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HEMATOLOGICAL DISORDERS AND MENTAL HEALTH: PSYCHOSOCIAL AND NEUROBIOLOGICAL INTERCONNECTIONS

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Abstract

The hematological conditions, such as hereditary hemoglobinopathies to malignant leukemia's, pose a considerable challenge that goes beyond the domain of physiological pathology to the ultimate psychological and societal torment. This review summarizes the existing literature to study the two-way interaction of blood diseases with mental health, in particular with reference to the biological and psychosocial processes causing psychiatric comorbidity. There is biological evidence that shows that hematological patients have clinical signs of anxiety, and mostly have depression, which are direct antecedents of clinical depression, anxiety, and fatigue of the central nervous system. These results are aggravated by stressors induced by treatment, including the neurotoxicity caused by chemotherapy and the high stakes of bone marrow transplantation. The psychosocial aspects of patients are burdened with such factors as social stigma, the economic burden of life-long therapies, and serious educational and job loss. These problems are exacerbated by the absence of integrated psycho-oncology support in developing countries such as Pakistan and the cultural stigma of a dual diagnosis. The review ends with the conclusion that the only way forward on the task of improving patient-reported outcomes is multidisciplinary change towards integrated care. Regular psychiatric assessment with validated instruments such as the PHQ-9 and HADS is critical to the early identification. Moreover, it is essential to integrate low-cost lifestyle changes and family-level counseling into routine hematological care to improve the quality of life of this risk group.

INTRODUCTION

Hematological diseases are multifaceted disorders that are connected with mutations of hematopoietic stem cells and chromosomal abnormalities like aneuploidy, translocations, or deletions (Awan et al., 2021). These conditions encompass an extensive range of clinical diseases, including life-threatening malignancies, such as acute and chronic leukemia's, and non-malignant but severe diseases, such as aplastic anemia (Awan et al., 2021; Javed et al., 2023).The disease burden is especially high in Pakistan; a study by Awan et al. (2021) suggests that Pre-B Acute Lymphoblastic Leukemia is the most common malignancy (33%), followed by Chronic Myelogenous Leukemia that accounts for 20% of the cases (Awan et al., 2021).Moreover, cytogenetic culture failure, which reaches up to 20% in some Pakistani centers, is a major problem in the diagnostic process. These failures are statistically

linked to persistent induction of chemotherapy and the low quality of clinical samples (Javed et al., 2023).

Mental health refers to the state of emotional and social well-being that allows individuals to be in a position to cope with the normal stressors in life (Masood et al., 2024). Nevertheless, Pakistan is experiencing a widespread mental health crisis, in which the number of individuals with psychiatric distress is almost 50 million, and the lack of professionals is critical (Masood et al., 2024; Weng Hong et al., 2022). In the group of hematological patients, 38.6% of the population is symptomatic of anxiety, and 42.4% of the patients have clinical depression (Kuang et al., 2023).

The hematological disorders have physiological effects as they are associated with the disruption of the hypothalamic-pituitary-adrenal (HPA) axis, which controls the stress response. Constant systemic inflammation and intermittent hemoglobin levels, in chronic anemic patients or those with malignant blood disorders, may cause cortisol secretion with an additional predisposition to depressive and cognitive fatigue symptoms in patients (Dantzer et al., 2008). Such a biological susceptibility, combined with the neurocognitive impairment of persistent physiological hypoxia, forms a vicious cycle in which physiological decline enhances psychological decline (Papathanasiou et al., 2020).

Such a connection between mental health and hematological disorders is complex, as it can be provoked by physiological and environmental factors (Papathanasiou et al., 2020).In biological terms, bone marrow suppression is brought about by biochemical effects resulting in cytotoxicity of chemotherapy regimens, which serve as a direct predictor of psychological distress (Javed et al., 2023; Weng Hong et al., 2022). On the psychosocial front, the chronic conditions, such as Thalassemia or CML, as well as the heavy therapeutic process, result in social isolation and impairments in emotional functioning (Masood et al., 2024; Papathanasiou et al., 2020). Neurocognitive deficits and depression associated with chronic physiological hypoxia affect adult anemic patients, while pediatric patients face academic and social disruptions with bleeding disorders (Papathanasiou et al., 2020).

The mental health burden in the particular case of the healthcare system of Pakistan is exacerbated by the stigma of a double diagnosis in which a patient is subject to the social disgrace of having been diagnosed with a life-threatening blood disorder and a psychiatric disorder. Families do not receive any integrated psycho-oncology support due to economic barriers that usually compel them to focus on life-saving hematological therapies instead of invisible mental health issues (Shafiq& Shahzadi, 2023). As a result, there is a pressing necessity of local studies into the ways in which low-cost lifestyle interventions and family-based counseling can be incorporated into routine hematological practice to enhance the Quality of Life of Pakistani patients (Salman & Mohammed, 2025).

There are significant gaps in the research related to Pakistan, where clinical hematology is not commonly combined with psychiatric support (Awan et al., 2021; Javed et al., 2023). Also, no localized data is available on how lifestyle changes can counter the mental health burden in active treatment (Salman & Mohammed, 2025). Thus, the goal of this review is to synthesize clinical patterns and psychological effects to promote a new comprehensive care approach to Pakistani patients (Salman & Mohammed, 2025).

Overview of Hematological Disorders

Hematological disorders comprise a wide spectrum of diseases that affect the blood and many other components of the blood, including red, white blood cells and platelets. The diseases may be caused by various reasons, including nutritional deficiencies, genetic factors, infections, and chronic diseases. The diseases may be malignant and non-malignant (Saito & Niwa, 2016).

Hereditary diseases of the erythrocyte type are common in many parts of the world, including the Middle East. In some parts of the Middle East, more than 10 percent of the population may be carriers of a gene that codes for one of the following diseases. When patients from the Middle East present themselves to medical facilities in the West, unsuspected but significant anomalies of the erythrocyte may cause life-threatening consequences from routine medical care, such as a drug-induced hemolytic crisis, as well as diseases such as sickle cell

anemia, thalassemia, and anemia (Steensma et al., 2001).

The manifestations of hemolysis include a syndrome of acute or chronic anemia, reticulocytosis, or jaundice. The diagnosis of hemolysis is confirmed by the presence of reticulocytosis, elevated levels of unconjugated bilirubin and lactate dehydrogen (Dhaliwal et al., 2004).The etiologies of hemolysis may be grouped as either acquired or hereditary in nature. The most common causes of acquired hemolytic anemia include autoimmunity, microangiopathies, and infection. Immune-mediated hemolytic anemia, resulting in the production of antierythrocyte antibodies, may result from malignancy, autoimmune diseases, medications, and transfusion reactions. Microangiopathic hemolytic anemia is characterized by damage to the red cell membrane, resulting in intravascular hemolysis and the presence of schistocytes (Jacobasch & Rapoport, 1996). Malaria and babesiosis are examples of infectious agents that infect red blood cells. Disorders of red blood cell enzymes, cell membranes, and hemoglobin are examples of hereditary hemolytic anemia. Glucose-6-phosphate dehydrogenase is a disorder that results in hemolysis when oxidative stress is present (Shahidi& Diamond, 1959).

Sickle cell anemia (SCA) is a genetic disorder that occurs due to abnormal hemoglobin production, which deforms the shape of the red blood cells, making them sickle-shaped. This deforming of the red blood cells makes the blood flow abnormal, leading to a number of complications. Sickle cell anemia occurs due to a genetic mutation in the HBB gene. This gene follows an autosomal recessive inheritance pattern. (Pauling et al., 1949).Sickle cell anemia (SCA) is an illness that is brought about by the production of abnormal hemoglobin, which combines with abnormal hemoglobin in the red cell, leading to rigidity in the cell's shape. This interferes with the cell's ability to pass through the small vessels, leading to sludging, thereby causing the vessels to become congested, resulting in infarction in the tissues served by the vessels. Infarction is seen in the body of the patient with SCA, leading to the first manifestation of the illness, the pain crisis, believed to result from infarction in the marrow. Eventually, the patient develops infarcts in the medullary bones, leading to osteonecrosis in the epiphyseal plates. In the brain, infarcts in the white matter and gray matter are seen, leading to cognitive function and functional neurological deficits (Lonergan et al., 2001).

Thalassemia is common hereditary anemia in the world which is caused by a reduction or complete cessation in the production of the alpha-like (alpha-thalassemia) or beta-like (beta-thalassemia) globin chains that are synthesized to make the hemoglobin tetramers in fetal (Aydinok, 2012).

Alpha thalassemia is caused by a deletion in the gene called alpha-globin, which leads to a reduction or lack of alpha globin chains. The alpha globin gene has four alleles; the severity of alpha thalassemia varies from mild to severe depending on the number of deleted alpha globin alleles. The deletion of four alpha globin alleles is the most severe form; no alpha globin is produced, and excess gamma globin chains (produced during fetal development) form tetramers. This is nonviable and leads to hydrops fetalis. One alpha globin allele deletion is the mildest form; it is usually asymptomatic (Muncie Jr & Campbell, 2009).Beta thalassemia is caused by point mutations in the beta globin gene. It is classified into three types depending on the zygosity of the mutation occurring in the beta gene. When a heterozygous mutation occurs in the beta gene, it is called beta-plus thalassemia, causing beta thalassemia minor, which is characterized by a reduction in beta chains. It is mild and asymptomatic. When a homozygous mutation occurs in the beta globin gene, it is called beta-zero thalassemia, causing beta thalassemia major, which is characterized by a total absence of beta chains (Galanello& Origa, 2010). It presents with jaundice, growth retardation, hepatosplenomegaly, endocrine abnormalities, and severe anemia that requires lifelong blood transfusions. The type of thalassemia that occurs between these two types is known as beta thalassemia intermedia with mild to moderate clinical symptoms (Origa, 2017).

White blood cells (WBCs), both granulocyte (e.g., neutrophils, eosinophil's, and basophils) and mononuclear cell (e.g., monocytes and lymphocytes), play a crucial role in the innate and adaptive immune response to mitigate infectious, traumatic, and malignant diseases. Normal development and

function of the various types of leukocytes is essential to understand the impact of their absence and/or function on the manifestation of diseases (Walkovich & Connelly, 2022).

Leukemia is caused by a transformed hematopoietic stem cell that results in a clone of cancerous cells and an overproduction of abnormal white blood cells, which is central to its development and progression (Lowenberg et al., 1999). Leukemic transformation is a multi-step process, and normal regulation of cell growth, differentiation, and programmed cell death is disrupted, resulting in a clone of self-renewing cells, often arrested in maturation, which becomes detectable in the bone marrow and/or blood as a result of expansion of this clone (Gilliland et al., 2004).

Lymphoma is characterized by its heterogeneous nature, where it is categorized as a malignant cell disorder of the lymphocytes, involving the lymphoid tissues, the bone marrow, or the extra nodal sites. The classification of the lymphomas is according to the World Health Organization, where there are over 90 distinct types of the disease. The initial classification is done according to whether the cell is of B cell, T cell, or NK cell origin. The classification of the distinct types of the lymphomas is beyond the scope of this article, although they are characterized by their morphologic, immunophenotypic, genetic, molecular, and clinical characteristics (Lewis et al., 2020).

When the blood vessel is injured, the platelets stick to the exposed sub-endothelium (platelet adhesion), become activated (platelet activation), and release the contents of their granules (platelet secretion), which include some platelet agonists (adenosine diphosphate, serotonin) that through interaction with specific receptors on the surface of platelets, are involved in the aggregation of more platelets (platelet aggregation). Moreover, platelets are involved in the coagulation mechanism; they are required to provide the surface of procoagulant phospholipids (Cattaneo, 2003).

Hemophilia A and B are rare bleeding disorders caused by the lack of clotting factor VIII and IX, respectively (Franchini& Mannucci, 2014).The severity of the disease in patients suffering from hemophilia is determined based on the plasma level of FVIII and FIX activity. The severe disease state is determined when the factor level is <1% of normal plasma levels, moderate disease state when the factor level is 1-5%, and mild disease state when the factor level is >5 and <40%.2 Patients suffering from severe cases of hemophilia usually suffer from spontaneous bleeding in their joints, muscles, and soft tissues without any apparent reason. They may suffer from the life-threatening bleeding situations such as intracranial hemorrhage (Castaman& Matino, 2019).

Thrombocytopenia is defined as a platelet count of less than 150,000/μL. It can be caused by a decrease in platelet production, platelet sequestration, or increased platelet destruction (Greenberg & Kaled, 2013).

Pain level and reduced functionality, as well as varied degrees/severity of problems, can greatly influence the patient's overall well-being, as these can increase not only their health problems but also negatively impact their quality of life. It is one of the most frequently applied measures in assessing therapeutic interventions and strategies that seek to enhance mental health. "Quality of Life" was also widely applied in studies that examined patients suffering from serious health conditions and those experiencing chronic pain (Papathanasiou et al., 2020).

Depression is the most common psychiatric complications noted among patients with hematological diseases, especially those with chronic anemias and hematologic cancers, including Leukemia, Lymphoma, and Multiple Myeloma, as well as bone marrow failure syndromes, including Aplastic anemia.

Prevalence of clinically significant depression among cancer patients varies between 15-25%. Higher rates of depression are noted among those undergoing intensive chemotherapy and/or hematopoietic stem cell transplantation (Mitchell et al., 2011).

Patients awaiting or undergoing bone marrow transplantation have very high levels of anxiety due to the awareness of mortality risks involved in the procedure and immunosuppression. Blood transfusion procedures required in chronic anemia and thalassemias may also create procedural anxiety and dependency anxiety (Pitman et al., 2018). Moreover, fear of relapse is a continuing psychological problem for survivors of leukemia and

lymphoma, which often results in anxiety disorder or panic attacks as given in figure 01. The biological mechanisms of anxiety may also be mediated by alterations in hypothalamic-pituitary-adrenal (HPA) axis function, which is a consequence of chronic stress and systemic inflammation. Increased concentrations of cortisol and pro-inflammatory cytokines are known to modulate amygdala function, making individuals more likely to suffer from anxiety disorders (Costanzo et al., 2011).

Cognitive Impairment

Cognitive impairment is a well-recognized complication of both benign and malignant disorders of the blood, including various aspects of cognitive functioning such as memory, attention, and processing speed. Cognitive impairment from disorders of the blood is caused by various biological mechanisms, including chronic cerebral hypoxia from anemia, neurotransmitter disruption from iron deficiency, inflammatory cytokine-induced neurotoxicity from leukemia and myelodysplastic syndromes, and chemotherapy-induced neurotoxicity (Ahles et al., 2012). Patients who undergo therapies such as chemotherapy or hematopoietic stem cell transplantation are especially at risk. Other factors that may contribute include vitamin B12 deficiency, the use of corticosteroids, metabolic abnormalities, sleep problems, and the presence of co-existing depression or fatigue. These factors combine to affect cognitive-related neural networks despite the absence of direct central nervous system involvement (Cella et al., 2011).

Patient experience brain fog, forgetfulness, slowness of thought, and problems with multiple tasks, sometimes during remission or even after treatment is over (Meyers et al., 2005). Cognitive dysfunction greatly impacts the quality of life, work performance, academic performance, and treatment compliance. Early detection of cognitive impairment using screening tests like the Montreal Cognitive Assessment (MoCA) or neuropsychological tests is crucial. Cognitive impairment is common, with a prevalence of up to 75% of patients with MS. Cognitive problems can be the presenting symptom of MS, occurring before (Wefel et al., 2015).

Mechanisms Linking Blood Disorders and Mental Health

Blood disorders such as anemia and sickle cell disease not only influence the body's hematologic status but also have important neurobiological associations to mood, cognitive, and emotional states. Blood disorders are increasingly being examined in relation to the influence they can have on mental health outcomes such as depression, anxiety, and cognitive functioning (Skibsbye, 2016).

Systemic chronic inflammation is a common feature among blood disorders and plays a major role in the pathophysiology of mood disorders (Oprica, 2005).

Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are secreted in excess in the presence of chronic inflammation. These cytokines can cross the blood-brain barrier or affect it indirectly, altering neurotransmitter synthesis, neural plasticity, and stress responses. Elevated levels of IL-6 have been linked to reduced brain-derived neurotrophic factor (BDNF) expression in limbic regions, which is implicated in depression and altered neural connectivity in mood disorders (Kyle, 2007). Systemic chronic inflammation is a common feature among blood disorders and plays a major role in the pathophysiology of mood disorders.

Pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) are secreted in excess in the presence of chronic inflammation. Increased IL-6 has also been implicated as being causally related to decreased expression of brain-derived neurotrophic factor (BDNF) in limbic structures, depression, and disrupted neural connectivity that is implicated in the regulation of mood states (Kapsimalis, 2008). Research has increasingly pointed to the role that inflammatory processes play by activating microglia, disrupting neuronal circuits, and affecting the hippocampus and prefrontal cortex, which regulate mood states (Elliott, 2011). There has been an association between cytokines and depression, as well as cognitive impairment, regardless of the presence of any neurodegenerative disease (Hyman, 2023).

Blood disorders like sickle cell anemia have chronic immune activation and increased levels of inflammatory markers. This may contribute to cognitive and mood disturbances that cannot be

accounted for by pain or psychosocial factors alone (Franke, 2020).

Cytokines have a variety of mechanisms to affect brain functions, Inflammation may affect the metabolism of tryptophan through the metabolism pathway, which shifts away from serotonin production towards neuroactive metabolites associated with mood disorders (Colatsky, 1990). Cytokines may activate microglia cells, which have a role in brain immunity, leading to alterations in brain connectivity associated with depression and cognitive impairment (Colatsky, 1990).

Painful crises in SCD not only cause physical pain but also emotional distress. SCD is associated with a state of continuous inflammation, endothelial activation (increased adhesion molecules), and oxidative stress, which increase the susceptibility for microvascular occlusion (van Brakel, W. H, 2014).

Recurring hypoxia caused by sickling of red blood cells in microvascular occlusions leads to enhanced cytokine production, not only contributing to local tissue injury but also affecting the systemic immune response (Skibsbye, 2016). Neuroinflammation along with pain and stress contributes to a higher incidence of depression and anxiety disorders in SCD patients. The complex relationship between pain, immune activation, stress, and the nervous system may also influence cognitive outcomes (van Brakel, W. H, 2014).

There are additional layers of biological stressors related to cancer and its treatment that can influence mood states and cognitive processes (van Brakel, W. H, 2014). Systemic chemotherapy, in addition to its effects on malignant cells, also has effects on normal tissues and the immune system. Chemotherapeutic agents can cause peripheral inflammation, which can increase the levels of cytokines such as IL-6 and TNF-alpha, potentially affecting the central nervous system (Luna, 2016).

Chemotherapy can cause inflammation in the brain, leading to the activation of microglial cells and oxidative stress, which can impair the process of neurogenesis. Chemotherapy can cause mitochondrial dysfunction in the brain, leading to cognitive and mood disorders (McKeever, 2024). Though the exact mechanisms that interlink chemotherapy and depression/anxiety disorders are complex and multifaceted, inflammation is believed to play a major role in the development of depression and anxiety disorders, and its role should be investigated in more depth (Luna, 2016).

Psychosocial Factors Linking Blood Disorders and Mental Health

Chronic blood disorders such as anemia, thalassemia, sickle cell anemia, and blood malignancies not only have a biological impact but also a psychosocial one. Besides the physiological effects of blood disorders, the psychological effects of long-term illness, social stigmas, economic difficulties, educational and work-life challenges, and caregiver stress also play an important role in the mental health status of the patient. This article seeks to discuss the psychosocial factors linking blood disorders and mental health (Luna, 2016).

Chronic illness, such as sickle cell anemia, entails living with the disease, medical monitoring, hospitalizations, taking medications, and making lifestyle changes. For sickle cell anemia, sickle cell disease (SCD), and thalassemia major, the disease process begins during childhood, and the patient is under medical care for the rest of the life span (Li, 2022).

Chronic illness burden results in Health-related anxiety, Fear of disease complications, Emotional exhaustion, Loss of autonomy. According to the study by Moussavi et al. (2007), individuals living with chronic illness experience more depression than the general population. Levenson et al. (2008) found that sickle cell anemia patients experience more psychological distress due to painful crises that occur during the disease process (Kapsimalis, 2008).

Social stigma is another important psychosocial stressor. In the case of hereditary blood diseases, misconceptions and stigma often cause discrimination and social isolation. According to research studies, individuals with sickle cell disease often perceive stigma and experience significant associations with depression and low self-esteem. Youths with sickle cell disease may also face social stigma due to the critical role peer relationships play during this period (Edwards, 2005).

The economic consequences of hereditary blood diseases can be significant. Chronic care for these diseases includes frequent blood transfusions, Iron chelation, Hydroxyurea, Chemotherapy, Frequent

diagnostic tests (Colatsky, 1990). For developing countries, the direct costs of medical care can include:

Frequent blood transfusions, Iron chelation, Hydroxyurea, Chemotherapy, Frequent diagnostic tests. These costs can cause considerable financial stress and have been identified as a significant predictor of psychological distress and depression. For individuals with hereditary blood diseases and their families, the consequences include: Frequent debt accumulation, Work interruption, Non-compliance with treatment due to economic constraints (Colatsky, 1990).

Economic insecurity can lead to chronic stress, which can have serious consequences for the health and well-being of individuals and communities (Camerino, 2007).

Children suffering from blood disorders may not attend school as a result of frequent hospitalizations and illness episodes. Cognitive problems may also affect the child's performance in school. Research has shown that children suffering from sickle cell anemia are at a high risk of poor academic performance and absenteeism in school. This may cause a lack of confidence and socioeconomic problems in the child's life (van Brakel, W. H, 2014).

Adults living with blood disorders may experience problems in maintaining employment as a result of fatigue, frequent clinic appointments, and physical limitations. It has been found that chronic illness results in a high rate of unemployment and discrimination in the workplace

Unemployment has a strong association with depression and anxiety disorders. Loss of identity also causes psychological problems (van Brakel, W. H, 2014). The whole family system is impacted by chronic blood disorders. Parents and caregivers have to bear the responsibility and burden of the illness. It has been observed in several studies that the level of stress, anxiety, and depression is high in the caregivers of children with chronic illness. The burden on the caregiver is characterized by the following factors: Emotional exhaustion, financial pressure, Sleep disturbance, Fear regarding the future of the patient (Blows, 2021).

High levels of stress in the caregiver may have an impact on the family and may indirectly affect the coping mechanisms of the patient. At times, the siblings may feel neglected, and the marital relationship may also be impacted due to the demands of the illness on the couple (Franke, 2020).

Impact on Different Age Groups

Chronic blood disorders have varying psychological, functional, and social impacts on people of different ages. The impacts of chronic blood disorders differ depending on the stage of life, from children and young people to adults and the aged, each of whom has their own challenges that affect their mental well-being, quality of life, and functioning (Franke, 2020).

Chronic blood disorders affect children and adolescents with a combination of biological and psychosocial stressors that have a significant effect on their mental health and psychosocial development. Some studies on children with sickle cell disease have revealed that children with SCD who experience painful crises often have increased levels of depression and anxiety, which have also been found to be related to levels of stress and anxiety among their families (Elliott, 2011).

Recent observational studies have revealed that children and adolescents with SCD have reduced health-related quality of life, low self-esteem, and increased levels of depression and anxiety, which are related to their long duration of illness, the number of times they have been hospitalized, and the complications of vaso-occlusive crises (Elliott, 2011).

Further studies from SCD-endemic countries, like Sudan, have revealed that children with SCD have increased levels of emotional problems, conduct problems, and hyperactivity, with a significant proportion of children experiencing moderate to severe psychosocial symptoms (Elliott, 2011).

Chronic hemoglobinopathies have also been found to affect the health behaviors of adolescents, which suggests that chronic blood disorders have a significant effect on the psychosocial adaptation of children and adolescents during their adolescent years (Colatsky, 1990). Moreover, specific population research has identified that the rates of clinical depression in adolescents with sickle cell anemia are substantially high, and the symptoms of depression correlate with the severity and occurrence of painful episodes (Colatsky, 1990).

These findings underscore the significance of psychological support, coping strategy development,

and family-centered care in the management and care of children and adolescents with chronic blood disorders (Elliott, 2011).

Adults living with chronic blood disorders have unique psychosocial issues that are related to the management and care of the disease, their family and professional obligations, and their life expectancy. Specific research on the psychosocial health and well-being of adults living with sickle cell disease has identified that this population has a high risk of stress and psychosocial problems, such as anxiety, depression, and social and professional maladjustment. The psychosocial problems in adults living with sickle cell disease are attributed to the chronic pain, unpredictable nature, and long-term complications associated with the disease (Anderson, 2021).

Narrative reviews on the psychosocial experiences of adults living with sickle cell disease have identified that the psychosocial problems are related to the stigmatization, lack of engagement in professional activities, and financial instability associated with the disease. While fewer studies have specifically focused on adults with other forms of chronic blood diseases (e.g., thalassemia and anemia), the studies examining hereditary and acquired bleeding disorders have shown that the self-reported health-related quality of life is significantly lower in adults with these diseases compared to healthy controls. These studies highlight the continued impact of chronic hematologic disease in adulthood (Burkhardt, 2006).

While less well-studied than the pediatric and adult populations, the evidence also indicates that the elderly population with chronic blood diseases can have compounding factors due to the process of aging. With the process of aging, individuals can experience physiological changes in their hematologic parameters even if they do not have any underlying disease. However, in the context of underlying disease, these changes can have significant consequences for the individual (Camerino, 2007).

This means that the elderly have to deal with other health complications such as cardiovascular diseases and diabetes, which, in turn, can be exacerbated by the underlying blood disorders. While there has been little literature on the mental health of the elderly with blood disorders, the general trend of the literature on multi-morbidity among different age groups indicates that the elderly have a higher chance of developing mental health complications as a result of the co-occurrence of different health conditions. This indicates that the elderly with blood disorders are a particularly vulnerable group that requires a holistic approach to healthcare, taking into consideration the complexities of aging with multi-morbidity (Burkhardt, 2006).

Psychiatric Screening, Evaluation, and Treatment of Hematology Patients

The psychological distress experienced by the patients who have experienced hematologic malignancies, lymphoma, multiple myeloma, aplastic anemia, sickle cell disease (SCD) and myelodysplastic syndromes is quite significant. The depressive symptoms and anxiety are prevalent among patients with hematologic cancer that is commonly seen in 3050% of patients up until the active treatment and recurrent stage. Timely resolution of depression, anxiety and distress in hematology patients is linked to improved clinical outcome, improved recovery, and better quality of life and decreased cost of healthcare usage. Research indicates that untreated psychological symptoms are associated with high levels of pain, compromised immune system, diminished compliance to chemotherapy/transfusion regimens and even death. Besides, it is not uncommon to be psychologically distressed even after treatment; even as many as 60% of the survivors of hematologic cancer have continued emotional problems that linger in the wake of remission. Early detection makes it possible to provide interventions that are better adjusted, resulting in better coping, symptom control, and patient satisfaction (Cella et al., 2010).

Psychological distress assessment in hematology patients requires carefully selected screening instruments because many physical symptoms, such as fatigue, sleep disturbance, and appetite changes can overlap with psychological symptoms. Therefore, validated tools specifically designed or tested in medical populations are preferred (Fann et al., 2008).

Psychometric properties in cancer populations, with sensitivity frequently exceeding 80% and specificity above 75%. Importantly, HADS minimizes emphasis

on somatic symptoms, thereby reducing false-positive findings in medically ill patients. A score of 8 or higher on either subscale is commonly used as an indicator of clinically significant anxiety or depression. Its reliability and validity have been consistently supported in research (Fann et al., 2008).

It is recommended by the National Comprehensive Cancer Network (NCCN) is a brief, single-item screening tool using a 0–10 scale to measure overall distress. A designated cut-off score indicates clinically significant distress requiring further evaluation. The tool is typically administered alongside a Problem List, which helps identify practical, emotional, family, and spiritual concerns contributing to distress. This approach enables rapid identification of psychosocial needs in oncology and hematology settings (Jacobsen & Thors, 2003).

This is a nine-item instrument widely validated in medical oncology populations for assessing depressive symptoms. It has strong diagnostic accuracy, with sensitivity and specificity rates of approximately 88% for major depressive disorder. Its brevity and alignment with DSM criteria make it particularly useful in routine clinical screening (Kroenke et al., 2001).

It provides computer-adaptive tests assessing anxiety, depression, fatigue, and social functioning. These measures offer high precision and are useful both in clinical research and routine hematology practice. PROMIS tools allow efficient monitoring of symptom burden over time and support individualized patient care. Evidence suggests that regular screening with brief, validated instruments improves the detection of psychological distress and increases timely referral and intervention compared to reliance on clinician judgment alone (Cella et al., 2010).

Following initial screening, structured and comprehensive assessments should be conducted for patients who screen positive. These may include formal psychiatric diagnostic evaluations using semi-structured clinical interviews such as the Structured Clinical Interview for DSM Disorders (SCID) or the Mini-International Neuropsychiatric Interview (MINI). Functional impairment should also be assessed using instruments like the Sheehan Disability Scale to determine the impact of symptoms on occupational, social, and family functioning. Quality of life can be evaluated using oncology-specific tools such as the EORTC QLQ-C30 or the Functional Assessment of Cancer Therapy–General (FACT-G). Additionally, pain and fatigue should be assessed using validated scales such as the Brief Pain Inventory and the FACIT-Fatigue scale, as these symptoms frequently overlap with mood disturbances in hematology patients (Chasiotis et al., 2012).

Psychological Interventions

Patients with blood disorders like disorders have a really tough time. They have to deal with a lot of stress because they're sick for a long time. They have to go to the hospital a lot they are in pain they get tired easily. They do not know what is going to happen to them in the future. People with Sickle Cell Disease, Anemia, Leukemia and Thalassemia often feel depressed, anxious. Their life is not as good as it could be. So it is very important to help these patients with their problems. Psychological help is a part of taking care of patients, with blood disorders (Bjelland et al., 2002).

CBT is believed to be ranked among the most studied psychological therapies in the management of depression and anxiety among the medically ill population, such as cancer and hematology patients. The meta-analyses show that effect sizes of depressive symptom reduction in cancer patients compared to those with usual care are 0.45-0.65. CBT is applied to modify maladaptive beliefs, improve coping, and reduce the interference of symptoms. Follow-up is at 3-6 months, where the benefits are maintained. The studies have revealed moderate effects of anxiety, depression, and quality of life among cancer survivors in mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). Between effects 0.30- 0.50 on mood improvement (Bjelland et al., 2002).

The supportive-expressive therapy is directed to the display of emotions and social support, and it is demonstrated to reduce psychological distress, particularly in a highly advanced cancer institution. Psychoeducational interventions and support groups are organized, have moderate to strong effects on patient-reported distress levels, and are associated

with coping, social support, and compliance with treatment (Bjelland et al., 2002).

Pharmacological management is key in dealing with health issues related to blood disorders. Patients with long-term blood conditions like Sickle Cell Disease, Thalassemia, Leukemia and Anemia often have health problems such as depression, anxiety, sleep issues and chronic pain (Fann et al., 2012).

Selective serotonin reuptake inhibitors (SSRIs) ofsertralineand paroxetine are preferred among cancer and hematologic patients due to their favorable safety profile. Sertraline has been moderately successful in reducing symptoms of depression with quite low interaction potential with chemotherapy. The tricyclic antidepressants (TCAs) are reduced in usage due to the anticholinergic side effects. Meta-analytic estimates reveal that the number needed to treat (NNT) of antidepressants to respond to major depressive disorder is 5-7 in the medically sick population (Ali et al., 2019).

Benzodiazepines (alprazolam) may be taken temporarily (acute anxiety or panic symptoms), particularly at times of hospitalizations or during surgery, but prolonged usage is not recommended due to the occurrence of tolerance and sedation. In the long-term, buspirone and part of the SSRIs (anti-anxiety) may be used. Pharmacotherapy should also take into account interactions with drugs (e.g., SSRIs with some chemotherapy agents), hepatic/renal impairment with metabolism of drugs, and overlapping reactions (e.g., nausea or fatigue). Medical support is advised through collaboration with psychiatrists (Fann et al., 2012).

Comprehensive psychosocial oncology interventions: mental health screening, psychology/psychiatry, nursing, and hematology teams are more effective in identifying psychological symptoms more promptly, more effectively, and result in improved patient outcomes (e.g., better quality of life, less distress, fewer emergency department visits). Regular screening of treatments (e.g., DT or PHQ-9) three times lessens untreated depression by more than 40 percent relative to customary care (Sharif et al., 2020).

Gaps in Current Research and Need for Further Studies

The several gaps in current research are mostly the poor research on mental health mostly in developing countries.

Poor Research on Mental Health among Hematology Patients in Developing Countries. Although there is an overall shift in emphasis in cancer and chronic illnesses populations in high-income countries toward psychological distress, the literature that has addressed mental health in patients with hematology of low- and middle-income countries is sparse. Most of the evidence is European, North American, and Australian, and relatively few studies are based in Asia, Africa, and Latin America, limiting the generalizability of the results to other healthcare systems, cultures, and resource settings (Mehta et al., 2022; Chaturvedi et al., 2014).

Incidentally, a methodical survey of the occurrence of psychological distress among cancer cohorts showed that only a minor part (<15) of the research was performed and it showed that a vast majority of them failed to discriminate or reveal the outcome in blood malignancies and solid tumors. It creates a knowledge gap to understand the effect of the cultural, economic, and health systems variables on the psychological outcome and the operation of the screening tools within the hematology patients in the developing settings (Patel et al., 2018). Moreover, the psychometric properties of the instrument that is accepted within the population of Western countries may not be as strong when it is used in the developing countries, which are not culturally adjusted or validated. It was also observed by a scoping review that not a large number of standardized tools have been formally verified in non-European/North American settings or other local languages, and therefore the validity of the screening suffers and eventually leads to under- or over-diagnosis (Sharif et al., 2020).

The majority of published studies on mental health and hematologic populations are cross-sectional studies that only give the picture of distress at one moment. Longitudinal research is essential to appreciate the course of nature of anxiety, depression, and distress with time, which includes how mental health varies on a diagnosis basis to treatment and survivorship, the impact of disease

relapse or progression and the effects of treatment side effects on psychological well-being. A longitudinal study in cancer populations showed that depressive symptoms at diagnosis strongly predicted subsequent functional impairment and quality of life at 12 months; however, equivalent longitudinal data specifically in hematology cohorts are lacking (Fann et al., 2008).

In the hematologic conditions, some groups of patients lack research regarding the mental health outcomes. Most studies focus on leukemia and lymphoma, multiple myeloma, and sickle cell disease. Nevertheless, other diseases like myelo dysplastic syndromes (MDS), aplastic anemia, hemophilia with chronic hemorrhage, and some rare hematologic diseases do not have any specific psychological studies. This brings about poor knowledge about the distress burden of these groups, suitable screening cut-offs and custom-made intervention plans (Syrjälä, 2022).

As an example, a survey on MDS survivorship reported a high rate of unmet psychosocial needs, with 1–2 empirical studies of depression/anxiety specifically in MDS, although it is chronic with a heavy symptom burden (Syrjälä, 2022).

CBT, mindfulness, and pharmacotherapy for anxiety and depression have proven to be effective in the general population with cancer and in chronic disease populations; however, fewer intervention studies have been conducted on hematology patients. Not many randomized controlled trials (RCTs) are available to compare various psychotherapeutic methods (e.g., CBT and MBCT) and to evaluate stepped care models. In a systematic review, fewer than one out of five studies of psychological interventions involved any hematologic cancer patients, and those that did were frequently not sufficiently powered or had long-term follow-up (Osborn, 2011).

Although screening and referral guidelines may be present (NCCN distress management), these recommendations remain poorly implemented into the routine hematology activity, particularly in the resource-poor environment. Barriers include Inadequately trained mental health professionals, time limitations in clinics that are busy, and lack of reimbursement of psychosocial care, the studies of effective integration strategies, models of task-sharing (e.g., screening/interventions provided by nurses), and telepsychiatry systems in hematology care are underrepresented in the implementation science research. The latest review showed that implementation research is necessary to reduce the difference between the guideline recommendations and the real practice (Smith et al., 2021).Research suggests cross-cultural validation and adaptation guidelines to make sure that the sensitivity and specificity of the tests are achieved in local circumstances, yet they are not performed systematically in hematological studies (Ali et al., 2019).

The overlap between hematology and mental health is an important paradigm of contemporary medicine whereby physiological pathology and mental distress are in a mutually strengthening, bidirectional relationship. This review highlights the fact that the pathology of blood diseases, which spans non-malignant anemia through malignant leukemia, has a much more reaching impact than abnormal cell formation, which significantly changes the emotional, social, and cognitive environment of a patient. Systemic chronic inflammation, intermittent hemoglobin levels, and disruption of the HPA axis are the direct biological antecedents of psychiatric symptoms, such as depression, anxiety, and cognitive fatigue (Dantzer et al., 2008).

Although life-saving, interventions, including intensive chemotherapy and hematopoietic stem cell transplantation, are associated with high levels of clinical depression and neurocognitive impairment statistically (Mitchell et al., 2011; Ahles et al., 2012). In such areas as Pakistan, the psychological load is heightened by the double stigma of life-threatening disease and mental health diagnosis, and a high degree of financial stress and absence of integrated psycho-oncology care (Masood et al., 2024; Shafiq & Shahzadi, 2023).

Results in a wide variety of clinical cohorts have affirmed that deteriorating physical and cognitive functioning are two of the best predictors of low health-related quality of life (Alliu et al., 2025; Fleming et al., 2013).

Conclusion

Hematological patients need a changing approach to management based on a multidisciplinary, integrated

care model rather than a strictly curative physiological model. Psychiatric screening should be done early with the help of validated tools like PHQ-9, HADS, or Distress Thermometer to identify at-risk individuals as early as possible. The inclusion of psychological interventions, such as Cognitive Behavioral Therapy and pharmacological support, in the daily practice of hematology needs to be a priority of the healthcare system in order to promote better long-term clinical outcomes and satisfaction of patients. The key clinical study on filling the research gaps left by the existing literature on longitudinal trajectories and culturally validated screening tools should be a priority in the future (Awan et al., 2021; Javed et al., 2023).

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