тяжести течения происходит и увеличение частоты возникновения слабости (86% при А стадии, 100% при В и С стадиях). Увеличение ПЛУ при А стадии встречалось в 26,6%, при В стадии – 83%, при С стадии – 100%. Спленомегалия при А стадии выявлялась в 18,3% случаев, при В стадии в 50% случаев, при С стадии в 50% случаев. При А стадии пациенты в 33,3% случаев отмечали жалобы на головокружение и головную боль, что не встречалось при более тяжелых стадиях течения.

В клинической картине пациентов с прогрессирующим течением ХЛЛ в А стадии реже отмечались жалобы на слабость и общее недомогание, чем у пациентов с такой же стадией, но без прогрессирующего течения (61,9% против 86%), однако чаще отмечали увеличение ПЛУ и спленомегалию (57,1% и 19,0% против 26,6% и 18,3% соответственно).В клинической картине ХЛЛ с прогрессирующим течением в В стадии, 100% пациентов отмечали слабость, спленомегалию, увеличение ПЛУ и ночную потливость. Медиана количества лимфоцитов при ХЛЛ в А стадии пришлась на $23,8*10^9$/литр, при В стадии – $61,7*10^9$/литр.

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CHRONIC LYMPHOCYTIC LEUKEMIA IN PAKISTAN

Introduction

In Pakistan, CLL is considered a rare hematological malignancy, with an overall prevalence of 0.9% and accounting for approximately 9.7% of leukemia cases. This disease primarily affects older individuals, with the incidence rate rising after the age of 60, and there is a slight male predominance. In the Western countries, it is the most prevalent leukemia in adults, accounting for 25–35% of all leukemia cases. However, in Asia, the prevalence of CLL is relatively low, comprising of only 10% of the cases observed in the Western countries. The current understanding of CLL emphasizes the heterogeneity of the disease, characterized by variations in clinical presentation, genetic mutations, and treatment responses among different demographics. This is particularly relevant in Pakistan, where factors such as socioeconomic status, access to healthcare, and genetic predispositions can influence disease management and outcomes. In recent years, targeted therapies, such as Bruton tyrosine kinase inhibitors (BTK inhibitors) and BCL2 inhibitors, have transformed the treatment paradigm for CLL, offering improved survival rates and

quality of life for patients. However, the integration of these therapies into clinical practice in Pakistan presents unique challenges, including financial constraints and limited access to novel agents. Moreover, the ongoing research efforts aim to address the gap in data concerning the epidemiology and treatment outcomes of CLL in the Pakistani population. [1] As we move through 2024, it is crucial to explore the current studies and findings that contribute to a deeper understanding of CLL, focusing on local research initiatives that aim to bridge the knowledge gap and enhance patient care.

Goal

The primary goal of this research is to determine the frequency of TP53 mutation at diagnosis of B-cell Chronic Lymphocytic Leukemia (B-CLL) in Pakistani patients.

Material and methods of research

This cross-sectional descriptive study was conducted at Liaquat National Hospital, Karachi. A total of 128 B-CLL patients who attended the hematology outpatient department (OPD) between January 2020 and December 2022 were registered and monitored. Inclusion criteria included Pakistani patients aged between 30–90 years who were recently diagnosed with B-CLL, according to iwCLL criteria, which relied on immuno-phenotyping results. Patients who had previously been diagnosed with other forms of cancer, whether hematological or non-hematological, and already had a confirmed TP53 gene mutation were not included in the study. Additionally, patients who had undergone chemotherapy or radiotherapy as part of their treatment for any type of cancer were also excluded from the study. Clinical research on chronic lymphocytic leukemia (CLL) in Pakistan, focusing on studies published up to 2024 were also evaluated. A comprehensive literature search was conducted using databases such as PubMed, ClinicalTrials.gov, and Google Scholar. Inclusion criteria comprised clinical studies specific to CLL patients in Pakistan published in peer-reviewed journals. Excluded were case reports and non-clinical studies. Data extracted included study design, sample size, patient demographics, clinico-hematological profiles, and treatment outcomes. The findings were qualitatively summarized, noting key trends and gaps in the literature.

The results of the research and their discussion

The study included 128 patients who had recently been diagnosed with B-CLL. Among these patients, 89 (69.5%) were males, and 39 (30.5%) were females. The mean age of the patients was 62 years, ranging from 35 to 88 years. TP53 mutation analysis was conducted on all patients using the FISH technique with peripheral blood samples. The results showed that 10 patients (7.8%) tested positive for the mutation, while 118 patients (92.2%) tested negative. Further analysis of chronic lymphocytic leukemia (CLL) research in Pakistan revealed significant insights based on the data from the systematic review. A total of 6 studies encompassing 365 patients were evaluated. The predominant study design remained cross-sectional, accounting for 5 of the studies, while one was prospective as shown in table 1.

Table 1 – Summary of studies evaluating clinical and laboratory profile of CLL patients

Year	Sample Size(n)	Mean Age (Years)	Gender Distribution	Study Design	Study Objective	Results
Ehsan et al., 2013	31	62.8	Male: 20 Female:11	Cross-sectional	Evaluate the prevalence of autoimmune cytopenias in CLL patients	Autoimmune cytopenias were found in 22% of patients, with autoimmune hemolytic anemia occurring more frequently than immune thrombocytopenia purpura (19.4% vs. 3.2%).
Rafiq et al., 2014	50	41.5±20.86	Male: 30 Female: 20	Cross-sectional	Analyze the clinic-hematological profile of CLL patients	CLL patients showed increased rates of anemia, thrombocytopenia, along with profile of CLL elevated levels of creatinine, total patients bilirubin, and urea
Abbas et al., 2015	60	59±9.2	Male: 35 Female:25	Cross-sectional	Investigate the relationship between coombs test results and disease staging.	A notable association was observed between Coomb's positivity and advanced Rai stage III disease, along with lower mean hemoglobin levels.
Zeeshan et al., 2015	60	59.0±9.2	Male:34 Female:26	Prospective observational	Examine the clinic-hematological profile of CLL patients.	Anemia and thrombocytopenia were observed in 26.7% and 21.7% of cases, respectively, and 21.7% of patients were at Rai Stage IV. [3]
Haider et al., 2019	64	65	Male: 40 Female:24	Cross-sectional	Determine the prevalence of autoimmune cytopenias in CLL patients.	Autoimmune hemolytic anemia was found to be more prevalent than immune thrombocytopenia purpura (7.8% vs. 3.1%). [4]
Rashid et al., 2020	100	65.8±1.33	Male:48 Female:52	Cross-sectional	Assess the overall prevalence and complications of CLL patients.	The overall Coomb's positivity rate was 26.7%, with Coomb's positive patients having a mean hemoglobin of 7.69 g/dL ±2.3. [4]
2020–2022	128	62	Male: 89 Female:39	Cross-sectional	Determine the frequency of TP53 mutation at diagnosis of B-CLL in Pakistani patients, and to investigate whether LDT of less than 1 year could be used as a surrogate marker for TP53 mutation.	TP53 mutations may be associated with shorter LDT, indicating aggressive disease. Further research is needed to fully comprehend the relationship between TP53 mutation and LDT in B-CLL.

During the follow-up period, 26 patients were lost to follow-up, with one patient from the TP53 positive group and 25 patients from the negative group. In the TP53 positive group, 55.6% (n=5/9) of patients had an LDT of less than 1 year, indicating aggressive disease, compared to 30.1% (n=28/93) of patients in the negative group (55.6% vs. 30.1%; p <0.1). Similarly, in the TP53 mutation with B-CLL group, 44.4% (n=4/9) of patients had an LDT of more than 1 year, while 69.9% (n=65/93) of patients in the TP53 negative group had an LDT of more than 1 year (44.4% vs. 69.9%; p <0.1).

Six studies evaluated the clinic-hematological profiles of CLL patients, reporting high rates of anemia and thrombocytopenia. Increased liver enzymes and serum creatinine levels were discovered among CLL patients; though causal links were unclear due to unaccounted comorbidities. Autoimmune complications were prevalent, with Comb's positivity rates reported at 23.3% and 26.7% in different studies, indicating a correlation with higher disease grades. Several studies assessed cytogenetic abnormalities using fluorescence in situ hybridization (FISH). The prevalence of TP53 mutations was found to be 13.7%, while 17p deletions were associated with poor prognosis. 2-year overall survival (OS) rate of 65% was found among patients with 17p deletion, highlighting the need for targeted therapies.

Conclusion

Relatively low frequency of TP53 mutation was revealed at the time of B-CLL diagnosis, specifically at 7.8%. Patients with a positive TP53 mutation tend to experience an early increase in lymphocyte count, with lymphocyte count doubling between 12 to 18 months, compared to patients without the TP53 mutation. TP53 mutations may be linked to a shorter LDT in patients with CLL. The systematic review underscores the increasing incidence of CLL within the country, yet emphasizes the critical gaps in comprehensive data due to the lack of a national cancer registry. Financial and logistical obstacles hinder the conduct of larger, impactful clinical trials in Pakistan. The lack of funding, combined with underrepresentation in global clinical trials, emphasizes the need for localized research that addresses demographic-specific issues. While several studies have been conducted, there is an urgent need for larger, well-funded clinical trials that incorporate modern therapeutic approaches and advanced diagnostic techniques like next-generation sequencing (NGS) thereby enhancing insight into CLL among the Pakistani population. Moreover, improving healthcare infrastructure and access to novel therapies is essential for better patient outcomes.

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