SUPPLEMENTAL FILES

SUPPLEMENTAL METHODS

Patients and Treatment Protocol

The detailed treatment protocols and eligibility criteria for HOVON trials were described previously.[1,2] All HOVON patients received intensive chemotherapy induction followed by risk-based assignment to either chemotherapy or stem cell transplantation as consolidation treatment. Patients from the MLL cohort were treated either with intensive chemotherapy, non-intensive chemotherapy or were given supportive care, all according to the standard treatment protocols in Germany. For survival analyses only MLL patients treated with intensive chemotherapy were included, in combination with all HOVON patients. All three HOVON protocols (H42A, H92 and H102) included the same therapeutic backbone with high dose chemotherapeutics and investigational drugs. Specifically, H102 study, included patients 18 to 65 years of age, investigated Clofarabine, H92 randomly assigned Laromustine as investigational drug while in H42A, patients 18 to 60 years of age, received similar induction chemotherapy but were randomly administered G-SCF. The MLL patients were treated with the same 7+3 backbone as the HOVON patients without the addition of an investigational drugs. No significant differences in overall survival were found between HOVON (N=889) and intensively treated MLL patients (N=334; Figure S9A), which may be expected since, the investigational drugs did not render survival benefits. In addition, we included an analysis of patients who achieved complete remission only since for both H42A (N=133) and H92 (N=43) only patients with complete remission were included in the current study (due to lack of availability of data on the presence of SF mutations in patients who did not reach CR from H42A and H92 studies). It should be noted that the majority of patients in our study were treated on the H102 protocol (N=889, including both CR and non-CR patients) and therefore the relatively small number of patients from H42A and H92 result in only a minor overrepresentation of CR patients in our cohort, which is not expected to substantially affect the conclusions. Accordingly, all patients with complete remission presented comparable outcome for both HOVON and MLL patients (Figure S9B).
A specific subgroup of patients was defined as secondary AML and included patients with antecedent myeloid disorder (N=61). Since this is supposed to be a subgroup with substantially different characteristics, they were analysed separately together with MDS (N=72) and treatment related AML (N= 43; Supplemental Table S6).

Sample preparation

Mononuclear cell fraction was isolated from bone marrow (BM) or peripheral blood (PB) by Ficoll-Hypaque (Nygaard, Oslo, Norway) density centrifugation and cryopreserved for further processing. For targeted NGS (see below), following thawing, cells were lysed in RLT buffer with the addition of DTT (Qiagen, Venlo, The Netherlands). Subsequently DNA was isolated as described previously.[3]

Mutational profile

The mutational status was determined for 41 commonly mutated genes in AML, including 7 splicing factors (ASXL1, BCOR, BCORL1, BRAF, CBL, CEBPA, CSF3R, CUX1, DNMT3A, ETV6, EZH2, FLT3-ITD, FLT3-TKD, GATA2, IDH1, IDH2, IKZF1, JAK2, KDM6A, KIT, KRAS, NOTCH1, NPM1, NRAS, PHF6, PTPN11, RAD21, RUNX1, SETBP1, SF1, SF3A1, SF3B1, SMC1A, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, U2AF2, WT1, ZRSR2).

Whole genome sequencing

Whole genome sequencing (WGS) libraries were generated from 1µg of DNA extracted from bone marrow or peripheral blood samples using the TruSeq PCR free library prep kit, following the manufacturer's recommendations (Illumina, San Diego, CA, USA) and sequenced on a NovaSeq6000 or HiSeqX Illumina instruments following a 2x150bp paired-end reads standard protocol at a mean depth of coverage of >100x. Bioinformatic analysis of WGS data was performed using Illumina's BaseSpace Sequence Hub and in-house pipelines. Reads were aligned against human genome build GRCh37/hg19 with the tool Isaac3.[4] Variant calling was performed using Strelka2[5] and additional variant annotation was performed using Ensembl VEP.[6] Only exonic (non-synonymous single nucleotide variants (SNVs) and small insertions/deletions (indels)) and variants at splicing acceptor/donor sites were considered in this study. Because matched normal samples were not available, tumor-unmatched normal variant calling was performed using a pool gender-matched DNA (Promega, Madison, WI, USA). In order to remove germline and benign variants as well as technical artifacts from the dataset a strict filtering strategy was applied as described below.

Filtering whole genome sequencing data

Upon variant calling the following in-house filtering strategy[7] was applied to remove sequencing artifacts as well as germline and likely benign variants, resulting in a dataset consisting of reliable and likely somatic, pathogenic variants.

Sequencing artifacts

Repetitive regions and regions potentially troublesome for variant calling were annotated based on Ensembl repeat database and the Global Alliance for Genomics and Health (GA4GH) database. Firstly, variants located in regions of established low confidence variant calling (as specified in Genome in a Bottle Consortium using sample NA12878/HG001, https://github.com/genome-in-a-bottle). Subsequently, we discarded variants with low frequency (VAF < 15%) located in low complexity regions (homopolymers), tandem repeats (i.e. microsatellites), segmental duplications or repetitive regions interspersed throughout the genome (i.e. transposable elements). Finally, variants supported by ≤ 3 reads for the alternative allele as well as with the total depth of coverage ≤ 5 were removed from downstream analysis.

Germline variants

First, variants with the global population frequency ≥ 0.001 (based on the genome aggregation database; gnomAD) were discarded. Next, variants labelled as germline in ClinVar or COSMIC databases were filtered out. Finally, variants not well annotated in hematological malignancies with a VAF between 40-60% or > 90% in all samples were eliminated. This strategy was applied in order to remove as many of the germline variants as possible although it should be noted that due to the lack of matched germline control some residual germline variants are likely to be retained in our dataset. However, since this study focuses on genes recurrently mutated in AML these residual germline variants are not expected to affect the analysis.

Likely benign variants

First, variants listed as benign/likely benign in ClinVar database were removed. Subsequently, we used an in-house developed tool HePPy (Hematological Predictor of Pathogenicity)[8] to remove missense variants with HePPy score < 0.75 (indicating low pathogenicity).

Statistical Analysis

In our study, OS was defined as time from the initial diagnosis to death or last follow-up. EFS was defined as time from initial diagnosis to an event (refractoriness, relapse, death or last follow-up, whichever occurred first). In the multivariable Cox proportional hazards model, the prognostic value of SF mutations was evaluated in the context of demographic and clinical variables (including age, gender, type of AML, white blood cell count, type of stem cell transplantation administered) as well as the ELN 2017 risk classification or modified ELN 2017 classification (all of which were also significantly associated with OS and EFS in univariable Cox model, Supplemental Table S8). In order to assess the individual and combined prognostic value of *RUNX1* and *ASXL*1 with SF mutations, a modified ELN 2017 classification was generated by excluding *RUNX1* and *ASXL*1 from the list of genetic criteria due to their frequent co-occurrence with SF mutations (hence patients carrying these mutations were re-classified based on the remaining criteria). The proportional hazard assumption was evaluated for each variable using the Schoenfeld test and upon examination of the plots of Schoenfeld residuals. Type of stem cell transplantation violated the proportional hazard assumption and therefore it was used as strata variable in all the multivariable Cox regression models (for variables used in the model as strata the statistics are not calculated and therefore, they do not appear in the results). In addition, the interaction between SF mutations and *RUNX1* variables violated the proportional hazard assumption and was additionally evaluated as time-dependent co-variate. The Akaike Information Criterion (AIC) was used to compare the fit of the baseline models with the fit of models containing variables of interest (SF mutations or their interaction with other genetic mutations). This AIC criterion informs not only about the goodness of fit of the model but also penalizes on the number of variables in the model which makes it an attractive method to compare models (the lower the AIC value the better, regardless of the magnitude of difference). To further substantiate the differences in the fit of the models, we have additionally performed ANOVA analyses to compare the fit of the baseline and new model for each tested variable. In all analyses p-value < 0.05 was considered statistically significant (for Fisher's test the 0.05 cut-off was applied to BH-corrected p-values). All statistical analyses were carried out in R version 3.6.3/R studio version 1.2.5, including the following packages: survminer (version 0.4.6)[9], survival (version 3.1-11, https://CRAN.R-project.org/package=survival)[10], ggplot2 (version 3.2.1)[11], ComplexHeatmap (version 2.2.0)[12]. The patient numbers in particular analyses vary depending on the amount of available data for specific variables.

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SUPPLEMENTAL RESULTS

Study Design

In this study, two independent cohorts of AML patients were included (the HOVON and MLL cohort, see Materials and Methods in the main paper). Acknowledging the heterogenous origin of our cohort, the genetic landscape as well as clinical features and treatment outcome of patients of both cohorts were carefully compared to assure that the inter-cohort heterogeneity will not bias the analysis.

The mutational profiles of patients included in both cohorts were primarily defined based on routine molecular diagnostics. In case of MLL patients, molecular diagnostics were additionally complemented by whole genome sequencing (WGS). The routine diagnostics data for 430 patients of the HOVON dataset were complemented by targeted sequencing using Illumina TruSight Myeloid Panel. The complete genetic landscape of both HOVON as well as MLL patients was found to be consistent and typical of AML with frequencies of cytogenetic and molecular aberrations being consistent with those reported in previous studies (data not shown).[1,2] In agreement, no significant differences in overall survival were found between HOVON (with all patients treated with intensive chemotherapy) and intensively treated MLL patients (Figure S9A). The experimental drugs included in HOVON studies (Clofarabine, Laromustine and G-SCF) did not improve treatment outcome, corresponding previously reported results (more details regarding treatment protocols can be found in the methods section).[3-5] Altogether, this cohort of 1447 patients, of which 1223 were treated with intense chemotherapy, allowed us to address our research questions, including the assessment of effects of relatively low frequency events such as SF mutations in subgroups of patients, and maximized the benefits to be derived from existing cohort studies.

Co-occurring SF mutations

Nine patients in the analyzed cohort had coinciding mutations in two different SF genes (Supplemental Table S5). In almost all cases a common (recurrent) allele for a particular SF was paired with a less common allele of the second SF. Furthermore, these patients were almost exclusively over 65 years of age and in majority presented with mutations in *ASXL1*. Interestingly, a recent study uncovered that less common alleles with reduced effects on alternative splicing were enriched in patients with double SF mutations as compared to single mutants.[2]

The Influence of Gene Interactions on Survival in Younger AML Patients

It was previously shown that in AML patients younger than 60 years harboring *RUNX1* mutations had an independent negative prognostic value.[6] Therefore, we assessed the association of the interaction between SFmut4 (as well as *SRSF2* mutations) and *RUNX1* mutations within this subgroup of patients (Figure S10). Again, the co-occurrence of *SRSF2* or SFmut4 with *RUNX1* mutations was associated with adverse outcome, while the presence of *RUNX1* mutations without SFmut4 or *SRSF2* mutations did not indicate inferior survival. In this subset of patients (with age below 60 years) the observed associations were even stronger than in the total cohort.

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SUPPLEMENTAL TABLES

Supplemental Table 1. Additional Patient Characteristic	
Prior Disease, n (%)	
None	1079 (88.2)
Hematological Disorder	68 (5.6)
Other Cancer	53 (4.3)
Other Disease	1 (0.1)
Missing	22 (1.8)
Prior Treatment, n (%)	
None	1139 (93.1)
Chemo- or Radiotherapy	60 (4.9)
Missing	24 (2.0)

Table S1. Additional characteristics of patients treated with intensive chemotherapy.

FAB, French American British Classification; RAEB, Refractory Anemia with Excess Blasts.

Gene	Evaluated cases	Positive cases	Negative Cases	Percentage Positive (among evaluated)	Percentage Positive (among total cases)
SF1	558	2	556	0.36	0.14
SF3A1	558	1	557	0.18	0.07
SF3B1	1447	41	1406	2.83	2.83
SRSF2	1447	148	1299	10.23	10.23
U2AF1	988	31	957	3.14	2.14
U2AF2	558	2	556	0.36	0.14
ZRSR2	988	15	973	1.52	1.04
SFmut7	661	231	430	34.90	15.96
SFmut4	1039	229	810	22.00	15.80

Table S2. The frequencies of SF mutations.

Table S3 and S4 can be found in attached Excel File.

Tables S3, S4 and S6-S13.xlsx

Sample ID	Gender	Age	SF Mutations (VAF)	Other Mutations (VAF)	Cytogenetics and Karyotype
#1	M	67,9	*SRSF2* P95H (0.4693) *SF3B1* T871I(0.3964)	*IDH2* (0.3885), *RUNX1* (0.1513), *SMC3* (0.4646)	Trisomy 11
#2	M	75,1	*SRSF2* P95H (0.5407) *SF1* G497S (0.4834)	*ASXL1* (0.5192), *NRAS* (0.1724), *TET2* (0.9794)	Normal Karyotype
#3	F	84	*SRSF2* P95H (0.5229) *SF1* K341N (0.4877)	*ASXL1* (0.2857), *TET2* (0.4154), *WT1* (0.3875)	Trisomy 8
#4	M	78,3	*SRSF2* P95H (0.1053) *ZRSR2* R169X (0.2449)	*CUX1* (0.092), *IDH1**, *TET2* (0.381)	Normal Karyotype
#5	F	63,3	*SF3B1* K666N (0.4567) *ZRSR2* G438R442dup (0.4713)	*NRAS* (VAF 0.0989)	Monosomy 7
#6	M	80,3	*SF3B1* D781Q (0.3364) *U2AF2* - (0.1132)	*ASXL1* (0.4302), *RUNX1* (0.2804)	Normal Karyotype
#7	M	80,1	*U2AF1* Q157P (0.2595) *ZRSR2* Q120RfsX10 (0.7391)	*ASXL1* (0.4145), *KRAS* (0.0693)	Del7q
#8	M	64,6	*U2AF1* Q157P (0.4142) *ZRSR2* S445R448dup (1)	*ASXL1* (0.4057), *BCOR* (0.0506), *EZH2* (0.4828), *FLT3*^{ITD} (AR >0.5), *RUNX1* (0.4706), *SMC1A* (0.8116), WT1 (0.5263)	Trisomy 8
#9*	F	45	*SF3B1* - *U2AF1* -	*RUNX1, NRAS, STAG2*	Trisomy 8

Table S5. Characteristics of patients with co-occurring SF mutations at diagnosis. Note: Copy number variation data was not included in the analysis and therefore VAFs should be interpreted with caution. * - no VAF data available; Male; F, Female; VAF, Variant Allele Frequency.

Tables S6-S13 can be found in attached Excel File.

Tables S3, S4 and S6-S13.xlsx

SUPPLEMENTAL FIGURE LEGENDS

Figure S1. Overall survival of AML patients in the relation to the presence of individual SF mutations. Kaplan-Meier curves for overall survival in relation to the mutation status of *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *SF3A1* or *U2AF2* are depicted.

Figure S2. Event-free survival of AML patients in the relation to the presence of individual SF mutations. Kaplan-Meier curves for event-free survival in relation to the mutation status of *SRSF2*, *SF3B1*, *U2AF1*, *ZRSR2*, *SF3A1* or *U2AF2* are depicted.

Figure S3. The influence of SF mutations on survival within ELN risk groups. The figure depicts Kaplan-Meier curves for event-free survival and overall survival in relation to SFmut4 status (A), mutation status of *SRSF2* (B) or mutation status of *SF3B1* (C) within the favorable, intermediate or adverse risk groups as defined by the ELN 2017 classification.

Figure S4. Multivariable analysis of overall survival of AML patients in relation to the presence of SF mutations. A,B. - Multivariable Cox regression analysis of overall survival in relation to SFmut4 with complete (A) and modified (B) ELN 2017 classification. In the modified ELN 2017 classification *RUNX1* and *ASXL1* mutations were excluded, so that patients carrying *RUNX1* or *ASXL1* mutations were re-classified based on the presence of the rest of aberrations in this classification system. Type of stem cell transplantation violated the proportional hazard assumption and therefore it was used as strata variable in all the multivariable Cox regression models (for variables used in the model as strata the statistics are not calculated and therefore, they do not appear in the results). WBC – white blood cell count; sAML – secondary AML, tAML - treatment-related AML.

Figure S5. Survival of AML patients in relation to the presence of a mutation in *RUNX1* or *ASXL1*. A - Multivariable Cox regression analysis of event-free (left) or overall survival (right) in relation to mutations in *RUNX1* including modified ELN 2017 classification. B - Multivariable Cox regression analysis of event-free (left) or overall survival (right) in relation to mutations in *ASXL1* including modified ELN 2017 classification. In the modified ELN 2017 classification *RUNX1* and *ASXL1* mutations were excluded, so that patients carrying *RUNX1* or *ASXL1* mutations were re-classified based on the presence of the rest of aberrations in this classification system. In both models type of stem cell transplantation was included as strata. WBC – white blood cell count; sAML – secondary AML, tAML - treatment-related AML.

Figure S6. Influence of interactions between SF mutations and *RUNX1* as well as *ASXL1* mutations on overall survival. A - Kaplan Meier curves for overall survival in relation to the mutation status of *SRSF2* (left) or SFmut4 (right) in combination with *RUNX1* mutations. B - Kaplan Meier curves for event-free and overall survival based on the mutation status of *SRSF2* (left) or SFmut4 (right) in combination with *ASXL1* mutations.

Figure S7. Analysis of survival in relation to interactions of SF mutations with *RUNX1* and *ASXL1* mutations in adverse risk category according to ELN 2017 classification. A **-** Kaplan Meier curves for event-free survival (left) and overall survival (right) in relation to the mutation status of *SRSF2* and *RUNX1* within the adverse ELN 2017 risk group. B - Kaplan Meier curves for event-free survival (left) and overall survival (right) in relation to the SFmut4 and *RUNX1* mutations.

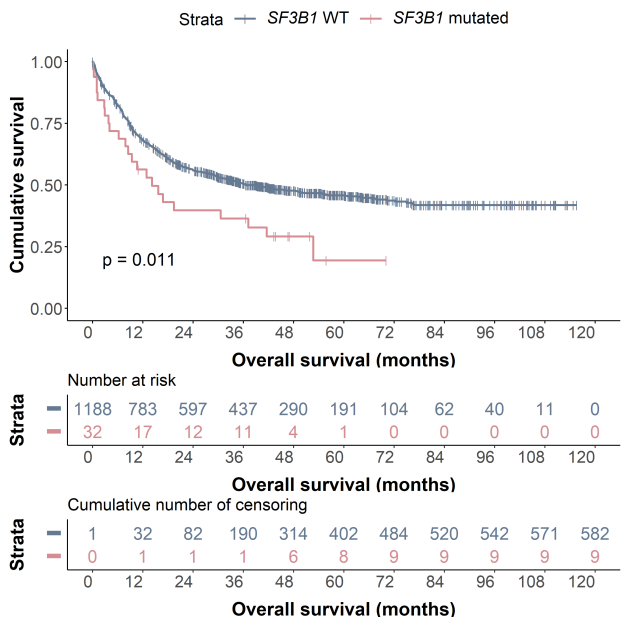
Figure S8. Multivariable analysis of survival of AML patients in relation to the interaction of SF mutations with mutations in *RUNX1* or *ASXL1*. A – Multivariable Cox regression analysis of overall survival in relation to the mutation status of *SRSF2* or SFmut4 and *RUNX1* including modified ELN 2017 classification. B,C – Multivariable Cox regression analysis of event-free (B) and overall survival (C) in relation to the mutation status of *SRSF2* or SFmut4 and *ASXL1* including modified ELN 2017 classification. In the modified ELN 2017 classification *RUNX1* and *ASXL1* mutations were excluded, so that patients carrying *RUNX1* or *ASXL1* mutations were re-classified based on the presence of the rest of aberrations in this classification system. Type of stem cell transplantation violated the proportional hazard assumption and therefore it was used as strata variable in all the multivariable Cox regression models (for variables used in the model as strata the statistics are not calculated and therefore, they do not appear in the results). WBC – white blood cell count; sAML – secondary AML, tAML - treatment-related AML.

Figure S9. Survival analysis of our combined cohort. The figure depicts Kaplan-Meier curves for overall and event free survival in all HOVON and MLL patients (A) and patients with complete remission only (B).

Figure S10. Survival of young and old AML patients in relation to the presence of SF mutations and *RUNX1* mutations. A - Kaplan Meier curves for overall survival in relation to the mutation status of *SRSF2* in combination with *RUNX1* mutations in AML patients younger than 60 years (left), or 60 years and older (right). B - Kaplan Meier curves for overall survival in relation to the presence of SFmut4 in combination with *RUNX1* mutations in AML patients younger than 60 years (left), or 60 years and older (right). C - Kaplan Meier curves for event-free survival in relation to the mutation status of *SRSF2* in combination with *RUNX1* mutations in AML patients younger than 60 years (left), or 60 years and older (right). D - Kaplan Meier curves for event-free survival in relation to the presence of SFmut4 in combination with *RUNX1* mutations in AML patients younger than 60 years (left), or 60 years and older (right).

SUPPLEMENTAL FIGURES

Figure S1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Number at risk
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Overall survival (months)
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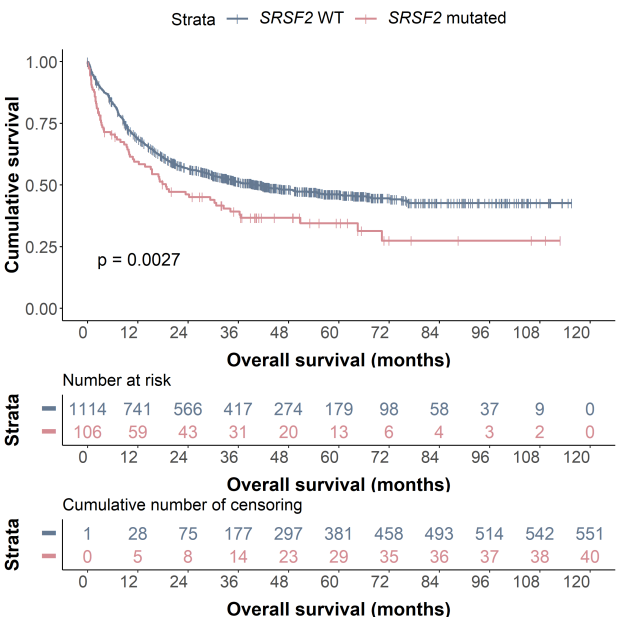
Overall survival (months)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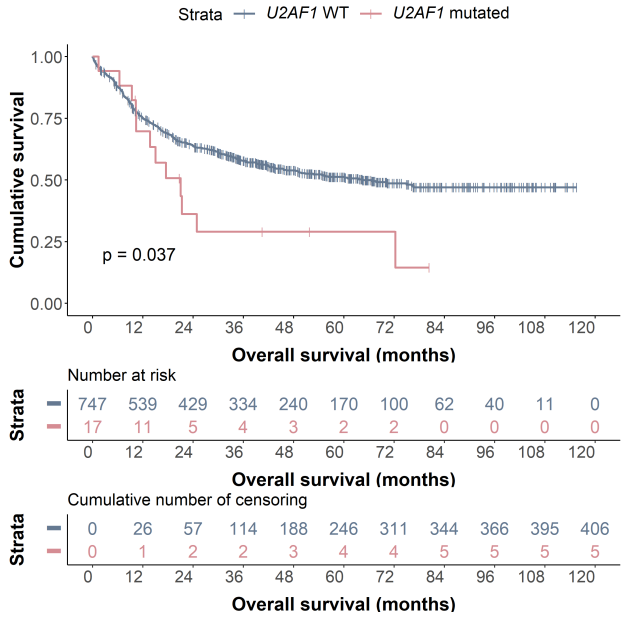
Overall survival (months)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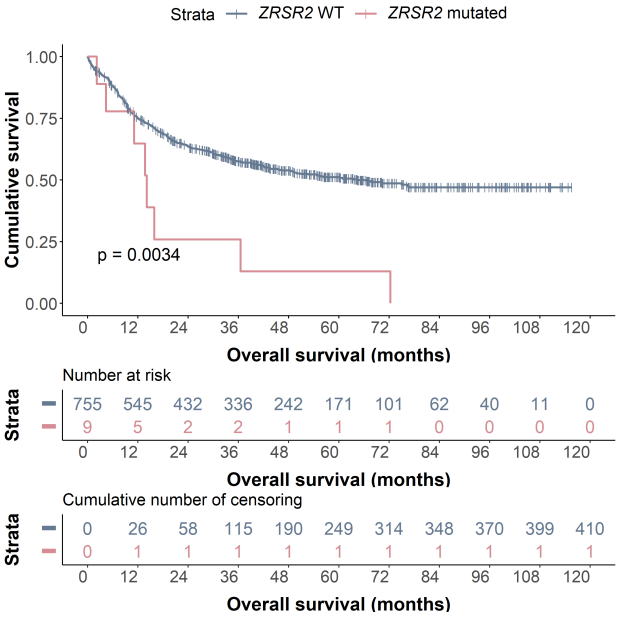
Overall survival (months)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Number at risk
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Overall survival (months)
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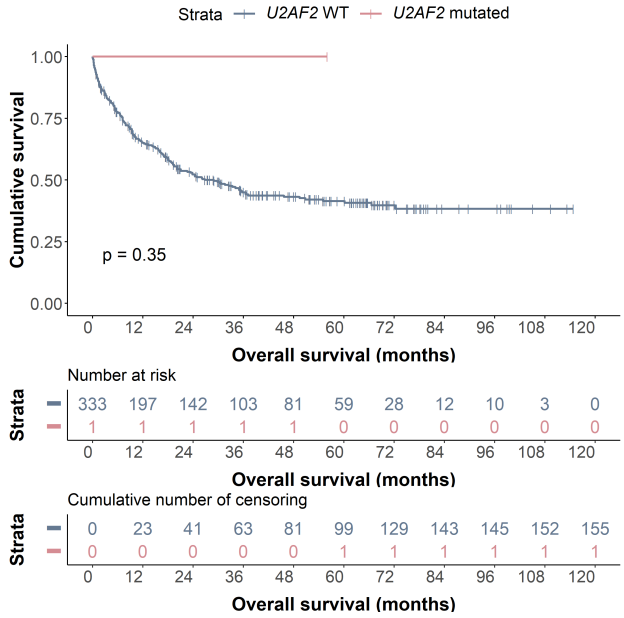
Overall survival (months)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Overall survival (months)
Number at risk
Strata
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Overall survival (months)
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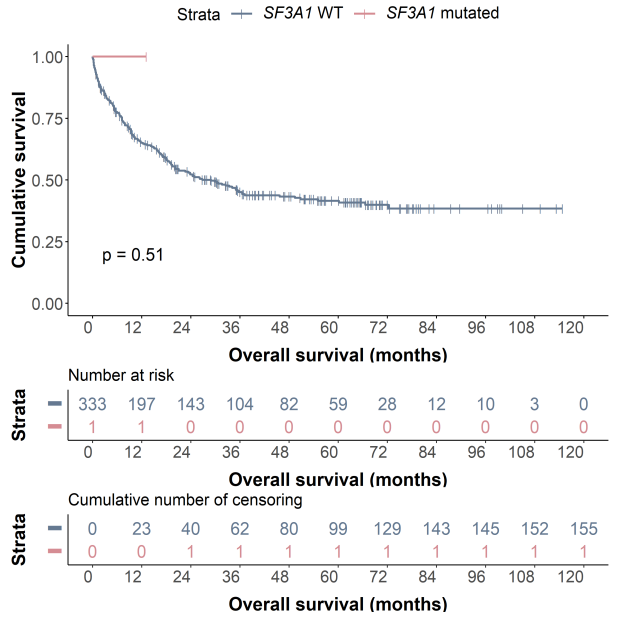
Overall survival (months)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Overall survival (months)
Number at risk
Strata
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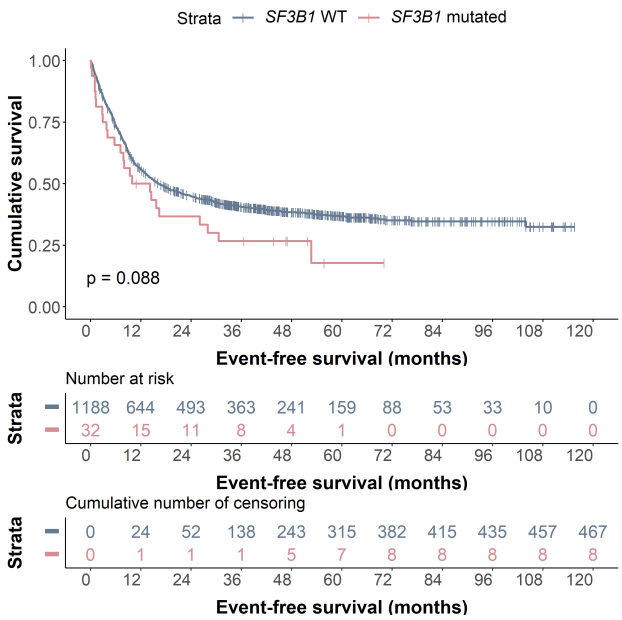
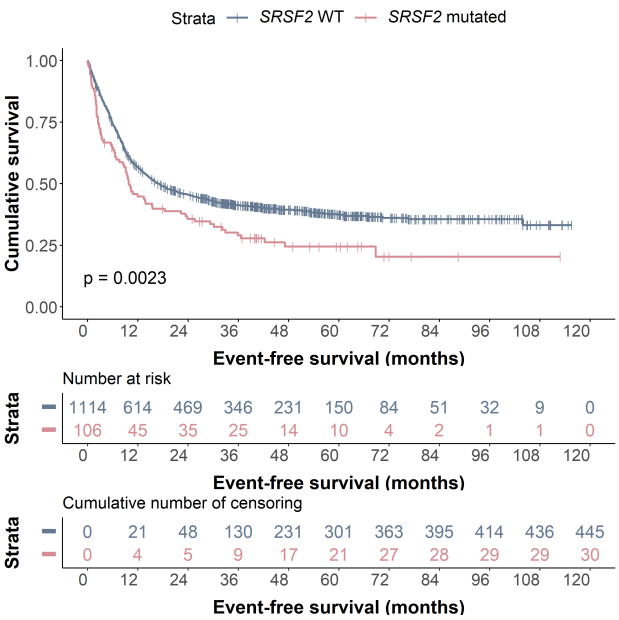
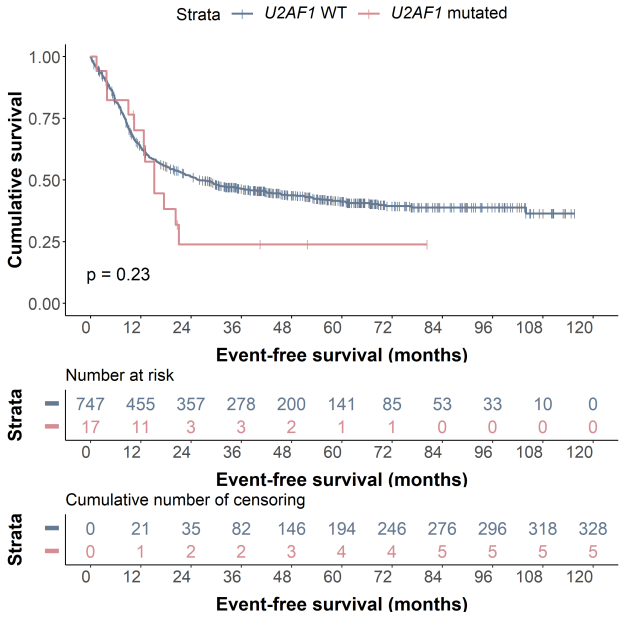
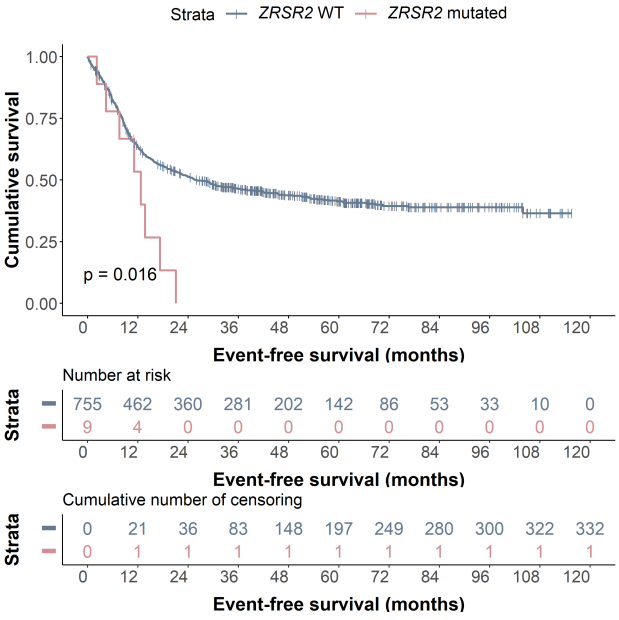
1 1 0 0 0 0 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Overall survival (months)
Cumulative number of censoring
Strata
0 23 40 62 80 99 129 143 145 152 155
0 0 1 1 1 1 1 1 1 1 1
0 12 24 36 48 60 72 84 96 108 120
Overall survival (months)

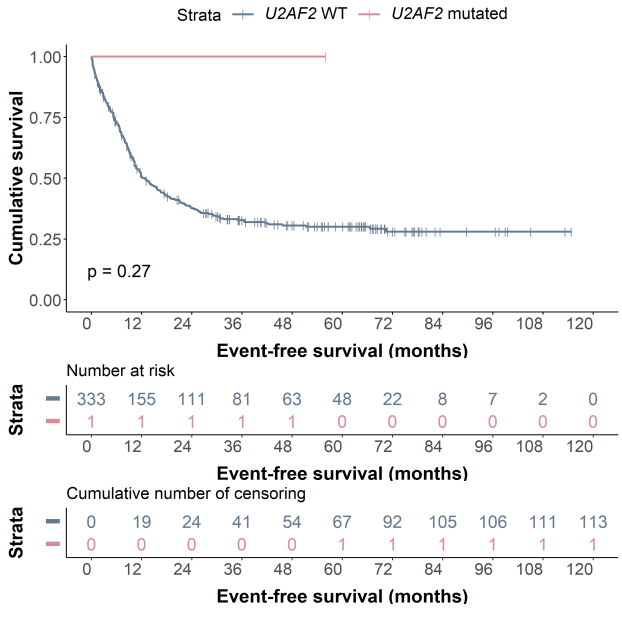
Figure S2


Strata SF3B1 WT SF3B1 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.088
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
1188 644 493 363 241 159 88 53 33 10 0
32 15 11 8 4 1 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 24 52 138 243 315 382 415 435 457 467
0 1 1 1 5 7 8 8 8 8 8
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)


Strata SRSF2 WT SRSF2 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.0023
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
1114 614 469 346 231 150 84 51 32 9 0
106 45 35 25 14 10 4 2 1 1 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 21 48 130 231 301 363 395 414 436 445
0 4 5 9 17 21 27 28 29 29 30
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)


Strata U2AF1 WT U2AF1 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.23
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
747 455 357 278 200 141 85 53 33 10 0
17 11 3 3 2 1 1 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 21 35 82 146 194 246 276 296 318 328
0 1 2 2 3 4 4 5 5 5 5
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)


Strata ZRSR2 WT ZRSR2 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.016
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
755 462 360 281 202 142 86 53 33 10 0
9 4 0 0 0 0 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 21 36 83 148 197 249 280 300 322 332
0 1 1 1 1 1 1 1 1 1 1
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)


Strata U2AF2 WT U2AF2 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.27
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
333 155 111 81 63 48 22 8 7 2 0
1 1 1 1 1 0 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 19 24 41 54 67 92 105 106 111 113
0 0 0 0 0 1 1 1 1 1 1
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)

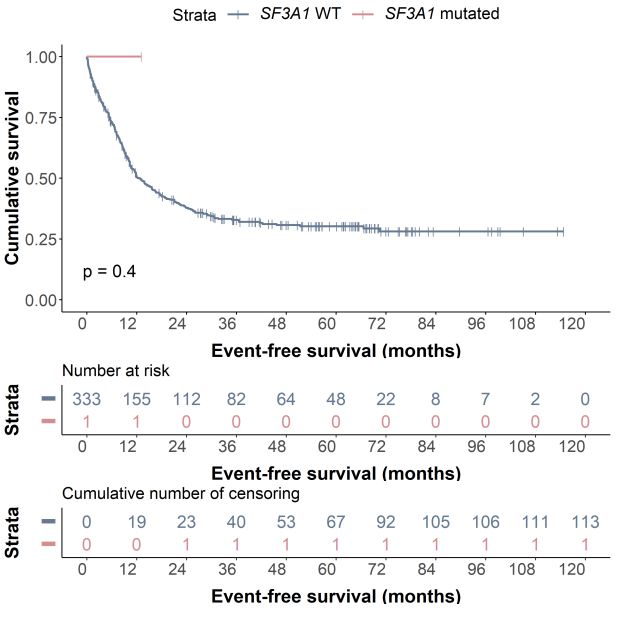

Strata SF3A1 WT SF3A1 mutated
Cumulative survival
1.00 0.75 0.50 0.25 0.00
p = 0.4
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Number at risk
Strata
333 155 112 82 64 48 22 8 7 2 0
1 1 0 0 0 0 0 0 0 0 0
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)
Cumulative number of censoring
Strata
0 19 23 40 53 67 92 105 106 111 113
0 0 1 1 1 1 1 1 1 1 1
0 12 24 36 48 60 72 84 96 108 120
Event-free survival (months)

Figure S3

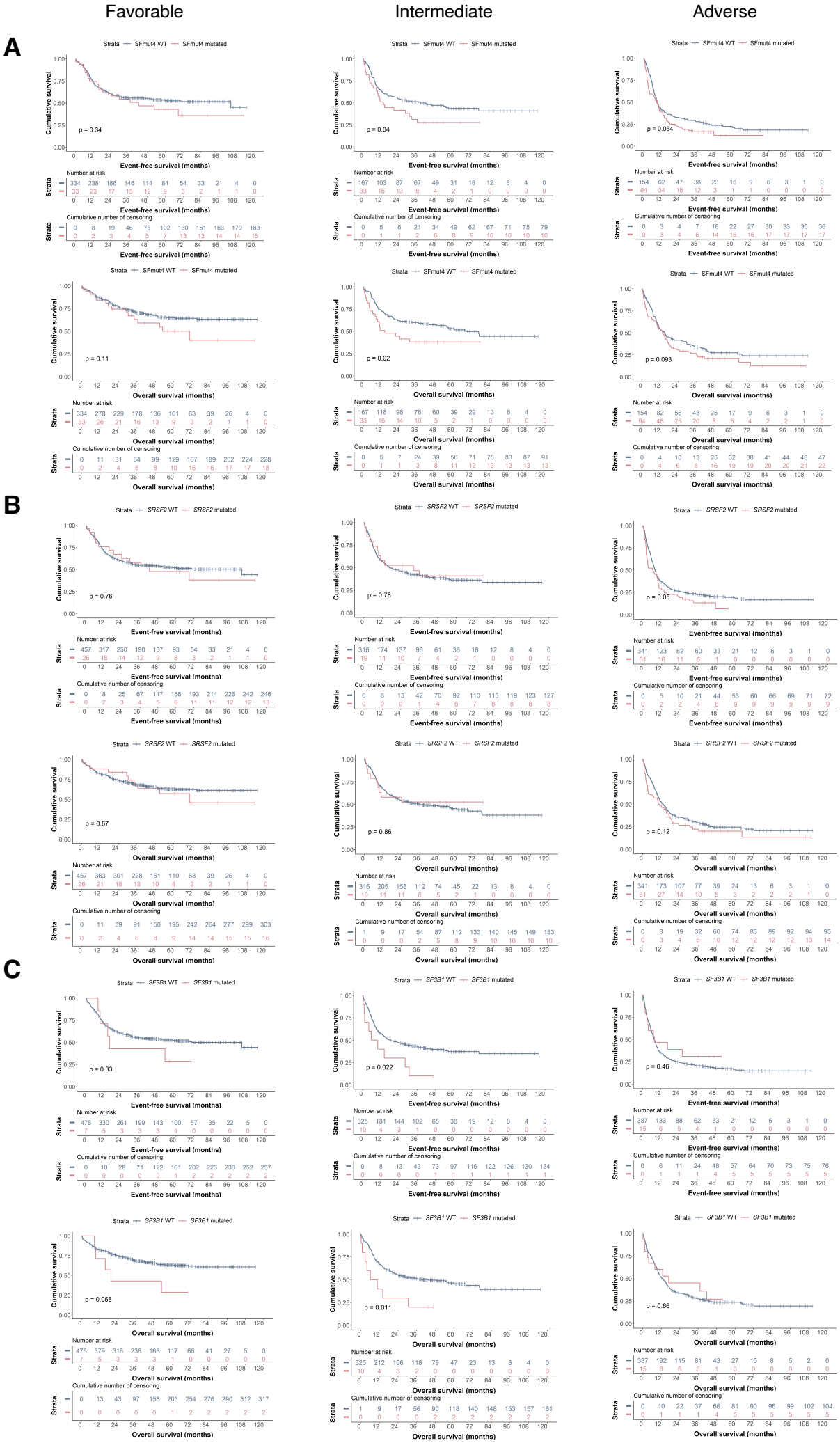
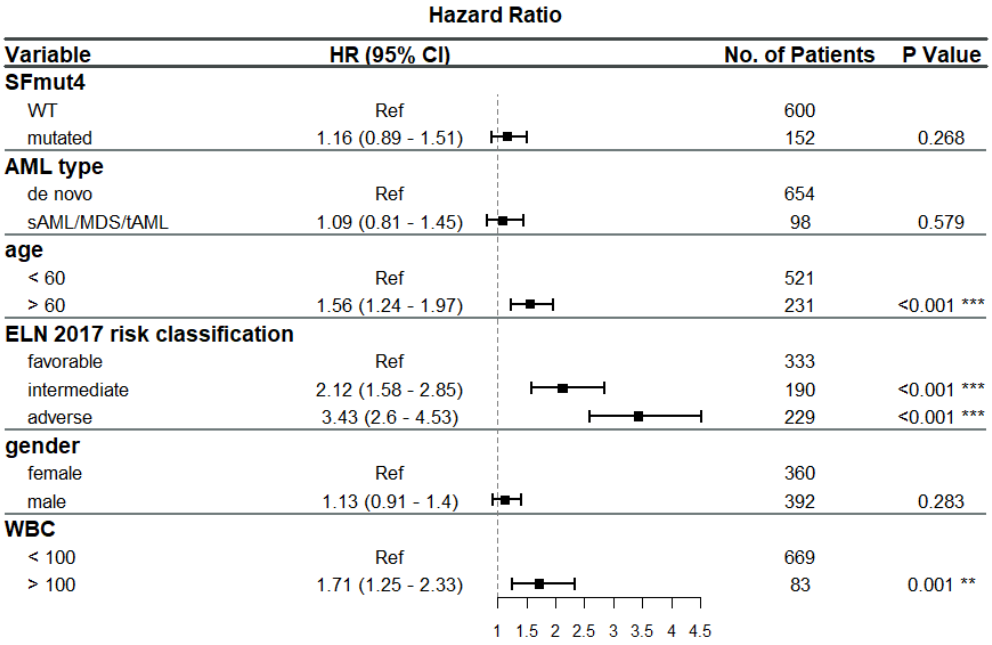

Favorable
Intermediate
Adverse
A
Strata SFmut4 WT SFmut4 mutated
Cumulative survival
p = 0.34
p = 0.04
p = 0.054
Event-free survival (months)
Number at risk
Cumulative number of censoring
p = 0.11
p = 0.02
p = 0.093
Overall survival (months)
B
Strata SRSF2 WT SRSF2 mutated
p = 0.76
p = 0.78
p = 0.05
p = 0.67
p = 0.86
p = 0.12
C
Strata SF3B1 WT SF3B1 mutated
p = 0.33
p = 0.022
p = 0.46
p = 0.058
p = 0.011
p = 0.66

Figure S4

A


Hazard Ratio
Variable | HR (95% CI) | No. of Patients | P Value
SFmut4
WT | Ref | 600 |
mutated | 1.16 (0.89 - 1.51) | 152 | 0.268
AML type
de novo | Ref | 654 |
sAML/MDS/tAML | 1.09 (0.81 - 1.45) | 98 | 0.579
age
< 60 | Ref | 521 |
> 60 | 1.56 (1.24 - 1.97) | 231 | <0.001 ***
ELN 2017 risk classification
favorable | Ref | 333 |
intermediate | 2.12 (1.58 - 2.85) | 190 | <0.001 ***
adverse | 3.43 (2.6 - 4.53) | 229 | <0.001 ***
gender
female | Ref | 360 |
male | 1.13 (0.91 - 1.4) | 392 | 0.283
WBC
< 100 | Ref | 669 |
> 100 | 1.71 (1.25 - 2.33) | 83 | 0.001 **
1 1.5 2 2.5 3 3.5 4 4.5

B

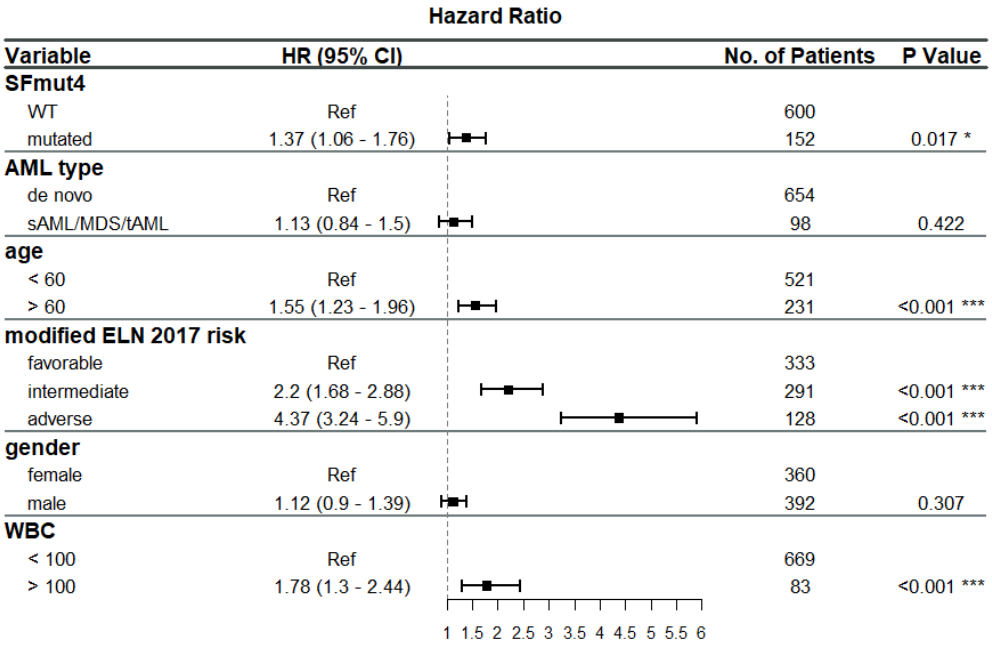

Hazard Ratio
Variable | HR (95% CI) | No. of Patients | P Value
SFmut4
WT | Ref | 600 |
mutated | 1.37 (1.06 - 1.76) | 152 | 0.017 *
AML type
de novo | Ref | 654 |
sAML/MDS/tAML | 1.13 (0.84 - 1.5) | 98 | 0.422
age
< 60 | Ref | 521 |
> 60 | 1.55 (1.23 - 1.96) | 231 | <0.001 ***
modified ELN 2017 risk
favorable | Ref | 333 |
intermediate | 2.2 (1.68 - 2.88) | 291 | <0.001 ***
adverse | 4.37 (3.24 - 5.9) | 128 | <0.001 ***
gender
female | Ref | 360 |
male | 1.12 (0.9 - 1.39) | 392 | 0.307
WBC
< 100 | Ref | 669 |
> 100 | 1.78 (1.3 - 2.44) | 83 | <0.001 ***
1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6

Figure S5

A

Variable	HR (95% CI)	No. of Patients	P Value
RUNX1			
WT	Ref	1022	
mutated	1.13 (0.91 – 1.41)	133	0.264
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.07 (0.87 – 1.32)	171	0.497
age			
< 60	Ref	799	
> 60	1.48 (1.26 – 1.73)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	1.79 (1.47 – 2.17)	461	<0.001 ***
adverse	3.48 (2.81 – 4.31)	246	<0.001 ***
gender			
female	Ref	532	
male	1.25 (1.07 – 1.45)	623	0.004 **
WBC			
< 100	Ref	1044	
> 100	1.87 (1.47 – 2.37)	111	<0.001 ***

Hazard Ratio

1 1.5 2 2.5 3 3.5 4 4.5

Variable	HR (95% CI)	No. of Patients	P Value
RUNX1			
WT	Ref	1022	
mutated	1 (0.79 – 1.27)	133	0.98
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.21 (0.98 – 1.5)	171	0.079
age			
< 60	Ref	799	
> 60	1.57 (1.32 – 1.87)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	2.33 (1.88 – 2.89)	461	<0.001 ***
adverse	4.61 (3.64 – 5.83)	246	<0.001 ***
gender			
female	Ref	532	
male	1.17 (0.99 – 1.38)	623	0.063
WBC			
< 100	Ref	1044	
> 100	1.86 (1.44 – 2.41)	111	<0.001 ***

Hazard Ratio

1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6

B

Variable	HR (95% CI)	No. of Patients	P Value
ASXL1			
WT	Ref	1040	
mutated	1.02 (0.8 – 1.29)	115	0.895
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.08 (0.88 – 1.33)	171	0.473
age			
< 60	Ref	799	
> 60	1.48 (1.26 – 1.75)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	1.82 (1.5 – 2.21)	461	<0.001 ***
adverse	3.53 (2.85 – 4.37)	246	<0.001 ***
gender			
female	Ref	532	
male	1.25 (1.07 – 1.45)	623	0.005 **
WBC			
< 100	Ref	1044	
> 100	1.86 (1.47 – 2.37)	111	<0.001 ***

Hazard Ratio

1 1.5 2 2.5 3 3.5 4 4.5

Variable	HR (95% CI)	No. of Patients	P Value
ASXL1			
WT	Ref	1040	
mutated	0.97 (0.76 – 1.25)	115	0.823
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.22 (0.98 – 1.51)	171	0.076
age			
< 60	Ref	799	
> 60	1.58 (1.32 – 1.88)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	2.34 (1.89 – 2.9)	461	<0.001 ***
adverse	4.62 (3.66 – 5.84)	246	<0.001 ***
gender			
female	Ref	532	
male	1.17 (0.99 – 1.38)	623	0.061
WBC			
< 100	Ref	1044	
> 100	1.86 (1.44 – 2.41)	111	<0.001 ***

Hazard Ratio

1 1.5 2 2.5 3 3.5 4 4.5 5 5.5 6

Figure S6

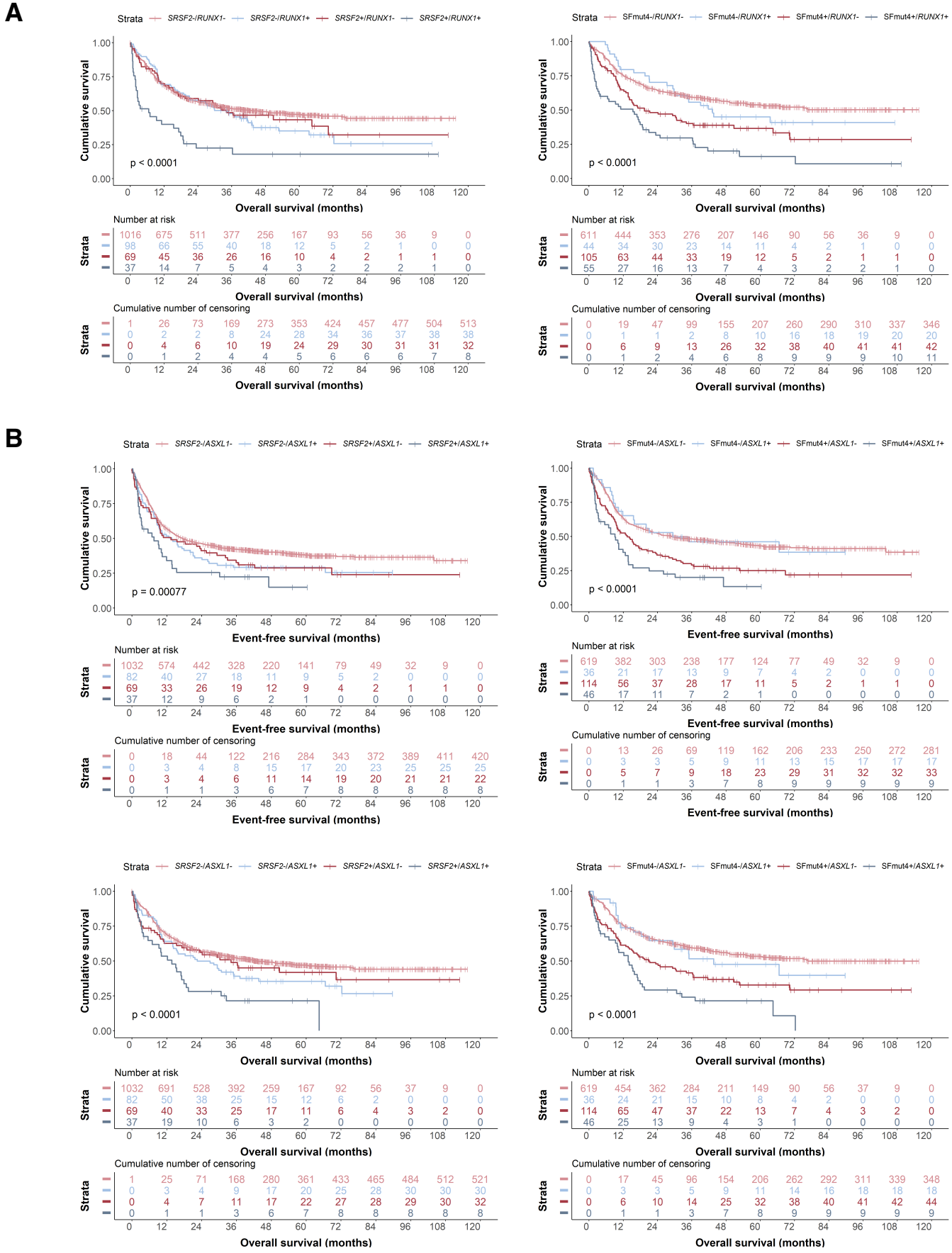

A
Strata SRSF2-/RUNX1- SRSF2-/RUNX1+ SRSF2+/RUNX1- SRSF2+/RUNX1+
Cumulative survival
p < 0.0001
Overall survival (months)
Number at risk
1016 675 511 377 256 167 93 56 36 9 0
98 66 55 40 18 12 5 2 1 0 0
69 45 36 26 16 10 4 2 1 1 0
37 14 7 5 4 3 2 2 2 1 0
Cumulative number of censoring
1 26 73 169 273 353 424 457 477 504 513
0 2 2 8 24 28 34 36 37 38 38
0 4 6 10 19 24 29 30 31 31 32
0 1 2 4 4 5 6 6 6 7 8
Strata SFmut4-/RUNX1- SFmut4-/RUNX1+ SFmut4+/RUNX1- SFmut4+/RUNX1+
p < 0.0001
611 444 353 276 207 146 90 56 36 9 0
44 34 30 23 14 11 4 2 1 0 0
105 63 44 33 19 12 5 2 1 1 0
55 27 16 13 7 4 3 2 2 1 0
0 19 47 99 155 207 260 290 310 337 346
0 1 1 2 8 10 16 18 19 20 20
0 6 9 13 26 32 38 40 41 41 42
0 1 2 4 6 8 9 9 9 10 11
B
Strata SRSF2-/ASXL1- SRSF2-/ASXL1+ SRSF2+/ASXL1- SRSF2+/ASXL1+
p = 0.00077
Event-free survival (months)
1032 574 442 328 220 141 79 49 32 9 0
82 40 27 18 11 9 5 2 0 0 0
69 33 26 19 12 9 4 2 1 1 0
37 12 9 6 2 1 0 0 0 0 0
0 18 44 122 216 284 343 372 389 411 420
0 3 4 8 15 17 20 23 25 25 25
0 3 4 6 11 14 19 20 21 21 22
0 1 1 3 6 7 8 8 8 8 8
Strata SFmut4-/ASXL1- SFmut4-/ASXL1+ SFmut4+/ASXL1- SFmut4+/ASXL1+
p < 0.0001
619 382 303 238 177 124 77 49 32 9 0
36 21 17 13 9 7 4 2 0 0 0
114 56 37 28 17 11 5 2 1 1 0
46 17 11 7 2 1 0 0 0 0 0
0 13 26 69 119 162 206 233 250 272 281
0 3 3 5 9 11 13 15 17 17 17
0 5 7 9 18 23 29 31 32 32 33
0 1 1 3 7 8 9 9 9 9 9
Strata SRSF2-/ASXL1- SRSF2-/ASXL1+ SRSF2+/ASXL1- SRSF2+/ASXL1+
p < 0.0001
Overall survival (months)
1032 691 528 392 259 167 92 56 37 9 0
82 50 38 25 15 12 6 2 0 0 0
69 40 33 25 17 11 6 4 3 2 0
37 19 10 6 3 2 0 0 0 0 0
1 25 71 168 280 361 433 465 484 512 521
0 3 4 9 17 20 25 28 30 30 30
0 4 7 11 17 22 27 28 29 30 32
0 1 1 3 6 7 8 8 8 8 8
Strata SFmut4-/ASXL1- SFmut4-/ASXL1+ SFmut4+/ASXL1- SFmut4+/ASXL1+
p < 0.0001
619 454 362 284 211 149 90 56 37 9 0
36 24 21 15 10 8 4 2 0 0 0
114 65 47 37 22 13 7 4 3 2 0
46 25 13 9 4 3 1 0 0 0 0
0 17 45 96 154 206 262 292 311 339 348
0 3 3 5 9 11 14 16 18 18 18
0 6 10 14 25 32 38 40 41 42 44
0 1 1 3 7 8 9 9 9 9 9

Figure S7

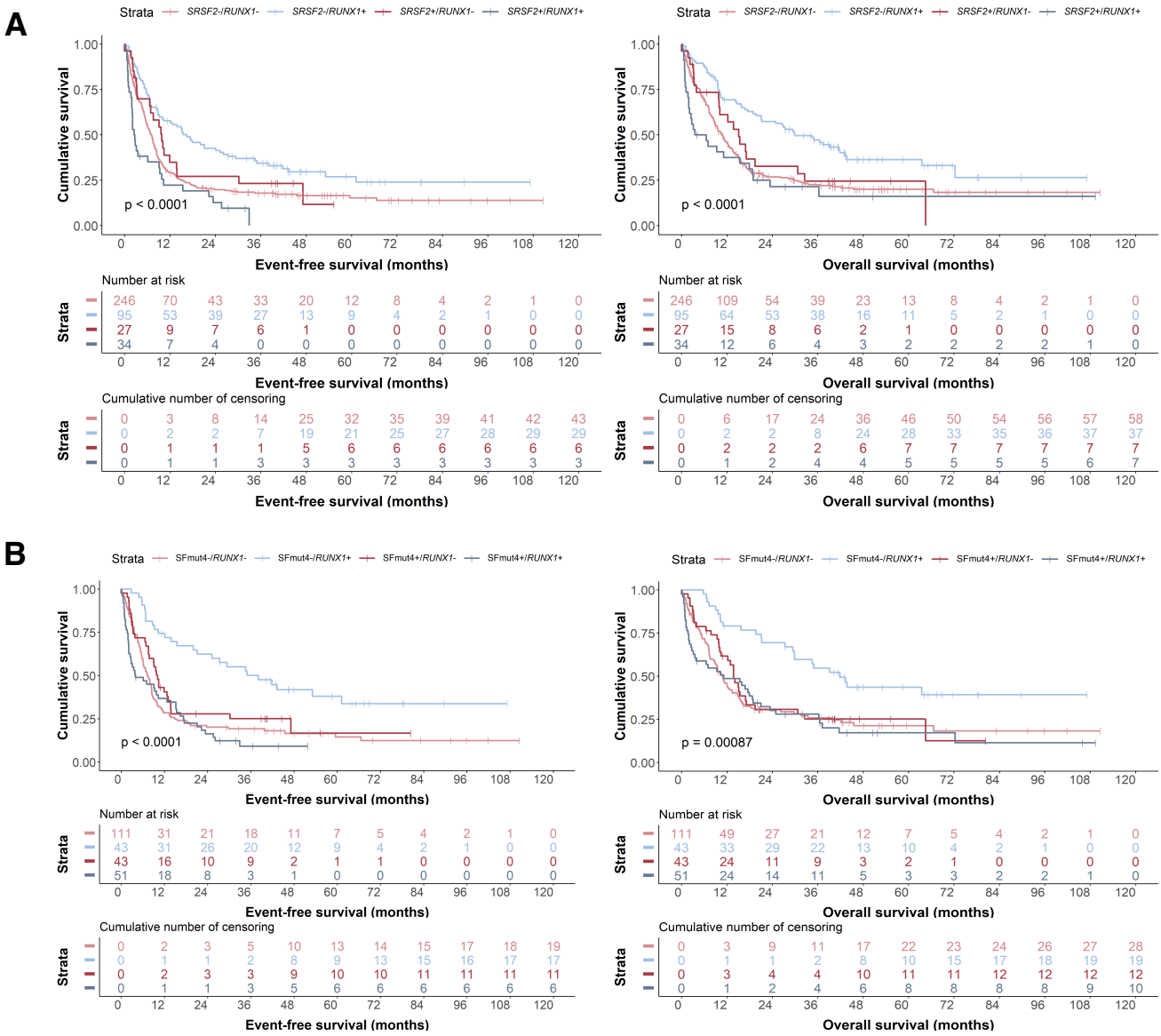
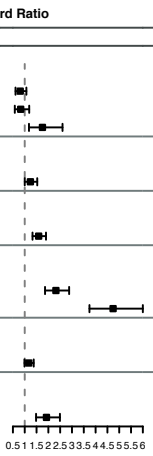

A
Strata SRSF2-/RUNX1- SRSF2-/RUNX1+ SRSF2+/RUNX1- SRSF2+/RUNX1+
Cumulative survival
p < 0.0001
Event-free survival (months)
Number at risk
246 70 43 33 20 12 8 4 2 1 0
95 53 39 27 13 9 4 2 1 0 0
27 9 7 6 1 0 0 0 0 0 0
34 7 4 0 0 0 0 0 0 0 0
Cumulative number of censoring
0 3 8 14 25 32 35 39 41 42 43
0 2 2 7 19 21 25 27 28 29 29
0 1 1 1 5 6 6 6 6 6 6
0 1 1 3 3 3 3 3 3 3 3
Overall survival (months)
p < 0.0001
246 109 54 39 23 13 8 4 2 1 0
95 64 53 38 16 11 5 2 1 0 0
27 15 8 6 2 1 0 0 0 0 0
34 12 6 4 3 2 2 2 2 1 0
0 6 17 24 36 46 50 54 56 57 58
0 2 2 8 24 28 33 35 36 37 37
0 2 2 2 6 7 7 7 7 7 7
0 1 2 4 4 5 5 5 5 6 7
B
Strata SFmut4-/RUNX1- SFmut4-/RUNX1+ SFmut4+/RUNX1- SFmut4+/RUNX1+
Cumulative survival
p < 0.0001
Event-free survival (months)
Number at risk
111 31 21 18 11 7 5 4 2 1 0
43 31 26 20 12 9 4 2 1 0 0
43 16 10 9 2 1 1 0 0 0 0
51 18 8 3 1 0 0 0 0 0 0
Cumulative number of censoring
0 2 3 5 10 13 14 15 17 18 19
0 1 1 2 8 9 13 15 16 17 17
0 2 3 3 9 10 10 11 11 11 11
0 1 1 3 5 6 6 6 6 6 6
Overall survival (months)
p = 0.00087
111 49 27 21 12 7 5 4 2 1 0
43 33 29 22 13 10 4 2 1 0 0
43 24 11 9 3 2 1 0 0 0 0
51 24 14 11 5 3 3 2 2 1 0
0 3 9 11 17 22 23 24 26 27 28
0 1 1 2 8 10 15 17 18 19 19
0 3 4 4 10 11 11 12 12 12 12
0 1 2 4 6 8 8 8 8 9 10

Figure S8

A

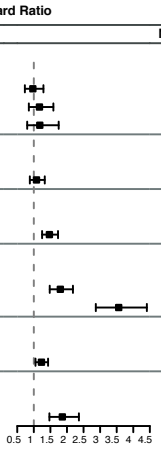
Variable	HR (95% CI)	No. of Patients	P Value
***SRSF2* and *RUNX1* interaction**			
SRSF2–/RUNX1–	Ref	957	
SRSF2–/RUNX1+	0.81 (0.61 – 1.07)	96	0.14
SRSF2+/RUNX1–	0.83 (0.58 – 1.19)	65	0.302
SRSF2+/RUNX1+	1.75 (1.18 – 2.6)	37	0.005 **
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.24 (1 – 1.53)	171	0.05
age			
< 60	Ref	799	
> 60	1.59 (1.33 – 1.9)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	2.32 (1.86 – 2.88)	461	<0.001 ***
adverse	4.74 (3.74 – 6)	246	<0.001 ***
gender			
female	Ref	532	
male	1.17 (0.99 – 1.38)	623	0.07
WBC			
< 100	Ref	1044	
> 100	1.92 (1.48 – 2.49)	111	<0.001 ***



Variable	HR (95% CI)	No. of Patients	P Value
SFmut4 and *RUNX1* interaction			
SFmut4–/*RUNX1*–	Ref	557	
SFmut4–/*RUNX1*+	0.76 (0.49 – 1.18)	43	0.217
SFmut4+/*RUNX1*–	1.14 (0.83 – 1.55)	98	0.419
SFmut4+/*RUNX1*+	1.72 (1.2 – 2.46)	54	0.003 **
AML type			
de novo	Ref	654	
sAML/MDS/tAML	1.18 (0.88 – 1.58)	98	0.265
age			
< 60	Ref	521	
> 60	1.58 (1.25 – 1.99)	231	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	333	
intermediate	2.21 (1.68 – 2.9)	291	<0.001 ***
adverse	4.44 (3.28 – 6.01)	128	<0.001 ***
gender			
female	Ref	360	
male	1.11 (0.89 – 1.38)	392	0.359
WBC			
< 100	Ref	669	
> 100	1.82 (1.33 – 2.5)	83	<0.001 ***

B

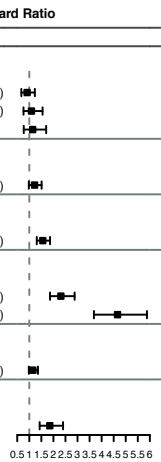
Variable	HR (95% CI)	No. of Patients	P Value
***SRSF2* and *ASXL1* interaction**			
SRSF2–/ASXL1–	Ref	975	
SRSF2–/ASXL1+	0.97 (0.73 – 1.29)	78	0.824
SRSF2+/ASXL1–	1.17 (0.85 – 1.59)	65	0.337
SRSF2+/ASXL1+	1.18 (0.8 – 1.75)	37	0.408
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.08 (0.88 – 1.33)	171	0.455
age			
< 60	Ref	799	
> 60	1.47 (1.25 – 1.73)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	1.8 (1.48 – 2.18)	461	<0.001 ***
adverse	3.56 (2.87 – 4.41)	246	<0.001 ***
gender			
female	Ref	532	
male	1.23 (1.05 – 1.43)	623	0.009 **
WBC			
< 100	Ref	1044	
> 100	1.86 (1.47 – 2.36)	111	<0.001 ***



Variable	HR (95% CI)	No. of Patients	P Value
SFmut4 and *ASXL1* interaction			
SFmut4–/*ASXL1*–	Ref	568	
SFmut4–/*ASXL1*+	0.73 (0.43 – 1.24)	32	0.244
SFmut4+/*ASXL1*–	1.26 (0.96 – 1.64)	106	0.091
SFmut4+/*ASXL1*+	1.36 (0.92 – 1.99)	46	0.12
AML type			
de novo	Ref	654	
sAML/MDS/tAML	0.99 (0.75 – 1.32)	98	0.966
age			
< 60	Ref	521	
> 60	1.55 (1.25 – 1.91)	231	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	333	
intermediate	1.61 (1.26 – 2.05)	291	<0.001 ***
adverse	3.23 (2.46 – 4.26)	128	<0.001 ***
gender			
female	Ref	360	
male	1.22 (1 – 1.5)	392	0.048 *
WBC			
< 100	Ref	669	
> 100	1.83 (1.38 – 2.44)	83	<0.001 ***

C

Variable	HR (95% CI)	No. of Patients	P Value
***SRSF2* and *ASXL1* interaction**			
SRSF2–/ASXL1–	Ref	975	
SRSF2–/ASXL1+	0.91 (0.67 – 1.23)	78	0.529
SRSF2+/ASXL1–	1.09 (0.76 – 1.55)	65	0.641
SRSF2+/ASXL1+	1.14 (0.77 – 1.7)	37	0.517
AML type			
de novo	Ref	984	
sAML/MDS/tAML	1.22 (0.98 – 1.51)	171	0.072
age			
< 60	Ref	799	
> 60	1.56 (1.31 – 1.86)	356	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	448	
intermediate	2.31 (1.86 – 2.88)	461	<0.001 ***
adverse	4.66 (3.68 – 5.88)	246	<0.001 ***
gender			
female	Ref	532	
male	1.15 (0.98 – 1.36)	623	0.094
WBC			
< 100	Ref	1044	
> 100	1.85 (1.43 – 2.4)	111	<0.001 ***



Variable	HR (95% CI)	No. of Patients	P Value
SFmut4 and *ASXL1* interaction			
SFmut4–/*ASXL1*–	Ref	568	
SFmut4–/*ASXL1*+	0.72 (0.42 – 1.25)	32	0.245
SFmut4+/*ASXL1*–	1.33 (1 – 1.77)	106	0.053
SFmut4+/*ASXL1*+	1.33 (0.89 – 1.97)	46	0.163
AML type			
de novo	Ref	654	
sAML/MDS/tAML	1.15 (0.86 – 1.54)	98	0.356
age			
< 60	Ref	521	
> 60	1.57 (1.24 – 1.98)	231	<0.001 ***
modified ELN 2017 risk			
favorable	Ref	333	
intermediate	2.24 (1.71 – 2.94)	291	<0.001 ***
adverse	4.42 (3.27 – 5.97)	128	<0.001 ***
gender			
female	Ref	360	
male	1.12 (0.89 – 1.39)	392	0.329
WBC			
< 100	Ref	669	
> 100	1.78 (1.3 – 2.44)	83	<0.001 ***

Figure S9

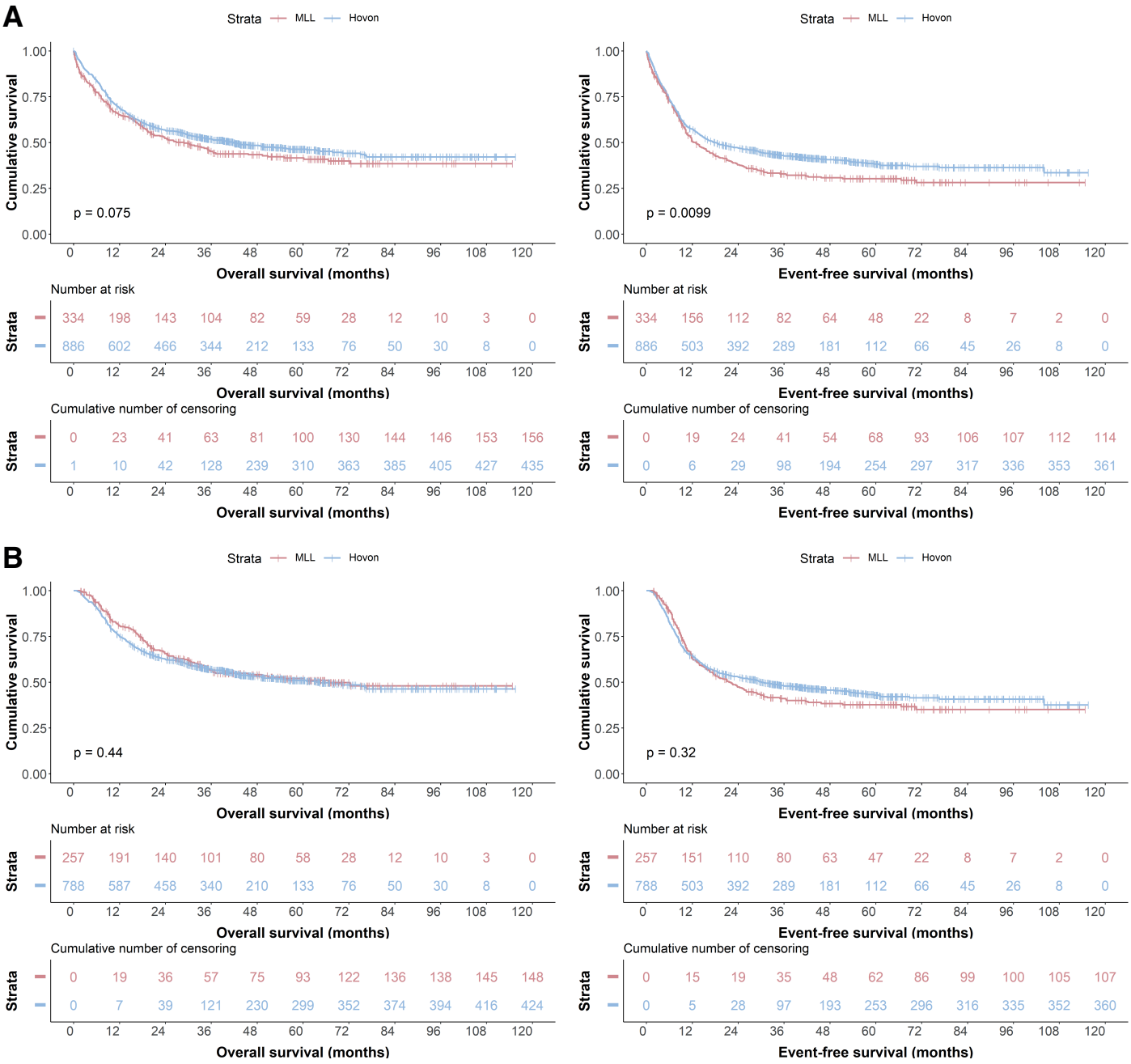
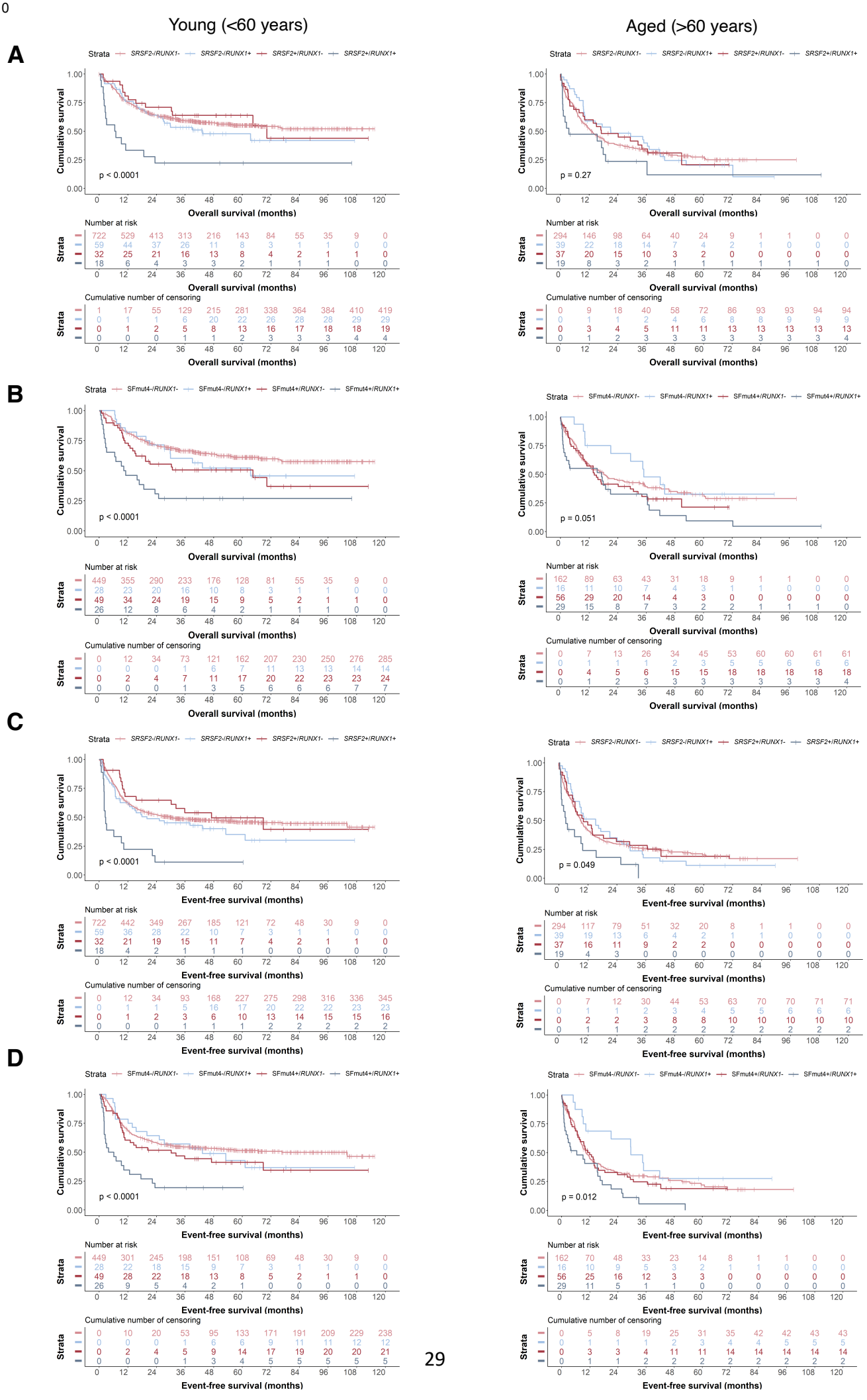

A
Strata MLL Hovon
Cumulative survival
1.00
0.75
0.50
0.25
0.00
p = 0.075
0 12 24 36 48 60 72 84 96 108 120
Overall survival (months)
Number at risk
Strata
334 198 143 104 82 59 28 12 10 3 0
886 602 466 344 212 133 76 50 30 8 0
Overall survival (months)
Cumulative number of censoring
Strata
0 23 41 63 81 100 130 144 146 153 156
1 10 42 128 239 310 363 385 405 427 435
Overall survival (months)
Strata MLL Hovon
Cumulative survival
p = 0.0099
Event-free survival (months)
Number at risk
Strata
334 156 112 82 64 48 22 8 7 2 0
886 503 392 289 181 112 66 45 26 8 0
Event-free survival (months)
Cumulative number of censoring
Strata
0 19 24 41 54 68 93 106 107 112 114
0 6 29 98 194 254 297 317 336 353 361
Event-free survival (months)
B
Strata MLL Hovon
Cumulative survival
p = 0.44
Overall survival (months)
Number at risk
Strata
257 191 140 101 80 58 28 12 10 3 0
788 587 458 340 210 133 76 50 30 8 0
Overall survival (months)
Cumulative number of censoring
Strata
0 19 36 57 75 93 122 136 138 145 148
0 7 39 121 230 299 352 374 394 416 424
Overall survival (months)
Strata MLL Hovon
Cumulative survival
p = 0.32
Event-free survival (months)
Number at risk
Strata
257 151 110 80 63 47 22 8 7 2 0
788 503 392 289 181 112 66 45 26 8 0
Event-free survival (months)
Cumulative number of censoring
Strata
0 15 19 35 48 62 86 99 100 105 107
0 5 28 97 193 253 296 316 335 352 360
Event-free survival (months)

Figure S10


Young (<60 years)
Aged (>60 years)
A
B
C
D
Strata
SRSF2-/RUNX1-
SRSF2-/RUNX1+
SRSF2+/RUNX1-
SRSF2+/RUNX1+
SFmut4-/RUNX1-
SFmut4-/RUNX1+
SFmut4+/RUNX1-
SFmut4+/RUNX1+
Cumulative survival
p < 0.0001
p = 0.27
p = 0.051
p = 0.049
p = 0.012
Overall survival (months)
Event-free survival (months)
Number at risk
Cumulative number of censoring