ASXL1/TET2 genotype-based risk stratification outperforms *ASXL1* mutational impact and is independent of mutant variant allele fractions in chronic myelomonocytic leukemia

Truncating *ASXL1* mutations are a high-risk feature in chronic myelomonocytic leukemia (CMML)[1] and are associated with inferior overall survival (OS) and acute myeloid leukemia-free survival (LFS).[2] Conversely, we previously showed that loss-of-function/hypomorphic mutations in *TET2* are associated with better outcomes, with the *ASXL1* wild-type *TET2* mutant (*ASXL1*^{wt}/*TET2*^{mut}) genotype conferring a survival advantage independent of treatment.[3] However, contemporary prognostic scoring systems - including the Groupe Francophone des Myelodysplasies (GFM),[4] Mayo Molecular (Mayo-Mol),[5] and CMML-specific prognostic scoring system molecular (CPSS-Mol)[6] models - do not consider mutational variant allele fractions (VAF) or *TET2* mutational status. Here, we expand upon our prior work by assessing mutation VAF, reconsidering the use of binary mutation status, and integrating *TET2* into the prognostic models.

After Institutional Review Board approval, we cataloged CMML patients seen at two centers, Mayo Clinic (N=466, 52%) and MD Anderson Cancer Center (N=422, 48%). Next-generation sequencing (NGS) was carried out as described at CMML diagnosis.[3,7] Variants were annotated against international normal allele and pathologic mutation databases, and variants of uncertain significance (VUS) were excluded from analysis. As *TET2* mutations occur in multiple clonal states,[3,8] we considered the mutation with highest VAF when assessing the impact on outcomes. Copy number alterations and loss of heterozygosity data were only available for a small number of patients, as reported elsewhere,[9] and thus were not considered for this analysis. Statistical analyses considered the parameters at the time of presentation to the respective institution. Categorical variables were compared by Fisher exact or Pearson χ^2 tests and continuous variables by Mann-Whitney U test or two-way ANOVA with Tukey *P* value correction for pairwise comparisons. Univariate and multivariate analyses were performed using Cox proportional hazards regression models. Models were compared using concordance indices (C-statistic), where higher values indicate a better fit, and receiver operator curve (ROC) analyses.[10] Survival was assessed via the Kaplan-Meier method. *P* values <0.05 were considered significant. Calculations were performed using BlueSky Statistics (v10.3.1) or MedCalc (v22.016).

The median age of the cohort (N=888) was 71 years (range, 20-94), 33% were female, 46% had proliferative CMML (pCMML), and 19% had CMML-2 by current criteria[1,11] (Table 1). The most frequently mutated genes were *ASXL1* (45%), *TET2* (44%), *SRSF2* (41%), *NRAS* (15%), and *RUNX1* (15%). The median number of mutations in *ASXL1* was 1 (range, 1-3) and in *TET2* was 1 (range, 1-5); however, multiple *ASXL1* mutations were rare (3%) in comparison to multiple *TET2* mutations (47%; Figure 1A). Most patients had ≥1 mutation in an epigenetic regulator (79%) or spliceosome gene (57%). RAS pathway mutations were observed in 37%. Transformation to AML occurred in 168 patients (19%) and there were 586 deaths (66%). The median OS (mOS) and mLFS of the cohort were 31.8 and 28.4 months, respectively, with a median follow-up of 63.1 months. Risk stratification according to the GFM, Mayo-Mol, and CPSS-Mol models is shown in *Online Supplementary Figure S1A-C*.

In order to evaluate the impact of *ASXL1* and *TET2* mutations on OS and LFS, the cohort was divided into four genotype-based subgroups: *ASXL1*^{wt}/*TET2*^{wt} (N=244, 28%), *ASXL1*^{mu}*t*/*TET2*^{wt} (N=254, 29%), *ASXL1*^{wt}/*TET2*^{mut} (N=241, 26%), and *ASXL1*^{mut}/*TET2*^{mut} (N=149, 17%) (Table 1). Patients with *ASXL1* mutations were more likely to be male (*P*=0.0135), have a higher white blood cell (WBC) count (*P*=0.0129), and harbor mutations in transcriptional and RAS pathways (*P*<0.0001). Patients with *TET2* mutations were more likely to have a higher hemoglobin (*P*<0.0001) and a normal karyotype (*P*=0.0005). As previously documented,[3,12,13] those with isolated *TET2* mutations had the longest mOS of 58 months whereas those with isolated *ASXL1* mutations had the shortest mOS of 21 months (Figure 1B). Patients with the *ASXL1*^{wt}/*TET2*^{wt} and *ASXL1*^{mut}/*TET2*^{mut} genotypes fared similarly with mOS of 30 and 27 months, respectively (*Online Supplementary Figure S1F*). The same pattern was observed for LFS (Figure 1C).

We hypothesized that the *ASXL1* or *TET2* mutation VAF would be more predictive of outcomes than a binary metric. The respective median VAF were 37% and 45% (Figure 1A). When treated as a continuous variable, there was no correlation between VAF and OS or LFS by either Pearson linear or Cox regression (*P*>0.39 for all correlations in both models; Figure 1D). Similarly, amongst patients with multiple *ASXL1* or *TET2* mutations, there was no association between the number of mutations and OS or LFS (*P*≥0.06). There was also no survival difference between those with 1 *versus* ≥2 mutations in either gene (*P*>0.05 for each). Although prior studies have inconsistently shown associations between the number of *TET2* mutations and survival,[3,8] these results support the practice of considering *ASXL1* and *TET2* mutation status as binary metrics in prognostic models.

Unlike in the overall cohort, the *ASXL1/TET2* genotypes did not accurately stratify patients with pCMML, CMML-2, or those considered high-risk by the prognostic models (*Online Supplementary Figure S1J, K*). In contrast, patients

Table 1. Characteristics of the four *ASXL1/TET2* genotypes within the CMML cohort.

Variable	Cohort	*ASXL1*^{wt}/*TET2*^{wt}	*ASXL1*^{mut}/*TET2*^{wt}	*ASXL1*^{wt}/*TET2*^{mut}	*ASXL1*^{mut}/*TET2*^{mut}	P[a]
N	888	244	254	241	149	-
Demographics, either median (range) or N (%)						
Age in years	71 (20-94)	71 (20- 94)	70 (27-90)	70 (36 - 90)	71 (39-91)	0.1027
Male	593 (66.8)	151 (61.9)	183 (72)	150 (62.2%)	109 (73.2)	0.0135
Female	295 (33.2)	93 (38.1)	71 (28)	91 (37.8%)	40 (26.8)	-
Laboratory parameters, either median (range) or N (%)						
Hemoglobin g/dL	10.8 (4.2-17.3)	10.4 (4.2-17.3)	10.2 (5.3-16.9)	11.6 (6.6-16.0)	11.6 (6.3-15.8)	<0.0001
MCV fL	92.4 (59.0-121.0)	92.8 (59.0-119.4)	91.7 (59.0-121)	93.3 (60.6-114.5)	91.1 (69.0-120.1)	0.2723
Platelets x10^9/L	97 (8-1,264)	95 (8-820)	105 (10-1264)	103 (12-840)	81 (10-308)	0.0033
WBC x10^9/L	12 (1.2-264.8)	11.1 (1.2-235.0)	14.8 (2.0-264.8)	9.2 (1.8-185.7)	13 (1.8-264.8)	0.0129
ANC x10^9/L	5.9 (0.0-151.0)	5.2 (0.0-67.5)	7.7 (0.0-151.0)	4.3 (0.0-142.9)	7.2 (0.2-142.9)	0.0283
AMC x10^9/L	2.3 (0.0-47.5)	2 (0.0-37.9)	2.8 (0.3-37.8)	2 (0.0-39.5)	2.7 (0.6-47.5)	0.0027
ALC x10^9/L	1.8 (0.0-22.0)	2 (0.3-11.0)	1.9 (0.4-22.0)	1.7 (0.0-11.0)	1.9 (0.0-7.9)	0.1914
IMC present	437 (49.5)	115 (47.3)	146 (57.9)	97 (40.4)	79 (53.7)	0.0015
Peripheral blasts %	0 (0-19)	0 (0-16)	0 (0-19)	0 (0-12)	0 (0-14)	<0.0001
Marrow blasts %	4 (0-31)	4 (0-31)	4 (0-20)	3 (0-17)	3 (0-18)	< 0.0001
Ringed sideroblasts	68 (15.8)	17 (14.2)	19 (14.6)	22 (19.8)	10 (14.5)	0.6162
LDH units/L	246 (84-6,075)	268 (98-6,075)	256 (109-3,615)	225 (85-1,808)	247 (84-4,464)	0.2315
Subtype, N (%)						
Dysplastic	474 (53.6)	133 (54.7)	108 (42.7)	160 (66.9)	73 (49)	0.0005
Proliferative	410 (46.4)	110 (45.3)	145 (57.3)	79 (33.1)	76 (51)	-
WHO category, N (%)						
CMML-1	708 (80.7)	117 (48.5)	189 (75)	216 (90.4)	126 (86.9)	0.0005
CMML-2	169 (19.3)	64 (26.6)	63 (25)	23 (9.6)	19 (13.1)	-
Karyotype, N (%)						
Normal	569 (66.9)	124 (54.4)	155 (62.2)	178 (76.7)	112 (78.9)	0.0005
Abnormal	282 (33.1)	104 (45.6)	94 (37.8)	54 (23.3)	30 (21.1)	-
Spanish cytogenetic risk category, N (%)						
Low	591 (69.4)	128 (56.1)	158 (63.5)	196 (84.5)	115 (81)	0.0005
Intermediate	124 (14.6)	43 (18.9)	42 (16.9)	24 (10.3)	15 (10.6)	-
High	136 (16)	57 (25)	49 (19.7)	15 (6.5)	15 (10.6)	-
GFM risk category, N (%)						
Low	275 (41.3)	103 (55.4)	28 (14.4)	120 (68.6)	24 (21.6)	0.0005
Intermediate	243 (36.5)	67 (36)	84 (43.3)	46 (26.3)	46 (41.4)	-
High	148 (22.2)	16 (8.6)	82 (42.3)	9 (5.1)	41 (36.9)	-
Mayo molecular risk category, N (%)						
Low	55 (8.3)	24 (12.9)	0 (0)	31 (17.7)	0 (0)	0.0005
Intermediate-1	192 (28.8)	73 (39.2)	26 (13.4)	77 (44)	16 (14.4)	-
Intermediate-2	192 (28.8)	51 (27.4)	55 (28.4)	47 (26.9)	39 (35.1)	-
High	227 (34.1)	38 (20.4)	113 (58.2)	20 (11.4)	56 (50.5)	-

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Variable	Cohort	*ASXL1*^{wt}/*TET2*^{wt}	*ASXL1*^{mut}/*TET2*^{wt}	*ASXL1*^{wt}/*TET2*^{mut}	*ASXL1*^{mut}/*TET2*^{mut}	P[a]
CPSS-molecular risk category, N (%)						
Low	83 (9.8)	32 (14)	0 (0)	51 (22.1)	0 (0)	0.0005
Intermediate-1	206 (24.2)	53 (23.2)	29 (11.6)	91 (39.4)	33 (23.2)	-
Intermediate-2	337 (39.6)	98 (43)	101 (40.6)	77 (33.3)	61 (43)	-
High	224 (26.4)	45 (19.7)	119 (47.8)	12 (5.2)	48 (33.8)	-
Mutation profile, either median (range) or N (%)						
Number of mutations	3 (0-8)	1 (0-5)	3 (1-7)	2 (1- 6)	4 (2-8)	<0.0001
ASXL1	403 (45.4)	0 (0)	254 (100)	0 (0)	149 (100)	<0.0001
BCOR	18 (2)	4 (1.6)	8 (3.1)	4 (1.7)	2 (1.3)	0.5899
BRAF	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
CALR	7 (0.8)	3 (1.2)	0 (0)	4 (1.7)	0 (0)	0.0800
CBL	118 (13.3)	15 (6.1)	34 (13.4)	36 (14.9)	33 (22.1)	<0.0001
CEBPA	31 (3.5)	8 (3.3)	11 (4.3)	7 (2.9)	5 (3.4)	0.8588
CSF3R	7 (1.5)	1 (0.8)	2 (1.4)	3 (2.4)	1 (1.3)	0.84.9
CUX1	1 (9.1)	0 (0)	1 (50)	0 (0)	0 (0)	0.5455
DNMT3A	51 (5.7)	21 (8.6)	10 (3.9)	17 (7.1)	3 (2)	0.0172
ETNK1	10 (1.1%)	1 (0.4)	4 (1.6)	4 (1.7)	1 (0.7)	0.5128
ETV6	2 (0.9)	0 (0)	2 (4.1)	0 (0)	0 (0)	0.1392
EZH2	34 (3.8)	2 (0.8)	15 (5.9)	3 (1.2)	14 (9.4)	<0.0001
FLT3	15 (1.7)	1 (0.4)	7 (2.8)	1 (0.4)	6 (4)	0.0062
GATA2	1 (0.5)	1 (2.3)	0 (0)	0 (0)	0 (0)	0.2028
IDH1	11 (1.2)	4 (1.6)	5 (2)	2 (0.8)	0 (0)	0.3127
IDH2	49 (5.5)	21 (8.6)	27 (10.6)	0 (0)	1 (0.7)	<0.0001
JAK2	52 (5.9)	15 (6.1)	14 (5.5)	13 (5.4)	10 (6.7)	0.9383
KIT	23 (2.6)	7 (2.9)	7 (2.8)	2 (0.8)	7 (4.7)	0.1038
KRAS	73 (8.2)	19 (7.8)	22 (8.7)	19 (7.9)	13 (8.7)	0.9749
MPL	14 (1.6)	3 (1.2)	1 (0.4)	7 (2.9)	3 (2)	0.1191
NPM1	18 (2.0)	14 (5.7)	0 (0)	4 (1.7)	0 (0)	< 0.0001
NRAS	137 (15.4)	27 (11.1)	50 (19.7)	33 (13.7)	27 (18.1)	0.0361
PHF6	20 (2.3)	2 (0.8)	6 (2.4)	7 (2.9)	5 (3.4)	0.2460
PTPN11	37 (4.2)	11 (4.5)	17 (6.7)	7 (2.9)	2 (1.3)	0.0463
RAD21	2 (0.9)	1 (2.3)	1 (2)	0 (0)	0 (0)	0.3228
RUNX1	129 (14.5)	27 (11.1)	47 (18.5)	24 (10)	31 (20.8)	0.0025
SETBP1	82 (9.2)	12 (4.9)	52 (20.5)	7 (2.9)	11 (7.4)	<0.0001
SF3B1	45 (5.1)	18 (7.4)	3 (1.2)	22 (9.1)	2 (1.3)	<0.0001
SH2B3	4 (0.9)	0 (0)	2 (1.4)	2 (1.6)	0 (0)	0.4739
SRSF2	363 (40.9)	70 (28.7)	108 (42.5)	106 (44)	79 (53)	<0.0001
STAG2	12 (1.4)	2 (0.8)	6 (2.4)	0 (0)	4 (2.7)	0.0226
SUZ12	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	N/A
TET2	390 (43.9)	0 (0)	0 (0)	241 (100)	149 (100)	<0.0001
TP53	37 (4.2)	24 (9.8)	1 (0.4)	7 (2.9)	5 (3.4)	<0.0001
U2AF1	69 (7.8)	19 (7.8)	33 (13)	7 (2.9)	10 (6.7)	0.0004
WT1	4 (0.5)	2 (0.8)	2 (0.8)	0 (0)	0 (0)	0.4413
ZRSR2	44 (5.0)	6 (2.5)	8 (3.1)	17 (7.1)	13 (8.7)	0.0083

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Variable	Cohort	*ASXL1*^{wt}/*TET2*^{wt}	*ASXL1*^{mut}/*TET2*^{wt}	*ASXL1*^{wt}/*TET2*^{mut}	*ASXL1*^{mut}/*TET2*^{mut}	*P*[a]
Mutation groups, N (%)						
RAS oncogenes	326 (36.7)	60 (24.6)	113 (44.5)	85 (35.3)	68 (45.6)	<0.0001
Epigenetic regulators	698 (78.6)	54 (22.1%)	254 (100)	241 (100)	149 (100)	<0.0001
Spliceosome components	505 (56.9)	108 (44.3)	151 (59.4)	145 (60.2)	101 (67.8)	<0.0001
Signaling pathways	26 (2.9)	2 (0.8)	11 (4.3)	6 (2.5)	7 (4.7)	0.0392
Transcription factors	227 (25.6)	43 (17.6)	102 (40.2)	36 (14.9)	46 (30.9)	<0.0001
Tumor suppressors	41 (4.6)	26 (10.7)	3 (1.2)	7 (2.9)	5 (3.4)	<0.0001
Outcomes, N (%)						
Transformation	168 (18.9)	45 (18.4)	50 (19.7)	36 (14.9)	37 (24.8)	0.1108
Death	586 (66.0)	177 (72.5)	181 (71.3)	133 (55.2)	95 (63.8)	0.0001

[a]*P* values represent two-way ANOVA comparisons with Tukey corrections between the four genotypes. Oncogenic RAS mutations include *NRAS*, *KRAS, BRAF, CBL*, and *PTPN11*. Epigenetic mutations include *ASXL1, TET2, BCOR, DNMT3A, EZH2, IDH1/2*, *PHF6*, and *STAG2*. Spliceosome mutations include *SF3B1, SRSF2, U2AF1*, and *ZRSR2*. Signaling mutations include *CSF3R, FLT3, JAK2*, and *SH2B3*. Transcription mutations include *CEBPA, ETV6, GATA2, RUNX1*, and *SETBP1*. Tumor suppressor mutations include *TP53* and *WT1*. WHO: World Health Organization; GFM: Groupe Francophone des Myelodysplasies; MCV: mean corpuscular volume; WBC: white blood cell; ANC: absolute neutrophil count; AMC: absolute monocyte count; ALC: absolute lymphocyte count; IMC: immature myeloid cells; LDH: lactate dehydrogenase.

considered intermediate- and low-risk by the Mayo-Mol and CPSS-Mol models were further stratified by the *ASXL1/TET2* genotypes. Therefore, we sought to improve the existing molecular models by incorporating *TET2* mutation status as a favorable prognosticator. Given that *TET2* mutations balanced detrimental *ASXL1* mutations in the Kaplan-Meier analyses, *TET2* mutation status was given equal weight as *ASXL1* in the GFM (-2 points), Mayo-Mol (-1.5 points), and the genetic risk scoring of the CPSS-Mol models (-1 point) (*Online Supplementary Table S1A*). Sex-specific hemoglobin thresholds were used as a surrogate for transfusion dependency in the CPSS-Mol model.[6,14,15]

After adjusting the risk category cutoffs to accommodate *TET2* scoring (*Online Supplementary Table S1A*), the number of patients downstaged was 122 (18.4%), 215 (25.3%), and 97 (14.6%) in the Mayo-Mol, CPSS-Mol, and GFM models, respectively (Figure 2). Although 2% of patients in the Mayo-Mol and 6% in the CPSS-Mol were upstaged, no patients with *TET2* mutations were upstaged. With the addition of *TET2* status, the intermediate-1 and intermediate-2 risk groups were not significantly different in the Mayo-Mol model (*P*=0.49), whereas the low and intermediate-1 risk groups were not significantly different in the CPSS-Mol model (*P*=0.084); thus, these were each combined into a single group, yielding a three-tiered stratification in both models. In the GFM with *TET2* mutational status, this resulted in a mOS of 42, 21, and 14 months for the low-, intermediate-, and high-risk groups, respectively. In the Mayo-Mol with *TET2*, the mOS was 58, 31, and 15 months, respectively. In the CPSS-Mol with *TET2*, the mOS was 63, 30, and 16 months, respectively (Figure 1E-G). Similar results were obtained when patients in the Mayo Clinic subgroup (where hematopoietic cell transplantation data were available, N=18, 4%) were censored at the time of transplant. In all three models, the addition of *TET2* mutation status improved prognostication compared to the parental model, as indicated by higher concordance indices for each model (*Online Supplementary Table S1B*). Likewise, the models with *TET2* status performed similar to or better than the parental models in ROC analyses.

These findings were then validated in an external database from Moffitt Cancer Center (N=265, 31% female) with median age 71 years (range, 17-88 years) and 55% pCMML and 15% CMML-2 cases (*Online Supplementary Table S2*). The mOS and mLFS of the external cohort were 41 (95% confidence interval [CI]: 33-51) and 37 (95% CI: 28-46) months, respectively, with 55 (21%) blast transformation events and 136 (51%) deaths. The external cohort was grouped by *ASXL1/TET2* genotype, providing: *ASXL1*^{wt}/*TET2*^{wt} (N=50, 19%), *ASXL1*^{mut}/*TET2*^{wt} (N=44, 17%), *ASXL1*^{wt}/*TET2*^{mut} (N=105, 40%), and *ASXL1*^{mut}/*TET2*^{mut} (N=66, 25%). As in the primary cohort, the *ASXL1*^{wt}/*TET2*^{mut} genotype conferred the longest mOS (61 months) and the *ASXL1*^{mut}/*TET2*^{wt} genotype the shortest mOS (22 months; *Online Supplementary Figure S1L*). The same trend was observed for LFS. Again, the pCMML (*P*=0.056) and CMML-2 (*P*=0.12) subgroups were not stratified by the genotypes, and there was no correlation between *ASXL1* or *TET2* VAF with either OS or LFS (*P*>0.25 for all comparisons). While patients were stratified by existing molecular models (as expected), the addition of *TET2* mutation status to the Mayo-Mol and CPSS-Mol models again defined three risk groups (low, intermediate, and high) with respective mOS values of 77, 39, and 20 months for the Mayo-Mol (*P*<0.0001) and 77, 39, and 22 months for the CPSS-Mol model (*P*<0.0001; Figure 1I-J). The mOS with the GFM model incorporating *TET2* status was 61, 31, and 15 months, respectively (*P*<0.0001; Figure 1H). Again, models

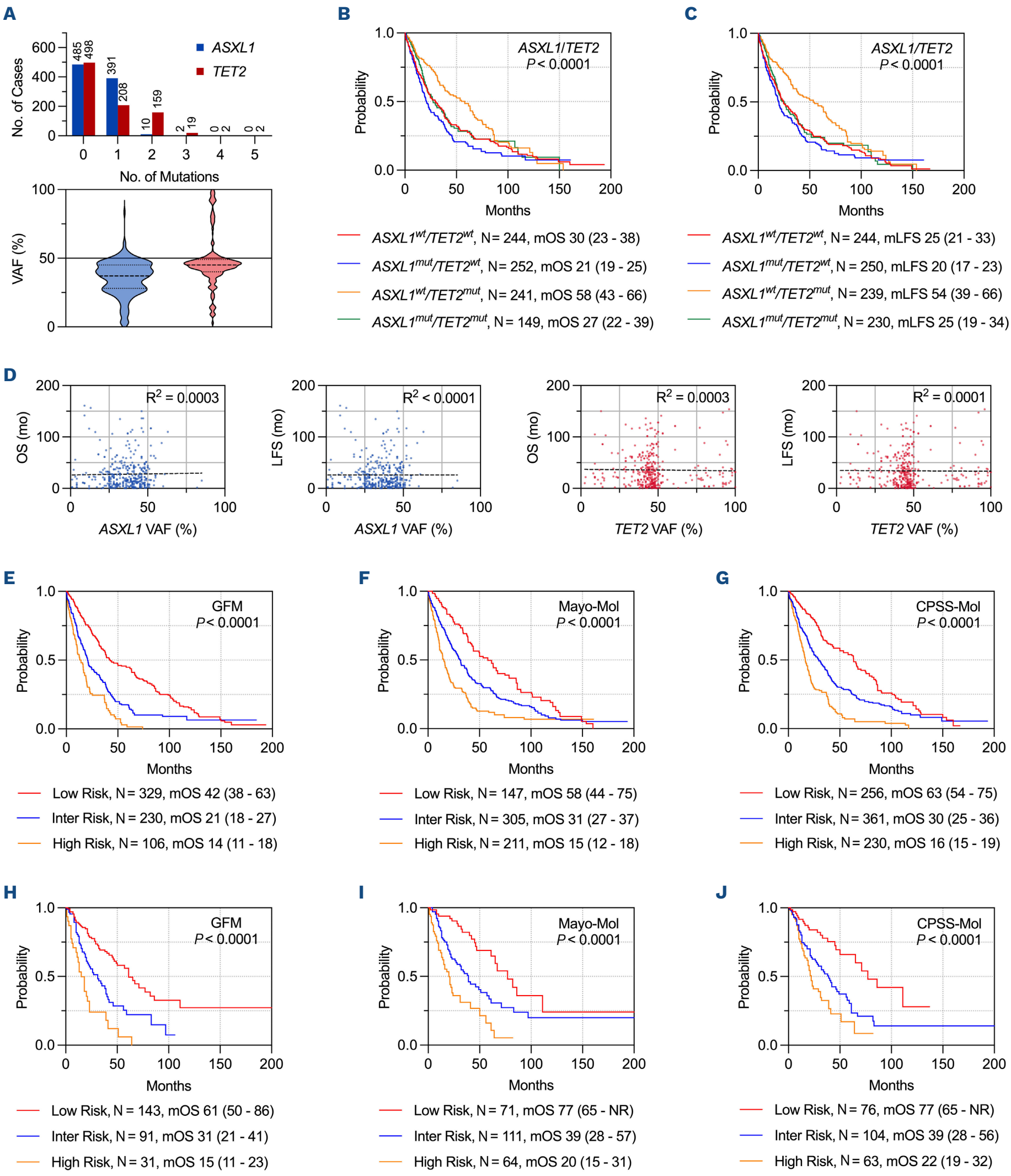

Figure 1. Prognostic implications of *ASXL1/TET2* co-mutation status in chronic myelomonocytic leukemia. (A) The upper panel (histogram) shows the distribution of cases with the indicated number of mutations in *ASXL1* or *TET2*. The lower panel (violin plot) shows the distribution of mutational variant allele fractions (VAF) for *ASXL1* in blue (median 37%, quartiles 28-45%) and *TET2* in red (median 45%, quartiles 40-49%). (B) Median overall survival (mOS) and (C) acute myeloid leukemia-free survival (LFS) of the cohort stratified by *ASXL1/TET2* genotype. (D) No correlation was observed between mutation VAF and either OS or LFS. *P*>0.39 for all correlations by both Pearson linear regression and Cox proportional hazard modeling. The mOS of the primary cohort strat-

ified into low-, intermediate- (inter), and high-risk subgroups by the (E) Groupe Francophone des Myelodysplasies (GFM), (F) Mayo-Molecular (Mayo-Mol), and (G) CPSS-Molecular (CPSS-Mol) models each with the addition of *TET2* mutation status The mOS of the external cohort stratified by the (H) GFM, (I) Mayo-Mol, and (J) CPSS-Mol models each with the addition of *TET2* mutation status. In all Kaplan-Meier analyses, data are presented as median survival (95% confidence interval) in months with log-rank *P* values.

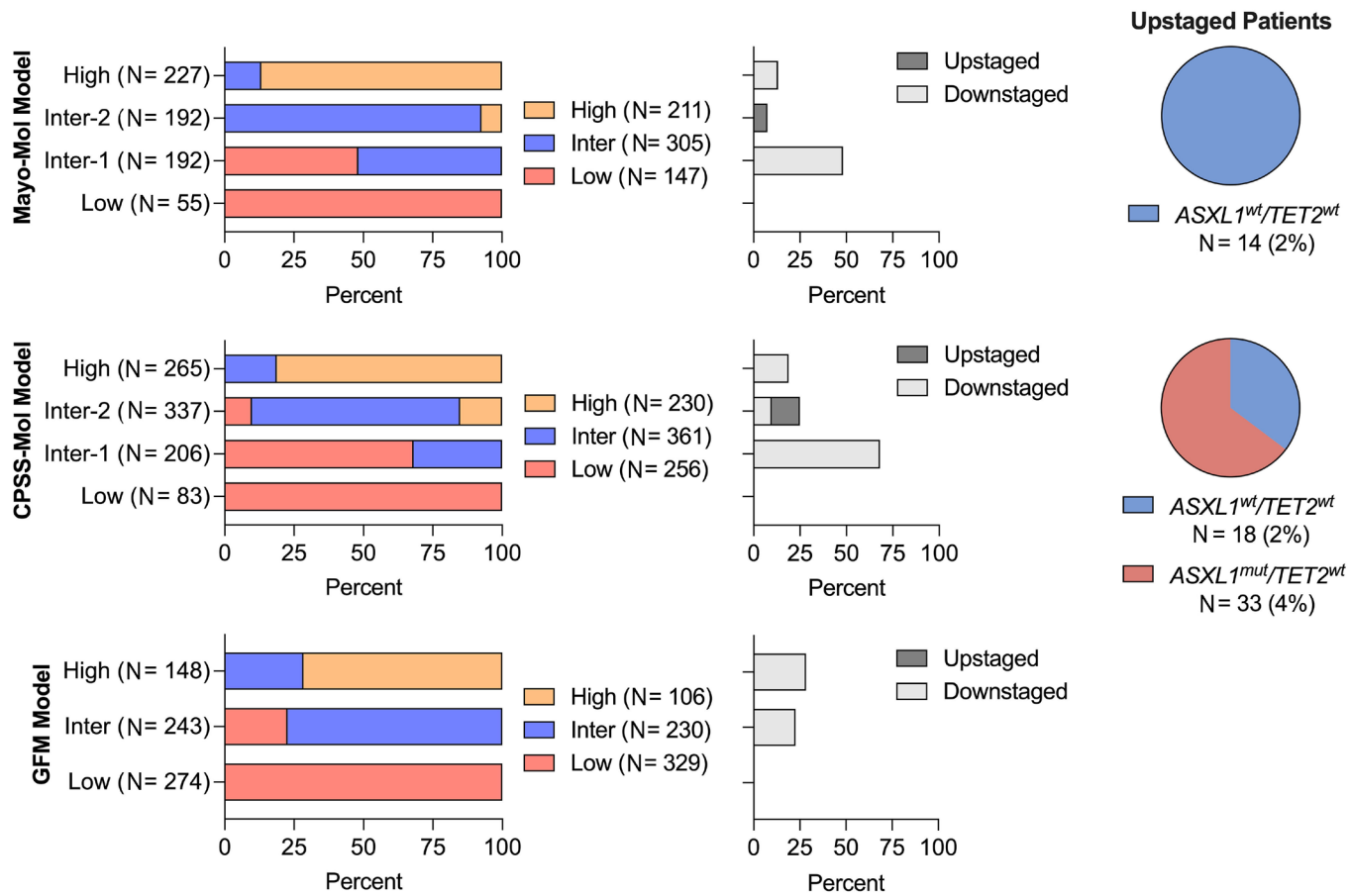

Figure 2. Risk restratification from existing chronic myelomonocytic leukemia prognostic models to models incorporating *TET2* mutation status. Stacked colored bar plots show the restratification of existing prognostic models to the updated models incorporating *TET2* mutation status for patients whom both scores could be calculated. Each bar corresponds to one existing risk category while colors represent the new risk categories with *TET2* status. The gray bar plots represent the percentage of restratified patients within each contemporary model's stratum. The pie charts depict the *ASXL1/TET2* genotypes of the patients who were upstaged in each model. The addition of *TET2* status to the Groupe Francophone des Myelodysplasies (GFM) model did not upstage any patients, and therefore no pie chart is depicted for this model. Inter: intermediate.

incorporating *TET2* mutation provided higher concordance indices and similar AUC values compared to parental models (*Online Supplementary Table S1B*).

In summary, our data validates the positive prognostic impact of *TET2* mutations in CMML, highlighting the importance of considering the *ASXL1/TET2* co-mutational status for prognostication.[3,12,13] Expanding upon prior work, we further show that *ASXL1* and *TET2* mutational VAF does not impact prognostic outcomes, supporting the ongoing practice of binary assessments for molecularly-based CMML prognostication. Furthermore, in a large database and an external validation cohort, the addition of binary *TET2* mutation status to existing molecularly-integrated CMML prognostic models simplified and refined risk stratification. Regardless of whether they are statistically superior, by downstaging some patients and harmonizing the models into three-tiered systems, these refined models may simplify risk stratification and clinical decision making. In this regard, the low-risk tiers of these models represent the lowest-risk patients whereas the intermediate- and high-risk tiers identify "higher-risk" patients. Finally, the favorable impact of *TET2* mutations in hematological neoplasms is largely associated with CMML3 and biological studies understanding the underlying mechanism are needed.

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Contributions

CMC collected data, performed the primary analyses, and drafted the manuscript. MG, RKS, KC, DH, TLL, CMF, CD, AN, AAM, AA, NG, AT, HA, GC-M, RSK, NAA, EP, and GM-B assisted with data collection and study design. EP, GM-B, and MMP conceived the study. MMP provided principal oversight. All authors critically reviewed and approved the manuscript.

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Data-sharing statement

Original data will be provided to collaborating investigators upon reasonable request to the corresponding authors after requisite institutional review board approval.

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