International Journal of Nursing and Medical Science 2026:15(02), 58-76

IJNMS ISSN: 2454-6674

INTERNATIONAL JOURNAL OF NURSING AND MEDICAL SCIENCE

Nursing Education Health Science Research

PANACEA INTERNATIONAL JOURNAL

PRL PUBLISHER

Review Article **Volume 15 Issue 02** **March - April 2026**

MANAGEMENT OF PATIENTS WITH CHRONIC LEUKEMIA IN THE EARLY PERIOD OF SPLENECTOMY

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Abstract. Splenectomy is performed in patients with chronic leukemia—including chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), hairy cell leukemia (HCL), and chronic myelomonocytic leukemia (CMML)—to manage hypersplenism, symptomatic splenomegaly, refractory cytopenias, and disease-related complications. The early postoperative period carries significant risks, including reactive thrombocytosis, thromboembolic events, infectious complications, hematological instability, and hemorrhage. This narrative review examines evidence-based approaches to the management of chronic leukemia patients during the early post-splenectomy period (first 30 days). Early management encompasses monitoring of reactive thrombocytosis (which occurs in approximately 75–82% of patients), venous thromboembolism

prophylaxis, antimicrobial prophylaxis against encapsulated organisms, hematological monitoring, continuation of disease-specific therapy, and multidisciplinary supportive care. Structured early post-splenectomy management protocols are critical to minimizing morbidity and mortality in this high-risk population, and disease-specific nuances must be integrated into individualized care plans.

Keywords: Splenectomy; chronic leukemia; post-splenectomy management; reactive thrombocytosis; venous thromboembolism prophylaxis; overwhelming post-splenectomy infection; hypersplenism.

Introduction. Chronic leukemia encompasses a heterogeneous group of hematological malignancies characterized by the clonal proliferation of mature or maturing lymphoid or myeloid cells. The principal subtypes include chronic lymphocytic leukemia (CLL), the most common adult leukemia in the Western world with an age-adjusted incidence of approximately 4.9 per 100,000 in the United States; chronic myeloid leukemia (CML), a myeloproliferative neoplasm defined by the Philadelphia chromosome and BCR-ABL1 fusion gene, the management of which has been transformed by tyrosine kinase inhibitor (TKI) therapy; hairy cell leukemia (HCL), a rare indolent B-cell malignancy accounting for approximately 2% of all leukemias; and chronic myelomonocytic leukemia (CMML), a clonal disorder with overlapping myelodysplastic and myeloproliferative features (Rosenthal et al., 1987; Modi et al., 2025). Each subtype presents unique pathophysiological characteristics, clinical trajectories, and therapeutic paradigms, yet all may necessitate splenectomy under specific clinical circumstances.

The spleen performs several critical physiological functions relevant to the management of chronic leukemia patients. As the largest lymphoid

organ in the body, the spleen is responsible for the filtration and clearance of senescent erythrocytes and platelets from the circulation, immunological surveillance through lymphocyte maturation, antigen presentation, and antibody production, sequestration of approximately one-third of the body's platelet pool and a significant proportion of formed blood elements, and the production of opsonins such as tuftsin and properdin that facilitate phagocytosis of encapsulated bacteria (Horowitz et al., 1996). Loss of these functions following splenectomy has profound immunological and hematological consequences that shape the postoperative management strategy.

Splenectomy is performed in patients with chronic leukemia for several indications. These include symptomatic massive splenomegaly causing abdominal discomfort, early satiety, and mechanical complications; hypersplenism resulting in refractory cytopenias including anemia, thrombocytopenia, and neutropenia; autoimmune hemolytic anemia (AIHA) refractory to corticosteroids and rituximab, particularly in CLL; immune thrombocytopenia (ITP) associated with CLL; disease control in HCL (historically as first-line therapy) and in CML when TKI-resistant disease is accompanied by giant splenomegaly; and preparation for allogeneic hematopoietic stem cell transplantation (HSCT) (Iberri et al., 2020; Alqatta, 2025). Although the frequency of splenectomy has decreased with the advent of novel targeted therapies, it remains an important intervention for selected patients with refractory disease.

The surgical context of splenectomy in hematologic malignancies is associated with considerable morbidity and mortality. Horowitz et al. (1996) reported an overall postoperative complication rate of 52% and a mortality rate of 9% in patients undergoing splenectomy for hematologic malignancies. Notably, the complication rate was significantly higher for

spleens weighing more than 2000 grams (63%) compared with those weighing less than 2000 grams (29%, p = 0.001). More than 50% of CLL and CML patients experienced postoperative complications in this series, underscoring the high-risk nature of these procedures (Horowitz et al., 1996; Iberri et al., 2020). These data highlight the imperative for evidence-based, structured postoperative management protocols.

The objective of this narrative review is to synthesize current evidence on the management of patients with chronic leukemia during the early post-splenectomy period, defined as the first 30 days following surgery. The review addresses hematological monitoring, thromboembolic prophylaxis, infectious complications, disease-specific management considerations, and general supportive care, with the goal of providing a comprehensive framework for clinicians managing this complex patient population.

Research methods. This study was designed as a narrative review to synthesize existing evidence on the management of chronic leukemia patients in the early post-splenectomy period. A comprehensive literature search was conducted using the electronic databases PubMed and Scopus, supplemented by targeted searches in key journals including the Annals of Surgery, Blood, Haematologica, and the Journal of Hematology. The search strategy employed the following keywords and their combinations: "splenectomy," "chronic leukemia," "CLL," "CML," "hairy cell leukemia," "postoperative management," "thrombocytosis," "VTE prophylaxis," "post-splenectomy infection," and "hypersplenism."

Inclusion criteria were as follows: peer-reviewed original research articles, case series, retrospective analyses, and clinical guidelines addressing post-splenectomy management in adult patients (aged 18 years

and older) with chronic leukemia subtypes (CLL, CML, HCL, or CMML); publications from recognized guideline bodies including the European Society for Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the European Society for Blood and Marrow Transplantation (EBMT); and studies published between 1987 and 2025 in the English language. Exclusion criteria included studies focused exclusively on acute leukemias, pediatric populations, or splenectomy performed solely for traumatic indications without relevance to hematologic malignancy management.

Data were extracted regarding indications for splenectomy, perioperative outcomes, hematological changes, thromboembolic and infectious complications, disease-specific management strategies, and general supportive care protocols. Given the heterogeneity of the available literature and the relatively low volume of prospective studies in this specific clinical niche, a formal meta-analysis was not performed. Instead, findings are presented as a narrative synthesis organized by thematic domains corresponding to the principal clinical challenges encountered in the early post-splenectomy period.

Results and Discussion. Hematological Changes in the Early Post-Splenectomy Period

The early post-splenectomy period is characterized by predictable and clinically significant hematological changes that require vigilant monitoring. The most prominent of these is reactive thrombocytosis, which occurs in approximately 75–82% of patients following splenectomy (Horowitz et al., 1996; Iberri et al., 2020). Under physiological conditions, the spleen sequesters approximately one-third of the circulating platelet pool and is responsible for the destruction of aged and activated platelets.

Following splenectomy, the loss of this sequestration and destructive capacity results in a rapid rise in the peripheral platelet count. The platelet count typically begins to increase within 2–5 days postoperatively, peaks at 1–3 weeks (often exceeding 500,000–1,000,000/μL), and normalizes within 4–8 weeks in uncomplicated cases. In chronic leukemia patients, however, the interpretation of post-splenectomy thrombocytosis is complicated by pre-existing disease-related thrombocytopenia, which may blunt or delay the reactive response, and by concomitant bone marrow disease that may alter platelet production kinetics (Tsujita et al., 2025).

Reactive leukocytosis is also common after splenectomy, reflecting the loss of splenic white blood cell sequestration and marginal pool. In CLL and CML patients, this presents a particular diagnostic challenge, as it may be difficult to distinguish reactive leukocytosis from disease-related leukocytosis or disease progression. A complete blood count (CBC) with manual differential and peripheral blood smear morphology assessment is essential to differentiate reactive changes (characterized by mature neutrophilia and left shift) from disease progression (characterized by the presence of blast forms, increased lymphocytosis in CLL, or rising basophil and eosinophil counts in CML) (Horowitz et al., 1996).

Anemia may transiently worsen in the immediate postoperative period due to operative blood loss and hemodilution. In HCL patients, anemia typically improves over 2–4 months as hairy cell sequestration in the spleen is eliminated and the bone marrow recovers (Tsujita et al., 2025). In CLL and CML patients, however, the degree of anemia recovery is limited by underlying marrow disease, and transfusion support may be required during the early postoperative period. The recommended hematological monitoring protocol consists of daily CBC during hospitalization, twice-weekly CBC for the first 4 weeks post-discharge, and

peripheral blood smear assessment at regular intervals to evaluate both disease status and reactive hematological changes.

Management of Post-Splenectomy Thrombocytosis and Thromboembolic Prophylaxis

Reactive thrombocytosis following splenectomy does not, by itself, require cytoreductive treatment in uncomplicated, low-risk patients. However, in patients with chronic leukemia, the risk of thromboembolic complications is substantially elevated by a confluence of factors: the underlying hypercoagulable state associated with malignancy, the inflammatory and prothrombotic response to surgical trauma, reactive thrombocytosis with platelet hyperreactivity, postoperative immobility, and the loss of the spleen's physiological role in filtering activated platelets and clearing prothrombotic microparticles from the circulation (Iberri et al., 2020; Alqatta, 2025).

Venous thromboembolism (VTE) is a well-recognized complication following splenectomy for malignancy, with a significantly higher incidence compared with splenectomy for traumatic indications. Portal vein thrombosis (PVT) and splenic vein thrombosis (SVT) represent specific and particularly serious complications, occurring in 4.5–14% of cases. These present with abdominal pain, fever, nausea, and elevated liver enzymes, and are diagnosed by Doppler ultrasound or computed tomography (CT) angiography. The risk of PVT/SVT is highest in patients with spleen weight exceeding 1000 grams and prolonged operative time (Horowitz et al., 1996; Tefferi et al., 2018). Deep vein thrombosis and pulmonary embolism also occur at increased rates in this population.

Anticoagulation prophylaxis is therefore a cornerstone of early post-splenectomy management in chronic leukemia patients. Low-molecular-

weight heparin (LMWH), such as enoxaparin 40 mg subcutaneously once daily, should be initiated 24–48 hours postoperatively (once hemostasis is secured) and continued for a minimum of 21–28 days. When the platelet count exceeds 500 × 10^9/L, the addition of low-dose aspirin (acetylsalicylic acid, 100 mg daily) may be considered. Routine Doppler ultrasound screening at day 7–10 post-splenectomy is advisable, particularly in patients with large spleens (greater than 20 cm) or marked thrombocytosis, to detect subclinical PVT/SVT (Alqatta, 2025; Iberri et al., 2020).

For extreme reactive thrombocytosis (platelet count exceeding 1,000,000/μL) accompanied by clinical symptoms such as erythromelalgia, visual disturbances, or headache, cytoreductive therapy is indicated. Hydroxyurea is the agent of choice for rapid platelet count reduction, administered at doses of 15–20 mg/kg/day with close monitoring. Platelet apheresis is reserved for symptomatic emergencies with acute thrombotic or hemorrhagic manifestations. Anagrelide, a phosphodiesterase III inhibitor that selectively reduces platelet production, represents an alternative cytoreductive agent. Importantly, asymptomatic reactive thrombocytosis alone is not an indication for cytoreduction, as the thrombotic risk of reactive thrombocytosis is substantially lower than that of clonal thrombocytosis (Tefferi et al., 2018).

In CML patients, TKI therapy should be continued or resumed as early as possible in the postoperative period. TKIs, including imatinib, dasatinib, and nilotinib, have independent antiplatelet and antithrombotic properties mediated through inhibition of BCR-ABL-dependent platelet activation pathways. Continuation of TKI therapy is therefore critical not only for disease control but also for its potential contribution to thrombosis

risk mitigation in the context of post-splenectomy reactive thrombocytosis (Alqatta, 2025).

Infectious Complications and Antimicrobial Prophylaxis

The spleen provides critical immunological defense against encapsulated bacteria, most notably Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type b (Hib). The splenic marginal zone contains specialized B lymphocytes responsible for the rapid production of immunoglobulin M (IgM) antibodies in response to polysaccharide antigens from encapsulated organisms. Additionally, the spleen produces opsonins, including tuftsin and properdin, that facilitate the phagocytosis of bacteria by macrophages and neutrophils. Loss of the spleen abolishes these immunological functions, placing patients at lifelong risk of overwhelming post-splenectomy infection (OPSI), a fulminant sepsis syndrome characterized by rapid onset, disseminated intravascular coagulation, and multiorgan failure, with an associated mortality rate of 50–70% (Horowitz et al., 1996; He et al., 2025).

In patients with chronic leukemia, the immunodeficiency conferred by asplenia is compounded by disease-intrinsic and treatment-related immune dysfunction. CLL patients characteristically exhibit hypogammaglobulinemia (affecting 25–50% of patients at diagnosis and increasing with disease duration), defective T-cell function, and impaired complement activation. CML patients receiving TKIs experience immune modulation, including reduced natural killer cell activity and altered dendritic cell function. HCL patients have severe monocytopenia, which is a hallmark of the disease and persists after splenectomy, further impairing innate immune defense against intracellular pathogens (Tsujita et al., 2025). These compounded immunodeficiencies render chronic leukemia

patients among the highest-risk groups for post-splenectomy infectious complications.

Infection is the leading cause of postoperative mortality following splenectomy in hematologic malignancy patients. Horowitz et al. (1996) reported that 73% of postoperative deaths were attributable to septic complications. Bacterial pneumonia was identified as the most frequent infectious complication in HCL patients following splenectomy, while bloodstream infections with encapsulated organisms were predominant in CLL patients with concurrent hypogammaglobulinemia (Iberri et al., 2020).

Vaccination is the first pillar of infection prevention and should ideally be administered at least 2 weeks before elective splenectomy to allow adequate immune response generation. The recommended vaccination protocol includes pneumococcal conjugate vaccine (PCV13) followed by pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later; quadrivalent meningococcal conjugate vaccine (MenACWY) and serogroup B meningococcal vaccine (MenB); Haemophilus influenzae type b (Hib) conjugate vaccine; annual influenza vaccine; COVID-19 vaccine according to current guidelines; and hepatitis B vaccine if the patient is not already immune. When emergency splenectomy precludes preoperative vaccination, vaccines should be administered at least 14 days postoperatively to optimize immunogenicity (He et al., 2025).

Antibiotic prophylaxis constitutes the second pillar of infection prevention. Oral phenoxymethylpenicillin (penicillin V) at a dose of 250–500 mg twice daily is recommended for a minimum of 2 years post-splenectomy, with many guidelines advocating lifelong prophylaxis in immunocompromised patients. Amoxicillin 250 mg twice daily is an acceptable alternative. In penicillin-allergic patients, erythromycin or

azithromycin may be substituted. In CLL patients with profound hypogammaglobulinemia (IgG levels below 5 g/L), intravenous immunoglobulin (IVIG) replacement therapy should be administered concurrently to provide passive humoral immunity (Horowitz et al., 1996; Tsujita et al., 2025).

Patient education is an essential component of post-splenectomy infection prevention. All patients must be informed about the signs and symptoms of OPSI, instructed that any fever of 38.5°C or higher should prompt immediate medical evaluation and empirical broad-spectrum antibiotic treatment (without waiting for culture results), and advised to wear a medical alert bracelet identifying their asplenic status. In heavily immunocompromised patients—including those with HCL and persistent monocytopenia or CLL patients with prior purine analog therapy and prolonged lymphopenia—prophylaxis against Pneumocystis jirovecii with co-trimoxazole (trimethoprim-sulfamethoxazole) should be maintained as long as lymphopenia persists (Iberri et al., 2020).

Disease-Specific Early Postoperative Management

Chronic Lymphocytic Leukemia (CLL)

In CLL, the indications for splenectomy include refractory AIHA, immune thrombocytopenia, hypersplenism with refractory cytopenias, and massive symptomatic splenomegaly unresponsive to systemic therapy. Surgical mortality is variable and is influenced by patient comorbidities, disease stage, and surgeon experience. Rosenthal et al. (1987) demonstrated that splenectomy significantly improved survival in CLL patients presenting with hemoglobin levels of 10 g/dL or lower or platelet counts of 50×10^9/L or lower ($p = 0.025$), establishing an evidence base for the procedure in selected patients with advanced cytopenias.

In the early post-splenectomy period, CLL patients can be expected to demonstrate improvement in cytopenias within 2–6 weeks, with platelet counts and hemoglobin levels gradually recovering as the hypersplenic component is eliminated. The white blood cell count may transiently rise due to a combination of reactive leukocytosis and the removal of splenic lymphocyte sequestration. The risk of AIHA relapse remains substantial, and serial monitoring with the direct antiglobulin test (Coombs test) is recommended throughout the postoperative period (Petroianu, 2003; Modi et al., 2025).

Continuation of CLL-directed therapy—including Bruton tyrosine kinase (BTK) inhibitors (ibrutinib, acalabrutinib), BCL-2 inhibitors (venetoclax), and anti-CD20 monoclonal antibodies (obinutuzumab, rituximab)—should not be interrupted unless the bleeding risk is prohibitive. BTK inhibitors, particularly ibrutinib, carry an established risk of increased bleeding due to inhibition of collagen-mediated platelet aggregation. Platelet counts and wound healing must therefore be monitored closely, and dose modification or brief perioperative interruption (3–7 days) may be required per hematologist guidance. Hypogammaglobulinemia management with IVIG supplementation should be maintained post-splenectomy, targeting IgG levels above 5 g/L to mitigate the compounded infectious risk of asplenia and CLL-related immunodeficiency (Rosenthal et al., 1987; Modi et al., 2025).

Hairy Cell Leukemia (HCL). Splenectomy in HCL was historically the first-line treatment, with overall response rates of 60–100% and a median response duration of 5–20 months. With the introduction of purine analogs (cladribine, pentostatin) and interferon-alpha (IFN-α), splenectomy has been relegated to a second- or third-line role. Current indications include massive symptomatic splenomegaly with low bone marrow infiltration, disease presenting during pregnancy (when systemic therapy is contraindicated), and disease refractory to purine analogs and IFN-α (Rosenthal et al., 1987; Tsujita et al., 2025). The NCCN guidelines do not include splenectomy as a first- or second-line option for HCL, while ESMO

guidelines permit splenectomy for massive splenomegaly with low-level bone marrow infiltration, progressive disease in pregnancy, or disease refractory to nucleoside analogs and IFN-α.

Post-splenectomy hematological recovery in HCL follows a characteristic pattern. Thrombocytopenia resolves within approximately 1–2 weeks as the splenic platelet sequestration is eliminated. White blood cell counts improve gradually over 2–4 months. Anemia shows the slowest recovery, improving over approximately 4 months. Circulating hairy cells decrease following splenectomy, with BRAF V600E mutation-driven cells becoming morphologically smoother—a phenomenon that may involve immunological and molecular changes beyond the simple elimination of splenic sequestration (Tsujita et al., 2025). Post-splenectomy management in HCL includes a recommended waiting period of at least 6 months before initiating further systemic therapy (cladribine or pentostatin) to allow full assessment of the hematological benefit of splenectomy. Profound monocytopenia, a hallmark of HCL, persists after splenectomy and confers an elevated risk of infection with Pneumocystis jirovecii and atypical mycobacteria. Prophylaxis with co-trimoxazole is therefore recommended for the duration of monocytopenia.

Early post-splenectomy management in chronic leukemia presents a uniquely complex clinical challenge owing to the convergence of multiple risk factors. Pre-existing immune dysfunction, whether disease-intrinsic (hypogammaglobulinemia in CLL, monocytopenia in HCL) or treatment-related (TKI-mediated immunomodulation in CML, chemotherapy-induced lymphopenia), is compounded by the loss of splenic immunological function. Disease-specific hematological profiles—ranging from the lymphocytosis of CLL to the leukocytosis and basophilia of CML—complicate the interpretation of postoperative laboratory changes and

require disease-specific expertise for appropriate clinical decision-making. The concurrent administration of disease-directed therapies, each with its own side-effect profile and drug interactions, introduces additional layers of complexity to perioperative management (Tefferi et al., 2018; Iberri et al., 2020).

The evolution of therapeutic paradigms across all chronic leukemia subtypes has fundamentally altered the role and context of splenectomy. The shift from splenectomy as primary therapy—particularly in HCL and, to a lesser extent, in CML—to its current status as a second- or third-line option has reduced the overall frequency of the procedure but has simultaneously increased the clinical complexity of patients undergoing surgery. Contemporary patients selected for splenectomy are typically more refractory to first-line therapies, more heavily pretreated, and often have greater comorbidity burdens than historical cohorts. This selection bias toward higher-risk patients underscores the critical importance of multidisciplinary coordination between hematologists, surgeons, anesthesiologists, and infectious disease specialists throughout the perioperative continuum, from preoperative planning through post-discharge follow-up (He et al., 2025).

Several important clinical questions remain unresolved and merit further investigation. The optimal anticoagulation agent and duration for post-splenectomy VTE prophylaxis in chronic leukemia patients have not been established by prospective randomized trials. The role of novel targeted agents, including BTK inhibitors and BCL-2 inhibitors, in influencing perioperative bleeding and thrombosis risk is incompletely characterized and represents an important area for pharmacovigilance studies. The optimal timing of chemotherapy resumption, particularly for hypomethylating agents in CMML and purine analogs in HCL, requires

further investigation to balance the risks of disease progression against the risks of impaired wound healing and infectious complications. Finally, the optimal duration of VTE prophylaxis in CML patients with persistent reactive thrombocytosis on TKI therapy remains undefined (Tefferi et al., 2018; He et al., 2025).

Conclusion. The early post-splenectomy period in patients with chronic leukemia is characterized by predictable hematological changes—most notably reactive thrombocytosis and reactive leukocytosis—and carries significant risks including venous thromboembolism, overwhelming post-splenectomy infection, hemorrhage, and disease progression. Evidence-based management of these patients requires a multifaceted and individualized approach that integrates vigilant CBC monitoring with daily assessment during hospitalization and twice-weekly monitoring post-discharge; individualized VTE prophylaxis with LMWH initiated 24–48 hours postoperatively and continued for a minimum of 21–28 days, supplemented by low-dose aspirin when platelet counts exceed 500 × 10^9/L; preoperative vaccination against encapsulated organisms and sustained postoperative antimicrobial prophylaxis with oral penicillin or alternatives; early resumption of disease-specific therapy tailored to the individual patient's leukemia subtype and treatment regimen; ERAS-compatible supportive care including multimodal analgesia, early mobilization, and nutritional optimization; and comprehensive patient education regarding OPSI recognition and emergency management protocols.

Disease-specific nuances must be incorporated into individualized care plans. In CLL, the management of BTK inhibitor interruption and IVIG supplementation requires close coordination between surgeon and hematologist. In CML, the prompt resumption of TKI therapy and molecular

monitoring with BCR-ABL1 PCR are essential for disease control. In HCL, the recommended 6-month waiting period before systemic therapy and co-trimoxazole prophylaxis for persistent monocytopenia represent unique management considerations. In CMML, the timely resumption of hypomethylating agent therapy is critical to preventing disease progression. Across all subtypes, multidisciplinary coordination and structured postoperative protocols are essential to optimizing outcomes.

Prospective multicenter studies are urgently needed to establish standardized, evidence-based protocols for post-splenectomy management in chronic leukemia patients. Such studies should address the optimal anticoagulation regimen and duration, the perioperative management of novel targeted therapies, and the development of risk-stratification tools to identify patients at highest risk for thromboembolic and infectious complications. As the therapeutic landscape for chronic leukemia continues to evolve, the management of post-splenectomy patients must adapt accordingly to ensure the best possible outcomes in this complex and high-risk population.

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