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REVIEW

Pan et al: Passenger lymphocyte syndrome review

Passenger lymphocyte syndrome – epidemiology, pathogenesis, diagnosis, treatment and future directions: A review

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ABSTRACT

Passenger lymphocyte syndrome (PLS) is a hematological complication that can occur following transplantation, characterized by donor-derived memory B lymphocytes producing antibodies against the recipient's blood cells. This review examines the pathophysiology, diagnostic approaches, and treatment strategies aimed at enhancing clinical management and standardizing therapeutic protocols for PLS. A literature search was conducted using Web of Science and PubMed to identify relevant publications on PLS, resulting in 79 studies. Studies were selected based on predefined criteria, including a focus on human donor-derived alloimmunity, documented blood group antigen-antibody interactions, transplantation context, clinical data on outcomes or management, and methodological validity. Only studies containing actual patient data and substantive discussions about PLS were included. PLS commonly presents as hemolytic anemia, accompanied by elevated lactate dehydrogenase (LDH) levels, indirect hyperbilirubinemia, and reduced haptoglobin levels. Diagnosis is primarily based on clinical manifestations and laboratory tests, including the direct antiglobulin test (DAT) and antibody screening. Differential diagnosis is crucial for excluding drug-induced hemolytic anemia and thrombotic microangiopathy. Current treatment strategies for PLS focus on halting hemolysis and restoring hematological balance. First-line treatment includes donor-compatible red blood cell transfusions and high-dose corticosteroids, while refractory cases may necessitate rituximab or plasmapheresis. Despite advancements in PLS management, challenges persist, including delayed diagnosis due to self-limiting cases and a lack of standardized treatment protocols. Future research should incorporate genomic and proteomic biomarkers for accurate diagnosis and risk prediction. Developing mechanism-driven therapies targeting donor lymphocytes and establishing global consensus frameworks can enhance monitoring, improve graft survival, and optimize transplant recipient outcomes.

Keywords: Passenger lymphocyte syndrome, transplantation, epidemiology, graft survival, red blood cell transfusion, blood group incompatibility, hemolytic anaemia.

INTRODUCTION

Transplantation is considered the most efficacious therapeutic approach for organ failure, improving long-term survival in patients with end-stage organ disease[1]. However, the limited availability of donor organs remains a major barrier to further advancement in clinical organ transplantation[2]. Advances in medicine have led to the development of ABO-incompatible (ABOi) organ transplantation, which has expanded the donor pool and partially mitigated organ shortages[3]. Notably, ABOi transplantation has shown comparable outcomes between blood group-mismatched and compatible transplants for hematopoietic stem cells, liver, and kidneys[4], challenging the traditional notion suggesting that ABO compatibility is essential for transplant success. Despite its advantages, ABOi transplantation presents unique challenges. Transplantation is often associated with hematological complications, including passenger lymphocyte syndrome (PLS), immune cytopenia, and transplant-associated thrombotic microangiopathy (TA-TMA)[5, 6]. Among these complications, the incidence of PLS has increased, garnering increased attention from experts in the fields of transplantation and blood transfusion. This trend is attributed to the widespread adoption of transplantation technology, including the rise in incompatible transplants involving the aforementioned blood types. Additionally, advancements in clinical diagnostic techniques, enhanced monitoring awareness, and determination of donor and recipient factors have contributed to this increased incidence. PLS was initially proposed by Beck et al. in 1971 as a mechanism regarding donor lymphocytes that underlie hemolysis and was first documented in humans. This is wherein a transplant recipient with type A blood exhibited elevated titres of anti-A antibodies following the receipt of a type O lung transplant. The term ‘PLS’ was later introduced by Stevens et al. in 1981[7]. PLS occurs when donor memory B lymphocytes transferred during transplantation generate antibodies targeting recipient red blood cells (RBCs), platelets, or other blood components, leading to complement-mediated hemolysis, thrombocytopaenia, or neutropenia[8].

PLS incidence varies significantly depending on the type of transplant. Although historically linked to ABO- or Rhesus (Rh)-incompatible solid organ transplants (e.g., heart, lung, liver, kidney, and small bowel), recent evidence has highlighted its growing relevance in hematopoietic stem cell transplantation (HSCT), particularly in ABO-minor mismatched donors[5, 9]. In minor ABO-mismatched transplants (e.g. donor O to recipient blood group A/B), the reported incidence rates range between 14% for liver transplants (LTs) and 20% for renal ones[10, 11]. Although PLS is typically self-limiting within 3 months, severe cases necessitate interventions such as transfusion support or corticosteroids, plasmapheresis, or rituximab administration. Notably, PLS manifestations extend beyond hemolysis; emerging reports associate PLS with severe thrombocytopaenia post-transplantation, termed transplant-mediated alloimmune thrombocytopaenia (TMAT), particularly in recipients of organs from donors with immune thrombocytopenic purpura (ITP)[12, 13]. TMAT and PLS have been reported in various organ transplants, including liver, kidney, and lung[14]. Additionally, donor-derived anti-human leukocyte antigen (HLA) antibodies in multi-organ transplant recipients suggest novel PLS variants, prompting a re-evaluation of its classification[15]. Recent studies have further highlighted the systemic impact of PLS, with documented cases of small bowel, lung, and pancreatic kidney transplants[16-18]. This broadening of the clinical spectrum of PLS, coupled with its recognition in patients receiving HSCT, necessitates a comprehensive re-evaluation of its mechanisms, organ-specific risk factors, and management strategies. This review synthesises decades of research to elucidate the pathophysiology, heterogeneity across transplant types, and evolving therapeutic approaches, ultimately enhancing diagnostic precision and prognostic assessment.

METHODS

To conduct a thorough literature review, we extensively searched the Web of Science and PubMed databases using specific keywords to identify the most pertinent publications. Keywords comprising ‘Passenger Lymphocyte Syndrome,’ ‘Blood

Group Incompatibility,' and 'Transplantation' were employed to perform an extensive literature search for publications from approximately 1978 to 2024. The initial search yielded 116 relevant articles. A subsequent screening was conducted to refine this initial selection, focusing on studies that specifically addressed cases of PLS, rather than solely on other transplantation-related hemolytic conditions. Furthermore, we prioritised research involving human participants with clinical data, thereby excluding animal studies and in vitro experiments. This rigorous selection process eventually resulted in the inclusion of 79 articles for our analysis. During the subsequent selection phase, we implemented rigorous screening criteria evaluating the following: 1) PLS-related focus on human donor-derived alloimmunity; 2) documented blood group antigens/antibodies implicated in PLS pathogenesis; 3) transplantation type (solid organ vs. hematopoietic stem cell); 4) clinical data on outcomes, manifestations, or management strategies; 5) study design validity (case reports, observational studies, or systematic reviews); 6) inclusion of actual patient data versus theoretical models; 7) clinical relevance beyond laboratory-based investigations; and 8) substantive discussion about PLS rather than peripheral mentions. This multidimensional assessment ensured that the selected studies met stringent methodological and clinical relevance criteria for inclusion.

Epidemiological Characteristics

The epidemiological features of PLS are closely linked to the transplantation type, extent of blood-type mismatch, and donor immune status. PLS predominantly occurs in transplants with minor ABO blood group incompatibilities. It develops when donors have blood type O or A/B and recipients have type A, B, or AB or Rh blood group mismatches[19]. In patients receiving solid organ transplantation, the incidence of PLS varies across different organ types. Specifically, it ranges between 9% to 20% in kidney, approximately 40% in liver, and up to 70% in heart–lung transplantation patients[20]. Although rare in small intestinal transplantation (ITx), PLS can cause

severe hemolysis. In patients receiving HSCT, PLS is relatively uncommon but can be triggered by either ABO or non-ABO antibodies, such as anti-RhD[21].

Specific age or sex predisposition to PLS remains unestablished. However, children might exhibit increased susceptibility to severe hemolysis due to their relatively immature immune systems, particularly because adults have a fully developed complement system[10]. Additionally, no well-defined regional distribution patterns for PLS have been identified; however, its prevalence may correlate with the frequency of ABO blood group mismatch transplants in different regions.

Risk factors for PLS include donors with abundant lymphoid tissue, such as in the liver and small intestine, prior donor sensitisation to the recipient's RBCs through transfusion or pregnancy, and insufficient immunosuppression, which allows donor lymphocytes to evade immune control[22, 23].

Pathogenesis of PLS

The pathophysiology of PLS involves the following three key steps (**Figure 2**):
First, regarding transfer of donor lymphocytes: Immunocompetent B lymphocytes from the graft migrate into the recipient’s bloodstream. Liver and intestinal grafts, which contain abundant lymphoid tissue, pose the highest risk of PLS[8, 24, 25]. Notably, lung transplants exhibit a high incidence of Rh-associated PLS due to donor-derived anti-D antibodies[22], whereas intestinal transplants often involve anti-A/B-mediated hemolysis[26].
Second, considering antibody production: Donor B lymphocytes generate antibodies targeting recipient RBC antigens, including anti-A/B antibodies in cases of ABOi transplants, anti-D antibodies in cases of Rh incompatibility, and antibodies against platelet antigens. This risk is further exacerbated if the donor has been previously alloimmunised with antibodies such as anti-K, anti-Jk(a), and platelet-specific antibodies[27-29]. For instance, donors with a history of autoimmune disorders (e.g., Hashimoto’s thyroiditis) might transfer autoreactive B lymphocytes, leading to

post-transplantation acute hemolysis[30].

Third, in terms of hemolysis or thrombocytopaenia: Antibodies trigger complement activation (C3d deposition) and/or induce Fc-mediated phagocytosis, leading to RBC destruction or thrombocytopaenia. The severity of hemolysis correlates with antibody titres and antigen density in RBCs[31-33]

Role of Blood Group Antigens in PLS

PLS is primarily driven by donor-derived antibodies that target recipient RBCs within the transplant recipient. It is predominantly associated with antibodies from the ABO blood group, followed by those from the Rh blood group. Additionally, it includes antibodies such as anti-K, Jka, M, and N[34]. ABO minor mismatches (e.g., O→A/B) are the most common triggers; however, non-ABO antibodies (e.g., anti-D, anti-K, anti-E, anti-Jk(a), anti-Kpb, anti-Lea) account for 15–20% of cases[23, 29]. Notably, PLS occurs in ABOi transplant patients primarily regarding minor ABO incompatibility (e.g., O→A). Rarely, bidirectional ABO incompatibility (e.g., A→B) may lead to simultaneous donor and recipient antibody-mediated hemolysis[35]. Hemolysis induced by anti-A/B antibodies is typically self-limiting and mild, whereas anti-D-mediated hemolysis generally persists longer, lasting for up to 6 months[22, 36].

ABO incompatibility is the primary risk factor, with the highest risk linked to minor ABO mismatches, such as O→A or O→B transplants. Kohl et al. reported an 18.18–30.77% PLS incidence rate in type A recipients of type O grafts[37], 5.13% in type B recipients of type O grafts, and 20% in type AB recipients of type O grafts. Rh incompatibility represents a secondary risk factor. Additionally, other blood group systems, such as Kidd and MNS, may contribute to PLS development[38]; however, their relative influence is unclear owing to insufficient data. Furthermore, numerous documented cases of transient lymphatic syndrome associated with Jka antibody-induced hemolysis require significant attention[27, 29]. Concurrently, PLS mediated by non-ABO/Rh antigens has been frequently reported in individual case

studies, highlighting a range of severities that generally correlate with the immunogenic properties of blood group system antigens. Some studies have identified cases of anti-HPA-3a/HPA-1a-mediated alloimmune thrombocytopaenia in liver, kidney, and combined hepatorenal transplantation, including severe thrombocytopaenia induced by liver grafts[14, 39-41]. These observations raise the question regarding whether antigens on RBCs, platelets, and leukocytes could contribute to PLS.

Overall, the data indicate that during transplantation, the severity and clinical outcomes of PLS vary across blood group systems, with ABO incompatibility showing the highest incidence compared with Rh and other blood group systems.

Diagnosis and Differential Diagnosis

PLS typically manifests 5–30 days post-transplantation, with the timing of onset influenced by graft type and immune interactions. In liver and small-bowel transplants, PLS often presents early (days 5–15) due to the high lymphocyte load inherent in these organs. By contrast, ABO-minor mismatched HSCT may exhibit delayed onset (days 20–30) as donor lymphocytes gradually engraft[24, 42-44]. The hallmark clinical features include hemolytic anaemia (median hemoglobin [Hb] nadir: 6–8 g/dL) accompanied by biochemical evidence of intravascular hemolysis, such as elevated lactate dehydrogenase (LDH) > 500 U/L, indirect hyperbilirubinaemia (> 2 mg/dL), and profoundly reduced haptoglobin (< 0.1g/L)[11, 42, 45, 46]. Organ dysfunction, including hepatic impairment (bilirubin > 5 mg/dL in 40% of LTs) and acute kidney injury (25% of severe cases), further highlights the systemic impact of PLS[47, 48]. Risk stratification highlights key predictors of PLS, including lymphoid-rich grafts (odds ratio [OR]: 4.8, 95% confidence interval [CI]: 2.1–10.9), minor ABO/Rh mismatches (OR: 3.2, 95% CI: 1.8–5.6), and cyclosporine-based regimens (OR: 2.4, 95% CI: 1.3–4.5)[10, 24, 44, 49].

Diagnosis follows a structured algorithm. The initial evaluation focuses on

unexplained jaundice and an Hb drop of > 2 g/dL within 24 h, prompting serial screening on days 5, 10, and 15 for Hb trends, LDH, and bilirubin[11, 42]. Confirmatory testing begins with the direct antiglobulin test (DAT), which detects IgG/C3d positivity in 85% of cases, alongside antibody identification to detect donor-derived anti-A/B antibodies (98% specificity)[36, 50-52]. In ambiguous cases, advanced techniques such as ABO/Rh genotyping resolve serological discrepancies (e.g., weak subgroups), chimerism analysis quantifies donor lymphocytes (>1% correlates with severity), and HLA antibody screening detects thrombocytopaenic variants[20, 28, 41, 52].

PLS may manifest atypically, necessitating specialised testing. Non-hemolytic PLS, characterised by DAT positivity without Hb decline (anti-D/M antibodies), requires antibody elution and RBC phenotyping. Sandler et al. proposed a unified classification system that included both hemolytic and non-hemolytic PLS manifestations to improve the correlation between clinical presentation and laboratory findings, particularly emphasising the role of lymphocytes rather than solely hemolysis[36]. Promoting the identification of subcategories that incorporate both types of manifestations, we provide a more comprehensive representation of the full spectrum of PLS[22, 34]. Thrombocytopaenic PLS, defined by a platelet count < 50×10^9/L, involves anti-HPA-1a/b antibodies, detectable via platelet glycoprotein-specific assays. If concurrent hemolysis and thrombocytopaenia occur (Evans syndrome-like presentation), CD20+ B cell quantification (by peripheral blood flow cytometry or tissue biopsy) is warranted.

A differential diagnosis is crucial for excluding conditions mimicking PLS (Table 3). Drug-induced hemolytic anaemia (e.g., tacrolimus) is characterised by temporal drug exposure and drug-dependent antibody testing[53]. Thrombotic microangiopathy (TMA) represents a rare yet clinically significant syndrome characterised by microangiopathic hemolytic anaemia, thrombocytopaenia, and organ damage resulting from microcirculatory thrombosis. Critical diagnostic indicators that differentiate TMA from other forms of hemolytic anaemia include the schistocyte

count and assessment of ADAMTS13 activity. Acute graft-versus-host disease (GVHD) manifests with skin rash, diarrhoea, and a negative DAT, as confirmed by biopsy and donor chimerism analysis [54, 55]. In HSCT, distinguishing between post-transplant, PLS, and pure red cell aplasia (PRCA) is crucial due to their different mechanisms and treatments. PRCA, often following ABO major mismatch transplants (e.g., A→O), is caused by recipient isoagglutinins blocking donor erythroid cell differentiation[56], leading to reticulocytopenia (<0.1%), normal LDH and haptoglobin, absence of erythroid progenitors in the bone marrow, and a negative DAT. PLS involves donor antibody-mediated hemolysis, with reticulocytosis, abnormal LDH and haptoglobin levels, and a positive DAT. Treatment of PRCA involves reducing immunosuppressants, whereas PLS requires B-cell targeted therapy like rituximab. During the diagnostic process, exercising vigilance is imperative. Anaemia accompanied by a positive DAT occurring shortly after HSCT, specifically within 7 to 21 days, should prompt consideration of PLS as a priority. In contrast, anaemia onset beyond 30 days, particularly when associated with transfusion dependence and reticulocytopenia, strongly indicates PRCA. This diagnosis can be established using flow cytometry, which detects CD71+ erythroid progenitor cells in the bone marrow.

Several diagnostic challenges complicate PLS identification. In approximately 30% of cases, the self-limiting nature of the syndrome may delay confirmation and ABO-identical transplants where anti-Kell/Jka/Jkb antibodies are overlooked without extended phenotyping[51]. To address these challenges, antibody screening every 48 h is recommended for cases of unexplained cytopenia until PLS is either confirmed or excluded. This structured approach ensures timely recognition and intervention, particularly in high-risk transplantation cohorts.

Based on these considerations, we established a straightforward monitoring protocol from a laboratory perspective (**Figure3**). First, basic information of the donors and recipients was comprehensively collected before transplantation. In recipients, this information included age; sex; medical history; ABO and RhD blood types; surgical

details (procedure type and time); and disease-related risk factors. In donors, data included age, sex, blood type, and medical history (omitted from living donors), with deceased donors requiring additional documentation regarding the cause of death. These foundational data facilitate risk assessment of disease onset and influencing factors. Second, during the monitoring period, blood samples from both parties were stored at 2–4 °C. In deceased donors, multiple blood samples were collected simultaneously, with plasma separated and stored at −20 °C, whereas RBCs were cryopreserved to ensure their availability for follow-up analysis and critical research. Dynamic multi-parameter monitoring involves three key aspects: (1) Symptom observation—close monitoring of skin/sclera jaundice, a common indicator of PLS-related hemolysis, which reflects disease progression and supports early diagnosis; (2) antibody monitoring—antibody screening and cross-matching with homologous RBCs, with further specificity identification if screening results are positive, effectively distinguishing ABO antibodies from irregular antibodies; and (3) Hemolysis/anaemia indicators—regular assessment of Hb, bilirubin, reticulocyte count, LDH, haptoglobin, and DAT results to assess hemolytic severity. A decline in Hb levels, elevated bilirubin, or a positive DAT suggests active hemolysis, aiding tracking disease progression.

Finally, a comprehensive analysis integrating clinical symptoms, antibody results, and hemolysis trends correlates antibody emergence with hemolytic reactions. For instance, PLS is strongly suspected if pre-transfusion testing reveals self-controlled positivity or incompatible cross-matching (excluding alloantibodies). In ABOi transplants (e.g., O donor to an A recipient), ABO antibody-mediated PLS is confirmed if crossmatching with multiple homologous donors fails, eluates agglutinate with homologous RBCs, and hemolysis markers are abnormal. Conversely, irregular antibody-mediated PLS is considered if antibody screening is positive, specificity is confirmed, or other factors are excluded. Special cases, such as unexplained thrombocytopaenia, require evaluating PLS-associated complications, such as TMAT. This systematic approach ensures the timely diagnosis and tailored

management of transplant-related complications.

Treatment and Prognosis

Treatment Strategies

The current treatment modalities for PLS encompass multiple aspects, with management primarily aimed to terminate hemolysis and restore hematological stability (Table2). In blood product management, transfusing donor-type, compatible, or antigen-negative RBCs (such as type O red blood cells for anti-A/B PLS) to avoid exacerbating hemolysis is emphasised, with the transfusion dose adjusted according to specific conditions. Early identification and rational product selection are crucial. First-line interventions also include combining high-dose glucocorticoids (methylprednisolone, 1 mg/kg/day) to suppress donor B cell activity[10, 44, 57, 58]. B-cell targeting and antibody depletion therapy, particularly using rituximab, has shown promise for treating refractory PLS and other autoantibody-associated autoimmune diseases. PLS occurs when donor B-lymphocytes produce antibodies against recipient RBCs, causing hemolysis[8]. Rituximab, an anti-CD20 antibody, has been proved effective in preventing and treating PLS in various transplant settings[59, 60]. The therapy works by depleting B-cells, which are precursors to antibody-producing plasma cells[61]. In refractory cases, rituximab (anti-CD20) achieves remission in 80% of patients by depleting antibody-producing lymphocytes, whereas plasmapheresis rapidly reduces circulating antibodies in patients with life-threatening hemolysis[26, 59, 62, 63]. Improvement in PLS appears measurable by tracking changes in ABO antibody titres alongside clinical signs of hemolysis[64]. In one kidney transplant case, the IgG anti-A titre fell from 64 pre-transplant to 4 after plasma exchange, corresponding with resolution of hemolysis. Another report noted an anti-A1 titre of 8 at diagnosis, with hemolysis resolving after plasma exchange and a switch to group O transfusions. In addition, one study documented clinical improvement within 28–30 days and antibody clearance by roughly three months, whereas a case series recorded hemolysis

resolution spanning 0–776 days (mean, 148 days)[46]. Higher transfusion needs were observed when the titres remained elevated[37]. The immunosuppressive protocols require individualised formulation. Transplant-related factors such as organ type and blood group mismatch influence risk and management, with onset typically occurring 1–3 weeks after transplantation. Supportive measures include erythropoietin, folic acid, and iron supplementation to mitigate anaemia-related complications[11, 65]. Emerging therapies such as eculizumab (anti-C5 monoclonal antibody) and efgartigimod (neonatal Fc receptor inhibitor) show potential for targeting complement activation or accelerating antibody clearance, particularly for PLS cases complicated by TMA or resistant to conventional therapy[47, 66, 67].

Prognostic Considerations

PLS is typically self-limiting, resolving within 2–6 weeks as donor lymphocytes are cleared. However, severe cases may lead to transfusion dependence (median, 2–8 units), graft dysfunction from hemoglobinuria-induced injury, or TMA (5% incidence)[42, 44, 47, 54]. Mortality remains rare (<5%) but increases with delayed diagnosis, multiorgan failure, or pre-existing comorbidities[12, 68]. Long-term outcomes are generally favourable, with most patients achieving normal graft function after recovery. Early recognition and tailored therapy—balancing immunosuppression intensity to avoid infection risks—are essential for optimising prognosis.

Clinical Classification in Passenger Lymphocyte Syndrome

PLS manifests distinct characteristics across organ transplants, driven by organ-specific immunological and anatomical factors (**Table 3)**.

Liver Transplants

The incidence of PLS in liver transplant (LT) recipients varies significantly across studies. In ABO minor-incompatible LTs, it ranges between 5% and 20%, with the rates being higher in paediatric patients[69]. A retrospective study involving 333

paediatric LT recipients reported a 14% PLS prevalence (7/51 ABO-compatible cases), particularly in blood group A+ recipients of O+ grafts. Similarly, among 1,217 adult LT recipients, 12 PLS cases were identified (10/56 ABO minor-incompatible and 2/147 Rh-incompatible cases)[10]. LTs have the highest PLS incidence, likely due to the abundance of passenger lymphocytes and presence of donor-derived B-cell activating factor (BAFF), which promote B-cell survival and antibody production[70]. Severe hemolysis, often characterised by a median Hb nadir of 6–8 g/dL, frequently requires transfusion. Hyperbilirubinaemia (> 5 mg/dL) is a common complication. PLS incidence in LT recipients shows considerable variability, ranging between 0.5% in large cohorts (14/2,772 patients) and 30–40% or even 100% in smaller case series. The onset of PLS typically develops 7–14 days after transplantation; however, cases have been reported to occur immediately post-transplantation and up to 120 days later[38].

ABO minor incompatibility is the most commonly reported risk factor, with Rh and other minor antigen mismatches also observed. Hemolytic anaemia is the primary clinical feature, with hemoglobin levels dropping by 1.5 g/dL to 5.4 g/dL[71] in several cases, often necessitating blood transfusions. Jaundice is frequently reported. Moreover, isolated complications such as thrombocytopaenia, renal injury, cardiovascular instability, and graft-related problems[57] have been documented.

Lung Transplants

In lung transplant recipients, PLS has an incidence rate of 0.5–2%, presenting as a treatable form of hemolytic anaemia with varying severity. Despite occasional severe complications, most patients achieve favourable outcomes. However, the reported PLS incidence rates vary widely[69]. In lung-specific cohorts, rates range between 0.5% to 2%, whereas heart–lung transplants show incidences as high as 70%[38]. In cases of minor ABO mismatches—particularly when an O donor is paired with an A, B, or AB recipient—the incidence rates are 18–31% (for A), 5% (for B), and 20% (for AB). Hematological manifestations are the primary clinical feature, with PLS

frequently manifesting as hemolytic anaemia. The severity varies, ranging between modest hemoglobin drops (e.g., 8.3 to 7.4 g/dL) and life-threatening reactions requiring blood transfusions, plasmapheresis, or targeted antibody therapy[37]. Although rare cases have resulted in severe complications, including cardiac death, studies generally report stable graft function and favourable patient outcomes with appropriate supportive care[38]. Additional factors, including HLA mismatch, transferred lymphoid tissue volume, and transplant technique variations, have been suggested as potential contributors; however, their exact roles remain unclear.

Kidney Transplants

A systematic review of 91 cases estimated a PLS incidence of approximately 20% in ABO-mismatched transplants[65], typically causing self-limiting anaemia managed with transfusions or erythropoietin; however, graft dysfunction or death rarely occurs. A case report [10] highlighted PLS manifesting as elevated indirect bilirubin without Hb decline[45], which resolved following donor-type RBC transfusion without affecting kidney function. However, Dirim et al. reported a refractory PLS case mimicking cold agglutinin disease[47], which was unresponsive to steroids, intravenous immunoglobulin (IVIG), and rituximab, necessitating immunoadsorption (IA) but ultimately leading to graft loss due to rejection. Another atypical PLS paediatric case involved gastrointestinal complications, manifesting as ischaemic colitis and disseminated intravascular coagulation (DIC), which required colectomy and therapeutic plasma exchange (TPE)[48]. These cases highlight the variability in PLS manifestation, ranging between mild hemolysis and life-threatening organ damage, emphasising the need for timely diagnosis (via DAT and antibody testing) and tailored therapies (transfusion, TPE, and IA). Although most PLS cases are self-limiting, refractory cases pose significant treatment challenges, highlighting gaps in standardised treatment protocols and the need for further research into prevention and management strategies.

Small Bowel Transplants

Although PLS occurrence in transplantation is well documented, its occurrence following ITx remains unclear. Intestinal graft-rich lymphoid tissue increases the risk of PLS, particularly in cases of ABO minor-incompatible or HLA leukocyte antigen mismatches. Regarding epidemiology, the incidence of PLS in ITx is estimated to be 9% among ABO minor-incompatible transplants[54]. The key risk factors include ABO minor incompatibility, where most cases involve O→A/B grafts, leading to donor lymphocyte-mediated production of anti-A/B antibodies[44, 72]. Lymphoid-rich grafts, such as small bowel or multivisceral transplants (including the spleen), carry a higher risk of PLS owing to abundant donor lymphocytes and HLA mismatch, as increased donor-recipient HLA disparity may exacerbate immune activation[63, 73]. In terms of clinical manifestation and diagnosis, PLS typically occurs 7–14 days after transplantation and manifests with severe hemolytic anaemia, characterised by an Hb drop > 20 g/L, jaundice, elevated LDH, and low haptoglobin levels[44]. A positive DAT can detect the presence of IgG- or complement-coated RBCs[74]. In ABO-mismatched cases, donor-derived antibodies, such as anti-A/B, are common, whereas non-ABO antibodies (e.g., anti-M) are rare but have been reported[34]. Notably, cases of non-hemolytic PLS (antibodies without overt hemolysis) have also been observed, highlighting the need for routine post-ITx antibody screening[22].

HSCT

HSCT represents a pivotal therapeutic strategy for the treatment of a variety of malignant and non-malignant disorders. Nonetheless, this strategy is frequently associated with a spectrum of immune-mediated complications that could substantially affect patient outcomes. A distinctive aspect of HSCT is its execution across the ABO blood group barrier, which entails the transfer of plasma, red blood cells, and immunocompetent cells from donor to recipient. This process might result in hemolytic anaemia due to red blood cell incompatibility[75]. PLS is one such

immune-mediated hemolytic complication that develops following allogeneic HSCT, primarily associated with minor or bidirectional ABO incompatibility. PLS is associated with the production of antibodies, including anti-A/B or non-ABO antibodies, by the donor's transplanted B cells, which subsequently target recipient's erythrocytes. Hemolytic events typically manifest within 1–3 weeks post-transplantation and are frequently correlated with GVHD and poor prognosis.[9, 27, 35, 76].

Regarding clinical features, sudden-onset intravascular hemolysis manifests as hemoglobinuria, jaundice, elevated LDH, and transfusion-refractory anaemia[21, 77]. Symptoms typically emerge 7–21 days post-HSCT and coincide with donor lymphocyte engraftment. Diagnostic evaluation includes a positive DAT for IgG/C3d, identification of donor-derived anti-recipient ABO or non-ABO antibodies in serum or eluates, and chimerism analysis to confirm donor-derived antibody production[5, 78].

Risk factors for PLS include minor or bidirectional ABO incompatibility, which increases in unrelated or HLA-mismatched donors due to exaggerated immune responses[5]. The absence of post-transplant methotrexate (MTX) increases the incidence of PLS, while cyclosporine-based prophylaxis without MTX further elevates risk. Additionally, peripheral blood stem cells may enhance susceptibility to PLS due to their higher lymphocyte content compared with bone marrow[21, 76].

Regarding complications and prognosis, severe hemolysis may lead to transfusion requirements exceeding the recipient's RBC mass, as both native and transfused RBCs undergo lysis. Moreover, PLS correlates with higher grades of acute GVHD and increased transplant-related mortality[79]. Laboratory findings typically show elevated LDH (> 1,000 U/L), indirect hyperbilirubinaemia (> 2 mg/dL), and positive DAT due to donor-derived anti-A/B antibody-coated recipient RBCs. Retrospective studies involving 310 patients have highlighted severe cases of transfusion-dependent

anaemia or fatal outcomes, emphasising the need for vigilant monitoring of high-risk cohorts.

The pathogenesis of PLS in patients receiving HSCT is driven by donor B lymphocytes producing anti-A/B antibodies, which is distinct from autoimmune hemolytic anaemia and plasma-derived hemagglutinin reactions. Although current management combines supportive care (erythropoietin and antigen-matched transfusions) and immunosuppression (rituximab achieves 80% remission), challenges persist in standardising HLA-matching documentation and clarifying transplant indications for hematologic diseases. Future research should prioritise standardising protocols for antibody profiling and HLA compatibility assessments to improve risk stratification and therapeutic precision.

CONCLUSION

PLS remains a significant challenge in transplantation medicine despite advancements in diagnostic and therapeutic strategies. Current management relies on risk stratification, including pre-transplant donor antibody screening (e.g., anti-ABO/Rh, anti-HLA) and cost-effective post-transplant monitoring (e.g., alternate-day DAT/LDH testing during days 5–30) to predict PLS onset, particularly in high-risk grafts such as liver and small bowel transplants. Although chimerism-based prediction holds theoretical promise, its clinical utility requires the further validation of cost-benefit ratios compared with conventional serologic monitoring. Novel therapeutic approaches, including complement inhibitors (e.g., ravulizumab) and B cell-targeted agents, demonstrate potentials for alleviating severe hemolysis and thrombocytopaenia (e.g., efgartigimod NCT04188379). Nonetheless, the effectiveness of these treatments necessitates confirmation through large-scale clinical trials. Notably, live-donor transplants carry a marginally higher PLS risk, attributed to factors such as shared haplotype-driven immune priming and smaller graft mass altering lymphocyte equilibration dynamics. Three key priorities define PLS research:

1. Practical diagnostics: Refining accessible biomarkers (e.g., donor B-cell clonality and BAFF/proliferation-inducing ligand signalling profiles) to pre-emptively predict severe PLS.
2. Mechanism-driven therapies: Developing biologics that target donor lymphocyte subsets (e.g., BAFF-R inhibitors and anti-CD38 CAR-T cells) while preserving graft tolerance.
3. Global consensus frameworks: Establishing organ-specific guidelines through multinational registries to standardise monitoring and intervention protocols.

Translational challenges persist, particularly in balancing immunosuppression to prevent PLS while minimising the risks of infection and GVHD. In self-limiting cases, vigilant clinical observation remains the cornerstone as early over-treatment may be unwarranted. Collaborative efforts among transplant immunologists, hematologists, and computational biologists are pivotal for transforming PLS from a reactive complication to a preventable condition. Prioritising biomarker discovery, therapeutic innovation, and data-driven guidelines can improve graft survival and transplant recipients' quality of life.

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REFERENCES

[1] Chaudhry D, Chaudhry A, Peracha J, Sharif A. Survival for waitlisted kidney failure patients receiving transplantation versus remaining on waiting list: systematic review and meta-analysis. Bmj 2022;376:e068769. https://doi.org/10.1136/bmj-2021-068769.

[2] Vanholder R, Domínguez-Gil B, Busic M, Cortez-Pinto H, Craig JC, Jager KJ, et al. Organ donation and transplantation: a multi-stakeholder call to action. Nature Reviews Nephrology 2021;17:554-568. https://doi.org/10.1038/s41581-021-00425-3.

[3] Lemoine CP, Brandt KA, Keswani M, Superina R. Outcomes after ABO incompatible pediatric liver transplantation are comparable to ABO identical/compatible transplant. Frontiers in Pediatrics 2023;11. https://doi.org/10.3389/fped.2023.1092412.

[4] Bentall A, Herrera LP, Cornell LD, Gonzales MA, Dean PG, Park WD, et al. Differences in chronic intragraft inflammation between positive crossmatch and ABO-incompatible kidney transplantation. Transplantation 2014;98:1089-1096. https://doi.org/10.1097/tp.0000000000000188.

[5] Migdady Y, Pang Y, Kalsi SS, Childs R, Arai S. Post-hematopoietic stem cell transplantation immune-mediated anemia: a literature review and novel therapeutics. Blood Adv 2022;6:2707-2721. https://doi.org/10.1182/bloodadvances.2021006279.

[6] Li A, Sartain SE. Transplant-associated TMA: the conundrum of diagnosis and treatment. Hematology Am Soc Hematol Educ Program 2024;2024:206-213. https://doi.org/10.1182/hematology.2024000545.

[7] Stevens J, Callender CO, Jilly PN. Emergence of red blood cell agglutinins following renal transplantation in a patient with systemic lupus erythematosus. Transplantation 1981;32:398-400. https://doi.org/10.1097/00007890-198111000-00012.

[8] Moosavi MM, Duncan A, Stowell SR, Roback JD, Sullivan HC. Passenger Lymphocyte Syndrome; a Review of the Diagnosis, Treatment, and Proposed Detection Protocol. Transfus Med Rev 2020;34:178-187. https://doi.org/10.1016/j.tmrv.2020.06.004.

[9] Worel N. ABO-Mismatched Allogeneic Hematopoietic Stem Cell Transplantation. Transfusion Medicine and Hemotherapy 2016;43:3-12. https://doi.org/10.1159/000441507.

[10] Woolfson JP, Vandriel SM, Stephens D, Dharmaraj BG, De Angelis M, Cattral MS, et al. Passenger Lymphocyte Syndrome After Pediatric Liver Transplantation. Journal of Pediatric Gastroenterology and Nutrition 2019;69:95-101. https://doi.org/10.1097/mpg.0000000000002337.

[11] Nadarajah L, Ashman N, Thuraisingham R, Barber C, Allard S, Green L. Literature review of passenger lymphocyte syndrome following renal transplantation and two case reports. Am J Transplant 2013;13:1594-1600. https://doi.org/10.1111/ajt.12219.

[12] Hill QA, Harrison LC, Padmakumar AD, Owen RG, Prasad KR, Lucas GF, et al. A fatal case of transplantation-mediated alloimmune thrombocytopenia following liver transplantation. Hematology 2017;22:162-167. https://doi.org/10.1080/10245332.2016.1240392.

[13] Aranda Escaño E, Prieto Calvo M, Perfecto Valero A, Ruiz Irastorza G, Gastaca Mateo M, Valdivieso López A. Transplantation-mediated alloimmune thrombocytopenia successfully treated by retransplantation. Lupus 2021;30:669-673. https://doi.org/10.1177/0961203320983450.

[14] West KA, Anderson DR, McAlister VC, Hewlett TJ, Belitsky P, Smith JW, et al. Alloimmune thrombocytopenia after organ transplantation. N Engl J Med 1999;341:1504-1507. https://doi.org/10.1056/nejm199911113412004.

[15] Kummrow M, Hiho S, Hudson F, Cantwell L, Mulley WR, D'Orsogna L, et al. Transfer of donor anti-HLA antibody expression to multiple transplant recipients: A potential variant of the passenger lymphocyte syndrome?

American Journal of Transplantation 2019;19:1577-1581. https://doi.org/10.1111/ajt.15262.

[16] Chiou FK, Beath SV, Morland B, Hartley J, van Mourik I, Abdel-Hady M, et al. Comparison of Clinical Features and Outcome of Pediatric Posttransplant Lymphoproliferative Disorder in Recipients of Small Bowel Allograft Versus Isolated Liver Transplantation. Transplantation 2020;104:1429-1436. https://doi.org/10.1097/tp.0000000000003004.

[17] Kataria A, Kumar D, Gupta G. Donor-derived Cell-free DNA in Solid-organ Transplant Diagnostics: Indications, Limitations, and Future Directions. Transplantation 2021;105:1203-1211. https://doi.org/10.1097/tp.0000000000003651.

[18] Hameed M, Hameed S, Harvey C, Moser S, Muthusamy A. Imaging in whole organ pancreatic transplants and a multimodality review of its complications. Br J Radiol 2021;94:20200106. https://doi.org/10.1259/bjr.20200106.

[19] Mathavan A, Krekora U, Kleehammer AC, Mathavan A. Passenger lymphocyte syndrome following minor ABO-mismatched liver transplantation. BMJ Case Reports 2024;17. https://doi.org/10.1136/bcr-2023-259259.

[20] Tsang HC, Samraj AN, Morse RJ, Krumm N, Hess JR, Pagano MB. Genetic testing to resolve the source of haemolytic antibody in solid organ transplantation. Blood Transfus 2019;17:307-311. https://doi.org/10.2450/2019.0054-19.

[21] Iwanaga S, Sakaguchi T, Nakanishi K, Furukuwa M, Ishizeki K, Kogawa K, et al. Passenger lymphocyte syndrome with hemophagocytic syndrome after peripheral blood stem-cell transplantation from an HLA-matched full biological sibling: Case report. Transfusion and Apheresis Science 2012;47:355-358. https://doi.org/10.1016/j.transci.2012.06.027.

[22] Cserti-Gazdewich CM, Waddell TK, Singer LG, Chaparro C, Pendergrast JM, Hawes J, et al. Passenger lymphocyte syndrome with or without immune hemolytic anemia in all Rh-positive recipients of lungs from rhesus

alloimmunized donors: three new cases and a review of the literature. Transfus Med Rev 2009;23:134-145. https://doi.org/10.1016/j.tmrv.2008.12.003.

[23] Squires JE. Passenger Lymphocyte Syndrome: A Case Report Involving Non-ABO Antibodies. Transfusion Medicine and Hemotherapy 2014;41:153-155. https://doi.org/10.1159/000357985.

[24] Audet M, Panaro F, Piardi T, Huang P, Cag M, Cinqualbre J, et al. Passenger Lymphocyte Syndrome and Liver Transplantation. Clinical and Developmental Immunology 2008;2008:1-4. https://doi.org/10.1155/2008/715769.

[25] Snell G, Hiho S, Levvey B, Sullivan L, Westall G. Consequences of donor-derived passengers (pathogens, cells, biological molecules and proteins) on clinical outcomes. The Journal of Heart and Lung Transplantation 2019;38:902-906. https://doi.org/10.1016/j.healun.2019.06.019.

[26] Zarei E, Shafiekhani M, Azadeh N, Shamsaeefar A, Lotfi M, Ahrami M, et al. Passenger Lymphocyte Syndrome as a rare cause of hemolysis in a patient after small intestine transplantation, A case report and review of the literature. Asian Journal of Transfusion Science 2022;16:135-139. https://doi.org/10.4103/ajts.ajts_18_21.

[27] Leo A, Mytilineos J, Voso MT, Weber-Nordt R, Liebisch P, Lensing C, et al. Passenger lymphocyte syndrome with severe hemolytic anemia due to an anti-Jk(a) after allogeneic PBPC transplantation. Transfusion 2000;40:632-636. https://doi.org/10.1046/j.1537-2995.2000.40060632.x.

[28] Seltsam A, Hell A, Heymann G, Salama A. Donor-derived alloantibodies and passenger lymphocyte syndrome in two of four patients who received different organs from the same donor. Transfusion 2001;41:365-370. https://doi.org/10.1046/j.1537-2995.2001.41030365.x.

[29] Hareuveni M, Merchav H, Austerlitz N, Rahimi-Levene N, Ben-Tal O. Donor anti-Jk(a) causing hemolysis in a liver transplant recipient. Transfusion 2002;42:363-367. https://doi.org/10.1046/j.1537-2995.2002.00075.x.

[30] Noubouossie DF, Zaanona MIA, Costa LJ, Pham HP, Marques MB, Di Stasi A, et al. Passenger Lymphocyte Syndrome and Autoimmune Hypothyroidism Following Hematopoietic Stem Cell Transplantation. Case Reports in Immunology 2022;2022:1-6. https://doi.org/10.1155/2022/1690489.

[31] Evangelidis P, Evangelidis N, Vlachaki E, Gavriilaki E. What is the role of complement in bystander hemolysis? Old concept, new insights. Expert Review of Hematology 2024;17:107-116. https://doi.org/10.1080/17474086.2024.2348662.

[32] Luo S, Hu D, Wang M, Zipfel PF, Hu Y. Complement in Hemolysis- and Thrombosis- Related Diseases. Front Immunol 2020;11:1212. https://doi.org/10.3389/fimmu.2020.01212.

[33] Flegel WA. Pathogenesis and mechanisms of antibody-mediated hemolysis. Transfusion 2015;55 Suppl 2:S47-58. https://doi.org/10.1111/trf.13147.

[34] Makuria AT, Langeberg A, Fishbein TM, Sandler SG. Nonhemolytic passenger lymphocyte syndrome: donor-derived anti-M in an M+ recipient of a multiorgan transplant. Immunohematology 2009;25:20-23.

[35] Prethika PA, Shastry S, Mohan G, Prabhu RA, Nagaraju SP, Rangaswamy D. Passenger lymphocyte syndrome in a bidirectional ABO-mismatched renal transplant. Asian J Transfus Sci 2020;14:63-66. https://doi.org/10.4103/ajts.AJTS_98_19.

[36] Sandler SG, Han S, Langeberg A, Matsumoto C, Fishbein TM. Nonhemolytic passenger lymphocyte syndrome. Transfusion 2017;57:2942-2945. https://doi.org/10.1111/trf.14383.

[37] Kohl MM, Schwarz S, Jaksch P, Muraközy G, Kurz M, Schönbacher M, et al. High Rate of Passenger Lymphocyte Syndrome after ABO Minor Incompatible Lung Transplantation. Am J Respir Crit Care Med 2024;209:995-1000. https://doi.org/10.1164/rccm.202306-1107OC.

[38] Marton A, Pendergrast JM, Keshavjee S, Singer LG, Hawes J, Cserti-Gazdewich CM. Passenger Lymphocyte Syndrome Following Solid

Organ Transplantation: Graft Source, Incidence, Specificity, Duration, and Severity Of Hemolysis. Blood 2013;122:37-37.

[39] Sönnerborg IV, Höglund P, Nordström J, Wikman A, Wennberg L, Nowak G. Severe Transplantation-Mediated Alloimmune Thrombocytopenia in 2 Recipients of Organs From the Same Donor. Transplantation 2017;101:e190-e192. https://doi.org/10.1097/tp.0000000000001669.

[40] Lindholm PF, Kwaan HC, Ramsey G, Curtis BR, Fryer J. Severe thrombocytopenia in a patient following liver transplantation caused by HPA-1a antibodies produced by the liver donor. Am J Hematol 2018;93:150-153. https://doi.org/10.1002/ajh.24944.

[41] French W, Hopkins M, Poles A, Mijovic A. Passenger lymphocyte thrombocytopenia due to human platelet antigen 3a antibodies: Case report and review of literature. Transfusion 2020;60:2185-2188. https://doi.org/10.1111/trf.15905.

[42] Romero S, Solves P, Lancharro A, Cano I, Moscardó F, Carpio N, et al. Passenger lymphocyte syndrome in liver transplant recipients: a description of 12 cases. Blood Transfus 2015;13:423-428. https://doi.org/10.2450/2015.0148-14.

[43] Peck JR, Elkhammas EA, Li F, Stanich PP, Latchana N, Black S, et al. Passenger lymphocyte syndrome: a forgotten cause of postliver transplant jaundice and anemia. Exp Clin Transplant 2015;13:200-202. https://doi.org/10.6002/ect.2013.0239.

[44] Foell D, Glasmeyer S, Senninger N, Wolters H, Palmes D, Bahde R. Successful management of passenger lymphocyte syndrome in an ABO-compatible, nonidentical isolated bowel transplant: a case report and review of the literature. Transfusion 2017;57:1396-1400. https://doi.org/10.1111/trf.14086.

[45] Zhou D, Leung J, Hu Z, Ye S, Ye Q. Passenger lymphocyte syndrome after ABO-mismatched kidney transplantation: A case report and literature review. Transplant Immunology 2023;76. https://doi.org/10.1016/j.trim.2022.101725.

[46] de Bruijn S, Philipse E, Couttenye MM, Bracke B, Ysebaert D, Michielsen P, et al. Passenger Lymphocyte Syndrome (PLS): A Single-center Retrospective Analysis of Minor ABO-incompatible Liver Transplants. Journal of Clinical and Translational Hepatology 2017;5:9-15. https://doi.org/10.14218/jcth.2016.00072.

[47] Dirim AB, Demir E, Safak S, Garayeva N, Artan AS, Oto OA, et al. An atypical case of refractory passenger lymphocyte syndrome after renal transplantation. Nefrología (English Edition) 2023;43:783-788. https://doi.org/10.1016/j.nefroe.2022.01.010.

[48] Yeom GE, Lim SH, Kim JH, Ahn YH, Kim H, Ha J, et al. Gastrointestinal involvement of passenger lymphocyte syndrome followed by minor ABO-incompatible renal transplantation: A case report. Pediatr Transplant 2023;27:e14556. https://doi.org/10.1111/petr.14556.

[49] Ainsworth CD, Crowther MA, Treleaven D, Evanovitch D, Webert KE, Blajchman MA. Severe hemolytic anemia post-renal transplantation produced by donor anti-D passenger lymphocytes: case report and literature review. Transfus Med Rev 2009;23:155-159. https://doi.org/10.1016/j.tmrv.2008.12.005.

[50] Zantek ND, Koepsell SA, Tharp DR, Cohn CS. The direct antiglobulin test: A critical step in the evaluation of hemolysis. American Journal of Hematology 2012;87:707-709. https://doi.org/10.1002/ajh.23218.

[51] Monfort M, Honoré P, Gothot A, Gérard C. Simultaneous passenger lymphocyte syndrome and multiple alloimmunization against donor's blood group antigens after liver transplantation. Vox Sanguinis 2015;109:86-90. https://doi.org/10.1111/vox.12253.

[52] Achkar R, Chiba AK, Zampieri-Filho JP, Pestana JOM, Bordin JO. Hemolytic anemia after kidney transplantation: a prospective analysis. Transfusion 2011;51:2495-2499. https://doi.org/10.1111/j.1537-2995.2011.03192.x.

[53] DiGiuseppe JA, Bastacky SI, Shirey RS, Silberman MA, Hutchins GM, Ness PM. Tacrolimus-related posttransplant lymphoproliferative disorder presenting as autoimmune hemolytic anemia. Arch Pathol Lab Med 1996;120:282-285.

[54] Thomas W, Foukaneli T, Cosgrove J, Massey D, Woodward J, Middleton S, et al. Transplant-associated thrombotic microangiopathy and immune haematological complications following intestine-containing organ transplantation: experience from over 100 consecutive cases. Br J Haematol 2021;193:961-970. https://doi.org/10.1111/bjh.17430.

[55] Renaudon-Smith E, De La Fuente J, Bain BJ. Transplant-associated thrombotic microangiopathy. Am J Hematol 2016;91:1160. https://doi.org/10.1002/ajh.24459.

[56] Zhu P, Wu Y, Cui D, Shi J, Yu J, Zhao Y, et al. Prevalence of Pure Red Cell Aplasia Following Major ABO-Incompatible Hematopoietic Stem Cell Transplantation. Front Immunol 2022;13:829670. https://doi.org/10.3389/fimmu.2022.829670.

[57] Koepsell SA, Landmark JD. Passenger Lymphocyte Syndrome: Use of Archived Donor Organ Biopsy Obtained at the Time of Transplantation for Diagnosis. American Journal of Transplantation 2013;13. https://doi.org/10.1111/ajt.12343.

[58] Nishide S, Uchida J, Kabei K, Iwai T, Kuwabara N, Naganuma T, et al. Passenger Lymphocyte Syndrome in the ABO-Incompatible Kidney Transplant Recipient Receiving Rituximab. Exp Clin Transplant 2019;17:558-560. https://doi.org/10.6002/ect.2016.0261.

[59] Lee HJ, Gulbis A, De Padua Silva L, Hosing C, Khouri I, de Lima M, et al. Rituximab for passenger lymphocyte syndrome associated with allogeneic

SCT. Bone Marrow Transplantation 2008;42:67-69. https://doi.org/10.1038/bmt.2008.79.

[60] Tsujimura K, Ishida H, Tanabe K. Is Efficacy of the Anti-Cd20 Antibody Rituximab Preventing Hemolysis Due to Passenger Lymphocyte Syndrome? Therapeutic Apheresis and Dialysis 2016;21:22-25. https://doi.org/10.1111/1744-9987.12483.

[61] Leandro MJ, de la Torre I. Translational Mini-Review Series on B Cell-Directed Therapies: The pathogenic role of B cells in autoantibody-associated autoimmune diseases--lessons from B cell-depletion therapy. Clin Exp Immunol 2009;157:191-197. https://doi.org/10.1111/j.1365-2249.2009.03978.x.

[62] Thomas W. Comment: Passenger lymphocyte syndrome as a rare cause of hemolysis in a patient after small intestine transplantation - A case report and review of the literature. Asian Journal of Transfusion Science 2024;18:373-374. https://doi.org/10.4103/ajts.ajts_147_22.

[63] Panaro F, DeChristopher PJ, Rondelli D, Testa G, Sankary H, Popescu M, et al. Severe hemolytic anemia due to passenger lymphocytes after living-related bowel transplant. Clin Transplant 2004;18:332-335. https://doi.org/10.1111/j.1399-0012.2004.00158.x.

[64] Shastry S, Prethika PA, Mohan G, Prabhu R, Nagaraju S, Rangaswamy D. Passenger lymphocyte syndrome in a bidirectional ABO-mismatched renal transplant. Asian Journal of Transfusion Science 2020;14. https://doi.org/10.4103/ajts.AJTS_98_19.

[65] Zhao H, Ding Z, Luo Z, Liu H, Peng P, Wang X, et al. Passenger lymphocyte syndrome in renal transplantation: A systematic review of published case reports. Transplant Immunology 2022;73. https://doi.org/10.1016/j.trim.2022.101605.

[66] Low M, Gregory G. Passenger lymphocyte syndrome after lung transplant. Blood 2012;120:4122. https://doi.org/10.1182/blood-2012-06-438614.

[67] Chase RC, Koop AH, Shaikh M, Imperial RJ, Harnois DM, Loo NM, et al. Successful treatment of severe passenger lymphocyte syndrome with efgartigimod synergy. Transfusion 2024;64:755-760. https://doi.org/10.1111/trf.17748.

[68] Udagawa T, Kamei K, Ogura M, Tsutsumi A, Noda S, Kasahara M, et al. Sequential liver-kidney transplantation in a boy with congenital hepatic fibrosis and nephronophthisis from a living donor. Pediatr Transplant 2012;16:E275-280. https://doi.org/10.1111/j.1399-3046.2011.01611.x.

[69] Aujayeb A, Lordan J, Kilner M, Wallis J. The passenger lymphocyte syndrome – experience from a cardiothoracic transplant unit. Transfusion Medicine 2014;24:423-425. https://doi.org/10.1111/tme.12158.

[70] Brunetta DM, de Barros Carlos LM, Da Silva VFP, de Oliveira Alves TM, Macedo ÊS, Coelho GR, et al. Prospective evaluation of immune haemolysis in liver transplantation. Vox Sanguinis 2019;115:72-80. https://doi.org/10.1111/vox.12865.

[71] Aluwihare CM, Abayadeera A, Jeganathan G. Passenger Lymphocytic Syndrome following orthoptic diseased donor liver transplantation. Sri Lankan Journal of Anaesthesiology 2018;26. https://doi.org/10.4038/slja.v26i2.8318.

[72] Davis SL, Vaidya A, Timbs A, Schuh A, Staves J, Murphy MF. Severe haemolysis due to passenger lymphocyte syndrome after an ABO mismatched bowel transplant--a case report. Transfus Med 2011;21:65-69. https://doi.org/10.1111/j.1365-3148.2010.01045.x.

[73] Botija G, Ybarra M, Ramos E, Molina M, Sarría J, Martínez-Ojinaga E, et al. Autoimmune cytopaenia after paediatric intestinal transplantation: a case series. Transplant International 2010;23:1033-1037. https://doi.org/10.1111/j.1432-2277.2010.01091.x.

[74] Barcellini W. Immune Hemolysis: Diagnosis and Treatment Recommendations. Semin Hematol 2015;52:304-312. https://doi.org/10.1053/j.seminhematol.2015.05.001.

[75] Holbro A, Passweg JR. Management of hemolytic anemia following allogeneic stem cell transplantation. Hematology Am Soc Hematol Educ Program 2015;2015:378-384. https://doi.org/10.1182/asheducation-2015.1.378.

[76] Gajewski JL, Petz LD, Calhoun L, O'Rourke S, Landaw EM, Lyddane NR, et al. Hemolysis of transfused group O red blood cells in minor ABO-incompatible unrelated-donor bone marrow transplants in patients receiving cyclosporine without posttransplant methotrexate. Blood 1992;79:3076-3085.

[77] Hoegler W, Nachbaur D, Kropshofer G, Wehl G, Schoenitzer D, Nussbaumer W. Abrupt onset of severe passenger lymphocyte syndrome after HLA-mismatched unrelated bone marrow transplantation in a seven-year-old boy. Med Pediatr Oncol 2002;38:143-144. https://doi.org/10.1002/mpo.1295.

[78] Zaimoku Y, Takami A, Sato H, Utsumi M, Nakao S. IgM anti-recipient ABO antibodies predict acute graft-versus-host disease following allogeneic hematopoietic stem cell transplantation. International Journal of Hematology 2013;98:96-101. https://doi.org/10.1007/s12185-013-1360-6.

[79] Watz E, Remberger M, Ringden O, Lundahl J, Ljungman P, Mattsson J, et al. Analysis of Donor and Recipient ABO Incompatibility and Antibody-Associated Complications after Allogeneic Stem Cell Transplantation with Reduced-Intensity Conditioning. Biology of Blood and Marrow Transplantation 2014;20:264-271. https://doi.org/10.1016/j.bbmt.2013.11.011.

TABLES AND FIGURES WITH LEGENDS

Table 1. Differential diagnosis of passenger lymphocyte syndrome

Condition	Key differentiators
Drug-induced haemolysis	Temporal relation to drug initiation (e.g., tacrolimus) and drug-dependent antibodies
Thrombotic microangiopathy (TMA)	Schistocytes, reduced ADAMTS13 activity, and microvascular thrombosis
Acute graft-versus-host disease (GVHD)	Skin rash, diarrhoea, negative DAT, and donor chimerism confirmed by biopsy
Pure red cell aplasia (PRCA)	Onset >30 days post-HSCT, reticulocytopenia (<0.1%), normal LDH/haptoglobin, and negative DAT

DAT: Direct antiglobulin test; HSCT: Haematopoietic stem cell transplantation; LDH: Lactate dehydrogenase.

Table 2. Treatment strategies for passenger lymphocyte syndrome (PLS)

Treatment	Timing	Efficacy
Blood transfusion	Severe or refractory haemolysis	Highly effective in most cases
Corticosteroids	If transfusion fails or severe haemolysis	Moderate efficacy, often combined with other therapies
B-Cell and antibody-targeting therapies		
Rituximab (RTX)	After steroid/transfusion failure	~80% remission (CD20+ B-cell depletion)
IVIG	Acute haemolysis or adjunct to RTX	Short-term reduction in antibody titers
Plasmapheresis (e.g., centrifugal exchange or Glycosorb-ABO immunoadsorption)	Emergent cases (e.g., renal failure)	Rapidly reduces antibody titres (e.g., anti-A IgG from 64→4)
Efgartigimod	Refractory cases	Case reports show synergy with plasmapheresis
Complement-targeting therapies		
Eculizumab	Evidence of complement activation	Anecdotal efficacy (risk of infections)
Sutimlimab	Cold agglutinin-like haemolysis	Theoretical (similar to cold agglutinin disease)
Supportive care	Chronic anaemia	Adjunctive role

Treatment	Timing	Efficacy
	management	

Note: “Blood transfusion and supportive care” is considered throughout the entire process of transplantation, while the remaining treatments are all therapeutic measures taken after the transplantation.

Table 3. Characteristics of PLS in diverse organ transplantations

Transplant type	Incidence rate	Clinical manifestations	Treatment and prognosis	Special risk factors
Liver transplantation	Highest incidence, approximately 17.9% in minor ABO incompatibility cases. In paediatric LT, the incidence is 14%, with a higher risk when the recipient is A+ and the donor liver is O+.	Marked hyperbilirubinaemia, often misdiagnosed. In some cases, elevated indirect bilirubin is the initial manifestation without significant haemoglobin decrease.	Generally good prognosis, most cases resolve within 2–3 weeks. Severe haemolysis can lead to graft dysfunction.	Donor's previous
Kidney transplantation	Approximately 20% in cases of minor ABO incompatibility. Overall incidence is lower than that of liver transplantation. Slightly higher risk in living-related kidney donation.	Anaemia is the primary manifestation. Renal function is usually not affected, but acute kidney injury induced by haemolysis may occur.	Usually self-limiting with a low mortality rate, but graft rejection may occur.	
Small intestine	Low incidence rate	More severe	Higher mortality	

transplantation	but may be potentially severe	haemolysis, often requiring multidisciplinary intervention	rate, possibly related to insufficient immunosuppression intensity.	immune history, immunosuppressive regimen (influence of cyclosporine), graft abundant in lymphoid tissue.
Lung transplantation	Approximately 18.2%–30.8% in cases of minor ABO incompatibility	May be complicated with thrombotic microangiopathy, significantly increased transfusion requirements	Haemolysis does not affect graft survival, but long-term monitoring of antibody titres is required.	
Hematopoietic HSCT	Low incidence rate, accompanied by severe haemolysis, especially in cases of minor ABO incompatibility	Share common features with other transplants such as haemolytic anaemia and positive DAT. Symptoms appear within 1–3 weeks after surgery and can be delayed for months.	Self-limiting in most cases, low mortality rate.	

DAT: Direct antiglobulin test; HSCT: Haematopoietic stem cell transplantation.

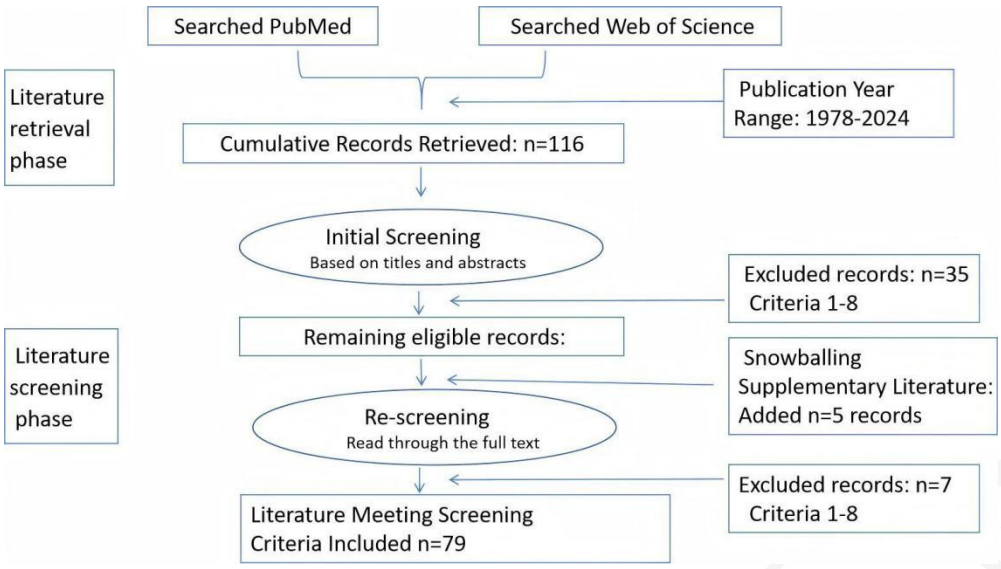

Figure 1. Flowchart of methodological and clinical relevance criteria for inclusion

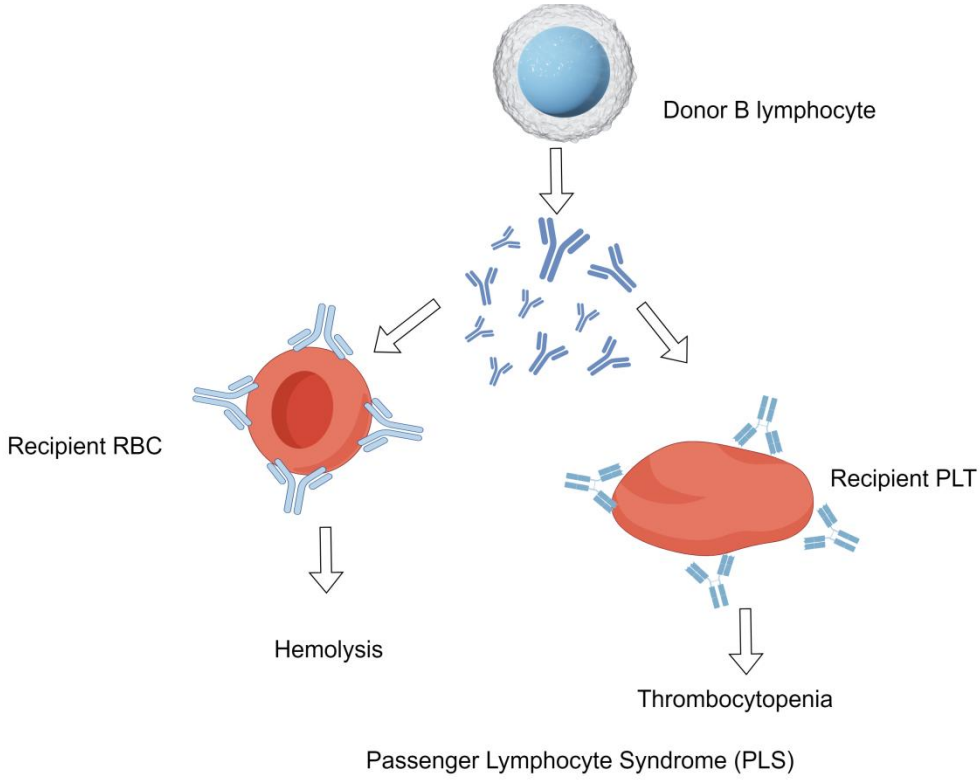

Figure 2. Pathogenesis of passenger lymphocyte syndrome (PLS)

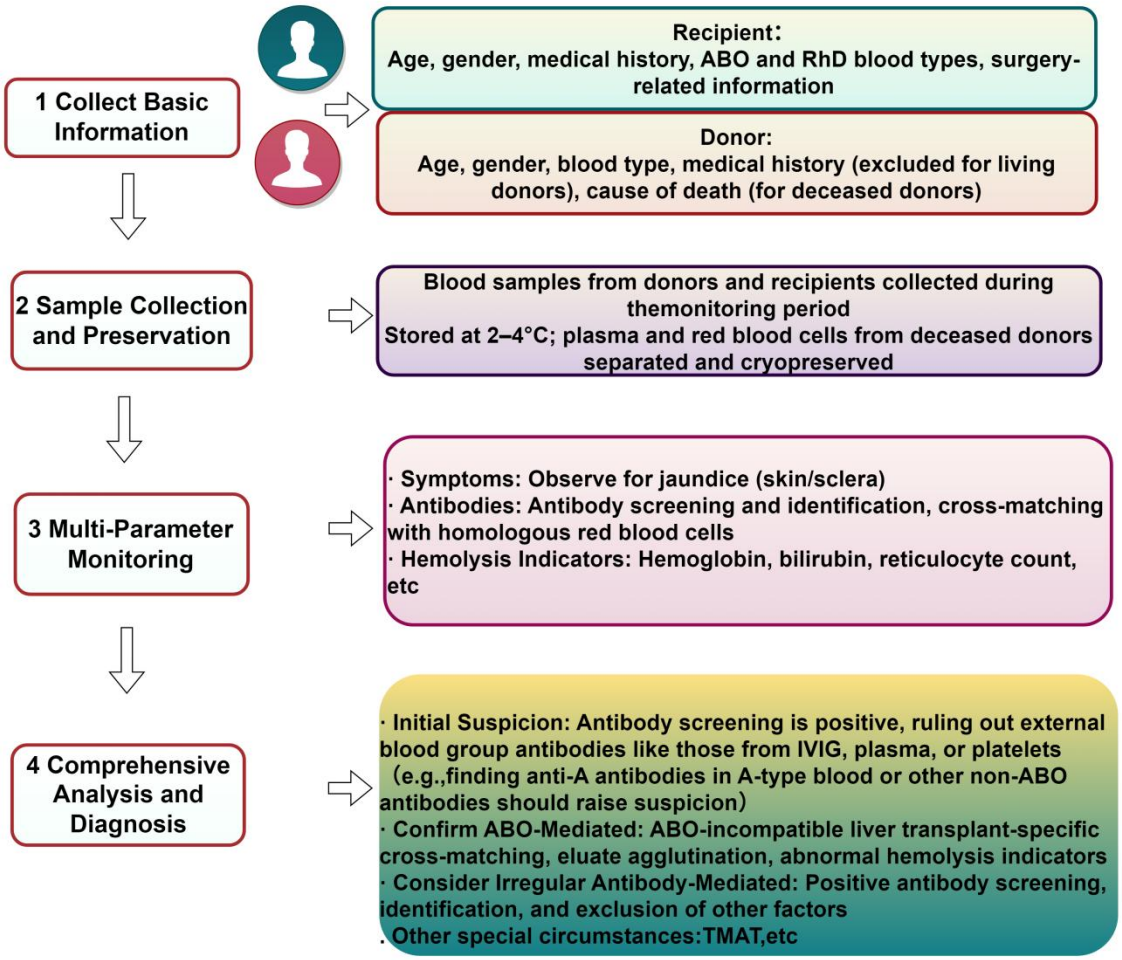

Figure 3. Monitoring process of passenger lymphocyte syndrome (PLS)