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RESEARCHARTICLE

Integrin alpha 7 expression in newly diagnosed Egyptian chronic lymphocytic leukemia patients

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ABSTRACT

Background: The landscape for chronic lymphocytic leukemia (CLL) has undergone a full makeover since the emergence of effective targeted therapies. Searching for novel biomarkers in CLL patients is critical to improve outcomes in CLL patients. Integrins, which play a key role in the tissue localization of both normal and malignant cells, are now known to be expressed in cells as well as in tumor and immune cell exosomes that can affect endothelial cells' proliferation, migration, and gene expression. **Aim**: Here, we aimed to assess the role of integrin α7 gene expression in de novo CLL patients. **Materials and Methods**: Integrin alpha7 gene expression by real-time PCR was evaluated in 40 De novo CLL patients as well as 40 age and sex-matched controls at the Medical Research Institute, Alexandria University, Egypt. **Results**: Levels of integrin α7 gene expression were significantly higher in CLL cases compared to normal controls. **Conclusion**: Integrin α7 gene expression can be used as a prognostic marker in de novo CLL patients.

Keywords: CLL, gene expression, Integrin α7.

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INTRODUCTION

Chronic lymphocytic leukemia (CLL) is a B-cell neoplasm characterized by progressive clonal expansion of monoclonal mature-looking CD5, CD23-positive B cells in the peripheral blood, bone marrow and lymphoid organs (Shishido et al., 2014, Bannerji et al., 2000). The Rai and Binet systems are the two main staging systems currently used for CLL evaluation in both routine practice and clinical trials (Catovsky et al., 2019). Before the start of therapy, there were certain indications that the disease was active, and treatment should be commenced. Progressive marrow failure, bulky lymph nodes, splenomegaly (i.e. ≥ 6 cm below the costal margin), steroid-refractory autoimmune complications and B symptoms are all indications of treatment initiation (Hallek et al., 2018). 17p deletion and IGHV mutation should be assessed to categorize treatment selection (Baliakas al., 2015).

Progression of CLL can occur due to the acquisition of certain mutations, mainly 17p deletion and TP53. There is a continuous search for novel target drug therapy in cases of chronic leukemia, aiming to overcome drug resistance and achieve a cure for patients, as well as MRD negativity (Baliakas et al., 2015). Among the promising targets that can affect treatment categorization and selection in the future of CLL are the integrins. Recirculation of the malignant lymphocytes (making them able to bypass the endothelium and migrate inside the tissues) is facilitated by integrins, which have a crucial role in this setting (Rossi et al., 2013).

Integrins are a big family of cell adhesion receptors made up of one alpha and one beta subunit. Adhesion of integrins to either extracellular matrix or stromal cell proteins activates intracellular signaling in hematopoietic and epithelial cells, which is required for cell proliferation, migration, survival, and resistance to death. Also, Recent studies have shown that integrin expression and function are pivotal in the migratory behavior of cancer cells, which use them to promote cell cycling within tissues and colonization of distal organs. Intercellular cohesion is essential for structural organization and communication between cells in multicellular animals (Danen et al., 2013, de la Fuente et al., 2002).

One member of the large integrin family in chronic lymphocytic leukemia (CLL) is α4β1integrin (CD49d), which has several pathological features, including participation in cell survival and migration. Subsequently, High expression of α4 integrin (≥30% cells) constitutes an adverse prognostic marker. CD 49d is considered a powerful predictor of overall and progression-free survival in CLL (Scharff et al., 2020).

CD49d/CD29 mediates cell-cell and cell-matrix interactions in CLL-affected tissues, delivering pro-survival signals and inhibiting drug-induced

apoptosis. Furthermore, CD49d/CD29 plays an important function in pushing CLL cells to the lymphoid organs. This is supported by the link between high levels of CD49d expression and lymphadenopathy at diagnosis, the progression of lymphadenopathy along the course of the disease, and practically ubiquitous CD49d expression in CLL subgroups with widespread nodal disease (Till et al., 2002, Hamidi et al., 2018, Dal Bo et al., 2016).

Trisomy 12 has been linked to high levels of CD49d expression caused by hypomethylation of the ITGA4 promoter, which encodes CD49d. This connection may explain the significant LN adenopathy frequently reported in patients bearing the trisomy 12 anomaly and the tropism of these cells toward the LN (Gutiérrez-González et al. 2019).

Another interesting integrin is the Integrin α7 (ITGA7), which is located on chromosome 12p13, forms a heterodimer with Integrin β1 in the plasma membrane, and facilitates contact between the extracellular matrix and cells. The ITGA7/integrin β1 heterodimer binds laminins 1 and 2. ITGA7 affects cell differentiation and migration as well as the interaction between cells and the extracellular matrix (Tan et al., 2013)

Targeting adhesion molecules in CLL may have multiple benefits, including blocking CLL cell homing and recirculation of cells into protective niches, promoting malignant cell exit from those niches into the PB, where they are more susceptible to chemotherapeutic agents, and finally inhibiting microenvironment-mediated drug resistance (Pasikowska et al., 2016, Zhu et al., 2010, Zucchetto et al., 2013).

This study was designed to investigate ITAG7 in Egyptian CLL patients for the first time. ITAG7 was evaluated in multiple solid tumors, including colorectal cancer, oesophageal carcinoma, gliomas, and AML. It is characterized as a potential stem cell marker, where its high expression is associated with a worse prognosis (Haas et al., 2017, Ming et al., 2016, Elaggan et al., 2024)

Subjects and Patients

We conducted this study on 40 newly diagnosed CLL patients and 40 matched healthy subjects as a control group. Patients were enrolled from the Hematology Department, Medical Research Institute, Alexandria University.

Ethical approval

This study was performed after approval 0306727 by the local ethics committee at the Medical Research Institute and Faculty of Medicine, Alexandria University, Egypt. Before sample collection, Informed consent from the patients was taken after an explanation of the study objectives. This study was conducted following the 1964 Declaration of Helsinki.

Inclusion criteria, exclusion criteria, rationale, and specifications

Patients were eligible for inclusion based on the WHO criteria for diagnosis of CLL patients which requires the presence of $\geq 5 \times 10^9$/L B lymphocytes in the peripheral blood, sustained for at least 3 months (Hallek et al., 2018). The clonality of these B lymphocytes was confirmed by demonstrating immunoglobulin light chain restriction using flow cytometry. The leukemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm and a dense nucleus lacking discernable nucleoli and partially aggregated chromatin (Catovsky et al., 2019).

CLL cells co-express the surface antigen CD5 together with the B-cell antigen CD19, CD20, and CD23. The levels of surface immunoglobulin, CD20, and CD79b are characteristically low compared with those found on normal B cells with restricted expression of either κ or λ immunoglobulin light chains. A large harmonization effort has confirmed that a panel of CD19, CD5, CD20, CD23κ, and λ is usually sufficient to establish the diagnosis (Hallek et al., 2018). Patients with active second malignancies were not considered for enrollment in the present study.

Clinical and Laboratory Assessment

CLL patients in our study had a full checkup, such as clinical examination, complete blood count (CBC) with blood film examination, Peripheral blood immunophenotyping, and imaging studies were performed. Patients were classified according to RAI and Binet staging system .

The following investigations were done at diagnosis (Reticulocyte count, LDH, DAT, B2 microglobulin, ZAP 70, CD 38, and 17p deletion). Bone marrow examination was performed at diagnosis if indicated.

Integrin alpha7 gene expression

Integrin alpha7 gene expression was done by quantitative real-time PCR. RNA extraction was performed on peripheral blood samples via RNeasy Mini Extraction Kit (QIAGEN, Maryland, USA) according to the manufacturer's instructions and under sterile conditions using a UV laminar flow cabinet. Reverse transcription (RT) was utilized using Thermo Scientific Revert Aid First Strand cDNA Synthesis Kit and Veriti 96–well thermal cycler. SYBR Green real-time PCR preparation for ITAG7 (target

gene) and GAPDH (housekeeping gene) using UV laminar flow, where the reaction was performed using a Rotor-Gene Q cycler from Qiagen. Primers (Thermo Fischer Scientific™); details were supplied in Table 1. Ct values were evaluated for cases and controls, ΔΔCt values (ΔCt case - ΔCt control), and the relative gene expression was calculated using $2^{-\Delta\Delta Ct}$.

Table (1): Primer sequences used in the gene expression assay.

Target gene	***Integrin Alpha7***
Forward	5'-GCC ACT CTG CCT GTC CAA TG-3'
Reverse	5'-CGG AGG TGC TAA GGA TGA GGT A -3'
Housekeeping gene	***GAPDH***
Forward	5'-TGA CCA CAG TCC ATG CCA TCA C-3'
Reverse	5'-GCC TGC TTC ACC ACC TTC TTG A -3'

These genes were supplied by Invitrogen from Thermo Fischer Scientific™, USA.

Statistical analysis

Data was fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). Categorical data were represented as numbers and percentages. A chi-square test was applied to compare between two groups. Alternatively, Fisher Exact test was applied when more than 20% of the cells had an expected count of less than 5. A chi-square test was applied to investigate the association between the categorical variables. Alternatively, the Monte Carlo correction test was applied when more than 20% of the cells had an expected count of less than 5. For continuous data, they were tested for normality by the Shapiro-Wilk test.

Quantitative data were expressed as range (minimum and maximum), mean, standard deviation and median. Student's t-test was used to compare two groups for normally distributed quantitative variables. For non-normally distributed quantitative variables, Mann-Whitney test was used to compare two groups, while Kruskal-Wallis test was used to compare more than two groups. Spearman coefficient was used to correlate non-normally distributed quantitative variables. The receiver operating characteristic curve (ROC) was used to determine the diagnostic performance of the marker area of more than 50% indicates acceptable performance and an area of about 100% is the best performance for the test. The significance of the results obtained was judged at the 5% level.

Results

The study cohort comprised 40 Egyptian CLL patients with a median age of 65 years. CLL patients were further sub-grouped according to those fulfilling the criteria for initiating treatment vs those on active surveillance (without indication to be treated) according to iwCLL guidelines (Hallek et al., 2018)

CBC results for our patients revealed that the median Hb concentration was 12.9 gm/dl for those on watchful waiting, 9.5 gm/dl for those indicated for treatment, respectively .

As regards WBCs at diagnosis median count was 40.4 × 109/L, with ALC median was 31.9 × 109/L for the watchful waiting group vs 111× 109/L and ALC median was 93.2× 109/L in the group indicated for therapy, as illustrated in Table 2.

As for reticulocyte count, biochemical parameters, including LDH and beta2 microglobulin results, were higher in those indicated for treatment in comparison to the watchful waiting group. As regards prognostic markers, ZAP70 expression (17.5%), CD38 expression (32.5%) and 17p del (20.0%), with no difference between the 2 subgroups as shown in Table.(2) splenomegaly and lymphadenopathy were present in 63.6% and 90.9%, respectively, in the CLL patients indicated for therapy, which was significantly higher than those on watch and wait.

There was a statistically significant difference as regard Integrin α 7 expressions in CLL patients compared to normal controls. The vast majority of CLL cells express Integrin α 7, with a median 22.5 (range 18.1 – 36.6) in the patients' group in comparison to the control group 19.6 (range 15 – 27.2), with no statistically significant difference between the 2 subgroups (watchful waiting and those indicated for treatment subgroups) as shown in Table (3).

Table (3): Comparison between CLL patients and control groups according to integrin α-7

	CLL (n = 40)	**Control (n = 40)**	**U**	**p**
Integrin α-7				
Mean±SD	24.7 ± 5.2	20.3 ± 4.2		
Median (Min. –Max.)	22.5 (18.1 – 36.6)	19.6 (15 – 27.2)	458*	0.001*

U: Mann-Whitney test SD: Standard deviation

Statistically significant at p ≤ 0.05 :*

A cutoff value >20.57 using the ROC curve for Integrin α-7 was used to discriminate patients from normal controls had a sensitivity of 80% and specificity of 55%. As described in Figure 1 and Table 4.

Correlation between integrin α-7 and different lab and biochemical parameters revealed insignificance with all parameters except for the percentage of smudge cells in peripheral blood *P*-value (0.028*) as shown in Tables (5,6).

Table 2: Relation between treatment plans with different parameters in the parameters in the cases group and subgroups cases group and subgroups

	Total (n = 40)	Treatment plan: PATIENTS INDICATED FOR TREATMENT (n = 22)	Treatment plan: Watchful waiting (n = 18)	Test of Sig.	p
Sex					
Male	21 (52.5%)	10 (45.5%)	11 (61.1%)	χ^2=	0.324
Female	19 (47.5%)	12 (54.5%)	7 (38.9%)	0.973	
Age (years)					
Mean ± SD.	63.9 ± 10.6	64.4 ± 11.0	63.2 ± 10.3	t=	0.730
Median (Min. – Max.)	65.0 (42.0 – 85.0)	66.0 (45.0 – 82.0)	62.0 (42.0 – 85.0)	0.348	
HB					
Mean ± SD.	10.9 ± 2.3	9.26 ± 1.48	12.96 ± 1.35	t=8.179*	>0.001*
Median (Min. – Max.)	11.0 (6.4 – 15.9)	9.50 (6.40 – 11.60)	12.9 (11.0 – 15.9)		
PLT					
Mean ± SD.	169.8 ± 78.2	147.4 ± 90.1	197.2 ± 50.65	t=2.200*	0.035*
Median (Min. – Max.)	170.0 (33.0 – 338.0)	116.0 (33.0 – 338.0)	190.5 (115.0 – 296.0)		
WBCs					
Mean ± SD.	113.5 ± 134.2	154.7 ± 162.4	63.0 ± 62.2	U=	0.017*
Median (Min. – Max.)	63.9 (14.2 – 722.7)	111.0 (14.43 – 722.7)	40.4 (14.20 – 250.0)	111.00*	
ALC					
Mean ± SD.	101.5 ± 123.2	140.3 ± 147.3	54.0 ± 60.5	U=	0.007*
Median (Min. – Max.)	52.2 (8.6 – 635.9)	93.2 (12.99 – 635.9)	31.9 (8.57 – 245.0)	100.00*	
DAT	3 (7.5%)	3 (13.6%)	0 (0.0%)	χ^2=2.654	FEp=0.238
17p	8 (20.0%)	5 (22.7%)	3 (16.7%)	χ^2=0.227	FEp=0.709
Splenomegaly	18 (45.0%)	14 (63.6%)	4 (22.2%)	χ^2=6.861*	0.009*
Lymphadenopathy	29 (72.5%)	20 (90.9%)	9 (50.0%)	χ^2=8.310*	FEp=0.006*
Hepatomegaly	9 (22.5%)	6 (27.3%)	3 (16.7%)	χ^2=0.639	FEp=0.476
RETIC					
Mean ± SD.	1.9 ± 3.3	2.68 ± 4.29	0.88 ± 0.45	U=	0.001*
Median (Min. – Max.)	0.9 (0.6 – 19.3)	1.14 (0.60 – 19.25)	0.75 (0.60 – 2.60)	77.500*	
LDH					
Mean ± SD.	284.9 ± 95.1	321.3 ± 110.0	240.4 ± 44.3	U=	0.006*
Median (Min. – Max.)	255.5 (183.0 – 562.0)	294.5 (199.0 – 562.0)	241.0 (183.0 – 321.0)	98.00*	
B2microglobulin					
Mean ± SD.	2.7 ± 1.5	3.26 ± 1.48	1.95 ± 1.30	U=	0.013*
Median (Min. – Max.)	2.9 (0.7 – 5.7)	3.35 (0.70 – 5.70)	1.40 (0.70 – 4.80)	107.500*	
Smudge cells (%)					
Mean ± SD.	26.8 ± 15.3	23.59 ± 12.46	30.7 ± 17.8	U=	0.325
Median (Min. – Max.)	23.5 (8.0 – 73.0)	20.0 (10.0 – 60.0)	34.0 (8.0 – 73.0)	161.500	
ZAP70	8 (20.0%)	6 (27.3%)	2 (11.1%)	χ^2=1.616	FEp=0.258
CD38	13 (32.5%)	7 (31.8%)	6 (33.3%)	χ^2=0.010	0.919
Binet					
A	16 (40.0%)	3 (13.6%)	13 (72.2%)	χ^2=	MCp
B	7 (17.5%)	2 (9.1%)	5 (27.8%)	27.417*	>0.001*
C	17 (42.5%)	17 (77.3%)	0 (0.0%)		
RAI					
No	9 (22.5%)	0 (0.0%)	9 (50.0%)		
I	5 (12.5%)	0 (0.0%)	5 (27.8%)		
II	4 (10.0%)	0 (0.0%)	4 (22.2%)	χ^2= 42.850*	MCp >0.001*
III	12 (30.0%)	12 (54.5%)	0 (0.0%)		
IV	10 (25.0%)	10 (45.5%)	0 (0.0%)		

Hb: hemoglobin, ALC: absolute lymphocytic count, DAT: direct Coombs test, RETIC, reticulocyte count, LDH: lactate dehydrogenase, ZAP70: zeta chain associated protein kinase 70, SD: Standard deviation

*: Statistically significant at $p \leq 0.05$

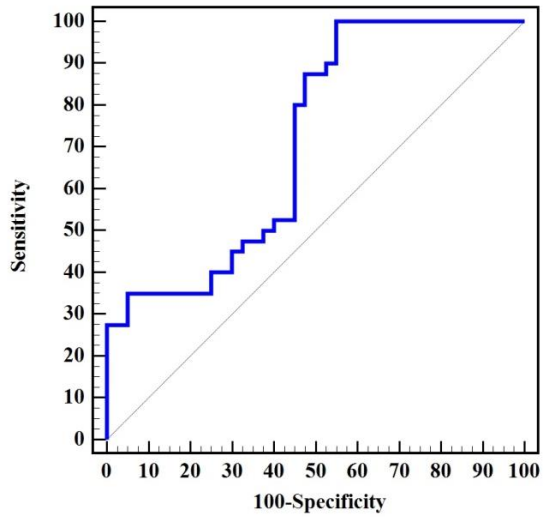

Figure 1: ROC curve for Integrin α-7 to discriminate patients (n = 40) from control (n = 40).

Table (4): Diagnostic performance for Integrin α-7 to distinguish patients (n = 40) from control (n = 40)

	AUC	P	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
Integrin α-7	0.714	0.001*	0.600 – 0.828	>20.57	80.0	55.00	64.0	73.3

AUC: Area Under a Curve *P*-value: Probability value
CI: Confidence Intervals NPV: Negative predictive value
PPV: Positive predictive value
*: Statistically significant at p ≤ 0.05

	Control	Cases
≤20.57	22	8
>20.57	18	32

Discussion

Integrins are a diverse family of receptors that mediate cell adhesion receptors which activate signaling in hematopoietic and epithelial cells. Integrins mediate their action through binding to some glycoproteins, such as collagens and laminins. Integrin α7 expression has been linked to AML and granulocytic sarcoma, while integrin α4:β1 (VLA-4) is an independent prognostic factor in chronic lymphoblastic leukemia (CLL) and has been linked to chemoresistance in those patients. (Cerreto et al., 2023). Many immune-related diseases, such as arthritis, cancer and certain other diseases, have been linked to dysregulation of integrins due to the interaction between integrins and immune cell receptors.

Strikingly, this connection between integrins and different ligands on the surface of various immune and cancer cells has been implicated in the pathogenesis of cancer by promoting or inhibiting its occurrence. Most of the studies done before on integrins proposed three precancerous mechanisms, which are: mediating the expansion of cancer cells, increasing invasion, and spreading of cancer cells, and producing immunological tolerance effects by inhibiting immune cell responses (Kobayashi et al., 2020)

Table (5): Correlation between Integrin α-7 with some hematological parameters in the cases group (n = 40)

Integrin α-7	r_s	p
Age (years)	-0.194	0.231
HB	0.020	0.903
PLT	-0.003	0.983
WBCs	-0.108	0.507
ALC	-0.087	0.593
RETIC	0.190	0.240
LDH	0.009	0.958
B2microglobulin	0.006	0.969

Regarding CBC parameters in our CLL patients, our results were like many published data as Kaasuhan et al. and Hayran M et al. (Kassahun et al., 2020, Zhang et al., 2023). Smudge cells (SCs) have many synonyms, known as Gumprecht shadows and basket cells, which are commonly seen on CLL patients' blood films. In CLL, almost all SCs are damaged lymphocytes. However, this has a considerable impact on the accuracy of differential WBCS cell counts. In our study, Smudge cells percent was the same as published by Marionneaux et al and Sall et al. (Hayran et al., 2006, Marionneaux et al., 20121)

As for important prognostic markers in CLL as 17p was 20% in our study, and it was more in the global range, as stated by Puiggros 2014 for newly diagnosed CLL patients. But it was 5% in those indicated for treatment, which is like the global range. Regarding ZAP70, we found that it was 17.5% and it is a reliable prognostic marker in CLL (Orchard et al., 2004, Sall et al., 2022, Baliakas et al., 2022).

There was a significant overexpression of Integrin Alpha 7 in CLL patients compared to normal controls. Unfortunately, we did not find any correlation between Integrin Alpha 7 and other hematological parameters as Hb, PLT, WBCs, LDH, and reticulocyte count etc. Also, there was no significant correlation with different prognostic markers, genetic markers and staging systems. To the far of our knowledge, we are the first to spotlight the role of Integrin Alpha 7 as an emerging novel prognostic marker in de novo

Table (6): Relation between Integrin α-7 with different parameters in cases group (n = 40)

	No.	Integrin α-7		Test of Sig.	p
		Mean ± SD.	Median (Min. – Max.)		
Sex					
Male	**21**	24.08 ± 4.80	22.07 (18.09 – 36.58)	U= 182.50	0.649
Female	**19**	25.30 ± 5.65	24.34 (18.49 – 36.58)		
DAT					
Negative	**37**	24.89 ± 5.25	22.73 (18.09 – 36.58)	U= 33.00	0.273
Positive	**3**	21.77 ± 4.05	19.83 (19.05 – 26.43)		
17p					
Negative	**32**	24.29 ± 5.12	22.20 (18.09 – 36.58)	U= 95.00	0.278
Positive	**8**	26.12 ± 5.57	24.09 (21.06 – 36.58)		
Splenomegaly					
Negative	**22**	25.11 ± 5.17	23.11 (18.78 – 36.58)	U= 169.00	0.443
Positive	**18**	24.11 ± 5.32	22.04 (18.09 – 36.58)		
Lymphadenopathy					
Negative	**11**	23.98 ± 5.36	22.73 (18.78 – 36.58)	U= 145.00	0.676
Positive	**29**	24.92 ± 5.20	22.33 (18.09 – 36.58)		
Hepatomegaly					
Negative	**31**	24.68 ± 5.26	22.73 (18.09 – 36.58)	U= 134.00	0.874
Positive	**9**	24.60 ± 5.27	21.74 (19.05 – 31.79)		
ZAP70					
Negative	**32**	23.99 ± 5.13	21.96 (18.09 – 36.58)	U= 73.000	0.065
Positive	**8**	27.33 ± 4.84	27.17 (21.06 – 34.24)		
CD38					
Negative	**27**	24.58 ± 5.49	22.07 (18.09 – 36.58)	U= 155.500	0.568
Positive	**13**	24.82 ± 4.72	23.48 (19.05 – 36.58)		
Binet					
A + B	**23**	24.83 ± 5.22	22.73 (18.09 – 36.58)	U= 176.00	0.607
C	**17**	24.43 ± 5.31	21.84 (18.49 – 36.58)		
RAI					
No	**9**	24.78 ± 5.63	23.48 (18.78 – 36.58)	H= 4.885	0.299
I	**5**	28.81 ± 5.29	27.91 (20.95 – 34.24)		
II	**4**	21.50 ± 2.44	22.04 (18.09 – 23.84)		
III	**12**	24.78 ± 4.55	23.21 (18.49 – 31.79)		
IV	**10**	23.59 ± 5.79	21.38 (19.05 – 36.58)		

CLL patients. Integrin Alpha 7 overexpression correlates with higher pathological grade in solid tumors, e.g., renal cell carcinoma and colorectal cancer (Chen et al., 2020, Cloutier et al., 2023).

As regards our results, there was a significant over-expression of Integrin Alpha 7 in CLL patients compared to normal controls. Unfortunately, we did not find any correlation between Integrin Alpha 7 and other hematological parameters as Hb, PLT, WBCs, LDH, and reticulocyte count etc. Analyses of mRNA profiles revealed that high ITGA7 expression negatively correlated with the survival of patients with both low- and high-grade glioma. It was found that targeting of ITGA7 by RNAi or blocking mAbs impaired signaling, and it led to a significant delay in tumor engraftment, plus a strong reduction in tumor size and invasion (Haas et al., 2017). It is recommended to perform a larger cohort study and follow-up for CLL patients to evaluate its role as a prognostic marker. As well as further studies are recommended to evaluate its correlation with treatment response (a prognostic marker). As well as further studies are recommended to evaluate its correlation with treatment response.

Conclusion

Our study highlighted that integrin alpha 7 expression is significantly increased in de novo CLL patients. Further studies are recommended to elucidate the role of higher Integrin alpha7 gene expression levels in de novo CLL patients and their correlation to treatment response.

Statements and Declarations

Competing interests

The authors declare that they have no competing interests.

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Author contributions

All authors declared equal contribution.

Data Availability statements

Data supporting this study are available upon request.

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Not applicable

Data Availability statements

Data supporting this study are available upon request.

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This manuscript has been read and approved by all the authors, and the requirements for authorship as stated by the journal have been met, and each author believes that the manuscript represents honest work.

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