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

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Table 1 and 2 are available in the Supplementary Files section.

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

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Abstract

IPSS-M has improved prognostication in MDS by integrating clinical, cytogenetic, and molecular data. Here, we investigate the potential added value of considering frailty and comorbidity for improving prognosis prediction. Using data from a training set of 412 subjects with newly diagnosed MDS, we develop "Integrated IPSS-M", a risk-stratification model that recalibrates IPSS-M based on age, frailty, and comorbidity. We then confirm the model's performance on a validation set of 275 subjects. The Integrated IPSS-M showed higher concordance scores for overall survival compared with the IPSS-M (training set, 0.77 [95-percent confidence interval [CI], 0.73, 0.80] *vs.* 0.68 [0.64, 0.72], $P < 0.001$; validation set, 0.73 [0.68, 0.78] *vs.* 0.69 [0.64, 0.74], $P = 0.03$). Our study indicates that integration of IPSS-M, age, frailty, and comorbidity enhances prognostic accuracy in MDS. These findings suggest that Integrated IPSS-M may inform treatment decision-making and trial enrollment for new therapies.

Keywords Myelodysplastic neoplasms; Prognostic model; Frailty; Comorbidity

Introduction

Myelodysplastic neoplasms (MDS) are a heterogeneous group of clonal haematopoietic stem cell disorders characterized by ineffective haematopoiesis, peripheral blood cytopenia, cellular dysplasia, and risk of leukaemic transformation [1]. Patients with MDS are diverse in clinical characteristics and physical fitness. These differences are especially pronounced in older or less fit patients, in whom treatment tolerance may outweigh disease biology in determining outcomes [2]. Due to this heterogeneity, accurate prognostic assessment and risk stratification of MDS are essential for guiding clinical decision-making [3, 4].

The Revised International Prognostic Scoring System (IPSS-R) is widely used for risk assessment based on disease biology, including bone marrow blast percentage, peripheral blood counts, and cytogenetic abnormalities [5]. Recent research indicates that sequencing data provides additional prognostic information [6-8]. This has led to the development of the Molecular IPSS (IPSS-M), which integrates clinical characteristics and genetic mutation [9]. IPSS-M outperforms IPSS-R in predicting clinical outcomes [10, 11].

However, both IPSS-R and IPSS-M fail to consider additional host-related factors, including frailty and comorbidity. Frailty refers to cumulative deterioration of multiple physiological systems, which leads to poor treatment response, diminished treatment tolerance, and shorter overall survival [12-19]. Comorbidities refer to the chronic conditions that coexist with MDS and are common in older adults. A higher comorbidity burden reduces the ability to tolerate intensive treatment and is independently associated with shorter overall survival [18, 20, 21]. Frailty and comorbidity are independent prognostic

indicators in patients with MDS, especially those who are older or less fit [2, 15, 22-27].

In this study, we incorporated frailty and comorbidity into IPSS-M to develop an integrated scoring system called “Integrated IPSS-M”. This model was designed to improve prognostic accuracy and better inform treatment decisions in patients with MDS.

Materials and Methods

Subjects

We analyzed data from 687 subjects newly diagnosed with *de novo* MDS with complete clinical records at the Institute of Hematology, Chinese Academy of Medical Sciences (IHCAMS; Tianjin, China) between August, 2016 and June, 2023. MDS diagnosis was based on the 2016 revised World Health Organization (WHO) criteria [28]. The flowchart for data compilation is displayed in **Figure 1**. Targeted next-generation sequencing (NGS) was performed as described [29]. IPSS-R and IPSS-M were calculated for all subjects. Overall survival was defined as the time from diagnosis until death or latest follow-up. Patients who underwent allogeneic hematopoietic stem-cell transplantation (allo-HSCT) were considered as censored at the time of transplantation. The last follow-up date was October 1st, 2025, with a median follow-up duration of 36.1 (Inter-Quartile Range [IQR], 18.2 – 52.8) months after diagnosis.

Frailty assessment: “FS-13”

We assessed frailty using an adapted version of the 15-item Frailty Scale (FS-

15). The FS-15 evaluates 15 variables that are associated with frailty, including global fatigue score, 4-minute walk test, self-care ability (*i.e.*, the ability to plan, prepare, and serve adequate meals independently), body mass index (BMI), cancer history, alanine aminotransferase (ALT), alkaline phosphatase (ALP), bilirubin, creatinine clearance, ferritin, lactate dehydrogenase (LDH), mean corpuscular volume (MCV), red blood cell distribution width (RDW), reticulocyte count (RET), and white blood cell count (WBC) [23].

Because global fatigue score and result of the 4-minute walk test were unavailable in most of the study subjects, we focused on the other 13 variables. Impaired self-care ability was defined as an Eastern Cooperative Oncology Group (ECOG) Score ≥ 3 [30]. In 13 subjects, ECOG score was unavailable and impaired self-care ability was defined as a Barthel index (BI) ≤ 35 [31]. Abnormal ALT, ALP, bilirubin, ferritin, LDH, MCV, RDW, RET, and WBC values were defined as values outside their respective reference ranges at the IHCAMS (**Supplementary Table S1**). Impaired creatinine clearance was defined as severe (< 30 mL/min) or moderate (≥ 30 and < 60 mL/min) based on the Cockcroft-Gault formula [32]. (Severe and moderate impaired creatinine clearance score as 1 and 0.5, respectively.) Abnormal BMI was defined as severe (< 18.5 or ≥ 30 kg/m²) or moderate (25 – 29.9 kg/m²). (Severe and moderate abnormal BMI score as 1 and 0.5, respectively.)

Finally, we calculated an FS-13 score in our cohort based on the 13 available FS-15 variables. The score was defined as the ratio of the weighted sum of deficits present to the total number of evaluated variables for each subject, with higher scores indicating greater frailty. Its value ranged from 0 to 1 .

Comorbidity assessment: MDS-CI

Comorbidity data were retrospectively collected from electronic health records. The MDS-specific Comorbidity Index (MDS-CI) was a sum of 5 separate scores for extra-haematologic comorbidity: cardiac disease (2 points if disease exists), moderate-to-severe hepatic disease (1 point), severe pulmonary disease (1 point), renal disease (1 point), and a history of solid tumor (1 point) [20]. The MDS-CI's value ranged from 0 to 6, and the scores were classified into high (≥ 3), intermediate (1 or 2), and low (0).

We defined comorbidities in accordance with Sorror et al. [33]. Cardiac disease was defined as arrhythmia, heart valve disease, congestive heart failure or ejection fraction ≤ 50%, coronary artery disease, or myocardial infarction. Moderate-to-severe hepatic disease was defined as liver cirrhosis or fibrosis, total bilirubin > 1.5× the upper limit of normal (ULN), or AST/ALT > 2.5× ULN. Severe pulmonary disease was defined as dyspnea at rest or requiring oxygen support, or pulmonary function impairment, with diffusing capacity of the lungs for carbon monoxide (DLCO) or forced expiratory volume in 1 second (FEV1) ≤ 65%. Renal disease was defined as persistent creatinine > 177 μmol/L, undergoing renal dialysis treatment, or prior renal transplantation. Solid tumor was defined as history of any solid malignancy, excluding non-melanoma skin cancer.

Model development and validation

Patients were randomly divided into training (60%, n = 412) and validation (40%, n = 275) sets. Using the training-set data we built a random survival forest (RSF) model, which is a non-parametric, ensemble, tree-based machine learning method for survival prediction, based on 4 co-variates: age (in years), FS-13 (theoretical range, 0 – 1), MDS-CI (0 – 6), and IPSS-M (1 = "very low risk"; 2 =

"low risk"; 3 = "moderate low risk"; 4 = "moderate high risk"; 5 = "high risk"; 6 = "very high risk") [34, 35]. Model tuning was conducted based on 5-fold cross-validation (with 3 repeats) within the training set, optimizing 3 key parameters: ntree (the total number of trees grown in the forest), mtry (the number of candidate variables randomly selected for splitting at each node), and nsplit (the number of random split points considered for each continuous variable). The parameteric value combination attaining the highest average concordance score (*i.e.*, C-statistic) in the cross-validation experiments was: ntree = 800, mtry = 4, and nsplit = 15. These optimized values were used for the final round of model training on the entire training set, and the resultant final model was termed "Integrated IPSS-M". Based on the distribution of the "Integrated IPSS-M" model outputs in the training-set subjects, we designated 5 cut-off values to divide the subjects into six risk-strata.

We subsequently applied the "Integrated IPSS-M" model to the validation-set subjects and used the same set of 5 predesignated cut-off values to divide the validation cohort into six risk-strata. Performance of Integrated IPSS-M was evaluated by computing the concordance score between model output and all-cause mortality.

Statistical analysis

Continuous variables were summarized as medians and IQRs. Categorical variables were presented as frequency and percentage values. Group comparisons for continuous variables were performed using the Wilcoxon test. Categorical variables were compared using the chi-squared test. Survival was estimated using the Kaplan-Meier method, and the log-rank test was used to compare different groups' survival. We used Gini index to quantify unevenness

of model-defined risk-strata sizes. (Values of the Gini index ranged from 0 [most even] to 1 [most uneven].) RSF modeling was done using the R function 'randomForestSRC' package (ver. 3.3.1). A two-sided *P* value of less than 0.05 was considered statistically significant. All analyses were performed using the R computing language (version 4.2.2).

Results

Characteristics of study subjects

The study subjects' clinical characteristics at diagnosis are summarized in **Table 1** and **Supplementary Table S2**. 29 (4%), 147 (21%), 212 (31%), 167 (25%), and 132 (19%) subjects were very low-, low-, intermediate-, high-, and very high-risk according to IPSS-R. Three-year survival of these 5 risk-strata were 88%, 71%, 64%, 35%, and 21%, respectively (overall $P < 0.001$). 19 (3%), 116 (17%), 97 (14%), 93 (14%), 175 (25%), and 187 (27%) subjects were very low-, low-, moderate low-, moderate high-, high-, and very high-risk according to IPSS-M. More than half (53% [362/687]) of the study subjects were high to very high risk according to IPSS-M. Gini index of IPSS-M-defined risk-strata sizes was 0.32. Three-year survival of the 6 risk-strata were 90%, 79%, 71%, 62%, 42%, and 23% (overall $P < 0.001$).

Median score of FS-13 was 0.42 (IQR, 0.31 – 0.54). Higher frailty score (> 0.42) was associated with shorter survival compared with lower frailty score (≤ 0.42): median = 30.2 *vs.* 73.5 months ($P < 0.001$; **Figure 2 A**). Compared with North American patients (the Myelodysplastic Syndromes-Canada cohort) [22], our

study subjects exhibited higher incidences of abnormal values of ALP (15.9% [China] *vs.* 10.5% [North America]; $P = 0.010$), bilirubin (5.7% *vs.* 1.9%; $P = 0.002$), ferritin (62.7% *vs.* 52.4%; $P = 0.001$), RET (44.1% *vs.* 30.3%; $P < 0.001$), RDW (85.9% vs. 77.8%; $P < 0.001$), and WBC (81.8% vs. 63.4%; $P < 0.001$) (**Supplementary Figure 1**).

The most prevalent comorbidity in our study subjects was hepatic disease(s) (26.5% [183/687]), followed by pulmonary disease(s) (24.4% [168/687]), hypertension (16.3% [112/687]), and cardiac disease(s) (9.7% [67/687]). 492 (71.6%), 75 (10.9%), 99 (14.5%), 20 (2.9%), and 1 (0.1%) subjects had an MDS-CI score of 0, 1, 2, 3, and 4, respectively. Median survival of subjects with high, intermediate, and low MDS-CI scores was 21.2, 21.8, and 65.6 months, respectively (overall $P < 0.001$; **Figure 2 B**).

Integrating age, FS-13, and MDS-CI with IPSS-M

We randomly split the study subjects into two sets: training (n = 412) and validation (n = 275). There was no statistically significant difference between the two sets in age, sex, WHO subtypes, peripheral blood counts, blast percentages, IPSS-R, IPSS-M, treatment, comorbidities, and frailty co-variates (all $P > 0.05$) **(Table 1** and **Supplementary Table S2)**.

Using the training-set data, we constructed an RSF model we termed “Integrated IPSS-M”. Distribution of natural logarithmic values of RSF model outputs in the training set is displayed in **Figure 3 A**. The median logarithmic value of model outputs was 3.9. We defined “very low risk” as $\log_e$(Integrated IPSS-M) ≤ 2; “low risk”, (2, 3.5]; “moderate low risk”, (3.5, 3.9]; “moderate high risk”, (3.9, 4.3]; “high risk”, (4.3, 5]; and “very high risk”, > 5. 30 (7%), 103 (25%), 57 (14%), 108 (26%),

76 (19%), and 38 (9%) subjects in the training set were classified as very low, low, moderate low, moderate high, high, and very high risk, respectively (**Figure 3 B**). Hazard ratios (HRs) for all-cause mortality were 0 (95-percent confidence interval [CI] not computable), 0.05 (95-percent CI, 0.03, 0.09), 0.12 (0.06, 0.21), 0.24 (0.15, 0.37), and 0.55 (0.36, 0.84) for the subjects classified as very low, low, moderate low, moderate high, and high risk, respectively, compared with those classified as very high risk. Concordance between Integrated IPSS-M and survival was 0.77 (95-percent CI, 0.73, 0.80), significantly higher (P < 0.001) compared with that between IPSS-M and survival (0.68 [0.64, 0.72]; **Figure 3 C**).

Validation of Integrated IPSS-M

21 (8%), 70 (25%), 48 (17%), 58 (21%), 46 (17%), and 32 (12%) subjects in the validation set were very low, low, moderate low, moderate high, high, and very high risk according to Integrated IPSS-M (**Figure 3 D**). In the validation set, HRs for all-cause mortality were 0.02 (95-percent CI, 0.01, 0.17), 0.09 (0.05, 0.19), 0.21 (0.11, 0.40), 0.37 (0.21, 0.64), and 0.64 (0.38, 1.09) for subjects classified as very low, low, moderate low, moderate high, and high risk compared with very high risk subjects. Concordance between Integrated IPSS-M and survival was 0.73 (95-percent CI, 0.68, 0.78), significantly higher (P = 0.030) compared with concordance between IPSS-M and survival (0.69 [0.64, 0.74]; **Figure 3 E**).

Subgroup analysis by treatment

185 (27% of 687) study subjects received hypomethylating agent (HMA) therapy. 3 (2%), 23 (12%), 24 (13%), 54 (29%), 53 (29%), and 28 (15%) were classified as very low, low, moderate low, moderate high, high, and very high risk by Integrated IPSS-M (**Figure 4 A**). HRs for all-cause mortality were 0 (95-percent

CI not computable), 0.09 (95-percent CI, 0.03, 0.26), 0.18 (0.08, 0.40), 0.33 (0.19, 0.58), and 0.63 (0.38, 1.05) for very low, low, moderate low, moderate high, and high risk compared with very high risk. Concordance between Integrated IPSS-M and survival (0.69 [95-percent CI, 0.64, 0.75]) was significantly higher (P < 0.001) compared with concordance between IPSS-M and survival (0.65 [0.59, 0.70]).

Notably, among the HMA-treated patients, subjects classified as low to very low risk by Integrated IPSS-M had better survival compared with those classified as low to very low risk by IPSS-M (HR = 0.26 [95-percent CI, 0.06, 1.07; P = 0.04]; three-year survival, 88% [95-percent CI, 75%, 100%] *vs.* 61% [34%, 100%]; **Figure 4 B**). On the other hand, survival was worse in the subjects classified as high to very high risk by Integrated IPSS-M compared with those classified as high to very high risk according to IPSS-M (HR = 1.54 [95-percent CI, 1.11, 2.15; P = 0.01]; three-year survival, 17% [95-percent CI, 10%, 29%] *vs.* 29% [21%, 40%]; **Figure 4 C**).

177 (26% of 687) patients received immune modulation therapy. Integrated IPSS-M classfied 24 (13%), 72 (39%), 26 (14%), 30 (16%), 18 (10%), and 7 (4%) of them as very low, low, moderate low, moderate high, high, and very high risk (**Figure 5 A**). HRs for all-cause mortality were 0 (95-percent CI not computable), 0.09 (95-percent CI, 0.03, 0.24), 0.20 (0.06, 0.65), 0.37 (0.14, 0.96), and 1.08 (0.41, 2.86) for very low, low, moderate low, moderate high, and high risk compared with very high risk. Concordance between Integrated IPSS-M and survival (0.77 [95-percent CI, 0.71, 0.83]) was significantly higher (P < 0.001) compared with concordance between IPSS-M and survival (0.66 [0.58, 0.74]).

Among the patients treated with immune modulation therapy, subjects classified as low to very low risk by Integrated IPSS-M had survival comparable to those classified as low to very low risk by IPSS-M (HR = 0.70 [95-percent CI, 0.29,1.70; *P* = 0.43]; three-year survival, 89.7% [95-percent CI, 83.5%, 96.3%] *vs.* 85.9% [76.7%, 96.2%]; **Figure 5 B**). In contrast, survival was worse in the subjects classified as high to very high risk by Integrated IPSS-M compared with those classified as high to very high risk according to IPSS-M (HR = 2.49 [95-percent CI,1.36, 4.56; *P* = 0.002]; three-year survival, 9.8% [95-percent CI, 2.6%, 36.5%] *vs.* 49.3% [36.4%, 66.6%]; **Figure 5 C**).

Correspondence between IPSS-M- and Integrated IPSS-M-defined risk-strata

Correspondence between IPSS-M-defined and Integrated IPSS-M-defined risk-strata in the study subjects is displayed in **Table 2**. Gini index for Integrated IPSS-M-defined risk-strata sizes was 0.27 in the study subjects. A total of 211 (31% of 687) study subjects were “stay-putters”, they remained in the same risk category under both IPSS-M and Integrated IPSS-M, including 6 very-low-risk, 56 low-risk, 10 moderate-low-risk, 30 moderate-high-risk, 39 high-risk, and 70 very-high-risk subjects. 409 (60%) subjects were “down-graders”, whose risk-stratification was adjusted downward by Integrated IPSS-M compared with IPSS-M. 67 (9%) were “up-graders”, whose risk-stratification was adjusted upward by Integrated IPSS-M.

Down-graders had better survival compared with stay-putters (**Figure 6**). Down-graders also tended to be younger and/or have lower FS-13 and/or MDS-CI scores. For example, 136 subjects were downgraded from high risk in IPSS-M

to moderate high risk or below in Integrated IPSS-M (**Figure 6**). These down-graders tended to be younger compared with the 39 stay-putters who were high risk according to both IPSS-M and Integrated IPSS-M (median age, 54 *vs.* 69; $P < 0.001$) (**Supplementary Table S3**). Similarly, 117 subjects were downgraded from very high risk in IPSS-M to high risk or below in Integrated IPSS-M. 97% (114/117) of these down-graders had low MDS-CI scores (**Supplementary Table S4**). On the other hand, of the 70 subjects who were very high risk according to both IPSS-M and Integrated IPSS-M, only 11% (8/70) had low MDS-CI scores. Median FS-13 score of the 117 down-graders was 0.42 (IQR, 0.35 – 0.50), significantly lower ($P < 0.001$) compared with the median score (0.50; IQR, 0.39 – 0.62) of the 70 stay-putters.

In contrast, "up-graders" tended to have higher FS-13 scores, higher MDS-CI risk-stratification, and poorer survival (**Figure 6**). For example, 30 subjects were upgraded from low risk in IPSS-M to moderate low risk or higher in Integrated IPSS-M. 57% (17/30) of these up-graders had intermediate to high MDS-CI scores, significantly ($P < 0.001$) worse than the 56 stay-putters who were low risk according to both IPSS-M and Integrated IPSS-M, of whom only 16% (9/56) had intermediate to high MDS-CI scores. The 30 up-graders also had higher FS-13 scores (median, 0.62 *vs.* 0.38 [$P < 0.001$]) compared with the 56 "low risk" stay-putters (**Supplementary Table S5**).

Discussion

The heterogeneity of MDS and the advanced age of most patients, along with wide variability in disease outcomes, make it challenging to determine the most

appropriate treatment strategy. IPSS-M has greatly improved prognostication in MDS by integrating clinical, cytogenetic, and molecular data. However, when applied to East Asian populations, IPSS-M classifies a disproportionately large number of patients with MDS as ≥ high risk [9, 36, 37]. In contrast, only 31% of MDS patients in the Europe/US population are high to very high risk according to IPSS-M [9]. We speculated that a portion of IPSS-M-defined high-to-very-high-risk patients might have better prognosis compared with what is suggested by their IPSS-M risk level, because they are young and/or have low frailty scores and low comorbidity burden. Frailty and comorbidity are two host-related factors that influence treatment tolerance and survival in patients with MDS but are omitted in IPSS-M [15-21, 38].

We developed and validated Integrated IPSS-M, an improved risk-stratification scheme for MDS that recalibrates IPSS-M according to age, frailty, and comorbidity. Risk level of patients with lower FS-13 scores and lower comorbidity burden is adjusted downward by Integrated IPSS-M, and vice versa. Integrated IPSS-M has better concordance with survival compared with IPSS-M in the Chinese population. Integrated IPSS-M-defined risk-strata also have a wider spread of mortality risks compared with IPSS-M-defined risk-strata. Three-year survival rate ranges from 94% in the very low-risk stratum to 17% in the very high-risk stratum in Integrated IPSS-M. In contrast, the range of three-year survival rate across IPSS-M-defined risk-strata is considerably narrower: from 78% in the very low-risk stratum to 30% in the very high-risk stratum. Furthermore, subgroup analyses indicate that Integrated IPSS-M continues to be more prognostic of survival compared with IPSS-M when focus is limited to patients receiving HMA

or immune modulation therapy. In conclusion, age, frailty, and comorbidity provide prognostic information across different therapies.

We have made the proposed model publicly accessible as an online calculator at https://skirt-calculator.shinyapps.io/Integrated_IPSS-M_for_MDS/. We propose our approach can be easily adapted to other ethnicities after appropriate recalibration. Because frailty and comorbidity are relatively easy to assess in routine practice, this model may have broad clinical applicability.

We acknowledge several limitations. First, our study was a retrospective analysis with potential attendant bias. Second, it was a single-center study. Our results need further external validation.

In conclusion, Integrated IPSS-M improves risk stratification in MDS by jointly considering disease-related and host-related factors, including clinical features, genetic mutations, age, frailty, and comorbidity. This model may help improve prognostic assessment and support enrollment in clinical trials of new treatment strategies.

Author contributions Z.Xiao and J.C. designed the study. X.W. led the study. X.W., S.Z., B.L., T.Q., Z.Xu, S.Qu, L.P., M.J., Q.G., J.Z., Y.L., F.L., B.J., Y.Z., and L.L. collected the data. J.C. designed the analysis plan. X.W. and Q.S. performed the analysis with assistance from X.G., W.Z., X.Z., and Y.F. S.Qi and Q.S. built the online calculator. X.W., Q.S., and J.C. prepared the manuscript, with contribution from Z.Xiao. All authors read, approved the final manuscript, and agreed to submit for publication.

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Conflict of interest No relevant conflicts of interest to declare about the manuscript.

Data availability statement Data supporting the findings of this study are available upon reasonable request made to the corresponding authors and in compliance with the People's Republic of China's regulations on human data management.

Ethics statement This study was approved by the Ethics Committee of the Institute of Hematology, Chinese Academy of Medical Sciences (IHCAMS; QTJC2023020-EC-1). All study subjects provided written informed consent compliant with the Declaration of Helsinki.

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Figure Legends

Figure 1. Flowchart for subject selection.

FS-13, 13-item frailty score.

Figure 2. Survival according to frailty and comobodity in 687 subjects with MDS.

A. Lower *vs*. higher FS-13 score.

B. High (≥ 3) *vs*. intermediate (1 or 2) *vs*. low (0) MDS-CI score.

FS-13, 13-item frailty score; MDS-CI, MDS-specific Comorbidity Index.

Figure 3. Development and validation of Integrated IPSS-M.

A. Distribution of log(Integrated IPSS-M) in the training set. The median log(Integrated IPSS-M) is 3.9.

B. Integrated IPSS-M *vs.* survival in the training set.

C. IPSS-M *vs.* survival in the training set.

D. Integrated IPSS-M *vs.* survival in the validation set.

E. IPSS-M *vs.* survival in the validation set.

Figure 4. Survival in subjects receiving hypomethylating agent therapy.

A. Integrated IPSS-M- vs. IPSS-M-defined risk-strata.

B. Integrated IPSS-M- *vs.* IPSS-M-defined low-to-very-low-risk subjects.

C. Integrated IPSS-M- *vs.* IPSS-M-defined high-to-very-high-risk subjects.

Figure 5. Survival in subjects receiving immune modulation therapy.

A. Integrated IPSS-M- vs. IPSS-M-defined risk-strata.

B. Integrated IPSS-M- *vs.* IPSS-M-defined low-to-very-low-risk subjects.

C. Integrated IPSS-M- *vs.* IPSS-M-defined high-to-very-high-risk subjects.

Figure 6. Re-stratification of subjects in separate IPSS-M-defined risk-strata by Integrated IPSS-M.

Figure 1

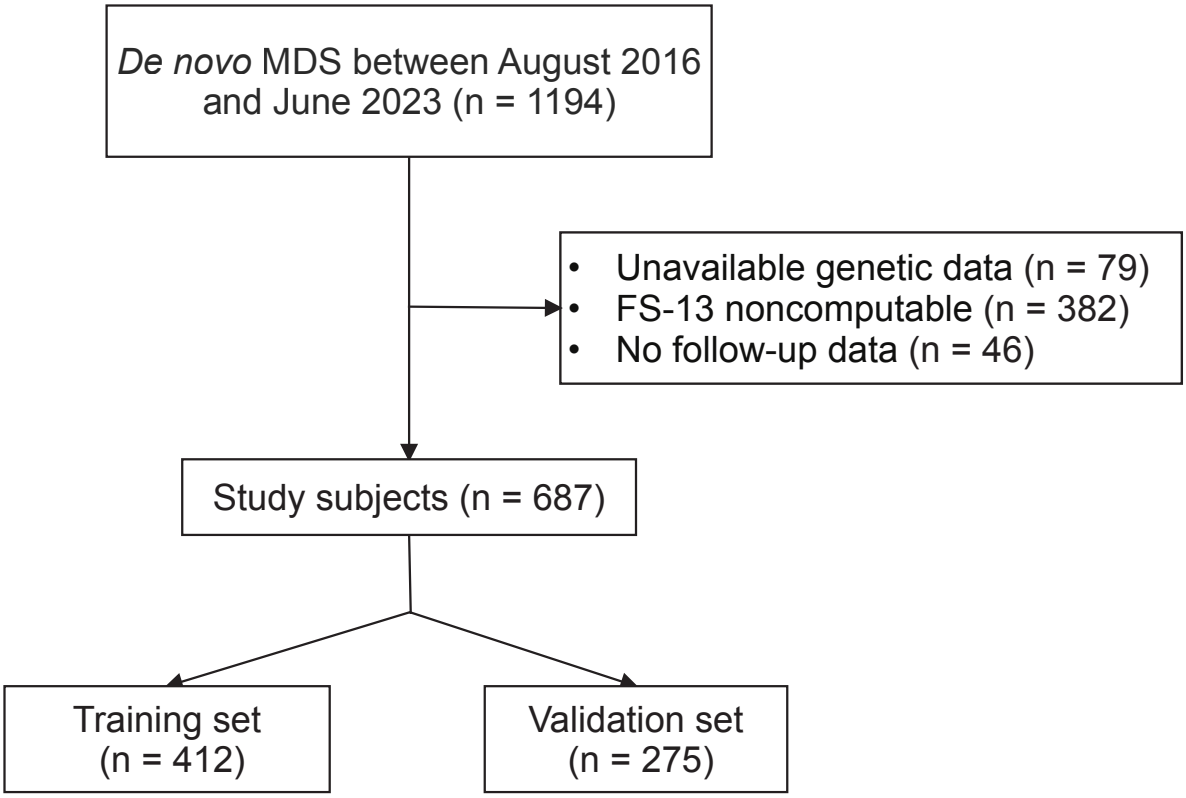

De novo MDS between August 2016 and June 2023 (n = 1194)
• Unavailable genetic data (n = 79)
• FS-13 noncomputable (n = 382)
• No follow-up data (n = 46)
Study subjects (n = 687)
Training set (n = 412)
Validation set (n = 275)

Figure 2

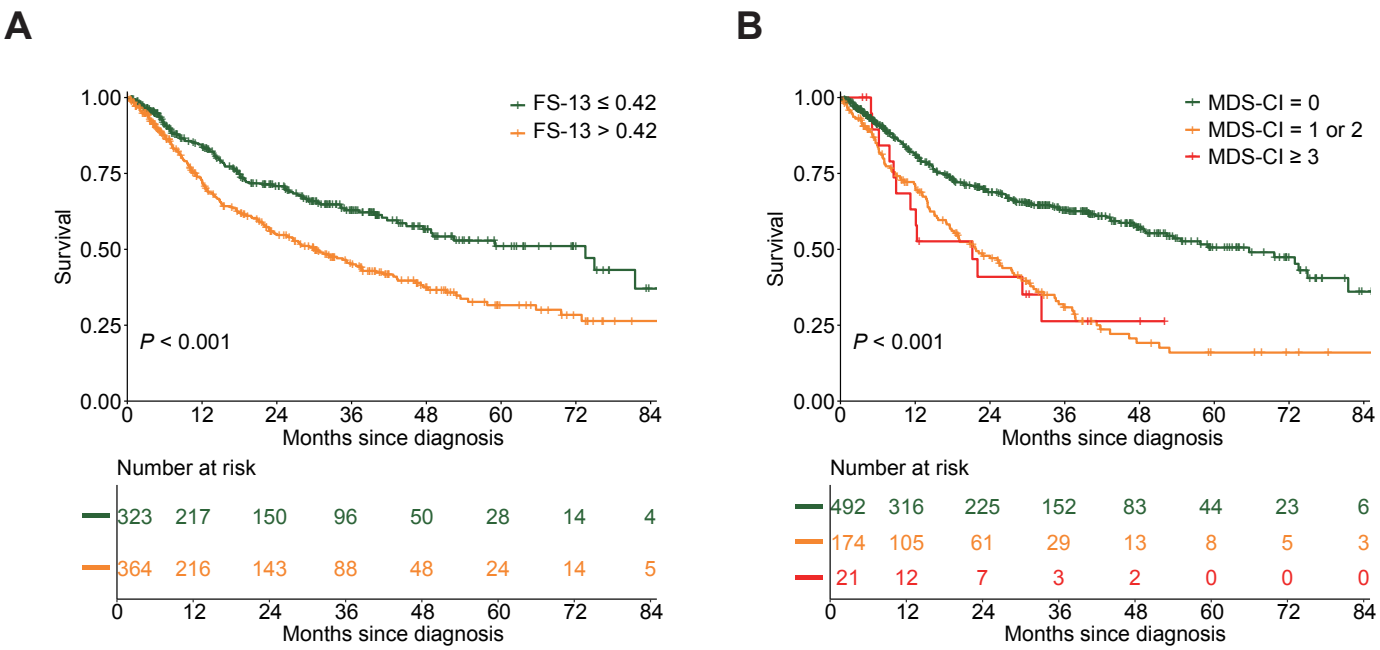
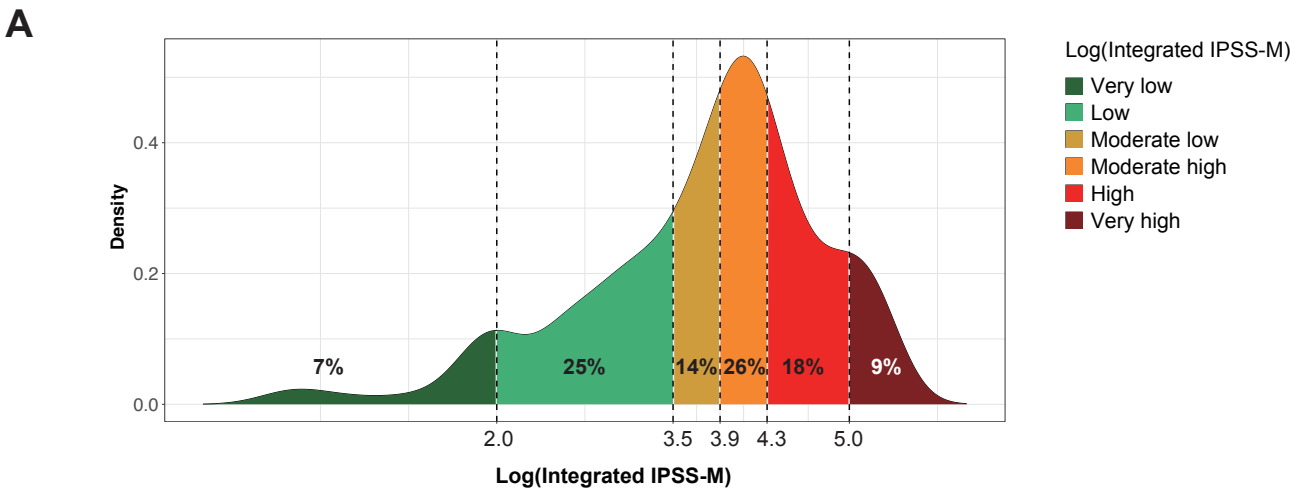
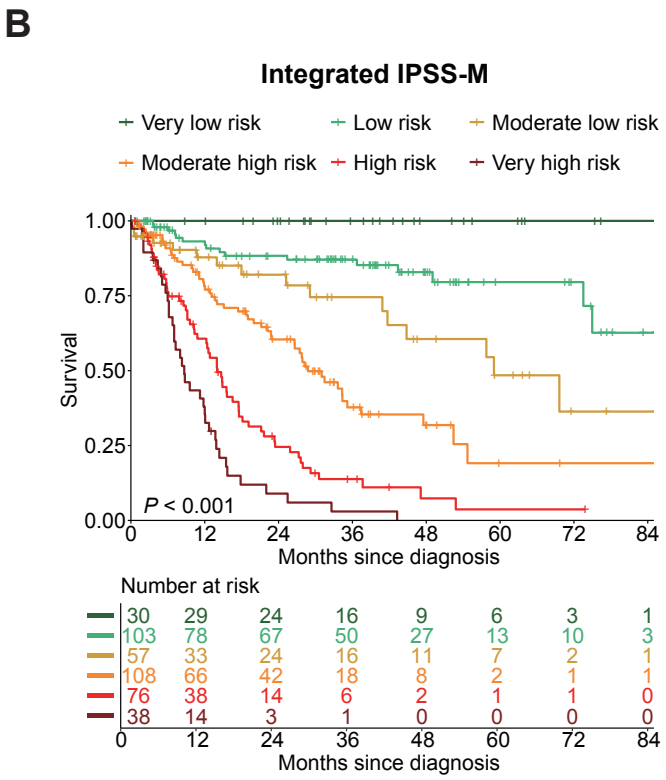
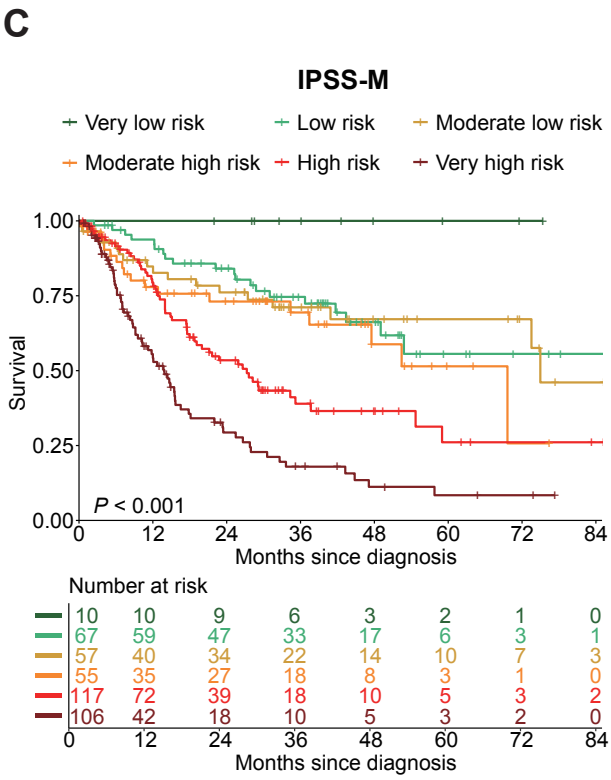
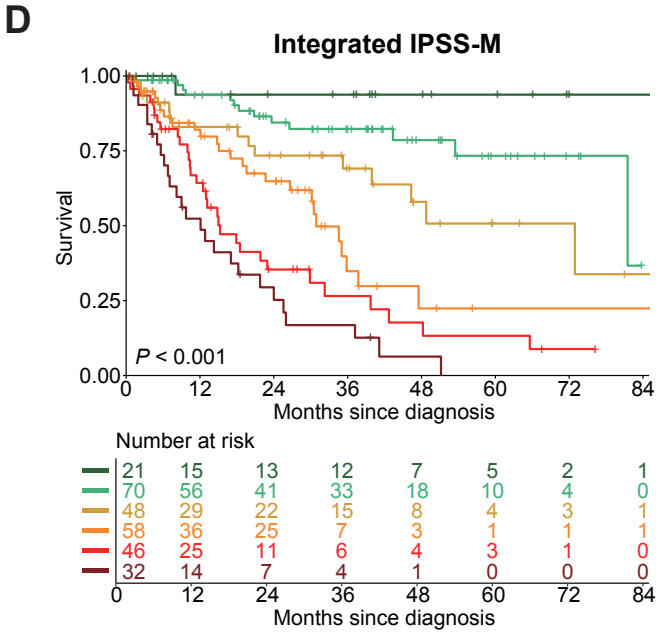

A
1.00
0.75
0.50
0.25
0.00
Survival
FS-13 ≤ 0.42
FS-13 > 0.42
P < 0.001
0
12
24
36
48
60
72
84
Months since diagnosis
Number at risk
323 217 150 96 50 28 14 4
364 216 143 88 48 24 14 5
Months since diagnosis
B
MDS-CI = 0
MDS-CI = 1 or 2
MDS-CI ≥ 3
P < 0.001
Months since diagnosis
Number at risk
492 316 225 152 83 44 23 6
174 105 61 29 13 8 5 3
21 12 7 3 2 0 0 0
Months since diagnosis

Figure 3


A
Density
0.4
0.2
0.0
7%
25%
14%
26%
18%
9%
2.0
3.5
3.9
4.3
5.0
Log(Integrated IPSS-M)
Log(Integrated IPSS-M)
Very low
Low
Moderate low
Moderate high
High
Very high


B
Integrated IPSS-M
Very low risk
Low risk
Moderate low risk
Moderate high risk
High risk
Very high risk
Survival
1.00
0.75
0.50
0.25
0.00
P < 0.001
0
12
24
36
48
60
72
84
Months since diagnosis
Number at risk
30 29 24 16 9 6 3 1
103 78 67 50 27 13 10 3
57 33 24 16 11 7 2 1
108 66 42 18 8 2 1 1
76 38 14 6 2 1 1 0
38 14 3 1 0 0 0 0
Months since diagnosis


C
IPSS-M
Very low risk
Low risk
Moderate low risk
Moderate high risk
High risk
Very high risk
Survival
1.00
0.75
0.50
0.25
0.00
P < 0.001
0
12
24
36
48
60
72
84
Months since diagnosis
Number at risk
10 10 9 6 3 2 1 0
67 59 47 33 17 6 3 1
57 40 34 22 14 10 7 3
55 35 27 18 8 3 1 0
117 72 39 18 10 5 3 2
106 42 18 10 5 3 2 0
Months since diagnosis


D
Integrated IPSS-M
Survival
1.00
0.75
0.50
0.25
0.00
P < 0.001
0
12
24
36
48
60
72
84
Months since diagnosis
Number at risk
21 15 13 12 7 5 2 1
70 56 41 33 18 10 4 0
48 29 22 15 8 4 3 1
58 36 25 7 3 1 1 1
46 25 11 6 4 3 1 0
32 14 7 4 1 0 0 0
Months since diagnosis

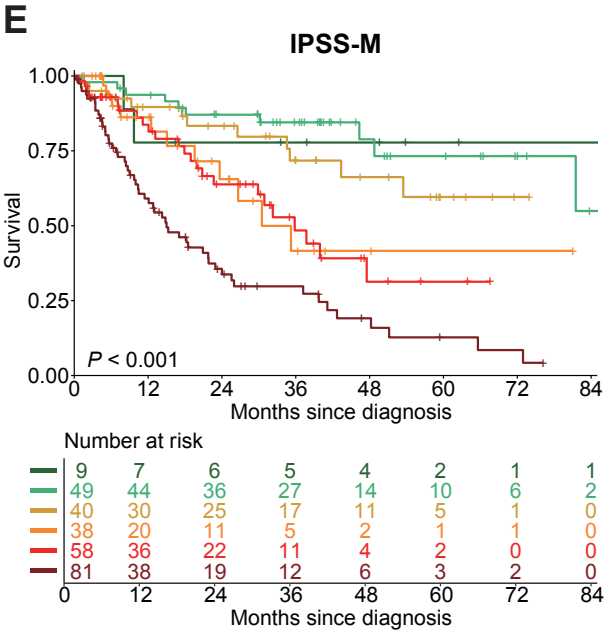

E
IPSS-M
Survival
1.00
0.75
0.50
0.25
0.00
P < 0.001
0
12
24
36
48
60
72
84
Months since diagnosis
Number at risk
9 7 6 5 4 2 1 1
49 44 36 27 14 10 6 2
40 30 25 17 11 5 1 0
38 20 11 5 2 1 1 0
58 36 22 11 4 2 0 0
81 38 19 12 6 3 2 0
Months since diagnosis

Figure 4

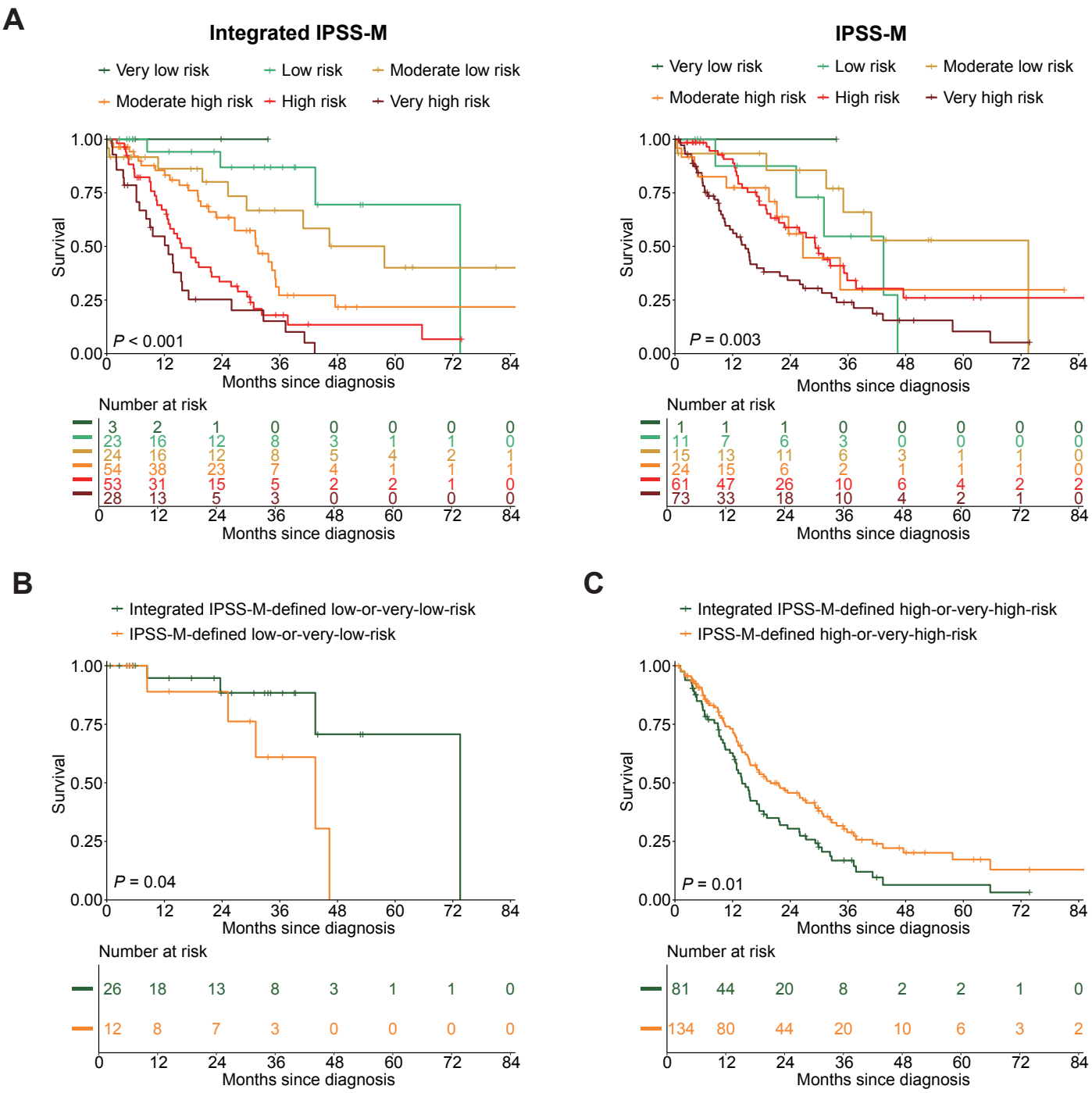
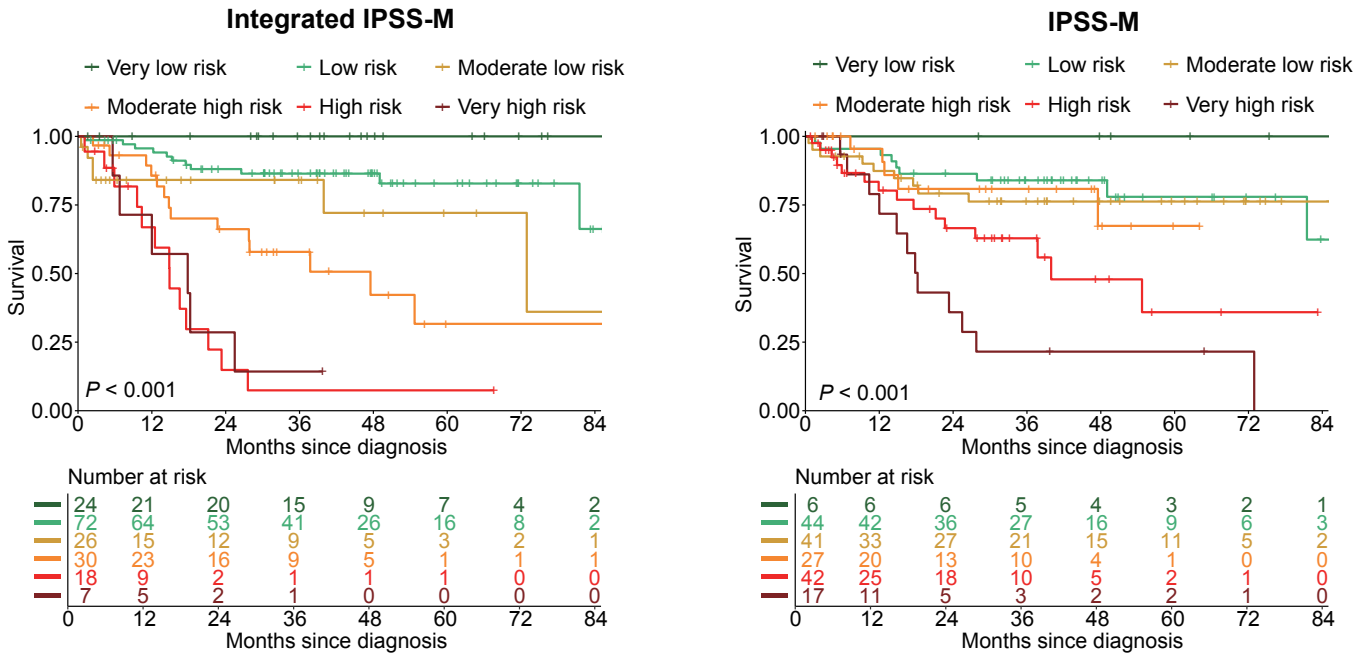
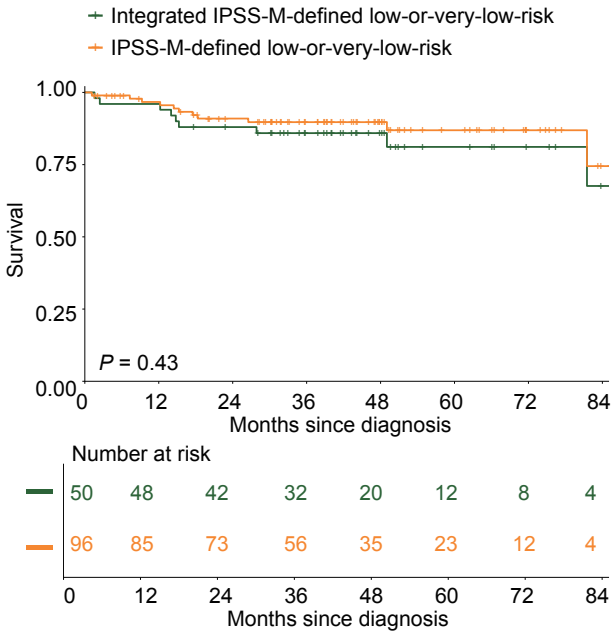

A
Integrated IPSS-M
Very low risk
Low risk
Moderate low risk
Moderate high risk
High risk
Very high risk
Survival
P < 0.001
Months since diagnosis
Number at risk
3 2 1 0 0 0 0 0
23 16 12 8 3 1 1 0
24 16 12 8 5 4 2 1
54 38 23 7 4 1 1 1
53 31 15 5 2 2 1 0
28 13 5 3 0 0 0 0
IPSS-M
P = 0.003
1 1 1 0 0 0 0 0
11 7 6 3 0 0 0 0
15 13 11 6 3 1 1 0
24 15 6 2 1 1 1 0
61 47 26 10 6 4 2 2
73 33 18 10 4 2 1 0
B
Integrated IPSS-M-defined low-or-very-low-risk
IPSS-M-defined low-or-very-low-risk
P = 0.04
26 18 13 8 3 1 1 0
12 8 7 3 0 0 0 0
C
Integrated IPSS-M-defined high-or-very-high-risk
IPSS-M-defined high-or-very-high-risk
P = 0.01
81 44 20 8 2 2 1 0
134 80 44 20 10 6 3 2

Figure 5

A


Integrated IPSS-M
Very low risk
Low risk
Moderate low risk
Moderate high risk
High risk
Very high risk
Survival
P < 0.001
Months since diagnosis
Number at risk
24 21 20 15 9 7 4 2
72 64 53 41 26 16 8 2
26 15 12 9 5 3 2 1
30 23 16 9 5 1 1 1
18 9 2 1 1 1 0 0
7 5 2 1 0 0 0 0
IPSS-M
Very low risk
Low risk
Moderate low risk
Moderate high risk
High risk
Very high risk
Survival
P < 0.001
Months since diagnosis
Number at risk
6 6 6 5 4 3 2 1
44 42 36 27 16 9 6 3
41 33 27 21 15 11 5 2
27 20 13 10 4 1 0 0
42 25 18 10 5 2 1 0
17 11 5 3 2 2 1 0

B


Integrated IPSS-M-defined low-or-very-low-risk
IPSS-M-defined low-or-very-low-risk
Survival
P = 0.43
Months since diagnosis
Number at risk
50 48 42 32 20 12 8 4
96 85 73 56 35 23 12 4

C

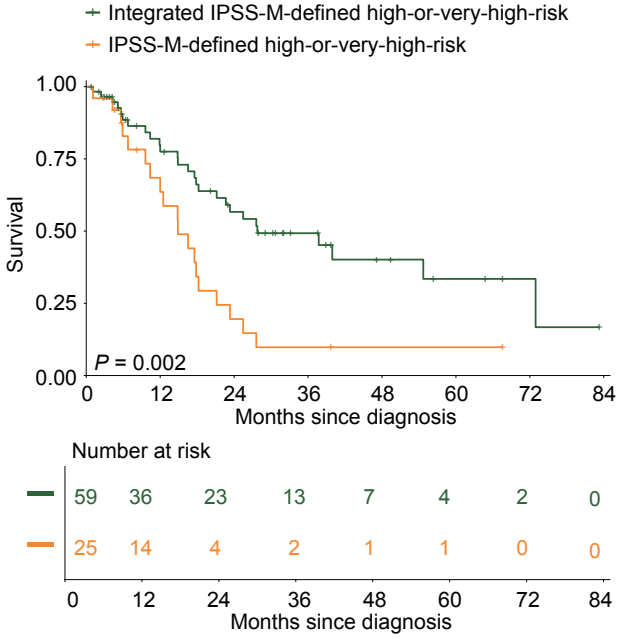
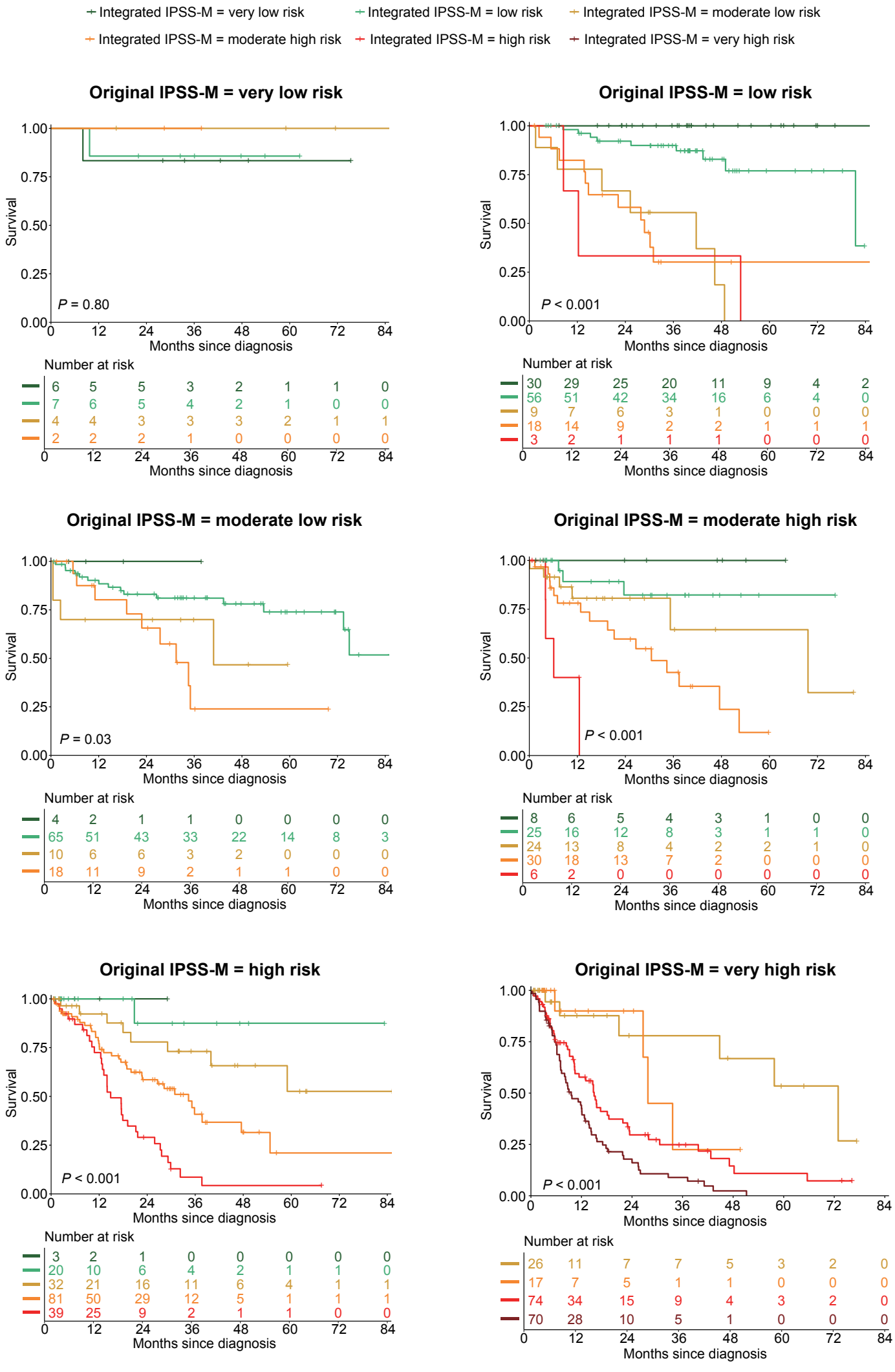

Integrated IPSS-M-defined high-or-very-high-risk
IPSS-M-defined high-or-very-high-risk
Survival
P = 0.002
Months since diagnosis
Number at risk
59 36 23 13 7 4 2 0
25 14 4 2 1 1 0 0

Figure 6


Integrated IPSS-M = very low risk
Integrated IPSS-M = low risk
Integrated IPSS-M = moderate low risk
Integrated IPSS-M = moderate high risk
Integrated IPSS-M = high risk
Integrated IPSS-M = very high risk
Original IPSS-M = very low risk
Survival
P = 0.80
Months since diagnosis
Number at risk
6 5 5 3 2 1 1 0
7 6 5 4 2 1 0 0
4 4 3 3 3 2 1 1
2 2 2 1 0 0 0 0
Original IPSS-M = low risk
P < 0.001
30 29 25 20 11 9 4 2
56 51 42 34 16 6 4 0
9 7 6 3 1 0 0 0
18 14 9 2 2 1 1 1
3 2 1 1 1 0 0 0
Original IPSS-M = moderate low risk
P = 0.03
4 2 1 1 0 0 0 0
65 51 43 33 22 14 8 3
10 6 6 3 2 0 0 0
18 11 9 2 1 1 0 0
Original IPSS-M = moderate high risk
P < 0.001
8 6 5 4 3 1 0 0
25 16 12 8 3 1 1 0
24 13 8 4 2 2 1 0
30 18 13 7 2 0 0 0
6 2 0 0 0 0 0 0
Original IPSS-M = high risk
P < 0.001
3 2 1 0 0 0 0 0
20 10 6 4 2 1 1 0
32 21 16 11 6 4 1 1
81 50 29 12 5 1 1 1
39 25 9 2 1 1 0 0
Original IPSS-M = very high risk
P < 0.001
26 11 7 7 5 3 2 0
17 7 5 1 1 0 0 0
74 34 15 9 4 3 2 0
70 28 10 5 1 0 0 0

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