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# ATRIAL FIBRILLATION IN HEMATO-ONCOLOGIC PATIENTS: EPIDEMIOLOGY, MECHANISMS, AND CLINICAL IMPLICATIONS

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**ABSTRACT**

**Background:** Atrial fibrillation (AF) is a common cardiac arrhythmia that affects approximately 2% of the population. In the population of patients with hematological neoplasms, there is an increased risk of developing atrial fibrillation. Despite growing evidence linking AF with hematological malignancies, current research rarely differentiates individual malignancies, leaving significant gaps in understanding disease-specific mechanisms.
**Objective:** The aim of this study is to demonstrate the correlation between an increased risk of atrial fibrillation in hemato-oncological patients, to present the mechanisms underlying the onset of AF in these patients, and to outline the challenges associated with arrhythmia management in this group of patients
**Materials and Methods:** The article is based on scientific literature sourced from PubMed, SpringerLink and Google Scholar.
**Results:** Patients with hematological malignancies have a markedly increased risk of developing atrial fibrillation compared to cancer-free patients. Multiple factors may explain this linking; for example, anemia, electrolyte disruption, cytokine-mediated atrial remodeling, radiation exposure, and side effects of various therapies, including anthracyclines, CAR-T, or tyrosine kinase-inhibitors. AF in this population is often complicated by higher rates of bleeding, thromboembolic events, and treatment interactions.
**Conclusions:** Atrial fibrillation represents a growing clinical challenge in hematology and oncology, requiring individualized treatment and close multidisciplinary collaboration, especially between cardiologists and oncologists. Current data suggest the need for disease-specific testing, improved risk stratification models, and the identification of predictive biomarkers. A more profound understanding of the mechanisms linking AF and hematologic malignancies could ultimately improve prevention, diagnosis, and tailored therapeutic strategies.

**KEYWORDS**

Atrial Fibrillation, Hematologic Malignancies, Oncology, Arrhythmia, Biomarkers

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## Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia that constitutes a significant worldwide problem, especially in the elderly age group. According to statistics, in 2017 there were 37.5 million cases of prevalent AF and 3.05 million incident cases of AF globally. [1] The prevalence of atrial fibrillation in the general population is estimated at 2%. [2] This arrhythmia gives rise to serious clinical consequences. AF is correlated with various clinical outcomes, including stroke, extracranial systemic thromboembolism, dementia, heart failure, myocardial infarction, venous thromboembolism, and death. [3] In addition to the well-known risk factors of atrial fibrillation, such as age, male gender, and hypertension, malignancy and cancer have been increasingly associated with the development of AF. [4] Hemato-oncologic patients constitute an increasingly larger group of subjects. Studies have shown that among individuals aged 75 and above, the incidence of certain hematologic malignancies (HM) has increased over the years. [5] The co-occurrence of AF and HM poses a serious therapeutic and diagnostic challenge. The aim of this study is to provide a comprehensive overview of atrial fibrillation in hemato-oncological patients, focusing on epidemiology, pathophysiological mechanisms resulting from the presence of malignancy, and clinical consequences.

**Epidemiology**

In a 2022 Austrian analysis, authors reported that the age-stratified random-effects relative risk ratio for AF in patients with cancer compared with no cancer diagnosis was calculated at a value of 10.45. The data shows that cancer patients, particularly those with advanced-stage disease, have been shown to have an elevated risk of developing AF; however, one of the largest degrees of association has been observed in individuals with hematologic malignancies. [6,7] The 2020 cohort study indicates that the risk of AF incidence in patients with HM is significantly higher than in the study population with solid cancer (HR 1.53). [8] Based on the 2021 scientific study, the adjusted subdistribution for leukemia was HR: 2.64; for lymphoma, the adjusted subdistribution was HR: 2.29. [9] Furthermore, the 2024 study focused on the influence of multiple myeloma (MM) on the risk of atrial fibrillation manifestation, grouping subjects depending on their age. The results showed that in the age group <65 years old, the prevalence of AF was estimated as 6.6%; 65–80 years old, 18.4%; and >80 years old, 28.2%, which emphasizes that MM provides a higher risk of AF onset than in the general population. [10] Also, the studies have proven that the association of AF and cancer is stronger in younger subjects. [6] Despite numerous studies examining the incidence of atrial fibrillation in patients with hematologic malignancies, there is a significant gap in the literature. Most of the studies group various hematologic entities into a single category, rarely providing data separated by the disease.

**Pathophysiology**

Atrial fibrillation is caused by a number of factors that contribute to arrhythmia. This section will explore the possible pathophysiological mechanisms in hemato-oncologic patients that cause the development and, in some cases, increase of mortality in individuals with AF.

**1. Hematological and metabolic disorders**

Hematological malignancies often cause hematological and metabolic disorders. The common complication accompanying HM is anemia. [10] The studies strongly suggest that the presence of anemia might be a significant risk factor for developing AF. [11] The mechanism linking anemia and AF development is unclear. Anemia leads to dyspnea, fatigue, and decreasing exercise capacity, in turn bringing about heart failure (HF) symptoms. HF gives rise to intracellular dysregulation in calcium ion level and neurohormonal activation. Furthermore, heart failure affects the progression of atrial remodeling, which may cause AF onset. [12]

On the other hand, hyperviscosity is frequent in patients with AF. It has been reported that hyperviscosity accompanies hematological malignancies, especially those that secrete high levels of paraprotein (i.e., IgM, IgA). It is most commonly observed in Waldenstrom macroglobulinemia (WM), affecting 10–30% of patients, and has been reported in 2–6% of patients with MM. [13] The role of hyperviscosity as a determinant of atrial fibrillation stays unclear; however, the studies suggest that co-occurrence of those two factors might increase already elevated risk of life-threatening complications such as cerebral ischemia. [14] Another possible factor causing AF in HM individuals worth looking at is hypercalcemia. Hypercalcemia is a common manifestation of multiple myeloma. That electrical disturbance may increase the excitability of myocardial cells and enhance the activity of ectopic pacemakers, thereby predisposing to atrial fibrillation. [15,16] The association of other electrolyte disturbances with hematologic malignancies has also been observed. For instance, acute leukemia patients may develop hypokalemia and hypomagnesemia. [17] Those two electrolyte disturbances have been proved to be the risk factors for developing AF. [18]

**2. Radiation**

Radiotherapy is used in the approach to a wide range of hematological malignancies in various ways. [19] The mechanism by which radiation might increase the risk of AF is cardiotoxicity, especially when radiation is placed in the thoracic range. [7] The studies strongly suggest that incidental radiation on the sinoatrial node during radiotherapy might be associated with developing AF as well as increasing mortality. [20]

**3. Inflammation and cytokines**

Cancers, including hematological malignancies, are associated with inflammation in the human body. There is a bidirectional correlation between inflammation and AF. The inflammation may lead to atrial fibrillation; however, AF promotes inflammation as well. A growing amount of research shows that inflammatory mediators contribute to both structural and electrical remodeling of the atria. The key mechanisms involve atrial fibrosis, changes in gap junctions, and disturbances in intracellular calcium handling. These changes enhance ectopic activity in the atria and reduce conduction velocity, which disrupts impulse

propagation and favors the development of reentry mechanisms. [21] Interleukin 6 (IL-6) plays a crucial role in chronic inflammation and is closely related to chronic inflammatory diseases, autoimmune diseases, and cancer. [22] It has been observed that elevated levels of IL-6 and sIL-6 receptor are frequently present in the various HM, and are considered as an indicator of poor prognosis for patients. [23] In vitro studies in which murine atrial cardiomyocytes were directly exposed to IL-6 indicate that this cytokine influences the expression of gap-junction channels and helps create a substrate for AF. IL-6 has also been shown to directly affect mouse and rat cardiomyocytes by modifying their electrophysiological behavior, including increasing ionized calcium and reducing the activity of sarco/endoplasmic reticulum calcium ATPase-2. Furthermore, IL-6 has been reported to be a useful biomarker for predicting the development of AF in a limited group of patients, including individuals with chronic kidney disease or coronary artery disease. [24] Nevertheless, there is a gap in the literature correlating IL-6 level as a biomarker of predicting the AF development in subjects with HM.

**4. Chimeric Antigen Receptor T-cell therapy**

Chimeric Antigen Receptor T-cell therapy (CAR-T) is a decisive breakthrough in the treatment of hematological malignancies. In particular, CAR-T has revolutionized the treatment and achieved unprecedented responses in malignancies such as multiple myeloma, non-Hodgkin lymphoma (NHL), and B-cell acute lymphocytic leukemia. [25]

Chimeric antigen receptors are being engineered to possess the ability to bind specific antigens with the capacity to activate T cells. CAR-T cells detect tumor-associated antigens independently of MHC molecules, triggering their antitumor response. When the CAR binds to its target antigen, T cells become activated through phosphorylation of ITAMs, leading to cytokine release, T cell proliferation, and cytotoxic activity. [26,27] One of the most common complications of CAR T-cell therapy is Cytokine Release Syndrome (CRS). CRS is a systemic inflammatory process that is the result of massive cytokine production by the proliferating activated CAR T cells, with IL-6 as the major mediator for the onset of that complication. Arrhythmias, among the most common complications from CAR T-cell therapy, have been reported mostly in the context of CRS. [28] While the precise mechanisms underlying arrhythmia development in these patients remain unclear, it is thought that atrial fibrillation may result from the direct impact of cytokines on the cardiac electrical system. The proposed mechanisms include the cytokines influence on changing the expression of calcium and potassium channels in the cardiomyocytes, abnormal calcium homeostasis, downregulation of connexins 43 and 40, and changes in ion channel gene expression. The above-mentioned factors favor the development of AF. [28]

**5. Allogeneic Hematopoietic Cell Transplantation**

Allogeneic hematopoietic cell transplantation (HCT) is a potentially curative procedure for various malignant and non-malignant hematologic diseases. HCT requires depletion of the recipient’s blood and immune system, followed by administration of donor hematopoietic stem cells (HSCs) which reach the recipient's bone marrow, implant into it, and restore all blood cell lines. Hematopoietic recovery after transplantation typically occurs in phases: innate immune cells and platelets usually recover within a few weeks after HCT, whereas full recovery of adaptive immunity may take months or even years. [29] Several mechanisms have been proposed to explain the potential of stem cell transplantation to induce arrhythmias. Proposed mechanisms include lack of electromechanical integration, transplantation of non-cardiomyocyte derivatives, local injury and edema, nerve sprouting leading to increased sympathetic tone, and immunologic mechanisms leading to rejection and inflammation. [30] The studies have indicated that the risk of onset of AF after HCT is significant and is associated with a worse survival rate. [31]

**6. Anthracyclines**

Anthracyclines are a group of chemotherapy drugs commonly used in treating various types of cancer, including hematological malignancies. The example of drugs used in individuals with HM may be idarubicin or daunorubicin. [7,32] Anthracyclines are commonly known for their cardiotoxicity effect; nevertheless, the results are dose dependent. [33] Research studies have shown a relationship between the use of anthracyclines and the occurrence of arrhythmia. [34] Furthermore, incidents of anthracycline-induced AF amplified the risk of developing heart failure. [35] However, the exact mechanism of inducing AF by anthracyclines is not fully understood. Scientists cite several hypotheses that cause AF. The factors include damage to cardiomyocytes caused by oxidative stress, resulting in cardiomyopathy and impaired electrical conduction; direct interference with ion channels leading to their dysfunction; myocarditis accompanied by cardiac remodeling; and disturbances in autonomic regulation. [7]

**7. Tyrosine kinase inhibitors**

Tyrosine kinase inhibitors are another group of drugs that have been linked to causing atrial fibrillation. Especially ibrutinib has a well-described connection with developing AF. The studies proved that almost 30-38% of individuals with chronic lymphocytic leukemia taking ibrutinib had the onset of AF. [7] The development of atrial fibrillation (AF) with ibrutinib or other tyrosine kinase inhibitors (TKIs) may be linked to off-target inhibition of C-terminal Src kinase, which can trigger structural changes, myocardial fibrosis, and inflammation in the atria. [36]

**8. Genetic and molecular predispositions**

Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition caused by somatic mutations in hematopoietic stem cells, leading to the expansion of mutant clones. The genes most frequently involved in CHIP are DNMT3A, TET2, ASXL1, and JAK2. These mutations are also commonly observed in myeloid hematologic malignancies, with JAK2V617F being the predominant mutation in JAK2 and the primary driver of myeloproliferative neoplasms (MPN). (37) The studies have shown that TET2 mutation and increased IL-1β were independent risk factors of AF in patients with JAK2V617F-positive MPN. The correlation between JAK2 mutations and the onset of AF is observed in healthy populations as well; however, the stronger link has been reported in MPN individuals with JAK2 variation and the development of AF. Furthermore, the co-occurrence of MPN with JAK2V617F and AF in patients increased the risk of stroke and mortality. [37] It establishes the fact that genetic mutations have the potential to become future biomarkers of the onset and the mortality ratio of atrial fibrillation in patients with HM.

**Clinical manifestations**

The palpitations are the most typical symptom of atrial fibrillation (AF); however, many patients in clinical practice present with other symptoms or may even be completely asymptomatic. Scientists have observed that over half of patients with AF present with atypical or no symptoms. [38] The study of Bin Salih et al. grouped the frequency of atrial fibrillation symptoms depending on whether the disease was acute or chronic. The results showed that palpitations, dizziness, and syncope were the most frequent symptoms in acute AF. On the other hand, dyspnea and palpitations were the most common symptoms in the chronic type. [39] There is the gap in the literature considering clinical manifestations of AF associated with specifically hematologic malignancies. Studies tend to focus on epidemiology, risk, treatment, or complications rather than symptomatology. This suggests the need for prospective studies to understand how AF manifests in this group of patients.

**Therapeutic approach**

Atrial fibrillation is a clinical condition with a wide array of therapeutic approaches. Management strategies encompass both ventricular rate control and rhythm restoration, in addition to the prophylaxis of thromboembolic events. [40] This section aims to provide a comparative analysis of AF management in oncological patients versus non-cancer patients, focusing on the incidence of complications and associated mortality.

**1. Anticoagulation**

Anticoagulation is the primary method of preventing thromboembolic complications such as stroke in individuals with atrial fibrillation. Malignancy increases both the risk of thromboembolic events and the risk of bleeding, particularly in the presence of thrombocytopenia and intracranial disease. The CHA2DS2-VASc scale, which assesses the risk of thromboembolic complications in patients with AF, and the HAS-BLED scale, which assesses the risk of bleeding associated with anticoagulation therapy, have not been validated in patients with active malignancy. [41] This requires the development of an individual stratification tool for this population that will allow a more accurate assessment of the risk of thrombosis and bleeding in patients with neoplasm. Despite unresolved questions regarding the risks of venous thromboembolism, bleeding, and arterial thromboembolism, stroke prevention still fundamentally relies on anticoagulation with warfarin or direct oral anticoagulants (DOACs). (7) However, several issues related to neoplasm can complicate warfarin therapy. That includes drug interactions and changes in nutritional status related to nausea, vomiting, and weight loss. Oncologic patients on warfarin, compared with matched controls, tend to spend a shorter duration within the target INR range, exhibit greater INR variability, and experience a higher incidence of thrombotic events. [41,42] DOACs may be an alternative for oncologic patients due to the lack of laboratory monitoring

requirements. [41] However, scientific studies comparing the effectiveness of treatment in atrial fibrillation between apixaban, dabigatran, edoxaban, rivaroxaban, and warfarin did not include oncological patients. [43,44,45,46] On the other hand, low-molecular-weight heparin (LMWH) is recommended for managing venous thromboembolism in patients with active cancer; however, its effectiveness and safety in atrial fibrillation have not been thoroughly investigated. [41]

**2. Left atrial appendage closure**

An alternative to oral anticoagulants that reduces the risk of thromboembolic complications of atrial fibrillation is left atrial appendage closure (LAAC) intervention. It had been observed that nearly 90% of intracardiac thrombi are being formed in the left atrial appendage. [47] If patients with atrial fibrillation achieve sinus rhythm, the resulting thrombus may break off and lead to the development of an embolism. LAAC prevents this complication with similar efficacy as warfarin [48]. The study conducted by Zweiker et al. showed that LAAC short-term complications and, importantly, long-term survival were similar in both oncologic individuals and patients without neoplasm. [47] Nevertheless, studies by Zhang et al. have not been that optimistic. The authors also proved that there was no contrast in hospital mortality or total hospitalization costs between both groups; however, patients with malignancy tended to have a longer hospital stay. [49] Additionally, among complications, oncology patients were more likely to require open or percutaneous pericardial drainage and experience major bleeding. [49]

**3. Ablation**

Catheter ablation has become the first-line option for rhythm control in atrial fibrillation. Catheter ablation has been shown to be similarly effective in maintaining sinus rhythm in patients with and without neoplasm. The database indicated a higher likelihood of periprocedural complications and bleeding in cancer patients compared to those without cancer [7] However, the study conducted by Alves de Carvalho et al. demonstrated that there were no significant differences in AF recurrence, the need for ablation repeat within 1 year, higher bleeding risk, or mortality. [50] Advancements in technology—including 3D electroanatomic mapping, intracardiac ultrasound, and pulsed field ablation—may address safety concerns in performing catheter ablation for cancer patients, thus preserving the availability of invasive yet efficacious therapies. [7]

**4. Drug Interactions**

The coexistence of hematologic malignancy and atrial fibrillation also has implications for pharmacotherapy. Some medications used in cancer therapy may interact with drugs used in AF therapy. This section is intended only to outline the issue, as a comprehensive discussion should address the individual therapeutic problems associated with specific drugs. An example is the previously mentioned tyrosine kinase inhibitor ibrutinib. Ibrutinib interacts with drugs that control ventricular rate, such as diltiazem, verapamil, and amiodarone. These drugs are CYP3A4 inhibitors, which are crucial for ibrutinib metabolism and may increase its serum levels. [51,52] Additionally, hematological malignancies cause changes in the body's homeostasis, often leading to malnutrition. [53] Severe malnutrition leads to alterations in body composition—extracellular body water increases while lean body mass decreases. As a result, the distribution of lipophilic drugs is reduced, whereas the distribution of hydrophilic drugs is increased. [54] This provides a basis for a thorough analysis of the inclusion of appropriate medications in appropriately selected doses by the physician in this group of patients. An example of an antiarrhythmic drug that can be used in the treatment of atrial fibrillation is dofetilide. Its clearance is directly dependent on creatinine clearance, and the half-life of dofetilide is prolonged as renal function deteriorates. The risk of QT interval prolongation and the associated ventricular arrhythmias is positively correlated with plasma dofetilide concentrations. [55] In patients with hematological malignancies, renal failure is a common complication of the underlying disease [56], which implies that particular caution is required when initiating dofetilide therapy in this population, along with appropriate pre-treatment assessment.

**Suggestions for further study**

This article highlights that patients with hematologic malignancies are at a higher risk of developing atrial fibrillation compared to the general population. However, current data remain insufficient to fully elucidate the coexistence of these two conditions. Future studies may identify disease-specific biomarkers that could enable earlier prevention and diagnosis. Moreover, a more comprehensive exploration of this topic would enhance understanding of the interplay between hematology and cardiology, fostering closer collaboration between specialists in the care of these individuals.

**Conclusions**

There is a significant correlation between the occurrence of atrial fibrillation and hematologic malignancies. Both AF and its associated therapies are linked to a higher rate of complications compared to the general population. Nevertheless, there is a lack of studies connecting specific hematologic disorders with the development of AF. The literature also reveals a gap in understanding the mechanisms underlying the onset of this arrhythmia in hemato-oncologic patients, as well as those specific to individual malignancies. What is clear, however, is that patients in this group require multidisciplinary collaboration and a comprehensive approach. Further research is needed to fully elucidate the interrelationship between AF and hematologic neoplasms and to potentially identify biomarkers that could help stratify the risk of arrhythmia in this patient population.

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