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Comparison of the Prognostic Utility of the Revised International Prognostic Scoring System and the French Prognostic Scoring System in Azacitidine-Treated Patients with Myelodysplastic Syndromes

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Summary

The revised International Prognostic Scoring System (IPSS-R) was developed in a cohort of untreated myelodysplastic syndromes (MDS) patients. A French Prognostic Scoring System (FPSS) was recently reported to identify differential survival among azacitidine-treated patients

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Author Contributions

AMZ conceived and designed the study, performed the research, analysed the data and wrote the manuscript. SDG, TP, PG designed the study, performed the research, analysed the data and critically reviewed the manuscript. JWL and ZS designed the study, performed the research, analysed the data, conducted the statistical analysis and critically reviewed the manuscript. MJ, MRS, EP, JG, HPE, and MST provided patients and critically reviewed the manuscript. All authors reviewed the final version and approved submission.

with high-risk MDS. We applied the FPSS and IPSS-R to 150 patients previously randomized to azacitidine monotherapy or a combination of azacitidine with entinostat (a histone deacetylase inhibitor). Neither score predicted response but both discriminated patients with different overall survival (OS) (median OS, FPSS: 9.7, 14.7, and 25.3 months, P=0.018; IPSS-R: 12.5, 11.3, 20.8, and 36 months, P=0.005). Statistical analysis suggested no improvement in OS prediction for the FPSS over the IPSS-R in azacitidine-treated patients.

Keywords

Myelodysplastic syndromes (MDS); azacitidine; Revised International Prognostic Scoring System (IPSS-R); French Prognostic Scoring System (FPSS); prognostic models

1. Introduction

Azacitidine is the only drug shown to prolong overall survival (OS) in patients with high risk (HR)-myelodysplastic syndromes (MDS) (Fenaux *et al*, 2009). Nevertheless, only about half of the patients respond to azacitidine therapy and the vast majority of responders lose their response within two years (Silverman *et al*, 2002, 2006, Fenaux *et al*, 2009). No cures are achieved with azacitidine therapy; upon failure the median survival is less than 6 months (Prebet *et al*, 2011). Therefore, identification of patients with differential baseline probabilities of achieving survival benefit from azacitidine therapy is highly warranted.

The International Prognostic Scoring System (IPSS) (Greenberg *et al* 1997), the most widely used prognostic tool for MDS, has recently undergone revision (Greenberg *et al*, 2012). Although the revised IPSS (IPSS-R) showed improved prognostic precision over the IPSS, both the IPSS and the IPSS-R were developed using cohorts of untreated patients (Greenberg *et al*, 1997, 2012). The IPSS-R has subsequently been shown to have prognostic value among treated MDS patients in retrospective analyses (Lamarque *et al*, 2012, Voso *et al*, 2013, Mishra *et al*, 2013, Savic *et al*, 2013, Neukirchen *et al*, 2014).

A new French prognostic scoring system (FPSS) has been shown to separate azacitidine-treated patients with HR-MDS into three prognostic groups with significantly different survivals based on 4 readily available clinical and laboratory parameters: Eastern Cooperative Oncology Group (ECOG) performance status (PS), cytogenetics, presence of circulating blasts, and red blood cell (RBC) transfusion-dependence (Itzykson *et al*, 2011b, 2012). The FPSS was validated by the same group in a cohort of patients in the AZA001 trial and by two other groups in two small European single-institution cohorts (Breccia *et al*, 2012, van der Helm *et al*, 2011). Most patients in the development and validation cohorts were European patients, and the two independent groups used retrospectively collected data for validation (Itzykson *et al*, 2011b, Itzykson *et al*, 2012, Breccia *et al*, 2012, van der Helm *et al*, 2011).

Therefore, we sought to determine the relative prognostic discriminatory power of FPSS and IPSS-R in a large cohort of azacitidine-treated patients whose data was collected prospectively in the context of a North American clinical trial.

2. Materials and Methods

2.1 Source population

The North American Leukemia Intergroup Trial E1905 was a randomized phase II trial that compared azacitidine monotherapy given at 50 mg/m^2/day on days 1–10 of each cycle (1 cycle=28 days) to a combination of azacitidine given at the same schedule with the histone deacetylase inhibitor entinostat (4 mg/m^2/day on days 3 and 10 of each of six cycles) (Prebet *et al*, 2014). Responding patients were treated for an additional 18 cycles of treatment in the absence of progression. No prior azanucleoside therapy or induction chemotherapy was allowed. Patients with chronic myelomonocytic leukaemia (CMML), MDS with high-risk features (IPSS of intermediate-2 and high) or those with low or intermediate-1 but with severe thrombocytopenia [platelet count < 50 × 10^9/l] and/or neutropenia [absolute neutrophil count < 0.5 × 10^9/l], and acute myeloid leukaemia (AML) with myelodysplasia-related changes (AML-MRC) were eligible. Therapy-related MDS or AML were ineligible. Responses were measured according to the International Working Group 2000 Criteria (Cheson *et al*, 2001).

A total of 150 patients were evenly randomized between the two treatment arms (93 with MDS, 52 with AML-MRC, and 5 with CMML), of whom 149 were analysed (74 patients in the azacitidine monotherapy arm vs. 75 in the combination arm). In the azacitidine monotherapy group, 32% achieved the primary endpoint (haematological normalization [HN], defined as complete response (CR) + partial remission [PR] + trilineage haematological improvement [HI-T]) compared to 27% in the combination regimen group (P=0.80). The median OS for all disease groups was 18 months for the azacitidine group compared to 13 months in the combination group (P=0.09). For patients with MDS and CMML, the median OS was 21.2 months in the azacitidine monotherapy arm vs. 14.7 months in the combination arm (P=0.06).

2.2 Study population

This was a nested retrospective cohort study of patients enrolled in the E1905 trial for whom the FPSS and IPSS-R could be calculated at baseline. The FPSS was calculated based on 4 prognostic factors: ECOG PS, presence of circulating blasts, RBC transfusion-dependence, and cytogenetics (Itzykson *et al*, 2011b). The IPSS-R was calculated based on karyotype, bone marrow (BM) blast proportion, haemoglobin, platelet and neutrophil levels (Greenberg *et al*, 2012). Oligoblastic AML was defined as AML up to 30% BM blasts (previously referred to as refractory anaemia with excess blasts in transformation [RAEB-t]).

2.3 Statistical analysis

Patient demographic factors and disease characteristics were compared by Wilcoxon rank sum tests and Fisher’s exact tests as appropriate. Best overall response rate (ORR) was defined as the proportion of patients with CR, PR, and any HI among all patients. OS was defined as time from registration to death from any cause. Follow-up was censored at last contact. Survival distributions were estimated by the Kaplan-Meier method and tested using the log-rank test. Multivariate Cox proportional hazards models were also fitted to evaluate the effect of FPSS and IPSS-R on OS after adjusting for covariates. The FPSS and IPSS-R

were compared using Akaike's information criterion (AIC; a measure indicating the relative quality of a statistical model based on a given set of data) and the C-statistic (a measure indicating overall adequacy of prediction models with censored survival data). P values are all two-sided and a level of 5% was considered statistically significant.

3. Results

3.1 Study cohort

The IPSS-R scores could be determined for 120 patients (**IPSS-R cohort**, 80%), of whom 59 received azacitidine monotherapy and 61 received azacitidine-entinostat combination. Of those 120 patients, 52 had IPSS HR-MDS, 20 IPSS lower-risk (LR)-MDS, 5 non-proliferative CMML (White blood cell [WBC] count $<12 \times 10^9$/l), and 43 had AML-MRC. Supplementary Table 1 summarizes baseline patient and disease characteristics for the IPSS-R cohort. The median follow-up for patients who were still alive (n=8) was 48.5 months. None of the patients belonged to the IPSS-R very-low risk group. Statistically significant differences were observed among the IPSS-R risk groups for ECOG PS (P=0.02), disease type (P<0.0001), RBC transfusion-dependence (P=0.007) and platelet-transfusion dependency (P=0.02). When limited to the patient group for whom the IPSS-R was originally developed (MDS and oligoblastic AML [defined with BM blast percentage up to 30%] and excluding those with CMML or with AML-MRC and >30% BM blasts), IPSS-R risk groups could be assigned to 96 patients (**intended IPSS-R subcohort**).

The FPSS scores could be determined for 116 patients (**FPSS cohort**, 77.3%), of whom 56 received azacitidine and 60 received the combination regimen. Those patients included 51 with IPSS HR-MDS, 21 with IPSS LR-MDS, 3 with non-proliferative CMML, and 41 with AML-MRC. The baseline characteristics and demographics of the FPSS cohort are shown in Supplementary Table 2. Statistically significant differences were noted among the FPSS risk groups for the baseline WBC count (P=0.02), haemoglobin level (P=0.008), disease type (P=0.005) and platelet transfusion-dependence (P=0.009). The median follow-up for patients who were still alive (n=8) was 48.5 months. When limited to the group of patients for whom the FPSS was originally developed (IPSS HR-MDS and oligoblastic AML and excluding those with IPSS LR-MDS, CMML, or AML-MRC with >30% BM blasts), the FPSS scores could be calculated for 73 patients (**intended FPSS subcohort**).

3.2 Survival probabilities by the prognostic model risk groups

A. IPSS-R cohort—Figure 1 depicts the Kaplan-Meier curves according to IPSS-R risk group in the **IPSS-R cohort** (n=120). The very-high (n=70), high (n=26), intermediate (n=14) and low (n=10) IPSS-R groups had significantly different OS (median OS 12.5, 11.3, 20.8 and 36 months, respectively, P=0.005). After adjustment for the ECOG PS and disease type (but not RBC-transfusion dependence and platelet-transfusion dependence because they are highly associated with IPSS-R risk categorization) the prognostic effect of IPSS-R risk category remained statistically significant (P=0.026) in a multivariate Cox model (Supplementary Table 3).

B. FPSS cohort—Figure 2 depicts the Kaplan-Meier survival estimates for the **FPSS cohort** (n=116) according to FPSS risk group. OS was significantly different among the high, intermediate, and low risk FPSS groups (median OS 9.7, 14.7, 25.3 months, respectively, P=0.018). When adjusted for the baseline WBC count, disease type, and platelet transfusion-dependence in a multivariate Cox model, the prognostic effect of FPSS risk groups was no longer statistically significant (P=0.09, Supplementary Table 4).

3.3 Survival probabilities by the prognostic models in cohorts limited to the originally modelled populations

A. Intended IPSS-R subcohort—Restricting evaluation to the 96 patients with MDS and oligoblastic AML (**intended IPSS-R subcohort**), the OS among the very high (n=55), high (n=21), intermediate (n=11) and low (n=9) risk IPSS-R groups remained significantly different (median OS 12.6, 21.5, 19.6, and 40.7 months, respectively, P=0.007, Figure 3). When adjusted for ECOG PS and the disease type in a multivariate Cox regression model, the prognostic effect of IPSS-R risk group remained statistically significant for this subcohort (P=0.025).

B. Intended FPSS subcohort—When limited to the 73 patients with IPSS HR-MDS and oligoblastic AML (**intended FPSS subcohort**), the difference between OS among the FPSS risk groups was statistically insignificant (n = 73; median OS 12, 14.2 and 16.4 months for the high [n=11], intermediate [n=58] and low [n=4] risk FPSS groups, respectively, P=0.52, Figure 4).

3.4 Comparison between survival prediction power of the FPSS and IPSS-R

In the AIC test, smaller values indicate a better model (as long as the AIC value is also lower than the one in the null model i.e. the model without any predictor). The AIC test suggested that the FPSS is not a better survival discriminator than the IPSS-R (687.28 vs. 684.80, respectively, for the 115 patients for whom both FPSS and IPSS-R scores could be calculated).

The model with FPSS (or IPSS-R) together with age as predictors produced a smaller AIC value than the one with FPSS (or IPSS-R) as a single predictor, implying age may be an important addition to the FPSS (and IPSS-R) for predicting OS. This observation was noted during the development of the IPSS-R and was the basis of providing a formula to adjust the IPSS-R for age. Combining FPSS and IPSS-R in the predicting model did not yield a smaller AIC value than either the FPSS or IPSS-R in univariate analysis (687.78), suggesting no extra power in predicting OS with both FPSS and IPSS-R scores combined in the model. Finally, when evaluation was limited to patients with IPSS HR-MDS and oligoblastic AML for whom both the FPSS and IPSS-R could be calculated (n=73), the IPSS-R appeared to be as good a predictor of OS as the FPSS (AIC=380.57 for FPSS and 380.33 for IPSS-R).

In the C-statistic test, results can range from 0 to 1, with 0.5 indicating the model is no better than chance at making a prediction, 1 indicating that the model perfectly predicts the outcome and 0 suggesting that the model is perfect in completely the opposite way. The C-

statistic results further supported the conclusion that FPSS is not superior to the IPSS-R in predicting OS. The C-statistic was higher with IPSS-R than with FPSS, but the 95% confidence interval (95% CI) of the C-statistic from the FPSS model was almost completely overlapping with the one computed, based on IPSS-R in the overall cohort (n=115, IPSS-R: 0.594, 95% CI, 0.493–0.695, FPSS: 0.562, 95% CI, 0.491–0.633) and when restricting to patients with IPSS HR-MDS and oligoblastic AML (n=73, IPSS-R: 0.555, 95% CI, 0.480–0.630, FPSS: 0.528, 95% CI, 0.452–0.604).

3.5 Response Analysis by the prognostic model risk groups

A. IPSS-R cohort and intended subcohort—There was no statistically significant association between the ORR and the IPSS-R risk group in the **IPSS-R cohort** (total n=120, very-high [n=70], high [n=26], intermediate [n=14] and low [n=10] risk groups, with ORRs of 44.3%, 42.3%, 50%, and 80%, respectively, overall P=0.19, Supplementary Table 5). Similarly, no statistically significant differences were found in ORR when the analysis was limited to the patient population with MDS and oligoblastic AML **(intended IPSS-R subcohort)**.

B. FPSS cohort and intended subcohort—There were no statistically significant differences in the ORR between the 3 FPSS risk groups in the overall FPSS cohort (35.3% 48.3%, 58.3% for the high [n=17], intermediate [n=87] and low [n=12] risk FPSS groups, respectively, P=0.45, Supplementary Table 6) or when limited to the patients with HR-MDS and oligoblastic AML (**intended FPSS subcohort**).

Discussion and conclusion

This is the first comparison of the FPSS and IPSS-R in a large cohort of azacitidine-treated MDS patients whose original data were collected prospectively in context of a clinical trial. Consistent with published data, our results indicate that while neither prognostic tool was able to identify patients with differential likelihood of achieving objective clinical response to azacitidine therapy, both models functioned well in separating azacitidine-treated patients into prognostic survival groups. These data confirm the prognostic utility of the IPSS-R in azacitidine-treated patients.

The fact that both the FPSS and the IPSS-R were prognostic for OS among the entire cohort of patients on a trial that included patients with CMML and AML-MRC with BM blasts >30%, raises the question of whether these prognostic tools should be specifically evaluated in these subgroups of patients. In fact, a recent study similarly demonstrated the prognostic utility of the IPSS-R in patients with AML with and without antecedent MDS (Stolzel *et al*, 2014). Nonetheless, our results could be driven by data from patients with HR-MDS and oligoblastic AML, who constituted the majority of the patients.

When we limited multivariate analysis to the group of patients for whom the FPSS was developed (IPSS HR-MDS and oligoblastic AML [n=73]), there were no statistically significant differences in OS among the FPSS risk groups. In contrast, when multivariate analysis was limited to the groups of patients for whom the IPSS-R was developed (MDS

and oligoblastic AML [n=96]), the difference in OS among the IPSS-R risk groups remained significantly different.

The impact of the effect of treatment arm (azacitidine monotherapy vs. azacitidine-entinostat combination) was also explored (Supplementary Figures 1 and 2). To address this question, we performed a Cox regression analysis evaluating the interaction between treatment group and the risk stratification for the prediction of OS (i.e. testing the 2-way interaction effect). That test did not show any statistically-significant difference between treatment arms and therefore the results of our analysis were reported by combining treatment arms.

Although the IPSS-R was developed using an untreated-patient cohort, our results indicate that the FPSS is not a better survival discriminator than the IPSS-R for azacitidine-treated patients. Still, several limitations are present in our analysis that makes this observation inconclusive. First, the FPSS was developed for patients who received the standard regimen of azacitidine (75 mg/m^2/day) for 7 days, while all patients in this analysis received azacitidine at 50 mg/m^2/day for 10 days, and approximately half of them received entinostat. Second, evaluation of peripheral blood blasts was not done systematically, and therefore patients excluded due to missing values could have biased the results. Third, the patients evaluated in IPSS-R analysis included patients with IPSS intermediate-1 and low risk scores, which were not included in the original development of the FPSS and therefore could have systematically affected the results by improving the accuracy of the IPSS-R. Fourth, as indicated earlier, the small sample size, especially in the low-risk FPSS group, in the cohorts and subcohorts means that these results should be interpreted with caution.

A prognostic/predictive clinical model or biomarker that identifies the differential likelihood of benefiting from azacitidine therapy at baseline remains a clinical and research priority (Zeidan *et al*, 2013, Zeidan & Komrokji, 2013). Despite several reports of potential predictive biomarkers, no baseline laboratory or clinical parameters consistently predicted benefit to azacitidine therapy (Steensma, 2012, van der Helm *et al*, 2011, Itzykson *et al*, 2011a).

Our data confirm the prognostic value of the IPSS-R and FPSS for OS in azacitidine-treated MDS patients. In our cohort, the FPSS does not seem to offer any advantage over the IPSS-R in prognostication of OS among azacitidine-treated MDS patients. Nonetheless, due to the previously mentioned limitations of this analysis, both prognostic tools warrant further evaluation as baseline predictors that can possibly define subgroups of patients with lower probabilities of clinical benefit from azacitidine therapy who might be candidates for alternative upfront therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Disclosures

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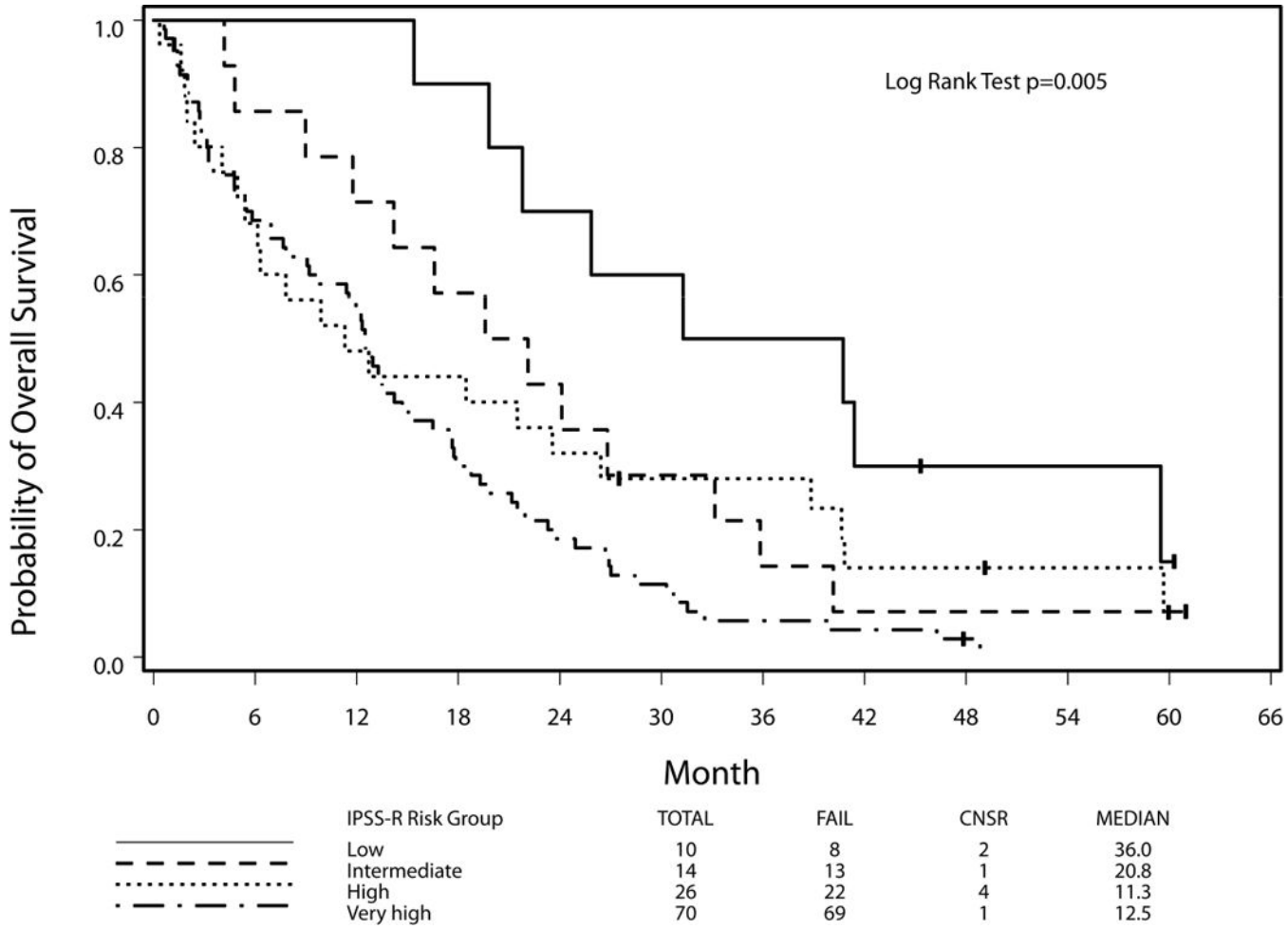

Figure 1.

Kaplan-Meier estimates of probabilities of overall survival for all the patients for whom the revised International Prognostic Scoring System (IPSS-R) scores could be calculated (n=120, the IPSS-R cohort). CNSR, censored.

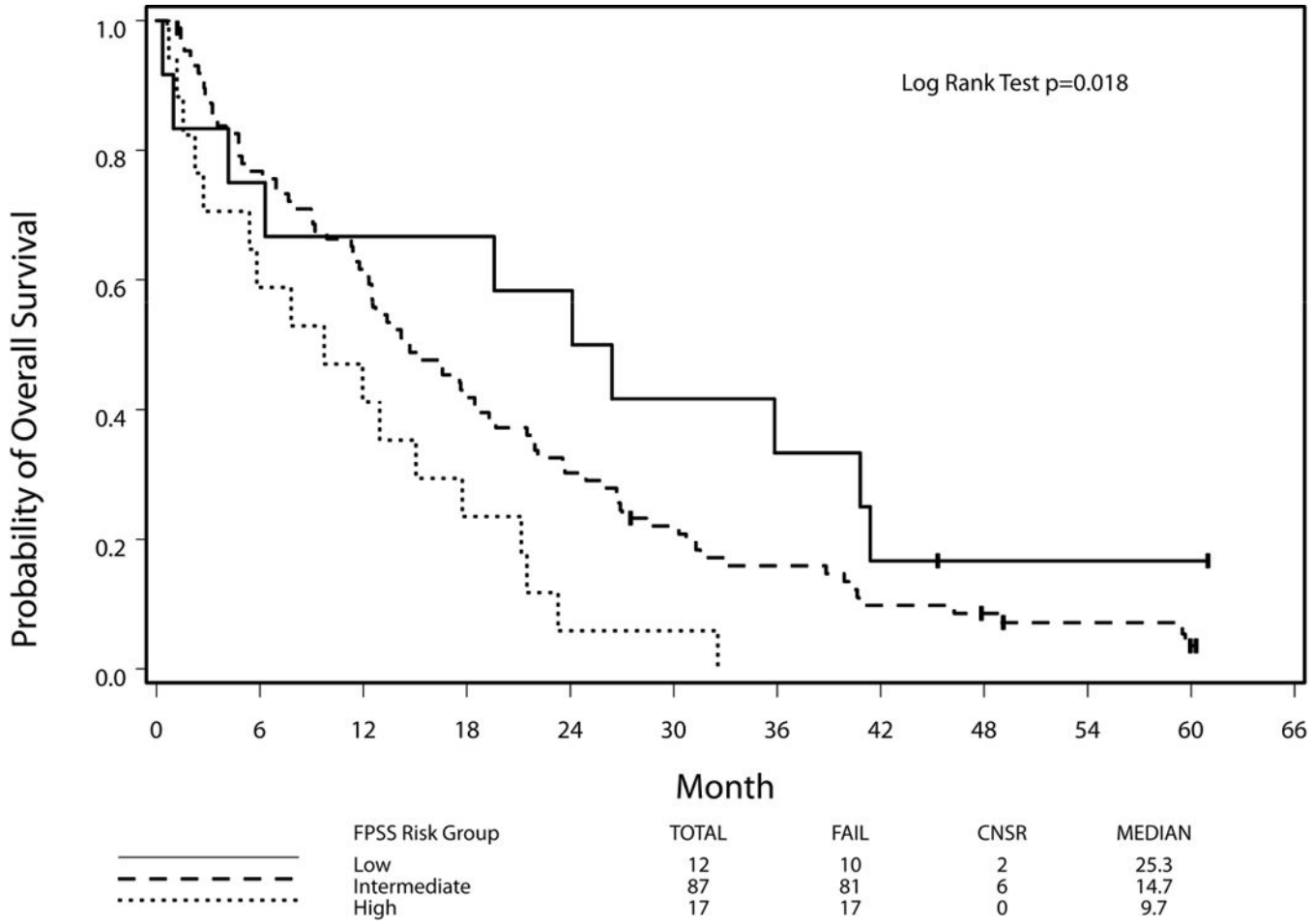

Figure 2.

Kaplan-Meier estimates of probabilities of overall survival for all the patients for whom the French Prognostic Scoring System (FPSS) scores could be calculated (n=116, the FPSS cohort). CNSR, censored.

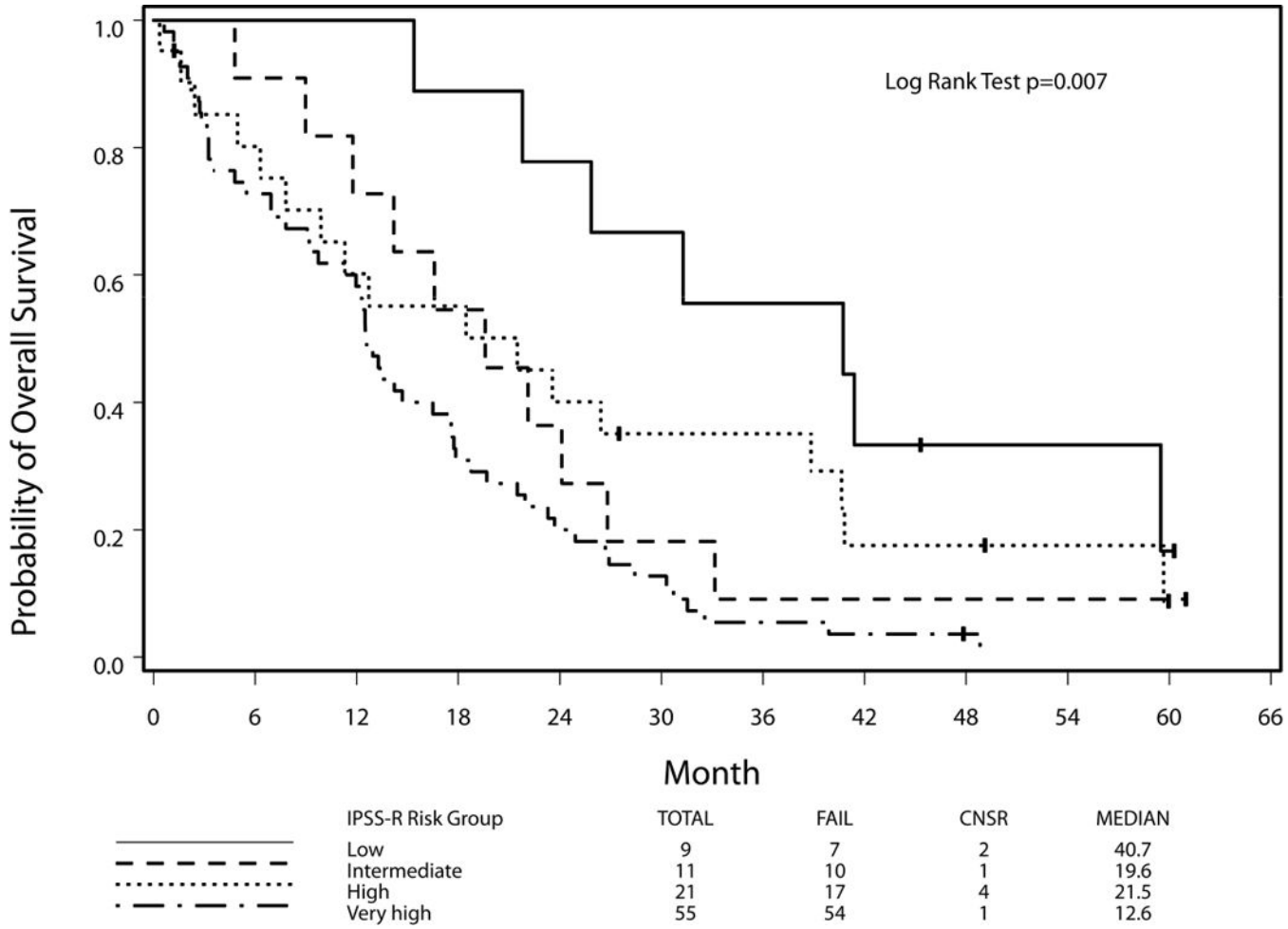

Figure 3.

Kaplan-Meier estimates of probabilities of overall survival for the patients with myelodysplastic syndromes and oligoblastic acute myeloid leukaemia (≤30% bone marrow blasts) for whom the revised International Prognostic Scoring System (IPSS-R) scores could be calculated (n=96, the intended IPSS-R subcohort). CNSR, censored.

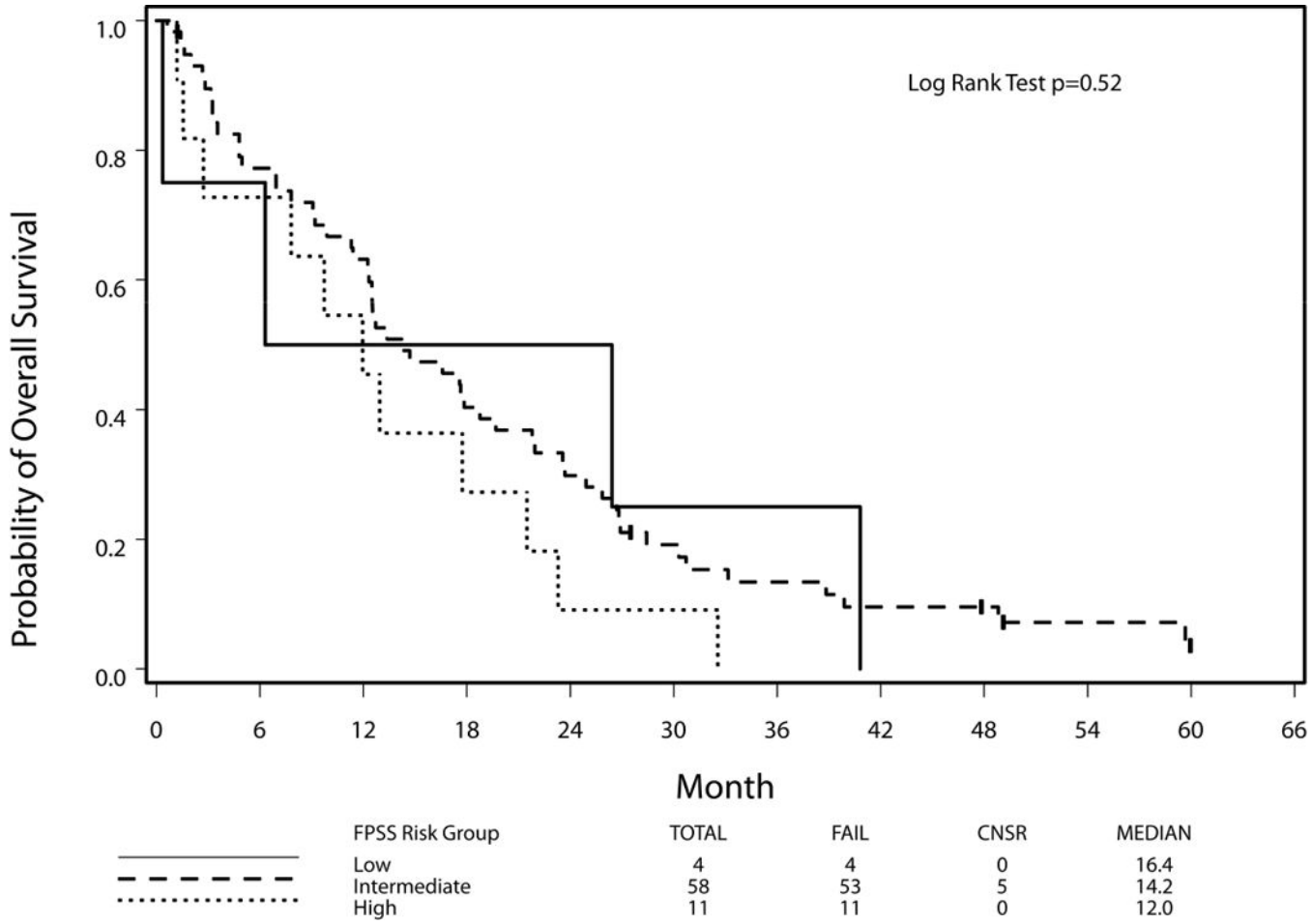

Figure 4.

Kaplan-Meier estimates of probabilities of overall survival (OS) for the patients with higher-risk myelodysplastic syndromes and oligoblastic acute myeloid leukaemia (≤30% bone marrow blasts) for whom the French Prognostic Scoring System (FPSS) scores could be calculated (n=73, intended FPSS subcohort). CNSR, censored.