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# WHEN PROGRESS MEETS AN OLD CHALLENGE

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EDITORIAL

# *When Progress Meets an Old Challenge*

***Elvana RISTA, MD, PhD***
Editor-in-Chief, Medicus

Medicine has always advanced, but rarely as quickly as it does today. Nowhere is this clearer than in transplantation, a field that within a single decade has advanced from refined immunosuppression and wider donor criteria to the threshold of xenotransplantation. Yet every step forward is shadowed by an old companion. Infection has challenged medicine in every century, and it challenges us still not as a problem of the past, but as one that grows alongside our progress.

This is the paradox at the centre of the present issue. The more we suppress the immune system to protect a graft, the more we expose the patient to the pathogens that the immune system once held back. Progress and vulnerability advance together. Three articles follow this thread closely: a scoping review of parvovirus B19 in kidney transplant recipients, showing how a "minor" virus can cause refractory anaemia and diagnostic difficulty; a practical review of cytomegalovirus management that adapts complex guidelines to resource-limited settings; and a serostatus-based approach to Epstein–Barr virus surveillance and the prevention of post-transplant lymphoproliferative disorder. Together, they make one point: infection is not what transplantation has left behind, but what it must keep pace with.

If infection is the constant, innovation is what carries us forward, and this issue reflects both. Alongside the transplant–infection theme, our authors look at artificial intelligence to make prescribing safer in polypharmacy: a fitting counterpoint, where the newest tools serve one of medicine's oldest duties, to do no harm. Others widen the view further: extreme proteinuria in a rare triple autoimmune overlap, multiple myeloma presenting as acute kidney injury, the laboratory picture of visceral leishmaniasis, the physical symptoms of anxiety and depression in Albanian adults, vertebral artery Doppler as an accessible diagnostic

tool, and the role of physiotherapy in cardiorespiratory function. Case reports, reviews, and original research stand side by side, a fair reflection of medicine as it is practiced today.

What ties this variety together is a single commitment: to meet both the lasting and the emerging challenges of our profession with rigour, curiosity, and care for the patient. I thank our authors, reviewers, and readers, and I invite you to explore a collection that looks ahead without losing sight of what remains constant.

# *Beyond Refractory Anaemia: A Focused Scoping Review of Parvovirus B19 Infection in Kidney Transplant Recipients*

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## Abstract

*Parvovirus B19 infection is a rare and underestimated complication encountered among kidney transplant recipients, with clinical implications extending beyond refractory anemia. This focused scoping review analyzed primary clinical evidence from 29 studies published over two decades, from 2002 to 2026, mapping current evidence across diagnostic, therapeutic and prognostic domains. Serological testing was found to be unreliable in this population, with quantitative PCR emerging as the essential diagnostic tool. Management is guided by a sequential immunosuppressive framework, though no standardised protocol exists and randomised controlled trial evidence is absent. Paediatric recipients represent a particularly vulnerable and underserved population. Prospective multicentre data and targeted paediatric research remain the most pressing unmet needs in this field.*

***Keywords:*** *Parvovirus B19; kidney transplantation; pure red cell aplasia; refractory anaemia; intravenous immunoglobulin; immunosuppression reduction; scoping review.*

## Introduction

Parvovirus B19 (B19V) is a single-stranded DNA virus belonging to the Parvoviridae family that shows selective tropism for committed erythroid progenitor cells. In immunocompetent individuals, it is responsible for the development of erythema infectiosum (Fifth disease) in the pediatric population. Among adults it often presents as a self-limiting illness characterized by mild constitutional symptoms. Primary infection is resolved through a humoral response with the generation of immunoglobulin G antibodies that commonly confer lasting immunity [1].

However, in immunocompromised patients the natural history of the infection is altered. This is particularly evident among solid-organ transplant recipients, who fail to mount a robust immunological response allowing B19V to persist in the bone marrow, eliciting lytic infection of erythroid progenitor cells and profound anemia. B19V infection in this population leads to the development of pure red cell aplasia (PRCA), characterized by severe normocytic anemia, reticulocytopenia and resistance to erythropoiesis-stimulating agents (ESAs). Due to their intense maintenance immunosuppressive regimens, kidney transplant recipients are especially vulnerable to this complication [1-4].

Despite decades of accumulated clinical experience, management of B19V infection remains unstandardized. Current literature on B19V infection among kidney transplant recipients comprises primarily case-reports or small case-series,

with evidence from randomized controlled trials lacking [1]. Diagnostic methods and treatment protocols are heterogenous and vary across institutions. Critical questions on the optimal PCR threshold for treatment initiation, IVIG dosing and duration, indications for immunosuppression modifications and treatment of refractory disease remain unanswered [1]. Moreover, recent data on B19V infection in this population, has revealed associations with antibody-mediated rejection (ABMR) and thrombotic microangiopathy (TMA) with important implications on allograft survival, pointing to clinical significance beyond refractory anemia [5-7].

This article aims to present a focused scoping review of primary clinical literature on B19V infection in kidney transplant recipients, by identifying and synthesizing key findings on the timing and clinical presentation of B19V infection following kidney transplantation, diagnosis and current treatment strategies, while highlighting priority evidence gaps for future research.

## Design and Methods

This focused scoping review was conceptualized in accordance with established scoping review methodology and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [8,9]. However, no protocol was prospectively registered, representing one of the limitations of our study. A systematic search was conducted across PubMed/MEDLINE, PubMed Central, Google Scholar, ScienceDirect, Frontiers, Wiley Online Library, MDPI, and Oxford Academic from January 2000 to March 2026. The search combined terms for Parvovirus B19 (including B19V and erythrovirus) with kidney or renal transplantation. A supplementary targeted search was subsequently performed by reference-list tracking to identify additional eligible records not captured by the database search. Only English-language publications were considered.

To be included as primary studies records were considered eligible if they: a) reported primary patient-level data, b) included adult or paediatric recipients of a kidney transplant, c) described Parvovirus B19 infection confirmed by PCR, serology, or bone marrow histology and d) were published as full-text peer-reviewed articles. Excluded study types were narrative reviews, systematic reviews, meta-analyses, editorials, and conference abstracts without full-text data.

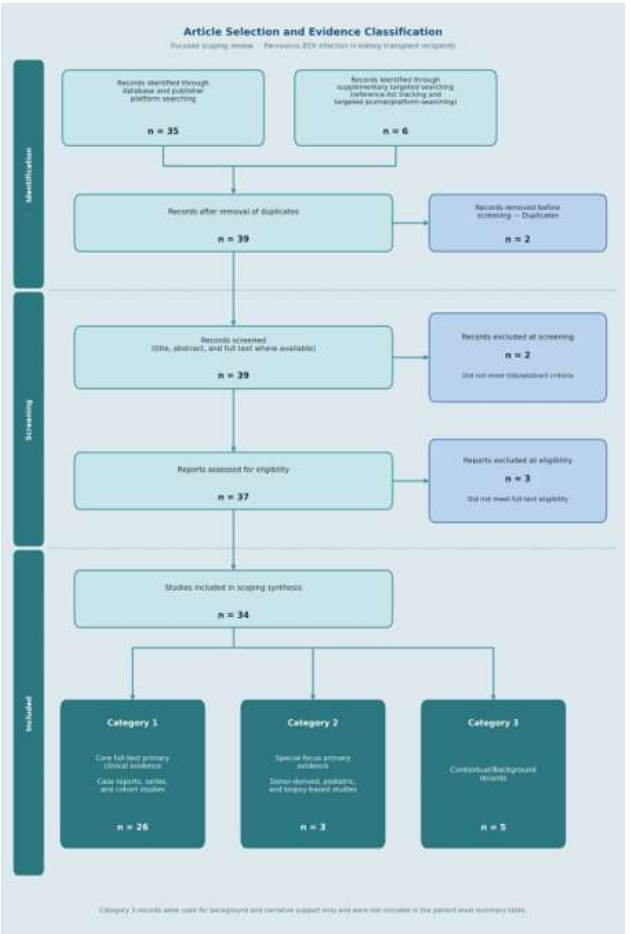
Titles, abstracts, and full texts were initially screened and categorised into three main groups, with the first two categories comprising the primary clinical evidence that was analyzed, and the third category representing records that were only utilized for narrative and background reference.

Given the heterogeneity of study designs and outcome reporting, thematic narrative synthesis was conducted across the main domains: timing and clinical presentation, diagnosis, treatment strategies and response, donor-derived transmission, graft outcomes and paediatric disease.

## Results
## Study Selection

Our initial database search identified 35 records, and the supplementary manual search identified a further six. After removal of two duplicate records, a total of 39 records were screened. We excluded two records at title and abstract screening, and the remaining 37 records underwent full-text review. Three were excluded at this stage as they did not meet eligibility criteria. A total of 34 records were included in the final review framework, further classified into three main categories: 29 primary studies (26 Category 1 and 3 Category 2), and five contextual records (Category 3) used for background and narrative support only. The selection process is summarized in Figure 1.

**FIGURE 1.** PRISMA flow diagram of study selection and evidence classification



## Characteristics of included studies

The 29 primary studies were published between 2002 and 2026 across geographically diverse settings, including South Korea, the United States, India, China, Brazil, Switzerland, Italy, Japan, Vietnam, Albania, Spain, the United Kingdom, Iran, Turkey, and Greece [2-6,11-34]. Twenty-two of 29 studies were published in 2017 or later. Study designs comprised 14 single case reports, six case series (two to 21 patients), six retrospective or prospective observational cohort studies, and three special-focus primary studies. The three Category 2 studies addressed: donor-derived B19V transmission across 2,048 kidney transplants (Yu et al. [24]); intrarenal B19V infection and ABMR in 106 paediatric recipients with prospective protocol biopsy (Bertazza Partigiani et al. [5]); and a paediatric case compilation yielding 50 cases (Jia et al. [12]). Table 1 summarises all included study characteristics (Figure 2, Figure 3 and Figure 4).

**TABLE 1.** Characteristics of included primary studies

| Study (Year) Country | Design (N) | Timing | Key findings | Treatment/Outcome |
|---|---|---|---|---|
| Yango, 2002 USA | CR; 1 | Early | Pancytopenia; donor-derived transmission | IVIG 0.4 g/kg/d x10 + RIS; stabilized |
| Ki, 2005 South Korea | Cohort; 167 (52 PCR+) | Serial | PRCA in 2; PCR+ → lower Hb; graft unaffected | Variable; graft survival unaffected |
| Egbuna, 2006 USA | Series; 3 | Mean 40 mo | EPO-resistant anemia/PRCA; 1 recurrence | RIS + IVIG 0.5 g/kg ×4; resolved |
| Beckhoff, 2007 Switzerland | CR; 1 | Early; relapse 3.5 mo | Relapsing PRCA; low-level viremia persisted | 2× IVIG + RIS; resolved |
| Carraturo, 2012 Italy | Cohort; 64 (2 active) | ≥6 mo post-Tx | B19V in 2/64; no severe anaemia in cohort | None required |
| Alves, 2013 Brazil | CR; 1 | Late; 3–4 years post-Tx | Severe PRCA; IgM/IgG negative (PCR+) | IVIG 0.4 g/kg/d x5; Hb recovered |
| Krishnan, 2015 USA | Retrospective series; 3 | Mean 8.6 wk | PCR-positive in 3/3; BM confirmed PRCA in 2/3; Cr↑ in 2/3; | IVIG + RIS + transfusion; 1 relapse |
| Baek, 2017 South Korea | Cohort; 39 PCR+ | 89.7% in year 1 | PCR+ → lower Hb; graft survival = controls | IVIG/RIS per severity; graft survival preserved |
| Hai An, 2019 Vietnam | Cohort; 9/663 | 8/9 within 3 mo | Severe anemia + reticulocytopenia; graft dysfunction 4/9; 1 relapse | RIS + IVIG; 1 relapse |
| Inamdar, 2019 India | CR; 1 | Recurrent course | Recurrent PRCA; collapsing glomerulopathy and allograft loss | IVIG + RIS; graft lost; re-transplantation |
| Inoue, 2020 Japan | CR; 1 | Early | Relapsing PRCA; allograft-mediated donor transmission | IVIG + RIS; Relapse → IVIG + RIS; Hb recovered |
| Mascia, 2020 Italy | CR; 1 | ~15 mo | Aplastic/PRCA + hemolytic-microangiopathic features; atypical | IVIG 400 mg/kg ×10 + transfusion; stable |
| Gang, 2020 South Korea | CR; 1 | Recurrent episodes | Recurrent PRCA; high VL; TAC → CsA conversion | Repeated IVIG; TAC → CsA; controlled |

| Study (Year) Country | Design (N) | Timing | Key findings | Treatment/Outcome |
|---|---|---|---|---|
| Sharma, 2020 USA | CR; 1 | <3 mo | B19V-associated anemia + concurrent BK & rhinovirus co-infection; no BM confirmation | IVIG weekly ×5 + RIS + cidofovir; resolved |
| Rodríguez-Espinosa, 2021 Spain† | CR; 1 | Early; ~1 mo | Relapsing PRCA; repeated IVIG ineffective† | TAC → EVR; sustained favorable response† |
| Yu, 2021 China | Cohort; 2,048 KTRs | Early | Donor-derived: 0.4% (living), 1.5% (deceased) | IVIG + RIS; all resolved; low-level asymptomatic viremia observed; donor kidneys acceptable |
| Huang, 2022 China | Prospective; 12/118 | Mostly within 2 wk | Anemia 100%; liver dysfunction 75%; platelet reduction 8.3%; kidney dysfunction 16.7%; PCR detected early | IS ± IVIG; Hb improved; favorable prognosis |
| Singh, 2023 India | Cohort; 7/714 | Median 6 wk | Refractory anaemia; leukopenia 57%; no relapse | RIS ± IVIG; all resolved |
| Bertazza Partigiani, 2023 Italy | Peds biopsy; 106 KTRs | Biopsies 6–24 mo | Intrarenal B19V 24% at Tx; peak 40.4% at 12 mo; ABMR 50% vs TCMR 19% (p=0.04) | No protocol; Tissue PCR/DSA surveillance recommended |
| Yaghoubi, 2023 Iran† | CR; 1 | 18 mo | Relapsing anaemia; IVIG efficacy waning discussed† | IVIG + RIS; TAC/MPA stopped and TAC → CsA IVIG + RIS† |
| Jia, 2024 China | Peds cohort (50 TR total); 14 KTR | Median 14 wk | IgM+ 26%, IgG+ 24% only; anemia 100%; graft dysfunction/loss 36% overall; HSCT worse than SOT | IVIG/RIS; highlights severe/ atypical pediatric transplant phenotype |
| Choudry, 2024 UK† | CR; 1 | Within 1 mo | Very early PRCA; high transfusion requirement; ABMR episode subsequently† | IVIG courses + RIS; MMF stopped and TAC → CsA; improvement; later ABMR episode† |
| Ersal, 2024 Turkey† | Series; 2 | One early; one late | Relapsing PRCA; IgM/IgG negative in both patients (PCR+); BM confirmed† | IVIG + RIS; Relapses → EVR added; no recurrence† |
| Sabanci, 2024 Turkey† | CR; 1 (peds) | 4 wk | Recurrent PRCA; mild leukopenia/ thrombocytopenia;13-yr-old; no peds protocol (authors' statement)† | RIS + IVIG + transfusions; persistent 15 mo; MMF → EVR with Hb improvement† |
| Hegde, 2025 India | Cohort; 21/1,164 | Median 39 d | Anemia 100%; leukopenia 14%; thrombocytopenia 9.5%; fever 47%; graft dysfunction 62%; 1 graft loss | RIS in all; IVIG in 8; Hb normalized median 30 d |
| Najar, 2025 USA | Series; 2 (donor-derived) | POD 53–73 | Donor-derived; VL >10 copies/mL; same deceased donor; Refractory anemia | IVIG + MMF withdrawal/RIS; improved |
| Shankar, 2025 India | Series; 10/117 | Median 6 wk (range 2–462 wk) | Hypoproliferative anemia in all; retic <1%; leukopenia/thrombocytopenia 30%; Hb↓ 3.72 g/dL; desidustat adjunct | RIS + IVIG (60%) + desidustat; most recovered; 2 deaths unrelated to B19V |
| Eleftheriadis, 2025 Greece† | CR; 1 | 22 yr post-Tx; PRCA 4 mo after EVR → TAC† | Late PRCA; IgM+; mTOR inhibitor withdrawal trigger† | IVIG; Hb normalized 3 wk; follow-up PCR negative† |
| Strakosha, 2026 Albania* | CR; 1 | Early | EPO-resistant PRCA; living-donor KTR; IgM positive; PCR unavailable; BM confirmed | IVIG + RIS + transfusions; Hb recovered; graft preserved; recurrent anemia required second IVIG |

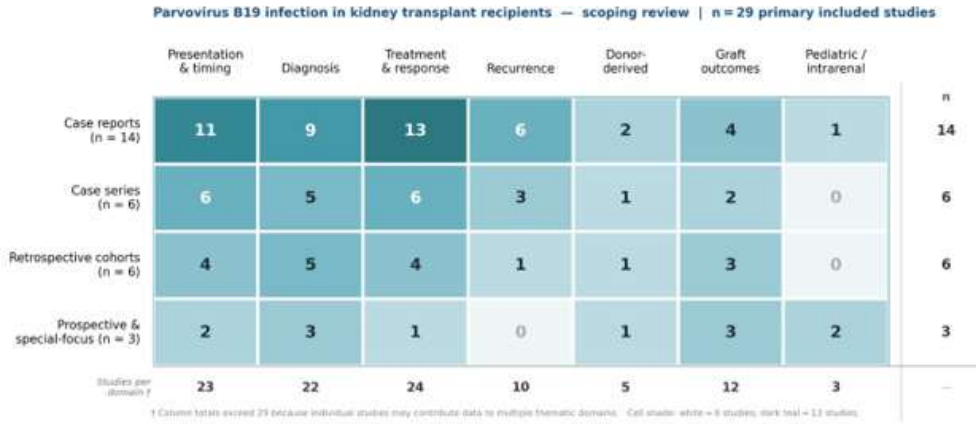
*† Identified via supplementary targeted searching.*
** Co-authored by review team. Studies ordered chronologically.*
Abbreviations: ABMR, antibody-mediated rejection; B19V, Parvovirus B19; BM, bone marrow; CR, case report; CsA, cyclosporine; DCD, donation after circulatory death;

EPO/ESA, erythropoiesis-stimulating agent; EVR, everolimus; Hb, haemoglobin; HSCT, haematopoietic stem cell transplant; IVIG, intravenous immunoglobulin; KTR, kidney transplant recipient; MMF, mycophenolate mofetil; mo, months; mTOR, mammalian target of rapamycin; NR, not reported; PCR, polymerase chain reaction; POD, post-operative day; PRCA, pure red cell aplasia; peds, paediatric; RIS, reduction of immunosuppression; TAC, tacrolimus; TCMR, T-cell-mediated rejection; Tx, transplantation; VL, viral load; wk, weeks; yr, years. Diagnosis confirmed by PCR in all studies; bone marrow biopsy performed in selected cases

## Timing and Clinical Presentation

B19V infection developed predominantly within the first three months post-transplantation [2,4,11,18,33]. Reported medians ranged from 39 days in Hegde et al. [11] to 14 weeks in pediatric transplant recipients in Jia et al. [12]. The earliest case occurred within the first month of the post-operative period [17] and the latest case developed 22 years post-transplant, following an immunosuppressive regimen change from everolimus to tacrolimus [13]. Therefore, timing alone cannot exclude a B19V infection. The primary clinical presentation was PRCA characterized by severe, normocytic, hypoproliferative anemia with profoundly low reticulocyte counts and ESA resistance [2-3,28,30-31,34]. Typical clinical features in immunocompetent patients such as arthropathy and rash were generally absent in this population [1]. Leukopenia and thrombocytopenia developed in 30% of recipients in the largest single-centre cohort analyzed in our study (Shankar et al. [14]), with a mean haemoglobin decline of 3.72 ± 1.22 g/dL from baseline.

**FIGURE 2.** Evidence map of thematic domain coverage by study design



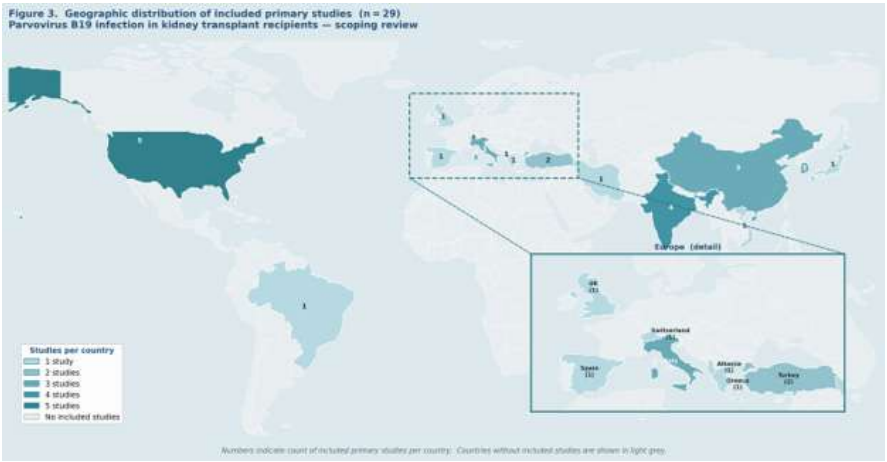
## Diagnosis

Our analysis showed serology testing to be an unreliable diagnostic tool, both in the pediatric population with the largest dataset showing IgM positivity in only 26% of cases and IgG positivity in only 24% of cases [12], as well as the adult cohort with multiple studies confirming seronegativity despite PCR-positive disease both as primary infection [15] and relapsing infection [16].

Quantitative PCR emerged as the gold standard diagnostic modality, outperforming serology testing that resulted negative even in cases of active viremia established by PCR-testing [1,4,11,14,18,33]. Furthermore PCR-testing enables evaluation of viral burden and monitoring of treatment response. However, presence of low-level viremia in the absence of a clinical and hematological constellation consistent with hypoproliferative anemia, should not prompt immediate treatment and should be interpreted with caution [24,29]. Additionally, Bertazza Partigiani et al. [5] confirmed presence of intra-renal B19V through tissue-PCR, without systemic viremia in a pediatric cohort, findings that were further solidified among adult patients by Choudry et al. [17], suggesting that tissue PCR can be incorporated as an additional diagnostic tool particularly in patients with graft dysfunction or de-novo DSA.

Bone marrow examination characterized by giant pronormoblasts with intranuclear viral inclusions, marked erythroid hypoplasia, and maturation arrest was performed selectively and reserved mainly in atypical presentations, when PCR-testing was not readily available or when a broader differential diagnosis was considered, to rule out drug-induced marrow suppression, hematological malignancy, hemophagocytic syndrome, or other viral infections [1,3,28,30,34].

**FIGURE 3.** Geographic distribution of included primary studies



## Treatment and Recurrence

Across included studies, the management strategy was primarily composed of two pillars: reduction of immunosuppression and administration of intravenous immunoglobulin (IVIG) [1,3-4,11,14,18]. Current literature lacks formal randomized trial evidence, and reported treatment protocols reflect institutional practices and expert clinical experience [1].

Immunosuppression regimen modification typically involves reduction or temporary discontinuation of mycophenolate mofetil (MMF), the antiproliferative agent most commonly associated with erythropoietic suppression [18,20-21,23,27,31]. This may or may not be combined with calcineurin inhibitor reduction. IVIG therapy was employed in most cases with significant hematological compromise. IVIG dosing regimens and duration varied across institutions. Mascia et al. [6] used 400 mg/kg/day for ten days, while other reports described total courses of 2 g/kg administered over two days or modified shorter regimens. Decisions to initiate IVIG treatment varied based on institutional practice as well, with Hegde et al. [11] using IVIG in 38% of the cohort and Shankar et al. [14] in 60% of their cohort. Singh et al. [18] used low-dose IVIG only in patients who did not respond to immunosuppression reduction alone and Najar et al. [19] described successful IVIG administration in two suspected donor-derived cases with exceptionally high viral loads ($>10^8$ copies/mL). Yaghoubi et al. [20] observed that the protective benefits of IVIG tended to diminish over time, in their report of relapsing B19V-associated anemia treated with both therapeutic strategies.

Hematological outcomes were generally favorable in adult recipients, with most reported cases experiencing hemoglobin recovery within several weeks [4,18,33]. Singh et al. [18] described hemoglobin improvement in some patients after immunosuppression reduction alone, and sustained hemoglobin recovery following IVIG administrations in patients who did not respond to immunosuppression modification. Transfusion dependence was a common feature across our analysis, with Shankar et al. [14] reporting need for transfusions, ranging from one to eight units of packed red blood cell transfusion, in eight out of ten patients. Of note, Shankar et al. [14] reports the first documented use of Desidustat, a novel oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI), as an adjunct erythropoiesis-stimulating agent in all cases, in kidney transplant-associated B19V infection.

Emerging evidence from supplementary studies supports the consideration of mTOR inhibitor-based immunosuppression regimens in patients with recurrent or refractory disease, with multiple studies showing sustained treatment response after switching from tacrolimus to an everolimus-based regimen [16,21].

Furthermore, Eleftheriadis et al. [13] reported the development of PRCA four months following a switch from everolimus to tacrolimus, emphasizing the important antiviral properties of mTOR inhibitors.

An important distinction between haematological and virological clearance emerged across the included evidence. Patients frequently achieved haemoglobin normalisation despite incomplete or absent virological clearance, and persistent B19V DNA was associated with subsequent clinical relapse in documented cases [23,28,31]. Virological surveillance by quantitative PCR should therefore continue after apparent clinical recovery and should not be substituted by haemoglobin monitoring alone.

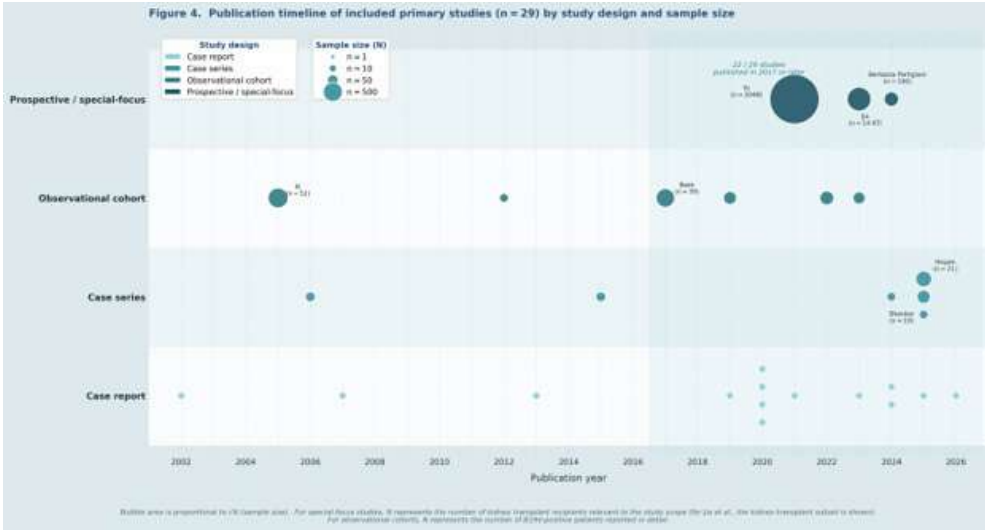
## Donor-derived transmission, graft-level pathology, and paediatric disease

Donor-derived transmission is a well-established phenomenon documented by multiple case-level data from Yango et al. [22] and Inoue et al. [23]. Najar et al. [19] confirmed simultaneous transmission in two distinct recipients that developed exceptionally high viral loads up to $10^8$ copies/mL, from the same deceased donor. The most informative data emerged from Yu et al. [24], who analysed 2,048 kidney transplants retrospectively: among living donors, 15 had detectable B19V DNAemia at donation and three recipients developed donor-derived infection corresponding to a transmission rate of 0.4%, whereas in deceased donation B19V DNAemia was observed concurrently in 18 recipients and their nine corresponding donors, with a transmission rate of 1.5%. All affected recipients responded to treatment, and the authors concluded that kidneys from B19V-infected donors are clinically acceptable and that routine pre-donation screening is not currently warranted [24]. Baek et al. [25] confirmed that allograft outcomes following B19V infection did not differ significantly from controls in the adult population. Transient declines in allograft function were generally attributed to anemia-induced hemodynamic compromise. Irreversible graft loss requiring re-transplantation was documented by Inamdar et al. [26], in the context of recurrent B19V infection.

Our analysis showed that B19V impact extends beyond hematological disease, with significant implications in allograft outcomes. Mascia et al. [6] reported development of thrombotic microangiopathy and Najar et al. [19] documented biopsy findings of borderline T-cell-mediated rejection and acute tubular damage in two donor-derived cases. Bertazza Partigiani et al. [5] showed in a pediatric cohort of 106 kidney transplant recipients, with 218 specimens analysed at 6, 12, and 24 months, persistence of intra-renal B19V independent of systemic viremia. B19V was detectable by tissue PCR in 24% of grafts at the time of transplantation,

consistent with preexisting donor-derived intrarenal infection. Overall intrarenal viral infection increased significantly between 6 and 12 months (24% vs. 44%, p = 0.007), while B19V prevalence peaked at 40.4% before declining to 14% at 48 months (p = 0.02) [5]. Notably, intra-renal B19V was more prevalent in biopsies demonstrating antibody-mediated rejection than in T-cell-mediated rejection (50% vs. 19%, p = 0.04), implicating intragraft viral presence in endothelial injury and de novo donor-specific antibody development [5]. These authors recommended tissue PCR for B19V in high-risk recipients, active DSA surveillance during the first post-transplant year, and consideration of IVIG in recipients with concurrent intrarenal B19V and DSA positivity even in the absence of formal ABMR criteria [5]. These findings were corroborated in the adult population as well by Choudry et al. [17], who documented ABMR development in an adult DCD kidney recipient with early-onset B19V-associated PRCA.

**FIGURE 4.** Publication timeline of included primary studies




Paediatric transplant recipients, including kidney transplant recipients, demonstrated a consistently more severe disease profile across the included evidence. Jia et al. [12] compiled 50 paediatric transplant cases and documented a median time to positive B19V DNA detection of 14 weeks post-transplantation, B19V IgM positivity in only 26% and IgG in only 24% of cases, graft loss or dysfunction in 36% of recipients, and more frequent multi-lineage cytopenia than in adult series. The prognosis was reported worse among haematopoietic stem cell transplant recipients compared to solid-organ transplant recipients [12]. Bertazza Partigiani et al. [5] further demonstrated that intrarenal B19V infection, often clinically silent, was detectable in nearly one quarter of paediatric

grafts at transplantation and was independently associated with ABMR. Cases of recurrent B19V-associated anaemia have been reported after pediatric kidney transplantation [27]. The absence of a standardized management protocol for both primary and recurrent infections alongside the severity data identify the pediatric kidney transplant recipient populations as a high-risk cohort and one of the most underdeveloped management domains.

## Discussion

Our focused scoping review analyzed data from 29 primary studies spanning 24 years and found that Parvovirus B19 infection among kidney transplant recipients had a heterogenous, but consistent clinical presentation characterized predominantly by pure red cell aplasia and severe hypoproliferative anemia [2-6,11-34]. The classic presentation involving rash and generalized arthralgias commonly found in the general population, were scarcely present among transplant recipients [1]. Quantitative blood PCR emerged as the most reliable and non-invasive diagnostic test, with multiple studies both in the adult and pediatric population confirming negative serological testing can frequently be present in PCR-positive disease [12,15-16]. This lack of seroconversion potentially reflects the impaired immunological response to active infection, in these highly immunosuppressed individuals. In this context, PCR-testing for B19V when available, should represent the first-line diagnostic approach in kidney transplant recipients with unexplained, ESA-resistant anemia [1,4,10,11,14,18,33].

Bone marrow biopsy can be reserved for atypical or uncertain presentations. Complementary tissue PCR on allograft biopsy may present a potential new avenue in recipients with unexplained graft dysfunction and de-novo DSA, supported by the findings of a recent study by Bertazza Partigiani et al. [5] confirming intra-renal presence of B19V in bioptic samples in the absence of systemic viraemia and association with ABMR.

Concerning treatment strategies, a sequential therapeutic approach is preferred. First-line treatment involves reduction of immunosuppression, primarily reduction or temporary cessation of MMF depending on the severity of the presentation [1,3,4,11,18]. IVIG therapy showed significant success rates among the adult population; however, optimal dosing, duration and retreatment criteria in refractory cases remains uncertain [1,3,6,18]. The emerging evidence on the efficacy of mTOR inhibitor conversion, documented in separate case-level studies of relapsing disease and the risk of PRCA following everolimus removal, provides a rationale for considering mTOR inhibitor-based regimens in recurrent or refractory cases [13,16,21]. It is important to emphasize that while the data are not abundant enough to merit a formal recommendation, it warrants further evaluation.

Notably, a significant distinction between haematological and virological endpoints was observed. Patients experienced haematological improvement and hemoglobin normalization despite incomplete virological clearance [23,28,31]. In this context, virological surveillance should be guided by quantitative PCR-testing that should continue after apparent clinical recovery, particularly when initial infection is associated with graft loss and re-transplantation is being considered [26].

The association between B19V infection and ABMR first established in the pediatric population, and later suggested among adult recipients by Choudry et al. [17], introduces a new dimension of immunological surveillance and treatment approach [5,17]. The significantly higher prevalence of intra-renal B19V in ABMR biopsies compared with T-cell-mediated rejection biopsies, can potentially point to causality with the viral intra-renal presence contributing to endothelial activation, complement deposition, or de novo DSA development [5]. B19V-infected kidney transplant recipients, particularly those with DSA positivity may warrant a lower threshold for IVIG. Beyond ABMR the intra-renal presence of B19V has been linked to the development of allograft vascular injury and thrombotic microangiopathy (TMA) [6-7]. A proposed mechanistic basis involves a specific tropism of B19V for glomerular endothelial cells through the globoside receptor (Gb4)/P antigen, which is expressed on the erythroid progenitor cells as well [1,7]. The histological pattern of vascular injury mimics that of vascular rejection, posing a significant diagnostic challenge. Furthermore, evidence of significant glomerular injury due to development of collapsing glomerulopathy, characterized by nephrotic-range proteinuria, progressive graft dysfunction, and eventual graft loss was documented by Inamdar et al [26]. The endothelial tropism of the virus provides a unifying biologic pathway explaining the intra-renal presence of B19V and its potential link to the development of ABMR, glomerular injury and TMA.

Current literature reveals that B19V infection is more prevalent in the first year following transplantation [2,4,11,25,33]. Nevertheless, several case-level data shows that infection can develop even years after kidney transplantation, with the most extreme case being reported 22 years following transplantation [13,15,20]. In this respect, timing alone cannot reliably exclude the presence of B19V infection. The development of severe, hypoproliferative anemia or new-onset pancytopenia at any point in a kidney transplant recipient should prompt testing and evaluation for B19V. Moreover, since B19V infection may reflect an increased net state of immunosuppression, concomitant viral infections, particularly CMV, EBV, and BK virus, should be actively considered during evaluation and follow-up [32].

Finally, our analysis found the pediatric population to be particularly vulnerable to B19V infection, beyond the hematologic disease with moderate rates up to 36% of graft dysfunction or loss, compared to more benign graft outcomes in adults [5,12,25]. The humoral response impairment was more pronounced in this population, with negative serologic test results hindering timely diagnosis

[12]. The clinical phenotype among pediatric kidney transplant recipients is more heterogenous as well with patients presenting with constitutional symptoms, multilineage cytopenias and graft dysfunction, highlighting the need to adopt a lower PCR testing threshold among these patients [5,12,27]. The lack of a standardized, pediatric specific treatment or monitoring protocol emerged as an important gap in current literature [27] (Figure 5).

**FIGURE 5.** Clinical summary: suspicion, diagnosis, management and evidence gaps


## Study Limitations and Research Priorities

Our review is subject to limitations inherent to the available evidence and our focused scoping review methodological approach. The evidence base is dominated by case reports and small case series, precluding quantitative analysis. Furthermore, the geographic distribution of the included primary studies, with limited representation from Europe and the Middle East, may affect the generalizability of our findings to these regions. The supplementary search was not systematic in scope and may not have captured all eligible records. Publication bias toward severe presentations is likely.

The most important gaps in need of addressing in additional research are conducting a prospective multicentre registry with standardized virological and haematological outcome endpoints and developing a consensus-based definition of virological clearance and retreatment thresholds. Additionally, adult protocol biopsy data incorporating B19V tissue PCR is imperative to characterize the ABMR association and designing dedicated prospective studies in paediatric kidney transplant recipients addressing treatment dosing and surveillance protocols. Finally, the development of a prospective trial to evaluate mTOR inhibitor conversion in recurrent disease, is paramount to evaluate the efficacy of this management approach.

## Conclusion

Parvovirus B19 infection in kidney transplant recipients is an underrecognised and diagnostically challenging complication with clinical implications that extend well beyond refractory anaemia. This scoping review confirms that the current evidence base, while informative, remains insufficiently standardised to support definitive diagnostic or treatment protocols. Quantitative PCR testing and a sequential immunosuppression management approach represent the best-supported clinical framework to emerge from this review. Prospective multicentre studies and randomised controlled trial evidence, alongside a dedicated paediatric research agenda, are paramount to building an evidence-based clinical practice and moving beyond current expert consensus.

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## Declarations

**Conflicts of interest:** The authors declare that they have no competing interests.
**Editorial independence:** E.R. is Editor-in-Chief of Medicus. To avoid any conflict of interest, this manuscript was handled entirely by an independent member of the editorial board, and E.R. was excluded from all editorial decisions regarding its peer review and acceptance.
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previously published, peer-reviewed literature and did not involve new studies on human participants or animals performed by the authors.

**Author contributions:** All authors contributed to the conception and design of the review, the literature search, study screening and data extraction, interpretation of the findings, and drafting and critical revision of the manuscript, and approved the final version.

**Data availability:** All data analysed in this review are derived from the published studies listed in the reference list; no new datasets were generated or analysed.

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# *Cytomegalovirus Infection After Kidney Transplantation: From Recent Guidelines to Feasible Strategies in Resource-Limited Settings*

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## Abstract

*Cytomegalovirus (CMV) remains one of the most frequent and clinically relevant opportunistic infections after kidney transplantation. Its importance is related not only to direct viral effects, including asymptomatic viremia, CMV syndrome and tissue-invasive disease, but also to indirect immunomodulatory effects that may contribute to acute rejection, graft dysfunction and other opportunistic infections. In recent years, CMV management has progressively moved toward a more individualized and risk-adapted approach, based on donor and recipient serostatus, net status of immunosuppressive therapy, recipient-related risk factors, quantitative viral-load monitoring and early recognition of refractory or resistant disease.*

*Current guidelines provide a detailed framework for prevention, diagnosis and treatment of CMV after solid organ transplantation. However, their application may be difficult in resource-limited settings, where access to standardized real-time quantitative PCR, repeated viral-load monitoring, rapid laboratory reporting, antiviral drugs and resistance testing may be limited. In this context, kidney transplant programs need feasible strategies able to translate guideline recommendations into daily clinical practice.*

*This review summarizes the clinical impact of CMV after kidney transplantation, focusing on risk stratification, diagnostic monitoring, prevention strategies, treatment of CMV infection and disease, antiviral resistance and toxicity. Particular attention is given to the practical management of CMV in resource-limited settings. In these contexts, CMV care should be based on a structured but adaptable approach, integrating donor–recipient serostatus, net state of immunosuppression, clinical presentation and locally available diagnostic resources. A practical risk-based algorithm may help clinicians identify patients who require universal prophylaxis, closer viral monitoring or early therapeutic intervention, improving CMV management while considering real-world limitations.*

***Key Words:*** *Cytomegalovirus Infection (CMV), Kidney Transplantation, Immunosuppressive therapy, CMV prophylaxis, resource limited-setting*

## Introduction

Cytomegalovirus (CMV) is a double strand virus with widespread prevalence among the general population. It is estimated that around 60-90% of people get infected during their lives, with higher prevalence in developing countries (1,2).

CMV has different transmission routes including horizontal transmission through blood, saliva, urine, organ transplantation and vertical transmission through placenta and potentially breast-feeding.

In immunocompetent individuals first infection is characterized by self-limiting primary replication, which can be asymptomatic or associated with mild flu-like syndrome, followed by a latent, non replicating infection in CD34+ cells. As it represents a globally widespread infection most people result immunized with positive IgG; therefore previous exposure does not assure long-last protective immunity but can reduce the risk of reinfection and severe disease.

In immunodepressed patients, both reactivation and primary infection can be severe and lead to tissue invasive disease with life threatening complications.

In kidney transplant, CMV remains one of the most frequent and relevant viral infections associated with direct and indirect effects. It may present with asymptomatic viremia, general systemic manifestations such as fever, arthralgia, asthenia, or tissue invasive disease. In this case nearly every organ can be involved but most frequent complications are colitis, myocarditis, ground-glass pneumonia, encephalitis and uveitis (3,4). In addition to these direct effects there are some indirect effects of CMV mediated by its immunomodulatory properties which may contribute to acute rejection, rise of other opportunistic infections and Esptein-Barr virus (EBV) associated Post-Transplant-Lymphoproliferative Disease (PTLD)(3-5). For this reason CMV careful management represents a cornerstone in post-kidney transplant management.

Diagnostic evaluation of CMV in kidney transplant management is spread over two levels. Before kidney transplant it is crucial to define serological status of both donor and recipient in order to assess the associated risk. Based on donor/recipient immunological status there are two main strategies to prevent CMV infection or reactivation: universal prophylaxis with an antiviral drug used for a certain amount of time and pre-emptive therapy consisting in close monitoring of CMV replication and start of treatment after a certain threshold. After kidney transplant real time quantitative PCR for the determination of CMV DNA is the gold standard to monitor, diagnose and evaluate therapy's response to CMV disease. It is important to emphasize that since CMV is a virus with potential multiorgan tropism it may affect every organ posing an important diagnostic challenge in post-transplant management.

CMV therapy is based on modulation of immunosuppressive therapy and the use of antiviral drugs that inhibit viral replications. It may be used as prophylaxis or treatment of well established infection or disease but requires a careful balance between antiviral efficacy, nephrotoxicity and rejection risk.

Prophylactic use aims to prevent replication in high risk patients, particularly D+/R- status, patients treated with thymoglobuline for post-transplant induction, HIV+ patients, or those who underwent desensibilization or treatment for

acute rejection. In this context oral Valganciclovir is the preferred agent with close monitoring of CMV DNAemia, renal function and evaluation of gastrointestinal adverse effects. In the last years Letermovir has emerged as an alternative prophylactic agent, particularly in high-risk patients or in those with valganciclovir-related myelotoxicity.

Therapeutic use is required in clinically significant infection where oral Valganciclovir is preferred for mild to moderate disease while intravenous Ganciclovir is preferred in severe or invasive disease.

Antiviral resistance is present in 1-5% of cases and must be suspected in case of rising or persistence of CMV DNA despite appropriate dose therapy and adequate compliance. Risk factors for resistance are long-term exposure to low dose antiviral drugs, D+/R- status and high or repeated immunosuppressive treatment. It must be suspected if CMV replication starts during prophylaxis or CMV viremia persists after 6 weeks of treatment. When available it is possible to test for viral genetic mutations that induce drug resistance by inhibiting drug phosphorylation particularly in UL54 and UL97, which codes for two crucial proteins in viral replication.

In confirmed cases of antiviral resistance first is important to reassess immunosuppressive intensity, drug levels and compliance. In confirmed antiviral resistance to first line therapy, alternative agents such as Foscarnet, Cidofovir and Maribavir are available although their use is limited by high nephrotoxicity, elevated cost and availability.

Recent guidelines for CMV management in solid organ transplantation emphasizes a more individualized and risk-adapted approach based on serologic status, immunosuppressive intensity, standardized viral testing, personalized use of new antiviral agents as Letermovir and Maribavir for prophylaxis in patients with risk factors (6).

Although these guidelines provide a comprehensive and personalized framework for CMV management, their implementation in resource-limited setting remains challenging where access to molecular tests, frequent monitoring and use of new antiviral drugs isn't yet fully implemented.

## Methods

This article is a narrative review prepared in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria. PubMed/MEDLINE and Scopus were searched for English-language literature on cytomegalovirus in solid organ and kidney transplantation, combining the terms "cytomegalovirus," "kidney/renal transplantation," "prophylaxis," "pre-emptive therapy," "viral load / PCR monitoring," "antiviral resistance," and "resource-limited settings." Priority

was given to current international consensus guidelines and recent studies, complemented by foundational references identified through citation tracking. Studies were selected and interpreted by the authors by consensus according to their relevance to risk stratification, diagnosis, prevention, treatment, and the feasibility of CMV care in resource-limited kidney transplant programs.

## Clinical Impact of CMV after Kidney Transplantation

CMV burden in kidney transplant remains relevant despite advances in diagnosis, prevention and treatment. The wide spread of clinical manifestation associated with CMV is due to its capability to infect a large variety of cells thanks to a broad spectrum of surface proteins present in the viral envelope.

A key distinction is between CMV infection, which means the presence of viral replication, and CMV disease when viral infection is associated with systemic symptoms or tissue invasive disease. Nonspecific constitutional symptom may present as fever, malaise, fatigue, arthralgia, swollen lymph nodes, tonsillitis, splenomegaly often associated with hematological abnormalities such as leukopenia, thrombocytopenia and mild hepatic enzyme elevation (6,7)

Although tissue-invasive disease may involve nearly every organ system, in kidney transplant recipients, the most frequent clinical manifestation is gastrointestinal involvement. It may present as abdominal pain, dysphagia, diarrhea, vomiting and can be caused by esophagitis, enteritis and/or colitis. Diagnosis often requires endoscopic evaluation with histological confirmation since CMV viremia may be low (6,8).

Other tissue-invasive manifestations are less common but clinically relevant. CMV hepatitis is characterized by elevation in liver enzymes in absence of any other cause. CMV pneumonia may present with fever, cough, respiratory distress associated with ground-glass pattern on CT scan plus CMV detection in bronchoalveolar lavage fluid. Guillain-Barrè syndrome may be the first manifestation of CMV encephalitis and anterior uveitis may also present in late stages. Myocarditis and pericarditis are rare but also potentially severe presentations(6,7). In addition a direct involvement of kidney allograft, also mentioned as CMV nephritis, has been described in the presence of histologic features, mostly as collapsing focal segmental glomerulonephritis, resulting in progressive deterioration of renal function (9,10).

Accordingly, CMV should always be considered whenever aspecific systemic symptoms or organ dysfunction occur in the presence of the rise of active viral replication.

**TABLE 1.** CMV effects and clinical manifestations after kidney transplantation [3–10].

| Effect / category | Clinical features |
|---|---|
| Direct — viremia / CMV syndrome | Asymptomatic viremia; fever, malaise, fatigue, arthralgia, lymphadenopathy, tonsillitis, splenomegaly; leukopenia, thrombocytopenia, mild hepatic enzyme elevation |
| Direct — tissue-invasive, gastrointestinal (most frequent) | Esophagitis, enteritis, colitis: abdominal pain, dysphagia, diarrhea, vomiting; often requires endoscopy with histological confirmation |
| Direct — other organs | Hepatitis; pneumonia (ground-glass pattern + BAL detection); encephalitis (may present as Guillain–Barré); uveitis; myocarditis/pericarditis (rare); CMV nephritis (collapsing FSGS) |
| Indirect (immunomodulatory) | Acute rejection and graft dysfunction; increased risk of other opportunistic infections; EBV-associated PTLD |

## Risk Stratification: Serostatus, Immunosuppression, and Host Factors

Risk stratification represents the first step in CMV management after kidney transplant and should guide the choice between prophylaxis and a pre-emptive approach.

It is based on immunologic status of both donor and recipient, the intensity of immunosuppressive therapy and the presence of secondary host factors such as concomitant transplant or infections.

Immunological status of both donor and recipient represent the strongest predictor of CMV infection and must be defined before kidney transplant through serology in order to assess the risk of transmission and reactivation. The most risky case is when the donor is positive for CMV-IgG while the recipient is negative (D+/R-) as the transplant procedure itself may become a new route of transmission with primary disease in the immediate post-transplant time (6,11).

The overall state of immunosuppression is also an important aspect of risk stratification and relies on type, intensity and frequency of induction and maintenance therapy used during transplant. In induction therapy lymphocytes T depleting agents such as rabbit anti-thymocyte globulin (rAtg) or Alemtuzumab induces a strong and prolonged lymphocyte depletion, thereby increasing susceptibility to CMV complications compared to non-depleting agents such as antiCD25 monoclonal antibody known as Basiliximab(6,12). Long-term maintenance therapy also plays an important role in CMV risk after kidney transplant. Widely used combination of prednisone, calcineurine-inhibitor and Mofetil Mycophenolate may increase susceptibility to CMV replication. Conversely, several evidences suggest that mTOR inhibitors may be associated with a lower risk of CMV infection which may reflect a direct effect on host-cell

pathways resulting in a less permissive environment for CMV replication and a lower impact of these drugs on antiviral cellular immune responses(13,15).

Host-related factors are also important in defining risk stratification. First of all impaired cellular immunity is central to CMV susceptibility therefore older recipient age, comorbidity, frailty, and long dialytic treatment before kidney transplant are considered important contributing factors. Transplant-related factors may also contribute as happens in second/third or multiorgan transplant.

**TABLE 2.** Determinants of CMV risk after kidney transplantation [6,11–15]

| Risk domain | Higher risk | Lower risk |
|---|---|---|
| Donor–recipient serostatus | D+/R− (primary infection via graft) | R+ (pre-existing immunity); D−/R− |
| Induction therapy | Lymphocyte-depleting agents (rATG, alemtuzumab) | Non-depleting agents (basiliximab) |
| Maintenance therapy | Prednisone + calcineurin inhibitor + mycophenolate mofetil | mTOR inhibitor–based regimens |
| Host / transplant factors | Older age, comorbidity, frailty, long pre-transplant dialysis, re-/multi-organ transplant | — |

## Diagnosis and Monitoring: From Guidelines to Real-World Constraints

Diagnosis and monitoring of CMV in kidney transplant is evolving to a multilevel and personalized approach. It is important to distinguish between CMV infection, determined by the presence of CMV viremia without systemic signs or tissue invasive disease and CMV disease characterized by increasing viremia and symptoms/signs of organ involvement.

Gold standard for diagnosis and monitoring is made by real time PCR performed on whole blood or plasma samples; both methods are accepted but they must not be used interchangeably(6,17). Indeed whole blood CMV viremia reflects circulating and intracellular viremia resulting in more sensitive tests; on the other hand plasma viremia may offer greater clinical specificity for active viral replication(6,16). Real time PCR for CMV can be quantitative or qualitative: qualitative assays can just detect the presence of CMV viremia but are unable to differentiate the grade of replication, which is important to predict the risk of CMV disease and response to therapy; consequently quantitative assays are the most diffused test as they can measure viral load distinguishing low from high-level replication allowing treatment to be started promptly when necessary.

The clinical value of quantitative testing, however, depends heavily on the reliability and comparability of viral-load measurements. Until the introduction of Who International Standard for CMV DNA quantification, viral load results were commonly reported in assay-specific units, making comparison across laboratories

highly problematic. In 2010 Who introduced an International standard for CMV DNA quantification, allowing viral-load results to be reported in IU/mL and improving comparability across PCR assays (18,19). Even if Who standardization has reduced results variability different pre-analytic factors influence viral load such as: type of assay, specimen use (whole blood vs plasma), storage conditions, amplification targets, serostatus of both donor and recipient, organ transplanted and type of immunosuppression.

Although these advances in standardization of CMV viral load have improved sensitivity and comparability, no universal CMV viremia cut-off has been established across all transplant settings. Clinically relevant thresholds vary according to analytic and pre-analytic factors mentioned before; therefore most recent guidelines suggest that CMV viremia should still be interpreted using institution-specific thresholds and, more importantly, viral-load kinetics rather than isolated absolute values (6,17,20)..

When a CMV tissue invasive disease is suspected, histologic examination may be needed. Cultural tests for CMV are commonly used but their sensitivity is not ideal because body fluid can contaminate tissue and viral shedding can occur in the absence of clinical disease. For this reason the preferred method is by the identification of CMV inclusions or a positive immunohistochemistry for CMV. This technique is preferred to usual histology because tissue can be contaminated with body fluid and viral shedding can occur from some sites in the absence of clinical disease. However, the absence of viral inclusion does not exclude tissue invasive disease especially in lung, gastrointestinal and retinal involvement where the inclusion detection can be missed.

Viral load assays are also used for monitoring the load during CMV treatment. Since the differences between test type and assays is essential to use the same assay and specimen type to evaluate viral kinetic during treatment.

Although uncommon antiviral resistance is an important complication of CMV disease. It must be suspected in patients who take longer than six weeks to test negative or who show ongoing viral replication during prophylaxis. Risk factors for antiviral resistance include suboptimal or prolonged exposure to antivirals, inadequate dose adjustment based on renal function, D+/R- immune status, lymphopenia, induction therapy based on lymphocyte-depleting agents or repeated rejection treatment.

The latest guidelines distinguish between refractory and resistance to CMV therapy; refractory is when the viral load does not decrease adequately after at least 2 weeks of therapy while resistance requires the demonstration of viral mutations associated with drug resistance. In this setting, mutations generally involve viral genes encoding proteins crucial for viral DNA replication and antiviral drug activation, such as UL97 phosphotransferase, which is mainly associated with ganciclovir/valganciclovir resistance, and, less frequently, UL54 DNA polymerase, which may confer broader cross-resistance to ganciclovir/valganciclovir, cidofovir,

and/or foscarnet. When suspected, genotypic sequencing of viral genes can be performed; testing requires sufficient viral DNA so it results most informative in patients with persistent or clinically significant DNAemi (6,21,22).

Given the complex distinction between CMV infection and disease, the extent organ tropism, the absence of specific clinical manifestations and the risk of recurrence in IgG positive patients CMV diagnosis in transplant recipients relies primarily on quantitative real-time PCR requiring sequential monitoring performed where its reliability depends on sequential monitoring using the same specimen type, assay platform and laboratory, with rapid response in order to allow timely interpretation and appropriate therapeutic decisions.

For these reasons, in resource-limited settings, CMV diagnosis and monitoring in transplant recipients may be very challenging. Updated recommendations are largely based on the availability of real time quantitative PCR, standardized assay platforms, consistent sample processing, and rapid turnaround times. However, in many developing transplant systems these conditions may be difficult to guarantee. Real time quantitative PCR for CMV may be limited by cost, restricted laboratory capacity, delayed reporting, lack of assay harmonization, and fragmented follow-up between transplant centres and peripheral hospitals.

These limitations are especially relevant for pre-emptive strategies, which depend on frequent viral-load monitoring and prompt initiation of therapy when clinically significant DNAemia is detected. The same diagnostic constraints also affect post-treatment and long-termpost-transplant management. After antiviral therapy has been started, serial quantitative PCR is essential to assess virological response, guide treatment duration, detect recurrent CMV DNAemia, and identify patients with refractory or resistant infection.

As a result, clinicians may need to adapt guideline-based recommendations to local resources, combining donor–recipient serostatus, intensity of immunosuppression, clinical presentation, and feasible PCR monitoring schedules. In such settings, improving CMV care requires not only access to antiviral drugs, but also investment in standardized diagnostic pathways, laboratory continuity, and national protocols for post-transplant viral surveillance.

**TABLE 3.** Key diagnostic definitions in CMV after kidney transplantation. Whole blood is more sensitive and plasma more specific; the two are not interchangeable. Use the same specimen, assay and laboratory over time, report in IU/mL (WHO standard) and interpret viral-load kinetics rather than isolated cut-offs [6,16–22].

| Term | Definition |
|---|---|
| CMV infection | Viral replication (viremia) without systemic symptoms or tissue-invasive disease |
| CMV disease | Viremia with systemic symptoms (CMV syndrome) or tissue-invasive organ involvement |
| Refractory | Viral load that does not decrease adequately after at least 2 weeks of appropriate therapy |
| Resistant | Refractoriness with a demonstrated resistance mutation (UL97, less often UL54) |

## Prevention Strategies: Universal and Pre-emptive Approaches

CMV is one of the most clinically relevant opportunistic infections in kidney transplantation due to its extensive seroprevalence in the general population, ability to establish lifelong latency, and strong dependence on T-cell immune control. Under immunosuppression the risk of primary disease or reactivation of CMV after kidney transplant is very high, leading not only to direct viral disease but also to indirect effects on graft function, rejection risk, and susceptibility to other infections. Because CMV is associated with considerable morbidity and mortality and has been identified as a risk factor for rejection in kidney transplant recipients, it is crucial to define a correct prevention strategy in order to reduce CMV burden in this group of patients. Two approaches are generally accepted in post-transplant management: antiviral prophylaxis, which consist in the administration of antiviral drug in the first post-transplant months when immunosuppression is the highest or pre-emptive therapy, which consist in sequential monitoring of viral load with prompt start of therapy if significant increase is detected (6,23,34)

The choice between them depends on several aspects taking into account the patient's related factors such as serological status, net state of immunosuppression, concomitant infection, and local feasibility of virological monitoring. International guidelines do not define one preferred approach except in the case of high risk patients with D+/R- status where antiviral prophylaxis is highly recommended since the risk of a transplant transmitted primary disease is very high and potentially fatal (6,25).

Antiviral prophylaxis is generally started from day 10 to 3-6 months with Valganciclovir as the most common agent while intravenous ganciclovir can be used in severe disease and letermovir as an emerging alternative in patients at risk of myelotoxicity(25,26). Antiviral prophylaxis, however, may be associated with myelotoxicity, gastrointestinal intolerance and neurological symptoms, elevated costs, late-onset CMV after discontinuation, and potential resistance. In the last years Letermovir has emerged as an alternative prophylactic agent, particularly in high-risk patients or in those with valganciclovir-related myelotoxicity, because it inhibits the CMV terminase complex and has a more favourable hematological safety profile(27).

Pre-emptive therapy is based on close monitoring, usually on a weekly basis, of viral kinetics in the first 4-6 months thereby reducing unnecessary drug exposure but requiring strict laboratory and clinical follow-up in order to assure a prompt initiation of therapy if active viral replication is detected. Therefore, CMV prevention represents a dynamic, risk-adapted strategy that integrates virological risk, immunosuppressive burden, drug safety but must be adapted to real-world diagnostic capacity.

**TABLE 4.** Risk stratification and recommended CMV prevention strategy after kidney transplantation. *Additional risk factors: lymphocyte-depleting induction (rATG/alemtuzumab), mycophenolate mofetil–based maintenance, lymphopenia, re-/multi-organ transplant, HIV infection [6,11,12,25].

| Donor–recipient serostatus | Risk | Recommended prevention strategy | Monitoring |
|---|---|---|---|
| D+/R− | Very high | Universal prophylaxis (strongly recommended) | CMV PCR after prophylaxis (late-onset disease) |
| D+/R+ or D−/R+ | Intermediate | Universal prophylaxis or pre-emptive | Weekly CMV PCR for 4–6 months if pre-emptive |
| D−/R− with additional risk factors* | Intermediate | Universal prophylaxis 3–6 months (especially if reliable monitoring is not available) | According to locally available resources |
| D−/R− without additional factors | Low | Pre-emptive | Weekly CMV PCR for 4–6 months |

**TABLE 5.** Universal prophylaxis versus pre-emptive therapy for CMV prevention [6,23–27].

| Feature | Universal prophylaxis | Pre-emptive therapy |
|---|---|---|
| Approach | Antiviral from the early post-transplant period | Monitor viral load; treat on significant rise |
| Typical timing | From day ~10, 3–6 months | Weekly CMV PCR during first 4–6 months |
| Preferred when | High risk (D+/R−) or reliable monitoring not feasible | Lower risk with reliable laboratory follow-up |
| Main agent | Valganciclovir (letermovir if myelotoxicity) | Valganciclovir started on trigger |
| Advantages | Prevents early disease and indirect effects | Less drug exposure and toxicity |
| Limitations | Myelotoxicity, cost, late-onset CMV, resistance | Requires strict laboratory organization and rapid response |

## Treatment, Refractory Disease and Antiviral Toxicity

The treatment of CMV viremia or disease in kidney transplant is based on two major cornerstones: immunosuppressive modulation and antiviral drugs. It should be modulated based on viral load kinetics, severity of clinically symptomatic disease, net state of immunosuppression, graft function and risk of rejection. Asymptomatic viremia, defined as a progressive increase in viral load, is usually targeted for treatment because it can rapidly evolve in CMV syndrome or disease and to prevent its indirect effects on graft and immune system. In this case, if viral load is low, the first step is to modulate immunosuppressive therapy by stopping anti-methabolite (Mofetil Mycophenolate or Azathioprine) followed by close monitoring of viral load in order to assess the need of adding antiviral therapy. Evidence on the long-term impact of antimetabolite discontinuation after asymptomatic CMV viremia remains limited: in a retrospective study of 52

kidney transplant recipients, antimetabolite withdrawal led to CMV clearance in 98% of patients, but 10% subsequently developed biopsy-proven acute rejection, mostly low-grade T-cell-mediated rejection. Since rejection occurred more than one year after discontinuation, causality remains uncertain; therefore, long-term antimetabolite withdrawal cannot currently be routinely recommended and personalized strategy must be assessed.

If the viral load shows rapid increase, or if it persists despite stopping anti-methabolite, antiviral therapy must be started at full dose. The most used agent is oral Valgancyclovir at the dose of 900 mg twice a day which must be continued until viral replication is no longer detectable (28).

In case of symptomatic infection, whether manifested as CMV syndrome or tissue invasive disease both immunosuppressive reduction and start of antiviral treatment must be initiated promptly. In this case, given that CMV symptomatic disease suggests an excessive state of immunosuppression most centres opt for a long-term anti-methabolite suspension; in high risk context of rejection anti-methabolite reinitiation must be balanced and can be restored at low dose after CMV treatment conclusion.

The choice of antiviral therapy is based on initial viral load, severity of illness, adequate gastrointestinal absorption and tolerance of oral therapy. For patients with mild to moderate disease (rapid increase in viral kinetic, CMV syndrome without organ involvement) oral Valganciclovir is preferred as first line agent at the dose of 900 mg twice daily, adjusted for renal function as it is better tolerated and avoid hospitalization and need for central venous access. In a trial of more than 300 solid organ recipients with mild/moderate CMV disease oral Valganciclovir resulted comparable to intravenous Ganciclovir in viraemia eradication and treatment success(28).

In case of severe manifestation with tissue invasive disease, intravenous Ganciclovir at 5 mg/kg twice daily is the treatment of choice with possible transition to oral Valganciclovir after clinical improvement (6,28).

Treatment duration is typically 21 days but it depends on severity and is guided by clinical and virological courses. Generally antiviral therapy is continued until symptoms resolvation and viral replication become undetectable .

In some cases there is a persistence or progression of CMV infection despite correct reduction of immunosuppressive therapy and appropriate and tolerated antiviral treatment. If after six weeks of treatment there is no clear viral response refractory or drug resistance must be suspected. In this case resistance mutations can be confirmed by genotypic sequencing of viral genes giving a useful tool in selecting second line agents.

There are three available agents approved for CMV disease with confirmed resistance but their use must be guided by disease severity, resistance mutations, kidney function and drug availability. Foscarnet, an intravenous pyrophosphate

analogue that inhibits CMV DNA polymerase,is active against UL 54 and UL97 mutations. Its use is limited by elevated nephrotoxicity requiring intense intravenous hydration and close monitoring of renal function and electrolytes during administration. Cidofovir, another viral DNA polymerase inhibitor, is highly nephrotoxic. It results active against UL97 mutations but generally not against UL54. Its use is limited by marked nephrotoxicity and possible uveitis, making a latter- line option(6,21,29). At least Maribavir has emerged as an important option for refractory or resistant CMV infection, particularly because it avoids Ganciclovir related myelotoxicity and Foscarnet/Cidofovir nephrotoxicity but its use is limited in mild to moderate disease (30,31).

In selected complex cases, treatment may also require further reduction of immunosuppression, by stopping corticosteroid and lowering calcineurin-inhibitor, resistance-guided antiviral switching, and, where available, adjunctive strategies such as CMV-specific immunoglobulin or adoptive T-cell therapy.

**TABLE 6.** Treatment of CMV by clinical scenario. *Adjusted for renal function; duration is typically about 21 days and is guided by clinical and virological response until viremia is undetectable [6,28].

| Clinical scenario | First step | Antiviral agent | Dose / route |
|---|---|---|---|
| Asymptomatic viremia, low load | Stop antimetabolite; monitor load | Add antiviral only if load rises | — |
| Mild–moderate / CMV syndrome | Reduce immunosuppression + antiviral | Valganciclovir (oral) | 900 mg twice daily* |
| Severe / tissue-invasive disease | Reduce immunosuppression + antiviral | Ganciclovir (intravenous) | 5 mg/kg twice daily* |
| Refractory / resistant | Reassess dose, adherence, immunosuppression; genotype UL97/UL54 | Maribavir / foscarnet / cidofovir | Per mutation and renal function |

**TABLE 7.** Antiviral agents used in CMV prophylaxis and treatment. UL54 mutations may confer cross-resistance to ganciclovir/valganciclovir, cidofovir, and/or foscarnet [6,21,27,29,30].

| Agent | Mechanism / target | Main use | Key toxicity / limitation |
|---|---|---|---|
| Valganciclovir (oral) | Ganciclovir prodrug; UL97-dependent activation | Prophylaxis; mild–moderate treatment | Myelotoxicity, gastrointestinal intolerance |
| Ganciclovir (IV) | DNA polymerase inhibitor (UL54) | Severe / tissue-invasive disease | Myelotoxicity |
| Letermovir | CMV terminase complex inhibitor | Prophylaxis (especially myelotoxicity risk) | Limited treatment data; drug interactions |
| Foscarnet | Pyrophosphate analogue (UL54, UL97) | Resistant disease | Nephrotoxicity, electrolyte disturbance |
| Cidofovir | DNA polymerase inhibitor | Resistant disease (later-line) | Marked nephrotoxicity, uveitis |
| Maribavir | UL97 kinase inhibitor | Refractory / resistant CMV | Limited to mild–moderate disease; dysgeusia |

## CMV Management in Resource-Limited Settings

Numerous evidences along the years confirmed that kidney transplant resulted superior to hemodialysis in terms of patient and graft survival and quality of life. According to that, numerous transplant programmes in low and middle income countries, where chronic kidney disease is even higher, have started. Unfortunately many diagnostic, follow up and treatment tools, necessary to ensure a proper long-term follow-up of post transplant complications, are missing.

As mentioned, CMV represents a wide spread and complex opportunistic infection in kidney transplant due to its elevated organ tropism, aspecific clinical manifestations, immuno-modulatory capability and risk for antiviral resistance-gaining mutations. These characteristics make CMV management particularly challenging in a limited-resources context.

While current guidelines emphasize risk stratification, repeated quantitative PCR monitoring, timely antiviral therapy and resistance testing when needed, these components may be difficult to implement consistently in developing transplant systems (35).

Limited access to regular CMV quantitative PCR, delayed laboratory turnaround, assay variability, high costs of antivirals, and restricted availability of second-line agents may compromise both prevention and treatment strategies. In this context, CMV care should be based on a structured but feasible approach that prioritizes donor–recipient serostatus, intensity of immunosuppression, clinical risk factors, and locally available monitoring schedules. Universal prophylaxis may be favored when reliable pre-emptive surveillance cannot be ensured, whereas pre-emptive therapy requires strong laboratory organization and rapid clinical response. Standardization of national diagnostic pathways, use of the same specimen type and laboratory over time, careful adjustment of antiviral dosing, and early recognition of refractory or recurrent infection are essential to improve outcomes(6,23,24,32). Therefore, in resource-limited settings, effective CMV management depends not only on applying guideline-based recommendations, but also on building sustainable systems for post-transplant surveillance, laboratory harmonization, and equitable access to antiviral treatment (35).

Beyond CMV, other viral complications of kidney transplantation — such as parvovirus B19, a frequently under-recognized cause of severe, erythropoietin-resistant anemia — may be particularly difficult to detect and to treat with the most current diagnostic and therapeutic tools in resource-limited settings, where a high index of clinical suspicion and a tailored, multidisciplinary approach remain essential (34).

**TABLE 8.** Adapting guideline recommendations to resource-limited settings [6,23,24,32].

| Guideline standard | Feasible adaptation in resource-limited settings |
|---|---|
| Frequent real-time quantitative PCR monitoring | Favor universal prophylaxis when reliable surveillance cannot be ensured |
| Standardized assay platforms, IU/mL reporting | Use the same specimen type and laboratory over time |
| Rapid turnaround enabling pre-emptive therapy | Risk-prioritized, simplified monitoring schedules |
| Genotypic resistance testing | Clinical reassessment of dose, adherence and immuno-suppression first |
| Access to newer antivirals (letermovir, maribavir) | Careful antiviral dosing; standardized national diagnostic pathways |

## A Practical Risk-Based Algorithm for Kidney Transplant Programs

A practical risk-based algorithm for CMV disease in kidney transplant programs should integrate immunological risk, net immunosuppression status, comorbidities, diagnostic feasibility and therapeutic availability. The first step is to define the pre-transplant immunological status in order to identify low to high risk patients based on CMV serology of both donor and recipient. Second is crucial to define the presence of additional risk factors such as use of lymphocyte-depleting agents, Mofetil Mycophenolate based maintenance therapy, profound or persistent lymphopenia, previous or concomitant transplant, HIV infection.

If low risk patient (e.g. D-/R- without additional risk factors) pre-emptive therapy can be adopted, in the other cases a 3 to 6 months universal prophylaxis is generally considered acceptable even in a limited-resources setting where access to sequential molecular monitoring may be difficult.

If available, real time quantitative PCR should be performed using the same specimen type, assay platform, and laboratory whenever possible, avoiding isolated decisions based on non-standardized cut-offs. In patients with persistent, recurrent, or rising CMV DNAemia despite appropriate treatment, the algorithm should include reassessment of antiviral dosing, adherence, gastrointestinal absorption, immunosuppressive intensity, and possible resistance testing. In resource-limited settings, such an algorithm should remain simple, reproducible, and adaptable, prioritizing high-risk patients for closer surveillance while promoting standardized national pathways for prevention, diagnosis, treatment, and long-term post-transplant monitoring.

**FIGURE 1.** Practical risk-based algorithm for CMV management in kidney transplant programs, integrating donor–recipient serostatus, net state of immunosuppression, diagnostic feasibility and treatment of refractory or resistant disease.


*D, donor; R, recipient; MMF, mycophenolate mofetil; PCR, polymerase chain reaction; GI, gastrointestinal.*

## Conclusions

CMV remains a major challenge after kidney transplantation because of its direct viral effects, indirect impact on graft outcomes, and strong relationship with the net state of immunosuppression. Although recent guidelines provide a more standardized and risk-adapted framework, their application may be difficult in resource-limited settings, where access to quantitative PCR, rapid reporting, antiviral drugs and resistance testing is not always guaranteed. For this reason, CMV management should be adapted to local resources. Pre-transplant donor–recipient serostatus, induction therapy, maintenance immunosuppression and host-related factors should guide prevention and monitoring strategies. Universal prophylaxis may be preferred in high-risk patients or when strict PCR surveillance is not feasible, while pre-emptive therapy requires reliable and repeated viral-load monitoring.In resource-limited transplant programs, a simple and reproducible risk-based algorithm may help prioritize high-risk patients, standardize follow-up, ensure timely treatment and reduce unnecessary antiviral exposure. Therefore, effective CMV care should combine guideline-based recommendations with feasible local pathways for diagnosis, monitoring and treatment.

## Declarations

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# *Leishmaniasis from a Laboratory Perspective*

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## Abstract

*Visceral leishmaniasis is a severe infectious disease caused by Leishmania spp., characterized by a strong host immune response and significant hematological abnormalities. Clinically, the disease presents with prolonged fever, splenomegaly, severe anemia, pancytopenia, and hypergammaglobulinemia, and delayed diagnosis may worsen patient outcomes. This retrospective descriptive study included 23 patients with confirmed visceral leishmaniasis admitted between January 2022 and March 2023 to the Infectious Diseases Service and the Pediatric Infectious Diseases Service at the Mother Teresa University Hospital Center in Tirana. Demographic characteristics, clinical manifestations, and laboratory parameters—including hematological indices, inflammatory markers, biochemical tests, and bone marrow examination—were collected and analyzed. The disease was more frequent in the pediatric population, with most affected children under 5 years of age, while the mean age among adults was 48 years. HIV–Leishmania coinfection was identified in three patients. Anemia was present in all cases and was frequently associated with neutropenia and thrombocytopenia. Bone marrow examination confirmed the presence of the parasite in all evaluated samples, supporting its role as the diagnostic gold standard. Additional laboratory abnormalities included changes in inflammatory markers, liver enzyme levels, and the albumin–globulin ratio. The correlation of laboratory findings with clinical manifestations may facilitate earlier suspicion and diagnosis of visceral leishmaniasis, particularly in non-specialized centers, enabling timely confirmation and management of the disease.*

***Keywords:*** *Visceral leishmaniasis; laboratory findings; anemia; splenomegaly; bone marrow examination.*

## Introduction

Leishmaniasis is a vector-borne zoonotic disease caused by protozoan parasites of the genus *Leishmania*. Once considered primarily a disease of parasitological and veterinary importance, it has become a major global public health concern due to climate change, increasing human mobility, urbanization, and the growing number of immunocompromised individuals. Laboratory investigations play a central role in diagnosis, monitoring, and therapeutic management, particularly through parasitological, serological, and molecular methods, together with the evaluation of characteristic hematological abnormalities and their correlation with clinical findings. (1–4)

The disease has been recognized since antiquity, but the causative parasite was identified independently by Sir William Boog Leishman and Charles Donovan in 1903. Subsequent studies established the role of *Leishmania* species, domestic dogs as the principal reservoir in zoonotic visceral leishmaniasis, and sandflies of the genus *Phlebotomus* as the main vectors responsible for transmission in the Mediterranean region. (4,7–10)

Globally, approximately one billion people live in endemic areas, with transmission reported in nearly 100 countries across five continents. An estimated 700,000–1,000,000 new cases occur annually, including approximately 50,000–90,000 cases of visceral leishmaniasis, the most severe clinical form, which remains associated with substantial morbidity and mortality if left untreated. The highest burden is observed in the Americas, East Africa, the Mediterranean basin, the Middle East, and South Asia. (2,7–10)

Albania is an endemic country for zoonotic visceral leishmaniasis caused by *Leishmania infantum*. Since the first reported cases in 1937, several epidemiological studies have confirmed the persistent circulation of the disease. Between 1998 and 2004, 815 cases of visceral leishmaniasis were reported, predominantly in the districts of Shkodër, Lezhë, Kukës, Krujë, Tirana, Librazhd, and Gjirokastër. More recent surveillance data indicate approximately 20–30 new cases annually, confirming the continued endemicity of the disease in Albania. (2,5,6)

Leishmaniasis is classified as a metazoonosis because transmission occurs through the bite of infected female sandflies. The parasite exists in two morphological forms: the extracellular promastigote within the sandfly vector and the intracellular amastigote, which survives and multiplies inside macrophages of the vertebrate host. Following inoculation, promastigotes are rapidly phagocytosed by macrophages, transform into amastigotes, and proliferate within phagolysosomes, resulting in persistent intracellular infection. In the Mediterranean region, *Phlebotomus* species are the principal vectors, whereas dogs constitute the main reservoir of infection. (4,7,9,15)

Three major clinical forms are recognized: cutaneous, mucocutaneous, and visceral leishmaniasis. Visceral leishmaniasis typically presents with prolonged fever, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia. In children, the disease may initially mimic hematological malignancies, making laboratory confirmation essential for establishing the diagnosis. (7,10–12,21)

The host immune response plays a fundamental role in disease progression. Protective immunity is predominantly mediated by Th1-associated cytokines, including IFN-γ, IL-2, TNF-α, and IL-12, whereas Th2-mediated responses characterized by IL-4, IL-5, IL-6, and IL-10 promote parasite persistence and chronic infection. Persistent intracellular survival of *Leishmania* contributes to immune dysregulation, hypergammaglobulinemia, immune complex formation, and varying degrees of immunosuppression. (22,26,27)

Laboratory diagnosis of visceral leishmaniasis relies on both direct and indirect methods. Direct diagnosis includes microscopic demonstration of amastigotes in bone marrow, splenic, or other tissue aspirates stained with May–Grünwald–Giemsa, as well as molecular techniques such as polymerase chain reaction (PCR), which provide high sensitivity and permit species identification and parasite load assessment. Indirect diagnosis is based on serological methods, including ELISA, indirect immunofluorescence, direct agglutination tests, and rapid rK39 immunochromatographic assays. (12–20)

Routine laboratory investigations commonly reveal normocytic normochromic anemia, leukopenia, thrombocytopenia, hypoalbuminemia, hypergammaglobulinemia, and markedly elevated erythrocyte sedimentation rate. Although these findings are nonspecific, they frequently raise clinical suspicion and prompt definitive parasitological or molecular confirmation. (17–22)

## Aim of the Study

The aim of this study was to identify the principal laboratory findings in patients with visceral leishmaniasis and to evaluate their correlation with the clinical presentation, including the main signs and symptoms of the disease.

## Study Objectives

1. To evaluate hematological, biochemical, and inflammatory laboratory parameters in patients diagnosed with visceral leishmaniasis.
2. To analyze the relationship between laboratory abnormalities and clinical manifestations of the disease.
3. To assess the role of laboratory findings in supporting early diagnosis of visceral leishmaniasis.
4. To examine the evolution of the disease during the acute phase and following therapy, based on clinical and laboratory indicators.

## Materials and Methods

This retrospective descriptive study included 23 patients with a confirmed diagnosis of visceral leishmaniasis who were admitted between January 2022 and March 2023 to the Infectious Diseases Service and the Pediatric Infectious Diseases Service at the Mother Teresa University Hospital Center, Tirana.

Clinical records were reviewed, and demographic, clinical, and laboratory data were systematically collected and analyzed. The following variables were evaluated:

- **Demographic characteristics:** age, sex, place of residence, and confirmed diagnosis.
- **Laboratory parameters:** hematological indices including red blood cell count (RBC), hemoglobin (Hb), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC); leukocyte differential count; platelet count; and additional laboratory tests including ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen, creatinine, and bone marrow examination (myelogram).
- **Clinical findings:** presence of high fever, splenomegaly, hepatomegaly, skin changes, asthenia, and cough.

Information regarding HIV status was also collected to identify possible HIV–Leishmania coinfection among the study participants.

The study was conducted in accordance with the principles of the Declaration of Helsinki. Patient data were anonymized prior to analysis, and confidentiality was maintained throughout the study. Approval was obtained from the institutional ethics committee according to local regulations.

## Results

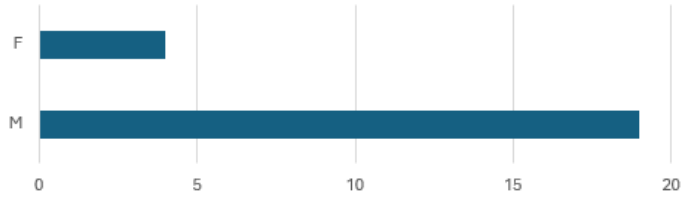
A total of 23 patients with confirmed visceral leishmaniasis were included in this study, of whom three were HIV-positive. Four pacients were female and nineteen were male. Fourteen patients were younger than 10 years of age, while nine were between 11 and 55 years old. All patients were hospitalized at the Mother Teresa University Hospital Center, Tirana, during the period January 2022 to March 2023. Patients were recruited from multiple regions of Albania, and no specific geographic area showed a higher incidence. Specifically, 3 patients were residents of Krujë, 2 from Shkodër, 2 from Fier, and 1 patient each from Gjirokastër, Burrel, Lezhë, Vlorë, and Durrës, while the remaining patients resided in Tirana.

**TABLE 1.** Age

| Age | Number of Patients |
|---|---|
| 0-4 years old | 12 |
| 5-10 years old | 3 |
| 11-55 years old | 8 |

Children younger than 4 years represented the most affected age group. The study identified a particularly high incidence among children under 2 years of age, with 7 recorded cases.

**FIGURE 1.** Distribution of Cases by Sex




Among our patients, males showed a higher prevalence of disease, accounting for approximately 70% of the cases.

**FIGURE 2.** Confirmed Diagnosis

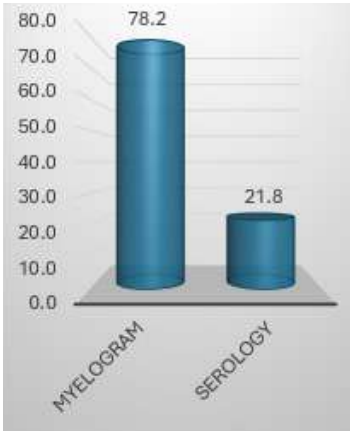
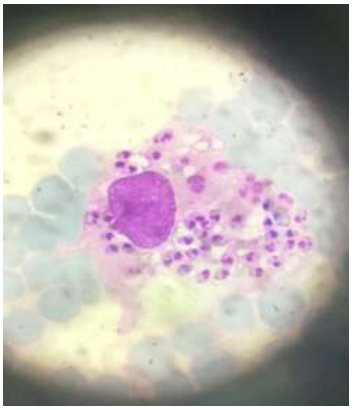



**FIGURE 3.** *Leishmania* in Bone Marrow



Of the 23 patients, 78.2% had their diagnosis confirmed through identification of *Leishmania* parasites on bone marrow examination (myelogram), where the organisms were observed in both intracellular and extracellular forms. The remaining patients had the diagnosis confirmed by *Leishmania* IgG serology.

Among the 23 patients with confirmed parasitic infection, clinical signs and symptoms consistent with this pathology were observed. The onset and evolution of clinical manifestations were assessed from the time of initial hospital admission. All patients presented with high fever, which in most cases persisted for more than 10 days and did not respond to antipyretic or antibiotic therapy. The majority reported weakness, asthenia, and myoarthralgia, while some experienced weight loss. Pallor was commonly observed, affecting both the skin and mucous membranes. No cases of other cutaneous lesions, such as erosions or nodules, were recorded. Less frequent and atypical symptoms included dry cough, although it was not possible to determine whether it was attributable to other underlying conditions. Vomiting and diarrhea were present in a small number of patients, particularly in the pediatric group. On physical examination, splenomegaly was detected in 100% of cases and confirmed by abdominal ultrasound, while hepatomegaly was present in 95% of patients. No hemorrhagic manifestations or edema were observed in our cohort.

It is noteworthy that approximately 59% of patients had experienced these symptoms within the previous 30 days, while a considerable proportion reported symptom onset within the last three months.

All laboratory investigations were performed at the Department of Laboratories of the Mother Teresa University Hospital Center. In the 23 patients with confirmed leishmaniasis, laboratory findings revealed alterations related to the inflammatory state as well as evidence of organ and tissue involvement. The presence of the parasite was demonstrated in patients' myelograms. Significant hematological abnormalities were observed, including anemia, deviations in the leukocyte differential count, and thrombocytopenia.

The biochemical parameters evaluated in this study, which showed significant alterations and correlation with the clinical presentation of these patients, include:

- Transaminases: In our study, most patients showed mildly elevated values, generally up to 100 IU/L, which is common in patients with visceral leishmaniasis. Seventeen patients had increased ALT and AST levels, with mean values of approximately 67.7 IU/L for ALT and 56.7 IU/L for AST. Transaminase levels exceeded 100 IU/L in only four cases, while two patients had normal values.
- Urea and Creatinine: Seven patients demonstrated reduced levels of urea and creatinine, with mean values of approximately 7.9 mg/dL and 0.3 mg/dL, respectively. These findings appeared closely related to the severity

of anemia, as well as to the patients' general condition, weight loss, and malnutrition.

- Lactate Dehydrogenase (LDH): Elevated LDH levels were observed in 13 patients. The mean value was 439.5 U/L, with a maximum recorded value of 747 U/L. The remaining patients had normal or minimally elevated values.
- Inflammatory Markers: 1.**C-reactive protein (CRP):** CRP levels were elevated in all patients ,ranging from 1.50 mg/dL to 20.72 mg/dL. 2. **White blood cell count (WBC):** WBC levels were reduced in almost all cases, except for one patient with normal values and one HIV-positive patient who showed leukocytosis (17.9 K/μL).
- Total Proteins: Normal reference values range from 6.0 to 8.04 g/dL. Results showed that total protein levels were generally within the normal range. However, all patients exhibited decreased albumin levels, accompanied by hyperglobulinemia. Protein electrophoresis performed in eight patients demonstrated reversal of the albumin/globulin ratio, with a mean A/G ratio of 0.82. Gamma-globulin levels increased to 19–29% of total proteins in five cases and to 30–35% in three cases. In several patients, elevations in α1- and α2-globulins were also observed.
- Complete Blood Count Analysis

The principal laboratory abnormalities observed in the complete blood count of our 23 patients were:

- Anemia
- Microcytic, hypochromic erythrocytes
- Thrombocytopenia
- Leukopenia (not present in all cases)
- Neutropenia
- Lymphocytosis
- Monocytosis
- Left shift of the leukocyte differential count

Marked alterations in these parameters were observed in all patients.

In the six patients in whom reticulocyte counts were measured, values ranged from 11% to 44%.

**TABLE 2.** Characteristics of Red Blood Cells

| | N | Minimum | Maximum | Mean | Normal Reference Range |
|---|---|---|---|---|---|
| MCV | 23 | 56.0 | 97.3 | 74.81 | 80-100 fL |
| MCH | 23 | 18.4 | 28.5 | 23.5 | 26-34 pg |

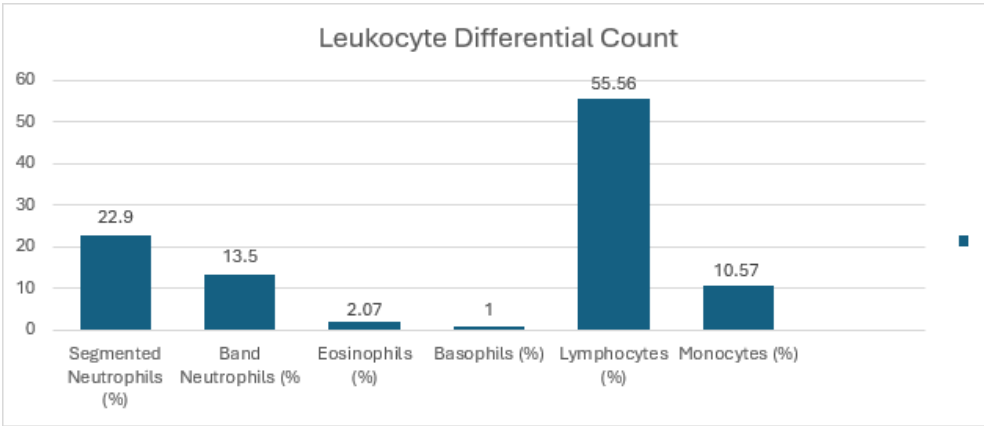
| | | | | | |
|---|---|---|---|---|---|
| MCHC | 23 | 28 | 35.50 | 31.00 | 31-35.5 g/dl |
| HCT | 23 | 20.3 | 36.8 | 26.6 | 35-55 % |
| RBC | 23 | $2.54x10^6$ | $4.6x10^6$ | $3.03x10^6$ | $4\text{-}5*10^6$ µL |

The table above summarizes the data regarding both the quantity and morphological characteristics of erythrocytes in these patients. As observed, the mean red blood cell count was reduced, reaching markedly low minimum values in some cases. On average, the cells did not consistently show reduced MCV, although microcytosis was noted in certain cases. Overall, most cases demonstrated hypochromic erythrocytes, with mean MCH and MCHC values below the normal range.

**TABLE 3.** Hemoglobin

| Severity of Anemia Hemoglobina (g/dl) | Number of Patients |
|---|---|
| I (12.8 - 9.6) | 7 |
| II (9.5 – 6.4) | 12 |
| III (6.3 – 3.2) | 4 |
| IV (<3.2) | 0 |

Anemia was consistently present and was evidenced by reduced mean hemoglobin values. As shown in the table above, 12 patients had hemoglobin levels below 9.5 g/dL, and 4 of them were classified as having severe (grade III) anemia, with hemoglobin values below 6.3 g/dL.




Another peripheral blood alteration characterizing these patients was leukopenia. The mean white blood cell (WBC) count was below the reference range in 17 patients. In one HIV-positive patient, the WBC count was elevated, while in five patients leukocyte counts remained within normal limits. In addition

to leukopenia, changes were observed in the leukocyte differential count. Overall, a reduction in the percentage of neutrophils was noted, with a mean value of 22.9%, along with an increased proportion of immature neutrophils, with a mean value of approximately 13.5%. No significant changes were observed in basophils or eosinophils. Lymphocyte levels were elevated, with a mean value of 55.56%. Platelet counts were below the normal range in 100% of the cases included in the study. The majority of patients (approximately 73%) had platelet counts between 100,000 and 150,000/mm³, followed by 20.3% of cases with counts ranging from 30,000 to 100,000/mm³. A small proportion of patients presented with platelet counts below 30,000/mm³.

## Bone Marrow Examination (Myelogram)

**TABLE 4.** Interpretation of the Myelogram

| | |
|---|---|
| Leishmania Present<br>Leishmania Absent | 17<br>0 |
| Myeloid to Erythroid Ratio (M/E) | 1/1 to 3,5/1 |
| Plasma Cells > 5 %<br>5-10 %<br>> 10 % | 17<br>0<br>0 |
| Megakaryocytic Series Present<br>Rare<br>Absent | 13<br>2<br>2 |

As observed from the bone marrow examinations of our patients, the presence of the parasite was identified in all smears, both extracellularly and intracellularly. The granulocytic-to-erythroid (M:E) ratio was preserved in nearly all patients. Plasma cells were present at levels below 5% in all cases. The megakaryocytic lineage was absent in two patients, while in the majority it was present at all stages of maturation. No abnormal cells were detected.

As highlighted above, the clinical presentation was characterized by prolonged high fever. Fever reflects an underlying pathological state, which in this case is caused by the presence of the parasite. By correlating the detection of *Leishmania* during the early stages of hospitalization—when persistent high fever was observed—with the markedly reduced blood cell counts indicating a longstanding infection, it can be inferred that fever correlates with the parasitic burden in these patients. Monocytosis, immune system hyperactivity, and hyperglobulinemia—present in nearly 100% of cases—further support the conclusion that the elevated temperature is also a consequence of these immunological changes.

The pronounced anemia observed in all patients correlated with their general condition and clinical manifestations, including pallor, weakness, fatigue, and overall poor health status.

As indicated by the epidemiology of the disease, leishmaniasis remains endemic and represents an ongoing health concern in our country. Delays in diagnosis and treatment worsen patients' conditions, leading to more severe clinical manifestations and significant laboratory abnormalities.

In our setting, all cases are confirmed at the Mother Teresa University Hospital Center, which may create logistical challenges and delays for patients living in regions distant from Tirana. The implementation of a standardized clinicopathological protocol could help minimize diagnostic delays, thereby reducing the morbidity and mortality associated with the disease.

## Discussion

Visceral leishmaniasis remains an important public health concern in endemic Mediterranean countries, including Albania. The findings of the present study are consistent with the classical clinical and laboratory profile of visceral leishmaniasis reported in previous studies [13,14]. Anemia, leukopenia, thrombocytopenia, and splenomegaly were the most common findings observed in our cohort, reflecting the combined effects of bone marrow involvement, hypersplenism, and chronic inflammation [6,7,13].

The predominance of pediatric cases, particularly among children younger than five years of age, is in accordance with the epidemiological pattern reported in Mediterranean countries, where *Leishmania infantum* is the principal causative species [8,20]. Previous Albanian studies have similarly demonstrated a higher incidence among young children, confirming the continued importance of visceral leishmaniasis in this vulnerable population [4,8].

The hematological abnormalities observed in our study are consistent with the known pathophysiology of the disease. Anemia, leukopenia, and thrombocytopenia are primarily related to bone marrow involvement, splenic sequestration, and chronic inflammatory processes [6,13,14]. The universal presence of anemia in our cohort highlights its importance as a key laboratory finding and supports consideration of visceral leishmaniasis in patients presenting with prolonged fever and unexplained cytopenias in endemic areas [7,21].

Hypoalbuminemia, hypergammaglobulinemia, and elevated inflammatory markers were common findings among our patients and reflect chronic immune activation induced by persistent parasitic infection [14,25] These laboratory abnormalities are well-recognized features of visceral leishmaniasis and may provide important diagnostic clues, particularly when associated with splenomegaly and hematological abnormalities [13,25].

Bone marrow examination demonstrated high diagnostic value and confirmed infection in the majority of patients. Although serological and molecular methods have become increasingly available, direct visualization of amastigotes remains a reliable diagnostic approach, particularly in patients presenting with prolonged fever, splenomegaly, and cytopenias [18,19,22].

Several limitations should be acknowledged. First, the retrospective design restricted data collection to information available in medical records. Second, the relatively small sample size may limit the generalizability of the findings. Nevertheless, this study provides valuable data regarding the clinical and laboratory characteristics of visceral leishmaniasis in Albania and highlights the importance of laboratory findings in facilitating early diagnosis and timely treatment.

## Conclusions

Visceral leishmaniasis continues to represent a significant diagnostic challenge in endemic regions. In our cohort, anemia, thrombocytopenia, leukopenia, splenomegaly, hypoalbuminemia, and hypergammaglobulinemia were the most consistent clinical and laboratory findings. Bone marrow examination remained a reliable method for confirming the diagnosis. Recognition of these characteristic laboratory abnormalities may facilitate earlier clinical suspicion, prompt diagnostic investigation, and timely treatment, thereby reducing disease-related morbidity and improving patient outcomes. Strengthening awareness of the laboratory profile of visceral leishmaniasis is particularly important in non-specialized healthcare settings.

## Declarations

**Ethics approval and consent:** This retrospective study was conducted in accordance with the Declaration of Helsinki. Data were obtained from routine clinical records and analysed anonymously.

**Conflicts of interest:** The authors declare no competing interests.

**Funding:** The authors received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Author contributions:** All authors contributed to the study conception and design, data collection and interpretation, and drafting and critical revision of the manuscript, and approved the final version.

**Data availability:** The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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# *Extreme Nephrotic-Range Proteinuria in Mixed Lupus Nephritis with Low Histologic Activity: Potential Contribution of Obesity-Related Hyperfiltration in a Triple Autoimmune Overlap Syndrome*

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## Abstract

***Background:*** *Mixed lupus nephritis (LN), combining proliferative and membranous lesions, is frequently associated with substantial proteinuria and increased risk of kidney injury. However, the occurrence of massive nephrotic-range proteinuria despite minimal histologic activity, persistently negative anti-double stranded DNA (anti-dsDNA) antibodies, and preserved serum creatinine represents an uncommon diagnostic challenge. The coexistence of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis (PsA) in a single patient is exceptionally rare and further complicates disease assessment and management.*

***Case Presentation:*** *We report a 39-year-old man with an 18-year history of triple autoimmune overlap syndrome (SLE, RA, and PsA) who presented with severe nephrotic-range proteinuria (10.7 g/24 h), urinary albumin-to-creatinine ratio (UACR) of 23,538 mg/g, hypoalbuminemia, persistent hypocomplementemia, pancytopenia, and severe obesity BMI 39.2 kg/m². Despite preserved serum creatinine (0.8 mg/dL), measured creatinine clearance was markedly elevated at 216 mL/min, consistent with extreme glomerular hyperfiltration. Serological evaluation demonstrated positive antinuclear antibodies (ANA) but persistently negative anti-dsDNA antibodies. Kidney biopsy revealed mixed lupus nephritis Class III+V according to the 2018 ISN/RPS classification, with full-house immunofluorescence, a low activity index (2/24), and minimal chronicity (0–1). The marked discrepancy between massive proteinuria and limited histologic activity raised the possibility that obesity-related hyperfiltration contributed to urinary protein losses in addition to immune-complex-mediated renal injury. Following treatment with pulse methylprednisolone, mycophenolate mofetil, hydroxychloroquine, and supportive nephroprotective therapy, the patient achieved substantial clinical and biochemical improvement. After nine months of follow-up, proteinuria decreased to 3.8 g/24 h, UACR declined to 238 mg/g, serum albumin improved to the lower limit of normal, and complement levels normalized, while body weight remained unchanged.*

***Conclusion:*** *This case highlights three important clinical messages. First, active lupus nephritis may occur despite persistently negative anti-dsDNA antibodies. Second, severe nephrotic-range proteinuria may be observed in mixed Class III+V lupus nephritis even when histologic activity appears limited. Third, obesity-related glomerular hyperfiltration may amplify proteinuria and contribute to clinicopathological discordance. The marked renal improvement despite unchanged body weight suggests that lupus nephritis represented the principal pathological process, whereas hyperfiltration acted as an important disease modifier. Kidney*

*biopsy remains indispensable for diagnosis and therapeutic decision-making in complex autoimmune overlap syndromes.*

***Keywords:*** *lupus nephritis; mixed lupus nephritis; overlap syndrome; systemic lupus erythematosus; rheumatoid arthritis; psoriatic arthritis; nephrotic syndrome; glomerular hyperfiltration; obesity-related kidney disease; mycophenolate mofetil.*

## Introduction

Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE), affecting approximately 40–60% of patients and representing a major cause of chronic kidney disease and kidney failure [1,2]. The revised 2018 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification recognizes mixed forms of LN in which proliferative lesions (Class III or IV) coexist with membranous involvement (Class V), a histological pattern frequently associated with substantial proteinuria and distinct therapeutic implications [3,4].

Although anti-double stranded DNA (anti-dsDNA) antibodies and complement levels are widely used as markers of disease activity, the correlation between serological findings and renal histopathology is often imperfect. A substantial proportion of patients with biopsy-proven lupus nephritis may present with negative anti-dsDNA antibodies, particularly in longstanding disease or membranous-predominant forms, highlighting the indispensable role of kidney biopsy in diagnosis and treatment decisions [1,5]. Furthermore, the relationship between urinary protein excretion and histological activity is not always linear, particularly in mixed proliferative–membranous disease and in the presence of additional hemodynamic stressors.

The coexistence of multiple autoimmune rheumatic diseases further complicates disease assessment and management. Overlap syndromes involving SLE and rheumatoid arthritis (RA), commonly referred to as "Rhupus syndrome," are uncommon, whereas the simultaneous presence of SLE, RA, and psoriatic arthritis (PsA) has only rarely been described in the literature [6–8]. In such patients, clinical manifestations, serological markers, and therapeutic responses may differ substantially from classical disease patterns.

Obesity has emerged as an important modifier of kidney disease. Severe obesity may induce glomerular hyperfiltration through increased intraglomerular pressure, activation of the renin–angiotensin–aldosterone system, and altered tubuloglomerular feedback [9]. Persistent hyperfiltration may amplify urinary protein losses and obscure clinicopathological correlations in glomerular disease [10].

We report a patient with an exceptionally rare triple autoimmune overlap syndrome (SLE, RA, and PsA) who developed biopsy-proven mixed lupus nephritis Class III+V presenting with massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and marked obesity-related glomerular hyperfiltration. The case highlights the diagnostic value of kidney biopsy and suggests that obesity-associated hyperfiltration may have amplified urinary protein losses and contributed to the apparent discrepancy between extreme proteinuria and limited histologic activity.

## Case Presentation

A 39-year-old Albanian man was referred to the Department of Nephrology, University Hospital Center "Mother Teresa" (QSUNT), Tirana, for evaluation of newly detected nephrotic-range proteinuria in the setting of longstanding autoimmune disease.

The patient had been diagnosed with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in 2007 and subsequently fulfilled diagnostic criteria for psoriatic arthritis (PsA), establishing a rare triple autoimmune overlap syndrome. His long-term treatment included glucocorticoids, hydroxychloroquine, non-steroidal anti-inflammatory drugs, and antihypertensive therapy. At presentation, he had severe obesity, with a body weight of 128 kg and BMI 39.2 kg/m2.

Three weeks before admission, he developed progressive fatigue, photosensitivity, facial erythema, scalp desquamation, periorbital edema, xerostomia, polyuria, and worsening constitutional symptoms. Physical examination confirmed obesity, facial erythema, and bilateral periorbital edema. Blood pressure was 130/75 mmHg.

**Figure 1.** Cutaneous manifestations at presentation.

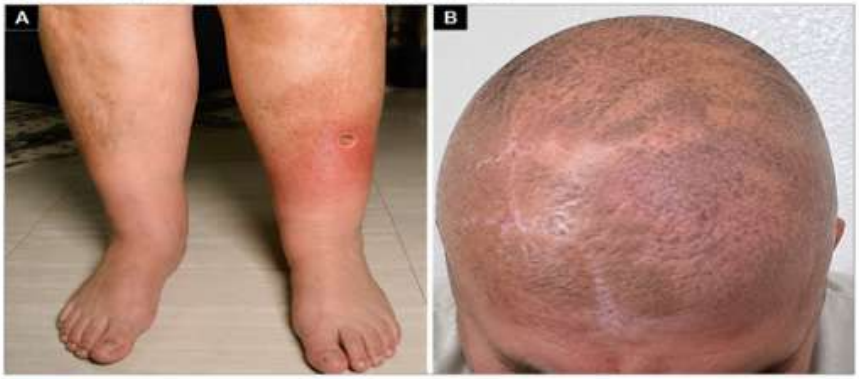


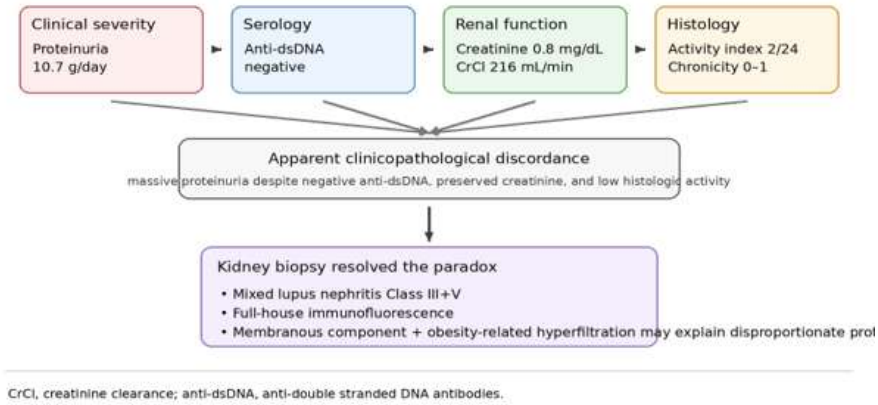

**Figure 1.** Cutaneous manifestations at presentation. (A) Pretibial ulcerative lesion with surrounding erythema and chronic skin changes of the lower extremity. (B) Chronic scalp lesion showing patchy hypopigmentation, alopecic changes, and cutaneous atrophy.

Initial laboratory evaluation revealed nephrotic-range proteinuria of 10.7 g/24 h and a urinary albumin-to-creatinine ratio (UACR) of 23,538 mg/g. Additional findings included hypoalbuminemia, normocytic anemia, thrombocytopenia, and marked hypocomplementemia (C3 34 mg/dL, C4 5.5 mg/dL). Antinuclear antibodies (ANA) were positive, whereas anti-double stranded DNA (anti-dsDNA) antibodies remained negative. Serum creatinine was preserved at 0.8 mg/dL; however, measured creatinine clearance reached 216 mL/min, indicating marked glomerular hyperfiltration

The coexistence of massive nephrotic-range proteinuria, preserved serum creatinine, persistently negative anti-dsDNA antibodies, and marked hyperfiltration represented a significant diagnostic challenge. Therefore, a kidney biopsy was performed.

Histopathological examination demonstrated mixed lupus nephritis Class III+V according to the 2018 ISN/RPS classification. Immunofluorescence revealed a characteristic full-house pattern with deposition of IgG, IgA, IgM, C3, and C1q. The modified NIH activity index was low (2/24), while chronicity was minimal (0–1), indicating limited inflammatory and chronic damage despite extensive urinary protein loss.

**FIGURE 2.** Diagnostic paradox at presentation.




Despite massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and marked glomerular hyperfiltration, kidney biopsy demonstrated mixed lupus nephritis Class III+V and resolved the apparent clinicopathological discordance. CrCl, creatinine clearance; anti-dsDNA, anti-double stranded DNA antibodies.

Supportive nephroprotective therapy with losartan and dapagliflozin was initiated. Following exclusion of active infection, induction immunosuppression was started with intravenous methylprednisolone pulses followed by mycophenolate mofetil. Hydroxychloroquine was continued throughout treatment.

The patient demonstrated progressive clinical and biochemical improvement during follow-up. Nine months after treatment initiation, 24-hour proteinuria had decreased from 10.7 g/day to 3.8 g/day, while UACR declined from 23,538 mg/g to 238 mg/g. Serum albumin improved to the lower limit of the normal range, complement levels (C3 and C4) normalized, and anti-dsDNA antibodies remained negative. ANA positivity persisted. Despite substantial improvement in renal and serological parameters, body weight remained unchanged at approximately 128 kg throughout follow-up and BMI 39.2 kg/m².

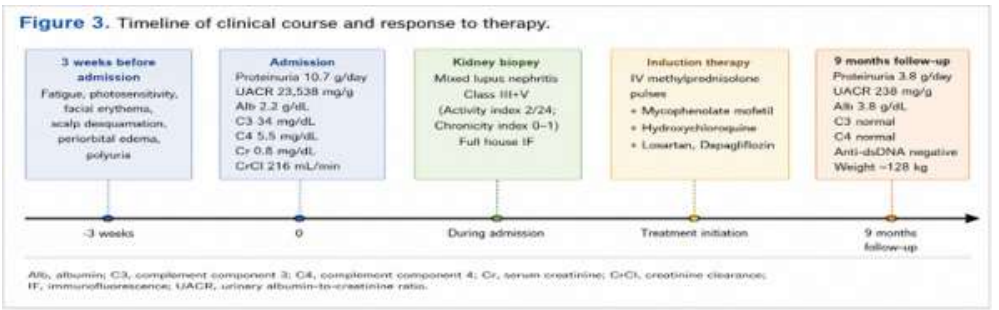
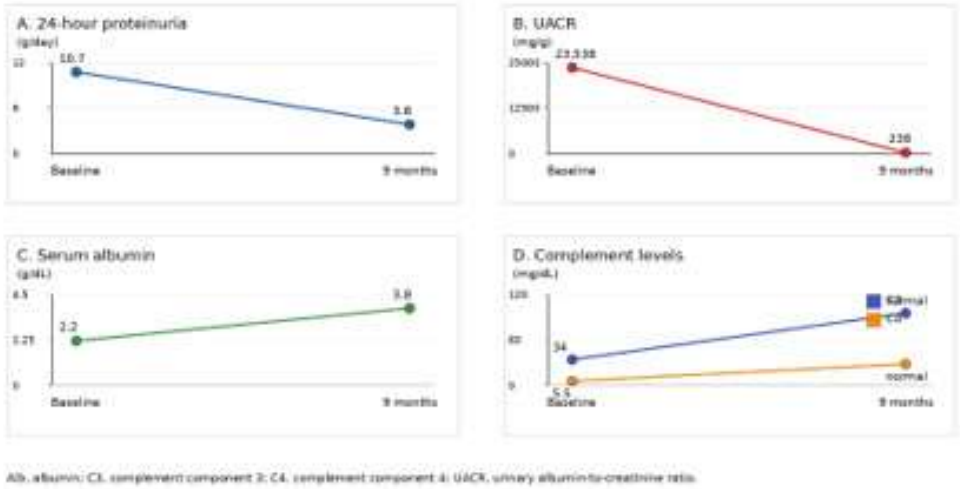



**FIGURE 4.** Trend of key laboratory parameters during follow-up. Changes in (A) 24-hour proteinuria, (B) urinary albumin-to-creatinine ratio (UACR), (C) serum albumin concentration, and (D) complement levels (C3 and C4) between baseline and 9-month follow-up. Marked improvement in proteinuria, albuminuria, hypoalbuminemia, and complement consumption was observed following immunosuppressive and nephroprotective therapy.




Alb, albumin; C3, complement component 3; C4, complement component 4; UACR, urinary albumin-to-creatinine ratio.

## Discussion

This case illustrates the complex interplay between autoimmune disease, renal pathology, and metabolic factors in a patient with an exceptionally rare triple overlap syndrome comprising systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and psoriatic arthritis (PsA). While overlap between SLE and RA ("Rhupus syndrome") has been increasingly recognized, the coexistence of SLE, RA, and PsA remains exceedingly uncommon and has been described only in isolated reports [6–8]. The simultaneous presence of three autoimmune diseases may generate atypical clinical and serological presentations, complicating diagnostic and therapeutic decision-making. In our patient, nephrotic-range proteinuria represented the first major renal manifestation after nearly two decades of systemic autoimmune disease.

An important feature of this case was the discordance between serological findings and renal histopathology. Despite biopsy-proven lupus nephritis, anti-dsDNA antibodies remained persistently negative throughout the disease course. Although anti-dsDNA antibodies are commonly used as biomarkers of disease activity, their sensitivity for active lupus nephritis is limited, particularly in membranous-predominant disease and in patients receiving chronic immunosuppressive therapy [1,5,11–13]. In contrast, our patient exhibited profound hypocomplementemia at presentation, with markedly reduced C3 and C4 levels that normalized following treatment. This evolution suggests that complement consumption reflected ongoing immune-complex activity more accurately than anti-dsDNA antibodies in this setting. The case therefore reinforces a fundamental principle of lupus nephritis management: serological quiescence does not exclude active renal disease, and kidney biopsy remains essential whenever clinical suspicion persists [3,5,12,13].

In the present case, the coexistence of massive nephrotic-range proteinuria, persistently negative anti-dsDNA antibodies, preserved serum creatinine, and a low histologic activity index created a diagnostic paradox that was ultimately resolved by kidney biopsy. Despite urinary protein excretion of 10.7 g/day, histopathology demonstrated a low activity index (2/24) and minimal chronicity (0–1). At first glance, this degree of proteinuria appeared disproportionate to the biopsy findings. However, the identification of mixed lupus nephritis Class III+V provides a biologically plausible explanation for this apparent discordance. Membranous lupus nephritis is characterized by subepithelial immune-complex deposition and podocyte injury and may produce severe nephrotic syndrome even in the absence of extensive proliferative lesions [4,14,15]. Consequently, the severity of proteinuria and the degree of histological activity do not necessarily correlate

linearly, particularly in mixed proliferative–membranous disease. Importantly, the substantial reduction in proteinuria from 10.7 g/day to 3.8 g/day following immunosuppressive therapy, together with normalization of complement levels and improvement in serum albumin, supports the biological and clinical relevance of the lupus nephritis despite the low activity index observed on biopsy.

A second mechanism may have contributed to the unusually severe proteinuria observed in this patient. At presentation, serum creatinine was normal (0.8 mg/dL), yet measured creatinine clearance reached 216 mL/min, indicating extreme glomerular hyperfiltration. Obesity-related glomerular hyperfiltration is a recognized consequence of severe obesity and results from increased renal plasma flow, activation of the renin–angiotensin–aldosterone system, hyperinsulinemia, and elevated intraglomerular pressure [9,10,16–18]. Persistent hyperfiltration increases mechanical stress on the glomerular filtration barrier and may enhance protein trafficking across damaged glomerular capillary walls [10,16,17]. Although obesity-related glomerulopathy was not demonstrated histologically in our patient, the extraordinary degree of hyperfiltration raises the possibility that obesity acted as a hemodynamic amplifier of proteinuria. We hypothesize that the coexistence of membranous lupus nephritis and severe obesity-related hyperfiltration contributed to the apparent mismatch between extreme urinary protein losses and the limited inflammatory activity observed histologically.

The patient's subsequent clinical evolution further supports this interpretation. Following induction therapy with methylprednisolone and mycophenolate mofetil, combined with hydroxychloroquine and nephroprotective treatment, proteinuria declined from 10.7 g/day to 3.8 g/day, while UACR decreased from 23,538 mg/g to 238 mg/g. Serum albumin improved to the lower limit of the normal range, complement levels normalized, and anti-dsDNA antibodies remained negative. Notably, these improvements occurred despite unchanged body weight of approximately 128 kg throughout follow-up. While lupus nephritis represented the primary pathological process, the patient's marked obesity and extreme glomerular hyperfiltration may have amplified urinary protein losses. Although obesity-related glomerulopathy was not demonstrated histologically, the measured creatinine clearance of 216 mL/min suggests a substantial hyperfiltration state that may have contributed to the apparent discrepancy between nephrotic-range proteinuria and the low histologic activity index observed on kidney biopsy. The case therefore highlights the importance of integrating clinical, serological, metabolic, and histopathological information rather than relying on any single parameter in isolation.

Current KDIGO 2024 and EULAR 2025 recommendations emphasize the importance of early diagnosis, kidney biopsy, hydroxychloroquine therapy, renin–angiotensin system blockade, and timely initiation of immunosuppressive treatment in patients with active lupus nephritis [2,5,19,20]. In the present case,

kidney biopsy proved crucial for establishing the diagnosis despite persistently negative anti-dsDNA antibodies and preserved serum creatinine. Conventional therapy with glucocorticoids and mycophenolate mofetil resulted in substantial clinical and renal improvement, supporting its continued effectiveness in appropriately selected patients, particularly in resource-limited settings.

In conclusion, this case highlights three clinically relevant messages. First, active lupus nephritis may occur despite persistently negative anti-dsDNA antibodies. Second, massive proteinuria may develop in mixed Class III+V lupus nephritis even when histologic activity appears limited. Third, severe obesity-related glomerular hyperfiltration may amplify urinary protein losses and contribute to clinicopathological discordance, thereby obscuring the relationship between proteinuria and histological activity. Recognition of these interacting mechanisms may facilitate earlier diagnosis and more individualized management in complex autoimmune overlap syndromes.

**Informed Consent**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying clinical data and images.

**Conflict of Interest**

The authors declare no conflict of interest.

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# *Artificial Intelligence in Polypharmacy: Moving Beyond Drug Alerts Toward Patient-Specific Medication Safety*

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## Abstract

*Polypharmacy is an increasing challenge in modern clinical practice, particularly among older adults and patients with multimorbidity, chronic kidney disease, heart failure, diabetes, frailty, or cognitive impairment. Its clinical impact extends beyond the number of prescribed medicines and reflects the interaction between therapeutic burden, comorbidities, organ dysfunction, fragmented care, changing physiological reserve, and multiple prescribers.*

*Traditional medication review remains essential but may be limited by incomplete medication histories, time constraints, fragmented records, and the difficulty of identifying clinically meaningful drug–drug, drug–disease, and drug–patient interactions. Artificial intelligence (AI) may support safer medication management by integrating prescribing data with diagnoses, laboratory values, clinical events, and patterns of healthcare use. Potential applications include medication reconciliation, prioritization of clinically relevant interactions, renal dose adjustment, adverse drug event prediction, recognition of prescribing cascades, and identification of patients most likely to benefit from structured medication review or deprescribing.*

*However, the value of AI in polypharmacy management should not be measured by the number of alerts generated. Its most useful role may be to help clinicians distinguish theoretical medication-related risks from those that are likely to be clinically important for an individual patient. This requires transparent recommendations, reliable data, local validation, integration into clinical workflow, and clear professional accountability.*

*This narrative clinical viewpoint discusses the opportunities, limitations, and ethical implications of AI in polypharmacy management. It argues that AI should function as a human-centered clinical decision-support tool that improves prioritization, supports multidisciplinary medication review, and preserves clinician-led and patient-centered prescribing decisions.*

***Keywords:*** *Artificial Intelligence; Polypharmacy; Medication Safety; Clinical Decision Support; Deprescribing; Patient-Specific Risk Stratification*

## Introduction

Polypharmacy is an increasingly common challenge in contemporary clinical practice, particularly among older adults and patients with multimorbidity, chronic kidney disease, heart failure, diabetes, frailty, or cognitive impairment. Although it is commonly defined as the concurrent use of five or more medications,

its clinical relevance extends beyond medication count. The central question is whether the overall treatment regimen remains appropriate, coordinated, and safe as the patient's health status, organ function, and therapeutic priorities change [1,2].

Medication-related harm is often difficult to recognize because it may arise from the interaction between multiple drugs, comorbidities, laboratory abnormalities, fragmented prescribing, and transitions of care. Clinicians must simultaneously consider drug–drug and drug–disease interactions, renal and hepatic function, therapeutic duplication, prescribing cascades, adherence, and patient preferences. In routine practice, this process may be limited by incomplete medication histories, time constraints, and information dispersed across different healthcare settings [3,4].

Artificial intelligence (AI) offers a potential opportunity to support safer medication management. By integrating prescribing data with diagnoses, laboratory values, clinical events, and patterns of healthcare use, AI-based systems may help identify medication-related risk, prioritize patients for review, detect clinically relevant interactions, support dose adjustment, and highlight opportunities for deprescribing [5,6].

However, AI should not be viewed as a substitute for clinical judgment. Its value depends on reliable data, transparent recommendations, local validation, and integration into real clinical workflows. This narrative clinical viewpoint examines the emerging role of AI in polypharmacy management, with particular focus on medication reconciliation, interaction prioritization, renal dose adjustment, adverse drug event prediction, and deprescribing support. It argues that the principal value of AI is not to generate more medication alerts, but to help clinicians identify which alerts are most likely to be clinically meaningful for the individual patient.

## *Literature scope and approach*

This narrative review and clinical viewpoint was informed by selected literature on polypharmacy, medication safety, medication reconciliation, clinical decision support systems, artificial intelligence, and deprescribing. Priority was given to systematic reviews, scoping reviews, international guidance documents, and recent studies describing clinically relevant applications of artificial intelligence in medication safety. The objective was not to provide a systematic evidence synthesis, but to critically discuss how artificial intelligence may support patient-specific prioritization of medication-related risk in routine clinical practice.

## Polypharmacy as a Complex Clinical and Digital Challenge

Polypharmacy is not only a prescribing challenge; it is also a problem of information integration across time, care settings, and clinicians. In patients with multimorbidity, each medicine may be appropriate when assessed in isolation. However, when multiple disease-specific recommendations are applied simultaneously, often by different prescribers, the overall regimen may become difficult to interpret as a whole [2,3].

This complexity is dynamic rather than static. Renal function may decline, acute illness may alter drug tolerance, new medicines may be added during hospitalization, and treatments initiated for short-term indications may remain active after the original clinical context has changed. A regimen that appears appropriate drug by drug may therefore become unsafe when considered in relation to the patient's full therapeutic burden, physiological reserve, and current goals of care [3,4].

Medication-related harm frequently emerges during transitions of care, particularly at hospital admission and discharge. At these points, discrepancies may arise between prescribed, documented, and actually taken medicines, including therapeutic duplication, omitted medicines, unintended continuation of discontinued therapies, and incorrect doses. Structured medication reconciliation, particularly when supported by pharmacists, can help identify and resolve clinically relevant discrepancies during these vulnerable transitions [3,7].

Traditional medication review remains essential, but it is often constrained by incomplete medication histories, fragmented electronic records, limited consultation time, and multiple prescribers. Drug–drug and drug-disease interactions, therapeutic duplications, renal dose issues, and prescribing cascades may therefore be missed, particularly in patients with high medication burden or rapidly changing clinical status [3,5,6].

For this reason, polypharmacy should also be understood as a digital challenge. The problem is not simply that clinicians receive too much information; it is that clinically relevant information is often distributed across different records, institutions, laboratory systems, discharge documents, and patient-reported histories. Digital tools may help organize this information, but their usefulness depends on whether they can distinguish clinically important risk from background noise [8,9].

The central clinical question is therefore not whether an interaction exists in theory, but whether a specific medication combination is likely to cause harm in the current patient, at the current moment, and within the patient's broader therapeutic priorities.

## Where Artificial Intelligence Can Add Value in Medication Safety

Artificial intelligence may support medication safety by helping clinicians process and prioritize information that is difficult to review manually in patients with complex therapeutic regimens. Its potential value is not limited to detecting whether a drug interaction exists, but to identifying which medication-related concerns may be most clinically relevant in a specific patient and at a specific moment of care [5,6].

One important application is medication reconciliation. AI-supported systems may compare medication information across outpatient records, hospital admissions, discharge summaries, pharmacy data, and specialist prescriptions. This may help identify duplicated therapies, recent dose changes, discontinued medicines that remain active in the record, and discrepancies between prescribed and actual treatment. More importantly, predictive models may help prioritize patients most likely to have clinically relevant discrepancies, directing pharmacist and clinician time toward those at highest risk rather than applying the same level of review to every patient [10,11].

AI may also improve the detection and prioritization of drug–drug and drug–disease interactions by incorporating patient-specific factors such as age, kidney function, liver function, laboratory abnormalities, frailty, recent acute illness, and concurrent medication burden. This may be more clinically useful than conventional rule-based alerts, which often identify theoretical interactions without distinguishing between low-risk warnings and situations likely to cause clinically meaningful harm [6,8].

Another promising area is dynamic monitoring of renal dose adjustment and adverse drug event risk. By integrating estimated glomerular filtration rate trends, creatinine values, potassium levels, glucose measurements, blood pressure, and medication exposure, AI-based tools may help identify patients at increased risk of drug accumulation, hyperkalemia, bleeding, hypoglycemia, hypotension, sedation, or acute kidney injury. However, these models should be viewed as risk-stratification tools rather than diagnostic systems: a prediction of increased risk does not establish causality, nor does it replace clinical assessment of volume status, acute illness, competing diagnoses, or treatment urgency [6,12].

AI may also assist in recognizing prescribing cascades and prioritizing deprescribing. Patients with recurrent falls, cognitive impairment, high anticholinergic burden, repeated hospitalizations, chronic kidney disease, or multiple prescribers may benefit from targeted medication review. In this context, AI may help identify patients or medication combinations that warrant closer attention, while the final decision regarding continuation, dose reduction,

substitution, or discontinuation remains clinician-led and based on expected benefit, prognosis, symptom burden, and patient preferences [5,13].

The practical value of AI will therefore depend on whether its recommendations are understandable, actionable, and integrated into clinical workflow. Systems that merely generate additional warnings may increase workload and alert fatigue. Systems that help clinicians prioritize meaningful risks, identify patients most likely to benefit from review, and explain why action may be needed are more likely to contribute to safer medication management.

**TABLE 1.** Potential applications of artificial intelligence in polypharmacy management.

| Clinical task | Potential AI-supported function | Potential clinical value | Key limitation | Clinician role |
|---|---|---|---|---|
| Medication reconciliation | Compare medication lists across hospital, outpatient, pharmacy, and specialist records | Detect discrepancies, duplicated therapies, omitted medicines, and recent changes | Incomplete or inaccurate records may produce misleading results | Confirm the actual medication regimen with the patient, caregivers, and available documentation |
| Drug–drug and drug–disease interactions | Identify and prioritize interactions using patient-specific data | Focus attention on interactions most likely to cause harm | Risk of false-positive alerts and alert fatigue | Assess clinical relevance, indication, severity, and alternatives |
| Renal dose adjustment | Integrate eGFR trends, creatinine, potassium, and medication exposure | Identify possible accumulation, hyperkalemia, hypotension, or nephrotoxicity | Laboratory values may not reflect rapidly changing clinical status | Interpret results alongside volume status, acute illness, and treatment urgency |
| Adverse drug event prediction | Recognize patterns associated with bleeding, falls, hypoglycemia, delirium, acute kidney injury, or sedation | Prioritize high-risk patients for medication review | Prediction does not establish causality | Evaluate competing diagnoses and confirm medication-related contribution |
| Prescribing cascades and therapeutic duplication | Detect temporal links between medication initiation, symptoms, diagnoses, and additional prescriptions | Identify potentially avoidable medication burden | Requires accurate longitudinal prescribing data | Decide whether symptoms represent an adverse effect, new disease, or both |
| Deprescribing prioritization | Identify patients with high medication burden, frailty, recurrent admissions, CKD, or high-risk medication combinations | Direct structured review toward patients most likely to benefit | Algorithms cannot determine patient goals or acceptable trade-offs | Lead shared decision-making and determine whether deprescribing is appropriate |

Note. AI, artificial intelligence; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

## From Alerts to Human-Centered Clinical Decision Support

Early digital medication-safety systems were largely based on rule-based alerts for drug interactions, duplicate therapies, contraindications, or dose-related concerns. Although these systems may improve awareness, their usefulness is often limited by insufficient clinical context. A technically correct alert may have little relevance for a specific patient, while an important medication-related risk may be missed when it depends on the combined effect of frailty, laboratory trends, acute illness, medication timing, organ dysfunction, and multiple comorbidities [8,14].

This limitation contributes to alert fatigue. When clinicians receive frequent, non-specific, or low-priority warnings, important alerts may be ignored, overridden, or delayed. The challenge is therefore not simply to generate more notifications, but to improve their relevance, timing, interpretability, and capacity to support a practical clinical response [15,16].

AI may help shift medication safety from generic alert generation toward patient-specific risk stratification. Rather than only identifying that two medicines may interact, an AI-supported system may help estimate whether that interaction is likely to be clinically important in the current patient. For example, the relevance of a potential interaction may depend on age, renal function, electrolyte disturbances, blood pressure, recent hospitalization, history of falls, frailty, or cumulative exposure to high-risk medicines [8,13].

A clinically useful system should also distinguish between different levels of urgency. Some situations may require immediate action, such as a high-risk medication combination in the setting of acute kidney injury, severe hyperkalemia, active bleeding, recurrent hypoglycemia, bradycardia, or excessive sedation. Other situations may require closer monitoring, dose adjustment, pharmacist review, medication reconciliation, or discussion at a subsequent outpatient visit. AI should support this prioritization, not replace the clinical evaluation needed to determine urgency and appropriate action [17].

However, AI-supported medication review should not be confused with automated prescribing. Algorithms may identify patterns, estimate risk, and highlight medication-related concerns, but clinicians must still assess indication, expected benefit, prognosis, functional status, symptom burden, treatment alternatives, and patient priorities. A recommendation to stop, reduce, or substitute a medicine may be technically reasonable yet clinically inappropriate if it disregards the patient's therapeutic goals or the risks of changing treatment.

The most valuable role of AI is therefore to make medication review more structured, selective, and clinically meaningful. It should reduce cognitive overload by helping clinicians identify which patients require urgent attention, which medication-related questions deserve closer review, and why a particular risk may matter for that individual patient [18].

## Risks, Ethics, and Human Oversight

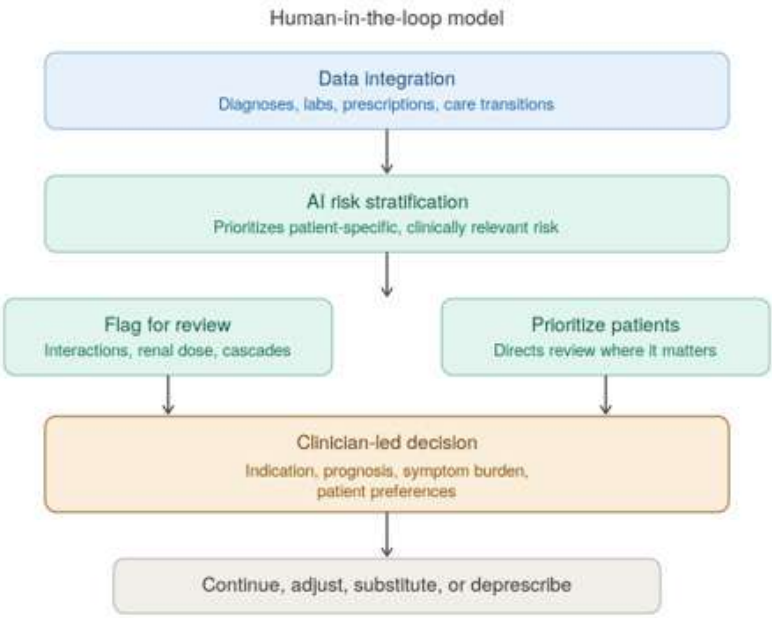
Despite its potential benefits, AI in polypharmacy management should be introduced cautiously. Algorithms depend on the quality, completeness, and timeliness of the data they receive. Missing information about over-the-counter medications, herbal products, adherence, recent dose changes, functional status, or patient preferences may substantially reduce the reliability of automated recommendations [3,5].

Algorithmic bias is another important concern. AI systems are often developed using data from specific populations and healthcare settings. If older adults, patients with frailty, chronic kidney disease, multimorbidity, or limited access to care are underrepresented, algorithmic recommendations may be less reliable precisely in the populations most vulnerable to medication-related harm. Local validation across relevant clinical settings is therefore essential before widespread implementation [19,20].

Explainability is equally important. Clinicians need to understand why a patient has been identified as high risk: for example, because of declining kidney function, cumulative sedative burden, laboratory abnormalities, therapeutic duplication, or a recent hospitalization, or a combination of these factors. Systems that provide transparent and clinically interpretable explanations are more likely to support safe decisions than opaque tools that generate unexplained recommendations [21,22].

AI must therefore operate within a human-in-the-loop model. It may identify patterns, estimate risk, and prioritize patients for review, but it cannot determine treatment goals or replace professional judgment. Decisions about deprescribing, dose reduction, treatment continuation, or therapeutic substitution require consideration of prognosis, symptom burden, expected benefit, patient preferences, family support, and the potential risk of therapeutic change [23,24].

**FIGURE 1.** The human-in-the-loop model of artificial intelligence in polypharmacy management. AI integrates clinical data and performs risk stratification to flag and prioritize patients for review, but the final therapeutic decision remains clinician-led and patient-centered.




Privacy and accountability must also be addressed. AI-supported medication review requires access to sensitive information, including diagnoses, laboratory data, prescribing history, care transitions, and sometimes patient-reported information. Health systems need secure data governance, clear standards for validation and monitoring, and explicit professional responsibility for decisions influenced by algorithmic recommendations [20,24].

The goal is not automated prescribing. It is intelligent clinical support that helps clinicians identify who needs closer medication review, which medication-related risks deserve attention first, and when a recommendation should be reconsidered in light of individual patient's circumstances.

## Implications for Clinical Practice and Health Systems

The successful integration of AI into polypharmacy management will require more than new software. Its usefulness depends on accurate medication lists, interoperable electronic health records, timely laboratory data, reliable documentation of care transitions, and clear communication between primary care, hospitals, pharmacies, and specialist services [6,25].

AI tools should be integrated into the clinical moments when medication decisions are already made: hospital admission, discharge, emergency assessment, chronic disease follow-up, pharmacy review, and multidisciplinary case discussions. Systems that require clinicians to open separate platforms, manually re-enter data, or interpret poorly explained risk scores are unlikely to be used consistently in routine practice [25,26].

Implementation should be gradual and clinically driven. In settings with limited digital infrastructure, the first priority is not advanced predictive modelling but the creation of reliable foundations for medication safety: structured medication reconciliation, accurate electronic medication lists, basic interaction screening, standardized monitoring of high-risk therapies, and clear documentation of renal function and other clinically relevant laboratory values. These steps may provide immediate safety benefits and create the data quality needed for more advanced AI-supported tools in the future [3,6].

A practical AI-supported medication-safety pathway should focus on identifying patients who require closer review rather than replacing routine clinical judgment. Patients with chronic kidney disease, recurrent falls, frailty, cognitive impairment, repeated hospital admissions, high anticholinergic burden, multiple prescribers, or high-risk medication combinations may be prioritized for multidisciplinary review. The final assessment should involve physicians, pharmacists, nurses, and, whenever possible, patients and caregivers.

Healthcare professionals also need training in the interpretation of AI-generated recommendations. Physicians, nurses, pharmacists, and clinical pharmacologists should understand what information an algorithm uses, how a risk score is generated, when a recommendation may be unreliable, and when clinical judgment should override an automated suggestion. Training should include communication with patients, especially when a medication is reduced, stopped, or changed on the basis of a structured medication review [27].

The relevant question is therefore not whether an algorithm can identify a theoretical interaction. It is whether AI can help prevent avoidable harm, reduce unnecessary medication burden, improve coordination across care settings, and support prescribing that remains aligned with the needs and priorities of the individual patient.

## Conclusion

Polypharmacy is a complex medication-safety challenge that cannot be addressed by medication count alone. It reflects the interaction between multimorbidity, changing physiological reserve, organ dysfunction, fragmented care, therapeutic burden, and the growing volume of clinical information that must be interpreted across different settings.

Artificial intelligence may support safer medication management by helping reconcile medication lists, identify clinically relevant interactions, recognize high-risk patterns, support renal dose adjustment, and prioritize patients for structured medication review or deprescribing. Its greatest value is unlikely to come from generating a greater number of alerts, but from improving the prioritization, timing, and clinical interpretation of medication-related risk.

However, AI is not a substitute for clinical judgment. Safe implementation requires accurate and complete data, transparent and explainable recommendations, local validation, secure data governance, and integration into real clinical workflows. Decisions about prescribing, deprescribing, and therapeutic priorities must remain clinician-led, multidisciplinary, and aligned with the patient's goals, preferences, and expected benefit.

When used within a human-in-the-loop model, artificial intelligence may help transform polypharmacy management into a more proactive, individualized, and safer component of modern clinical care. The aim is not automated prescribing, but better-informed clinical decisions for the patients most vulnerable to medication-related harm.

The future of AI in polypharmacy should not be judged by how many drug alerts it can generate, but by whether it helps clinicians recognize the right medication-related risk, in the right patient, at the right time.

**Conflict of Interest**

The authors declare no conflict of interest.

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# *From Pain to Diagnosis: Somatic Presentations of Anxiety and Depression in Albanian Adults*

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## Abstract

*This study explores the prevalence of, and relationships among, somatic symptoms, depressive symptoms, anxiety symptoms, and general help-seeking behaviors in the Albanian context. A cross-sectional quantitative design was employed using convenience and snowball sampling, involving 181 adult participants (116 women and 65 men). Data were collected through the standardized instruments PHQ-15, PHQ-9, GAD-7, and GHSQ. The results revealed significant associations between psychological and somatic symptoms, no significant differences across gender and age groups, and a strong orientation towards informal sources of help-seeking. Depressive and anxiety symptoms emerged as stronger predictors of help-seeking behavior than somatic symptoms or demographic factors such as gender and age. These findings highlight the need for a stronger integration of mental health services into primary healthcare in Albania.*

## Introduction

To the present day, the integration of psychological well-being into primary healthcare has remained limited, particularly in the Albanian context, where the Semashko model has historically predominated, focusing primarily on physical illnesses. The transition of the 1990s toward a less centralized system, combined with economic difficulties, led to the prioritization of emergency services and the neglect of the psychological dimension [38,20]. However, the literature emphasizes that quality care requires the integration of the health triad—physical, social, and psychological—reflecting the close link between physical symptoms and psychological disorders[12; 13]. Within this framework, somatic symptoms represent one of the most common ways in which psychological distress presents in primary care, characterized by physical complaints that often cannot be fully explained and are associated with biological, psychological, and sociocultural factors[32; 7; 30].

In contemporary diagnostics, somatization is included within the category of Somatic Symptom Disorder (SSD), which emphasizes cognitive, emotional, and behavioral reactions to bodily symptoms and their impact on everyday functioning. Epidemiological studies indicate a considerable prevalence of these disorders (approximately 4.6%), with higher rates among women[1; 6; 19]. The literature also highlights the prevalence of somatic symptoms among younger age groups and in high-stress contexts, where such symptoms often serve as a means of expressing emotional distress, particularly in cultures that discourage the direct expression of emotions[30, 35]. In primary care, patients with depression or anxiety often initially

present with physical complaints, whereas somatization may function as a defense mechanism and is associated with increased use of healthcare services and delayed diagnosis[30; 41].

The significance of this study lies in its contribution to a deeper understanding of the conjunction between somatic symptoms, depression, and anxiety, particularly in primary healthcare settings, where patients most commonly present with physical complaints. As somatic symptoms often conceal underlying psychological disorders, this study highlights the role that depressive and anxiety symptoms play in how somatization is experienced and intensified, thereby helping reduce the risk of misdiagnosis and fragmented care.

**The goal** of this study is to explore the relationship between somatic symptoms, depressive symptoms, and anxiety symptoms among the Albanian population, taking into consideration the impact of these symptoms on daily functioning and health-related help-seeking behavior. The study aims to provide a deeper understanding of somatization as a biopsychosocial phenomenon by analyzing the interconnection between bodily symptomatology and affective and emotional components, as well as the role that demographic and sociocultural factors may play in the presentation and subjective experience of somatic symptoms.

## *Somatization as a psychological phenomenon*

Somatic symptoms do not constitute a specific disease but rather a mode of presentation of an underlying pathology, often one that cannot be fully explained through traditional physiological assessments. It was not until the late 17th century that psychological factors began to be considered a possible cause of somatization[42]. These symptoms are closely linked to brain functioning and unprocessed emotional states and are interpreted as a means through which the body expresses psychological distress. Within this framework, somatization is defined as the tendency to experience and communicate psychological distress through physical symptoms and to seek medical help for those symptoms[32], while diagnostically it is characterized by an excessive focus on physical symptoms and disproportionate cognitive, emotional, and behavioral responses to them[2]. The literature distinguishes between two main forms of somatization: presentational somatization, in which symptoms serve as an expression of emotional concerns, and functional somatization, in which symptoms remain medically unexplained and persist over time[14].

Somatization is prevalent across many psychological disorders, particularly depression and anxiety, and is associated with reduced functioning, disability, and high healthcare costs. It is strongly linked to depressive and anxiety symptoms, moderately linked to other disorders, and more weakly linked to substance use[28], while factors such as childhood trauma and lack of family support contribute to its

development[8]. Other contributors are biological and psychosocial factors, while the symptoms are associated with negative affect, irrational health-related beliefs, and an increased focus on the body.

## *The relationship between somatization and depression*

Depression is one of the most prevalent mental disorders worldwide, affecting approximately 332 million people, and is characterized by low mood and cognitive and somatic disturbances that impair daily functioning[42; 3; 11]. In primary care settings, it often presents through somatization, with individuals reporting physical symptoms such as fatigue, sleep disturbances, and bodily pain[15; 22]. This relationship is associated with biological mechanisms, including alterations in serotonin and dopamine, as well as changes in the prefrontal cortex, amygdala, and hippocampus, which are involved in emotional processing and stress regulation[39; 22].

From a clinical and cultural perspective, individuals often present with physical complaints while avoiding emotional expression, which is associated with stigma and increases the risk of misdiagnosis[30; 40]. Studies show that a large proportion of individuals report only physical symptoms during initial visits (69%), with considerable cross-cultural variation[12; 30], while in cultures where emotional expression is limited, somatization becomes a dominant form of articulating stress26. This highlights the need for a biopsychosocial assessment, as focusing solely on physical symptoms may mask underlying disorders, whereas professional awareness improves their identification[6; 17;31].

## *The relationship between somatization and anxiety*

Anxiety is defined as a physiological and psychological response to stress, mediated by the sympathetic nervous system and the "fight-or-flight" mechanism, which activates the release of adrenaline and cortisol and increases heart rate and breathing. Although this response is adaptive in the short term, prolonged activation may lead to anxiety disorders and functional impairment[2; 36]. In this context, somatization represents the expression of psychological distress through physical symptoms that are not fully explained, such as pain and fatigue[23; 32; 37], while the relationship between anxiety and somatization is explained by the activation of stress systems and increased sensitivity to bodily sensations[28; 5].

From a clinical and epidemiological perspective, anxiety often co-occurs with somatization and depression, with a high prevalence of bodily symptoms and positive correlations among them16. In primary care settings, patients mainly present with physical complaints, while emotional symptoms remain underreported, leading to an underestimation of psychological causes[27; 35]. The co-occurrence of these disorders is associated with lower quality of life and increased

disability[33], while cultural factors influence how symptoms are expressed. This evidence emphasizes that somatic symptoms are part of an interconnected psychological network and require integrated biopsychosocial approaches to treatment[21; 18].

## Methodology

This study employed a cross-sectional quantitative design, aiming to explore the relationships between somatic symptoms, depressive symptoms, anxiety symptoms, and general help-seeking behaviors among the Albanian adult population. This study used non-probability convenience and snowball sampling, whereby a Google Forms questionnaire was distributed online through social media for data collection. Before completing the questionnaire, participants were clearly informed about the purpose of the study and were assured that all information would remain confidential. Participants were required to be over 18 years old and to have no diagnosis of chronic pain. These exclusion criteria were clearly stated in the form, and all personal information was handled with full respect for participants' privacy.

### *Assessment instruments*

The instruments used in this study were translated into Albanian and adapted for the purposes of the study. Before their administration in the main sample, the translated versions were piloted in order to assess clarity and suitability for the Albanian context. After data collection, internal consistency was examined using Cronbach's Alpha coefficients.

Somatic symptoms were assessed using the PHQ-15, an instrument derived from the Patient Health Questionnaire, which includes 15 items related to common somatic complaints. Participants reported symptoms experienced during the past four weeks on a 3-point Likert scale ranging from 0 to 2. The PHQ-15 showed very high internal consistency in the present study, with Cronbach's Alpha $\alpha = 0.944$. Depressive symptoms were measured using the PHQ-9, anxiety symptoms using the GAD-7, and help-seeking intentions using the General Help-Seeking Questionnaire. In the present study, the PHQ-9 demonstrated acceptable internal consistency, $\alpha = 0.785$, while the GHSQ also showed good reliability, $\alpha = 0.821$. The GAD-7 showed moderate internal consistency, $\alpha = 0.673$, which should be interpreted with some caution but was considered acceptable for exploratory use in this sample.

Overall, although the Albanian versions of the instruments were not previously validated, in this specific study population they were translated, adapted, and piloted before use. Their internal consistency values supported their use in the present study.

**TABLE 1:** Shapiro–Wilk test of normality for the main study variables

| Variables | W | df | p |
|---|---|---|---|
| Somatic symptoms (PHQ-15) | .977 | 181 | .005 |
| Depressive symptoms (PHQ-9) | .955 | 181 | < .001 |
| Anxiety symptoms (GAD-7) | .913 | 181 | < .001 |
| Help-seeking behaviors (GHSQ) | .990 | 181 | .246 |

**Note.** The Shapiro–Wilk test was used to assess the normality of the distribution of the variables. A p-value of < .05 indicates a statistically significant deviation from normality.

**TABLE 2:** Correlations *–PHQ15, PHQ9, GAD7 AND GHSQ*

| | PHQ-15 | PHQ-9 | GAD-7 | GHSQ |
|---|---|---|---|---|
| PHQ-15 | 1 | .668** | -.569** | -.171* |
| PHQ-9 | .668** | 1 | .768** | -.279** |
| GAD-7 | -.596** | .768** | 1 | -.117 |
| GHSQ | -.171* | -.279** | -.117 | 1 |

**. Correlation is significant at the 0.01 level (2-tailed), p < .01.
*. Correlation is significant at the 0.05 level (2-tailed), p < .05.

**TABLE 3:** Multiple linear regression predicting general help-seeking behaviors (GHSQ)

| Predictor | B | SE | β | t | p |
|---|---|---|---|---|---|
| Konstante | 29.19 | 1.95 | - | 14.99 | <.001 |
| Anxiety (GAD-7) | 0.44 | 0.21 | .24 | 2.10 | 0.037 |
| Depression (PHQ-9) | -0.73 | 0.20 | -.46 | -3.74 | <.001 |
| Somatic symptoms (PHQ-15) | -0.01 | 0.18 | -.01 | -0.08 | .938 |

**Note.** Dependent Variable: General Help-Seeking Behaviors (GHSQ)

**TABLE 4:** ANOVA: Gender differences in general help-seeking behaviors (GHSQ)

| Variance source | SS | df | Ms | F | P |
|---|---|---|---|---|---|
| Between groups | 3.71 | 1 | 3.71 | 0.04 | .840 |
| Within groups | 16268.52 | 179 | 90.98 | - | - |
| Total | 16272.23 | 180 | - | - | - |

**TABLE 5:** ANOVA: Differences in general help-seeking Behaviors (GHSQ) across age groups

| Variance source | SS | df | Ms | F | P |
|---|---|---|---|---|---|
| Between groups | 111.56 | 2 | 55.78 | 0.61 | .542 |
| Within groups | 16160.67 | 179 | 90.79 | - | - |
| Total | 16272.23 | 180 | - | - | - |

**Note.** Dependent Variable: General Help-Seeking Questionnaire (GHSQ).
The assumption of homogeneity of variances was met (Levene's test, p = .604).

## Statistical analysis

The statistical analyses used in this study included descriptive analyses, Pearson correlation analyses, ANOVA, and linear regression. First, descriptive analysis was conducted to describe the sociodemographic characteristics of the participants and the distribution of the main study variables. Normality was tested using the Shapiro–Wilk test and visual inspection, and although some deviations were statistically significant, the distributions were considered suitable for parametric analyses due to the sample size[34].

The analyses were conducted in IBM SPSS on a sample of 181 participants (64.1% female; mean age = 25.5 years), with the level of statistical significance set at $p < .05$. The descriptive results showed consistent symptom levels in line with the literature on non-clinical populations. Using standard cut-off scores, 41.6% (n = 77) of participants had clinically significant depressive symptoms (PHQ-9 ≥ 10), while 65.9% (n = 122) had anxiety symptoms (GAD-7 ≥ 10), indicating a high prevalence of psychological distress in the sample.

Pearson correlation analysis showed strong and statistically significant associations between somatic, depressive, and anxiety symptoms. Somatic symptoms were strongly associated with depression ($r = .668$, $p < .01$) and anxiety ($r = .596$, $p < .01$), while the strongest association was found between depression and anxiety ($r = .768$, $p < .01$), reflecting high comorbidity. In contrast, help-seeking behaviors showed weak negative correlations with symptoms, particularly depression, suggesting that higher symptom intensity may hinder help-seeking.

ANOVA analyses showed no statistically significant differences in help-seeking behaviors by gender ($F(1, 179) = 0.041$, $p = .840$) or age group ($F(2, 178) = 0.61$, $p = .542$), while the statistical assumptions were met according to Levene's test. This suggests that demographic factors are not significant determinants of these behaviors, highlighting the importance of psychological and sociocultural factors.

Multiple linear regression analysis showed that the model was statistically significant ($F(3, 177) = 6.59$, $p < .001$), explaining approximately 10% of the variance in help-seeking behaviors. Anxiety symptoms emerged as a positive

predictor, whereas depressive symptoms emerged as a negative predictor, while somatic symptoms did not contribute independently when emotional variables were controlled for. These findings indicate that emotional dimensions play a greater role in determining help-seeking behaviors.

GHSQ analysis showed that individuals have a greater tendency to seek help from informal sources, such as partners, family members, and friends, while formal sources, such as mental health professionals, are used less frequently. Some participants reported that they would not seek help from anyone, reflecting stigma, lack of trust, or the normalization of psychological suffering. Additionally, most participants had not consulted a family doctor, and only a small percentage had received a referral for professional help.

Overall, the findings indicate that help-seeking is primarily supported by informal social networks, while the use of professional services remains limited. This underscores the need to increase awareness, reduce stigma, and strengthen the role of primary care in the early identification and referral of mental health problems, thereby supporting a biopsychosocial approach to treatment.

## Discussion

This study aimed to explore the interactions among somatic, depressive, anxiety symptoms, and general help-seeking behaviors in a population of Albanian adults, providing empirical evidence on how psychological distress is manifested and addressed within the context of primary healthcare. The findings contribute to the existing literature by shedding light on the cultural and structural specificities that influence the trajectory of help-seeking in Albania. The results revealed significant associations among somatic, depressive, and anxiety symptoms, confirming the interconnected nature of these experiences. This finding is particularly meaningful for Albanian primary care, where bodily complaints often constitute the primary reason for presenting to a family physician.

In the absence of systematic identification of the psychological component, these symptoms risk being treated only at the somatic level, leading to the underdiagnosis of depression and anxiety. The fact that depressive and anxiety symptoms emerged as stronger predictors of help-seeking behaviors than somatic symptoms suggests that, although distress is often expressed bodily, subjective awareness of emotional suffering may be the key factor that encourages individuals to seek support. This has direct implications for assessment practices in primary care. A central finding of the study is the dominance of informal sources of help-seeking, such as intimate partners, friends, and family, compared to formal sources. This pattern reflects a familiar reality in societies with strong family ties, but it also signals limitations in the access to, and perception of, professional mental health services. Particularly meaningful is the relatively low use of the GP as a source of help for emotional

concerns. In the Albanian context, where the GP represents the first point of contact with the healthcare system, this finding suggests a discrepancy between the theoretical role of primary care and actual practice.

This may be related to a lack of specialized training, time constraints during consultations, or individuals' own expectations, as they may not consider mental health to fall within the competence of the general practitioner. The presence of a considerable percentage of individuals who state that they would not seek help from anyone reinforces concerns about structural and cultural barriers. These barriers have direct consequences for the efficiency of the healthcare system and for the early detection of cases in primary care. The absence of statistically significant differences in general help-seeking behaviors by gender and age group suggests that the patterns described are relatively consistent across the adult sample.

This finding may reflect a homogenization of help-seeking experiences in the online context, but it also underscores the need for systemic interventions that address the entire adult population, rather than only specific groups. The findings of this study highlight the need for stronger integration of mental health into Albanian primary care. Improving assessment for depression and anxiety during GP consultations, training primary care professionals, and developing clear referral pathways to specialized services are essential steps toward increasing the efficiency of the healthcare system.

This study should be interpreted in light of several limitations. First, the cross-sectional design does not allow conclusions about causal relationships between the symptoms and behaviors examined in this study. Secondly, the use of self-report instruments may have introduced response bias, as participants may have underreported or overreported symptoms based on personal perception, stigma, or social desirability. Third, the online convenience and snowball sampling method may have limited the representativeness of the sample, as participation was more accessible to individuals who use social media and are more willing to complete online questionnaires. In addition, the relatively young mean age of the sample may limit the generalizability of the findings to the wider Albanian adult population, particularly older adults, who may experience somatic symptoms and help-seeking behaviors differently. Nevertheless, despite these limitations, the study provides valuable exploratory evidence on the relationship between psychological distress, somatic presentation, and help-seeking patterns in the Albanian context.

As a methodological recommendation for future research, the inclusion of qualitative interviews with general practitioners is strongly suggested, with the aim of collecting direct information on their experience in identifying, managing, and referring patients with somatic and psychological symptoms. Such an approach would enable an assessment of the actual efficiency of the healthcare system from the perspective of primary care professionals and would help identify structural and organizational gaps.

In conclusion, this study provides important evidence on the interconnection between psychological and somatic symptoms and help-seeking patterns in the Albanian context. The findings emphasize the need for a more integrated and mental health-sensitive approach in primary care, laying the groundwork for evidence-informed interventions and further multidisciplinary research.

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# *Serostatus-Driven Epstein–Barr Virus Management After Kidney Transplantation: Screening, Surveillance, and Pre-emptive Prevention of PTLD*

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**Abstract**

*Epstein–Barr virus (EBV) is a principal driver of post-transplant lymphoproliferative disorder (PTLD), one of the most serious complications of kidney transplantation. Because the risk of EBV-related disease is determined primarily by donor–recipient EBV serostatus, post-transplant EBV management is increasingly conceptualised as*

*serostatus-driven. This narrative review synthesises evidence published predominantly within the last five years on EBV screening, post-transplant surveillance, interpretation of EBV DNA-emia, and pre-emptive prevention of PTLD in kidney transplant recipients, complemented by selected solid organ, paediatric, haematology, and laboratory-methodology studies. We argue that pre-transplant donor–recipient serology should define the baseline risk tier—high-risk donor-positive/recipient-negative (D+/R−), intermediate D−/R−, and lower-risk seropositive recipients—and thereby govern the intensity of monitoring, whereas viral-load kinetics, specimen type, assay calibration, immunosuppression exposure, and clinical context should govern intervention. Practical messages include the superiority of trend-based over single-threshold interpretation of EBV DNA-emia, the need for assay and specimen consistency in longitudinal follow-up, the limited role of antiviral prophylaxis, and the selective, evidence-informed use of immunosuppression reduction and pre-emptive rituximab in high-risk recipients. A six-step serostatus-driven algorithm is proposed to standardise screening, risk-adapted surveillance, interpretation of DNA-emia, pre-emptive intervention, and escalation to PTLD evaluation, while avoiding unnecessary testing or excessive immunosuppression reduction in lower-risk patients. Priorities for future research include international standardisation of EBV PCR, integration of EBV-specific immune monitoring into risk prediction, and prospective trials defining which recipients benefit from pre-emptive immune-directed therapy.*

***Keywords:*** *Epstein–Barr virus; kidney transplantation; post-transplant lymphoproliferative disorder; serostatus; EBV DNA-emia; viral load monitoring; rituximab; pre-emptive therapy.*

## Introduction

Kidney transplantation requires long-term immunosuppression, which improves graft survival but increases susceptibility to viral reactivation, opportunistic infections, and virus-driven malignancies. Epstein–Barr virus (EBV) is particularly relevant in this context because it establishes lifelong latency in B lymphocytes and, under impaired T-cell immune surveillance, may progress from asymptomatic DNA-emia to post-transplant lymphoproliferative disorder (PTLD). PTLD remains one of the most severe complications after kidney transplantation, with potential consequences including graft dysfunction, allograft loss, treatment-related morbidity, and death. Contemporary reviews emphasize that PTLD is biologically heterogeneous, ranging from EBV-positive early lesions to EBV-negative late lymphoid malignancies, and that management often requires a stepwise multidisciplinary approach involving nephrology, infectious diseases, hematology, oncology, pathology, and transplant surgery [1–4].

A central principle emerging from recent evidence is that EBV management after kidney transplantation should be serostatus-driven. Pre-transplant donor–recipient EBV serology identifies recipients at the highest risk for primary EBV infection after transplantation, especially donor-positive/recipient-negative mismatch (D+/R−). This group lacks pre-existing EBV-specific immune memory and is therefore particularly vulnerable to donor-derived EBV acquisition, early EBV DNA-emia, and PTLD. Large contemporary kidney transplant cohorts and registry-based analyses consistently show that donor–recipient EBV serostatus is strongly associated with post-transplant EBV-related outcomes, making serostatus the practical foundation for surveillance intensity and pre-emptive decision-making [5,6].

Serostatus alone, however, does not fully define risk. The intensity and type of immunosuppression modify EBV-related outcomes, especially in EBV-mismatched recipients. Lymphocyte-depleting induction therapies such as antithymocyte globulin and alemtuzumab may increase PTLD risk compared with non-depleting induction strategies, likely by weakening early EBV-specific T-cell control. Recipient age, pediatric status, rejection treatment, maintenance immunosuppression intensity, and viral co-infections also influence the transition from transient EBV DNA-emia to clinically significant disease. Thus, EBV serostatus should be viewed as the baseline risk determinant onto which dynamic clinical and immunological variables are added [7–9].

This review summarizes recent evidence on EBV in kidney transplant recipients and proposes a practical serostatus-driven framework for screening, surveillance, interpretation of EBV DNA-emia, and pre-emptive prevention of PTLD. The central argument is that EBV donor–recipient serostatus should guide the intensity of monitoring, while EBV viral load kinetics, assay methodology, and clinical context should guide intervention decisions. This approach aims to prevent PTLD while avoiding unnecessary testing or excessive immunosuppression reduction in lower-risk recipients [1–9].

## Scope and methodology of the review

This narrative review was prepared in accordance with the quality criteria of the Scale for the Assessment of Narrative Review Articles (SANRA). PubMed/MEDLINE, Scopus, and the Cochrane Library were searched from January 2014 to December 2025, with priority given to literature published within the last five years; older foundational studies were retained when they provided essential context for EBV PCR monitoring, PTLD diagnosis, or long-term kidney transplant outcomes. Search terms combined the concepts "Epstein–Barr virus," "EBV DNAemia/viraemia," "PCR/viral load monitoring," "post-transplant lymphoproliferative disorder," "serostatus," and "kidney/renal transplantation,"

complemented by selected solid organ, paediatric transplant, haematology, and laboratory-methodology references identified through citation tracking. English-language original studies, cohort and registry analyses, reviews, and methodological evaluations relevant to kidney transplantation, donor–recipient serostatus, EBV viral load surveillance, and PTLD prevention were eligible; non-English reports and studies without extractable transplant-relevant data were not prioritised. Study selection and interpretation were performed by the authors by consensus [1–4,10].

Because EBV surveillance literature is heterogeneous with respect to study design, population, organ type, specimen type, PCR platform, viral load units, and intervention thresholds, this article does not attempt a formal meta-analysis. Instead, it uses a structured narrative synthesis, emphasizing clinically interpretable patterns across recent cohorts and reviews. Particular attention is given to evidence that can inform practical transplant protocols: who should be monitored, when monitoring should be intensified, how EBV DNA-emia should be interpreted, and when pre-emptive intervention should be considered [5,6,10–12].

## Pre-transplant EBV serostatus and risk stratification

Pre-transplant EBV serological screening is the cornerstone of EBV risk stratification in kidney transplantation. Standard assessment generally includes EBV viral capsid antigen IgG and IgM and Epstein–Barr nuclear antigen IgG, allowing identification of prior infection versus EBV-naïve status. In clinical practice, the most important distinction is whether the recipient is EBV-seronegative before transplantation, because this defines susceptibility to primary EBV infection under immunosuppression. When donor and recipient serostatus are combined, recipients may be classified as high risk (D+/R−), intermediate risk (D−/R−), or lower risk when the recipient is EBV-seropositive regardless of donor status [5,6].

The D+/R− recipient represents the highest-risk phenotype. These patients may acquire EBV from the donor organ or early post-transplant exposure at a time when immunosuppression is strongest and EBV-specific immunity is absent. Recent cohort evidence shows that EBV-mismatched recipients have higher rates of EBV DNA-emia and PTLD than EBV-seropositive recipients. In a serostatus-driven management model, this group should therefore be identified before transplantation, flagged in the transplant record, and assigned an intensified post-transplant monitoring pathway [5,6,13].

Risk stratification should also incorporate clinical modifiers. EBV-mismatched adults receiving lymphocyte-depleting induction appear to be at higher PTLD risk than those receiving non-depleting induction, and pediatric kidney recipients are often EBV-seronegative at transplant and therefore disproportionately represented

among high-risk groups. Rejection episodes and intensified immunosuppression may further increase EBV replication risk. These modifiers do not replace serostatus, but they refine how aggressively a patient should be followed after transplantation [7,8,14].

**TABLE 1.** Serostatus-based EBV risk stratification a
nd surveillance intensity in kidney transplant recipients.

| Donor–recipient serostatus (risk tier) | EBV-specific immunity | Surveillance intensity | Pre-emptive considerations |
|---|---|---|---|
| D+/R− (high) | Absent (EBV-naïve) | Intensified, structured viral-load monitoring, especially months 0–6 and the first post-transplant year | Early stepwise immunosuppression reduction; consider pre-emptive rituximab if viral load rises or persists despite reduction |
| D−/R− (intermediate) | Absent (EBV-naïve) | Structured monitoring, generally less intensive than D+/R− | Immunosuppression reduction guided by viral-load kinetics |
| R+ (any donor) (lower) | Present (immune memory) | Selective, clinical-trigger-based testing rather than fixed high-frequency monitoring | Intervene only with persistent or high viral load or compatible clinical findings; avoid overreaction to isolated low-level DNA-emia |

D, donor; R, recipient; DNA-emia, EBV DNA in blood. Clinical modifiers (lymphocyte-depleting induction, paediatric status, rejection treatment) refine surveillance within each tier [5–8,13,14].

## Post-transplant EBV surveillance

EBV surveillance after kidney transplantation should be risk-adapted rather than uniform. High-risk D+/R– recipients should undergo structured EBV viral load monitoring, especially during the first post-transplant year and particularly during the early window when primary EBV infection is most likely. Evidence from EBV-mismatched solid organ transplant cohorts, including kidney recipients, suggests that donor-acquired EBV DNA-emia frequently emerges during the first months after transplantation, with a clinically important concentration of events between months 2 and 6. This supports intensified surveillance in this interval, followed by individualized monitoring according to prior viral load behavior and immunosuppression exposure [13].

In contrast, EBV-seropositive kidney transplant recipients may not benefit from the same high-frequency surveillance strategy. In these patients, low-level or intermittent EBV DNA-emia may reflect latent viral shedding rather than clinically meaningful progression toward PTLD. A more selective approach is therefore reasonable, with EBV PCR testing triggered by augmented immunosuppression, rejection treatment, unexplained cytopenias, lymphadenopathy, persistent fever, graft dysfunction, or clinical suspicion for PTLD. This approach avoids

overinterpretation of isolated low-level results while maintaining vigilance when clinical context changes [1,12,15].

Laboratory methodology is central to EBV surveillance. Whole blood and plasma EBV PCR assays may produce substantially different viral load values because whole blood detects both cell-associated and circulating viral DNA, whereas plasma may better reflect active viral replication. Prospective evaluations of WHO-standardized EBV PCR and comparative studies of specimen type show that assay and sample selection influence viral load interpretation, making universal numeric thresholds difficult to apply across centers. For this reason, each transplant program should use consistent specimen type and assay methodology for longitudinal follow-up whenever possible [10,11,16].

The most clinically useful interpretation of EBV monitoring is trend-based rather than threshold-based. A single viral load value is often less informative than the pattern of change over time, especially whether EBV DNA-emia is rising rapidly, persistent, or increasing despite immunosuppression adjustment. This is particularly important in D+/R− recipients, where rising EBV viral load may reflect primary infection and higher PTLD risk. Conversely, stable low-level DNA-emia in a clinically well EBV-seropositive recipient may require observation rather than immediate intervention [10–12,16].

## EBV DNA-emia: clinical interpretation and actionable findings

EBV DNA-emia is best understood as a spectrum rather than a diagnosis. It may represent transient viral replication, primary EBV infection, reactivation under immunosuppression, or early lymphoproliferation. Contemporary adult and pediatric solid organ transplant studies show that EBV DNA-emia is relatively common, but only a minority of patients progress to PTLD. This gap between viral detection and clinical disease explains why EBV PCR cannot be interpreted in isolation and must be integrated with serostatus, viral load kinetics, immunosuppression intensity, and symptoms [12,17,18].

There is no universally accepted EBV viral load cutoff for intervention. Differences in whole blood versus plasma testing, assay calibration, viral load units, transplant population, and baseline serostatus all limit comparability between studies. Even when WHO-standardized methods are used, clinically meaningful differences between specimen types remain. As a result, many experts favor center-specific thresholds combined with individualized assessment of viral kinetics, rather than a single universal cutoff applied to all kidney transplant recipients [10,11,16,19].

In D+/R− recipients, EBV DNA-emia is more likely to represent primary infection and carries greater concern when viral load rises, persists, or reaches high levels. Higher peak viral load and EBV viral load at the time of PTLD diagnosis have

been associated with worse outcomes in kidney transplant recipients with PTLD. Therefore, sustained or rapidly increasing DNA-emia in an EBV-mismatched recipient should prompt closer monitoring, evaluation of immunosuppression, and consideration of pre-emptive intervention [6,13,20].

In EBV-seropositive recipients, low-level DNA-emia is often less specific. Longitudinal data in adult renal transplant recipients suggest that EBV DNA-emia may occur beyond the early post-transplant period without necessarily predicting PTLD, especially when levels are low or transient. Overly aggressive responses to isolated low-level DNA-emia may increase rejection risk by prompting unnecessary immunosuppression reduction. In this group, intervention should be guided by persistent viral load increase, high peak viral load, compatible clinical findings, or additional risk modifiers rather than by detection alone [15,21].

EBV DNA-emia may also occur in complex clinical contexts involving other viral infections or immune perturbations. Studies of multiplex viral monitoring demonstrate that EBV, CMV, and BK virus replication may coexist in kidney transplant recipients, particularly during suspected rejection or intensified immunosuppression. In such cases, EBV viral load may reflect broader immune dysregulation rather than EBV-specific disease. Concurrent infection, graft dysfunction, and systemic inflammation should therefore be considered when interpreting EBV PCR results [9,22].

## EBV DNA-emia and PTLD

PTLD represents a heterogeneous group of lymphoid proliferations occurring under post-transplant immunosuppression. EBV-positive PTLD is classically linked to impaired T-cell control of EBV-infected B cells, especially in EBV-naïve recipients who acquire primary infection after transplantation. Early PTLD is more often EBV-associated and may arise within the first year, while later PTLD can be EBV-negative and may follow different oncogenic mechanisms. This biological heterogeneity explains why EBV DNA-emia is a valuable risk marker but not a definitive diagnostic test [1–4].

Clinically, PTLD in kidney transplant recipients may present with lymphadenopathy, fever, weight loss, cytopenias, graft dysfunction, gastrointestinal symptoms, or extranodal disease. Case series and reports illustrate that gastrointestinal involvement can be severe and may present with bleeding or ischemic complications, underscoring the need for tissue diagnosis when clinical suspicion is high. Imaging, hematology consultation, and biopsy remain essential because EBV PCR alone cannot distinguish benign viral replication from malignant transformation [23,24].

Prognosis in PTLD depends on several factors, including age, disease stage, histological subtype, EBV association, extranodal involvement, and EBV viral

load at diagnosis. Kidney transplant cohorts suggest that higher EBV viral load at PTLD diagnosis and older age are associated with worse survival. Regional experiences also demonstrate variability in presentation and outcomes, reflecting differences in surveillance intensity, access to diagnostic pathways, and treatment strategies. These findings support earlier recognition and standardized algorithms for high-risk kidney transplant recipients [20,24,25].

## Prevention and management strategies

The first-line response to clinically significant EBV DNA-emia is usually a reduction of immunosuppression. The goal is to restore EBV-specific immune surveillance while preserving graft function. Common approaches include reducing calcineurin inhibitor exposure and decreasing or temporarily withholding antimetabolite therapy. This strategy is biologically rational and widely recommended, but it requires careful balancing because excessive immunosuppression reduction can precipitate rejection, particularly in patients with recent rejection episodes or high immunological risk [1,4,9].

Rituximab has emerged as a potential pre-emptive or therapeutic option in selected high-risk patients. Retrospective solid organ transplant data suggest that rituximab exposure after EBV DNA-emia may reduce PTLD risk over time, although prospective randomized evidence remains limited. Pediatric kidney transplant series also suggests that pre-emptive rituximab may help clear EBV DNA-emia in EBV-naïve recipients who do not respond to immunosuppression reduction alone. Nevertheless, rituximab should not be applied routinely to all patients with EBV DNA-emia because B-cell depletion carries infection risk and may complicate immune recovery [8,26,27].

Antiviral therapy has a limited role in EBV prevention compared with CMV prevention because EBV often persists in latently infected B cells, where nucleoside analogues have limited effect. Current reviews do not support routine antiviral prophylaxis solely to prevent EBV-driven PTLD. More promising future approaches include immune-based monitoring and EBV-specific adoptive T-cell therapy, which has stronger precedent in hematopoietic stem cell transplantation but remains investigational in kidney and other solid organ transplant populations [2,28,29].

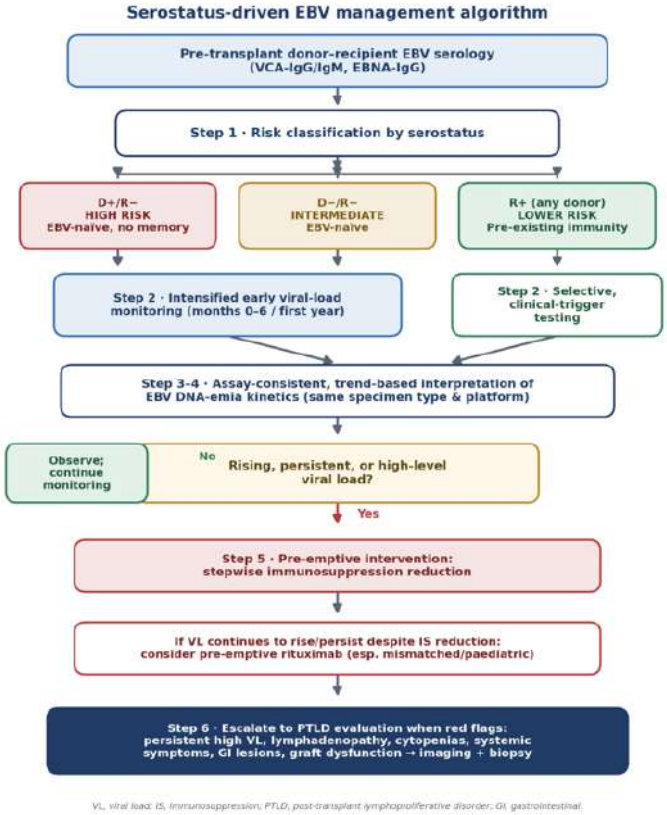
## A practical serostatus-driven algorithm

A practical EBV management algorithm should begin before transplantation with donor–recipient EBV serology. Step 1 is classification into high-risk D+/R–, intermediate D–/R–, or lower-risk R+ status. Step 2 is assignment of surveillance intensity: D+/R– recipients should undergo intensified early EBV viral load

monitoring, while R+ recipients may be monitored selectively according to clinical triggers. Step 3 and 4 is assay-consistent interpretation of EBV DNA-emia kinetics, with emphasis on rising, persistent, or high-level viral load rather than isolated values [5,10,13].

Step 5 is pre-emptive intervention when EBV DNA-emia becomes clinically actionable. In high-risk recipients, this generally begins with stepwise immunosuppression reduction and close reassessment of viral load and graft function. Rituximab may be considered when viral load continues to rise or persists despite immunosuppression adjustment, especially in EBV-mismatched pediatric recipients or other high-risk scenarios. Step 6 is escalation to PTLD evaluation when red flags appear, including persistent high viral load, lymphadenopathy, unexplained cytopenias, systemic symptoms, gastrointestinal lesions, or graft dysfunction [8,20,26,27].

**FIGURE 1.** Serostatus-driven EBV management algorithm in kidney transplant recipients. Schematic overview of a risk-adapted surveillance and intervention pathway integrating donor–recipient EBV serostatus, EBV DNA-emia kinetics, and assay-consistent viral load monitoring. The algorithm emphasizes trend-based interpretation, stepwise immunosuppression modulation, and escalation to PTLD evaluation when clinically indicated [5,10,13].



## Future directions

Future research should address three major gaps. First, EBV PCR monitoring requires better standardization across laboratories, including specimen type, reporting units, calibration, and clinically meaningful viral load kinetics. Second, risk prediction should move beyond viral load alone by integrating EBV-specific immune monitoring, recipient risk factors, immunosuppression exposure, and possibly viral or host biomarkers. Third, prospective studies are needed to define which patients benefit from pre-emptive rituximab or other immune-directed therapies, particularly among EBV-mismatched kidney transplant recipients [10,16,19,25].

Emerging contexts such as SARS-CoV-2 infection also highlight the dynamic nature of EBV immune control in transplant recipients. Reports of EBV reactivation after COVID-19 in kidney transplant recipients suggest that systemic immune perturbations may alter viral latency and surveillance needs. Regional studies from different healthcare settings further emphasize the need to adapt EBV protocols to local resources, laboratory capacity, and transplant population characteristics [25,30,31].

## Conclusions

EBV remains a major determinant of PTLD risk after kidney transplantation, but its management should not rely solely on viral load detection. The most practical framework is serostatus-driven: donor–recipient EBV serology defines baseline risk, while viral load kinetics, specimen type, immunosuppression exposure, and clinical context determine whether monitoring, observation, immunosuppression reduction, rituximab, or PTLD evaluation is appropriate. This approach is particularly important for D+/R– recipients, who require intensified early surveillance and proactive prevention strategies [5–8,13].

A structured serostatus-driven algorithm can help standardize EBV management across transplant programs while reducing unnecessary intervention in lower-risk recipients. Until better biomarkers and prospective trial data become available, clinicians should prioritize risk-adapted surveillance, assay consistency, multidisciplinary interpretation, and timely escalation when clinical red flags emerge. In this way, EBV monitoring can be transformed from a purely laboratory-based practice into a clinically integrated strategy for PTLD prevention and graft preservation [1–4,10,26].

## Declarations

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**Author contributions:** All authors contributed to the conception of the review, the literature search and interpretation, drafting and critical revision of the manuscript, and approved the final version.

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# *Diagnostic Challenges in Multiple Myeloma: A Case of Recurrent Acute Kidney Injury, Hypercalcemia, and Anemia*

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**Abstract**

*Multiple myeloma (MM) is a hematologic malignancy with heterogeneous clinical presentations, often delaying diagnosis [1,3,4]. Renal impairment is one of its most frequent and severe complications, primarily due to light-chain cast nephropathy,*

*hypercalcemia-induced nephropathy, or nephrotoxic exposures [2,5,10]. We present a case of recurrent acute kidney injury (AKI), episodic hypercalcemia, progressive anemia, and disproportionately elevated inflammatory markers, including hyperferritinemia and markedly elevated D-dimer (>10,000 ng/mL),which initially suggested alternative etiologies such as infection, thromboinflammation, or macrophage activation, but may also reflect tumor activity [9,11]. Serial clinical deterioration ultimately led to a bone marrow aspirate confirming MM [8,13]. This case underscores the diagnostic challenges of MM when renal involvement and inflammatory dysregulation dominate the early clinical picture [6,12]. It highlights the importance of timely hematologic evaluation, repeated assessment of monoclonal components, and early suspicion of myeloma kidney in patients with unexplained recurrent renal dysfunction [2,5,10].*

## Introduction

Multiple myeloma represents approximately 10% of hematologic malignancies and is characterized by clonal proliferation of plasma cells producing monoclonal immunoglobulin or free light chains [1,3,4]. Classical CRAB criteria—hyperCalcemia, Renal failure, Anemia, and Bone lesions—remain central to diagnosis; however, these features may evolve progressively, sometimes over months or years [1,3,4,15]. Delayed diagnosis is particularly likely when renal involvement presents before overt hematologic abnormalities, or when inflammatory markers mimic infectious or autoimmune disease [2,9,11].

Renal impairment occurs in 20–50% of MM patients at presentation and is an independent predictor of mortality [2,5,10]. Cast nephropathy is the most characteristic renal lesion, resulting from intratubular precipitation of monoclonal free light chains with Tamm-Horsfall proteins [5,10]. However, the clinical picture is often confounded by dehydration, medications (NSAIDs, ACE inhibitors, contrast), infections, and metabolic abnormalities [2,9].

This case report describes a patient with recurrent AKI, hypercalcemia, severe fluctuations in inflammatory markers—including ferritin >1000 ng/mL and D-dimer values persistently above 10,000 ng/mL—with delayed diagnosis of a hematologic malignancy [9,11]. The case illustrates how atypical laboratory patterns may overshadow the classical MM presentation and emphasizes the need for a high index of suspicion [6,12,13].

## Case Presentation

### *Clinical Course Overview*

Between July 2024 and June 2025, the patient experienced multiple distinct episodes of AKI, with creatinine peaks ranging 1.14–6.21 mg/dL and urea ranging 33.4–115.1 mg/dL. Renal function frequently improved after hydration and empiric therapy, only to deteriorate again within weeks . Early episodes were attributed to dehydration, infection, or subclinical sepsis due to elevated inflammatory markers.

The patient also developed progressive normocytic anemia, intermittent hypercalcemia, and constitutional symptoms including severe headache, hypotension, nausea, fatigue, anorexia, and mild bone discomfort, which were initially non-specific.

### *Patient History*

A 65-year-old woman with type 2 diabetes mellitus (on insulin glargine), hypertension (lercanidipine, carvedilol, furosemide), and dyslipidemia (atorvastatin) presented in July 2024 with severe headache, hypotension, oliguria, nausea, and vomiting. She had no prior chronic kidney disease and was not on calcium or vitamin D supplementation.

### *Initial Hospitalization (20–30 July 2024)*

Initial laboratory evaluation revealed severe acute kidney injury (AKI) with creatinine 6.21 mg/dL and urea 115.1 mg/dL, accompanied by anemia (Hgb 7.6 g/dL; RBC 2.23 $\times 10^6$/μL). Supportive management with intravenous fluids and blood transfusion resulted in substantial renal recovery at discharge (creatinine 1.14 mg/dL; urea 33.4 mg/dL).

A non-contrast CT scan demonstrated preserved renal morphology, mild bilateral pleural and pericardial effusions, hepatic steatosis, and mild ascites.

### *Second Major Hospitalization (5–20 Nov 2024)*

The patient was rehospitalized for dyspnea and CT-confirmed basal pleuropneumonia. She exhibited severe anemia requiring transfusion, markedly elevated inflammatory markers (including D-dimer >10,000 ng/mL), and progressive renal impairment. Imaging demonstrated osteolytic bone involvement, including

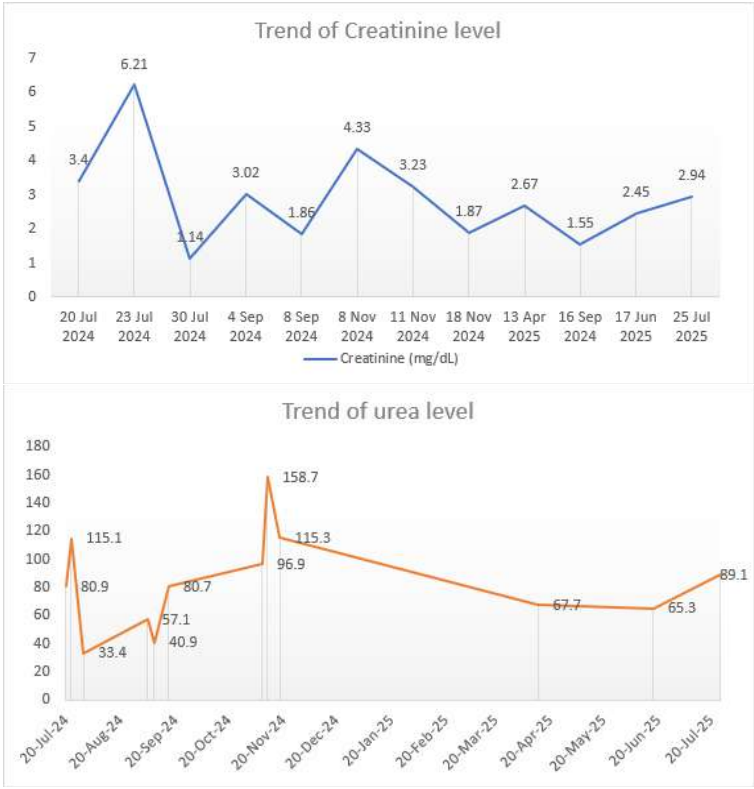
a compression fracture at T12 and lucent lesions at L1. During this interval, she developed hypercalcemia and significant proteinuria (3424 mg/24h) with Bence Jones protein positivity and the first appearance of a monoclonal spike, accompanied by worsening renal indices (creatinine 4.33 mg/dL, urea 96.9 mg/dL). Although supportive management led to partial renal improvement, the post-discharge period remained marked by clinical instability, characterized by recurrent episodes of acute kidney injury, persistent anemia, intermittent hypercalcemia, and progressive biochemical abnormalities.

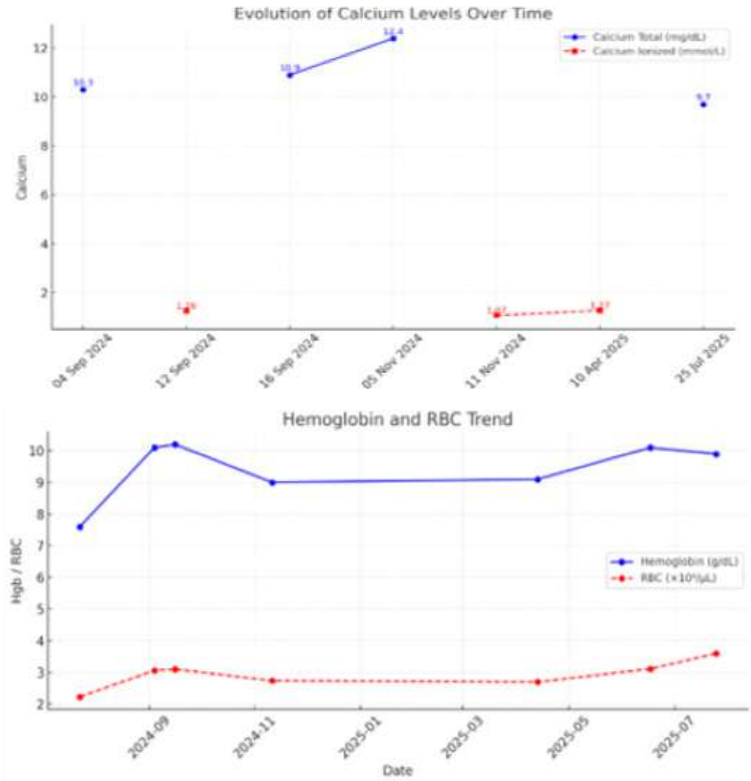
### *Definitive Diagnosis (May 2025)*

Delayed hematologic evaluation revealed early multiple myeloma. Bone marrow aspiration demonstrated 17% plasma cells, elevated monoclonal components (MC, MM, S, M, MBP), and dyspoiesis. MRI confirmed marrow involvement consistent with monoclonal gammopathy.

## Key Laboratory Data

**FIGURE 1.** Laboratory trends over time in a patient with suspected multiple myeloma.






**(A)** Serum creatinine levels demonstrating recurrent episodes of acute kidney injury (AKI). **(B)** Serum urea levels illustrating the same recurrent AKI episodes. **(C)** Total and ionized calcium levels over time, highlighting episodes of hypercalcemia coinciding with AKI recurrence. **(D)** Hemoglobin and red blood cell (RBC) counts showing trends of anemia across multiple hospitalizations and follow-up.

**TABLE 1.** Trends of Inflammatory and Coagulation Markers During the Clinical Course.

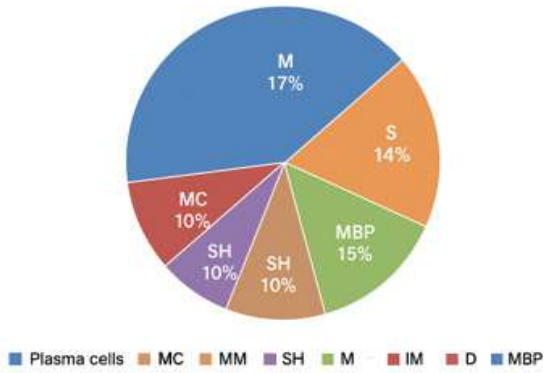
| Date | Ferritin (ng/mL) | D-dimer (ng/mL) | Interpretation |
|---|---|---|---|
| 13 sept 2024 | 870.97 | 9407.0 | AKI |
| 8 Nov 2024 | 1076.9 | 2500.2 | Hyperferritinemia |
| 11 Nov 2024 | 923 | >10,000 | AKI recurrence |
| 3 May 2025 | 3000 | 3759.7 | Hyperferritinemia,AKI |
| 17 Jun 2025 | 786 | >10,000 | New AKI episode |

This table illustrates the persistent and disproportionate elevation of ferritin and D-dimer levels, including marked hyperferritinemia and D-dimer values exceeding 10,000 ng/mL, which contributed to diagnostic uncertainty by suggesting alternative etiologies such as infection or thromboinflammatory states. These abnormalities were later recognized as part of the systemic inflammatory response associated with underlying multiple myeloma.

## Bone Marrow Evaluation

A bone marrow aspirate performed in May 2025 revealed an increased plasma cell population (>10%) with monoclonal morphology, findings that were consistent with and supportive of a diagnosis of multiple myeloma.

**FIGURE 2.** Bone marrow composition (May 2, 2025).




Percentage distribution of marrow elements highlighting plasma cell predominance, supporting the diagnosis of multiple myeloma.

## Imaging

### *CT Scan – July 2024*

Preserved renal morphology without evidence of obstruction, with mild pleural effusion and small-volume ascites. Small lytic lesions were identified on this initial CT scan, indicative of early bone involvement.

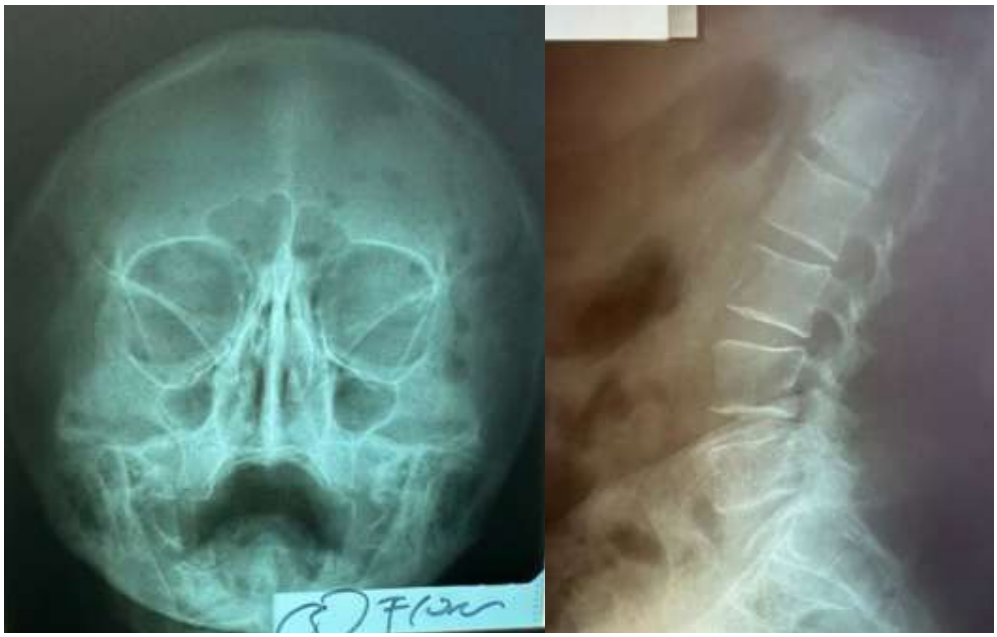
### *Skull X-ray (Rogafi Crani) – November 2024*

Small, well-defined rounded lucencies are observed in the cranial bones, suggestive of osteolytic lesions and consistent with early myeloma-related bone involvement.

### *Spine X-ray -November 2024*

Imaging demonstrates a compression fracture at T12, with additional small lucencies at L1, suggestive of early osteolytic involvement related to multiple myeloma.

**FIGURE 3.** X-ray ( November 2024 )



**(A)** **(B)**

**(A)** Skull X-ray showing small osteolytic lesions in the cranial bones. **(B)** Spine imaging demonstrating a compression fracture at T12 and small lucencies at L1.

## Discussion

This case highlights the diagnostic challenges of MM presenting with recurrent AKI, episodic hypercalcemia, and evolving anemia [1,2,3,4]. The patient experienced multiple AKI episodes over 12 months, characterized by rapid rises in creatinine, partial recoveries, and recurrences without clear external triggers [2,5,9]. This pattern is typical of cast nephropathy, where free light chains intermittently overwhelm tubular reabsorption thresholds [5,10]. Minor insults, including volume shifts, infections, or NSAID exposure, may precipitate acute declines [2,9]. Early testing for serum free light chains could have facilitated a timelier diagnosis [8,15].

Extremely elevated inflammatory markers, including ferritin (>1000 ng/mL) and D-dimer (>10,000 ng/mL), initially suggested sepsis, macrophage activation syndrome, or thromboinflammation [9,11]. In MM, these elevations can result from high tumor burden, cytokine overexpression, impaired renal clearance, or endothelial activation [10,15]. This emphasizes that atypical inflammatory patterns do not exclude MM and may contribute to diagnostic delays [2,9,11].

Hypercalcemia and anemia emerged sequentially, with episodic hypercalcemia contributing to renal vasoconstriction and tubular injury, and anemia gradually fulfilling CRAB criteria [1,3,4,15]. Repeated negative infectious or inflammatory workups illustrate a common real-world pitfall, where hematologic disease is considered only after prolonged evaluation [6,12].

Bone marrow evaluation ultimately confirmed plasma cell dyscrasia [8,13]. Earlier hematology referral, particularly after the second or third AKI episode, might have mitigated renal decline [2,5,10]. Timely initiation of disease-specific therapy correlates with better renal recovery [2,5,10].

## Conclusions

This case highlights that MM can present with a misleading pattern of recurrent AKI, episodic hypercalcemia, and anemia, even in the absence of classic skeletal lesions [1,2,3,4]. Disproportionate inflammatory markers, such as elevated ferritin or D-dimer, may further complicate the diagnostic pathway [9,11]. Clinicians should maintain a high index of suspicion for MM in patients with:

- Unexplained or recurrent AKI [2,5,10]
- Partial renal recovery followed by relapse [2,5,9]
- Anemia or hypercalcemia, even if initially mild [1,3,4,15]
- Disproportionate inflammatory marker elevations [9,11]

Early evaluation with serum free light chain analysis, SPEP/UPEP, and prompt hematology referral are essential [8,15]. Supportive care can temporarily maintain renal function, but definitive disease-specific treatment is required to control progression [2,5,10]. Addressing barriers to timely diagnostic evaluation, including patient reluctance, and providing counseling are critical to prevent irreversible organ damage [6,12,13].

**Informed Consent**

Written informed consent was obtained from the patient for the publication of this case report and any accompanying clinical data and images.

**Conflict of Interest**

The authors declare no conflict of interest.

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# *Vertebral Artery Doppler Ultrasonography: Anatomy, Examination Technique and Clinical Applications*

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**Abstract**

*The vertebral arteries form an essential part of the posterior cerebral circulation, supplying the brainstem, cerebellum, occipital lobes, and portions of the thalami. In routine neurovascular work, Doppler ultrasonography offers a safe, repeatable, non-invasive, and relatively inexpensive way to assess vertebral artery anatomy and flow patterns. CTA and MRA provide superior anatomic detail, particularly for distal*

*and intracranial segments, but duplex ultrasound remains valuable as an initial and follow-up examination in selected patients with suspected vertebrobasilar disease. This educational article reviews segmental anatomy, scanning technique, expected Doppler parameters, common anatomic variants, vertebral artery hypoplasia, atherosclerotic stenosis, occlusion, dissection, subclavian steal syndrome, frequent interpretive pitfalls, and a practical diagnostic algorithm. The aim is to provide a concise working guide for neurologists, radiologists, residents, and other clinicians involved in cerebrovascular imaging.*

***Keywords:*** *vertebral artery; Doppler ultrasound; posterior circulation; vertebrobasilar disease; stenosis; hypoplasia; subclavian steal syndrome.*

## Introduction

The vertebrobasilar system accounts for roughly 20-25% of cerebral blood flow, yet it supplies structures whose ischemia may produce disabling or life-threatening symptoms, including the brainstem, cerebellum, occipital lobes, and thalami [1,2]. Clinical presentation is often variable. Vertigo, dizziness, diplopia, dysarthria, ataxia, syncope, visual field disturbance, transient ischemic attack, and posterior circulation stroke may all be encountered [1,2].

Compared with carotid disease, pathology of the vertebral arteries tends to receive less attention in everyday ultrasound practice. Several reasons explain this: the arteries are smaller and deeper, their course is partly hidden by the cervical transverse processes, and Doppler criteria are less firmly standardized than those used for carotid stenosis. Despite these limitations, duplex ultrasound can provide useful information on vessel patency, flow direction, waveform morphology, and hemodynamic asymmetry when it is performed systematically [3,4].

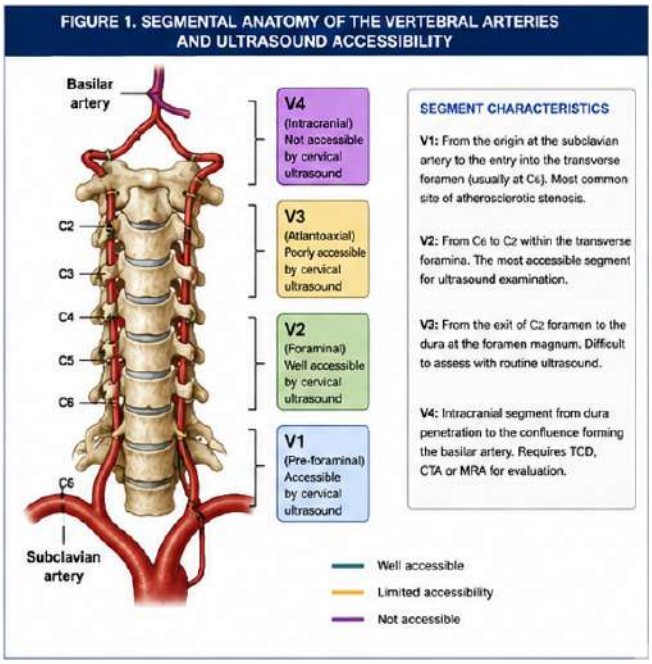
This article is intended as a practical educational review rather than a formal systematic review. It brings together the anatomic and Doppler findings that are most useful at the workstation, with emphasis on what should be recognized, what should not be overcalled, and when CTA or MRA should be recommended. The figures are placed next to the corresponding sections to reinforce the main diagnostic point of each finding. The supporting literature was identified through PubMed/MEDLINE and Scopus searches combining the terms "vertebral artery," "Doppler ultrasound," "posterior circulation," "stenosis," "hypoplasia," and "subclavian steal," supplemented by standard cerebrovascular ultrasound reference texts and citation tracking; the review was prepared in line with the SANRA criteria for narrative reviews.

## Segmental anatomy and ultrasound accessibility

The vertebral arteries most often originate from the superior-posterior aspect of the subclavian arteries and then ascend toward the skull base, where they unite to form the basilar artery. For imaging and reporting purposes, each vertebral artery is divided into four segments: V1, V2, V3, and V4 [3].

V1 extends from the origin at the subclavian artery to the point where the vessel enters the transverse foramen, usually at C6. This proximal segment is clinically important because it is a frequent site of atherosclerotic narrowing. V2 runs within the transverse foramina, typically from C6 to C2, and is the segment most consistently assessed during routine cervical duplex ultrasound. V3 curves around the atlas from C2 to the dura at the foramen magnum, while V4 is intracranial and continues to the vertebrobasilar junction [3].

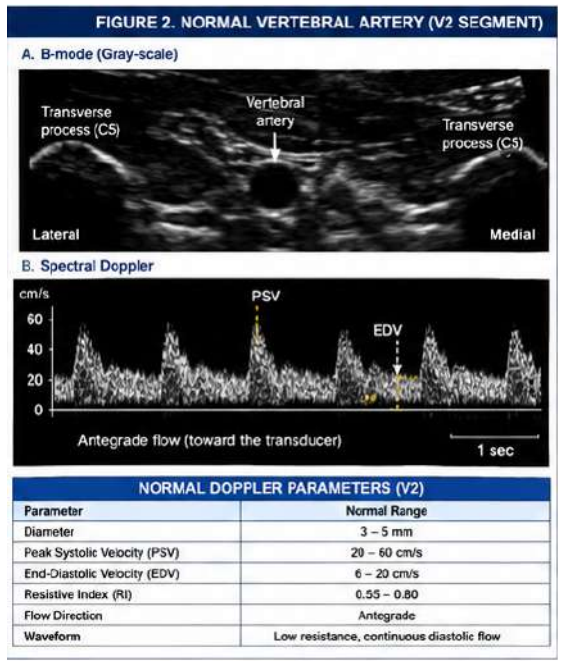
**FIGURE 1.** Segmental anatomy of the vertebral arteries and ultrasound accessibility. V1 and V2 can usually be evaluated by cervical duplex ultrasound, whereas V3 and V4 are less accessible and often require CTA, MRA, or transcranial Doppler for complete assessment [3].



## Examination technique

The examination is generally performed with a high-frequency linear probe, most often in the 5-12 MHz range. The patient lies supine, with the neck slightly extended and rotated gently away from the side being assessed. A complete study should combine gray-scale imaging, color Doppler, and spectral Doppler, because no single component is sufficient on its own [3]. In most patients the vertebral artery is easiest to find in the V2 segment, between the acoustic shadows of the transverse processes. During acquisition, the operator should document whether the vessel is patent, its diameter, flow direction, waveform shape, peak systolic velocity, end-diastolic velocity, and the presence of turbulence or aliasing. Angle correction is important; whenever possible, the Doppler angle should remain below 60 degrees to avoid unnecessary velocity error [3]. Both sides should be examined. A difference between the two vertebral arteries is common and may simply reflect dominance or hypoplasia. For this reason, asymmetry should be interpreted together with vessel caliber, velocities, flow volume, waveform morphology, and the clinical presentation rather than as an isolated abnormal finding.

**FIGURE 2.** Normal vertebral artery appearance in the V2 segment. The B-mode panel shows the artery between the cervical transverse processes. The spectral Doppler panel demonstrates antegrade low-resistance flow with preserved diastolic flow, typical of the posterior cerebral circulation [3,6].



## Normal Doppler parameters

In a normal study, vertebral artery flow is antegrade, directed cranially toward the posterior circulation. The spectral waveform is usually low resistance, with maintained diastolic flow. Published ranges vary according to equipment, technique, and patient factors, but the values summarized in Table 1 are useful as a practical frame of reference [3,6,9].

**TABLE 1.** Practical reference values for vertebral artery Doppler assessment. Values should be interpreted in clinical context and with attention to technique [3,6,9].

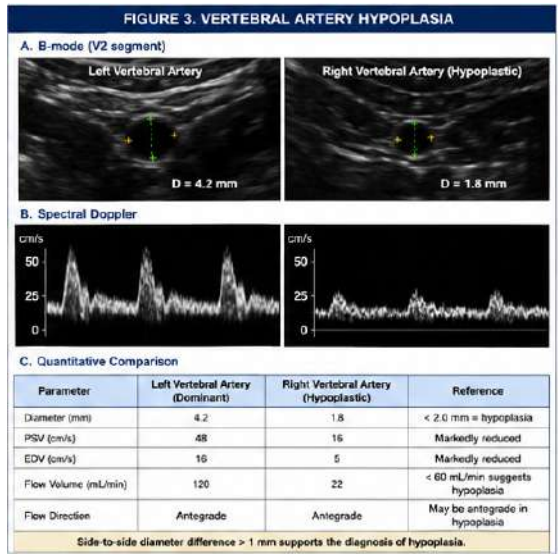
| Parameter | Typical normal range |
|---|---|
| Diameter | 3-5 mm |
| Peak systolic velocity (PSV) | 20-60 cm/s |
| End-diastolic velocity (EDV) | 6-20 cm/s |
| Resistive index (RI) | 0.55-0.80 |
| Flow direction | Antegrade |
| Waveform | Low resistance with preserved diastolic flow |

## Vertebral artery hypoplasia

Vertebral artery hypoplasia is a common anatomic variant. Many authors use a diameter below 2.0 mm as a practical cut-off, although definitions differ between studies. A side-to-side diameter difference greater than 1 mm is also helpful, particularly when one artery is clearly dominant. Hypoplasia is often an incidental finding, but in selected patients it has been associated with posterior circulation ischemia [5].

Sonographically, a hypoplastic vertebral artery is small in caliber and usually shows lower velocities and reduced flow volume, while the direction of flow remains antegrade. The main difficulty is separating a very small patent artery from an occluded one. Careful optimization of color gain, low pulse repetition frequency, power Doppler, and targeted spectral sampling may reveal residual flow. When doubt persists, especially in a symptomatic patient, CTA or MRA is appropriate.

**FIGURE 3.** Vertebral artery hypoplasia. Side-to-side comparison demonstrates marked caliber asymmetry with reduced Doppler velocities and flow volume in the hypoplastic artery. A diameter below 2 mm supports the diagnosis, but clinical context is essential [5,9].



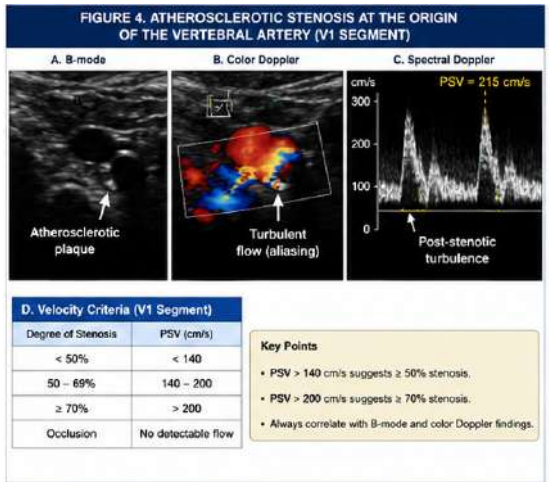

## Atherosclerotic stenosis of the vertebral artery

Atherosclerotic disease most often affects the vertebral artery origin, corresponding to the V1 segment [4,7,10]. The risk profile is similar to other atherosclerotic territories and includes hypertension, diabetes mellitus, smoking, dyslipidemia, and increasing age.

Diagnosis should not rely on one Doppler number alone. Gray-scale imaging may show plaque, calcification, or visible luminal narrowing. Color Doppler can demonstrate focal aliasing or a mosaic pattern, and spectral Doppler may show focal acceleration, spectral broadening, and post-stenotic turbulence [4,7]. The confidence of the examination increases when these findings are concordant.

Unlike carotid stenosis, vertebral artery stenosis has less universally accepted velocity criteria. A focal PSV rise is suspicious when it occurs at the vertebral origin and is accompanied by plaque and disturbed post-stenotic flow. In many educational protocols, PSV greater than 140 cm/s is used to suggest at least 50% stenosis, while PSV greater than 200 cm/s raises concern for more severe stenosis. These thresholds should be applied with caution and correlated with CTA or MRA if treatment decisions depend on the result [4,7,10].

**FIGURE 4.** Atherosclerotic stenosis at the origin of the vertebral artery. The key finding is the concordance between plaque on B-mode, aliasing and turbulent flow on color Doppler, and focal PSV elevation on spectral Doppler [4,7].




## Vertebral artery occlusion and dissection

Complete occlusion may occur as a consequence of advanced atherosclerosis, thromboembolism, dissection, trauma, or inflammatory vascular disease. On ultrasound, the expected findings are absence of color Doppler flow and absence of a spectral Doppler signal; echogenic intraluminal material may occasionally be seen. The distinction from severe hypoplasia can be difficult when the vessel is very small or the acoustic window is limited.

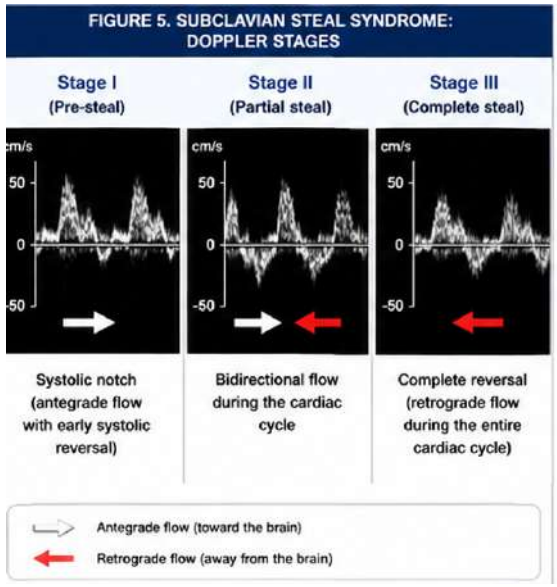
Vertebral artery dissection deserves particular attention because it is an important cause of posterior circulation stroke in young and middle-aged adults [2]. It may be spontaneous or follow cervical trauma, abrupt neck movement, sports injury, or neck manipulation. Ultrasound may raise suspicion when it shows long-segment narrowing, irregular stenosis, an intramural hematoma, or turbulent flow. Nevertheless, CTA and MRA remain the main confirmatory examinations, especially if V3 or V4 involvement is suspected [2,7].

## Subclavian steal syndrome

Subclavian steal syndrome develops when a severe stenosis or occlusion of the proximal subclavian artery reverses flow in the ipsilateral vertebral artery. In this setting, blood is diverted from the posterior circulation toward the upper limb. Patients may report dizziness, vertigo, syncope, visual symptoms, or arm claudication, although the finding may also be detected incidentally [8].

Ultrasound is particularly helpful in this situation because it shows the direction of flow in real time. The waveform may progress from an early systolic notch in the pre-steal stage, to bidirectional flow in partial steal, and finally to retrograde flow throughout the cardiac cycle in complete steal.

**FIGURE 5.** Doppler stages of subclavian steal syndrome.
The sequence moves from pre-steal to partial steal and complete reversal; persistent retrograde vertebral flow is the hallmark of complete steal [8].




## Flow volume assessment

Flow volume can add useful context, especially when one vertebral artery is dominant, when hypoplasia is suspected, or when symptoms suggest vertebrobasilar insufficiency. The calculated value depends on both vessel diameter and mean velocity. Reference data proposed by Seidel and colleagues support the use of vertebral artery flow volume as part of posterior circulation hemodynamic assessment [9].

Reduced flow volume may support hypoplasia, severe stenosis, or a low-flow state, but it should not be interpreted in isolation. Because the calculation is highly sensitive to small errors in diameter measurement, the result should always be checked against waveform morphology, side-to-side comparison, and the clinical context.

## Pitfalls and artifacts

Several technical and interpretive pitfalls are worth emphasizing. Incorrect angle correction may either overestimate or underestimate PSV. Cervical osteophytes may obscure the V2 segment. A markedly hypoplastic artery may be mistaken for occlusion. Color aliasing alone is not proof of stenosis unless spectral Doppler confirms focal acceleration. Finally, normal side-to-side asymmetry should not be labelled as disease without supporting hemodynamic or clinical evidence.

A reliable examination therefore starts with anatomic identification of the vessel, followed by confirmation of flow direction, optimization of color settings, careful angle correction, bilateral comparison, and correlation with symptoms and vascular risk factors.

## Role of CTA and MRA

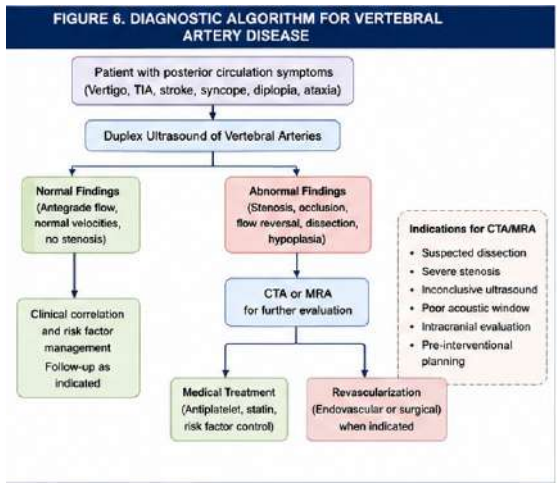
Duplex ultrasound and cross-sectional angiography answer related but different questions. Ultrasound is dynamic, inexpensive, repeatable, and well suited for assessing flow direction; however, it is operator dependent and has limited access to distal V3 and intracranial V4 segments. CTA offers high spatial resolution and is often useful for vertebral origin stenosis, calcified plaque, dissection, and pre-interventional mapping. MRA avoids ionizing radiation and may be preferable when iodinated contrast is contraindicated, although availability, cost, and flow-related artifacts can be limiting.

CTA or MRA is reasonable when ultrasound suggests severe stenosis, occlusion, dissection, or intracranial disease, or when the ultrasound result is inconclusive despite persistent posterior circulation symptoms [2,7,10].

## Practical diagnostic algorithm

Evaluation usually begins with the clinical question. In patients with symptoms suggestive of posterior circulation involvement, such as vertigo, diplopia, ataxia, dysarthria, syncope, transient ischemic attack, or stroke, duplex ultrasound can be used to assess the carotid and vertebral systems. Normal findings may be managed according to clinical risk and symptom evolution. Abnormal or uncertain findings--including suspected stenosis, occlusion, dissection, flow reversal, or marked hypoplasia--should lead to CTA or MRA when the result is likely to affect treatment or follow-up.

**FIGURE 6.** Diagnostic algorithm for suspected vertebral artery disease. Duplex ultrasound can serve as an initial test, while CTA or MRA is recommended for abnormal or inconclusive findings, suspected dissection, severe stenosis, intracranial assessment, or pre-interventional planning [2,7,10].




## Structured reporting template

A useful report should state whether both vertebral arteries are visualized and patent, which side is dominant, the vessel diameter, PSV, EDV, waveform morphology, and flow direction. It should also mention any evidence of focal stenosis, occlusion, dissection, or a subclavian steal pattern. When a clinically relevant abnormality is found, the report should indicate whether CTA or MRA is recommended.

Example: Right vertebral artery: diameter 3.8 mm, antegrade low-resistance flow, PSV 42 cm/s, EDV 14 cm/s, without Doppler evidence of hemodynamically significant stenosis. Left vertebral artery: diameter 1.8 mm, antegrade low-volume flow, in keeping with hypoplasia. No Doppler evidence of subclavian steal. Recommendation: clinical correlation; CTA/MRA if symptoms persist or posterior circulation ischemia remains suspected.

**TABLE 2.** Summary of vertebral artery Doppler findings by condition. Findings should always be interpreted together with clinical context and, where indicated, confirmed with CTA or MRA.

| Condition | Diameter | Typical Doppler Findings |
|---|---|---|
| Normal | 3–5 mm | Antegrade low-resistance flow |
| Hypoplasia | <2 mm | Reduced PSV and flow volume |
| Stenosis | Variable | Focal PSV increase, turbulence |

| | | |
|---|---|---|
| Occlusion | Not measurable | Absent flow signal |
| Dissection | Variable | Irregular narrowing / turbulence |
| Subclavian steal | Variable | Retrograde flow |

## Conclusion

Vertebral artery Doppler ultrasonography remains useful in daily cerebrovascular imaging because it provides information that is not limited to anatomy: patency, flow direction, waveform morphology, and hemodynamic asymmetry can all be assessed at the bedside or in the vascular laboratory. Its strongest applications include recognition of vertebral artery hypoplasia, stenosis at the origin, occlusion, and the different stages of subclavian steal. The method also has clear limitations, particularly for distal V3 and intracranial V4 segments, and abnormal or equivocal findings should be integrated with CTA or MRA when management may change. Accurate interpretation depends on careful technique, knowledge of segmental anatomy, and avoidance of common pitfalls.

## Declarations

**Funding:** This review received no external funding.

**Conflicts of interest:** The authors declare that they have no competing interests.

**Ethics approval and consent:** Not applicable. This is an educational review of published literature and did not involve new studies on human participants or animals performed by the authors.

**Author contributions:** All authors contributed to the conception of the review, the literature review and interpretation, drafting and critical revision of the manuscript, and approved the final version.

**Data availability:** Data sharing is not applicable; no new datasets were generated or analysed. All sources are cited in the reference list.

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# *The Role of Physiotherapy in Optimizing Cardiorespiratory Function Through the Treatment of Postural Dysfunctions*

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**Abstract**

*The growing prevalence of sedentary lifestyles and prolonged static working positions, particularly among office workers, has contributed significantly to the development of postural dysfunctions. These dysfunctions are commonly associated*

*with musculoskeletal pain, especially in the cervical region, but their influence on cardiorespiratory function remains underexplored in clinical practice.*

*This paper aims to analyze the relationship between postural alterations, muscular activity, and respiratory mechanics, emphasizing the role of physiotherapy in optimizing cardiorespiratory function through the treatment of postural dysfunctions.*

*A narrative and analytical review approach was adopted through the structured analysis of contemporary scientific literature indexed in PubMed, Scopus, PEDro, and Google Scholar. The review focused on studies investigating the interaction between posture, electromyographic activity, respiratory function, and neuromuscular control in sedentary populations and individuals with chronic neck pain.*

*The analyzed evidence demonstrates that forward head posture, thoracic kyphosis, and reduced thoracic mobility negatively influence respiratory mechanics and ventilatory efficiency. Postural dysfunctions are associated with increased activation of cervical and accessory respiratory muscles, reduced diaphragmatic contribution, and decreased respiratory muscle performance. Integrated physiotherapeutic interventions combining postural correction, respiratory training, and neuromuscular re-education were shown to improve respiratory efficiency, reduce pain, and enhance functional performance.*

*Postural dysfunctions should be considered multidimensional functional disorders that affect both musculoskeletal and cardiorespiratory systems. Physiotherapy plays a critical role in restoring the interaction between posture and respiration through integrated therapeutic approaches. Further empirical and longitudinal studies are needed to strengthen the evidence regarding the clinical effectiveness of these interventions.*

***Keywords:*** *Physiotherapy; posture; cardiorespiratory function; breathing; electromyography; musculoskeletal dysfunctions; sedentary lifestyle*

## Introduction

In recent decades, transformations in lifestyle and work organization have shifted a substantial proportion of the population toward sedentary activities, making the office environment one of the most characteristic contexts of this change. Prolonged computer use and sustained static postures have created a reality in which office workers spend approximately 70–85% of their working time in a seated position [1], a behavioral pattern strongly associated with the increasing prevalence of musculoskeletal disorders. Neck pain, reported by nearly 50–70% of individuals during their lifetime [2], represents one of the most common manifestations of this phenomenon, reflecting not only a significant clinical burden but also considerable socioeconomic implications. Recent evidence suggests that prolonged sedentary behavior affects not only the musculoskeletal

system but also systemic physiological functions, including cardiorespiratory and metabolic capacity [3].

Despite these findings, clinical management of such disorders remains predominantly focused on the treatment of local symptoms, particularly pain reduction. Although this approach may provide short-term relief, it often fails to address the functional mechanisms underlying the disorder. In this context, posture should not be interpreted solely as a static biomechanical element but rather as a dynamic factor influencing the organization and coordination of multiple physiological systems. Contemporary literature increasingly emphasizes that interactions among biological systems are essential for understanding both functional performance and dysfunction, supporting a transition toward more integrative interpretative models [4].

One of the least explored dimensions within this framework is the influence of postural dysfunctions on respiratory function. Alterations in head position and thoracic alignment may restrict thoracic cage mobility and negatively affect ventilatory mechanics, leading to shallower and less efficient breathing patterns. This interaction between biomechanics and physiology establishes a functional relationship in which musculoskeletal imbalances directly influence cardiorespiratory performance. Recent evidence demonstrates that postural restrictions may reduce respiratory capacity and increase reliance on accessory respiratory muscles, consequently impairing overall functional efficiency [5].

From this perspective, the analysis of the relationship between posture and breathing represents not only an expansion of the theoretical framework but also a clinical necessity for the development of more effective therapeutic approaches. By considering the human body as an integrated system in which structure and function are inseparable, a stronger basis is created for interventions aimed not only at symptom reduction but also at the optimization of overall function. Within this framework, physiotherapy emerges as a key discipline capable of mediating this interaction through the integration of postural correction, respiratory training, and neuromuscular control strategies. Such an approach is consistent with contemporary directions in research and clinical practice, where the focus is progressively shifting from segmental treatment toward restoration of systemic functional balance.

## Theoretical Framework

Within a scientific environment increasingly oriented toward understanding human function beyond traditional disciplinary boundaries, the analysis of the relationship between musculoskeletal structure and respiratory function represents an effort to redefine the interpretation of performance and dysfunction. Posture, as a dynamic equilibrium between skeletal structures and coordinated muscular

activity, should not be considered merely a static state but rather a continuous adaptive process responding to functional and environmental demands. Under conditions of prolonged exposure to static postures, this balance gradually deteriorates, contributing to the development of musculoskeletal imbalances and increased functional load on cervical and thoracic segments.

Evidence suggests that non-neutral postures may increase cervical muscle activation by up to 30–40%, creating a physiological basis for muscular fatigue and neuromuscular dysfunction [6]. More recent studies indicate that these adaptations are not exclusively mechanical but represent complex neurophysiological responses to prolonged postural stress [7].

In this context, muscular fatigue emerges as a multidimensional phenomenon involving both peripheral and central mechanisms that influence contractile capacity and motor activation patterns [8,9]. This process becomes particularly evident during prolonged static activities, where reductions in motor efficiency are associated with measurable changes in electromyographic (EMG) signals. Contemporary literature suggests that alterations in motor control and muscular load distribution represent key mechanisms in the transition from acute fatigue to chronic dysfunction [10].

A fundamental aspect of this framework is the direct interaction between posture and respiratory function. The respiratory system, which is closely integrated with the musculoskeletal structure, is significantly influenced by thoracic and cervical alignment. Postural deviations such as thoracic kyphosis and forward head posture may restrict thoracic expansion and promote a more superficial and less efficient breathing pattern. Individuals with chronic neck pain frequently demonstrate significant reductions in respiratory muscle strength and endurance [11], while dysfunctional breathing patterns have been associated with increased cervical muscle activity and altered neuromuscular coordination [12].

Recent investigations further demonstrate that thoracic mobility limitations and altered breathing strategies directly affect functional capacity and tolerance to physical activity [13], reinforcing the concept of an inseparable interaction between biomechanics and physiology.

Within this interaction, the diaphragm represents a critical structure linking respiratory and postural functions. Beyond its ventilatory role, the diaphragm contributes to trunk stability through the regulation of intra-abdominal pressure and coordination with stabilizing muscles, becoming activated even prior to movement initiation in response to postural demands [14]. More recent evidence suggests that diaphragmatic dysfunction influences not only respiration but also postural control and movement efficiency, placing the diaphragm at the center of a complex functional network [15].

In light of these findings, contemporary physiotherapy is progressively moving toward integrative models in which interventions target not only structural correction but also restoration of functional balance through postural exercises,

motor control re-education, and respiratory training. Evidence indicates that combined interventions improve neuromuscular coordination and functional performance [16], while the integration of electromyography with respiratory assessment provides a more advanced framework for targeted evaluation and intervention. Overall, this theoretical analysis highlights the necessity of understanding human function as an integrated process in which the interaction between posture and breathing plays a decisive role in maintaining efficiency and preventing chronic dysfunctions, reflecting the most recent developments in clinical research and physiotherapy practice.

## Methodology

### *Search Methodology*

This paper was developed using a narrative and analytical literature review approach aimed at exploring the interaction between postural dysfunctions and cardiorespiratory function. A structured search of scientific literature was conducted using the electronic databases PubMed, Scopus, PEDro, and Google Scholar. The literature search included studies published between 2000 and 2024 using combinations of the following keywords:

- forward head posture,
- respiratory dysfunction,
- thoracic mobility,
- chronic neck pain,
- electromyography (EMG),
- respiratory muscle activity,
- physiotherapy,
- posture and breathing.

Boolean operators (AND/OR) were applied to optimize the search strategy.

### *Inclusion Criteria*

The review included:

- peer-reviewed scientific articles,
- clinical and observational studies,
- systematic and narrative reviews,
- studies published in English,

- studies involving adults aged 18–65 years,
- studies investigating the relationship between posture, respiratory function, muscular activity, or neuromuscular control.

### *Exclusion Criteria*

The following studies were excluded:

- studies involving severe neurological or cardiorespiratory diseases,
- pediatric populations,
- non-scientific publications,
- conference abstracts without full-text availability,
- duplicate publications,
- studies lacking methodological clarity.

### *Literature Selection Process*

An initial screening identified approximately 65 potentially relevant articles. After title and abstract evaluation, 38 studies were selected for full-text analysis. Finally, 27 studies meeting the inclusion criteria were incorporated into the conceptual synthesis of this review.

**FIGURE 1:** PRISMA 2020 flow diagram illustrating the literature selection process

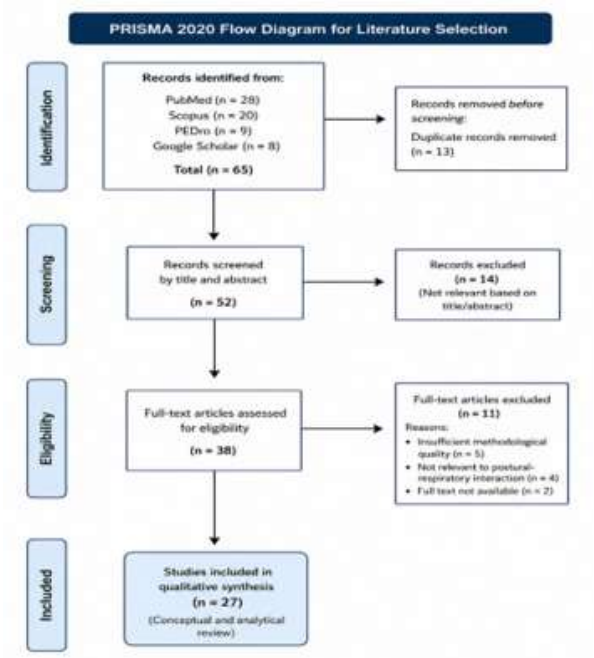


**TABLE 1:** Literature Synthesis Table

| Author | Population | Main Findings | Clinical Relevance |
|---|---|---|---|
| Kapreli et al. [11] | Patients with chronic neck pain | Reduced respiratory muscle strength and endurance | Demonstrates relationship between cervical dysfunction and respiratory impairment |
| Kocjan et al. [12] | Healthy adults | Altered breathing patterns increase cervical muscle activity | Supports interaction between respiration and postural muscles |
| Andersen et al. [6] | Office workers | Increased cervical muscle activation in non-neutral posture | Highlights biomechanical overload in sedentary work |
| Hodges & Gandevia [14] | Healthy adults | Diaphragm involved in postural stabilization | Supports integrated respiratory-postural model |
| Lee et al. [13] | Adults with thoracic postural alterations | Thoracic posture influences respiratory function | Reinforces importance of thoracic mobility |
| Janssens et al. [17] | Adults with respiratory dysfunction | Respiratory muscle dysfunction affects postural control | Suggests need for integrated rehabilitation |
| Tong et al. [18] | Adults undergoing respiratory training | Respiratory training improves functional performance | Supports physiotherapy-based interventions |

## Limitations of the Study

This paper presents several limitations that should be acknowledged. First, the study is based on a narrative analytical approach and does not include original experimental or clinical data. Second, the reviewed studies demonstrate methodological heterogeneity regarding population characteristics, assessment tools, and intervention protocols, limiting direct comparison between findings. Third, most available studies involve relatively small sample sizes and focus predominantly on chronic neck pain populations. Additionally, variations in electromyographic protocols and respiratory assessment methods may influence the consistency of findings. Finally, the absence of longitudinal evidence limits the ability to establish causal relationships between postural dysfunctions and cardiorespiratory impairment.

### *Future Research Directions*

Future studies should focus on:

- longitudinal investigations examining the long-term effects of postural dysfunctions on respiratory performance;
- randomized controlled trials evaluating integrated physiotherapy interventions;

- combined use of electromyography and spirometry for comprehensive assessment;
- investigation of diaphragm function during postural tasks;
- workplace prevention programs targeting sedentary populations;
- development of standardized rehabilitation protocols integrating postural and respiratory training.

Further multidisciplinary research may contribute to the development of evidence-based clinical guidelines for the management of postural-respiratory dysfunctions.

## Results

The literature analyzed in this review demonstrates a consistent relationship between postural dysfunctions and alterations in respiratory and neuromuscular function. Across the included studies, forward head posture, thoracic kyphosis, and reduced thoracic mobility emerged as the most frequently reported postural alterations associated with impaired respiratory mechanics.

Several studies identified increased cervical muscle activation during prolonged static postures, particularly among office workers and individuals with chronic neck pain. Electromyographic findings consistently demonstrated increased muscular activity and altered motor recruitment patterns in non-neutral postures, suggesting elevated biomechanical loading and neuromuscular fatigue [6,7].

Respiratory dysfunctions associated with postural alterations included reduced respiratory muscle strength, decreased thoracic expansion, inefficient ventilatory mechanics, and increased reliance on accessory respiratory muscles. Kapreli et al. [11] reported significant reductions in respiratory muscle performance in patients with chronic neck pain, while Kocjan et al. [12] demonstrated that altered breathing patterns significantly increased cervical muscle activity.

The reviewed evidence also highlighted the central role of the diaphragm in the interaction between posture and breathing. Studies indicated that impaired diaphragmatic activation negatively influences trunk stability, postural control, and respiratory efficiency [14,15].

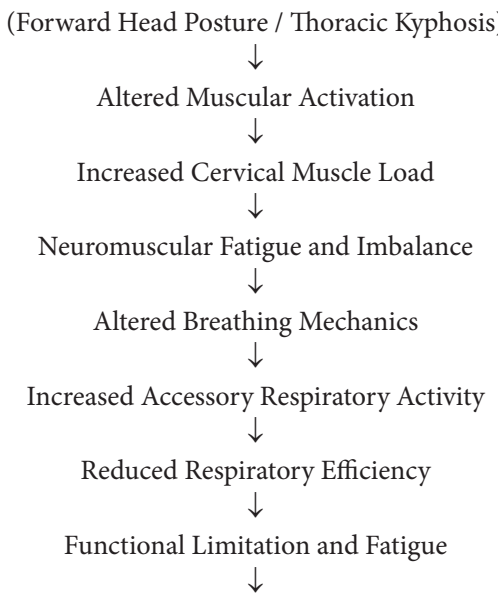
Integrated physiotherapy interventions combining postural correction, respiratory exercises, motor control re-education, and neuromuscular training demonstrated the most consistent improvements in pain reduction, respiratory efficiency, and functional performance. Several studies reported improvements ranging from 20–30% in functional and respiratory parameters following multidisciplinary rehabilitation approaches [16,18].

Overall, the findings suggest that postural dysfunctions and respiratory impairments are functionally interconnected and should be evaluated and treated through integrated physiotherapeutic strategies.

**TABLE 2.** Functional Interaction Between Postural Dysfunctions and Respiratory Impairment

| Functional Alteration | Physiological Consequence | Clinical Manifestation | Physiotherapy Implication |
|---|---|---|---|
| Forward head posture | Increased cervical muscle activation | Neck pain and muscular fatigue | Postural correction and motor control exercises |
| Thoracic kyphosis | Reduced thoracic expansion | Decreased ventilatory efficiency | Thoracic mobility and breathing exercises |
| Reduced diaphragmatic activation | Impaired trunk stabilization | Inefficient breathing mechanics | Diaphragmatic training |
| Increased accessory muscle activity | Increased energy expenditure | Respiratory fatigue | Respiratory re-education |
| Neuromuscular imbalance | Altered motor recruitment | Reduced functional performance | Neuromuscular retraining |

**FIGURE 2.** Conceptual Model of the Interaction Between Posture, Breathing, and Neuromuscular Function



↓ Integrated Physiotherapy ↓

• Postural Correction
• Respiratory Muscle Training
• Neuromuscular Re-education
• Motor Control Exercises
• Thoracic Mobility Exercises

↓

Improved Functional and Cardiorespiratory Performance

## Discussion

The findings of this review emphasize that postural dysfunctions should not be considered merely localized musculoskeletal problems, but rather functional disorders that significantly influence the coordination between muscular activity and respiratory function. The observed reduction in respiratory efficiency by approximately 10–20% and the decrease in respiratory muscle strength by 15–25% among individuals with chronic neck pain [11,19] demonstrate that the impact of posture is both measurable and functionally significant. These findings are further supported by contemporary literature highlighting the interaction between neuromuscular control and respiratory function under conditions of prolonged postural stress [20].

Within this context, traditional therapeutic approaches focusing exclusively on pain reduction appear limited. Treating symptoms without addressing alterations in muscular activity and neuromuscular coordination often fails to produce sustainable outcomes. The increase in cervical muscle activation by up to 30–40% in non-neutral postures [6] reflects a persistent functional overload associated with muscular fatigue and altered motor control strategies. Consistent with these observations, research in motor control suggests that changes in muscular recruitment and postural stability are closely related to the way the body manages functional loading [10].

Analyses of muscular activity further indicate that prolonged exposure to static positions is associated with measurable alterations in EMG signal characteristics, including increased amplitude and median frequency shifts, which are linked to muscular fatigue and reduced contractile efficiency [8,9]. These changes directly influence the activation of accessory respiratory muscles, promoting inefficient load distribution. More recent evidence suggests that such neuromuscular adaptations represent part of a broader process of functional reorganization in response to chronic stress exposure [21].

In this framework, the increased use of accessory respiratory muscles by approximately 20–30% above physiological levels [12] may be interpreted as a compensatory strategy that, over time, reduces respiratory efficiency and increases energy expenditure. Simultaneously, the reduction in diaphragmatic activation during postural tasks by approximately 10–15% [14] reflects a disruption in the coordination between postural and respiratory functions, further reinforcing the cycle of dysfunction.

These findings support the necessity for a more integrated physiotherapeutic approach. Postural correction combined with respiratory training and neuromuscular control re-education aims not only to reduce symptoms but also to restore functional activation patterns. Such interventions have demonstrated improvements of approximately 25–30% in functional parameters and pain reduction [16]. Furthermore, recent literature confirms that integrated rehabilitation programs may positively influence both biomechanical and respiratory performance, contributing to more sustainable functional outcomes [18].

Nevertheless, several limitations should be considered when interpreting these findings. Most of the studies included in the present review demonstrate methodological heterogeneity regarding population characteristics, assessment tools, intervention protocols, and outcome measures. Additionally, the majority of available studies involve relatively small sample sizes and predominantly focus on chronic neck pain populations, limiting the generalizability of findings. The narrative nature of this review also limits the possibility of quantitative synthesis and meta-analytic interpretation.

Future research should prioritize longitudinal and randomized controlled studies investigating the long-term effects of integrated physiotherapy interventions on respiratory and postural function. Further investigation combining electromyography, respiratory assessment, and functional performance measures may contribute to a more comprehensive understanding of the interaction between musculoskeletal and cardiorespiratory systems.

Overall, postural and respiratory dysfunctions appear to be inseparably interconnected. Alterations in muscular activity and neuromuscular control represent key mechanisms linking structure and function, reinforcing the argument for integrative approaches in both clinical management and scientific research.

## Practical Implications

The findings of this review have important implications for physiotherapy practice, particularly in sedentary populations where the interaction between postural dysfunctions and respiratory impairment is becoming increasingly prevalent.

Contemporary evidence indicates that rehabilitation programs integrating postural correction with respiratory training may produce clinically meaningful improvements in pain reduction, ventilatory efficiency, muscular coordination, and overall functional performance [16]. More recent investigations have further demonstrated that integrated physiotherapeutic interventions contribute not only to symptom management but also to the restoration of more efficient neuromuscular and respiratory activation patterns, thereby supporting sustainable functional recovery [20].

These findings suggest that fragmented therapeutic approaches focusing exclusively on isolated symptoms or anatomical regions may be insufficient for achieving long-term clinical outcomes. Instead, rehabilitation should be conceptualized as a multidimensional and system-oriented process in which structural, neuromuscular, and respiratory components are addressed simultaneously. Within this framework, postural correction should be combined with interventions targeting breathing mechanics, thoracic mobility, motor control, and muscular endurance in order to optimize functional integration between systems.

From a clinical perspective, improving respiratory mechanics through physiotherapeutic intervention may reduce excessive reliance on accessory respiratory muscles and minimize compensatory cervical muscle overactivation. This may subsequently decrease mechanical stress on cervical and thoracic structures, improve movement efficiency, and reduce fatigue during functional activities. In addition, contemporary literature emphasizes that motor control and breathing re-education contribute significantly to optimized load distribution and reduced functional stress across spinal segments [10].

Another relevant implication concerns the increasing importance of individualized rehabilitation strategies. The integration of electromyographic assessment, respiratory function evaluation, and postural analysis may facilitate a more precise identification of functional imbalances and compensatory neuromuscular strategies. Such an approach allows clinicians to develop more targeted and personalized rehabilitation protocols. Recent studies suggest that combining electromyography with respiratory assessment substantially improves clinical precision and intervention effectiveness [17], supporting the implementation of evidence-based physiotherapy models.

Furthermore, patient education should be considered a central component of rehabilitation. Increasing patient awareness regarding posture, breathing patterns, ergonomic habits, and sedentary behavior may contribute significantly to long-term adherence and prevention of symptom recurrence. In occupational settings, preventive physiotherapy programs focusing on ergonomics, postural awareness, workplace mobility, and respiratory exercises may reduce the incidence of chronic musculoskeletal and respiratory dysfunctions among office workers and sedentary populations.

Finally, these findings reinforce the importance of interdisciplinary collaboration in rehabilitation practice. Effective management of postural-respiratory dysfunctions may require coordinated interventions involving physiotherapists, rehabilitation physicians, occupational health specialists, ergonomists, and exercise professionals. Such multidisciplinary approaches may optimize both functional outcomes and quality of life in individuals affected by chronic postural dysfunctions.

## Conclusions

Postural dysfunctions should be understood as multidimensional functional disorders that influence not only the musculoskeletal system but also respiratory and cardiorespiratory function. The evidence analyzed in this review demonstrates a significant interaction between postural alignment, neuromuscular control, and breathing mechanics, particularly among sedentary populations and individuals with chronic neck pain.

Alterations such as forward head posture, thoracic kyphosis, and reduced thoracic mobility appear to contribute to inefficient breathing patterns, increased activation of accessory respiratory muscles, impaired diaphragmatic function, and reduced ventilatory efficiency. These physiological and biomechanical changes may negatively affect functional capacity, movement efficiency, and overall quality of life.

The findings further suggest that integrated physiotherapy approaches combining postural correction, respiratory training, motor control exercises, and neuromuscular re-education provide more effective and sustainable outcomes compared to isolated therapeutic interventions. Within this context, physiotherapy has the potential not only to optimize structural alignment but also to restore functional integration between respiratory and musculoskeletal systems.

Overall, the interaction between posture and respiration supports the concept of the human body as an interconnected functional system in which dysfunction in one component inevitably influences others. Consequently, rehabilitation strategies should adopt multidimensional and evidence-based approaches aimed at restoring systemic functional balance rather than focusing solely on symptom reduction.

Further longitudinal, experimental, and multidisciplinary studies are necessary to strengthen the current evidence base and support the development of standardized clinical protocols for the assessment and management of postural-respiratory dysfunctions.

**Conflict of Interest**
The authors declare no conflict of interest.
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