Risk Factors and Prognosis of Chronic Myeloid Leukemia in Saudi Arabia: A Systematic Review

Abstract

Background: Among adult leukaemias, chronic myeloid leukaemia (CML) is one of the most prevalent types. The Philadelphia chromosome, which constitutively activates tyrosine kinase through the BCR-ABL1 oncoprotein, is central to the pathophysiology of CML. **Objectives:**To study the risk factors and prognosis of chronic myeloid leukemia in Saudi Arabia. **Methods:** PubMed, SCOPUS, Web of Science, and Science Direct were systematically searched for relevant literature. Rayyan QRCI was employed throughout this comprehensive process. **Results & interpretation:** seven studies with a total of 658 patients and 357 (54.3) were males. Risk factors for the development of CML were shown to be limited to younger and middle-aged groups, with a slight male predominance. This study showed that imatinib for CML has both long-term efficacy and manageable side effects. Improved compliance, lower blast and basophil counts, increased haemoglobin, increased platelets, and a low-risk score were all associated with different molecular reactions to imatinib. Future research is required to assess the possible risk factors, management lines, and prognostic factors of CML in Saudi population.

Keywords: Chronic myeloid leukemia; Risk factors; Management; Saudi Arabia; Systematic review.

Introduction

Like all leukaemias, chronic myeloid leukaemia, also known as chronic myelogenousleukaemia (CML), is a disease of the hematopoietic stem cell (HSC). Translocation t(9;22)(q34;q11), which fuses the ABL1 and BCR genes to form the pathogenic BCR-ABL1 oncogene, is the hallmark of CML. This disease has numerous downstream implications [1, 2]. This fusion oncogene's primary pathway effect is constitutively activating the tyrosine kinase pathway, which gives mutant HSCs a proliferative advantage over normal HSCs and causes normal HSCs to gradually disappear [3].

Depending on the stage of the disease, leukostasis frequently develops during the blast phase of CML; symptoms can range from asymptomatic to overt. The most typical sign, on the other hand, is hyperleukocytosis, which frequently occurs in all phases (chronic phase, accelerated phase, and blast phase). Acute lymphocytic leukaemia (ALL) and acute myeloid leukaemia (AML) share similarities in the blast phase. Finding chromosomal abnormalities in addition to performing a basic haematology workup is frequently necessary for the diagnosis of CML. Clinical symptoms and blast percentage can be used to distinguish between different stages of CML [1].

The incidence of CML, a myeloproliferative neoplasm, is 1-2 occurrences per 100,000 persons. About 15% of adult leukaemia cases with a recent diagnosis are caused by it. Due to the disease's current high incidence, it is anticipated that 8860 new instances of CML will be identified in the US in 2022, and that 1220 patients will pass away from the disease. Imatinib was first introduced in 2000, and since then, the annual mortality rate for CML has dropped from 10% to 2% [4]. As a result, the anticipated 30 000 cases of CML in the US in 2000 have climbed to over 150 000 cases in 2022, an increase of roughly 8600 cases per year. According to early projections, by 2030–2040, the prevalence of CML patients will level at around 180 000 cases [5].

As previously mentioned, most CML patients have no symptoms, especially in the beginning.1. When leukocytosis and basophilia are discovered during a medical examination, patients are frequently suspected of having CML. When most CML patients are identified in the chronic phase, their symptoms include weight loss, weariness, chills, and abdominal pain or feeling full rapidly because of splenomegaly. Since spleen size affects CML prognostic scores like the ELTS and Sokal scores, it should be measured. Low-grade fever, haemorrhage, thrombosis, gouty arthritis, priapism, and gastric ulcers are other symptoms that may manifest, but infrequently [1].

This systematic review studies the risk factors and prognosis of chronic myeloid leukemia in Saudi Arabia.

Methodology

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed in the conduct of this systematic review [6].

Study Design and Duration

December 2023 marked the start of this systematic review.

Search strategy

To discover the pertinent literature, a thorough search was conducted across four main databases: PubMed, SCOPUS, Web of Science, and Science Direct. We limited our search to English and considered each database's specific needs. The following keywords were transformed into PubMed Mesh terms and used to locate the pertinent studies; "Chronic myeloid leukemia," "Chronic myelogenousleukaemia," "Risk Factors," "Management," and "Saudi Arabia." The Boolean operators "OR" and "AND" matched the required keywords. Publications

with full English text, available free articles, and human trials were among the search results.

Selection criteria

We considered the following criteria for inclusion in this review:

- Studies that the risk factors and prognosis of chronic myeloid leukemia in.
- Only studies conducted in Saudi Arabia.
- No age limits were restricted.
- Only human subjects.
- English language.
- Free accessible articles.

Data extraction

The output of the search method was verified twice with Rayyan (QCRI) [7]. The researchers assessed the titles and abstracts' relevance by adding inclusion/exclusion criteria to the combined search results. The reviewers carefully examined each paper that satisfied the inclusion requirements. The writers discussed conflict resolution techniques. The approved study was uploaded using an already-created data extraction form. The authors extracted data about the study titles, authors, study year, city, participants, gender, follow-up duration, objectives, and main outcomes. A separate sheet was created for the risk of bias assessment.

Strategy for data synthesis

A qualitative evaluation of the research components and conclusions was provided by the creation of summary tables utilising data from pertinent studies. The most effective method for using the data from the included study articles was selected once the data for the systematic review had been collected.

Risk of bias assessment

The quality of the included studies was assessed using the ROBINS-I risk of bias assessment technique for non-randomized trials of treatments [8]. Confounding, participant selection for the study, intervention classification, deviance from intended interventions, missing data, outcome assessment, and choice of reported result were the seven themes that were evaluated.

Results

Search results

A total of 256 study articles resulted from the systematic search, and 63 duplicates were deleted. Title and abstract screening were conducted on 193 studies, and 160 were excluded. 33 reports were sought for retrieval, and 3 articles were retrieved. Finally, 30 studies were screened for full-text assessment; 10 were excluded for wrong study outcomes, 11 for the wrong population type, and 2 articles were letters to the editors. Seven eligible study articles were included in this systematic review. A summary of the study selection process is presented in **Figure 1.**

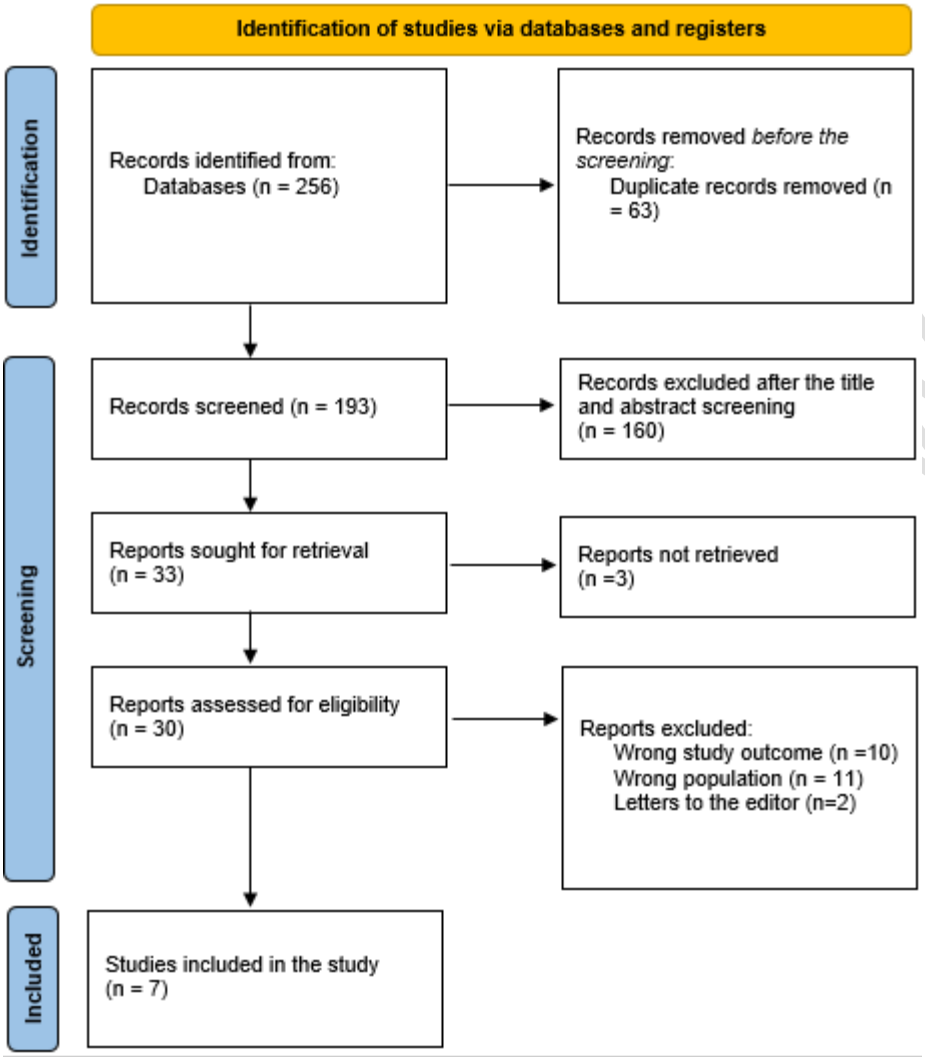

Figure (1): PRISMA flowchart summarizes the study selection process.

Characteristics of the included studies

Table (1) presents the sociodemographic characteristics of the included study articles. Our results included seven studies with a total of 658 patients, and 357 (54.3) were males. One study was prospective in nature [9], and six were retrospective in nature [10-15]. Three studies were conducted in Riyadh [9, 11, 15], one in Abha [10], one in Mecca [12], one in Jeddah [13], and one in Al-Khobar [14].

Table (2) presents the clinical characteristics. Only younger and middle-aged age groups were found to be risk factors for CML development, with slight male predominance. This study demonstrated the long-term efficacy and controllable side effects of imatinib on CML [12-14]. Greater haemoglobin, greater platelets, fewer blasts and basophils, a low-risk score, and improved compliance were all factors that influenced the molecular responses to imatinib [12]. Patients who did not respond to imatinib showed improvement in TKIs, first-generation TKIs exhibited fewer adverse events [10]. Adverse haematological characteristics, like anaemia and leukocytosis, were seen in a significant section of the research population [11].

Study	Study design	Country	Participants	Mean age	Gender (Males)
Roberts et al., 1991 [9]	Prospective	Riyadh	248	38.2	142 (57.3)
Fatima et al., 2021 [10]	Retrospective	Abha	80	41.6	40 (50)
Algahtani et al., 2020 [11]	Retrospective	Riyadh	56	43.3 + 18.1	25 (44.6)
Elsayed et al., 2021 [12]	Retrospective	Mecca	141	16-83 (range)	76 (53.9)
Alsobhi et al., 2015 [13]	Retrospective	Jeddah	101	14-73 (range)	53 (52.5)
Al-Amri, 2018 [14]	Retrospective	Al-Khobar	17	15-63 (range)	13 (76.5)
Khalil et al., 2010 [15]	Retrospective	Riyadh	15	14-56 (range)	8 (53.3)

Table (1): Sociodemographic characteristics of the included participants.

Table (2): Clinical characteristics and outcomes of the included studies.

Study	Objectives	Follow-up duration	Main outcomes	ROBIN-I
Roberts et al., 1991 [9]	To study patterns of blastic transformation in CML that are morphological and immunological	NM	The age range of this group of CML patients was lower than the average age recorded from the West, which may be related to Saudi Arabia's generally younger population. At diagnosis, the proportion of Ph′ was comparable to other reports. The	Moderate
Fatima et al., 2021 [10]	To examine the clinical aspects of CML patients as well as the effectiveness and safety of tyrosine kinase inhibitors (TKIs) as a treatment for CML.	12 months - 16 years	The majority of CML patients were middle-aged, with a little male preponderance. With a Sokal score in the intermediate-risk range, the majority of patients appeared during the chronic phase. TKIs were used to treat patients upfront; many of them received second-generation TKIs. Compared to second-generation TKIs, first-generation TKIs exhibited fewer adverse events, albeit these toxicities were minor.	High
Algahtani et al., 2020 [11]	To study the demographic, clinical, and hematological characteristics of CML patients	NM	Adverse haematological characteristics, like anaemia and leukocytosis, were seen in a significant section of the research population. As a result, it is imperative that a patient with a raised WBC count, hepato-splenomegaly, abdominal pain, and distension of the left side be tested for CML. Males 31 (55.4%) and females 25 (44.6%) did not have statistically significant differences in CML incidence (P = 0.2552), which may have been caused by ethnic variance.	Moderate
Elsayed et	To study the efficacy and	47.7 months	Greater haemoglobin, greater platelets, fewer blasts and	

al., 2021 [12]	tolerance of imatinib in patients who are treated outside clinical trial		basophils, a low-risk score, and improved compliance were all factors that influenced the molecular responses. It was discovered that imatinib has a safe safety profile in conjunction with a high level of efficacy in CML patients in a real-world context.	Moderate
Alsobhi et al., 2015 [13]	To study the efficacy and tolerance of imatinib in CML patients	45 months	When used to treat CML patients during their chronic phase, IM has been shown to produce long-lasting effects.	Moderate
Al-Amri, 2018 [14]	To study the efficacy and tolerance of imatinib in CML patients	8 years	This study demonstrated the long-term efficacy of Saudi patients with CML-CP and their controllable side effects.	High
Khalil et al., 2010 [15]	To evaluate the response and resistance of cases to CML therapy withTKI (imatinibmesylate) and to search for mutations in the BCR-ABL kinase domain prior to and during therapy	6-24 months	Mutations in the breakpoint cluster region (BCR)-Abelson murine leukaemia (ABL) are uncommon in the early stages of the chronic phase and become more common as the disease progresses.	High

Discussion

This qualitative review is limited by the small sample sizes included that were investigated for the risk and prognosis of CML among Saudi patients. This review found that only younger and middle-aged age groups were found to be risk factors for CML development, with slight male predominance. A growing number of patients with cancer who are diagnosed between the ages of teenagers and young adults are the focus of attention these days. With a median age of 67 years recorded in national registries, CML has traditionally been associated with older persons [16]. A rising percentage of CML patients, nonetheless, are receiving their diagnosis earlier in life [17]. Regarding the other leukemias, including CML, not much is known about the features of patients and their prognoses.

A previous analysis [18] demonstrated that the adult CML incidence logarithmic versus age displays a male line that is either left-shifted in relation to the female line or parallel to it. This is consistent with either longer CML latencies in men, higher risks per CML target cell, or combinations of these factors. In males, there are also more CML target cells. With just the Surveillance, Epidemiology, and End Results (SEER) [19] dataset, these mechanistically distinct options are indistinguishable. We demonstrate that the A-bomb survivor CML data favour a mixed interpretation that is more in line with a pure larger-amplitude approach (more target cells and/or higher risk per target cell) than a pure difference-in-latency one. It is less expected that other mechanisms, such as hormonal impacts, will result in concurrent male-female CML log occurrences.

The current study demonstrated the long-term efficacy and controllable side effects of imatinib on CML [12-14]. Greater haemoglobin, greater platelets, fewer blasts and basophils, a low-risk score, and improved compliance were all factors that influenced the molecular responses to imatinib [12]. The Food and Drug Administration (FDA) approved imatinibmesylate as the first TKI for the treatment

of individuals with CML-CP. It works by inhibiting protein phosphorylation implicated in cell signal transmission through competitive inhibition at the ATP-binding site of the BCR::ABL1 oncoprotein. In addition to blocking the platelet-derived growth factor receptor (PGDFR) and the C-KIT tyrosine kinase, it effectively inhibits the BCR::ABL1 kinase [20]. In the CML-CP International Randomised Study of Interferon and STI571 (IRIS), 1106 patients were randomised to receive either IFN-a plus low-dose cytarabine or imatinib 400 mg/day. Significant improvements were observed in the frequencies of CCyR (74% vs. 9%, p <.001) and independence from progression to AP or BP at 12 months (99% vs. 93%, p <.001) with imatinib therapy. The high proportion of IFN-a-related intolerance crossover to imatinib underscored the difficulties in employing IFN-a [21].

In the current study, patients who did not respond to imatinib showed improvement in TKIs, and first-generation TKIs exhibited fewer adverse events. Adverse haematological characteristics, like anaemia and leukocytosis, were seen in a significant section of the research population [10, 11]. In the CML-CP International Randomised Study of Interferon and STI571 (IRIS), 1106 patients were randomised to receive either IFN-a plus low-dose cytarabine or imatinib 400 mg/day. Significant improvements were observed in the frequencies of CCyR (74% vs. 9%, p <.001) and independence from progression to AP or BP at 12 months (99% vs. 93%, p <.001) with imatinib therapy. The high proportion of IFN-a-related intolerance crossover to imatinib underscored the difficulties in employing IFN-a [22].

The availability of effective salvage therapy may have contributed to the lack of benefit of second-generation TKIs on long-term survival, despite their higher rates of early optimum responses. Additionally, they were linked to greater incidences of major adverse events (10-year cumulative rate of adverse events with

nilotinib33%). Patients with high-risk diseases may benefit from second-generation TKIs; nilotinib, dasatinib, and bosutinib successfully reduced the rate of transition to the accelerated phase (AP) and blast phase (BP) [23].

Conclusion

Risk factors for the development of CML were shown to be limited to younger and middle-aged groups, with a slight male predominance. This study showed that imatinib for CML has both long-term efficacy and manageable side effects. Improved compliance, lower blast, and basophil counts, increased hemoglobin, increased platelets, and a low-risk score were all associated with different molecular reactions to imatinib. Future research is required to assess the possible risk factors, management lines, and prognostic factors of CML in the Saudi population.

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