RESEARCH ARTICLE

Editorial Process: Submission:11/27/2022 Acceptance:04/23/2023

Implication of Dynamin-2 (*DNM2*) Mutations in Adult T-cell Acute Lymphoblastic Leukemia

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Abstract

Background: The objective of the present study was to improve the risk stratification of T-cell Acute Lymphoblastic Leukemia (T-ALL) patients. It aimed to identify the frequency and clinical impact of *DNM2* gene mutations among adult T-ALL cases. **Methods:** The current study included 25 T-ALL patients before starting their treatment. Mutational analysis of *DNM2* gene (exons 18 and 22) was performed for all patients using Macrogen 3730 apparatus. **Results:** We identified *DNM2* gene mutations in 19 out of 25 (76%) patients. The detected mutations were either missense or deletion. Only active mutations (deletion) were associated with poor induction remission response and high frequency of relapse. Two novel mutations were addressed among the studied cohort of patients. They included c.1866G>C (p.V596L) and c.1872delA in exon 18. A high frequency of silent mutations was also found in T-ALL patients, but with no impact on clinical features. **Conclusion:** The *DNM2* mutations were prevalent among adult T-ALL patients and might have a role in the pathogenesis of the disease. Active *DNM2* mutations were associated with poor clinical outcome. Moreover, high frequency of *DNM2* mutations indicated that these mutations could be utilized in detection of minimal residual disease in T-ALL patients.

Keywords: *DNM 2*- mutations- adult T-cell acute lymphoblastic leukemia- prognosis

Asian Pac J Cancer Prev, **24 (4)**, 1257-1264

Introduction

T-cell Acute Lymphoblastic Leukemia (T-ALL) is an aggressive, malignant disorder that affects both pediatrics and adults (Bridges et al., 2023; Pui et al., 2008). It represents about 15% of pediatrics and 25% of adults (Chennamadhavuni et al., 2022; Iacobucci and Mullighan, 2017). In 2023, it was reported 6540 T-ALL new cases and 1390 deaths in a project done in the United States (Siegel et al., 2023). The diagnosis of T-ALL requires the presence of 20% or more blasts in bone marrow (Paul et al., 2016). Clinical features of T-ALL patients usually include elevation of the total leukocyte count (TLC) and may show organomegaly and CNS involvement (Chiaretti and Foà, 2009; Del Principe et al., 2014; Ikonomidou, 2021). T-ALL is divided into 5 subtypes according to molecular biology, gene expression and FISH results. These subtypes include pro-T, pre-T, cortical, mature T-ALL and ETP (Ferrando et al., 2002; Ge et al., 2016). T-ALL is associated with high risk of treatment failure (Trochet and Bitoun, 2021).

Previous studies indicated that genetic mutations might have an adverse impact on patient with T-ALL (Chiaretti and Foà, 2009; Neumann et al., 2015; Roberts and Mullighan, 2015). More than one hundred genes were identified to be mutated in ALL but with variable frequency. The most popular mutated genes were NOTCH1 and CDKN2A/2B. It was reported that mutations of these genes appeared in more than 50% of patients with T-ALL (Aref et al., 2020). According to the available genomic data, it was noticed that each T-ALL case contained more than 10 genes defects (Girardi et al., 2017, Aref et al., 2016, Aref et al., 2021).

Dynamin-2 (DNM2) is a large GTPase (100kDa) located on short arm of chromosome 19 (19p13.2). Its product was specified as a micro-tubule binding protein which composed of four isoforms 1, 2, 3 and 4. The *DNM2* gene is composed of 22 exons and consists of 5 domains: GTPase domain, intermediate domain (MD), pleckstrin homology domain (PH), GTPase effector domain (GED) and proline-arginine-rich domain (PRD) (Cao et al., 1998; Durieux et al., 2010; Ramachandran and Schmid, 2018; Sambuughin et al., 2015; Xu et al., 2014).

The GTPase *DNM2* is essential for a lot of physiological functions; it is responsible for membrane trafficking, cytokinesis and receptor endocytosis. It is also acting as a regulator of cytoskeletons. Overexpression of *DNM2* gene is associated with some cancer types and their

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progression. *DNM2* mutations are observed in early precursor T-ALL (EPT-ALL) with a high risk of induction failure or not achieving complete remission (Ge et al., 2016; Sambuughin et al., 2015). This study aimed to determine the frequency of *DNM2* gene mutations in adult T-ALL patients and relate them to clinical and pathological characters.

Materials and Methods

The study was approved by Mansoura University IRB and was done according to Helsinki regulation.

Patients and Samples

Five mls of EDTA blood sample were collected from 25 T-ALL patients (17 male, 8 females), with mean age 34.76 (age range 17-62), who were newly diagnosed with recruitment at Mansoura University Oncology Center (OCMU), Mansoura University, Mansoura, Dakahlia Governorate, Egypt. (Table 1). The examined T-ALL patients were followed up for 24 months.

Treatment protocol

Induction remission protocol for adult T-ALL cases, was by either augmented Berlin-Frankfurt-Münster (aBFM) protocol (Chang et al., 2008) or modified hyper CVAD (cyclophosphamide, vincristine, dexamethasone, doxorubicin) (anthracycline intensification) (Thomas et al., 2010) in relapsed or high risk ALL cases and gemcitabine was used in pediatric T-ALL cases (Angiolillo et al., 2006).

Follow up and prognostic criteria

Hematological remission was identified when the blast cells < 5% in bone marrow. Complete remission was addressed by minimal residual disease cut off levels of blast cells count < 0.01%. Relapse is identified as reappearance of blasts in blood smear or the presence of > 5% blast cells in BM smear. Disease free survival (DFS) is the time from complete remission to time of relapse, death or date of last contact with patient. Overall survival (OS) is the time from study entry until death from any cause or last contact with patient (Aref et al., 2020).

Methods

T-ALL diagnosis was done by morphological examination of bone marrow smear (Blast cells equal to or more than 20%) and immunophenotyping using flowcytometry panel including cytoplasmic CD3, CD5, CD7, CD2, CD4, CD8, CD34, TDT, CD19, CD79a, MPO, and CD117.

DNA Extraction and Amplification

Mini QIA amp DNA isolation kit (QIAGEN) (Cat. no.51104) was used to extract genomic DNA from T-ALL patient's bone marrow following the standard procedures according to the manufacturer's guidelines. Isolated DNA fragments were amplified using conventional PCR technique.

Conventional Polymerase Chain Reactions (PCRs) were done in a total volume of 50 µL containing 25 µL of Dream Taq master mix, 0.2 µl from the both primers (100 pmol), and 2 µL of extracted DNA and completed to 50 µL with distilled water. PCR was done using Thermo Scientific Arktik Thermal Cycler. Cycling conditions were 35 cycles with annealing temperature 54ºC for exon 18 and 56ºC for exon 20.

The primers used for PCR amplification of *DNM2* exons (18 and 20) were as follow:

Exon 18 forward, CTAGAGCCCATTCCTCTCGG and reverse, CATGATTTCAGAGACTCCTGGC and exon 20 forward, CCCGCCCTGTGAGAGATG and reverse, AGGACCCTGCAGGACACAC

The process included the following steps: initial denaturation at 95°C for 2 minutes, 35 cycles at 95°C for 30 seconds, 54°C (for exon 18) and 56°C (for exon 20) for 30 seconds, and 72°C for 30 seconds, and a final extension at 72°C for 10 minutes.

DNA Purification

Purification of PCR products was done using the DNA Clean and Concentrator®-25 PCR Purification Kit (Cat.no.D4005-USA) according to the manufacturer's guidelines. Cycle sequencing of the purified PCR products was performed using the Big Dye Terminator, version 3.1, Cycle Sequencing Kit.

DNA Sequencing

Macrogen3730 Applied Biosystem apparatus was used for performing mutational analysis of *DNM2* exons (18 and 22).

Statistical Analysis

The sample size of the T-ALL patients group was calculated statistically. The analysis of the data was performed using Excel and Statistical Package for Social Sciences (SPSS version 22). Qualitative data were presented in the form of numbers and percentages. Quantitative data were presented in the form of mean (M) ± standard deviation (SD). For evaluation of survival analysis (OS and DFS), we used Kaplan-Meier test. A p value was considered significant at level $p<0.05$.

Results

Demographic Data and Patients' Characteristics

This study was conducted upon 25 patients who were newly diagnosed with T-cell Acute Lymphoblastic Leukemia (T-ALL). The study group was formed of 8 females and 17 males, with mean age 34.76 (age range 17-62). Demographic data and laboratory findings of the studied T-ALL patients' group are shown in (Table 1).

Table 1. T-ALL Patients' Characteristics

Parameters	No	(Mean)Range
Age (year) Mean (range)	25	34.76 (17- 62)
TLCs (10^9/L)	25	84.56 (11.1-328.00)
Hemoglobin (g/dl)	25	9.98(5.09- 13.77)
Platelets count (10^9/L)	25	78.1 (9.00 – 328.00)
LDH (U/L)	25	1848.2 (263.32-11134.60)
Bone Marrow blast cells (%)	25	83.0 (40-95)

Table 2. Clinical criteria of adult T-ALL patients with active *DNM2* Mutations

Case no	TLC X10^9/L	Hb g/dl	PLT X10^9/L	LDH IU/ml	BM Blasts%	CNS infiltration	Abdominal ultrasound	Lymphadenopathy	Mutations
1	37.8	8.4	34	638	90%	Positive	Normal live and spleen with enlarged para aortic lymph nodes	Negative	c.1866G>C c.2219C>T
2	149	13	40.4	598	90%	Free	Mild enlarged liver Enlarged spleen	Few enlarged lymph nodes at portahepatis; largest one about 2 cm	c.1872delA c.2219C>T
3	164	8.8	32.52	1300	95%	Free	Normal Liver and spleen size	Negative	c.1872delA c.2219C>T
4	58	8.5	58.7	5623	90%	Positive	Enlarged liver and spleen	Multiple bilateral small axillary LNs	c.1872delA
5	328	8	24	4967	90%	Free	Enlarged liver and moderate splenomegaly.	Bilateral enlarged cervical L.N.s the largest in right posterior triangle. Few enlarged supraclavicular L.N.s left side. Enlarged bilateral axillary L.N.s right side	c.1872delA c.2219C>T

TLC, Total leucocyte count; Plat, Platelets count; Hb,Hemoglobin; Abd.US, Abdominal ultrasound; LN, lymph nodes

Clinical Criteria and Laboratory Data of Adult T-ALL Patients with Active DNM2 Mutations

Clinical and laboratory findings of adult T-ALL patients (with active *DNM2* mutations) showed organomegaly (hepatomegaly and splenomegaly) (50%), lymphadenopathy (60%), fever (60%), CNS infiltration (25%) and pallor (70%) (Table2).

DNM2 Mutations Characterization

Eighteen patients exhibited silent mutation (c.2219C>T) (p.A713A) in exon 20, one patient showed active mutation (c.1866G>C) (p.V596L) in exon 18 and 4 patients had frame-shift "deletion" mutations in exon 18 (c.1872delA). There were 4 patients who gained 2 kinds of mutations, one patient with (c.1866G>C and c.2219C>T) and 3 patients with (c.1872delA and c.2219C>T) (Figure 1, Table 3).

Frequency of Detected DNM2 Mutations

In the current study, 25 newly diagnosed T-ALL adult patients were tested for mutations in the *DNM2* gene for both exons 18 and 20. We found that 19 out of 25 (76%) patients had one or more kinds of mutations (point or frame shift) (Table 3, Figure 2).

Impact of DNM2 Mutations on T-ALL Patients' Outcomes

In the current study, we observed that 17 patients were induction remission responders and 8 patients were

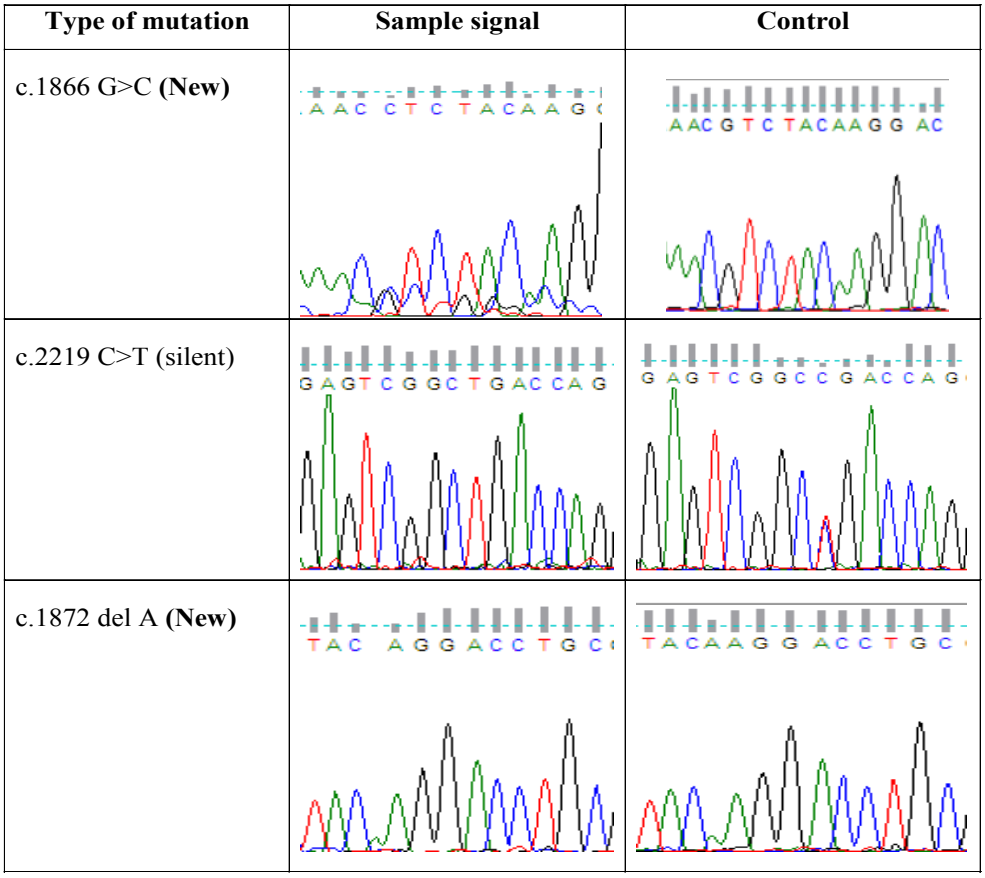

Figure 1. Types of *DNM2* Mutations in Adult T-ALL (active point mutation; Silent point mutation, and deletional mutation)

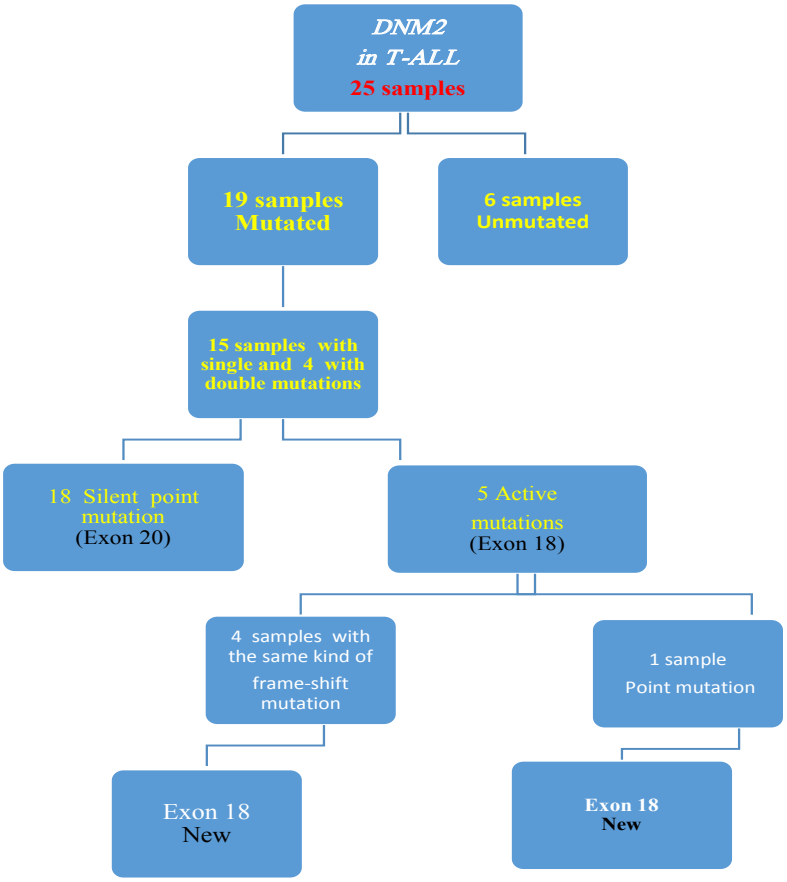

Figure 2. Types and Frequency of Detected Mutations in T-ALL patients

Table 3.The Detected MutationsTypes and Frequency in T-ALL Patients.

Types of mutations	Mutation: nucleotide	Mutation: amino acid
No. of mutated samples (19/25)		
Point mutation (19/25)(1 active and 18 silent)		
Exon 18: 1 Samples(active)	c.1866G>C	p.V596L
Exon 20: 18 Samples (silent)	c.2219C>T	p.A713A
Deletion mutation in Exon 18 (4 Samples)	c.1872delA	Frame shift mutation with unknown protein.

Among the detected mutations 2 novel ones were detected in exon 18, all of them were active, one was point mutation (c.1866G>C), and one was frame-shift mutation (c.1872delA) was detected in 4 samples.

non-responders. During the follow up process, 12 patients were relapsed and 13 patients continued in complete remission. After 24 months, 15 patients (60%) died and 10 patients (40%) were still alive (Table 4).

Clinical Criteria of Patients with DNM2 novel Mutations

Two novel detected mutations include: (c.1866G>C) (p.V596L) and (c.1872delA) in exon 18 (Figure 1) were detected in 6 patients. Clinical criteria of patients with *DNM2* novel mutations are shown in (Table 2). These patients exhibited high white blood cells count and increased initial LDH, CNS infiltration and organomegaly (Table 2).

Impact of DNM2 Silent Mutations on T-ALL Patients' Overall Survival

We analyzed the impact of *DNM2* silent mutations on T-ALL patients overall survival (OS) by Kaplan Miere Curve. This analysis revealed that there were no significant differences between mutated and non-mutated T-ALL cases regarding OS (Figure 3).

Table 4. Impact of *DNM2* Mutation on Adult T-ALL Patients' Outcome

Induction of remission response		Relapse During Follow up		Outcome after 24 months	
Responder	Non-responder	Relapsed	Non-relapsed	Died	Alive
(n=17)	(n=8)	(n=12)	(n=13)	15	10
68%	32%	48%	52%	60%	40%

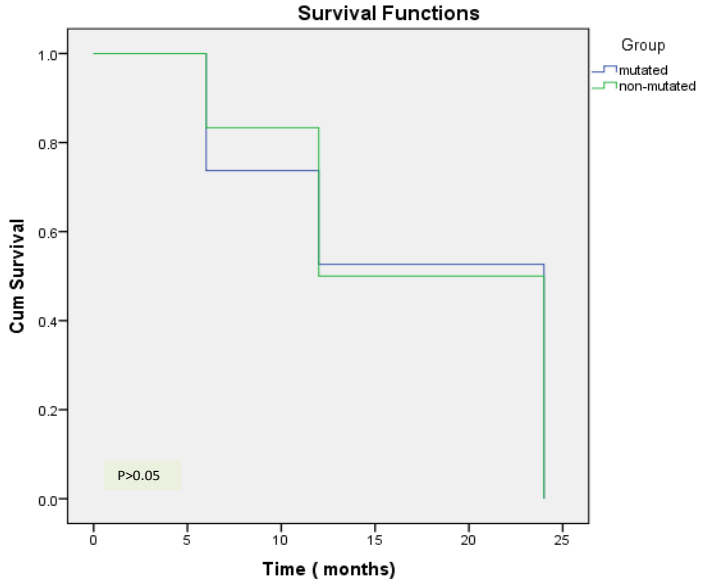

Figure 3. Kaplan Meier Curve for Overall Survival (OS) of T-ALL patients with DNM2 Mutations Compared to Non-Mutated Ones. The analysis revealed that there were no significant differences between mutated and non- mutated T-ALL cases regarding OS.

Impact of DNM2 Active Mutations on T-ALL Patients' Overall Survival

The impact of *DNM2* active mutation was evaluated by Kaplan Miere Curve. The results showed that patients with active mutations exhibited shorter OS compared to those with silent mutations or non mutated ones. T-ALL patients with active mutations had significantly shorter OS compared to those with silent or non-mutated (Figure 4).

Impact of DNM2 Mutations on T-ALL Patients' Disease Free Survival

The statistical analysis revealed that the mutated T-ALL patients displayed high frequency of relapse compared to non-mutated ones (Figure 5).

Discussion

The percentage of *DNM2* mutations detected in exons 18 and 20 was 76%. This high frequency of *DNM2* mutations indicated that these mutations might have an important role in the pathogenesis of T-ALL. Among the detected mutations, there are 2 active mutations detected in 5 out of 25 patients and 18 silent mutations were detected in 25 (72%) T-ALL patients.

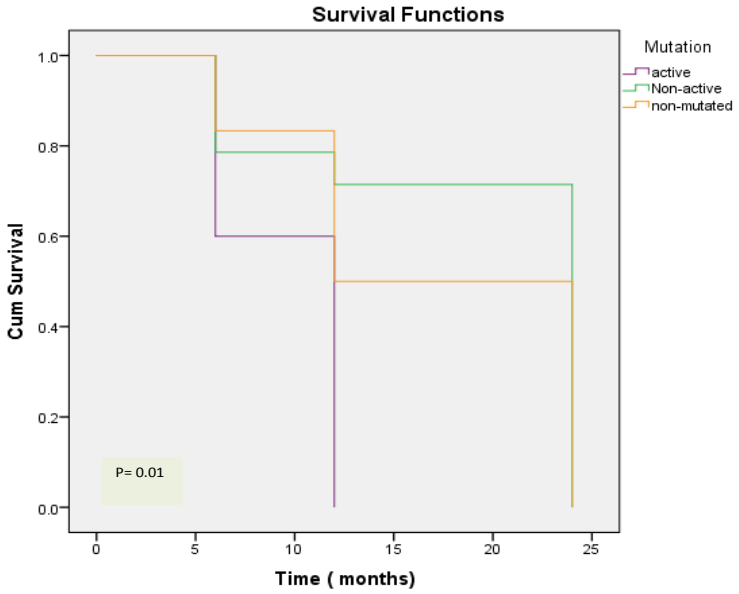

Figure 4. Kaplan Meier Curve for Overall Survival (OS) of T-ALL Patients with *DNM2* Active Mutation vs. Non Active (Silent) vs. Non Mutated Ones. Patients with active mutations exhibited shorter OS compared to those with silent mutations or non mutated ones. T-ALL patients with active mutations had significantly shorter OS compared to those with silent or no-mutation.

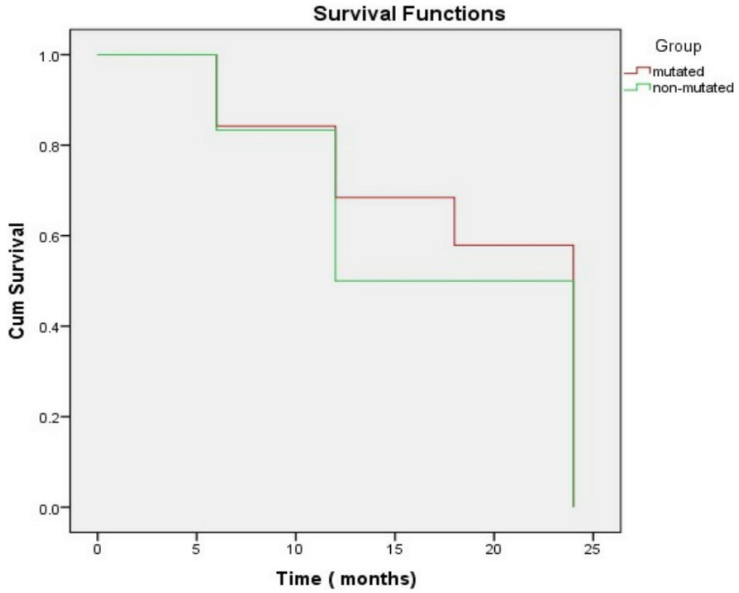

Figure 5. Impact of *DNM2* Mutation on DFS of T-ALL Patients. The mutated patients displayed high frequency of relapse compared to non-mutated ones.

Previous report stated that *DNM2* mutations induced elevation of the content of Interleukin 7 (IL-7) receptor in the plasma membrane in pre-leukemic thymocytes leading to enhancing IL-7 signaling and development of more immature T-ALL (Trochet and Bitoun, 2021). Also, it was reported that T-ALL was promoted by *DNM2* loss-of-function mutations resulted from enhancing IL-signaling. These mutations included: L354P, K562del, S698L and P791T. These mutations were found along the gene functional domains (Tremblay et al., 2016).

In the current study, 2 novel mutations were detected in 5 cases (20%). They included c.1866 A>C in one case and c.1872delA in 4 cases. Previous reported mutations included c.1081C>T, c.1453T>C, c.1609G>A and c.1801C>T, which were located in exons 8, 13, 16 and 18, respectively. Moreover, two silent amino acid mutations included Ala713Ala and Asp720Asp were reported in exon 20 (Ge et al., 2016).

In the current study, the silent mutations were not associated with characteristic clinic-pathological features. Similar finding was previously reported by (Ge et al., 2016) who suggested that the sites of silent mutations might represent the hot spots and the nucleotides at these sites could be quickly corrected and were easily changed.

Similar to *DNM2* mutations that located in functional domain, inherited *DNM2* mutations were associated with degenerative neurologic diseases like peripheral neuropathy, Charcot– Marie–Tooth, autosomal dominant Centro nuclear myopathy, lethal congenital contracture syndrome and Siberian family with hereditary spastic paraplegia (Sambuughin et al., 2015; Trochet and Bitoun, 2021).

Recurrent *DNM2* mutations were identified in patients with T-ALL through exons (18 and 20). Previous study found that there were two silent amino acid mutations including Ala713Ala and Asp720Asp in exon 20. The first mutation was found in 31 out of 42 patients and the other one was found in 3 out of 42 patients with 80.95% for both in the T-ALL patients. The two kinds of mutations of exon 20 were found in only one case (Ge et al., 2016). Consequently, we found additive novel mutations [(c.1866 G>C) (p.V596L), (c.1872delA)]. In another study, 13 ETP-ALL and 4 non-ETP ALL with *DNM2* mutations had been reported, 4 out of 17 mutations were reported in PH domain of the gene (Zhang et al., 2012).

The impact of *DNM2* mutations on induction of remission response revealed that 30% of patients were non-responders and 70% responded during 24 months of therapy. Responders included 5 patients with no mutations and 12 patients with mutations. Non-responders included 7 mutated and 1 non-mutated. Similar findings were reported in another study which stated that certain mutations were appeared in patients that exhibited induction failure and relapse (Ge et al., 2016).

During 24 months follow up after induction therapy, 12 out of 19 patients with *DNM2* mutations were relapsed. Three patients relapsed after 6 months, four after 8 months and two after 17 months. In addition, three patients relapsed three times, the first relapse was after 6 months, the second was after 11 months and the third was after 19 months. Previous studies reported that only one patient (1/4) with point mutations get relapsed, one patient had an increased TLC count, and 2 patients had lymph node metastasis and complex karyotypes (Ge et al., 2016).

In the current study, we assessed the impact of *DNM2* mutations on overall survival. The results revealed that 13 out of 19 mutated patients were died with ratio of 68.42% and with ratio of 52% of whole 25 patients diagnosed with T-ALL. Similarly, patients with *DNM2* mutations exhibited high-risk leukemia and possessed a poor prognosis (Ge et al., 2016).

We had evaluated the impact of *DNM2* active mutations on overall survival. From 19 mutated samples, there were only 5 samples with active mutations. We reported 4 deaths from 5 patients. It was reported that it needed more than 4 weeks for a complete remission in patients with *DNM2*

mutations (Ge et al., 2016). Previous reports stated that treatment of T-ALL with chemotherapy came with high overall survival especially for younger patients. However, this treatment showed more side effects and relapse with poor prognosis. Girardi et al., (2017) suggested that the whole-exome sequencing of relapsed patients could make a detailed view on the genomes of relapsed T-ALL cases. This result can help in the introduction of new targeted drugs and to reduce the toxicity of current chemotherapies.

DNM2 mutations are frequent in our cohort of T-ALL cases. Similar to our results, previous study reported that 34 out of 42 cases exhibited *DNM2* gene mutations with frequency of 80.95% (Ge et al., 2016). High frequency of *DNM2* mutations in T-ALL patients suggested that these mutations might have a role in the pathogenesis of the disease. Furthermore, these mutations could be a candidate for minimal residual disease detection in T–ALL patients.

In conclusion, The *DNM2* mutations were prevalent among adult T-ALL patients and might have a role in the pathogenesis of the disease. Active *DNM2* mutations were associated with poor clinical outcome. Moreover, high frequency of *DNM2* mutations indicated that these mutations could be used in detection of minimal residual disease in T-ALL patients.

Author Contribution Statement

Marwa Sobh: Laboratory Work and Analysis of Data; Salah Aref: Study Idea and Design; Mohamed Al Agdar: Laboratory Work; Maha El Zafrany: Patients' Follow up and Clinical Management; Ahmed M.A El Sokkary: Supervision of the Study.

Acknowledgements

The present study is the result of MSc thesis of the postgraduate student, Marwa Sobh and approved by the ethical committee of Faculty of Science, Mansoura University. The authors would like to thank the technicians in the Hematology laboratory at Mansoura University Oncology Center (MUOC).

Funding Statement

This study was funded in whole by the authors themselves. The authors did not receive any financial support from any organization for the submitted paper.

Ethical Statement

This study was approved by Mansoura Faculty of Medicine ethical committee and done according to declaration of Helsinki.

Availability of Data

The data that support the finding of the present study are available upon request from the corresponding author.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of the present paper.

References

Angiolillo A, Whitlock J, Chen Z, Krailo M, Reaman G (2006). Children's Oncology Group. Phase II study of gemcitabine in children with relapsed acute lymphoblastic leukemia or acute myelogenous leukemia (ADVL0022) a Children's Oncology Group Report. *Pediatric Blood Cancer*, **46**, 193–7.

Aref S, El Menshawy N, El-Ghonemy M, Abou Zeid T, El-Baiomy M (2016). Clinicopathologic Effect of DNMT3A Mutation in Adult T-Cell Acute Lymphoblastic Leukemia. *Clin Lymphoma Myeloma Leuk*, **16**, 43-8.

Aref S, El Agdar M, Salama O, Abouzeid Zeid T, Sabry M (2020). Significance of NOTCH1 mutations détections in T-acute lymphoblastic leukemia patients. *Cancer Biomark*, **27**, 157–62.

Aref S, Fawzy E, Darwish A, Aref M, Al Agdar M (2021). Cortactin Expression is a Novel Biomarker for Risk Stratification of T-Cell Acute Lymphoblastic Leukemia. *J Pediatr Hematol Oncol*, **43**, e798–e803.

Bridges CS, Chen TJ, Puppi M, Rabin KR, Lacorazza HD (2023). Antileukemic properties of the kinase inhibitor OTSSP167 in T-cell acute lymphoblastic leukemia. *Blood Adv*, **7**, 422-35.

Cao H, Garcia F, McNiven MA (1998). Differential distribution of dynamin isoforms in mammalian cells. *Mol Biol Cell*, **9**, 2595-609.

Chennamadhavuni A, Lyengar V, Mukkamalla SKR, Shimanovsky A (2022). Leukemia. In StatPearls. Treasure Island (FL): StatPearls Publishing.

Chang J, Medlin S, Kahl B, et al (2008), Augmented and standard Berlin-FrankfurtMunster chemotherapy for treatment of adult acute lymphoblastic leukemia. *Leuk Lymphoma*, **12**, 2298–307.

Chiaretti S, Foà R (2009). T-cell acute lymphoblastic leukemia. *Haematologica*, **94**, 160-2.

Del Principe MI, Maurillo L, Buccisano F, et al (2014). Central nervous system involvement in adult acute lymphoblastic leukemia: diagnostic tools, prophylaxis, and therapy. *Mediterr J Hematol Infect Dis*, **6**, e2014075.

Durieux AC, Prudhon B, Guicheney P, Bitoun M (2010). Dynamin 2 and human diseases. *J Mol Med (Berl)*, **88**, 339-50.

Ferrando AA, Neuberg DS, Staunton J, et al (2002). Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. *Cancer Cell*, **1**, 75-87.

Ge Z, Li M, Zhao G, Xiao L, et al (2016). Novel dynamin 2 mutations in adult T-cell acute lymphoblastic leukemia. *Oncol Lett*, **12**, 2746-51.

Girardi T, Vicente C, Cools J, De Keersmaecker K (2017). The genetics and molecular biology of T-ALL. *Blood*, **129**, 1113-23.

Iacobucci I, Mullighan CG (2017). Genetic Basis of Acute Lymphoblastic Leukemia. *J Clin Oncol*, **35**, 975-83.

Ikonomidou C (2021). Cerebrospinal Fluid Biomarkers in Childhood Leukemias. *Cancers*, **13**, 438.

Neumann M, Vosberg S, Schlee C, et al (2015). Mutational spectrum of adult T-ALL. *Oncotarget*, **6**, 2754-66.

Paul S, Kantarjian H, Jabbour EJ (2016). Adult Acute Lymphoblastic Leukemia. Mayo Clin Proc, 91, 1645-66.

Pui CH, Robison LL, Look AT (2008). Acute lymphoblastic leukaemia. *Lancet*, **371**, 1030-43.

Ramachandran R, Schmid SL (2018). The dynamin superfamily. *Curr Biol*, **28**, R411-6.

Roberts KG, Mullighan CG (2015). Genomics in acute lymphoblastic leukaemia: insights and treatment implications. *Nat Rev Clin Oncol*, **12**, 344-57.

Sambuughin N, Goldfarb LG, Sivtseva TM, et al (2015). Adult-onset autosomal dominant spastic paraplegia linked

to a GTPase-effector domain mutation of dynamin 2. *BMC Neurol*, **15**, 223.
Siegel RL, Miller KD, Wagle NS, Jemal A (2023). Cancer statistics, 2023. *CA Cancer J Clin*, **73**, 17-48.
Thomas D, O'Brien S, Faderl S, et al (2010). Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol*, **28**, 3880–9.
Tremblay CS, Brown FC, Collett M, et al (2016). Loss-of-function mutations of Dynamin 2 promote T-ALL by enhancing IL-7 signalling. *Leukemia*, **30**, 1993-2001.
Trochet D, Bitoun M (2021). A review of Dynamin 2 involvement in cancers highlights a promising therapeutic target. *J Exp Clin Cancer Res*, **40**, 238.
Xu B, Teng LH, Silva SD, et al (2014). The significance of dynamin 2 expression for prostate cancer progression, prognostication, and therapeutic targeting. *Cancer Med*, **3**, 14-24.
Zhang J, Ding L, Holmfeldt L, et al (2012). The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature*, **481**, 157-63.