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Serum LC-MS based untargeted metabolomics machine learning identified CLL/SLL patients with different metabolic features and predict TTFT

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OBJECTIVES

- Use serum LC-MS based untargeted metabolomics to reveal serum metabolites features in CLL/SLL patients.
- Reveal the relationship between biological and clinical characteristics and serum metabolites.
- Explore prognosis of CLL/SLL patients with different metabolic modules.

CONCLUSIONS

- Serum metabolome differs among CLL/SLL patients and can be divided into three metabolic clusters.
- Patients assigned to different metabolic clusters showed different biological features.
- Patients belong to cluster2 showed better prognosis in terms of TTFT free survival in watch and wait cohort.

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INTRODUCTION

- Metabolic reprogramming is a hallmark of cancer and may play a pivotal role in driving disease progression. However, studies focused on serum metabolite profiles of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) patients are scarce.
- Besides, heterogenous metabolite profiles and whether biological characteristics will influence serum metabolome is also uncertained.
- Prognosis of metabolome in watch and wait cohort were explored.

METHODS

- Between Oct 2020 and Nov 2024, newly diagnosed CLL/SLL patients in Jiangsu Province Hospital with available serum samples were enrolled in the cohort (N=182) among whom 68 pts were asymptomatic and 114 pts were symptomatic according to iwCLL2018 criteria.
- All serum samples were collected prior to any treatment and LC-MS based untargeted metabolomics analysis were performed.
- Unsupervised Learning was used to demonstrate heterogenous composition of serum metabolome.
- PCA(principal component analysis) and Partial least squares discriminant analysis (PLS-DA) was used to visualize differences among metabolic clusters.
- Baseline clinical and biological features were compared between different clusters.

RESULTS

- Serum untargeted metabolomics based on LC-MS method totally identified 1157 metabolites.
- Baseline clinical and biological characteristics is shown in Table1. 37.4% patients are asymptomatic and 62.6% patients are asymptomatic are symptomatic. 38.4% patients are IGHV unmutated. 6.6% patients have 17p deletion, 20.0% patients have TP53 mutation.
- By unsupervised learning method, patients enrolled in this study were divided into 3 metabolic clusters(Figure2). Both PCA and PLSDA visualized the distinct separation among different metabolic clusters(Figure3A-B).Metabolite set enrichment analysis (MESA) showed these metabolites enriched in glycerophospholipid metabolism, nitrogen metabolism, purine metabolism and arginine biosynthesis.
- Clinical and biological characteristics were compared between different clusters and clinical characteristics showed no difference among 3 clusters. However, cluster 1 had higher proportion of patients with KMT2D mutation and EGR2 mutation. Cluster 3 had higher proportion of patients with TP53 mutation(Table2).
- Median follow-up was 652 days in asymptomatic cohort(watch and wait cohort) . Patients featured with metabolic cluster 2 had higher 2 year TTFT free survival, suggesting serum metabolome may reflect metabolic clusters with biological features and prognosis.

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DISCLOSURES

None

Figure1. Study design.

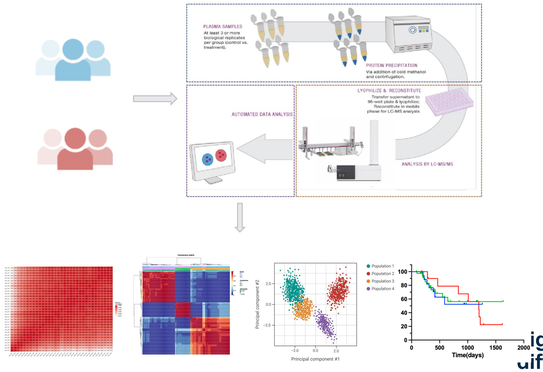

Figure2.CLL/SLL patients can be divided into three metabolic clusters by consensus NMF.

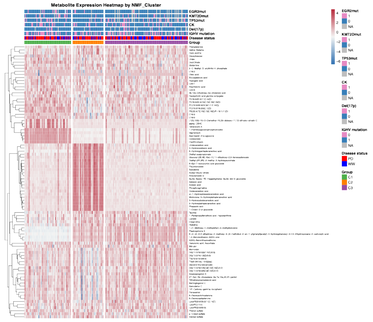

Table1.Clinical and biological characteristics of the cohort.

Characteristics	Overall (N = 182)
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Age, Mean ± SD	59 ± 12
Sex, n (%)	
Male	112 (61.5%)
Female	70 (38.5%)
BMI, n (%)	
<18.5	14 (7.7%)
18.5~24	85 (46.7%)
24~28	61 (33.5%)
≥28	10 (5.5%)
Missing	12 (6.6%)
B2MG, Mean ± SD	3.66 ± 1.84
LDH, Mean ± SD	220 ± 123
WBC, Mean ± SD	66 ± 72
ALC, Mean ± SD	55 ± 63
Disease status, n (%)	
PD	114/182 (62.6%)
WW	68/182 (37.4%)
Binet stage, n (%)	
A	45/182 (24.7%)
B	66/182 (36.3%)
C	71/182 (39.0%)
Bulky(>5cm), n (%)	
Yes	98/159 (61.6%)
No	61/159 (38.4%)
IGHV mutation, n (%)	
mutated	156/167 (93.4%)
unmutated	11/167 (6.6%)
Del(17p), n (%)	
No	87/154 (56.5%)
Yes	67/154 (43.5%)
Del(13q14), n (%)	
No	138/157 (87.9%)
Yes	19/157 (12.1%)
Del(11q), n (%)	
No	113/150 (75.3%)
Yes	37/150 (24.7%)
Trisomy12, n (%)	
No	113 (62.1%)
Yes	37 (20.3%)
Del(6q23), n (%)	
No	123/128 (96.1%)
Yes	5/128 (3.9%)
CK, n (%)	
No	139/179 (77.7%)
Yes	40/179 (22.3%)
TP53mut, n (%)	
No	128/160 (80.0%)
Yes	32/160 (20.0%)
NOTCH1mut, n (%)	
No	132/156 (84.6%)
Yes	24/156 (15.4%)
SF3B1mut, n (%)	
No	141/156 (90.4%)
Yes	15/156 (9.6%)
MYD88mut, n (%)	
No	138/157 (87.9%)
Yes	19/157 (12.1%)
ATMmut, n (%)	
No	135/156 (86.5%)
Yes	21/156 (13.5%)
KMT2Dmut, n (%)	
No	139/157 (88.5%)
Yes	18/157 (11.5%)
BIRC3mut, n (%)	
No	149/156 (95.5%)
Yes	7/156 (4.5%)
EGR2mut, n (%)	
No	145/156 (92.9%)
Yes	11/156 (7.1%)

Figure3. Serum Metabolome differs between different metabolic clusters.

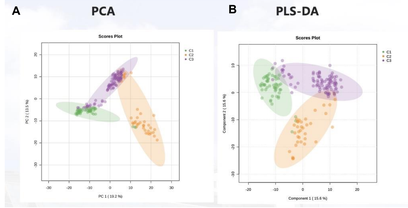

Table2. Biological characteristics differ between clusters

Percentage(%)	C1(N=53)	C2(N=35)	C3(N=94)	C1 vs C2	C1 vs C3	C2 vs C3
IGHV-UM	43.1%(22/51)	34.4%(11/32)	36.8%(28/76)	0.427[1]	0.579[1]	0.807[1]
TP53mut	20%(10/50)	8.8%(3/34)	25%(19/76)	0.165[1]	0.514[1]	0.050[1]
Del(17p)	7.8%(4/51)	3.0%(1/33)	7.2%(6/83)	0.644[2]	0.896[1]	0.671[2]
Trisomy	28.6%(14/49)	20.0%(6/30)	23.9%(17/71)	0.395[1]	0.569[1]	0.666[1]
CK	26.4%(14/53)	20.0%(7/35)	20.9%(19/91)	0.490[1]	0.446[1]	0.913[1]
NOTCH1mut	14.6%(7/48)	6.1%(2/33)	20.0%(15/75)	0.298[2]	0.445[1]	0.067[1]
KMT2Dmut	20.0%(10/49)	2.9%(1/33)	9.2%(7/75)	0.025[2]	0.083[1]	0.431[2]
EGR2mut	14.3%(7/48)	8.8%(3/33)	1.3%(1/75)	0.515[2]	0.006[2]	0.087[2]
ATMmut	14.6%(7/48)	6.1%(2/33)	16.0%(12/75)	0.298[2]	0.832[1]	0.219[2]
MYD88mut	12.2%(6/49)	15.2%(5/33)	10.7%(8/75)	0.749[2]	0.786[1]	0.531[2]
SF3B1mut	12.5%(6/48)	12.1%(4/33)	6.7%(5/75)	>0.999[2]	0.336[2]	0.451[2]

Figure4. Prognosis differs between different metabolic clusters in watch and wait cohort.