

Supplementary Information

Frailty and comorbidity improve IPSS-M prognostic stratification in myelodysplastic neoplasms

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Supplement Table S1. Reference ranges of variables for FS-13 calculation at the IHCAMS.

| Item | Full name | Reference range in adults | Unit |
|----------|------------------------|---------------------------|--------------------|
| ALP | Alkaline phosphatase | 50 – 135 | U/L |
| ALT | Alanine | 7 – 40 | U/L |
| Ferritin | Ferritin | 23.9 – 336.2 | ng/mL |
| LDH | Lactate | 120 – 250 | U/L |
| MCV | Mean corpuscular | 80 – 100 | fL |
| RDW | Red blood cell | 11 – 14.1 | % |
| RET | Reticulocyte count | 0.024 – 0.084 | $\times 10^{12}/L$ |
| TBIL | Total Bilirubin | 0 – 21 | $\mu\text{mol}/L$ |
| WBC | White blood cell count | 4 – 10 | $\times 10^9/L$ |

Abbreviations: *IHCAMS* Institute of Hematology, Chinese Academy of Medical Sciences.

Supplement Table S2. Comorbidity and frailty items in the training and validation sets.

| Variable | All (N = 687) | Training set (N = 412) | Validation set (N = 275) | P value ^a |
|------------------------------------|--------------------------|-----------------------------------|-------------------------------------|-----------------------------|
| Comorbidities, n (%) | | | | |
| Cardiac disease | 67 (10) | 46 (11) | 21 (8) | 0.13 |
| Cerebrovascular disease | 26 (4) | 19 (5) | 7 (3) | 0.16 |
| Diabetes | 92 (13) | 58 (14) | 34 (12) | 0.52 |
| Endocrine disease | 17 (2) | 10 (2) | 7 (3) | 0.92 |
| Gastrointestinal disease | 14 (2) | 9 (2) | 5 (2) | 0.74 |
| Hypertension | 112 (16) | 66 (16) | 46 (17) | 0.81 |
| Mild hepatic disease | 140 (20) | 85 (21) | 55 (20) | 0.84 |
| Moderate to severe hepatic disease | 43 (6) | 27 (7) | 16 (6) | 0.70 |
| Mild to moderate pulmonary disease | 148 (22) | 96 (23) | 52 (19) | 0.17 |
| Severe pulmonary disease | 20 (3) | 9 (2) | 11 (4) | 0.17 |
| Obesity | 8 (1) | 6 (2) | 2 (1) | 0.38 |
| Psychiatric disease | 7 (1) | 5 (1) | 2 (1) | 0.53 |
| Renal disease | 6 (1) | 3 (1) | 3 (1) | 0.62 |
| Rheumatological disease | 30 (4) | 20 (5) | 10 (4) | 0.44 |
| Solid tumor | 21 (3) | 13 (3) | 8 (3) | 0.85 |
| FS-13 items, n (%) | | | | |
| ALP abnormal | 109 (16) | 68 (17) | 41 (15) | 0.58 |
| ALT abnormal | 29 (4) | 17 (4) | 12 (4) | 0.88 |
| Bilirubin abnormal | 39 (6) | 26 (6) | 13 (5) | 0.38 |
| BMI with abnormal | 74 (11) | 49 (12) | 25 (9) | 0.49 |
| BMI with partial abnormal | 253 (37) | 148 (36) | 105 (38) | 0.49 |
| CCr with abnormal | 2 (0.3) | 2 (0.5) | 0 (0) | 0.22 |
| CCr with partial abnormal | 29 (4) | 14 (3) | 15 (6) | 0.22 |
| Ferritin abnormal | 431 (63) | 256 (62) | 175 (64) | 0.69 |
| LDH abnormal | 253 (37) | 142 (35) | 111 (40) | 0.12 |
| MCV abnormal | 369 (54) | 220 (53) | 149 (54) | 0.84 |
| RDW abnormal | 590 (86) | 350 (85) | 240 (87) | 0.39 |
| RET abnormal | 303 (44) | 183 (44) | 120 (44) | 0.84 |
| Selfcare ability abnormal | 22 (3) | 11 (3) | 11 (4) | 0.33 |
| WBC abnormal | 562 (82) | 335(81) | 227 (83) | 0.68 |

^a, Chi-squared test.

Abbreviations: *ALP* alkaline phosphatase, *ALT* alanine aminotransferase, *BMI* body mass index, *CCr* creatinine clearance, *LDH* lactate dehydrogenase, *MCV* mean corpuscular volume, *RDW* red blood cell distribution width, *RET* reticulocyte count, *WBC* white blood cell count.

Supplement Table S3. Baseline clinical characteristics of the down-graders and the stay-putters from the IPSS-M high-risk stratum.

| Variable | Down-graders from the IPSS-M high-risk stratum (N = 136) | Stay-putters from the IPSS-M high-risk stratum (N = 39) | P value |
|--|---|--|---------------------|
| Age at diagnosis, median years (IQR) | 54 (46 – 60) | 69 (65 – 72) | <0.001 ^a |
| Sex, n (%) | | | 0.68 ^b |
| Female | 49 (36) | 12 (31) | |
| Male | 87 (64) | 27 (69) | |
| 2016 revised WHO MDS subtype, n (%) | | | 0.09 ^b |
| MDS with del5q abnormality | 1 (1) | 0 (0) | |
| MDS MLD | 45 (33) | 8 (21) | |
| MDS SLD | 10 (7) | 3 (7) | |
| MDS with EB1 | 32 (24) | 14(36) | |
| MDS with EB2 | 45 (33) | 10 (26) | |
| MDS-SLD/MLD-RS | 3 (2) | 3 (7) | |
| MDS-U | 0 (0) | 1 (3) | |
| Haemoglobin, median g/L (IQR) | 72 (62 – 86) | 79 (66 – 93) | 0.15 ^a |
| Platelets, median 10⁹/L (IQR) | 59 (30 – 110) | 39 (23 – 72) | 0.04 ^a |
| White blood cell count, median 10⁹/L (IQR) | 2.38 (1.75 – 3.40) | 2.20 (1.36 – 2.94) | 0.12 ^a |
| Neutrophil count, median 10⁹/L (IQR) | 0.99 (0.64 – 1.88) | 0.90 (0.57 – 1.75) | 0.54 ^a |
| Blast percentage in bone marrow, median (IQR) | 4 (1 – 8) | 5.5 (1.25 – 8.25) | 0.38 ^a |
| Blast percentage in blood, median (IQR) | 0 (0 – 0) | 0 (0 – 0) | 0.61 ^a |
| IPSS-R risk-stratification, n (%) | | | 0.32 ^b |
| Very low | 0 (0) | 0 (0) | |
| Low | 6 (4) | 1 (3) | |
| Intermediate | 55 (40) | 13 (33) | |
| High | 55 (40) | 22 (56) | |
| Very high | 20 (15) | 3 (8) | |
| FS-13 score, median (IQR) | 0.38 (0.35 – 0.50) | 0.46 (0.35 – 0.58) | 0.04 ^a |
| MDS-CI score, n (%) | | | <0.001 ^b |
| Low | 106 (78) | 17 (44) | |
| Intermediate | 26 (19) | 17 (44) | |

High

4 (3)

5 (13)

^a, Wilcoxon test.

^b, Chi-squared test.

Abbreviations: *EB* excess blasts; *FS-13* 13-item frailty scale, *IPSS-R* the Revised International Prognostic Scoring System, *IQR* Inter-Quartile Range, *MDS* myelodysplastic neoplasms, *MDS-CI* MDS-specific Comorbidity Index, *MDS-U* MDS unclassifiable, *MLD* multilineage dysplasia, *RS* ring sideroblast, *SLD* single lineage dysplasia.

Supplement Table S4. Baseline clinical characteristics of the down-graders and the stay-putters from the IPSS-M very high-risk stratum.

| Variable | Down-graders from the IPSS-M very high-risk stratum (N = 117) | Stay-putters from the IPSS-M very high-risk stratum (N = 70) | P value |
|--|--|---|---------------------|
| Age at diagnosis, median years (IQR) | 54 (39 – 63) | 63 (58 – 68) | <0.001 ^a |
| Sex, n (%) | | | 0.09 ^b |
| Female | 40 (34) | 15 (21) | |
| Male | 77 (66) | 55 (79) | |
| 2016 revised WHO MDS subtype, n (%) | | | 0.10 ^b |
| MDS with del5q abnormality | 1 (1) | 0 (0) | |
| MDS MLD | 16 (14) | 12 (17) | |
| MDS SLD | 0 (0) | 3 (4) | |
| MDS with EB1 | 35 (30) | 18 (26) | |
| MDS with EB2 | 58 (49) | 36 (51) | |
| MDS-SLD/MLD-RS | 7 (6) | 0 (0) | |
| MDS-U | 0 (0) | 1 (2) | |
| Haemoglobin, median g/L (IQR) | 72 (61 – 85) | 70 (57 – 81) | 0.1 ^a |
| Platelets, median 10⁹/L (IQR) | 47 (26 – 89) | 51 (35 – 81) | 0.97 ^a |
| White blood cell count, median 10⁹/L (IQR) | 2.44 (1.61 – 3.71) | 2.56 (1.88 – 3.34) | 0.93 ^a |
| Neutrophil count, median 10⁹/L (IQR) | 1.00 (0.51 – 2.06) | 0.94 (0.44– 1.85) | 0.44 ^a |
| Blast percentage in bone marrow, median (IQR) | 8 (4 – 12) | 7 (4 – 12) | 0.75 ^a |
| Blast percentage in blood, median (IQR) | 0 (0 – 2) | 0 (0 – 2) | 0.92 ^a |
| IPSS-R risk-stratification, n (%) | | | 0.03 ^b |
| Very low | 0 (0) | 0 (0) | |
| Low | 0 (0) | 3 (4) | |
| Intermediate | 16 (14) | 4 (6) | |
| High | 38 (32) | 19 (27) | |
| Very high | 63 (54) | 44 (63) | |
| FS-13 score, median (IQR) | 0.42 (0.35 – 0.50) | 0.50 (0.39 – 0.62) | <0.001 ^a |
| MDS-CI score, n (%) | | | <0.001 ^b |
| Low | 114 (97) | 8 (11) | |

| | | |
|--------------|-------|---------|
| Intermediate | 3 (3) | 54 (78) |
| High | 0 (0) | 8 (11) |

^a, Wilcoxon test.

^b, Chi-squared test.

Abbreviations: *EB* excess blasts; *FS-13* 13-item frailty scale, *IPSS-R* the Revised International Prognostic Scoring System, *IQR* Inter-Quartile Range, *MDS* myelodysplastic neoplasms, *MDS-CI* MDS-specific Comorbidity Index, *MDS-U* MDS unclassifiable, *MLD* multilineage dysplasia, *RS* ring sideroblast, *SLD* single lineage dysplasia.

Supplement Table S5. Baseline clinical characteristics of the up-graders and the stay-putters from the IPSS-M low-risk stratum.

| Variable | Up-graders from the IPSS-M low-risk stratum (N = 30) | Stay-putters from the IPSS-M low-risk stratum (N = 56) | P value |
|--|---|---|---------------------|
| Age at diagnosis, median years (IQR) | 57 (52 – 68) | 60 (54 – 64) | 0.43 ^a |
| Sex, n (%) | | | 0.66 ^b |
| Female | 7 (23) | 17 (30) | |
| Male | 23 (77) | 39 (70) | |
| 2016 revised WHO MDS subtype, n (%) | | | 0.29 ^b |
| MDS with del5q abnormality | 1 (3) | 1 (2) | |
| MDS MLD | 11 (37) | 24 (42) | |
| MDS SLD | 3 (10) | 8 (14) | |
| MDS with EB1 | 6 (20) | 4 (7) | |
| MDS with EB2 | 1 (3) | 2 (4) | |
| MDS-SLD/MLD-RS | 7 (24) | 11 (20) | |
| MDS-U | 1 (3) | 6 (11) | |
| Haemoglobin, median g/L (IQR) | 105 (91 – 120) | 104 (86 – 120) | 0.62 ^a |
| Platelets, median 10⁹/L (IQR) | 87 (42 – 205) | 78 (55 – 170) | 0.65 ^a |
| White blood cell count, median 10⁹/L (IQR) | 3.43 (2.21 – 5.66) | 2.99 (2.19 – 4.05) | 0.25 ^a |
| Neutrophil count, median 10⁹/L (IQR) | 2.35 (1.11 – 3.39) | 1.52 (1.04 – 2.13) | 0.17 ^a |
| Blast percentage in bone marrow, median (IQR) | 0.5 (0 – 3) | 1.0 (0 – 2) | 0.85 ^a |
| Blast percentage in blood, median (IQR) | 0 (0 – 0) | 0 (0 – 0) | 0.41 ^a |
| IPSS-R risk-stratification, n (%) | | | 0.32 ^b |
| Very low | 3 (10) | 13 (23) | |
| Low | 20 (67) | 32 (57) | |
| Intermediate | 7 (23) | 11 (20) | |
| High | 0 (0) | 0 (0) | |
| Very high | 0 (0) | 0 (0) | |
| FS-13 score, median (IQR) | 0.62 (0.40 – 0.62) | 0.38 (0.30 – 0.46) | <0.001 ^a |
| MDS-CI score, n (%) | | | <0.001 ^b |
| Low | 13 (43) | 47 (84) | |
| Intermediate | 14 (47) | 9 (16) | |

High

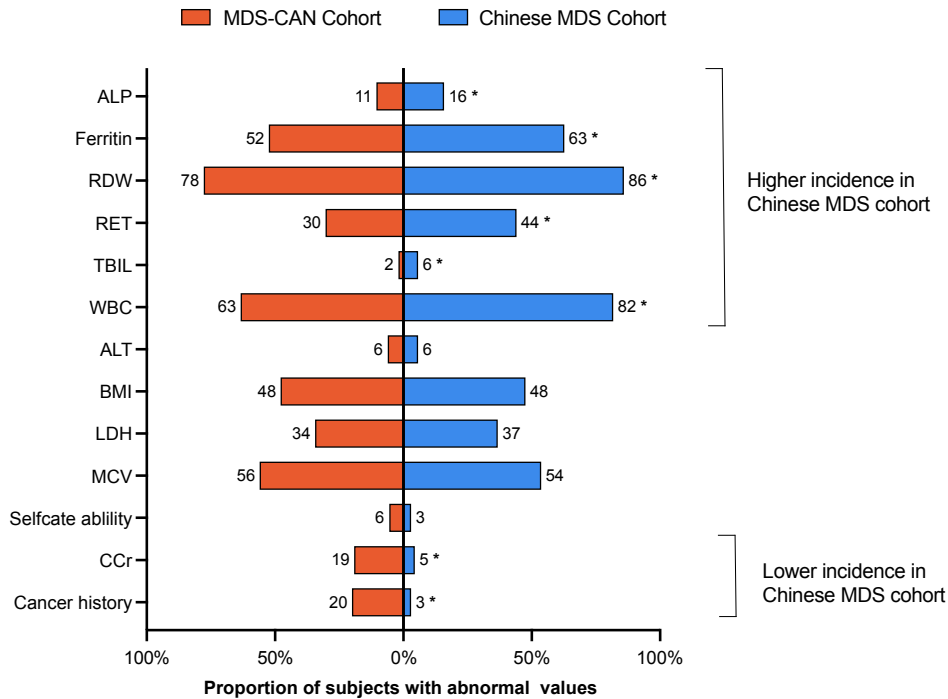
3 (10)

0 (0)

^a, Wilcoxon test.

^b, Chi-squared test.

Abbreviations: *EB* excess blasts; *FS-13* 13-item frailty scale, *IPSS-R* the Revised International Prognostic Scoring System, *IQR* Inter-Quartile Range, *MDS* myelodysplastic neoplasms, *MDS-CI* MDS-specific Comorbidity Index, *MDS-U* MDS unclassifiable, *MLD* multilineage dysplasia, *RS* ring sideroblast, *SLD* single lineage dysplasia.



Supplement Figure S1. Comparison of FS-13 items between the Chinese MDS cohort and the MDS-CAN cohort.

ALP alkaline phosphatase, *ALT* alanine aminotransferase, *BMI* abnormal body mass index, *CCr* creatinine clearance, *LDH* lactate dehydrogenase, *MCV* mean corpuscular volume, *MDS-CAN* Myelodysplastic Syndromes-Canada, *RDW* red blood cell distribution width, *RET* reticulocyte count, *WBC* white blood cell count. * $P < 0.05$ (Chi-squared test).