, cellphone...) and publish
• Improve the model – stage IV
  – Increase numbers of patients and variables
• Incorporate additional peripheral blood parameters
  • Flow cytometry
  • Genetic info
• Use the model for other purposes
  – Prognosis
  – Follow up
Summary and Conclusions

• **Stage 1:**
  – 6 variables, (48 and 63 patients), LoR model
  – Diagnose/exclude MDS in 50% of patients.

• **Stage 2:**
  – GB model, 178 and 178 patients
  – Model improvement

• **Stage 3:**
  – 10 variables, 502 and 502 patients, GB model diagnosed
  – PPV = 90%; NPV = 95%
  – Diagnose/exclude MDS in 86% of patients.

• **Conclusion:** For most patients, MDS can be diagnosed or ruled out noninvasively without a bone marrow examination.
Thank you

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Thank you