SEX BIAS IN MUTATIONAL LANDSCAPE OF CHRONIC LYMPHOCYTIC LEUKEMIA: ANALYSIS OF CLINICAL SEQUENCING DATA

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Abstract 1552424

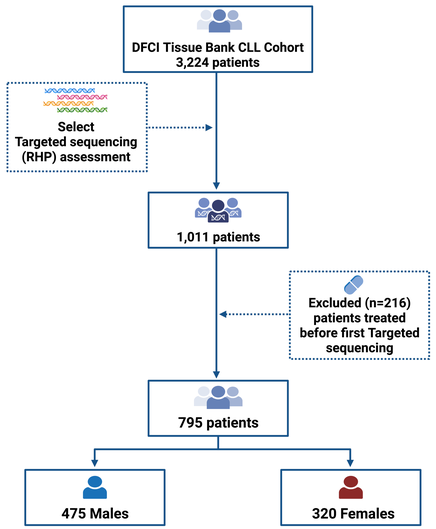
BACKGROUND

- Chronic lymphocytic leukemia (CLL) is more common in males and associated with worse outcomes in males, although the reasons for this remain poorly understood, despite well-established molecular markers defining prognostic impact in CLL.
- **Aim**: to identify potential sex-based differences in genomic data and their prognostic impact on time to first treatment (TTFT) as a primary clinical endpoint in an untreated CLL cohort.

METHODS

- Mutational screening was performed by a clinical targeted NGS panel, covering all or hotspots exons of 95 genes, called The Rapid Heme Panel (RHP), and implemented by BWH *(Kluk MJ, et al. J Mol Diagn. 2016;18(4):507-515).*
- The RHP was performed on a cohort of 795 treatment-naïve patients with CLL diagnosed based on iwCLL guidelines **(Figure 1).**
- **The median time from diagnosis to RHP analysis was 6.6 months (26.50 – 33.27, 95%CI).**
- Sex-based risk and association were analyzed via Cox proportional-hazards regression. TTFT was the time from diagnosis to initial treatment.

Figure 1. Study cohort selection process



RESULTS

- Characteristics of studied cohort are presented in **Table 1.**

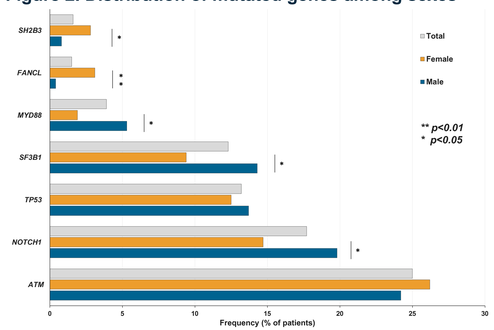
Table 1. Cohort characteristics

Characteristics	Male n=475	Female n=320	Total cases n=795	*p*-value [1]
Age at diagnosis (years)				
Median (IQR)	61 (53, 68)	62 (55, 69)	61 (53, 68)	.262
Range	23 – 88	20 – 88	20 – 88	
Age >65	154 (32.4%)	114 (35.6%)	268 (33.7%)	.349
Rai stage				
0	191 (40.2%)	158 (49.4%)	349 (43.9%)	
1-2	249 (52.4%)	151 (47.2%)	400 (50.3%)	**.038**
3-4	35 (7.4%)	11 (3.4%)	46 (5.8%)	**.007**
IGHV				.541
Mutated	221 (46.5%)	161 (50.3%)	382 (48.1%)	
Unmutated	222 (46.7%)	137 (42.8%)	359 (45.2%)	
Unknown[a]	32	22	54	
Chromosomal aberration				
del(11q)	66 (13.9%)	28 (8.8%)	94 (11.8%)	**.028**
del(13q)	238 (50.1%)	179 (55.9%)	417 (52.5%)	.106
del(17p)	53 (11.2%)	26 (8.1%)	79 (9.9%)	.161
del17p/TP53mut	33 (6.9%)	20 (6.3%)	53 (6.7%)	
del17p/TP53wt	20 (4.2%)	6 (1.9%)	26 (3.3%)	
no del17p/TP53mut	32 (6.7%)	20 (6.3%)	52 (6.5%)	
tri12	96 (20.2%)	68 (21.2%)	164 (20.6%)	.722
no abnormalities	113 (23.8%)	61 (19.1%)	174 (21.9%)	
FISH prognostic groups				
Favorable	165 (34.7%)	142 (44.4%)	307 (38.6%)	
Intermediate	195 (41.1%)	125 (39.1%)	320 (40.3%)	.075
Unfavorable	115 (24.2%)	53 (16.6%)	168 (21.1%)	**.002**
Karyotype				
Normal	260 (54.7%)	178 (55.6%)	438 (55.1%)	
Sole / Two abnormalities	132 (27.8%)	98 (30.6%)	230 (28.9%)	.679
Complex ≥3	83 (17.5%)	44 (13.8%)	127 (16%)	.256
Complex 3-4	54 (11.4%)	27 (8.4%)	81 (10.2%)	
Complex ≥5	29 (6.1%)	17 (5.3%)	46 (5.8%)	
ZAP-70				.069
Favorable	245 (51.6%)	186 (58.1%)	431 (54.2%)	
Unfavorable	230 (48.4%)	134 (41.9%)	364 (45.8%)	
ß2 microglobulin (B2M)				**.005**
≤3.5 mg/L	362 (76.2%)	269 (84.1%)	631 (79.4%)	
>3.5 mg/L	111 (23.4%)	47 (14.7%)	158 (19.9%)	
Unknown[b]	2	4	6	
Treatment status[c]				**.013**
Treatment-naïve	301 (63.4%)	230 (71.9%)	531 (66.8%)	
Treated	174 (36.6%)	90 (28.1%)	264 (33.2%)	
Vital status[c]				.858
Alive	456 (96%)	308 (96.2%)	774 (96.1%)	
Deceased	19 (4%)	12 (3.8%)	31 (3.9%)	

1 – Pearson's Chi-squared test; a – Analysis of IGHV mutational status was failed or was not done; b – ß2 microglobulin level was not tested; c – Status at timepoint of last follow-up.

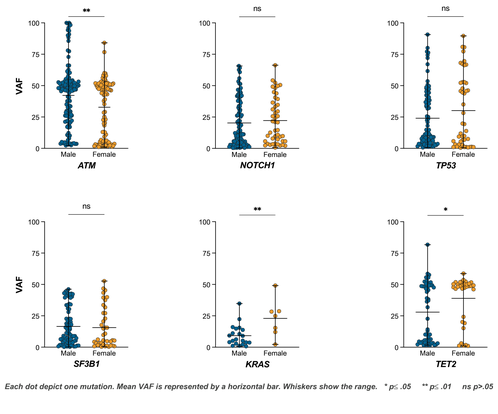
- The most mutated (≥10%) genes in the whole cohort were *ATM* (24.9%), followed by *NOTCH1* (18.0%), *TP53* (13.6%), and *SF3B1* (12.7%), **Figure 2.**

Figure 2. Distribution of mutated genes among sexes



- Males tended to have a higher variant allele frequency (VAF) in *ATM*, females had a higher VAF in *KRAS* and *TET2* **(Figure 3).**

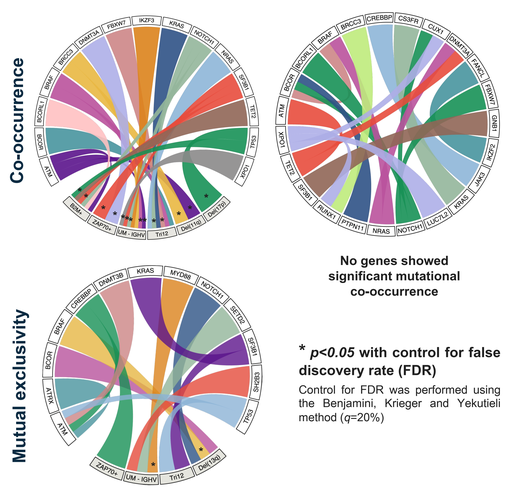
Figure 3. Distribution of VAF per genes



*Each dot depict one mutation. Mean VAF is represented by a horizontal bar. Whiskers show the range. * p≤.05 ** p≤.01 ns p>.05*

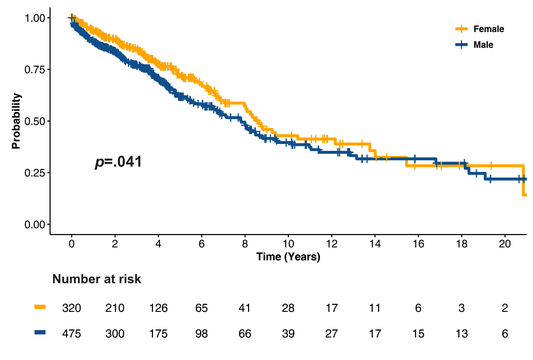
- We analyzed patients with a higher mutational burden (≥2 distinct mutated genes) for co-occurrence and mutual exclusivity patterns **(Figure 4)** using Fisher's exact test ($p<0.05$).

Figure 4. Pairwise association in CLL cohort



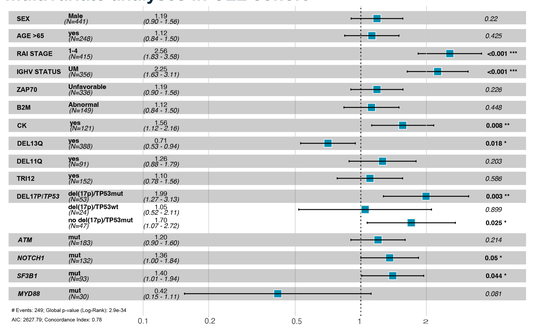
- **The median follow-up time for all patients was 3.91 years (range, 0 – 42.8).**
- Median TTFT in males was 7.83 yrs (6.54 – 8.81, 95% CI), in females – 8.62 yrs (7.96 – 13.76, 95% CI), **Figure 5.**

Figure 5. Kaplan-Meier curves of TTFT among sex



- In univariable (UV) analyses, male sex (p=0.041), age >65 (p=0.022), UM-*IGHV* (p<2.0E-16), CK3 (p=7.0e-10), each of del17p, del11q, and tri12 (p<0.001), as well as positive ZAP70 (p=0.00012) were associated with shorter TTFT.
- Mutated *MYD88* (p=0.029) and del13q (p=7.10e-06) were associated with prolonged TTFT in UV.
- In multivariable (MV) analysis **(Figure 6)** factors independently worsening TTFT were advanced Rai stages, UM-IGHV, CK, mutated *TP53* +/- del17p, mutated *SF3B1 and NOTCH1.*

Figure 6. Cox proportional hazard model for TTFT in multivariate analyses in CLL cohort



CONCLUSION

- In this study we identify a shorter TTFT in males vs females.
- Males had more advanced disease at diagnosis (Rai stage, B2M level) and higher frequency of unfavorable FISH.
- Mutated *SF3B1* (p=0.038) had a higher prevalence in males and independently associated with worsening TTFT.
- Sex is not a significant predictor of TTFT in MV analysis.

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