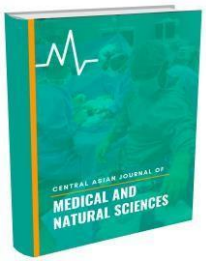

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Article

Sex-Based Disparities in Chronic Myeloid Leukemia: Insights from ASXL1 Mutations and Epidemiological Data

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Abstract: Chronic Myeloid Leukemia (CML) is a hematological tumor considered through the BCR-ABL1 fusion gene, instigating unrestrained growth of myeloid cells. Whereas Tyrosine Kinase Inhibitors (TKIs) have transformed CML management, differences in sickness proportions and results between sexes requirement additional training. This paper associations perceptions as of a new thesis on ASXL1 mutations and BCR-ABL1 transcript kinds in CML sick, along with wider epidemiological documents, to inspect sex-based alterations in CML vulnerability and advancement. Investigation consistently shows a higher incidence of CML in men compared to women, proposing that men might have a larger innate danger or a larger pool of objective cells susceptible to leukemic alteration. Moreover, research indicate that men with CML often have additional somatic mutations, comprising those in ASXL1, which stay related to worse medical results and sickness development. This evaluation accentuates the serious requirement for sex-disaggregated documents in CML investigation to uncover fundamental biological apparatuses, for example genetic and hormonal aspects, and to progress additional exact, sex-specific management. Accepting these changes is important for progressing personalized medication in CML.

Keywords: Chronic Myeloid Leukemia, ASXL1 Mutations, BCR-ABL1 Fusion Gene, Sex-Based Disparities, Tyrosine Kinase Inhibitors

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1. Introduction

Chronic myeloid leukemia is a well considered myeloproliferative neoplasm, illustrious through the existence of the (Ph), which outcomes as of a reciprocal translocation among chromosomes 9 and 22, t(9;22)(q34;q11). This genetic reordering hints to the creation of the BCR-ABL1 fusion gene, encoding a constitutively active tyrosine kinase. The initiation of (TKIs) directing this abnormal protein has greatly altered the natural history of CML, altering it as of a quickly fatal sickness into a controllable long-lasting disorder with near-normal life expectancy. Emerging evidence suggests that sex-based disparities impact disease presentation, progression, and prognosis[1],[2] . In spite of the outstanding achievement of TKI treatments, important heterogeneity occurs in CML patient reactions and illness development. A serious, yet frequently under-explored, feature of this heterogeneity is the effect of sex on CML. Epidemiological documents steadily propose a higher occurrence of CML in men matched to women [3[,]4]. Considerate the fundamental causes for these sex-based differences is critical for a widespread grasp of CML biology and for proceeding personalized medication methods. This paper purposes to investigate into the enquiry of whether men or women are

additional vulnerable to CML. By creating these different foundations, we seek to explain possible biological apparatuses, for instance genetic predilections (e.g., ASXL1 mutations) and hormonal effects that might donate to the detected sex-based disparities in CML vulnerability and development.In the chronic phase of CML, the presence of an ASXL1 mutation has been identified as an independent risk factor for poorer event-free survival [5].Understanding the interplay between sex, genetic mutations like ASXL1, and epidemiological patterns is essential for developing more accurate prognostic tools and personalized therapeutic strategies in CML.

Epidemiological and Molecular Findings

A. CML Incidence and Prevalence by Sex:

Reliable epidemiological documents as of numerous sources designate an upper occurrence of CML in men paralleled to women. For example, estimations for new issues analyzed in the United States in 2023 illustration that crudely 58% of these new issue are in males and 42% in females [6]. The SEER Tumor Stat Facts website likewise obviously conditions that CML is additional mutual in men [4].

A search analyzing SEER documents and Japanese A-bomb survivors additional provisions this statement [3]. It create that for persons older than 25 years, the occurrence of CML is dependably greater in males. The examination proposed that this sex alteration is additional probable an outcome of changes in danger instead of potential, suggesting that males might have a greater inherent vulnerability or a greater pool of objective cells at danger for CML beginning.

B. Sex-Related Differences in Mutational Profiles:

Elsewhere occurrence, exterior trainings expose an important sex-linked alterations in the genomic profiles of sick with CMN, comprising CML. A review of sex-linked alterations in CMN underscored that men often existing with an upper number of somatic mutations and an upper occurrence of particular mutations related with worse results [7].

Specially, the MDPI object illustrious that:

a. ASXL1 Mutations: In studies of Myelodysplastic Diseases/Myeloproliferative Neoplasms (MDS/MPN) sick, ASXL1 mutations stood institute to be additional mutual among men [7]. This outcome is mostly applicable assumed the attention on ASXL1 mutations in CML.
b. Other Mutations: Men with CMN incline to have a greater occurrence of mutations in genes complicated in RNA splicing and epigenetic parameter, for instance EZH2, IDH1/2, U2AF1, and SRSF2. These mutations are frequently related with an upper danger for illness progress and general inferior consequences [7]. Contrariwise, females with MDS have revealed a greater occurrence of DNMT3A and TP53 mutations [7].

C. Clinical Outcomes and Treatment Response by Sex:

Some trainings direct that men have general worse existence and an upper occurrence of transformation to acute leukemia paralleled to females across CMN [7]. Contrariwise, further investigation proposes that women might have analogous or even improved results in spite of bestowing with fewer promising predictive variables [8]. The relationship between imatinib fighting and gender has likewise been discovered, with some trainings representative an important friendship with diverse age groups, nevertheless less clear through relations to gender only [9]. These contradictory results underline the difficulty of sex-related changes in management reaction and highpoint the requirement for additional vigorous, sex-disaggregated medical trial documents.

Epidemiological and molecular experiments dependably display that (CML) arises more recurrently in males than in females. This proposes that men might have a greater prevalence of particular opposing somatic mutations, for instance ASXL1, which could rise their danger of illness development. The influence of sex on the reaction to (TKIs) quiet

requirements additional examination, predominantly concluded more inclusive investigates that revenue sex alterations into explanation.

2. Materials and Methods

Patients

The research complicated a whole of 51 patients, encompassing 28 men and 23 women, whose ages prolonged as of 20 to 70 years. Each person stayed opposite the contests postured through CML and stood vigorously receiving dealing with TKLs. These patients represented a diverse group, each with their unique journey through the complexities of their illness, united by their battle against this persistent form of cancer.

Study design, Patient recruitment, Setting, and Timing

This cross-sectional study stayed directed In the Department of Pharmacology and Therapeutics, College of Medicine, University of Al-Qadisiyah, Iraq, and in the Al-Diwaniyah Teaching Hospital both, for the dated as of July 2024 through January 2025. A whole of 51 sick with CML stayed registered in this training. A specialist caregiving physician/ Hematologist diagnosed and recruited all candidates' patients.

Patient Inclusion Criteria:

a. The Philadelphia chromosome has a long-established presence.
b. Definitively indicates chronic myeloid leukemia in individuals aged 12 and older, underscoring the necessity for prompt diagnosis and intervention.
c. Every patient with CML on TKI therapy

Patient exclusion criteria :

a. Pregnancy
b. TKI contraindication

Ethical approval: The approval was awarded by the Scientific Commission of the Branch of Basic Sciences in the College of Medicine (University of Al-Qadisiyah, Iraq). Testers were obtained after written conversant consensus was obtained as of completely patients.

3. Results

In this study, the number of male cases with CML is 29, 56.9 %; whereas, the number of female cases is 22, 43.1 %. Therefore, the male: female ratio, based on data collected in this study, is 1.32:1, as outlined in the following pie chart, see Figure 1

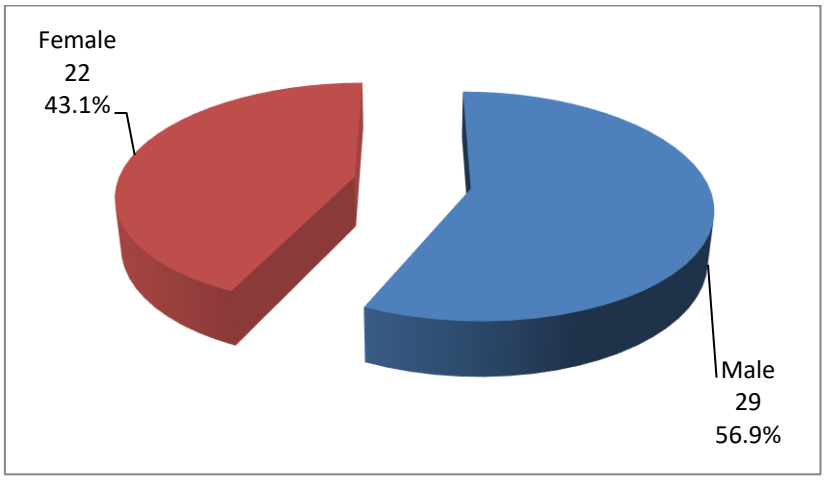

Figure 1. This figure shows the number of cases and proportions according to sex. The male: female ratio is 1.32:1.

It was observed that the average of age of males with CML was greater than that of female patients, 51.55 years versus 47.18 years, in that order; nonetheless, this apparent difference in age between two sexes carries no significancy from statistical point of view as the p-value is 0.292, as it is presented in the following bar chart, see Figure 2.

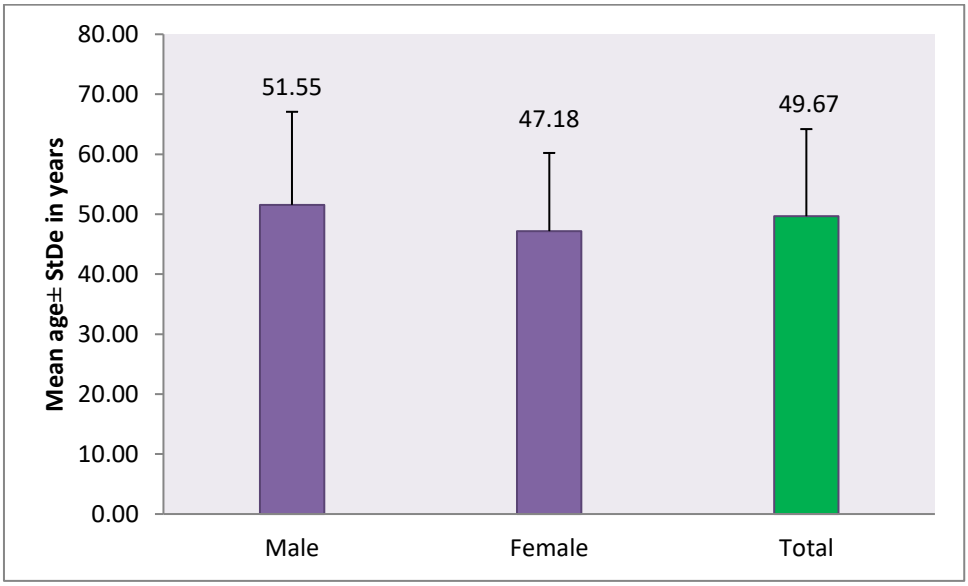

Figure 2. The influence of sex on the average of age in sick with CML.

4. Discussion

Explaining Sex Disparities in CML Incidence

The consistent finding of a higher CML incidence in men compared to women, as evidenced by SEER data and specific epidemiological studies [3, 4, 6], suggests that males are inherently more susceptible to the disease. This disparity is likely multifactorial, involving a complex interplay of genetic, hormonal, and potentially environmental factors:

a. Genetic Predisposition and Mutational Burden

The external literature highlights that men with CMN, including CML, tend to exhibit a higher overall burden of somatic mutations and a greater incidence of specific mutations, such as ASXL1, EZH2, IDH1/2, U2AF1, and SRSF2 [7]. In our study, we identified ASXL1. mutations in its cohort of (CML) patients. Although it did not examine a correlation with sex, external data suggest that these mutations may be more common in males and could contribute to a higher risk of disease progression. This increased mutational load in men might make hematopoietic stem cells more susceptible to leukemic transformation.

b. Hormonal Influences

Sex hormones play a crucial character in adaptable hematopoiesis and immune responses. Androgens, characteristically greater in males, and estrogens, predominant in women, could differentially influence the propagation, diversity, and survival of hematopoietic stem and progenitor cells. While direct evidence linking specific hormonal profiles to CML susceptibility is still emerging, it is plausible that the hormonal milieu in men creates a more permissive environment for CML development or progression. For instance, estrogens have been shown to have protective effects in some cancers, potentially offering women a degree of resilience against certain oncogenic processes[10],[11].

c. Target Cell Pool Hypothesis

The hypothesis that males possess a larger pool of target cells susceptible to leukemic transformation [3] offers a compelling explanation for the observed incidence rates. Differences in baseline hematopoietic stem cell numbers or their proliferative capacity

between sexes could contribute to a higher probability of acquiring oncogenic mutations in men.

d. Environmental and Lifestyle Factors

Although less directly supported by the reviewed literature for CML specifically, general epidemiological principles suggest that differential exposure to environmental carcinogens or lifestyle factors between sexes could contribute to cancer disparities. Nevertheless, additional targeted investigation is required to institute a clear relation in the context of CML[12], [13].

Implications for Clinical Management and Future Research

The observed sex disparities in CML incidence and the emerging understanding of sex-specific mutational landscapes have significant implications for both clinical practice and future research:

a. Personalized Medicine

Recognizing that men and women may present with different mutational profiles and potentially distinct disease trajectories underscores the importance of personalized medicine approaches in CML. Future research should investigate whether sex-specific risk stratification models or tailored treatment strategies, potentially including different TKI dosages or combinations, could optimize outcomes for both male and female patients [14], [15].

b. Sex-Disaggregated Data Collection

It is imperative for future CML research, including clinical trials and observational studies, to systematically collect and analyze sex-disaggregated data. This would allow for a more precise understanding of how sex influences disease presentation, molecular characteristics (including ASXL1 and other mutations), treatment response, and long-term survival. The absence of such data in the provided thesis highlights a common gap in current research practices.

c. Biological Mechanism Elucidation

Further investigation is required to elucidate the biological mechanisms underlying these sex differences fully. This includes in-depth studies on the role of sex (hormones, chromosomes, and sex-specific gene appearance patterns) in CML pathogenesis. Understanding these fundamental biological differences could chief to the detection of novel therapeutic objectives.

d. Prognostic Markers

The finding that certain mutations, like ASXL1, are additional predominant in men and associated with worse outcomes [7] suggests that these could serve as sex-specific prognostic markers. Validating such markers in larger, sex-stratified cohorts could improve risk assessment and guide treatment decisions.

5. Conclusion

This study highlights a consistent male predominance in chronic myeloid leukemia (CML) incidence, reflected in both global epidemiological data and our cohort findings, with a male-to-female ratio of 1.32:1. Although age differences between sexes were not statistically significant, evidence suggests that men may have a higher mutational burden—particularly involving ASXL1—and other adverse genetic alterations, which may contribute to poorer clinical outcomes. Potential mechanisms include genetic predisposition, hormonal influences, and the target cell pool hypothesis, wherein men may possess a greater number of hematopoietic stem cells susceptible to leukemic transformation. While the role of environmental and lifestyle factors in sex disparities for CML remains less defined, they warrant further investigation.

The observed differences underscore the need for integrating sex-specific perspectives into clinical management and research. Routine inclusion of sex-

disaggregated data in clinical trials, molecular profiling, and outcome analyses could refine prognostic tools and inform tailored therapeutic approaches. Additionally, exploring the interplay between sex hormones, mutational landscapes, and disease biology may reveal novel therapeutic targets. Overall, acknowledging and addressing sex-based disparities in CML could enhance precision medicine efforts, improve patient outcomes, and contribute to a deeper understanding of disease pathogenesis.

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