

Huntsman Cancer Institute Survival Analysis of Genetic Mutations in Patients with Chronic Myelomonocytic Leukemia

Joaquin Zetina Huesca^{1*}, Ahmad Halwani², Ami Patel², Srinivas Tantravahi²,
Vikas Patil², Sarah Soderborg², Kyle Hansen²

¹University of Utah School of Medicine, ²Huntsman Cancer Institute

Background

Chronic Myelomonocytic Leukemia (CMML) is a rare hematopoietic stem cell disorder that predominantly affects the elderly. Previous genetic analysis supports the presence of mutations including *ASXL1*, *TET2*, spliceosome components (*SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*), and the oncogenic RAS pathway (*NRAS*, *KRAS*, *CBL*, *PTPN11*, and *NF1*).

Objective

As part of a precision cancer surveillance to increase our basic, translational, and clinical understanding of rare diseases at the Huntsman Cancer Institute, we identified a cohort of patients with CMML treated at our institution. This report reports their clinical and molecular characteristics based on standard of care molecular profiling with myeloid next-generation sequencing. We also describe the overall survival of patients with molecular profiles of interest.

Design

We extracted data from 57 CMML patients from the Huntsman Cancer Institute electronic health record system. We categorized the patients using their first bone marrow myeloid malignancy panel diagnosis between October 2009 and September 2020. We reviewed their charts for the following information elements: date of birth, sex, vital status, bone marrow biopsy, CMML diagnosis, and date of death or last follow-up. Our analysis was performed by producing Kaplan-Meier survival curves.

Age Groups		
50-59	5	(8.8%)
60-69	10	(17.5%)
70-79	23	(40.4%)
80-89	15	(26.3%)
90+	4	(7.0%)
Gender		
Male	32	(56.1%)
Female	25	(43.9%)
Ethnicity		
White or Caucasian	53	(93.0%)
Hispanic	1	(1.8%)
Asian	2	(3.5%)
Other	1	(1.8%)
Vital Status		
Alive	26	(45.6%)
Deceased	31	(54.4%)

Table 1. Patient demographics included in the study, n=57.

<i>TET2</i>	32	(15.5 %)
<i>ASXL1</i>	31	(15.0%)
<i>SRSF2</i>	22	(10.6%)
<i>CBL</i>	12	(5.8%)
<i>NRAS</i>	11	(5.3%)
<i>U2AF1</i>	8	(3.9%)
<i>JAK2</i>	6	(2.9%)
<i>KRAS</i>	5	(2.4%)
<i>FLT3</i>	3	(1.4%)
<i>ZRSR2</i>	3	(1.4%)
<i>SF3B1</i>	1	(0.5%)
<i>PTPN11</i>	1	(0.5%)

Table 2. The distribution of *TET2*, *ASXL1*, RAS pathway mutations and spliceosome component mutations among 57 patients with a median age of 74, of which 56% were male.

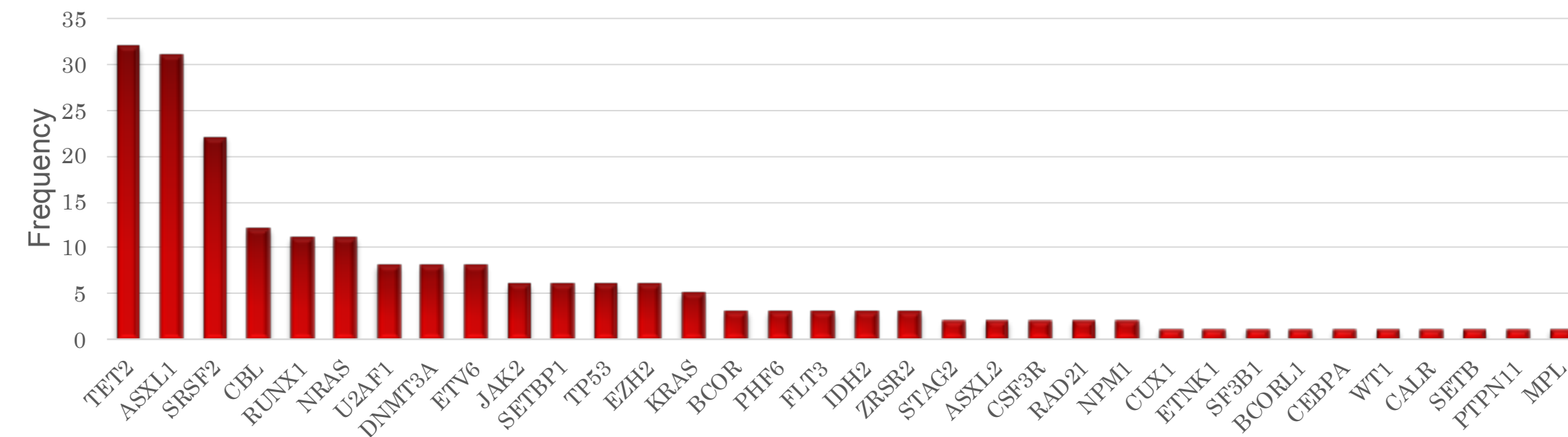


Figure 1. Bar graph displaying each myeloid mutation gene frequency, n=34.

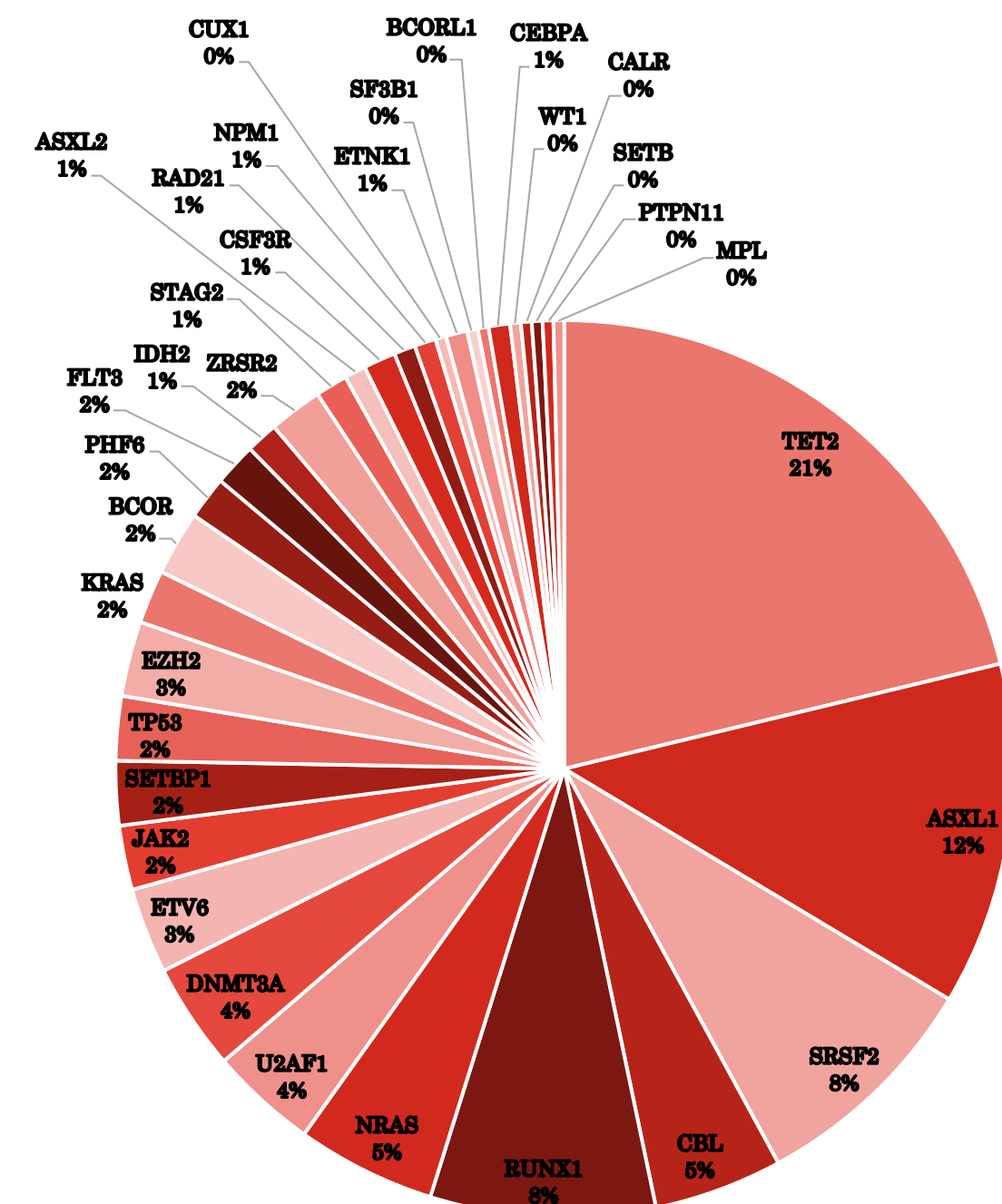


Figure 2. Pie graph distribution of tier 1 mutations from myeloid malignancies patient panels.

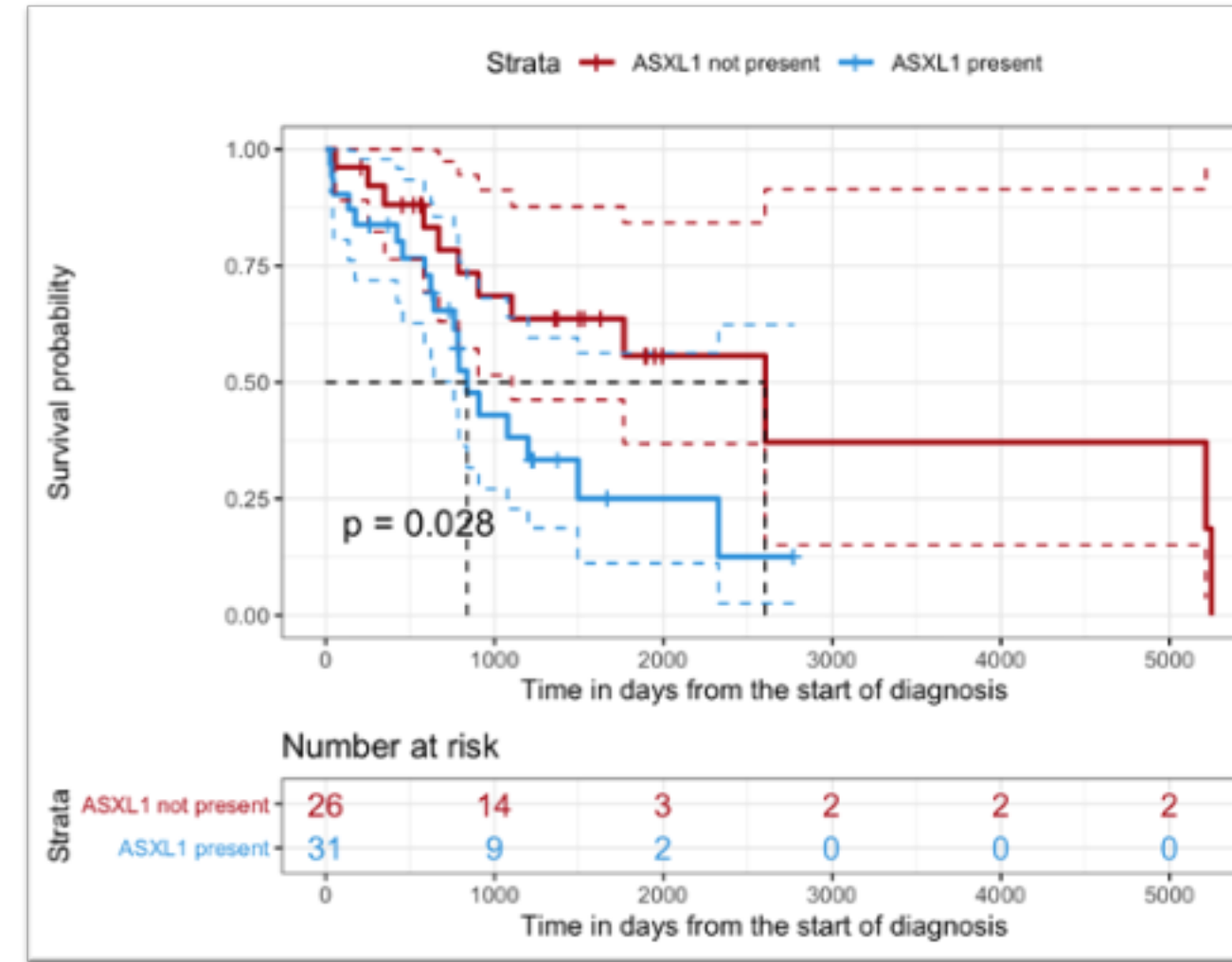


Figure 3. Kaplan-Meier estimate of overall survival in patients with *ASXL1* not present vs. patients with *ASXL1* present. Patients with *ASXL1* not present had a median overall survival of 2605 days compared to 838 days in patients with *ASXL1* present (p=0.028).

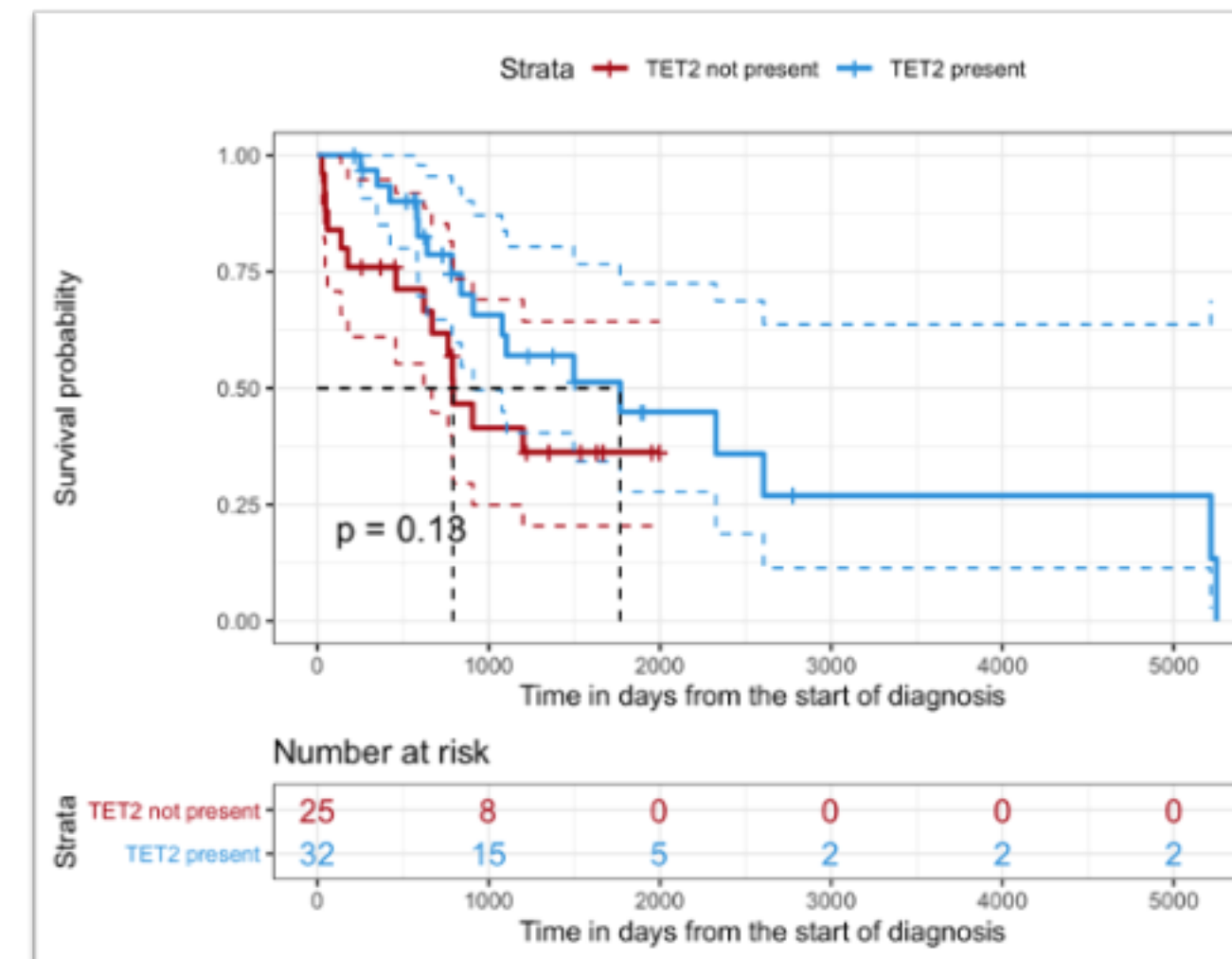


Figure 4. Kaplan-Meier estimate of overall survival in patients with *TET2* not present vs. patients with *TET2* present. Patients with *TET2* not present had a median overall survival of 790 days compared to 1767 days in patients with *TET2* present (p=0.13).

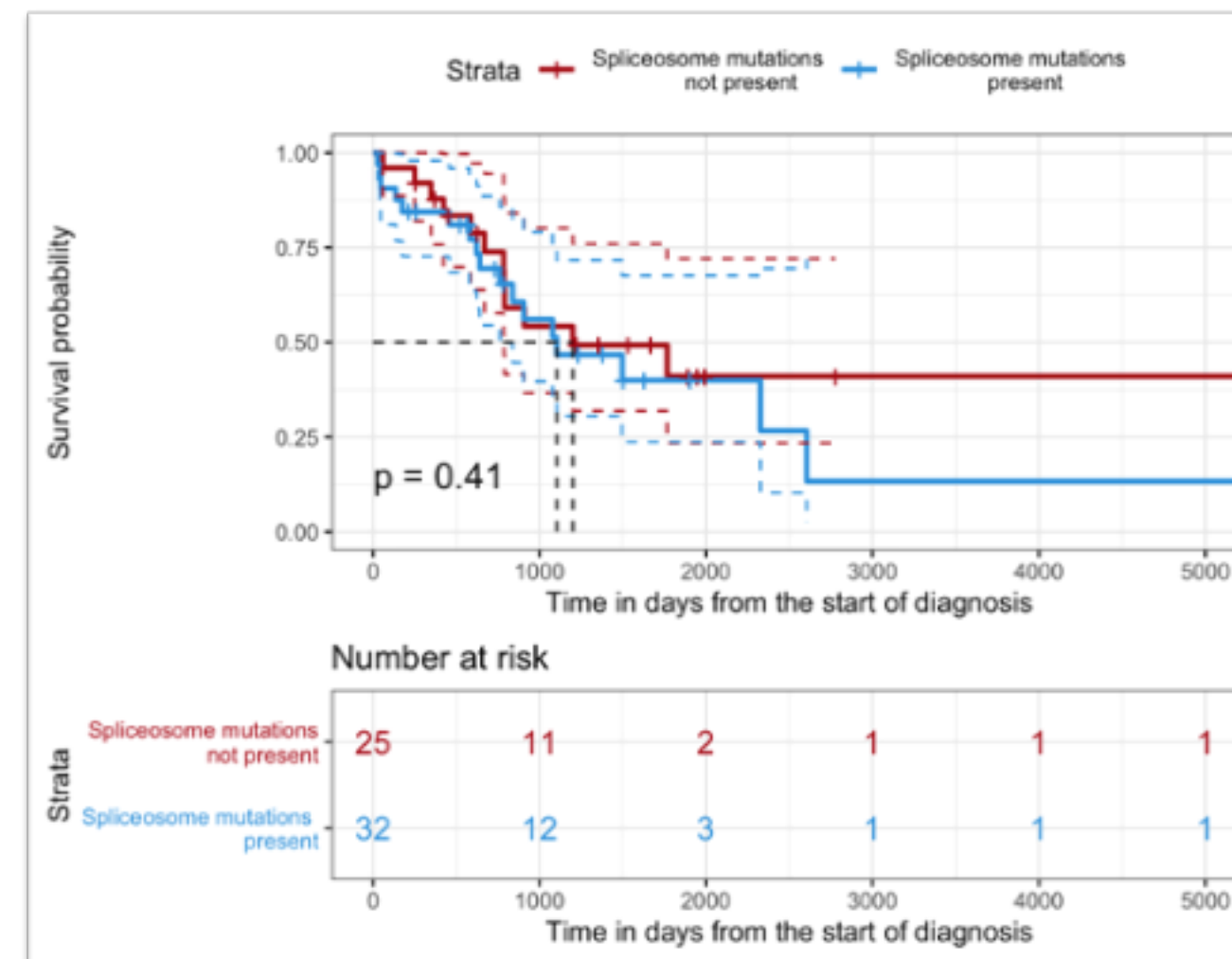


Figure 5. Kaplan-Meier estimate of overall survival in patients with a spliceosome mutation not present vs. patients with a spliceosome mutation present. Patients with a spliceosome mutation not present had a median overall survival of 1200 days compared to 1103 days in patients with a spliceosome mutation present (p=0.41).

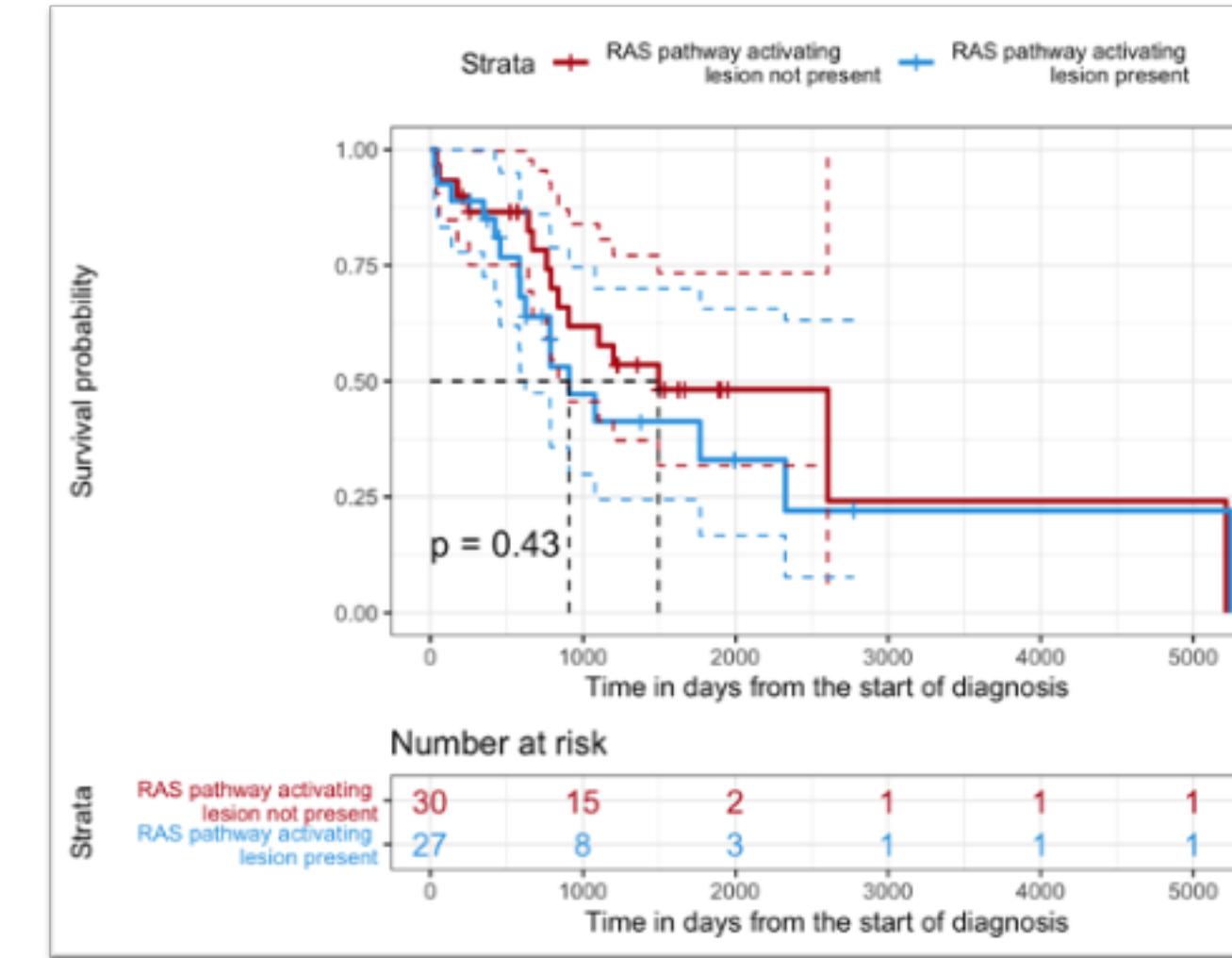


Figure 6. Kaplan-Meier estimate of overall survival in patients with a RAS pathway activating lesion not present vs. patients with a RAS pathway activating lesion present. Patients with a RAS pathway activating lesion not present had a median overall survival of 1496 days compared to 908 days in patients with RAS pathway activating lesion present (p=0.43).

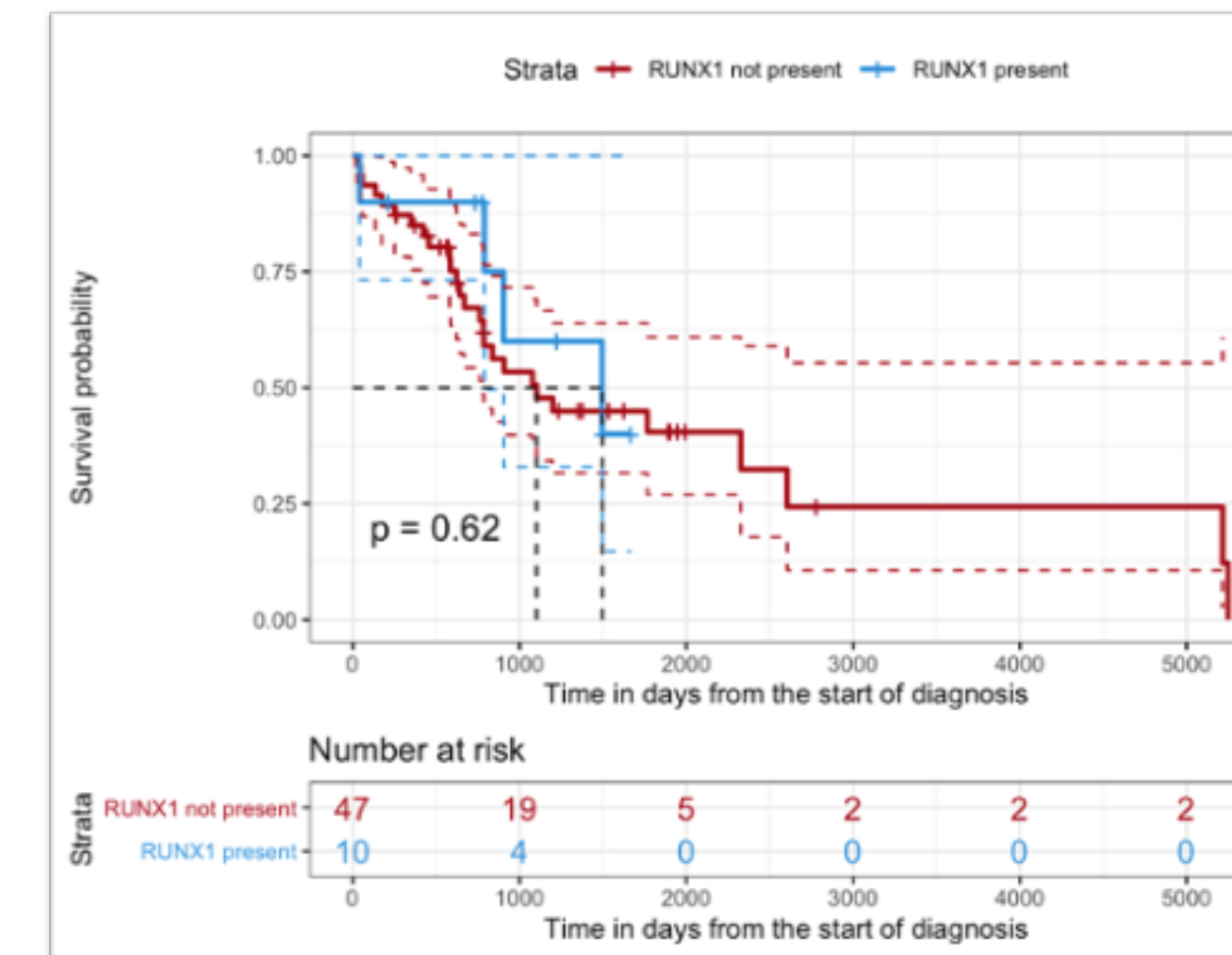


Figure 7. Kaplan-Meier estimate of overall survival in patients with *RUNX1* not present vs. patients with *RUNX1* present. Patients with *RUNX1* not present had a median overall survival of 1103 days compared to 1496 days in patients with *RUNX1* present (p = 0.62).

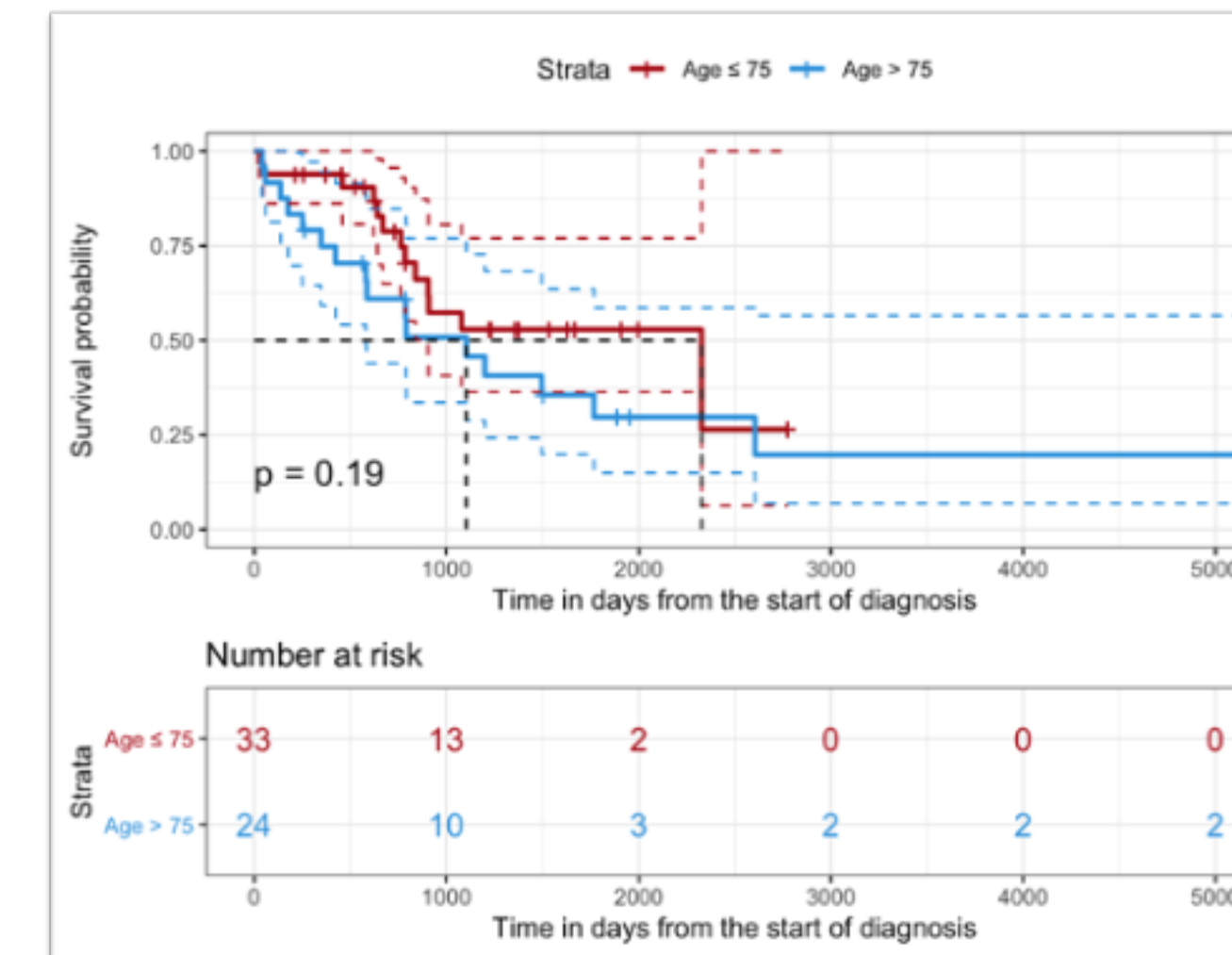


Figure 8. Kaplan-Meier estimate of overall survival in patients with age ≤ 75 vs. patients with age > 75. Patients with age ≤ 75 had a median overall survival of 2327 days compared to 1103 days in patients with age > 75 (p = 0.19).

Results

We identified a total of 34 gene mutations and found that more than fifty percent of mutation frequencies were distributed between *TET2* (15%), *ASXL1* (15%), *SRSF2* (11%), *CBL* (6%), and *RUNX1* (5%). There was a significant association between *ASXL1* mutation and worse overall survival (HR=2.34, p=0.028). We also found a tentative suggestion of improved survival with *TET2* (HR=0.56, p=0.13). Both RAS pathway mutations and spliceosome component mutations, although present in a significant portion of the patient cohort (47% and 16%, respectively), showed no apparent association with survival (HR=1.34, p=0.43, and HR=1.36, p=0.41). Older patients (>75 years) displayed a slightly better survival probability than their younger counterparts (HR=1.63, p=0.19).

Conclusion

In our hypothesis-generating report, we confirm the association of *ASXL1* mutation and worse prognosis and describe possible favorable overall survival from patients with the presence of a *TET2* mutation. Further work is planned to confirm these findings in larger cohorts and their impact on response to hypomethylating agents.

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