Are We Moving Toward Curative Approaches in Chronic Lymphocytic Leukemia?

Martin Šimkovič[1,*], Eva Vejražková[1], Dominika Écsiová[1], Pavel Vodárek[1]

ABSTRACT

Over the past decade, chronic lymphocytic leukemia (CLL) management has undergone a fundamental transformation driven by the introduction of oral targeted inhibitors. Continuous Bruton tyrosine kinase (BTK) inhibition and time-limited BCL-2–based therapy has replaced chemoimmunotherapy as the standard of care, improving survival and quality of life. Ibrutinib and its next-generation analogues, acalabrutinib and zanubrutinib, provide durable disease control with improved safety. At the same time, venetoclax combined with anti-CD20 antibodies enables deep and measurable residual disease (MRD)-negative remissions within fixed-duration regimens. Recent trials have demonstrated the feasibility of MRD-guided treatment cessation and the potential benefit of combining BTK and BCL-2 inhibition to achieve durable, chemotherapy-free responses. Ongoing research focuses on optimizing treatment sequencing, overcoming acquired resistance through non-covalent BTK inhibitors, and integrating immunotherapeutic modalities such as bispecific antibodies and CAR-T cells.

The current paradigm emphasizes individualized, biomarker- and comorbidity-driven therapy based primarily on *TP53* and IGHV status, with treatment selection tailored to patient fitness, tolerance, and long-term safety. This review summarizes contemporary evidence, clinical practice recommendations, and future directions in the targeted management of CLL.

KEYWORDS

chronic lymphocytic leukemia; BTK inhibitors; BCL2 inhibitors; venetoclax; acalabrutinib; targeted therapy; comorbidities; personalized medicine

AUTHOR AFFILIATIONS

[1] 4th Department of Internal Medicine, University Hospital Hradec Králové, Faculty of Medicine in Hradec Králové, Charles University, Hradec Králové, Czech Republic

* Corresponding author: 4th Department of Internal Medicine, University Hospital Hradec Králové, Sokolská 581, 500 05 Hradec Králové, Czech Republic; simkovicm@lfhk.cuni.cz

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INTRODUCTION

Over the past decade, the therapeutic landscape of chronic lymphocytic leukemia (CLL) has evolved more profoundly than at any other time in its history. Once regarded as an incurable malignancy treated with largely palliative intent, CLL has become a prototype of precision oncology. The emergence of oral inhibitors targeting key signaling and apoptotic pathways has redefined therapeutic goals and outcomes, thereby establishing them as cornerstones of targeted treatment approaches in CLL (see Fig. 1). These advances have led to unprecedented improvements in survival and have shifted the therapeutic paradigm from chemoimmunotherapy to targeted oral medications (1, 2).

The biological understanding of CLL has expanded considerably. Recurrent cytogenetic and molecular abnormalities, including deletions of 13q14.3, 11q22–23, and 17p13, together with mutations in TP53, NOTCH1, SF3B1, and BIRC3, have been identified as critical determinants of prognosis and treatment response (3). The mutational status of the immunoglobulin heavy-chain variable region (IGHV) remains among the most potent predictors of clinical course, distinguishing an indolent, antigen-experienced form of the disease from its aggressive, unmutated counterpart (showing <2% difference from the germline sequence) (4). Furthermore, insights into B-cell receptor (BCR) signalling, the influence of the tumour microenvironment, and dysregulation of apoptosis have provided the biological rationale for inhibiting the BCR pathway and the antiapoptotic protein B-cell lymphoma 2 (BCL-2) (5).

Introducing the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, the phosphoinositide-3-kinase δ inhibitor idelalisib, and the BCL-2 inhibitor venetoclax has revolutionized the management of CLL. Ibrutinib demonstrated sustained efficacy in treatment-naïve and relapsed settings, including patients with high-risk genomic features (6, 7). However, its off-target activity has been associated with cardiovascular adverse events and resistance mutations, prompting the development of next-generation, more selective BTK inhibitors such as acalabrutinib and zanubrutinib (8–10). In contrast, venetoclax induces deep remissions with frequent achievement of undetectable minimal residual disease (uMRD), thus enabling time-limited, chemotherapy-free treatment when combined with anti-CD20 monoclonal antibodies. These therapeutic advances have transformed CLL into a chronic, functionally curable condition in selected cases (11–13).

Despite remarkable progress, several clinically relevant questions remain unresolved. Optimal sequencing and duration of targeted therapies continue to be explored, as do the criteria for selecting patients suitable for fixed-duration versus continuous treatment. Moreover, the long-term immunologic consequences of these agents, the persistent risk of secondary malignancies, and the management of Richter transformation remain active research areas. Integrating genomic risk stratifi-

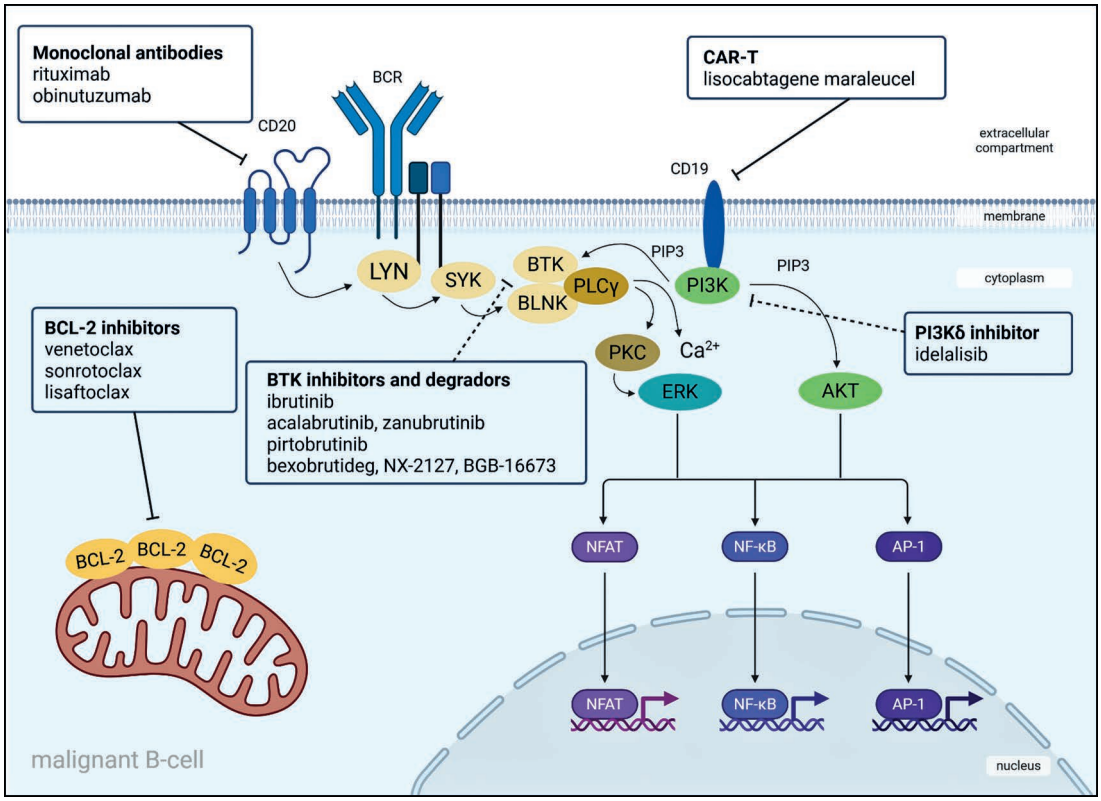

Fig. 1 Schematic representation of the sites of action of major therapeutic agents for CLL in the era of targeted oral inhibitors.
AKT, Ak Strain Transforming; BCR, B-cell receptor; Bcl-2, B-cell lymphoma 2; BLNK, B-cell linker protein; CAR-T, chimeric antigen receptor T cells; CD, cluster of differentiation; LYN, Lck/Yes novel tyrosine kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NFAT, nuclear factor of activated T cells; PI3K, phosphatidylinositol-3-kinase; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PLCγ, phospholipase C gamma; SYK, spleen tyrosine kinase. Created with BioRender.com.

cation and MRD monitoring into clinical algorithms may further refine individualized treatment approaches in the near future.

This review summarizes the current state of evidence and practical management of CLL in the era of targeted inhibitors, emphasizing treatment selection, sequencing strategies, immune implications, and challenges that will define the next decade of therapeutic development.

DIAGNOSIS AND PROGNOSTIC FACTORS

The diagnosis of chronic lymphocytic leukemia is based on the identification of a persistent clonal population of small, mature B lymphocytes in the peripheral blood exceeding 5×10^9/L, typically coexpressing CD5, CD19, CD23, and surface immunoglobulin of low density (14, 15). Flow cytometry remains the cornerstone of diagnosis, distinguishing CLL from other mature B-cell neoplasms, particularly mantle cell lymphoma, which is characterized by cyclin D1 overexpression and t(11;14)(q13;q32). Bone marrow examination is not routinely required for diagnosis, but may be helpful to clarify cytopenias or to confirm remission status after therapy. Lymph node biopsy should be reserved for cases with atypical immunophenotype or suspected Richter transformation.

The last decade has witnessed a significant shift toward molecularly informed risk stratification. Conventional clinical staging systems (Rai and Binet – see Table 1) remain relevant for initial assessment, yet their prognostic capacity is limited in the context of targeted therapies (16, 17). Modern prognostication relies on integrating cytogenetic, molecular, and immunogenetic parameters. Fluorescence in situ hybridization (FISH) is mandatory before initiating treatment and should include detection of del(17p), del(11q), trisomy 12, and del(13q). Among these, deletion 17p, usually accompanied by *TP53* mutation, confers the most adverse prognosis, predicting resistance to chemoimmunotherapy and inferior outcomes even with novel agents (15, 18, 19). Consequently, testing for *TP53* mutations and IGHV mutational status is now considered obligatory before selecting treatment.

The mutational status of IGHV divides CLL into two biologically distinct entities. Patients with mutated IGHV display an indolent clinical course and may achieve long-lasting remissions with time-limited therapy, whereas those with unmutated IGHV show increased dependence on B-cell receptor (BCR) signalling and derive greater benefit from continuous BTK inhibition. Specific stereotyped subsets, such as subset #2 utilizing *IGHV3-21*/*IGLV3-21* R110, are associated with aggressive disease irrespective of IGHV mutation status, underlining the complexity of CLL immunogenetics (4, 20, 21).

High-throughput sequencing studies have identified additional recurrently mutated genes affecting diverse cellular pathways – *NOTCH1*, *SF3B1*, *BIRC3*, *RPS15*, *MYD88*, *ATM*, and others – each conferring distinct biological and prognostic implications (3, 22, 23). While the cumulative number of driver mutations correlates with inferior outcome, only *TP53* and IGHV status currently influence therapeutic decision-making in routine practice. Nonetheless, broader genomic profiling provides valuable insight into clonal evolution, therapy resistance, and risk of Richter transformation.

Assessment of measurable residual disease (MRD) has emerged as an independent predictor of progression-free and overall survival, irrespective of treatment modality. Advances in flow cytometry and next-generation sequencing have enabled MRD detection below 10^{-5}, and uMRD has become a key endpoint in time-limited regimens combining venetoclax with anti-CD20 antibodies (24). Although MRD-guided therapy is not yet universally adopted outside clinical trials, its incorporation into future treatment algorithms is anticipated.

Finally, a comprehensive evaluation of comorbidities, performance status, and renal function remains essential for individualized management (25). Integrating biological and clinical variables – summarized in composite tools such as the CLL-International Prognostic Index (CLL-IPI, see Table 2) – allows refined risk stratification and optimization of therapy selection in the era of targeted inhibitors (26). Importantly, treatment initiation for CLL is indicated only after the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for active or symptomatic disease have been met (Table 3) (18).

FIRST-LINE TREATMENT IN THE ERA OF TARGETED INHIBITORS

GENERAL OVERVIEW

The introduction of oral targeted inhibitors has profoundly reshaped the therapeutic algorithm for treatment-naïve patients with CLL. Chemoimmunotherapy (CIT) regimens such as fludarabine-cyclophosphamide-rituximab (FCR) or bendamustine-rituximab (BR), once the standard of care, have been mostly replaced by chemotherapy-free strategies (27, 28). These novel regimens combine inhibit-

Tab. 1 Rai and Binet Staging Systems in CLL.

Rai stage	Risk category	Findings (Rai)	Binet stage	Findings (Binet)
0	Low	Lymphocytosis[1]	A	No cytopenia and ≤2 lymphoid areas involved
I	Intermediate	Lymphadenopathy[2]	B	No cytopenia and >3 lymphoid areas involved
II	Intermediate	Hepatosplenomegaly[2]	C	Presence of anemia or thrombocytopenia
III	High	Anemia[3]		
IV	High	Thrombocytopenia[4]		

[1] Lymphocyte count > 5×10^9/L; [2] On physical examination; [3] Hemoglobin level < 110 g/l; [4] Platelet count < 100×10^9/L

Tab. 2 International Prognostic Index for Chronic Lymphocytic Leukemia (CLL-IPI).

Domain	Factor or CLL-IPI score	Points	Risk category / 5-year TFS
Prognostic factors contributing to the CLLIPI score			
Prognostic factor	Del17p on FISH or TP53 mutation	4	
	Unmutated IGHV genes	2	
	Serum β2 microglobulin >3.5 mg/L	2	
	Binet B, C or Rai stage I–IV	1	
	Age >65 years	1	
Risk stratification based on cumulative CLLIPI score			
Risk group	Cumulative CLLIPI score 0–1		Low risk – 78% 5-year TFS
	Cumulative CLLIPI score 2–3		Intermediate risk – 54% 5-year TFS
	Cumulative CLLIPI score 4–6		High risk – 32% 5-year TFS
	Cumulative CLLIPI score 7–10		Very high risk – 0% 5-year TFS

Tab. 3 iwCLL Criteria for the Definition of Symptomatic or Active Disease.

Criterion	Definition
Progressive bone marrow failure	Development or worsening of anemia and/or thrombocytopenia. Cut-off levels of Hb < 10 g/dL or platelet counts < 100 × 10^9/L are generally regarded as indications for treatment.
Splenomegaly	Massive splenomegaly (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
Lymphadenopathy	Massive lymph nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
Progressive lymphocytosis	Increase of ≥ 50% over 2 months, or lymphocyte doubling time < 6 months, determined by linear regression of absolute lymphocyte counts measured at 2-weekly intervals.
Autoimmune cytopenias	Autoimmune anemia or thrombocytopenia poorly responsive to corticosteroids.
Extranodal involvement	Symptomatic or functional extranodal disease (e.g., skin, kidney, lung, spine).
Disease-related (B) symptoms	Any of the following: • Unintentional weight loss ≥ 10% within 6 months • Significant fatigue (ECOG PS ≥ 2; unable to work or perform usual activities) • Fevers ≥ 38.0 °C (≥ 100.5 °F) for ≥ 2 weeks without evidence of infection • Night sweats for ≥ 1 month without evidence of infection

ing key intracellular signalling pathways or apoptosis regulators with anti-CD20 monoclonal antibodies, achieving durable remissions and improved tolerability across diverse patient populations.

Bruton tyrosine kinase (BTK) inhibitors have become a cornerstone of first-line therapy. In several pivotal trials, Ibrutinib, the first-in-class covalent BTK inhibitor, demonstrated clear superiority over CIT (6, 24, 29). In the ECOG-1912 study, continuous ibrutinib plus rituximab significantly reduced the risk of progression and death compared with FCR in younger, fit patients (30). Similarly, in the RESONATE-2 and iLLUMINATE trials, ibrutinib-based regimens showed substantial improvements in progression-free survival (PFS) and overall survival (OS) versus chlorambucil-based chemoimmunotherapy in elderly or comorbid patients (6, 31). These results firmly established BTK inhibition as the evidence-based first-line approach irrespective of fitness status.

Nevertheless, the clinical use of ibrutinib is influenced by its off-target toxicity, including atrial fibrillation, hypertension, and bleeding, as well as by resistance mutations in *BTK* (*C481S, T474I, L528W, A428D*) or *PLCγ2* (8, 32). Developing second-generation covalent BTK inhibitors such as acalabrutinib and zanubrutinib, characterized by greater selectivity and improved safety, has represented a significant step forward (33). In the ELEVATE-TN trial, acalabrutinib – with or without obinutuzumab – significantly prolonged PFS compared with obinutuzumab-chlorambucil, demonstrating a more favorable cardiovascular safety profile (34). Likewise, the SEQUOIA study confirmed the efficacy of zanubrutinib in treatment-naïve patients, including those with deletion 17p, with an 18-month PFS rate approaching 90%. These data firmly support next-generation BTK inhibitors as the current standard of care for patients eligible for continuous therapy (35).

FIXED-DURATION VENETOCLAX-BASED THERAPY

In contrast to continuous BTK inhibition, venetoclax – an oral, selective BCL-2 inhibitor – enables time-limited therapy through deep remissions and frequent achievement of uMRD (Table 4). The phase 3 CLL14 study established venetoclax plus obinutuzumab (Ven-Obi) as the preferred first-line regimen for older or comorbid patients. After six years of follow-up, median PFS reached 76 months, markedly exceeding that of obinutuzumab-chlorambucil (36 months), with sustained benefit beyond treatment completion. MRD negativity at the end of therapy predicted both prolonged remission and improved survival (11). However, patients with *TP53* aberrations or deletion 17p

Tab. 4 Long-Term Outcomes of Fixed-Duration Chemo-Free Regimens in CLL.

Study	Phase	Line	Treatment	PFS / Median PFS
CAPTIVATE (FD cohort)	2	1st line	I + V	5.5year PFS ≈ 65%
GLOW	3	1st line	I + V	5.5year PFS 51.7%
FLAIR	3	1st line	I + V	4year PFS 93.5%
CLL13	3	1st line	VenG	4year PFS 81.8%
CLL14	3	1st line	VenG	Median PFS 76.2 months
MURANO	3	RR CLL	V + R	Median PFS 54.7 months

FD – fixed duration, I – ibrutinib, V – venetoclax, R – rituximab, VenG – venetoclax + obinutuzumab, PFS – progression-free survival, RR – relapsed/refractory.

derived less durable benefit, highlighting the need for alternative strategies in this subgroup.

Venetoclax-based regimens are generally well tolerated, though careful monitoring for tumor lysis syndrome remains mandatory during dose ramp-up. The main limitation of fixed-duration therapy is the uncertainty of long-term disease control in high-risk patients. Ongoing studies aim to determine whether MRD-guided re-treatment or extended therapy can further optimize outcomes.

COMBINATORIAL STRATEGIES

Given the complementary mechanisms of BTK and BCL-2 inhibition, combined regimens have been explored to achieve deep remissions while avoiding indefinite therapy. In the phase 2 CAPTIVATE trial, sequential ibrutinib-venetoclax therapy produced uMRD in over 70% of treatment-naïve patients, leading to sustained PFS after discontinuation (Wierda et al. 2024). The randomized phase 3 GLOW study confirmed the superiority of this fixed-duration combination over obinutuzumab-chlorambucil in elderly patients (Niemann et al. 2023). Similar efficacy was observed in the CLL13 trial, where venetoclax-obinutuzumab-ibrutinib achieved the highest MRD-negative rates and 3-year PFS exceeding 90%, surpassing both chemoimmunotherapy and venetoclax-obinutuzumab doublet therapy (18). These data support the feasibility of intensive, time-limited triplet approaches for selected patients.

The next frontier involves integrating MRD-driven treatment cessation into clinical practice. The FLAIR and CAPTIVATE-MRD cohorts demonstrate that tailoring therapy duration based on uMRD achievement can maintain durable responses while reducing cumulative toxicity, cost, and treatment fatigue (36).

PRACTICAL CONSIDERATIONS AND PATIENT SELECTION

Current guidelines recommend BTK inhibitors or venetoclax-based therapy as standard options for first-line treatment (2, 15). The choice between continuous versus time-limited therapy should be individualized according to patient preference, comorbidities, genomic risk, and tolerance profile.

Fixed-duration regimens achieve excellent outcomes, particularly in patients with mutated IGHV and without *TP53* aberrations, where venetoclax–obinutuzumab, venetoclax-ibrutinib or venetoklax-acalabrutinib is often selected for its limited duration and potential to induce deep remissions. In patients with del(17p) or *TP53* mutations, continuous BTK inhibitor therapy may be preferred due to its more favorable disease control.

For younger fit patients, chemoimmunotherapy (FCR regimen) may be considered only in rare cases with mutated IGHV without del(11q) and p53 abnormality, in situations where targeted therapy is unavailable due to reimbursement restrictions, as targeted inhibitors generally provide comparable or superior outcomes with lower toxicity.

The rapid evolution of CLL therapy underscores the need for dynamic, biomarker-driven treatment algorithms. Integrating MRD monitoring and genomic profiling into routine clinical decision-making will refine individualized treatment and may eventually allow a functional cure in a subset of patients.

MANAGEMENT OF RELAPSED OR REFRACTORY CLL

GENERAL PRINCIPLES

Targeted therapies have transformed the management of relapsed or refractory chronic lymphocytic leukemia (R/R CLL). The traditional distinction between "relapsed" and "refractory" disease – formerly defined by the duration of response to chemoimmunotherapy – has become less relevant in the era of continuous BTK and time-limited BCL-2 inhibition. The current therapeutic approach is guided primarily by the mechanism of prior therapy, the response duration, and the presence of specific resistance mutations.

For patients previously treated with chemoimmunotherapy, the introduction of BTK inhibitors or venetoclax-based regimens has led to significant improvements in survival (13, 37, 38, 39). For those relapsing after targeted therapy, optimal sequencing remains a matter of active investigation. Molecular profiling is increasingly applied to help guide treatment decisions, including assessment for *BTK* and *PLCγ2* mutations and *BCL2* resistance variants (40–42).

COVALENT BTK INHIBITORS

Ibrutinib has demonstrated durable disease control in relapsed CLL, with median progression-free survival (PFS)

exceeding five years in the RESONATE study's long-term follow-up (38, 39). However, continuous exposure frequently results in cumulative toxicity or the development of resistance, typically mediated by mutations in BTK or PLCγ2. Second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, retain efficacy in patients who discontinue ibrutinib for intolerance rather than progression, with substantially lower rates of atrial fibrillation and bleeding.

Direct head-to-head comparisons, such as ELEVATE-RR, confirmed equivalent efficacy between acalabrutinib and ibrutinib in R/R CLL, but with fewer cardiovascular adverse events in the acalabrutinib arm (9). Similarly, zanubrutinib demonstrated prolonged PFS and reduced toxicity in the ALPINE trial, establishing it as a preferred covalent BTK inhibitor in relapsed settings (43). Nevertheless, resistance due to *BTK* mutations remains a universal challenge for all covalent agents (32).

NON-COVALENT BTK INHIBITORS

The emergence of non-covalent (reversible) BTK inhibitors has provided an effective strategy for patients resistant to covalent BTK inhibitors. Pirtobrutinib, a highly selective, reversible BTK inhibitor, has shown high response rates across multiple studies, including heavily pretreated cohorts and those harboring *BTK C481* mutations. The BRUIN trial's overall response rate exceeded 70%, with a median PFS of 19 months and favorable tolerability (44).

BCL-2 INHIBITION AND SEQUENCING STRATEGIES

Venetoclax remains a potent option in relapsed CLL, particularly for patients who have not been previously exposed to BCL-2 inhibition. In the pivotal MURANO trial, time-limited venetoclax plus rituximab achieved a median PFS of 54 months, markedly superior to bendamustine-rituximab (13). Retreatment with VenR resulted in uMRD in 32% of patients, with a median PFS of 23 months, confirming the feasibility of VenR re-administration as an effective strategy for appropriately selected patients with relapsed/refractory CLL (13).

THE SEQUENCING OF THERAPY

In the current era of targeted CLL therapy, key questions remain regarding the optimal sequencing of treatment regimens and whether the efficacy of BTK and BCL2 inhibitors depends on their order of administration or on the reasons for discontinuing prior therapy. Time-limited therapy offers clear advantages, including lesser financial burden, long-term toxicity and a reduced risk of resistance development. It is therefore currently preferred in clinical practice, particularly for patients without p53 aberrations. Venetoclax-based regimens remain effective in patients previously exposed to BTK inhibitors (45, 46), and conversely, BTK inhibitors are effective in patients previously treated with venetoclax (47). However, these findings are based on small analyses, and a comprehensive overview of efficacy in treatment sequencing is lacking. Similarly, no randomized trial has yet directly compared continuous therapy and time-limited therapy using oral inhibitors. Initial data will be presented at the 2025 ASH Annual Meeting, where the first detailed results from the CLL17 study (NCT04608318) will become available.

CELLULAR AND IMMUNOTHERAPY APPROACHES

While targeted agents have improved outcomes for most patients, a subset with double-refractory disease – resistant to BTK and BCL-2 inhibitors – continues to represent an unmet need (48). Chimeric antigen receptor (CAR)-T cell therapy has emerged as a promising option for such patients, achieving durable remissions in approximately 40–50% of cases (49). Early results with bispecific antibodies targeting CD20 and CD3, such as epcoritamab and mosunetuzumab, show substantial activity in heavily pretreated CLL and Richter transformation (50, 51).

RICHTER TRANSFORMATION

Richter transformation (RT) remains one of the most challenging scenarios in CLL management. Historically treated with anthracycline-based chemoimmunotherapy (e.g., R-CHOP), outcomes have remained poor, with median overall survival rarely exceeding one year. Recent insights into the clonal and molecular heterogeneity of RT have led to the evaluation of targeted approaches. Venetoclax-based combinations (e.g., Ven-R-EPOCH) have yielded encouraging response rates and a median PFS of around 10 months. Early-phase studies combining venetoclax with immune checkpoint inhibitors (atezolizumab) or BTK inhibitors (zanubrutinib) have demonstrated promising activity and manageable toxicity. Cellular immunotherapy with CAR-T cells or allogeneic stem-cell transplantation remains the only potentially curative approach for eligible patients.

FUTURE DIRECTIONS

The treatment of relapsed or refractory CLL has evolved from empiric chemotherapy to a mechanism-based, genomically informed discipline. Covalent and non-covalent BTK inhibitors, BCL-2 inhibition, and emerging immunotherapeutic strategies offer durable control for most patients. The rational sequencing of these agents, guided by molecular resistance profiles and MRD dynamics, represents the cornerstone of modern CLL management. In the near future, integrating novel immune and targeted modalities may extend survival and achieve disease eradication in selected patients.

IMMUNE DYSREGULATION IN CLL

CLL is inherently associated with profound immune dysfunction (52–54). Impairments affect the innate and adaptive arms of the immune system, contributing to the characteristic susceptibility to infections, autoimmune phenomena, and secondary malignancies. Defects arise from quantitative hypogammaglobulinemia and qualita-

tive dysfunction of T and NK cells, monocytes, and dendritic populations.

Hypogammaglobulinemia occurs in up to 70% of patients during the disease course and correlates with both disease stage and cumulative therapy exposure (52–55). However, impaired T-cell synapse formation, T-cell exhaustion, and expansion of regulatory T cells further weaken antitumor immunity (56–59). Monocytes in CLL often acquire a nurse-like phenotype, supporting leukemic survival within the microenvironment (60–62). Together, these mechanisms result in an immunosuppressive milieu that occurs even in early disease stages such as monoclonal B-cell lymphocytosis (MBL) (63).

IMPACT OF TARGETED THERAPY ON IMMUNE FUNCTION

Unlike conventional cytotoxic chemotherapy, BTK and BCL-2 inhibitors exert variable but generally favorable effects on immune reconstitution. BTK inhibitors, particularly ibrutinib, increase total T-cell counts and reduce exhaustion markers (PD-1, CTLA-4), suggesting partial restoration of T-cell competence. They also diminish the proportion of regulatory T cells. However, their off-target inhibition of interleukin-2-inducible kinase (ITK) may transiently impair T-cell proliferation and antibody-dependent cellular cytotoxicity (ADCC) mediated by NK cells (6, 64, 65).

Second-generation BTK inhibitors, such as acalabrutinib and zanubrutinib, exhibit greater selectivity for BTK and minimize these off-target immune effects. Venetoclax, by contrast, has been associated with gradual immune recovery, including normalization of immunoglobulin levels, T-cell subsets, and NK-cell function (66, 67). Combined BTK and BCL-2 inhibition, as evaluated in the CAPTIVATE trial, has shown comparable immune restoration to monotherapy, suggesting that the observed immune improvement may primarily result from adequate CLL cytoreduction rather than direct immunomodulation (68).

INFECTIOUS COMPLICATIONS

Despite immune reconstitution during targeted therapy, infectious complications remain a significant cause of morbidity and mortality in CLL. The incidence of serious infections has been estimated at approximately 4–5 per 100 patient-years, increasing with age, prior therapy, and hypogammaglobulinemia (52, 53, 69, 70). Bacterial respiratory infections predominate, whereas opportunistic infections are less common than during chemoimmunotherapy but can occur with prolonged BTK or PI3K inhibitor use.

BTK inhibitors, especially ibrutinib, have been linked to invasive fungal infections such as *Aspergillus* and *Cryptococcus*, possibly due to off-target inhibition of macrophage signalling pathways. PI3K inhibitors carry additional risk for *Pneumocystis jirovecii* pneumonia and cytomegalovirus reactivation, warranting prophylaxis and close monitoring (71, 72). Conversely, venetoclax-based regimens appear to have a lower risk of opportunistic infections, provided neutropenia is appropriately managed.

The COVID-19 pandemic highlighted the vulnerability of CLL patients to viral infections -seroconversion after SARS-CoV-2 vaccination is frequently impaired, particularly during active BTK or BCL-2 inhibitor therapy. Booster doses, prophylactic monoclonal antibodies, and antiviral agents remain essential components of infection prevention strategies in this population (73–76).

SECONDARY MALIGNANCIES

Patients with CLL exhibit an increased risk of secondary neoplasms, reflecting a combination of disease-related immune suppression, genotoxic therapy exposure, and host susceptibility. Population-based studies report an incidence of secondary cancers nearly fourfold higher than in the general population, most commonly non-melanoma skin cancers, solid epithelial tumors, and therapy-related myeloid neoplasms (77, 78). The introduction of targeted therapy has not eliminated this risk. Monitoring and preventive strategies remain crucial. Regular dermatologic screening, avoidance of unnecessary immunosuppression, and adherence to vaccination programs are key components of survivorship care in CLL.

CLINICAL IMPLICATIONS

Recognition and management of immune dysfunction are integral to optimizing outcomes in CLL. Baseline evaluation of immunoglobulin levels, vaccination status, and infection history should guide preventive measures, including immunoglobulin replacement in selected patients. The overall immunologic impact of targeted therapy appears favorable compared with chemotherapy. However, long-term follow-up is required to determine its influence on infection risk, secondary malignancies, and immune senescence. The evolving integration of immune-monitoring biomarkers may ultimately refine patient stratification and enhance the safety of novel combination regimens.

FUTURE DIRECTIONS AND CHALLENGES

The rapid evolution of targeted therapy has fundamentally altered the natural history of CLL. However, the research trajectory suggests that the most transformative decade may remain. The overarching goals of modern CLL management are to achieve durable, chemotherapy-free remissions, individualize therapy based on biological risk, and ultimately attain a functional cure through time-limited, combination-based, or immune-mediated strategies.

TOWARDS MRD-GUIDED, TIME-LIMITED THERAPY

The concept of measurable residual disease (MRD) has evolved from a research endpoint into a potential clinical decision tool. As demonstrated in trials such as CLL14, CAPTIVATE, and GLOW, achieving uMRD strongly correlates with prolonged remission and survival (11, 79, 80). Future treatment paradigms will likely integrate MRD-guided therapy cessation and re-initiation strate-

gies, enabling dynamic adjustment of therapy duration according to disease kinetics rather than fixed schedules.

Several ongoing studies, including FLAIR, CLL18, and MAJIC, explore whether MRD-driven discontinuation of BTK and BCL-2 inhibitors can maintain durable control while reducing cumulative toxicity, cost, and patient burden (81, 82).

NEXT-GENERATION TARGETED INHIBITORS

BTK degraders (e.g., NX-2127, NX-5948, BGB-16673, ABBV-101, AC676) represent the emerging fourth generation of BTK-targeted therapy (83, 84). Unlike traditional inhibitors that block kinase activity, these agents induce ubiquitination and proteasomal degradation of the entire BTK protein, thereby eliminating its enzymatic and scaffolding functions. This strategy may overcome resistance mechanisms that persist despite kinase inhibition. Parallel progress has been achieved with next-generation BCL-2 inhibitors, including lisaftoclax and sonrotoclax, which aim to enhance potency and address acquired venetoclax resistance (85, 86). In preclinical models, sonrotoclax demonstrated superior cytotoxicity and retained activity against BCL-2 variants such as *G101V*, highlighting a convergent effort to refine targeted therapy through more complete and durable pathway suppression.

EMERGING IMMUNOTHERAPIES

Chimeric antigen receptor (CAR) T-cell therapy – particularly constructs optimized for the CLL microenvironment (e.g., 4-1BB–based or dual-target CARs) – continues to show promise for durable remission. However, careful patient selection and toxicity management remain critical (87). In 2024, the first CAR-T product for relapsed or refractory CLL, lisocabtagene maraleucel (liso-cel), an anti-CD19 construct incorporating a 4-1BB costimulatory domain, received regulatory approval in the United States. In the phase 1/2 TRANSCEND CLL 004 study, liso-cel achieved an overall response rate of 44% and complete remission in 20% of patients previously treated with BTK or BCL-2 inhibitors. Although the median duration of response for the overall cohort was approximately 12 months, patients who achieved complete remission experienced markedly prolonged disease control and durable survival outcomes.

In parallel, the convergence of targeted therapy and immunotherapy is reshaping clinical practice: CD3×CD20 bispecific antibodies, such as epcoritamab, have yielded encouraging responses in heavily pretreated CLL, including cases refractory to both BTK and BCL-2 inhibitors (50).

CONCLUDING REMARKS

Chronic lymphocytic leukemia has evolved from an indolent yet incurable malignancy into a largely controllable chronic condition, and for selected patients, a disease potentially curable through rationally designed, time-limited therapy. Integrating molecular diagnostics, MRD-directed strategies, and next-generation targeted and immune therapies defines the current research frontier. Continued collaboration between academic investigators, industry partners, and cooperative groups will be essential to transform these advances into a new standard of durable, individualized, and ultimately curative treatment for CLL.

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Hyperlipidemia Associated Oxidative Stress and Its Impact on Bone Regeneration and Dental Implant Osseointegration

Amalia Koutsoupia[1], Eleni Kotti[1], Kalliopi Topouzi[1], Maria Kateri[1], Panagiotis Kafas[2,*]

ABSTRACT

Hyperlipidemia is recently recognised as a factor that could impair bone regeneration and dental implant osseointegration. High fat diets raise oxidised lipid levels in blood, which accumulate in bone and suppress osteoblast function, tipping the balance toward bone resorption. Excess lipids also induce oxidative stress and inflammatory cytokine production in bone, further inhibiting bone formation. These changes may affect implant osseointegration. At the cellular level, high lipid levels cause overproduction of reactive oxygen species and inhibit Wnt/β-catenin signalling in osteoblasts. Health promotion strategies should address these mechanisms. Lipid lowering drugs such as statins may improve bone healing ability both by reducing blood lipids and by directly stimulating bone formation. Antioxidant nutrients or drugs may counteract lipid driven ROS and inflammation. Emerging approaches include epigenetic interventions to boost osteoblast gene expression and dampen inflammatory pathways. Improving lipid control alongside these future targeted therapies may help preserve bone health and implant success in patients with hyperlipidemia associated oxidative stress. While very exploratory, incorporating molecular level approaches into continuing clinical protocols could represent a path towards future therapies. Maximizing postoperative management is essential in order to limit the effects of hyperlipidemia induced negative microenvironment at implant sites. This could include controlling laboratory levels of lipids prior to surgery.

KEYWORDS

hyperlipidemia; oxidative stress; bone regeneration; dental implant osseointegration; osteoblast function; reactive oxygen species; inflammation

AUTHOR AFFILIATIONS

[1] Dental Students, School of Dentistry, Aristotle University of Thessaloniki, Greece
[2] Department of Oral Surgery and Radiology, School of Dentistry, Aristotle University of Thessaloniki, Greece
* Corresponding author: Oral Surgeon, Kassandrou 3, Kavala 65403, Greece; pankafas@yahoo.com, panos@kafas.gr

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INTRODUCTION

Hyperlipidemia is the condition where cholesterol and triglycerides elevated in circulation. Hyperlipidemia is a known risk factor for cardiovascular disease and increasing evidence suggests hyperlipidemia has important implications for skeletal biology and oral health (1). Hyperlipidemia can become dysregulated in such a way that alters lipid metabolism very quickly within the human body to the extent that it causes issues with normal bone remodeling and repair (2). The process of bone regeneration is a balance of forces between the formation of osteoblasts, and osteoclast resorption, that is mediated through a series complex mediators, including Wnt/β-catenin signalling, transcription factors Runx2 and Osterix that regulate osteoblast activity, and cytokines that control the activity of both osteoblasts, and osteoclasts (3–5). Hyperlipidemia, however, alters the balance of bone formation and resorption particularly by increasing oxidative stress and low grade chronic inflammation due to increased osteoclast activity (6). Additionally, oxidized lipid remnants alter the fate of mesenchymal derived stem cells from the (early) osteoblastic direction limit early osteogenic progenitors necessary for regenerative hypotheses towards developing more adipogenic pathways (7, 8). For the most part the consequences of an interaction between hyperlipidemia biology and implants are important.

BIOLOGY OF BONES IN HYPERLIPIDEMIC STATUS

Bone regeneration occurs, largely, through differentiation of osteoprogenitor cells to osteoblasts, regulating these processes through key transcription factors such as Runx2, Osterix (Sp7), and β-catenin in the canonical Wnt signaling cascade (9–11). Hyperlipidemia will not only affect these pathways, but also can initiate additional inflammatory cytokine release, oxidative stressors, and additional downstream effects through a variety of processes (12). One potential mechanism being explored is oxidized low-density lipoprotein (oxLDL), which in vivo inhibited Runx2 and promoted PPARγ (a transcription factor promoting adipogenesis) (13–15). These inflammatory mediators, initiated from hyperlipidemia, are inhibitory to the regeneration process by further inhibiting osteoblast differentiation through an innumerable pathway (16, 17). These cytokines downregulated osteoblastic differentiation markers, alkaline phosphatase (ALP) and osteocalcin, which were further upregulated by the osteoclastogenic stimulating cytokine RANKL's expression in stromal supporting cells, facilitating osteoclastogenesis (18, 19).

This ultimately adds up to support a net resorptive bone reaction, instead of a net deposition. The Wnt/β-catenin pathway may be the most sensitive cascade to external influences like dyslipidemia. Hyperlipidemia is related to increased expression of antagonists to Wnt, like Dkk1 and sclerostin (3). The impairment of signaling, and consequently signaling fidelity, remains exacerbated through unfavorable levels of oxidative stress due to changes in lipid metabolism. Epigenetic reprogramming is an interference with transcriptional control (12). Hyperlipidemia is associated with, but not limited to, broadly altered patterns of DNA methylation and histone acetylation in MSCs (7). In these processes, microRNA also plays important mediating roles, as miR-204 and miR-211 both use Runx2 as a target, suggesting these are potentially elevated during hyperlipidemia states, and miR-29 is diminished (this miRNA promotes osteogenesis), indicating that hyperlipidemia provides a complex narrative for regulatory pathways (13, 20). There may be therapeutic opportunities using methods to normalize or reduce oxidative stress, and/or target those specific pathways of gene expression to improve osteogenic gene expression (12). Statins may show some efficacy in increasing osteogenic BMP-2 gene expression while inducing biosynthetic osteoblastic differentiation characteristics, probably context-specific (9). Monoclonal antibodies to sclerostin may offer some support through decreasing Wnt inhibition, although again requires targeted studies and clinical relevance when hyperlipidemia exists (3, 21). Going forward, defining these mechanisms will potentially provide clearer clinical paths for linking lipid therapies to regenerative occasions and possibly better translate to improved clinical outcomes to promote bone health, repair, and regeneration.

BONE HOMEOSTASIS UNDER HYPERLIPIDEMIA

Bone homeostasis is only achieved through the concerted actions of osteoblasts and osteoclasts (5, 10, 18); imbalance can come from a variety of systemic and cellular stimuli, of which oxidative stress and inflammation, and altered osteoblast/osteoclast activity, are significant contributing factors (12, 16). The effects of oxidative stress in patients with metabolic disease can largely be attributed to the neural link with systemic stressors and the convergence of interrelated influences implicated in compromised bone health and poor quality of repair (22).

High levels of reactive oxygen species (ROS), usually produced from a metabolic state such as hyperlipidemia, can damage DNA, proteins, and lipids of the bone cells (osteoblasts and osteocytes) (23). Osteoblasts are especially sensitive to oxidative stress due to their role in bone regeneration, and show reduced proliferation, differentiation, and mineralization capabilities (24). Higher oxidative stress will lead to an increase in osteoclastogenesis and this favors bone loss due to a tipping of the balance of bone health (12, 22, 23). In all of its forms, oxidative stress is a regulator of bone remodeling (25). In addition, low-grade inflammation has been directly associated with metabolic states characterized by higher levels of lipids (26). Inflammatory cytokines can directly inhibit the properties of the osteoblasts while promoting differentiation and/or activity of the osteoclast. TNF-α can inhibit Runx2 and Osterix, both genes that have an influence on the maturation of osteoblasts and promote RANKL-mediated osteoclastic differentiation (4, 18). Likewise, signalling for IL-6 can promote bone resorption activity as well as mobilization of osteoclast precursors via activation of the JAK/STAT signaling pathway (5). These

inflammatory signals will promote bone resorption during the normal regulatory bone remodeling process and together, these may negatively influence skeletal regenerative capabilities (18).

Metabolic dysfunction, oxidative stress and inflammatory signals lead to impaired osteoblast differentiation and increased osteoclast differentiation (12). Impaired osteoblast differentiation directly affects bone formation, increased osteoclast activity will mean more bone resorption, and both of these circumstances result in disequilibrium of osteogenic health and bone health (10). The impaired osteoblast properties due to TNF and the lipid signaling have been suggested to lead to greater levels of PPARγ, a fate-determining transcription factor that promotes adipogenic fate over osteoblastic fate in mesenchymal stem cells, by significantly decreasing osteoblast progenitor availability (15, 27). These mechanisms connect with a complex intersection of oxidative stress and inflammatory signaling (Tab. 1).

Oxidative stress has been effectively linked to inflammation through ROS and by activation of NF-kB signaling in bone cells, but inflammation can also promote ROS (22).

The already elevated inflammatory cytokines of TNF-α, IL-1β, and IL-6 during and/or after surgery further compromise osteoblast differentiation and function by decreasing the level of osteogenic markers necessary for new bone formation at the implant site, like alkaline phosphatase and osteocalcin (18). Markers such as malondialdehyde and protein carbonyls indicate an increased level of reactive oxygen species (ROS) production and cellular injury (21). High levels of ROS will inhibit critical transcriptional networks such as Runx2 and β-catenin, which are necessary for osteoblast commitment and also promote adipocyte differentiation via stimulation of PPARγ, which will decrease osteogenesis (13).

HEALTH STRATEGIES

There is compelling evidence for lifestyle related hyperlipidemia exacerbating bone health so smoking cessation and decreasing the quantity of alcohol consumption should be highlighted as part of an inclusive education program for the patient (28). Weight loss, to normalize body mass index, may be also important to health status improvement in obesity related hyperlipidemia (29).

Pharmacological management of hyperlipidemia is still an important foundation in reducing cardiovascular risk and enhancing bone healing capability. Statins, widely used lipid lowering agents, may promote osteogenic differentiation by enhancing the upregulation of the bone morphogenetic protein-2 (BMP-2) actions and inhibiting osteoclastic activity in the process of implant osseointegration (30). A systematic review provides an overview of new antioxidant agents and synthetic analogues that act through targeting oxidative stress and inflammation signaling pathways (31). It highlights new opportunities for the management of oxidative stress-related diseases in the clinic. Given the often-compromised bone health profile of patients, it is necessary for clinicians to consider a patient's health status before prescribing any of these agents to enhance regional and possibly systemic outcomes for implant surgeries.

Health promotion interventions can also be targeted and creative methods aimed at normalizing profile changes in microRNA expressions (miR-29 promoted, and miR-204 and miR-211 inhibited), or normalizing aberrant epigenetic changes such as, DNA methylation and histone acetylation that influence skeletal health (20, 32, 33). These options could help define methods or protocols advancing the osteogenic capability of potential regenerative cells such as mesenchymal stem cells and possibly

Tab. 1 Effects of TNF and lipid signaling on osteoblast differentiation and mesenchymal stem cell fate.

Parameter	Measure	Notes	Citation Number(s)	Model / Source
Oxidative phosphorylation in osteoblasts	Elevated levels of Reactive Oxygen Species (ROS) are present in inflammatory tissue of peri-implantitis lesions	In inflammatory settings, ROS production is associated with local tissue breakdown and bone loss, linking oxidative stress to clinical bone pathologies	34	Human
Effect of oxidative stress on osteoblast markers	Significant reduction in alkaline phosphatase (ALP) and Runx2 in oxidative stress-exposed bone stromal cells	ROS inhibits osteoblast differentiation signaling pathways (p38 MAPK, NF-κB, ERK)	22	In Vitro
Correlation of oxidative stress marker & bone density	Malondialdehyde positively correlates with reduced bone mineral density (r=−0.45) and ultrasound speed of sound (r=−0.39)	Increased oxidative stress is associated with a shift toward bone loss	12, 22, 23	Human
Osteoblast apoptosis rate under oxidative stress	FoxO3 overexpression reduces apoptosis rate by 25%; antioxidants reduce TNF-α-induced apoptosis	ROS is associated with osteoblast apoptosis via JNK signaling	22	In Vitro
TNF-α increase & bone resorption	TNF-α levels increase ~40% in hyperlipidemic mouse models, associated with increased osteoclast activity	TNF-α promotes osteoclastogenesis via NF-κB signaling under oxidative stress	2	Animal
High glucose-induced ROS and osteoblast apoptosis	Intracellular ROS increase correlates strongly (r>0.8) with apoptosis markers in osteoblasts	Hyperglycemia-induced oxidative stress is associated with osteoblast dysfunction	27	In Vitro

improve results for hyperlipidemic patients undergoing implant therapy. While very exploratory, incorporating molecular-level approaches into continuing clinical protocols could represent a path towards future therapies.

ANIMAL STUDIES

Animal experiments have indicated that lipid excess may alter osteogenic signalling and reduce the structural integrity of regenerated bone (2). Work assessing progenitor cell fate in vivo has also shown shifts toward adipogenic commitment under lipid-driven cues (7, 8). Studies examining bone healing in hyperlipidemic models describe delayed regeneration, weaker biomechanical properties, and reduced osseointegration, although partial recovery has been noted when lipid-lowering agents were introduced (2, 30).

HUMAN STUDIES

Human studies have reported altered osteoblast behavior under inflammatory hyperlipidemic conditions, including changes in key transcriptional regulators and reduced expression of markers linked to maturation (18, 19, 27). Clinical assessment and biochemical examination of peri-implant tissues have identified increased ROS and inflammatory mediators in affected patients, which may be related to impaired healing response (34, 35). Additional evidence from cultured human osteoblasts has shown shifts in osteogenic marker expression and signaling when exposed to metabolic or oxidative stress, suggesting that hyperlipidemia could influence bone turnover dynamics (18, 19, 27).

DISCUSSION

A distinction between animal and human findings has been included, as differences in physiology could influence how each set of results informs clinical interpretation (Tab. 2). Although animal experiments provide interesting insights, their applicability to human metabolism is limited due to interspecies differences, which may also affect data consistency.

The downregulation of the Wnt/β-catenin pathway via lipid mediated antagonists, as the Wnt/β-catenin pathway is one of the main pathways involved with osteoblast activity and matrix production (3, 16). There are also accounts that refer to epigenetic features, and with crosstalk from microRNA regulation, having additional roles in how hyperlipidemia mediates progenitor cell fate and function (7). Specifically, two significant osteogenic associated transcription factors, miR-204 and miR-211, which act to inhibit osteogenesis are upregulated, whereas miR-29 that supports osteogenesis is downregulated (10, 32). This supports the complexity of metabolic regulation on regenerative potential. This class of molecular changes may represent a limitation of progenitor cells to regenerate and adapt to an implant osseointegration. Both oxidative stress and inflammatory cytokines work interactively through several of the NF-kB signal pathways, which may cause a self-reciprocating loop that promotes progressive tissue impairment with a decrease in repair abilities (12, 25). This interaction could be especially impacting the peri-implant microenvironment due to the effect of chronic inflammation and ROS buildup due to peri-implantitis and early implant failure (34, 35). Elevated inflammatory cytokines and oxidative stress are leading indicators of osseointegration compromise in hyperlipidemia (1, 2, 16, 17, 26). While reports have been made that provide a widely phrased approach to describe the negative influences from TNF-α, IL-6, and ROS in osseointegration, there is also an opportunity for research to employ potential antioxidant agents, Wnt pathway modifiers, and lipid lowering drug to facilitate improved osseointegration in dyslipidemic patients (3, 5, 18, 21, 22, 30, 35). Explaining some of the mechanisms, along with the typical downstream metabolic conditions associated with hyperlipidemia, will be critical for managing conditions and limiting the multiple problematic facets of each condition in achieving dental implant success. The possibilities of management of hyperlipidemia lie among the multitude of antioxidant modalities to mitigate ROS trauma, along with other novel pathways to therapy via inhibition of inflammatory cytokine action, which all would have the potential to yield some improvement with osteoblast viability and performance. Recent findings provide evidence showing inflammatory cytokines and oxidative stress typically occur in conjunction with one another, evidenced by their pro-inflammatory states being characterized by a poor prognosis in chronic disease processes (12, 18, 22, 25, 26, 31, 35). Inflammatory cytokines' principal duty is to affect a site of immune activity, thus rising cytokine levels are frequently described with the state of inflammation, further demonstrating alterations with cells and tissue outcomes. Overproduction of cytokines, battling with ROS, increased mitochondrial dysfunction, along with additional stimuli, all perpetuate the stress state, causing activation of nuclear factor-kappa B (NF-kB). NF-kB leads to pro-cytokine activation, promoting inflammatory processes (17, 23, 35). The whole process relies on the interactive complexities of the transcriptional involvement signatures with signaling pathways, where the epigenetic modifiers interface clearly defined fates for the mesenchymal stem cells (MSCs) toward respective gleaned fates of osteogenesis and adipogenesis.

Maximizing postoperative management is imperative to limit the effects of hyperlipidemia oxidative stress induced negative microenvironment at implant sites. This would include controlling laboratory levels of lipids as tightly as possible prior to surgery, or any presurgical outcomes anticipate that it would be feasible to administer antioxidants to the patient before the surgical procedure to dampen reactive oxygen species, and therefore, inflammatory potentials. This could take on prior details, and proactive attention to approaching surgical outcomes in optimized management of systematic control postsurgically, along with local steps to limit peri-implantitis, will support osseointegration. Providing education to patients about their systemic health challenges such as hyperlipidemia, and understanding the potential contributions or

Tab. 2 Comparison of animal and human study findings with consideration of physiological differences.

Parameter	Animal Studies	Human Studies	Citations
Scope and Focus	Studies investigate the impact of hyperlipidemia on bone regeneration and mechanics in animal models. They explore oxidative stress, lipid oxidation, inflammation, and impaired osteoblast function, including pathways like Wnt/β catenin and transcription factors (Runx2, Osterix). Animal studies highlight altered microRNA and epigenetic changes affecting osteogenesis.	Clinical and epidemiological studies report associations between serum lipid abnormalities and reduced bone mineral density, altered bone formation markers, and increased resorption markers. Observations suggest that hyperlipidemia may influence oxidative stress, inflammatory cytokines, and bone remodeling outcomes, including in dental implant patients. Evidence for microRNA or epigenetic involvement in humans remains preliminary and largely indirect.	(1–3, 7, 11–13, 20)
Oxidative Stress Role	Animal models show that hyperlipidemia-induced reactive oxygen species cause DNA, protein, and lipid damage in bone cells, impair osteoblast proliferation, and increase osteoclastogenesis, tipping the balance towards bone loss.	Hyperlipidemia is associated with elevated oxidative stress markers (malondialdehyde, protein carbonyls) and higher inflammatory cytokines (TNF-α, IL-6), which correlate with reduced osteoblast activity and altered bone remodeling markers. Direct causal links have not been established.	(12, 21–26)
Bone Metabolism Markers	Impaired canonical Wnt/β-catenin signaling and upregulated antagonists are observed. Key osteogenic transcription factors such as Runx2 are inhibited, while adipogenic factors like PPARγ are promoted. Altered miRNAs affect differentiation: i) miR-204 and miR-211 typically function as inhibitors of osteoblast differentiation, while ii) miR-29 acts as a promoter of osteogenesis.	Elevated inflammatory cytokines are associated with reduced serum markers of osteoblast function, such as alkaline phosphatase and osteocalcin. Serum bone formation and resorption markers indicate dysregulated bone turnover in people with hyperlipidemia. Most evidence derives from circulating measurements rather than direct bone tissue analyses.	(3–5, 11, 13–15, 18–20, 27)
Therapeutic Interventions	In animal studies, therapeutic interventions involve dietary modifications such as high-fat diet regulation and the use of pharmacologic agents including statins and fibrates which have demonstrated efficacy in reducing lipid levels, oxidative stress, and improving bone regeneration outcomes	Lifestyle modifications, including smoking cessation and weight loss, along with pharmacologic lipid-lowering therapies such as statins, are emphasized. Approaches, including miRNA regulation and epigenetic modulation, remain experimental and are not yet established in clinical practice.	(2, 7–9, 28–33)
Data Interpretation	Insights from animal studies illustrate how hyperlipidemia induces oxidative stress and molecular signaling alterations detrimental to bone regeneration and strength.	Findings from human studies primarily show associations rather than causation. The insights from animal studies cannot be directly extrapolated, highlighting the need for clearer clinical evidence on the effects of oxidative stress on osteoblast metabolism.	(1, 2, 6, 16, 17)

risk to the surgical outcome, and concurrent with the provision of presenting medication and oral health maintenance instructions, may lead to improved compliance to their overall recommended health prescription which may improve fidelity toward long term implant stability.

Although there is evidence that elevated oxidative stress could interfere with osteoblastic activity, the current data are largely correlative, and a direct cause-and-effect relationship in vivo has not been confirmed. The animal studies were based on experimental models, and the human findings were presented as correlations rather than direct evidence. In some quantitative studies, levels of oxidative stress markers, such as malondialdehyde and protein carbonyls in peri-implant tissues and cultured human osteoblasts, have been observed to be higher under hyperlipidemia or an inflammatory condition (18, 19, 35). Markers important for osteogenic metabolism, such as alkaline phosphatase and osteocalcin, were decreased, and mineralization was impaired, which is suggestive of a directed effect on osteoblast metabolism by reactive oxygen species (18, 19, 27). However, without controlled longitudinal studies, definitive proof of causality is lacking. Future studies using antioxidants or lipid-lowering methods might observe concordance in levels of reactive oxygen species and osteoblast activity and measure the extent of this direct relation at the biochemical level (1, 2, 30, 35).

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Statins and Dental Implant Osseointegration – Bridging Molecular Science and Next Generation Clinical Outcomes: A Review

Konstantinos Rallis[1], Georgios Gkinopoulos[1], Konstantinos Manolakos[1], Georgios Militsis[1], Eleftheria Kotopoulou[1], Panagiotis Kafas[2,*]

ABSTRACT

Statins, widely prescribed for dyslipidemia, may exert bone modifying effects through coordinated stimulation of osteoblast activity and suppression of osteoclastogenesis. Lipophilic statins, including simvastatin, lovastatin, and atorvastatin, have been shown in preclinical models to enhance osteoblast differentiation and matrix synthesis via BMP-2/Smad and Ras-PI3K-Akt-Erk signaling, while attenuating osteoclast development through modulation of the OPG/RANKL axis, NF-kB inhibition, and blockade of p38 MAPK pathways. Despite mechanistic consistency in experimental systems, human data remain inconclusive, with modest increases in bone mineral density and no confirmed reduction in fracture risk. In implant dentistry, hyperlipidemia has been linked to impaired osseointegration, likely via reduced osteoblastic function, increased osteoclast activity, and compromised collagen turnover. The interplay between obesity, lipid metabolism, and skeletal biology introduces additional confounding variables, emphasizing the need for patient stratification in clinical research. Current evidence supports the biological plausibility of statin mediated enhancement of peri-implant bone formation, but definitive clinical translation requires large-scale, stratified trials with controlled delivery approaches and extended follow-up.

KEYWORDS

statins; dental implants; osseointegration; bone metabolism; osteoblasts and osteoclasts

AUTHOR AFFILIATIONS

[1] School of Dentistry, Aristotle University of Thessaloniki, Greece
[2] Department of Oral Surgery and Radiology, School of Dentistry, Aristotle University of Thessaloniki, Greece
* Corresponding author: Spc Oral Surgeon, Kassandrou 3, Kavala 65403, Greece; pankafas@yahoo.com, panos@kafas.gr

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INTRODUCTION

Beyond their lipid lowering properties, statins may influence skeletal biology through pleiotropic mechanisms that converge on bone forming and bone resorbing cells (1). The inhibition of HMG-CoA reductase reduces isoprenoid intermediates, impairing prenylation-dependent signaling in small GTPases such as Rho and Ras (2). This molecular interference appears to enhance osteoblastic activity and limit osteoclastic differentiation in experimental systems (1, 3, 4). Currently there is an academic interest in the potential of statins to improve bone mineral density (BMD) and support osseointegration, particularly under conditions of metabolic disturbance such as hyperlipidemia.

The clinical relevance of these effects remains uncertain, as epidemiological associations and modest trial results have yet to translate into unequivocal fracture risk reduction. Moreover, the interplay between obesity, dyslipidemia, and bone metabolism introduces additional variables that complicate interpretation. In dental and orthopedic contexts, the possibility of local statin delivery to enhance bone healing warrants investigation, especially for patients with compromised lipid profiles.

STATINS AND OSTEOBLASTS

Statins may stimulate osteoblasts through multiple molecular pathways. In cell cultures, simvastatin enhances alkaline phosphatase activity and mineralization in MC3T3-E1 osteoblastic cells, acting in a dose-dependent manner and raising BMP-2 and ALP mRNA expression, while suppressing collagenase-1 expression – a signature of anabolic activity (5). More detailed mechanistic work shows simvastatin promotes osteoblast differentiation via a membrane-bound Ras/Smad/Erk/BMP-2 pathway. Treatment increases ALP activity and upregulates genes for BMP-2, sialoprotein, and type I collagen (6). Across animal and in vitro models, statins, especially lipophilic ones like simvastatin, lovastatin, and atorvastatin, appear to modulate small GTPases (Ras, Rho), suppressing their prenylation and thus enabling osteogenic signaling, while also engaging TGF-β/Smad3 pathways to reduce osteoblast apoptosis (7).

A broader review emphasizes these pleiotropic effects, noting that statins increase mediators such as BMP-2, TGF-β, ALP, type I collagen, and collagenase-1 to bolster bone formation (8). These findings suggest that statins may support bone tissue by enhancing osteoblastic survival, differentiation, and matrix production, though the clinical margin of effect on bone healing or osteoporosis remains to be fully confirmed.

STATINS AND OSTEOCLASTS

Statins appear to suppress osteoclast development and activity. Experimental studies report that statins increase osteoprotegerin (OPG), a decoy receptor that inhibits RANKL, and decrease RANKL levels, altering the OPG/RANKL/RANK axis in favor of reduced osteoclastogenesis (9). In vitro, simvastatin blocks RANKL-induced transcriptional activation of NF-kB by preserving IkBa, suppressing osteoclast differentiation. In vivo, simvastatin reduces osteoclast numbers and IRF4 expression in rodent models, increasing bone volume and preventing bone loss when RANKL is experimentally elevated (10). Lovastatin likewise inhibits osteoclastogenesis in a dose-dependent fashion in rat bone marrow cultures.

CORRELATION OF OBESITY TO HYPERCHOLESTEROLEMIA

Obesity and elevated cholesterol frequently coexist, though the causative threads are intricate. Excess adipose, especially visceral fat, releases adipokines and inflammatory signals that may boost hepatic lipid synthesis and compromise lipid clearance, potentially raising LDL cholesterol (11). Insulin resistance, common in obesity, may augment hepatic VLDL production and elevate circulating lipids. Epidemiological data frequently shows positive correlations between BMI or waist circumference and LDL or total cholesterol, though these correlations vary by age, diet, genetics, and ethnicity (12).

Obesity may act less as a direct driver and more as part of a metabolic profile that includes genetic predispositions, sedentary habits, dietary patterns, and, increasingly recognized, gut microbiome composition (13). Thus, while obesity increases the likelihood of hypercholesterolemia, particularly within metabolic syndrome, it is not sufficient to predict it. Instead, it contributes to a constellation of risk factors shaping lipid dysregulation.

HYPERCHOLESTEROLEMIA AND OSSEOINTEGRATION OF DENTAL IMPLANTS

Hyperlipidemia seems to impair the healing processes underpinning osseointegration. In mice, a high fat diet reduced peri-implant bone volume, decreased mechanical strength at the bone to implant interface, and increased implant loss (1); these effects reflect reduced osteoblastic activity, enhanced osteoclast differentiation, disrupted collagen processing, and impaired bone quality (14). Osseointegration, the direct structural and functional connection between bone and implant surface, depends heavily on osteoblast mediated matrix deposition and remodeling. Hyperlipidemia appears to disrupt both of those key processes.

Statin delivery strategies, including local application via coatings, hydrogels, nanoparticles, and bone graft materials, have shown promise in promoting bone formation and improving osseointegration in hyperlipidemic contexts (4). For example, simvastatin coated on β-tricalcium phosphate or delivered via PLGA-PEG hydrogels can enhance peri-implant bone healing, though evidence is largely preclinical and further validation is required (7, 15).

Consequently, while hypercholesterolemia may pose a risk to implant success, adjunctive strategies, particu-

larly localized statin delivery, may offer pathways to enhance healing around implants under adverse metabolic conditions.

STATINS AND BONE MINERAL DENSITY

Observational and trial data suggest statins may modestly improve bone mineral density (BMD). A meta-analysis involving over 34,000 participants (from both cohort and randomized controlled studies) found statistically significant increases in BMD at the lumbar spine (SMD 0.15), total hip (SMD 0.22), and femoral neck (SMD 0.19), with similar effect sizes across subgroups and ethnicities (16).

Preclinical studies reinforce that statins increase bone volume in animal models and suppress experimentally induced bone loss (10). These anabolic effects derive from both enhancement of osteoblast function and suppression of osteoclast activity, combined with potential improvements in bone vascularization and reduced apoptosis of bone cells (7, 8).

Currently, randomized trials focusing specifically on fracture outcomes are limited. The increase in BMD is modest and may not directly translate into reduced fracture risk for all patients. Differences in statin lipophilicity, dosage, duration, and baseline bone health may influence effectiveness. In short, statins may support BMD to a certain degree, especially over time, but their role in fracture prevention, osteoporosis and dental implant management remains suggestive rather than definitive (17).

OSTEOBLAST PATHWAYS: STATIN INDUCED BONE FORMATION

Statins inhibit HMG-CoA reductase, disrupting the mevalonate pathway and reducing synthesis of isoprenoids like farnesyl pyrophosphate and geranylgeranyl pyrophosphate molecules essential for prenylation of small GTPases such as Rho and Ras (18). This inhibition impairs the prenylation dependent activity of Rho associated kinase (ROCK), which may relieve suppression on osteogenic signaling. Pitavastatin increased BMP-2 and osteocalcin expression in human osteoblasts, effects nullified by geranylgeranyl pyrophosphate, suggesting Rho-kinase inhibition mediates this enhancement of bone formation (19).

Lovastatin activates Ras and downstream cascades. It stimulated tyrosine phosphorylation and activation of the PI3K catalytic machinery via membrane bound Ras in osteoblasts. PI3K then activated Akt and Erk1/2, both of which contributed to upregulation of BMP-2 expression and several osteogenic markers including alkaline phosphatase, type I collagen, and osteopontin (20)

Simvastatin harnesses a multi-pathway approach. It enhances osteoblast viability and differentiation through a membrane-bound Ras → Smad1 → Erk → BMP-2 signaling cascade. The activation of Smad1 (a BMP effector) and Erk underscores how multiple molecular conduits may converge to foster osteogenesis (6).

Summarizing, statins may foster bone formation by:
1. Inhibiting Rho/ROCK via impaired prenylation
2. Activating Ras-PI3K-Akt/Erk signaling
3. Engaging Smad-mediated BMP-2 induction

These strands coalesce in a coordinated promotion of osteoblast differentiation, matrix synthesis, and survival, though the degree to which this translates to clinical bone repair or density gains may vary.

OSTEOCLAST PATHWAYS: STATIN INDUCED INHIBITION OF RESORPTION

Statins modulate the OPG/RANKL/RANK axis, a critical control point in osteoclastogenesis. They elevate OPG (a decoy receptor) and reduce RANKL expression in bone-cell culture systems, dampening osteoclast formation (21).

They also suppress NF-kB activation, essential for osteoclast differentiation. Simvastatin inhibited RANKL-induced activation of NF-kB by blocking IκBα phosphorylation and degradation in RAW 264.7 cells, directly restraining osteoclastogenesis (9).

Atorvastatin further acts by interrupting inflammatory signaling. In synoviocytes from rheumatoid arthritis patients, it suppressed TNF-α-induced p38 MAPK phosphorylation and reduced RANKL expression and TRAP-positive osteoclast formation effects reversed by mevalonate supplementation, underscoring the role of the mevalonate pathway (22).

In essence, statins may attenuate bone resorption through multiple nodes:
1. Promoting OPG while suppressing RANKL
2. Blocking NF-kB activation required for osteoclastogenesis
3. Inhibiting p38 MAPK and related inflammatory triggers

DISCUSSION

The experimental evidence presents a consistent mechanistic narrative that statins promote osteoblast differentiation via BMP-2 induction and Ras-PI3K-Akt-Erk signaling, while reducing osteoclastogenesis through modulation of the OPG/RANKL axis and suppression of NF-kB and inflammatory kinase activation (20). These complementary pathways could, in theory, favor net bone formation and improved osseointegration of dental implants (Graph 1). In hyperlipidemic animal models, statins also appear to counteract impaired osseointegration, suggesting possible translational relevance for implant dentistry.

Nevertheless, translation to clinical outcomes is limited by the modest magnitude of BMD changes observed in human studies, the absence of large scale trials targeting fracture endpoints, and variability in statin type, dose, and treatment duration. Additionally, obesity's partial but nondeterministic correlation with hypercholesterolemia reflects a broader metabolic milieu influencing both bone and cardiovascular health, making causality difficult to isolate. Future research should address whether targeted delivery systems, patient stratification by metabolic status, and longer treatment durations can reveal more

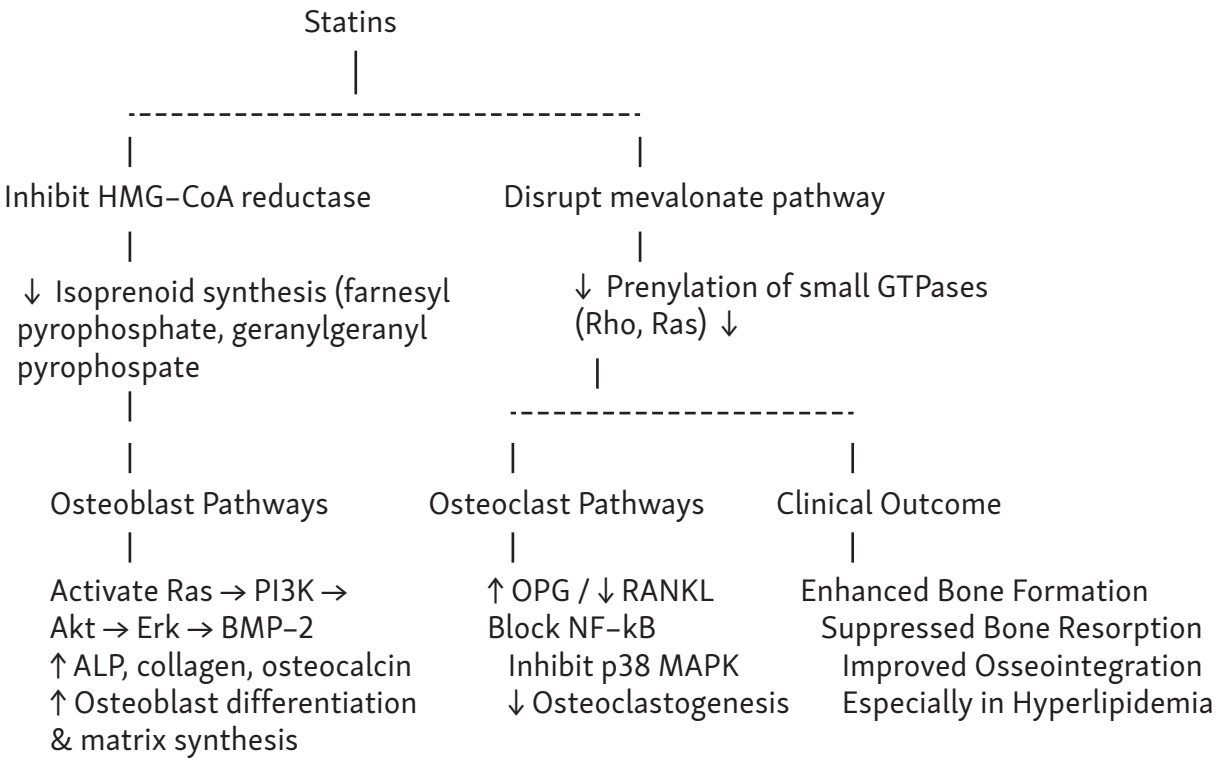

Fig. 1 Effect of statins on bone remodeling and implant osseointegration.

substantial skeletal benefits. The convergence of lipid metabolism, inflammation, and bone remodeling pathways positions statins as promising, but as yet incompletely validated, agents in skeletal health management.

Future studies should optimize delivery vehicles that provide controlled, site specific release to the peri-implant region, minimizing systemic exposure and maximizing local BMP-2 induction.

Detailed in vivo and ex vivo studies are needed to confirm whether the peri-implant microenvironment, including exposure to oral microbiota, local inflammation, and masticatory forces, alters these signaling pathways.

Statins' modulation of the OPG/RANKL axis and suppression of NF-kB-mediated osteoclastogenesis should be investigated within peri-implant tissues, particularly under conditions of early implant loading or in patients with a history of periodontitis.

Given the links between obesity, dyslipidemia, and altered bone metabolism (23, 24), clinical trials should stratify patients by metabolic profile to determine whether hyperlipidemic or insulin resistant individuals derive greater peri-implant benefits from statin therapy.

Statin release from implant surfaces or coatings could be combined with micro/nano-textured titanium or bioactive ceramic surfaces to achieve additive or synergistic effects on osseointegration.

Most existing studies assess short term bone implant contact and early stability. Randomized controlled trials with extended follow up should evaluate whether statin based interventions reduce late implant loss, particularly in medically compromised patients.

A trial should explore whether statin therapy interacts with microbiota mediated metabolic and inflammatory pathways to influence peri-implant bone maintenance.

The limitations in future research design could be the heterogeneity of study models, the dosage and delivery methods, the duration of the follow up, the small sample sizes, the population diversity, the interaction with other medications and conditions (such as osteoporosis and diabetes mellitus), the molecular mechanism clarity and study design biases. Addressing these limitations will be crucial for using statins in dental implantology within the clinic, and for the design of future research. This approach will also maximize meaningful, translatable outcomes in evidence for these medications.

CONCLUSION

Statins appear to be at least potentially bone friendly. They appear to enhance osteoblast activity, inhibit osteoclastogenesis, potentially provide some benefit in bone density along with the potential benefit in implant healing in the presence of hyperlipidemia. There is a relationship between obesity and hypercholesterolemia, yet non linearly, resembling the global form of metabolic interrelation involving obesity and hyperlipidemia. Therefore, this review will call for further clinical investigation, however, given what is presented in terms of mechanistic and preclinical evidence it is possible that the interrelated matrix discussed here deserves further examination.

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Surgical Management of Spondylodiscitis: A Single-Center Retrospective Analysis of 126 Cases

Pavel Trávníček[1,2,*], Lenka Ryšková[3], Tomáš Hosszú[1,2], Roman Kostyšyn[1,2], Pavel Ryška[4], Jan Trlica[5,6], Tomáš Česák[1,2], Miroslav Cihlo[1,2]

ABSTRACT

Background: Pyogenic spondylodiscitis is a severe spinal infection. Surgery can provide source control, neural decompression, and stability when indicated, but practice varies. We assessed outcomes of surgically treated cases at a tertiary neurosurgical center (2015–2024).

Methods: Retrospective cohort of consecutive adults admitted with pyogenic spondylodiscitis to a tertiary neurosurgical center (2015–2024). Surgical and non-surgical cases were recorded; analyses focus on surgically managed patients with whole-cohort descriptors where indicated.

Methods: We retrospectively analysed consecutive patients indicated for surgery. Variables included procedure type (decompression alone vs. instrumentation), presence of epidural abscess, reoperation for relapse or new-onset instability, microbiology, length of hospital stay (LOS), early outcomes, and admission clinical status.

Results: We included 126 patients (87 men, 69%); mean age 65 years (range 13–91). Surgery was performed in 108 (85.7%): decompression alone in 76/108 (70.4%), instrumented decompression in 21/108 (19.4%), standalone instrumentation in 4/108 (3.7%), and multistage combined procedures in 7/108 (6.5%). Epidural abscess was present at the index operation in 98/108 (90.7%). Relapse, either confirmed intraoperatively or on preoperative MRI occurred in 29/126 (23.0%); reoperation for progressive instability in 17/108 (15.7%). Among patients with confirmed etiology (121/126, 96.0%), the most frequent pathogens were Staphylococcus aureus 69/121 (57.0%), Enterobacterales 18/121 (14.9%), and streptococci 16/121 (13.2%). Mean LOS was 35.3 days (median 27). Multiorgan failure developed in 44/126 (35.0%); in-hospital mortality was 7/126 (5.6%). No implant-related complications were observed.

Conclusions: Early surgical source control with decompression without instrumentation was sufficient in most operated cases. When radiographic or intraoperative instability was present, instrumentation appeared safe despite active infection, provided meticulous debridement and pathogen-directed antibiotics were employed. Blood cultures and tissue samples should be taken timely and repeated if needed, as they both provide high diagnostic yield.

KEYWORDS

spondylodiscitis; spondylitis; epidural abscess; magnetic resonance imaging; antibiotic therapy; instrumentation; spine; intervertebral disc

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AUTHOR AFFILIATIONS
[1] Department of Neurosurgery, Charles University, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech Republic
[2] Department of Neurosurgery, University Hospital Hradec Králové, Hradec Králové, Czech Republic
[3] Department of Clinical Microbiology, University Hospital Hradec Králové, Hradec Králové, Czech Republic
[4] Department of Radiology, University Hospital Hradec Králové, Hradec Králové, Czech Republic
[5] Department of Surgery, University Hospital Hradec Králové, Hradec Králové, Czech Republic
[6] Department of Surgery, Charles University, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech Republic
* Corresponding author: Department of Neurosurgery, Charles University, Faculty of Medicine in Hradec Králové, Hradec Králové, Czech Republic; Department of Neurosurgery, University Hospital Hradec Králové, Hradec Králové, Czech Republic; pavel.travnicek@fnhk.cz

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INTRODUCTION

Infectious spondylodiscitis is a serious spinal infection involving the intervertebral disc and/or the adjacent vertebral bodies. It is an inherently multidisciplinary condition that engages multiple medical and surgical specialties. The incidence has been rising in recent decades, driven by population aging, a higher burden of comorbidities, and improved detection owing to broad availability of sensitive imaging modalities – particularly magnetic resonance imaging (MRI) with gadolinium-based contrast (1–3). Randomized controlled trials of antimicrobial therapy are lacking, and there is currently no national consensus guideline for diagnosis and treatment in the Czech Republic (1).

The source of infection is usually in another body system and the infection is spread via the hematogenous route. In adults, infection typically begins in the subchondral regions of the vertebral bodies with secondary spread to the intervertebral disc; in children it may more rarely start in the disc due to different vascularization (2, 3). Infection can extend into the paravertebral compartments and the epidural space with abscess formation; less commonly it involves the subdural space or the central nervous system (CNS) (meningitis, myelitis) (4). Microbiologically, Staphylococcus aureus predominates (up to ~60%), followed by Enterobacterales, streptococci; mycobacterial (e.g. *Mycobacterium tuberculosis*), fungal, and parasitic etiologies are less frequent but clinically important (3–5). In epidural abscesses, S. aureus and streptococci prevail (6). The most common location is the lumbar spine (≈58%), followed by thoracic (≈30%) and cervical (≈11%); multisegmental involvement is uncommon and more often associated with atypical pathogens (6, 7).

Risk factors for spondylitis development include diabetes mellitus, intravenous drug use, catheter-related infections, recent spinal surgery, infective endocarditis, urinary tract infection, chronic alcoholism, and conditions associated with immunosuppression (8). In complicated courses (e.g., subdural abscess), liver cirrhosis and chronic renal failure have also been reported (5). The disease shows two age peaks: a pediatric form (especially between 2–8 years) and an adult form peaking in the 5th–7th decades; males are more frequently affected (ratio ~1.5–2:1) (1, 2).

Clinical manifestations of spondylitis are nonspecific. Localized back or neck pain – often nocturnal and at rest – predominates; radicular radiation is common and may lead to misdiagnosis. Fever is absent in a substantial proportion of patients, it is found in only half of the cases (9–15). Neurological deficit is present in approximately one third of cases and more commonly accompanies delayed diagnosis, epidural abscess, cervical involvement, or tuberculous etiology; the spectrum ranges from sensorimotor deficits and radiculopathy to paraplegia or conus/cauda syndromes with sphincter dysfunction (3, 5).

Diagnosis relies on contrast-enhanced MRI and laboratory testing including repeated blood cultures and inflammatory markers. Early, high-quality microbiological sampling with culture and PCR diagnosis is crucial for targeted therapy; prematurely initiated empirical antibiotic therapy markedly reduces culture yield and increases the risk of relapse (3, 7). In uncomplicated cases, the standard approach is conservative management with immobilization and at least six weeks of antimicrobial therapy; percutaneous abscess drainage may be appropriate for early collections (1). Surgical treatment is indicated in case of instability, progressive or impending neurological deficit, failure of conservative therapy, extensive epidural/paravertebral abscess, or diagnostic uncertainty. The goals are eradication of the infectious focus, decompression of neural elements, and restoration of spinal stability (1–4).

The role of surgery, alongside antibiotics, is to obtain source control (decompression and debridement), eradicate devitalized tissue, drain abscess collections, protect neural elements, and restore spinal stability when instability is present. However, consensus varies regarding indications, timing, and the safety of instrumentation in the setting of active infection. This single-center retrospective study summarizes our surgical strategies, microbiological yield, and short-term outcomes over a 10-year period, with attention to relapse and reoperation for progressive instability.

The aim of this single-centre retrospective study is to describe the indication criteria, the range of surgical procedures, and early outcomes – including complications – in spondylodiscitis management at the authors' institution.

MATERIALS AND METHODS

STUDY DESIGN AND SETTING

Single-center retrospective observational study at a tertiary neurosurgical department (2015–2024). Consecutive hospitalized adults with pyogenic spondylodiscitis were screened.

INCLUSION/EXCLUSION CRITERIA

Included: MRI-confirmed pyogenic spondylodiscitis requiring surgery at our center during the index admission. Excluded: non-pyogenic etiologies (e.g., tuberculosis, fungal), purely conservative cases that never underwent a surgical procedure during the index episode, and pediatric-specific entities. (We report conservative cases descriptively where relevant.)

DIAGNOSTIC WORK-UP AND IMAGING

Diagnosis was based on clinical presentation and contrast-enhanced MRI of the affected segment; plain radiography was added as needed. Single-centre retrospective observational study conducted at the authors' institution in 2015–2024. Consecutive hospitalized patients with spondylodiscitis who were indicated for conservative or surgical management at our centre were included. The diagnosis was based on the clinical manifestation (localized back/neck pain, fever, neurological deficit, signs of sepsis) and contrast-enhanced MRI of the affected spinal segment (16); plain radiography was added as needed. Data were systematically extracted from the medical record. The following were recorded:

- demographics, comorbidities, and body-mass index (BMI) (with emphasis on diabetes mellitus and long-term corticosteroid therapy);
- clinical presentation at admission (pain, fever, neurological deficit, sepsis) and the Medical Research Council (MRC) muscle strength score (0–5);
- inflammatory and organ-function laboratory indices (complete blood count, C-reactive protein (CRP); as indicated, urea, creatinine, estimated glomerular filtration rate);
- microbiology (see below); imaging findings (contrast-enhanced MRI; plain radiography);
- treatment strategy (conservative vs. surgical), timing, and surgical approach/procedure type;
- hospitalization metrics and discharge status (pain at discharge categorized as none/improved/unchanged/worsened) and the need for reoperation.

MRI was obtained in all potentially operable patients.

MICROBIOLOGY

Blood cultures were drawn at admission whenever feasible prior to antibiotics. Tissue sampling from the spinal focus was performed in all patients (intraoperatively in operated cases; CT-guided biopsy otherwise). Culture was the in non-operated /deferred cases. The primary modality, in culture-negative cases with concomitantly negative blood cultures, PCR was added. Organism proportions are reported on the subset with confirmed etiology (n = 121/126, 96.0%) and explicitly labeled as such throughout. The presence of an epidural abscess was recorded. Conservative therapy comprised immobilization with an orthosis and targeted antibiotic therapy based on blood cultures or CT-guided biopsy results; empiric antibiotics were initiated only in case of sepsis, according to local recommendations.

SURGICAL STRATEGIES

Procedures were categorized as: (i) debridement + decompression without instrumentation; (ii) instrumented decompression; (iii) instrumentation alone; (iv) staged/combined procedures. Approach (anterior/posterior/combined) and the presence of epidural abscess were recorded. Timing categories (primary/early; delayed after antibiotics; after failure of conservative therapy) are mutually exclusive and refer to the index operation.

Outcome definitions:

- Relapse (primary endpoint, added): recurrent clinical signs compatible with spondylodiscitis within 90 days of index hospitalization plus ≥1 of: (a) microbiological confirmation concordant with the index episode; (b) MRI evidence of progression/recurrence (new/enlarging abscess or destructive changes); (c) sustained inflammatory response (CRP/ESR) with renewed focal pain or neurologic worsening requiring escalation (antimicrobials and/or reoperation). Events >90 days are reported descriptively but not counted toward the primary relapse rate. Reoperation for progressive

Primary outcomes:

- Presence of a drainable (pus-containing) epidural abscess, defined by intraoperative proof/finding of suppuration or preoperative MRI features of a fluid collection with rim enhancement and diffusion restriction.
- Reoperation for relapse/residual infection.
- Development or progression of spinal instability: any unplanned surgery prompted by radiographic/clinical worsening of stability after the index procedure.
- Spinal instability: increase in segmental kyphosisof the kyphotic angle ≥10° or >50% vertebral body height loss, or clear intraoperative instability prompting fixation, as per institutional practice.
- Microbiological yield: any positive culture from blood and/or tissue and/or positive PCR result (pooled as "confirmed etiology"). The denominator for pathogen percentages is n = 121.

STATISTICAL

Secondary outcomes:

- length of hospital stay and in-hospital mortality;
- pain status at the time of discharge (none/improved/unchanged/worsened);
- diagnostic yield of microbiology (blood cultures, tissue cultures, PCR results).

A DESCRIPTIVE ANALYSIS

Descriptive analysis only: categorical variables are presented as counts/numbers/sum and percentages; continuous variables as mean (SD) or median (IQR) depending on distribution. Missing data were left as missing; denominators are explicitly stated by variable (e.g., microbiology n = 121). Analyses were done instandard deviation (SD)) and/or median (interquartile range (IQR)) according to distribution). Statistical processing was performed using

NCSS (NCSS, LLC, East Kaysville, Utah, USA; version NCSS 2025, www.ncss.com).

RESULTS

We identified 126 patients (87 men, 69%); mean age 65 years (median 67, range 13–91). Surgery was performed in 108/126 (85.7%). An epidural abscess at the index operation was present in 98/108 (90.7%). Baseline characteristics are summarized in Table 1.

Tab. 1 Baseline cohort characteristics and laboratory indices.

Variable	Value
Number of patients, n	126
Age, mean (range), years	65 (13–91)
Sex, n (%)	Men **87** (69%) Women **39** (31%)
BMI[1], mean (min–max)	**29.15** (17.60–52.20)
Clinical presentation at admission, n (%)	Isolated pain **55** (43.6%); Isolated neurological deficit **16** (12.7%); Sepsis **16** (12.7%); Combination of symptoms **39** (31%)
Fever at admission, n (%)	**22** (17.5%)
MRC[2] score at admission–distribution, n (%)	5: **60** (47.6%); 4: **18** (14.3%); 3: **22** (17.5%); 2: **11** (8.7%); 1: **5** (4%); 0: **10** (7.9%)
MRC score - summary	Mean 3.69; median 4
Comorbidities / risk factors, n (%)	Type 2 diabetes mellitus **53** (42.1%); long-term corticosteroid therapy **41** (32.5%); tobacco use **24** (19%); chronic alcohol misuse **10** (7.9%); intravenous drug use **3** (2.4%)
Length of hospital stay, mean (days)	**35.3 (median 27, range...)**

[1] BMI = body-mass index; [2] MRC = Medical Research Council muscle strength score

LOCALIZATION

Spinal involvement was categorized as cervical, thoracic, lumbar, or multilevel disease. Proportions were cervical 12.0%, thoracic 20.6%, lumbar 46.0%, and multilevel 21.4%. These categories were treated as mutually exclusive for reporting; "multilevel" denotes contiguous or noncontiguous involvement spanning more than one region and is not summed with single-region categories.

SURGICAL MANAGEMENT

Among surgically treated patients (n = 108): decompression alone in 76/108 (70.4%); decompression with instrumentation in 21/108 (19.4%); standalone instrumentation in 4/108 (3.7%); multistage combined procedures in 7/108 (6.5%).

Early surgical intervention and a single-stage strategy predominated. Debridement with decompression without instrumentation was the most common procedure; instrumented procedures represented a minority. The cohort consisted predominantly of older patients (mean age 65 years) with a substantial comorbidity burden (type 2 diabetes 42.1%, long-term corticosteroid therapy 32.5%). Clinically, back/neck pain prevailed; fever was present in only 17.5%, underscoring the nonspecific presentation. The MRC distribution indicates that 52.4% of patients had a motor deficit, reflecting marked functional impairment at the time of admission.

MRI was performed in all patients. Distribution by spinal segment: cervical 12%, thoracic 20.6%, lumbar 46%; multilevel disease 21.4%. A pre-existing extra-spinal infectious focus was identified in 68 patients, while isolated spinal involvement without another primary focus was present in 58 patients.

Admission blood cultures were obtained in 103/126 patients; 89/103 (86.4%) were positive, corresponding to 89/126 (70.6%) of the entire cohort. Material from the spinal focus was obtained in all patients (intraoperatively in those undergoing surgery, CT-guided biopsy in non-operated /deferred cases). Tissue cultures were positive in 114/126, negative in 11/126, and contaminated/indeterminate in 1/126; PCR was performed in 10 culture-negative samples. The total number of patients with any microbiological confirmation (blood and/or tissue culture and/or PCR) was 121/126 (96.0%). The most frequently identified pathogen was *Staphylococcus aureus* (69/121, 57,0%), followed by Enterobacterales (18/121, 14.9%; most commonly *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella Enteritidis*) and Streptococci (16/121, 13.2%), see Figure 1.

Primary conservative therapy (combination of antibiotics and orthosis) was applied in 18/126 patients; it was successful in 14/18. Owing to failure of conservative management, 4 of these patients subsequently underwent surgery; an additional 17 patients were referred for surgery after failure of conservative treatment at referring hospitals (total 21 were operated after failed conservative care).

Early surgery (without previous conservative treatment) was indicated in 74/126 patients: a delayed procedure after antibiotics in 17/126. The posterior approach was dominant; a pure lateral approach was not used. The high prevalence of epidural abscesses at presentation reflects the severity of cases treated at a tertiary center and explains the predominance of decompressive procedures.

MICROBIOLOGY

Confirmed etiology was established in 121/126 (96.0%), see Figure 1. The most frequent pathogen was Staphylococcus aureus 69/121 (57,0%) (MSSA/MRSA distribution to be specified if available), followed by Enterobacterales 18/121 (14.9%) and Streptococci 16/121 (13.2%). Polymicrobial growth and contaminants were recorded according to institutional microbiology standards.

EARLY OUTCOMES, RELAPSE, AND REOPERATIONS

Relapse occurred in 29/126 (23.0%) by the primary 90-day definition. Reoperation for progressive instability occurred in 17/108 (15.7%). Mean LOS was 35.3 days (me-

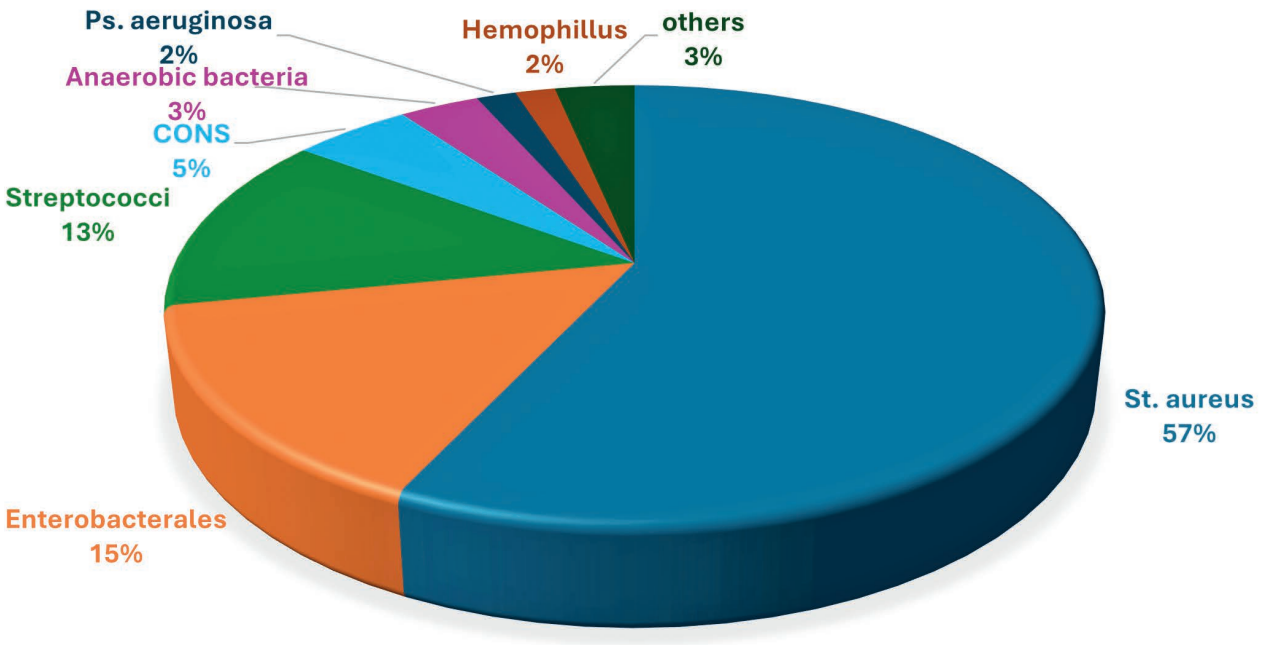

Fig. 1 Pathogen distribution among culture/PCR-confirmed cases (n = 121). Pie chart shows counts and proportions of the etiologic groups. CONS = Coagulase-Negative Staphylococci.

dian 27). Multiorgan failure developed in 44/126 (35.0%); in-hospital mortality was 7/126 (5.6%). No implant-related complications were observed within the recorded follow-up window.

Surgical management is summarized in Table 2.

Tab. 2 Surgical management of spondylodiscitis (N = 108). Values are n (% of operated patients). Timing categories are mutually exclusive and refer to the index operation.

		n	%
Timing of surgery	Primary (early) procedure	74	58.7
	Delayed procedure after antibiotics	17	13.5
	After failure of conservative therapy*	17	15.7
Number of stages	Single-stage procedure	85	78.7
	Multistage procedure	23	21.3
Type of surgical procedure	Debridement + decompression without instrumentation	76	70.4
	Instrumented decompression	21	19.4
	Instrumentation alone (no decompression)	4	3.7
	Combined multistage procedures	7	6.5
Surgical approach	Posterior	90	83.3
	Anterior	12	11.1
	Combined (anterior+posterior / lateral+posterior)	6	5.6
	Lateral alone	0	0.0

* Note: Patients did not respond to conservative therapy at regional hospitals.

Early surgical intervention and a single-stage strategy prevailed. Debridement with decompression without instrumentation was the most common procedure with lesser number of instrumented procedures our tertiary centre and explains the predominance of decompressive procedures.

Targeted antibiotic therapy was guided by culture results; when the pathogen was unknown, empiric therapy was used in severe septic presentations according to local microbiological treatment standards. The duration of antibiotic treatment could not be reliably retrieved in many cases and is therefore not reported.

Treatment course and outcomes are summarized in Table 3.

During hospitalization, multiorgan failure occurred in 35% and in-hospital mortality was 5.6%. Most patients were discharged to subsequent inpatient/rehabilitation care (73.8%), with 7.9% transferred directly to a rehabilitation institute. Relapse was documented in nearly one quarter of the cohort. Pain relief at discharge was achieved in the vast majority (80.9% with no pain or improved pain), and we observed no complications related to spinal instrumentation.

DISCUSSION

In this single-centre retrospective cohort of 126 consecutive patients with pyogenic spondylodiscitis managed at a tertiary neurosurgical center, surgery was indicated in 108/126 (85.7%). Early surgical source control with decompression alone sufficed in most operated cases (76/108; 70.4%). When radiographic or intraoperative instability was present, instrumented fusion appeared safe despite active infection (32/108; 29.6%), and no implant-related mechanical failures were observed. The cohort was char-

Tab. 3 Treatment outcomes in our spondylodiscitis cohort.
Cohort N = 126; survivors at discharge n = 119.

Domain	Outcome	n	%
In-hospital course	Multiorgan failure	44	35.0
	In-hospital mortality	7	5.6
Discharge disposition (of all 126)	Home	26	20.6
	Further inpatient/rehabilitation care	93	73.8
	Died in hospital	7	5.6
– of which (subset of "Further care")	Direct transfer to a rehabilitation institute[1]	10	7.9
Relapse (of all 126)	Disease relapse after treatment	29	23.0
****Pain at discharge (of survivors, n = 119)**[2]	None	12	9.5
	Improved	90	71.4
	Unchanged	17	13.5
	Worsened	0	0.0
Implant-related complications[3]	Complications related to spinal instrumentation	0	0.0

[1] Subset of the "Further inpatient/rehabilitation care" group.
[2] Pain assessed among survivors only (n = 119).
[3] Assessed among instrumented cases (denominator detailed in Table 2); no implant-related complications were observed.

acterized by a high prevalence of epidural abscess (98/108; 90.7%), a relapse rate of 23.0% (29/126), substantial systemic morbidity (multiorgan failure 44/126; 35.0%), and low in-hospital mortality (7/126; 5.6%). Microbiological confirmation was achieved in 96.0% of cases, with Staphylococcus aureus as the predominant pathogen.

SURGICAL STRATEGY AND THE ROLE OF INSTRUMENTATION

The predominance of decompression-only procedures reflects a pragmatic approach prioritizing source control and neural decompression while avoiding hardware when structural stability can be preserved. This contrasts with reports from centers employing instrumentation in >90% of surgically treated cases (17), likely reflecting differences in case mix, referral patterns, and stability assessment (18, 19). The absence of implant failures in our instrumented subgroup aligns with contemporary evidence that instrumentation, when combined with meticulous debridement and appropriate antibiotics, does not inherently increase reinfection risk (20–22).

Our broad definition of relapse (including clinical, radiographic, and microbiological recurrence at any time during follow-up) may capture events that other series classify differently. Some studies distinguish between early treatment failure (within 3 months) and late recurrence, or between same-site relapse and new-level disease (23, 24). Our relapse rate (23.0%) and reoperation for progressive instability (15.7%) exceed figures in many series (~8–14%) (18, 23, 25). This likely reflects (i) a more severe case mix with an exceptionally high burden of epidural abscess (26, 27); (ii) pathogen factors, including a high proportion of S. aureus with potential MRSA contribution (28, 29); (iii) limits on debridement scope imposed by neurological or anatomical considerations (24); and (iv) nuances of antimicrobial timing, penetration, and duration. Clinically, more liberal instrumentation at the index procedure may be considered in patients with substantial vertebral body destruction, three-column involvement, or clear intraoperative instability – balanced against operative risk in fragile hosts (30, 31).

The predominance of S. aureus (~57%) lies at the middle of published ranges, consistent with its central role in hematogenous vertebral infections (28, 29). Enterobacterales and streptococci comprised relevant minorities, often with identifiable bacteremic sources (32). These patterns support empiric anti-staphylococcal coverage with agents achieving therapeutic bone/disk levels and prompt de-escalation once susceptibilities are known.

In-hospital mortality (5.6%) falls within contemporary surgical series and reflects the severity of sepsis among patients referred for neurosurgical intervention (30, 32). The 35.0% rate of multiorgan failure underscores the need for multidisciplinary care (infectious diseases, critical care, rehabilitation). Hospital length of stay was prolonged (mean 35.3 days; median 27 days), consistent with requirements for intravenous therapy, stabilization of sepsis, wound healing, and mobilization. Pathways that enable early switch to high-bioavailability oral regimens, use of outpatient parenteral antimicrobial therapy (OPAT), and structured rehabilitation may shorten hospitalization without compromising outcomes (33).

A 96.0% microbiological confirmation rate exceeds many reports and likely reflects systematic practices: obtaining blood cultures before antibiotics, collecting multiple intraoperative tissue specimens, and close laboratory coordination. Blood and tissue sampling are complementary and should both be pursued; molecular diagnostics (e.g., 16S rRNA PCR) may aid culture-negative cases with strong clinical suspicion (34, 35).

This study has some limitations. The retrospective, single-center design with tertiary referral bias (high rates of epidural abscess and organ failure) limits generalizability. Absence of a nonoperative comparator precludes inference on relative effectiveness versus medical therapy

alone. Incomplete detail on antibiotic regimens and long-term functional outcomes constrains analysis of relapse determinants. Standardized definitions for relapse and instability would facilitate cross-study comparisons (36).

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Management should be individualized based on neurological status, biomechanical stability (imaging and intraoperative assessment), extent of osseous destruction, pathogen virulence/susceptibility, comorbidity burden, and response to initial therapy. We favor early source control, decompression when stability is preserved, and instrumentation when instability is documented. Priorities for future research include prospective, multicenter comparisons of surgical strategies and timing, validated risk models for relapse/instability, and optimization of perioperative antimicrobial pathways.

Limitations of our study are as follows: (i) retrospective design without a control group and without inferential analyses, limiting causal inference and exposing the data to selection and information bias; (ii) single-centre setting, which may limit generalizability; (iii) incomplete capture of the entire conservatively treated population across specialties, as spondylodiscitis is multidisciplinary and many patients are treated outside neurosurgery; (iv) imperfect post-discharge follow-up across multiple post-acute facilities, limiting precise ascertainment of antibiotic start/stop dates (intravenous and oral) and late complications/relapses; (v) absence of standardized cross-disciplinary protocols for follow-up imaging, potentially introducing heterogeneity in indications for re-intervention; (vi) antibiotic duration (IV and oral) was not analysed due to incomplete documentation and inter-facility variation in prescription, precluding adjustment for antimicrobial exposure in outcome comparisons.

Our findings support a pragmatic algorithm: early microbiological sampling; early decompression and debridement in case of epidural abscess or neurological deficit; and instrumentation when instability is confirmed, without an observed increase in implant-related complications in our series. Prospective multicentre studies should aim to: (i) standardize surgical indication criteria; (ii) optimize IV/PO antibiotic duration and the role of early switch to oral therapy; (iii) define follow-up MRI protocols, particularly in the post-operative and post-antibiotic periods; and (iv) validate predictors of relapse.

CONCLUSIONS

Conservative therapy remains the standard for uncomplicated spondylodiscitis, with targeted – often prolonged – antimicrobial treatment as a cornerstone. Staphylococcus aureus predominates microbiologically; early blood cultures and sampling from the spinal focus are therefore essential, with repeated sampling advisable when initial results are negative or inconclusive. Surgical indications include, in particular, diagnostic tissue sampling, neurological deficit or its progression, failure of conservative therapy, epidural abscess, and instability or extensive disease. In our cohort, early surgical source control with decompression without instrumentation sufficed in most cases; instrumentation was effective and safe when instability was demonstrated, and we observed no implant-related complications. Meticulous debridement and subsequent targeted antimicrobial therapy are crucial steps to success. CT-guided sampling proved a useful adjunct to establish etiology and guide therapy in unclear or non-surgical cases.

AUTHOR CONTRIBUTIONS

Conceptualization, P.T. and L.R.; methodology, P.T., L.R.; software, M.C.; validation, L.R.; formal analysis, L.R., T.H., T.Č.; investigation, P.T., R.K., T.H., P.R. L.R., J.T.; resources, P.T.; data curation – M.C.; writing – original draft preparation, P.T.; writing – review and editing, M.C., T.Č., L.R.; supervision, T.Č., T.H., L.R.; project administration, P.T., M.C.; funding acquisition, P.T. All authors have read and agreed to the published version of the manuscript. All authors participated in critical revision of the manuscript, contributed comments, and approved the final version.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Ethical Committee of the University Hospital Hradec Kralove, Hradec Kralove, Czech Republic (Chairperson Jiri Vortel, MD) determined that this retrospective chart review was exempt from full review, and that written informed consent was not required due to the use of de-identified data. The study adhered to the Declaration of Helsinki and applicable data-protection regulations. All data were de-identified prior to analysis; no direct patient identifiers were collected (GDPR-compliant).

CONSENT FOR PUBLICATION

Not applicable (no individual person's data are included).

DATA AVAILABILITY

The study protocol and de-identified dataset supporting the findings are available from the corresponding author upon reasonable request.

COMPETING INTERESTS

The authors declare no competing interests.

CONFLICTS OF INTEREST

The authors certify that there are no conflicts of interest with any financial organization regarding the materials discussed in this manuscript.

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Clinical Trajectories and Outcomes of Acute Heart Failure in Internal Medicine: A Real-World Single-Centre Study

Edgardo J. Kaplinsky[1,*], Silvia Masmitjà Comajuan[1], Josefa Torres Martínez[2], Ana Serrado Iglesias[2], Daniel Cuartero Guerrero[2], Francesc Planas Ayma[1], Lourdes Zurita[1], Gustavo Tolchinsky Wiesen[2], Esther Moreno Ariño[3], Àngels Fumàs Comas[4], Cristina Carod Pérez[5]

ABSTRACT

Purpose: To analyze the clinical characteristics and outcomes of patients with acute heart failure (AHF) admitted to an internal medicine department (IMD), with a focus on their trajectories, risk factors, and rehospitalisation/mortality rate.
Methods: This retrospective cohort study included 410 hospitalisations (280 patients; 28% readmissions) for AHF during 2023. Diagnosis was validated using the European Society of Cardiology age-specific NT-proBNP thresholds and echocardiographic criteria. Baseline clinical and laboratory data were analyzed, prognostic markers were identified, and a risk algorithm was developed.
Results: Mean patient age was 82 years (54% women). Most cases involved nonischemic etiology (80%) and HF with preserved ejection fraction (HFpEF, 69%). Frequent comorbidities included hypertension (85%), diabetes (45%), atrial fibrillation (44%), and multiple non-cardiac conditions. In-hospital mortality was 19.6%; 30-day readmission was 9.9%. Three clinical trajectories (index/first hospitalisation) were identified: single admission (n: 169), rehospitalisation (with/without death) (n: 73), and in-hospital death (n: 38). Prognostic markers included advanced age, elevated NT-proBNP, renal dysfunction, anemia, and non-cardiac cause of HF decompensation.
Conclusions: This elderly IMD-HF cohort, mainly female and multimorbid, showed high HFpEF prevalence and adverse outcomes. NT-proBNP, renal function, haemoglobin, and non-cardiac causes of HF decompensation were key prognostic indicators.

KEYWORDS

heart failure; hospitalization; rehospitalization; mortality; NT-proBNP

AUTHOR AFFILIATIONS

[1] Cardiology Unit, Hospital Municipal de Badalona, Barcelona, Spain
[2] Internal Medicine Department, Hospital Municipal de Badalona, Barcelona, Spain
[3] Emergency Department, Hospital Municipal de Badalona, Barcelona, Spain
[4] Management Control and Process Unit, Badalona Serveis Assistencials, Barcelona, Spain
[5] Healthcare Management, Badalona Serveis Assistencials, Barcelona, Spain
* Corresponding author: Cardiology Unit, Hospital Municipal de Badalona, Via Augusta 9–13, 08911 Badalona, Barcelona, Spain; ejkaplinsky@gmail.com

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INTRODUCTION

Heart failure (HF) remains one of the most pressing and complex challenges in modern cardiovascular medicine, with an estimated prevalence of 1–2% among the adult population in developed countries (1, 2). This condition not only imposes a substantial burden on healthcare systems but also significantly affects patients' quality of life and long-term prognosis. Within this spectrum, acute heart failure (AHF) stands out as a leading cause of hospital admissions among individuals aged 65 years and older – a population frequently characterized by the presence of multiple comorbidities and increased clinical vulnerability (3, 4).

In clinical practice, the setting of hospitalisation plays a pivotal role in shaping patient outcomes. Patients admitted to internal medicine departments (IMDs) tend to be older, exhibit greater frailty, and present with a higher burden of chronic illnesses compared to those managed in specialized cardiology units (5–7). These differences underscore the importance of tailoring therapeutic strategies and care pathways to the unique needs of this population.

This study presents a single-centre, retrospective descriptive analysis of patients admitted with AHF to an IMD. Our objectives are twofold: first, to characterize the baseline clinical conditions of these patients; and second, to delineate three distinct clinical trajectories emerging after the initial (index) hospitalization. Through this approach, we aim to contribute to a more nuanced understanding of AHF management in internal medicine settings and highlight potential avenues for improving care delivery in this high-risk group.

METHODS

OBJECTIVES

The primary objectives of this study were twofold. First, to describe the baseline demographic characteristics and clinical profiles of patients with acute AHF who were discharged from our IMD following decompensation, classified either as primary (cardiac-related cause of decompensation) or secondary (non-cardiac cause of decompensation). Second, to identify and describe three distinct clinical trajectories observed over the course of one year following the index (first) hospitalisation: (1) patients who experienced only a single hospitalization, (2) patients who underwent rehospitalisation, and (3) patients who died during their initial hospital stay

STUDY DESIGN AND ETHICAL ISSUES

This study is a retrospective, single-centre, observational analysis. Prior to its initiation, approval was obtained from the hospital's clinical research committee. All clinical data were handled in strict compliance with patient confidentiality protocols and ethical standards, in accordance with the principles outlined in the Declaration of Helsinki. Informed consent was waived in accordance with national legislation and institutional policies governing retrospective research.

CHARACTERIZATION OF THE URBAN AREA AND THE HEALTHCARE CENTER

The Hospital Municipal de Badalona (bsa.cat) is an adult university hospital located in Badalona, on the outskirts of Barcelona (Catalonia, Spain), approximately 11 km from the city center (calcularruta.com/barcelona-badalona.html). Badalona has a population of 219,786 inhabitants as of 2025, of whom about 162,000 are adults (≥18 years) (bdeex.com/es/naselenie/spain/Badalona).

The hospital offers a wide range of specialties, including cardiology and internal medicine. The IMD has a capacity of 50–70 inpatient beds and registered 2,168 hospitalizations in 2023 and 2,157 in 2024.

CATEGORIZATION OF PATIENTS

The study analyzed all patients discharged with AHF from our IMD during 2023 (January 1 to December 31), including both primary (cardiac-related) and secondary (non-cardiac-related) decompensation causes. Case selection involved reviewing all discharge summaries, encompassing both single hospitalizations and readmissions. All data was obtained from the hospital's clinical information system.

HEART FAILURE DIAGNOSIS

A total of 567 hospitalizations were reviewed, from which 410 confirmed discharges with a diagnosis of AHF were identified. Diagnostic validation required a positive clinical assessment, jointly conducted by specialists in internal medicine and cardiology. In addition, measurement of left ventricular ejection fraction (LVEF) was mandatory, and baseline N-terminal pro B-type natriuretic peptide (NT-proBNP) levels had to meet the age-specific diagnostic thresholds established by the European Society of Cardiology for AHF (see Figure 1).

COLLECTED INFORMATION

A total of 280 patients accounted for 410 hospitalizations, including readmissions, allowing for baseline demographic analysis. Data collected included sex, age, body mass index (BMI), HF etiology (ischemic or non-ischemic), LVEF, HF phenotype, and heart rhythm categorized as sinus rhythm, atrial fibrillation (AF), or pacemaker-dependent rhythm. Data was also collected on comorbidities including hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), sleep apnea syndrome, active cancer, hypothyroidism, stroke, and chronic kidney disease (CKD). To recognize each condition, the use of specific treatments was verified. Stroke was only included if the patient had previous hospitalization for this condition. Pre-existing CKD required an estimated glomerular filtration rate ≤30 mL/min/1.73 m² during a stable phase for inclusion. This analysis also incorporated admission values of blood pressure, NT-proBNP, haemoglobin, creatinine, and eGFR, along with differentiation of HF cause of decompensation (cardiac and non-cardiac)

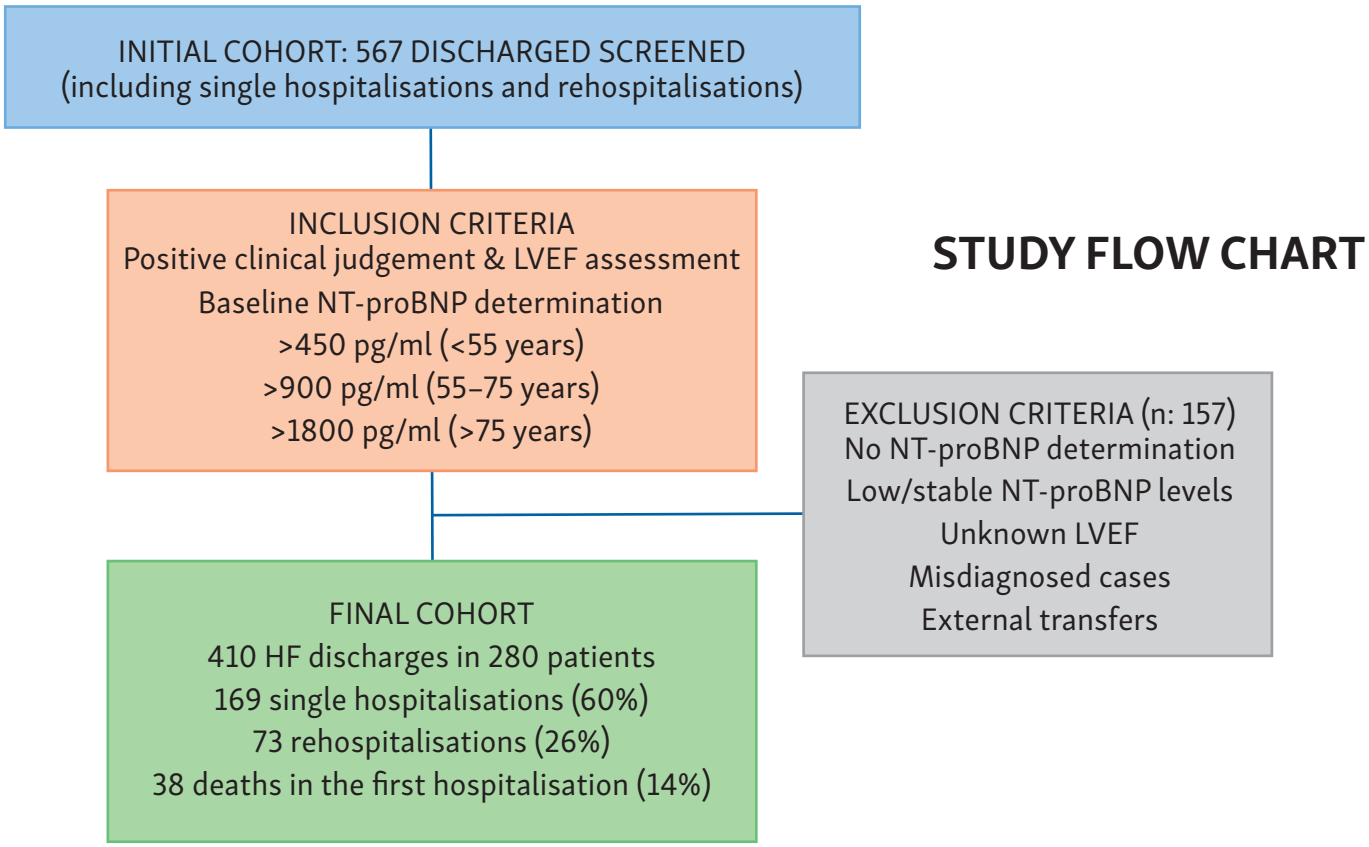


Fig. 1 Study flow chart.
A total of 567 hospitalizations were initially classified as heart failure (HF). After applying clinical criteria, assessing left ventricular ejection fraction (LVEF), and measuring peptide levels in accordance with European Society of Cardiology guidelines, 410 hospitalizations were confirmed as HF, corresponding to 280 individual patients (including readmissions).

STATISTICAL ANALYSIS

All categorical variables are presented as absolute numbers (n) and percentages (%), while continuous variables are expressed as mean ± standard deviation (SD) and range. NT-proBNP values, due to their significant skewness and dispersion, are reported as median and interquartile range (IQR, 25–75%). To compare qualitative data between groups, the Chi-square test (Pearson's χ^2) was used for categorical variables. For continuous variables, the Kruskal-Wallis test was applied to non-normally distributed data (screwed variables), while the ANOVA and Student's t-test were used for normally distributed variables.

Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated, and all statistical tests were two-sided, considering a p-value <0.05 as statistically significant. All statistical analyses were performed using Microsoft Excel 2021®. Multivariate analysis was not performed.

FOLLOW-UP AND CENSORING

Index hospitalisation was defined as the first admission for acute HF during the study period. For in-hospital mortality, time zero was the admission date, and patients were followed until discharge. For post-discharge outcomes, time zero was set at the discharge date. Patients were followed until administrative censoring on July 31, 2024. Readmissions within 30 and 100 days were assessed among patients who were alive at discharge and measured over fixed windows of 30 and 100 days from the discharge date. Mortality at 1-, 3-, and 6-months post-discharge was evaluated using fixed windows of 30, 90, and 180 days, or corresponding calendar months. Survivors without events were right censored on July 31, 2024.

RESULTS

BASELINE DEMOGRAPHICS

During 2023, our IMD recorded 410 AHF hospitalisations involving 280 patients (Table 1). The cause of HF decompensation was determined by identifying the initial or most significant contributing factor in its development, while acknowledging that overlapping or multifactorial mechanisms could not be excluded.

Our population was elderly (mean age 82), predominantly female (54%), and typically overweight (mean BMI 28.1). Women were generally older than men (84 vs 79 years) with nearly triple the proportion of nonagenarians (29% vs 10%). This cohort showed high prevalence of hypertension (85%), DM (45%), and AF (44%), with relatively low coronary artery disease (CAD) incidence (20%). This LVEF profile corresponded with predominantly (69%) HF with preserved ejection fraction (HFpEF) versus a minority of patients (20%) exhibiting HF with reduced ejection fraction (HFrEF). Men had higher CAD rates (25% vs. 16%), lower mean LVEF (50.2% vs.56.5%), and more HFrEF (30% vs 12%) (Table 2).

Tab. 1 Precipitating causes of heart failure (n: 410 hospitalizations).

Acute heart failure: precipitating factors	n (%)
Respiratory infection /insufficiency[1]	176 (43)
Worsening renal function[2]	49 (12)
Atrial fibrillation (new onset and worsening)[3]	38 (9)
Natural evolution (valvular disease/ amyloidosis)[4]	28 (7)
Sepsis[5]	27 (6)
Urinary infection[6]	19 (5)
Non-compliance[7]	17 (4)
Acute coronary syndrome	14 (3.3)
Anaemia (gastrointestinal bleeding)	11 (3)
Bradyarrhythmia[8]	8 (2)
Hip fractures	7 (1.7)
Ascitic decompensation	5 (1.3)
Stroke	5 (1.3)
Pulmonary embolism	3 (0.7)
Other	3 (0.7)

1: includes respiratory infections of viral or bacterial etiology (sepsis not included), respiratory insufficiencies partial pressure of oxygen <60 mmHg with no proven infectious origin and overlapped cases. 2: Marked increase in serum creatinine compared to basal level (conditioning issue). 3: includes new onset of atrial fibrillation cases and the exacerbation of previously known atrial fibrillation ones. 4: includes cases of acute heart failure without a documented trigger for decompensation, occurring in the context of advanced valvular disease (predominantly severe degenerative aortic stenosis) and prosthetic valve dysfunctions or, the detection of transthyretin (TTR) amyloidosis. 5: from any origin. 6: bacterial etiology (sepsis not included). 7: includes alcoholism, abandonment of treatment, low awareness of illness and social isolation. 8: requiring permanent pacemaker placement. Categorical variables are expressed as absolute number and percentage.

Tab. 2 Characteristics of the study population.

Item	All patients	Female	Male	*p*
Demography				
n	280 (100%)	152 (54%)	128 (46%)	
Age: years± SD (range)	83 (41–99)	85 (46–99)	79 (41–96)	**<0.001**
BMI: Kg/m^2± SD (range)	28.4 ± 5.6 (16–49.1)	28.4 ± 5.8 (16–49.1)	28.5 ± 5.3 (17.6–44.1)	0.948
Age distribution: n (%)				
≤59 years	10 (4%)	2 (1%)	8 (6%)	
60–69 years	18 (6%)	8 (5%)	10 (8%)	
70–79 years	65 (23%)	31 (20%)	34 (27%)	
80–89 years	130 (46%)	68 (45%)	62 (48%)	
≥90 years	57 (20%)	43 (28%)	14 (11%)	
Etiology n (%)				
CAD	55 (20%)	22 (14%)	33 (26%)	**0.019**
Non-CAD	225 (80%)	130 (86%)	95 (74%)	
Cardiac rhythm n (%)				
SR	134 (48%)	73 (48%)	61 (48%)	0.951
AF	119 (43%)	67 (44%)	52 (41%)	0.561
Pacemaker	27 (9%)	12 (8%)	15 (11%)	0.289
LVEF: % ± SD (range)	53.7 ± 12.3 (19–76)	56.8 ± 10.2 (20–76)	50.0 ± 13.5 (19–76)	
HFrEF: n (%)	57 (20%)	17 (11%)	40 (31%)	**<0.001**
HFmrEF: n (%)	30 (11%)	13 (9%)	17 (13%)	0.211
HFpEF: n (%)	193 (69%)	122 (80%)	71 (55%)	**<0.001**

BMI (body mass index); SD (standard deviation); CAD (coronary artery disease); SR (sinus rhythm); AF (atrial fibrillation); LVEF (left ventricular ejection fraction); HFrEF (heart failure with reduced ejection fraction); HFmrEF (heart failure with mildly reduced rejection fraction); HFpEF (heart failure with preserved ejection fraction). All categorical variables are expressed as absolute number and percentage and all continuous variables are expressed as mean ± SD, (range). Significant p values (between genders) are in bold (continuous variables required Student's t-test and categorical variable Pearson's χ^2 test).

Nearly half (49%) of patients had three or more non-cardiac comorbidities and men showed higher rates of chronic respiratory diseases (58% vs 35%) and sleep disorders (24% vs 14%), while hypothyroidism was more common in women (16% vs 6%). (Table 3). The distribution of HF phenotypes demonstrated a clear predominance of HFpEF, which accounted for 193 out of 280 cases. This group showed a notable female majority (64%). Beyond sex, HFpEF was significantly associated with older age, higher body mass index (BMI), and a greater prevalence of AF (48% vs. 30% in HFrEF). As anticipated, patients with HFrEF exhibited markedly lower LVEF and a higher prevalence of CAD (Table 4).

Tab. 3 Main non-cardiac comorbidities of the studied population.

Comorbidity	All patients	Female	Male	*p*
Hypertension	242 (86%)	133 (88%)	109 (85%)	0.572
DM	130 (46%)	63 (41%)	67 (52%)	0.069
COPD	127 (45%)	53 (35%)	74 (58%)	**0.001**
SAS	52 (19%)	21 (14%)	31 (24%)	**0.028**
Stroke	50 (18%)	30 (20%)	20 (16%)	0.368
CKD	42 (15%)	22 (14%)	20 (16%)	0.789
Hypothyroidism	33 (12%)	25 (16%)	8 (6%)	**0.006**
Active cancer	19 (7%)	7 (5%)	12 (9%)	0.125
≥3 comorbidities	136 (49%)	68 (45%)	68 (53%)	0.163

DM (diabetes mellitus); COPD (chronic obstructive pulmonary disease), SAS (sleep apnea syndrome), CKD (chronic kidney disease). Categorical variables are expressed as absolute number and percentage, and significant p values (between genders) are in **bold** (Pearson's χ^2).

Tab. 4 Clinical profile of heart failure phenotypes of the studied population.

Item	Total	HFpEF	HFmrEF	HFrEF	*P*
N = 100%	280	193	30	57	
Female: n (%)	152 (54)	124 (64)	12 (40)	16 (28)	**<0.001**
Male: n (%)	128 (46)	69 (36)	18 (60)	41 (72)	
Age: years	83 (41–99)	83 (46–99)	81 (53–96)	77 (41–98)	**0.020**
BMI: Kg/m2	28.4 ± 5.5 (16–49.1)	28.7± 5.2 (17–49.1)	28.3 ± 5.8 (19–42.3)	26.8 ± 5.8 (16–44.1)	**0.001**
CAD: n (%)	55 (20)	26 (14)	11 (37)	18 (32)	**0.005**
Non-CAD: n (%)	225 (80)	167 (86)	19 (63)	39 (68)	
LVEF: %	53.7 ±12.3 (19–76)	61.2 ±5.0 (50–76)	45.6 ±3.0 (41–49)	32.6 ± 5.7 (19–40)	<0.001
SR: n (%)	134 (48)	84 (43)	16 (53)	34 (60)	0.083
AF: n (%)	119 (43)	92 (48)	10 (33)	17 (30)	**0.032**
Pacemaker: n (%)	27 (9)	17 (9)	4 (14)	6 (10)	0.714
Single Hosp: n (%)	169 (60)	117 (61)	14 (47)	38 (67)	0.192
Rehosp: n (%)	73 (26)	52 (27)	11 (36)	10 (17)	0.137
Death: n (%)	38 (14)	24 (12)	5 (17)	9 (16)	0.706

BMI (body mass index); SD (standard deviation); CAD (coronary artery disease); SR (sinus rhythm); AF (atrial fibrillation); LVEF (left ventricular ejection fraction); HFrEF (heart failure with reduced ejection fraction); HFmrEF (heart failure with mildly reduced rejection fraction); HFpEF (heart failure with preserved ejection fraction). Hosp (hospitalization). Rehosp (rehospitalizations). Death (at first hospitalization) All categorical variables are expressed as absolute number and percentage and all continuous variables are expressed as mean ± SD, (range). Significant p values – between HF phenotypes are in **bold** (Anova for continuous variables / Pearson's χ^2 for categorical variables).

INDEX HOSPITALISATION: PATIENT PROFILES & CLINICAL TRAJECTORIES

Taking the first annual hospitalization for HF as the index episode, three distinct clinical trajectories were identified (Table 5): single admission (n: 169), rehospitalizations with possible deaths (n: 73), and death during initial hospitalization (n: 38). Across these groups, worsening outcomes correlated with increased age (81, 84, 86 years; p: 0.0018), higher NT-proBNP levels (8,264, 10,084, 17,001 pg/ml; p <0.001), reduced kidney function (eGFR: 50.9, 45.3, 38.9 mL/min/1.73m^2; p <0.001) and lower haemoglobin values (11.9, 11.3, 11.2 g/dl; p = 0.044). In addition, a progressively higher proportion of non-cardiac causes of AHF decompensation was observed across the three groups (63%, 75%, and 84%; p: 0.013), suggesting that AHF cases attributable to non-cardiac factors carry a worse prognosis than those precipitated by a clearly identifiable cardiac cause (e.g., arrhythmia, ACS).

Tab. 5 Patient profiles and trajectories according to index hospitalization.

Items	All patients	Single hospitalization	Rehospitalizations	Death First hospitalization	*p*
Total: n (%)	280 (100)	169 (60)	73 (26)	38 (14)	
Gender					
Female: n (%)	152 (54)	97 (57)	33 (45)	22 (58)	0.195
Male: n (%)	128 (46)	72 (43)	40 (55)	16 (42)	
Clinical findings					
Age (years)	83 (41–99)	81 (41–99)	84 (55–98)	86 (69–96)	**0.001**
BMI	28.4 ± 5.5 (16–49.1)	28.5 ± 5.9 (17.3–49.1)	28.2 ± 5.1 (16.0–40.0)	28.3 ± 4.6 (20.1–42.3)	0.885
SBP	135.3 ± 26.9 (60–230)	136.6 ± 27.0 (65–230)	134.3 ± 27.1 (60–195)	131.2 ± 26.4 (70–200)	0.498
DBP	76.3 ± 14.4 (30–115)	77.4 ± 14.2 (40–110)	75.3 ± 14.9 (30–115)	73.3 ± 14.0 (40–100)	0.222
Cr	1.52 ± 1.0 (0.42–6.63)	1.40 ± 0.9 (0.42–6.24)	1.55 ± 0.8 (0.47–5.09)	2.01 ± 1.5 (0.48–6.63)	**0.002**
eGFR	47.8 ± 21.9 (15–90)	50.9 ± 21.8 (15–90)	45.3 ± 20.8 (15–90)	38.9 ± 22.2 (15–90)	**0.004**
Hb (gr/dl)	11.6 ± 2.2 (3.5–17.3)	11.9 ± 2.3 (4.8–17.3)	11.3 ± 2.2 (3.5–16.4)	11.2 ± 2.0 (7.0–16.5)	**0.044**
NT (proBNP)	9938 (8841–11035)	8264 (6981–9547)	10084 (8083–12085)	17101 (13623–20579)	**<0.001**
Etiology: n (%)					
CAD:	55 (20)	33 (20)	19 (26)	4 (8)	0.074
Non-CAD	225 (80)	136 (80)	54 (74)	35 (92)	
Cardiac rhythm: n (%)					
SR	134 (48)	90 (53)	25 (34)	19 (50)	**0.023**
AF	119 (43)	68 (40)	38 (52)	13 (34)	0.126
Pacemaker	27 (9)	11 (7)	10 (14)	6 (16)	0.085
LVEF: %	53.7 ± 12.3 (19–76)	53.4 ± 12.9 (20–72)	54.8 ± 11.3 (19–76)	53.1 ± 11.4 (34–76)	
HF Phenotype: n(%)					
HFrEF	57 (20)	38 (22)	10 (14)	9 (24)	0.257
HFmrEF	30 (11)	14 (8)	11 (15)	5 (13)	0.257
HFpEF	193 (69)	117 (69)	52 (71)	24 (63)	0.679
AHF trigger n(%)					
Cardiac	87 (31)	63 (37)	18 (25)	6 (16)	**0.013**
Non-cardiac	193 (69)	106 (63)	55 (75)	32 (84)	

SBP (systolic blood pressure) mmHG; DBP (diastolic blood pressure) mmHG; BMI (body mass index) Kg/m2; Cr (creatinine) mg/dl, eGFR (estimated glomerular filtration rate) mL/min/1.73 m2; NT-proBNP (N-terminal pro-brain type natriuretic peptide) pg/ml; CAD (coronary artery disease); SR (sinus rhythm); AF (atrial fibrillation); SD (standard deviation); LVEF (left ventricular ejection fraction); HFrEF (heart failure with reduced ejection fraction); HFmrEF (heart failure with mildly reduced ejection fraction); HFpEF (heart failure with preserved ejection fraction).

MORTALITY AND REHOSPITALIZATION RATE

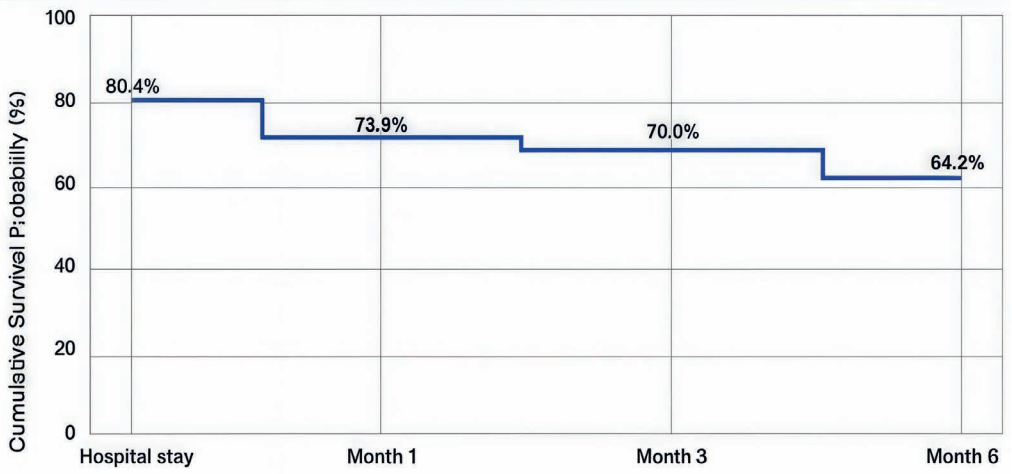
During the study period (2023), all-cause mortality was 19.6% (n: 55) all through hospitalization. Cumulative mortality rose to 26% (n: 73) at 3 months and 30% (n: 84) at 6 months after discharge, considering the last recorded event. Deaths were documented across all settings, including private residences, nursing homes for retired/older people, convalescence facilities, and during subsequent hospitalizations in 2024. These findings emphasize a pronounced early mortality burden that not only persists but progressively intensifies within this elderly cohort (Figure 2).

In our study, 410 hospitalizations were recorded among 280 patients, of which 113 (28%) represented rehospitalizations. The readmission rate was 9.9% within the first 30 days, rising to 22.7% by 100 days. Sequentially, 69 patients experienced a first readmission (second hospitalization), 27 patients a second readmission (third hospitalization), 13 patients a third readmission (fourth hospitalization), and 4 patients a fourth readmission (fifth hospitalization)

DISCUSSION

As was previously described, our cohort of AHF patients was elderly (mean age 82), predominantly female (54%), with high rates of hypertension (85%), DM (45%), and AF (44%), and a notably reduced presence of CAD (20%) and HFrEF (20%). These findings align with other European cohorts of patients with decompensated HF managed in IMDs including the RICA (9) and RICA-2 registries (10), the PRECIC study (11), the SMIT study (12), the ATHENA study (13), as well as the series reported by Davidge et al. (6), De

Matteis et al. (8), Chuda et al. (14), and Bazmpani et al. (15) (Table 6). In contrast, the large and broadly representative ESC-HF-LT registry (n: 4,449) included a younger cohort (mean age 69 years) with higher proportions of men (63%), CAD (53%), and HFrEF (67%), underscoring the age-related shift in heart failure phenotype (16).



Time Point	At Risk	Interval Deaths	Survival Probability	Cumulative Survival Probability
In-Hospitat	280	55	0.8036	0.8036
Month 1	225	18	0.9200	0.7393
Month 3	207	11	0.9469	0.6997
Month 6	196	18	0.9184	0.6424
Month 6	198	16	0.9184	0.6424

Fig. 2 Life curve for acute heart failure cohort.
Kaplan-Meier survival curve for patients discharged after acute AHF hospitalization, using actuarial estimates at 1, 3, and 6 months. Cumulative survival probabilities were 73.9% at 1 month, 70% at 3 months, and 64.2% at 6 months. Patients were followed until July 31, 2024, with right-censoring applied to those who survived beyond each interval. At Risk: Number of patients alive at the start of each interval. Interval Deaths: Number of deaths occurring during that interval. Survival Probability: Likelihood of surviving that specific interval. Cumulative Survival Probability: Overall chance of surviving from baseline to the end of that interval. So, by 6 months, the estimated survival probability is 64.2%, meaning roughly two-thirds of the cohort survived that long.

Tab. 6 Characteristics of acute heart failure patients admitted to internal medicine departments.

Item	**HMB**	**RICA** (9)	**RICA-2** (10)	**PRECIC Study** (11)	**SMIT Study** (12)	**ATHENA study** (13)	**Chuda et al** (14)	**De Matteis et al** (8)	**Davidge et al** (6)	**Bazmpani, et al** (15)
Country	Spain	Spain & Portugal	Spain & Portugal	Portugal	Italy	Italy	Poland	Italy	Sweden	Greece
N	280	5,644	1,000	429	770	276	75	6,930	5,029	137
Age	82	81	83	79	82	83	81	81	79	81
Women (%)	54	53	51	62	55	53	61	51	45	51
CAD (%)	20	26	24	34	31	30	39	48	46	44
Non-CAD (%)	80	74	76	66	69	70	61	52	54	56
AF (%)	43	53	68	52	47	47	48	45	58	72
LVEF	53	55	57		44	45	42			
HFrEF (%)	20	28	34	30	28	35	44			35
HFpEF (%)	69	61	52	70	40	47	56			52
DM (%)	46	46	50	48	36	37	44	30	26	47
Hypertension (%)	86	86	88	87	73	79	72	53	75	70

Acute heart failure patients admitted to internal medicine departments consistently exhibit (albeit with some variations), elevated mean age, female predominance and higher prevalence of hypertension, DM, and AF with comparatively lower rates of coronary artery disease (CAD) and (HFrEF).
HMB (Hospital Municipal de Badalona). DM (diabetes mellitus), AF (atrial fibrillation), CAD (coronary artery disease), LVEF (left ventricular ejection fraction) HFrEF (heart failure with reduced ejection fraction), HFpEF (heart failure with preserved ejection fraction). Blank boxes: data not available.

Returning to our cohort, we observed an all-cause in-hospital mortality rate of 19.6%, a figure substantially higher than those reported in major multicenter studies, including the KaRen study (2.4%) (17), OPTIMISE-HF (3.8%) (18), the ADHERE registry (4.0%) (19), the SMIT study (5.9%) (12), the PRECIC study (7.9%) (11), and the JROADHF registry (7.7%) (20). Despite these differences, our findings are consistent with single-center studies of older, comorbid populations, which have reported comparable in-hospital mortality rates: 20% in Lodz (14), 12.7% in Prague (21), 12% in Vellore (22), and 19% in Florence (geriatric ATHENA cohort) (13).

Focusing in rehospitalisations, these represent a critical inflection point in the HF trajectory, with the greatest vulnerability occurring within 30–90 days after discharge (5, 6, 23–25). In our cohort, readmissions were frequent, accounting for 28% of the total 410 hospitalisations, with 30-day and 100-day readmission rates of 9.9% and 22.7%, respectively. Figures from other series demonstrate notable variation: 30-day readmission rates of 24.8% in New York, USA (25) and 23.8% in Adelaide, Australia (7), while in Halmstad, Sweden, a 100-day rate of 33% was reported (6). Moreover, Sager et al. (Lund, Sweden) reported 30-day mortality and readmission rates of 40% and 24% with continuous furosemide infusion compared with 20% and 40% using bolus injection. In a real-world study, Wideqvist et al. (Gothenburg, Sweden) observed 30-day and 90-day readmission rates of 11.4% and 21% in patients with AHF (26). Taken together, these variations in both mortality and rehospitalisation rates underscore important differences across healthcare systems, discharge planning practices, patient demographics, and comorbidity burden.

As it was observed, three clinical trajectories emerged from the index hospitalization: (1) single admission, (2) rehospitalization – with some subsequent deaths, and (3) death during the initial stay. Across these groups, greater clinical severity was consistently associated with older age, renal dysfunction, and elevated NT-proBNP levels. Overall, the severity indicators identified in our cohort are in line with prior reports. For instance, De Matteis et al. demonstrated a 2.5-fold increase in in-hospital mortality among AHF patients aged ≥85 years (8). Similarly, the PRECIC study identified advanced age (≥80 years) as a significant predictor of one-year mortality (p: 0.001) (11), while the JROADHF registry confirmed age as an independent predictor of in-hospital mortality (p<0.001) (20). In addition, the ESC-HF-LT registry reported age as a key determinant of annual all-cause mortality in HF patients, with risk increasing per 5-year increment (p<0.0001) (16). Finally, Al-Omary et al. found advancing age (per 10-year increment; p<0.001) to be a univariate predictor – among other factors – of annual AHF readmissions (27)

In the context of renal dysfunction, Chuda et al. reported that AHF patients with CKD or more than three comorbidities (among other factors) had a higher risk of rehospitalisation (p<0.05) (14). Davidge et al. similarly observed a significantly increased admission rate among patients with severely impaired renal function (eGFR <30 ml/min; p: 0.005) (6). In addition, Wideqvist et al. and Al-Omary et al. found that readmitted patients had higher rates of CKD (p: 0.001 and p: 0.082, respectively) (26, 27). For its part, the ESC-HF-LT registry also identified renal dysfunction as a strong predictor of all-cause mortality in HF patients (p<0.001) (16).

Lastly, baseline NT-proBNP levels at index hospitalization emerged as a risk factor in our cohort for both mortality and rehospitalisation, consistent with prior well-established evidence (1–3). Udani et al. stratified 21,445 AHF patients into admission quartiles (<1,669; 1,670–4,274; 4,275–10,499; >10,500 pg/ml), showing progressively higher in-hospital mortality (0.9%, 1.4%, 2.5%, 4.7%; all p<0.005) and increased 60-day readmission in the highest quartile (p: 0.013 vs. group 1; p: 0.014 vs. group 2), persisting at 90 days only against group 1 (p: 0.021) (28). Sager et al. reported 30-day mortality of 20% in elderly AHF patients with mean NT-proBNP 9,640 pg/ml versus 40% with 15,901 pg/ml (25). The BIOSTAT-CHF program (n: 2,516) identified NT-proBNP >4,000 pg/ml as a major mortality predictor, alongside age >70 years, elevated blood urea nitrogen, and low hemoglobin (29). Similarly, Huang et al. found that AHF patients who died had significantly higher NT-proBNP than survivors (15,942 vs. 6,013 pg/ml; p<0.001), with risk rising from a cut-off of 8,100 pg/ml (30).

Therefore, our series aligns with published data on baseline characteristics of AHF patients hospitalised in IMDs. Moreover, our findings reaffirm the established association between adverse prognosis and advanced age, comorbidities, renal dysfunction, and elevated baseline NT-proBNP levels.

LIMITATIONS

The present study has several limitations that warrant consideration. First, the retrospective design of our analysis is inherently subject to multiple biases. Second, the single-centre nature of this series introduces an additional bias. Third, there is a low representation of younger patients, individuals with CAD or heart HFrEF, as the study was conducted in an IMD (not in a cardiology one).

CONCLUSIONS

This study offers a real-world snapshot of AHF patients admitted to an urban IMD. The cohort was predominantly elderly and female, with multiple cardiac and non-cardiac comorbidities, a low prevalence of CAD and HFrEF, and high rates of rehospitalization and in-hospital mortality. In addition, clinical data from index hospitalizations – including age, renal dysfunction, haemoglobin, NT-proBNP levels, and the proportion of non-cardiac versus cardiac AHF causes – were identified as severity markers.

In conclusion, highlighting experiences like ours underscores the challenges of this clinical scenario, while offering valuable lessons and supporting strategies to improve care for a highly vulnerable population.

AUTHOR CONTRIBUTIONS, FUNDINGS AND CONFLICT OF INTEREST

All authors have contributed significantly to the manuscript, meeting the criteria for authorship and approving its final version. EK was responsible for study design, data analysis and article writing. SMC, JTM, ASI, DCG, FPA and LZ were responsible for screening articles, data collection and clinical performance GTW, EMA and CCP were responsible for theoretical guidance and decision-making in case of disagreement and AFC was responsible for the statistical analysis.

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Age-Related Variations in Enteric Glial Cells: A Comprehensive Microscopic Analysis of the Human Colon

Anam Ahmed[1], Seema Singh[1,*], Anand Verma[1], Swati Rohilla[1], Vivek Dubey[1], Saba Sarwar[1]

ABSTRACT

Background: Constipation and other lower intestinal disorders are more common in the middle-aged population. According to recent research, enteric glial cells (EGCs) may have an impact on colonic motility. Little is known about how ageing impacts EGCs in the human colon. This study aims to compare the morphology of EGCs in the colons of young and middle-aged individuals.

Objective: To study the age-related morphological variations in the EGCs of the myenteric plexus in human transverse colon.

Materials and Methods: Colon specimens from 11 deceased individuals were obtained from a mortuary and categorized into two age groups: Group 1 (Young, n = 6) and Group 2 (Middle-Aged, n = 5). Immunohistochemistry for Glial Fibrillary Acidic Protein (GFAP) and routine staining were performed. Both qualitative and quantitative evaluations were conducted.

Results: In the middle-aged group 2, vacuolization was observed between Myenteric Ganglia (MG), and myenteric neurons appeared more scattered compared to the young group 1. The number of myenteric neurons and EGCs decreased with increasing age. The mean count of EGCs per MG and per mm² of ganglionic area was significantly higher in group 1 (young) as compared to group 2 (middle-aged). The MG density, expressed relative to the thickness of the inner circular muscle, was significantly greater in group 1 (young).

Conclusion: There is a significant decrease in the number of EGCs with advancing age, along with notable morphological changes. These changes may contribute to various gut motility disorders observed in the middle-aged, impacting their quality of life.

KEYWORDS

enteric nervous system; gastrointestinal; myenteric ganglia; myenteric neurons; immunohistochemistry

AUTHOR AFFILIATIONS

[1] Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India

* Corresponding author: Department of Anatomy, All India Institute of Medical Sciences, New Delhi 110029, India; drseemasingh@aiims.edu

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INTRODUCTION

Humans with advanced age are more likely to experience disorders such fecal impaction, constipation, and incontinence (1, 2). The gastrointestinal (GI) tract motility of the middle-aged can be affected by a variety of factors, including diet and exercise level (3) and the use of one or more prescription drugs – NSAIDs, calcium-channel antagonists, and calcium supplements (4). Human physiological and pharmacological research (5–8) also points to a decrease in afferent nerve and neuromuscular functions in the ageing colon, which is at least partially linked to "inflammageing" (9) and an increase in the expression of post-mitotic cellular senescence-like activity within enteric neurons (10).

Enteric Nervous System (ENS) is an intricate division of the peripheral nervous system (PNS) which is embedded in the wall of the gut. It exhibits plasticity and undergoes changes with ageing. The neurons and enteric glial cells (EGCs) are present in ganglia and are placed in the form of two major plexuses, the myenteric and the submucosal plexuses (11). The Myenteric Plexus (MP) lies between inner circular and outer longitudinal layers of smooth muscle of gut (12). Research on how ageing affects intestinal functions in humans has primarily looked at extrinsic, enteric, and muscular neurons (see above), but little is known about the existence or roles of EGCs as people age. Apart from their active functions in regulating several aspects of GI function (13) like mucosal permeability, EGCs surround neuronal cell bodies and processes, facilitating functional communication between EGCs and neurons (14). Moreover, EGCs have been implicated in the regulation of GI motility (15, 16), the provision of immunological support (17), and sufficient plasticity to generate new neurons or replace dead neurons (18).

It has been documented earlier that age-related changes in the ENS are seen such as neurodegeneration in colon as early as the fourth year of age in humans (19). It was also found that there was about 37% reduction in neurons between the ages of 20 to 35 and 65 years of age in humans. Animal model-based studies have been suggested that 40% neuronal loss in distal colon of the guinea pig at the age of 27 months, 60% loss of neurons in colon of rat at 6 and 24 months and 50–60% loss in distal colon of the mouse at 3 and 12 months (20). In rodent studies, the reduction of EGCs has been found to be proportional to the reduction of myenteric neurons (21). Loss of EGCs causes neuronal degeneration (22). Thus, neuronal integrity is maintained by EGCs by providing structural support, releasing neurotrophic factors and ensuring a protective environment. The EGCs are associated with many gut related disorders (23).

Currently, there is no universal marker that identifies all EGC populations in the GI system. The sex-determining region Y (SRY)-related HMG-box (Sox) 10 gene, a key marker for neural crest cell progenitors in the ENS, is the most recent marker that labels most, but not all, EGC populations (24). Additionally, EGCs are known to express the intermediate filament glial fibrillary acidic protein (GFAP) and the calcium-binding protein S100. To evaluate the impact of ageing on EGCs, it's crucial to identify distinct functional EGC subpopulations within the colonic wall sublayers. Currently recognized EGC populations based on morphology and location include: Type I: Intraganglionic, residing within the ganglia in the MP and submucosal plexus, Type II: Extraganglionic, located in the interganglionic fiber tracts connecting myenteric ganglia, Type III: Found in the mucosal region, Type IV: Located in the intramuscular layer (25, 26). Few studies have been done on the morphology of the EGCs and scant literature is there on ageing human subjects. Consequently, we looked into how ageing affected the morphology of EGCs (anti-GFAP) in the MP.

MATERIALS AND METHODS

The human transverse colon (n = 11) was collected from the mortuary of the Department of Forensic Medicine and Toxicology (Ethical clearance number IECPG-93/22.03.2017). All tissues were from males. Samples were obtained from cases of suicide and road traffic accidents (Table 1) with relevant medical and personal histories collected from relatives. The age and cause of death were determined from case sheets. Samples with known GI disorders or histories of alcohol and drug abuse were excluded. Most specimens were procured within 8 hours of death and washed before being preserved in 4% paraformaldehyde. The tissues were stored in the same solution at 4°C for further processing. A 4 cm segment of the transverse colon was resected and maintained in this preservative until subsequent analyses. For each tissue block, 3 serial sections were taken (each 5 µm thick). From each section, we captured 5–8 high-resolution images covering the MP across the entire circumference of the transverse colon segment. The average length of the myenteric plexus examined per sample was 12–15 mm, measured along the inner circular muscle.

Tab. 1 Parameters of postmortem cases.

S. No.	Age (years)	Sex	Cause of death
1	48	M	Hanging
2	42	M	Road traffic accident
3	17	M	Hanging
4	24	M	Hanging
5	30	M	Hanging
6	12	M	Hanging
7	20	M	Hanging
8	34	M	Hanging
9	51	M	Hanging
10	60	M	Myocardial Infarction
11	65	M	Myocardial Infarction

HISTOLOGICAL ANALYSIS METHODS

Hematoxylin and Eosin Staining: Paraffin sections were stained to visualize gut layers in the myenteric plexus (MP).

Glial Fibrillary Acidic Protein (GFAP) Immunohistochemistry: Cryosections were stained to visualize enteric glial cells (EGCs) in the MP, using a rabbit-derived GFAP antibody (Cell Signaling, 1:400).

Post-fixation, 4 cm longitudinal samples were dehydrated through graded alcohols, cleared in cedarwood oil, and embedded in paraffin. Paraffin blocks were sectioned at 7 µm using a microtome, floated in warm water, and mounted on glass slides coated with egg albumin and thymol. After air drying, slides were stained with hematoxylin and eosin.

IMMUNOHISTOCHEMISTRY

After fixation for 2 hours at 4 °C, longitudinal tissue slices were washed with chilled 0.1M phosphate buffer and cryoprotected in 15% sucrose for 3 hours and 30% sucrose for 8 hours at 4 °C. The tissues were then embedded in optimal cutting temperature compound and sectioned at 12 µm thickness using a LEICA cryostat microtome. The sections were mounted on 1% gelatin-coated glass slides [1% w/v gelatin, 0.01% w/v $Cr(SO_4)_2.12H_2O$] and air-dried, then stored at –20 °C for immunohistochemistry.

For antigen retrieval, Triton X was used, followed by quenching with methanol and hydrogen peroxide. Blocking was performed with 10% Normal Goat Serum (NGS) in 0.1M PBS-Tx for 2 hours. Sections were incubated with primary antibodies (anti-GFAP, Cell Signaling, 1:400) and secondary antibodies (ABC Kit, 1:10,000 dilution). Visualization was achieved using a DAB substrate kit. Finally, sections were dehydrated, counterstained with hematoxylin, and mounted with DPX coverslips

MORPHOMETRIC ANALYSIS

For morphometric analysis, sections were examined using a Nikon Eclipse 90i light microscope, and images were captured. These images were analyzed with ImageJ – Fiji software (National Institutes of Health, available at http://imagej.nih.gov/ij/). Volume density, defined as the volume of EGCs per unit volume of the MP, was measured using this software.

For quantitative analysis the samples were divided into two groups:

Group 1; Young (n = 6: 12, 17, 20, 24, 30, 34yrs) – lower age group <40yrs

Group 2; Middle-aged (n = 5: 42, 48, 51, 60, 65yrs) – middle age ≥40yrs

Parameters analyzed:

- Number of EGCs per myenteric ganglion. Glial cells were counted only when a clearly visible nucleus was present, and the surrounding cytoplasm was intact for more than half of the cell's circumference, consistent with established stereological criteria (42).
- Mean count of EGCs per mm^2 of ganglionic area.
- Myenteric fraction: The percentage of area occupied by the myenteric ganglia (neurons, EGCs and nerve fibers) with respect to the inner circular muscle was calculated with the help of Grid Cycloid Arc plugin in ImageJ software. The myenteric fraction per inner circular muscle was calculated over a standardized 10–mm length of the muscularis externa in each section. This length was selected because it consistently captured 2–3 myenteric ganglia per region.

STATISTICAL ANALYSIS

Statistical analysis was conducted with data presented as mean ± SEM using SPSS software, with assistance from the biostatistics department. The Mann-Whitney test was employed for comparing non-parametric data between groups. A probability level of ≤0.05 was considered statistically significant.

RESULTS

MICROSCOPIC FEATURES

Hematoxylin and eosin staining:

Myenteric ganglia (MG) were located between the two layers of the muscularis externa: the inner circular (IC) and outer longitudinal (OL) layers (Figure 1) across all age groups. The shape, size, and arrangement of MG varied with age in the human transverse colon. In younger individuals (12–30 years), MG appeared elongated (Figure 1 & 4). Elongated MG were also observed in middle-aged individuals (51–65 years), although the number of neurons and EGCs was significantly lower (Figures 4, 5). In middle-aged individuals (34–48 years), MG appeared spheroid (Figure 2). In younger ages, MG was continuous, but from middle age onwards, spaces appeared, making MG seem separated (Figure 2). The size of MG appeared reduced in middle-aged individuals (51–65 years) (Figures 10–13).

Changes in the shape, size, and distribution of myenteric neurons were observed with age. Myenteric neurons were either irregular or spherical to oval in shape (Figure neurons exhibited a horny profile. In younger individuals, myenteric neurons appeared smaller (Figure 1, 3), while in middle-aged individuals, they appeared larger (Figure 3). In middle-aged, myenteric neurons were predominantly located peripherally within the MG (Figure 3). The number of myenteric neurons and EGCs was observed to decrease starting from 42 years onwards (Figure 2, 3, 4, 5).

IMMUNOHISTOCHEMISTRY (IHC) FOR GFAP

GFAP is the primary marker for EGCs, and its expression in gut tissue confirms the presence of EGCs. IHC staining of cryo-sectioned transverse colon showed remarkable expression of GFAP in EGCs within the MG. Most ganglionic segments exhibited GFAP immunoreactivity, confirming the presence of a large number of EGCs. The non-reactive (unstained) portions of MG indicate a lack of GFAP expression. The GFAP expression patterns revealed well-developed small ganglionic plexuses between the IC and OL layers of the muscularis externa (Figure 6). Based on GFAP expression patterns, it was observed that the MG were highly populated with EGCs in the human transverse colon (Figure 6). EGCs were also distributed at the periphery of MG. In middle-aged individuals, no clear grouping of EGCs into distinct ganglia was found (Figure 9).

From 12 years onwards, the number of MG with EGCs increased with age until 34 years (Figure 7, 8). From 42 years onwards, the number of EGCs decreased with age (Figures 8, 9). In younger ages (12–24 years), MG appeared continuous and elongated (Figure 7). In middle age (30–42 years), MG appeared spheroid with spaces between them (Figure 8). In middle-aged individuals (51 years and above), MG again appeared elongated but with extensive spacing and significantly less expression compared to younger ages (Figure 9).

The number of EGCs and their processes increased with age until 34 years (Figure 7) and decreased from 42 years onwards (Figure 8, 9). The minimum expression of GFAP was observed at 65 years (Figure 9). No significant changes in the size and shape of EGCs were observed with increasing age. The bodies of EGCs were irregular in shape with many processes, which decreased in ageing MG. Minimal processes were observed in middle-aged individuals (Figures 8, 9). The irregular shape of EGC bodies was consistent across all ages in humans.

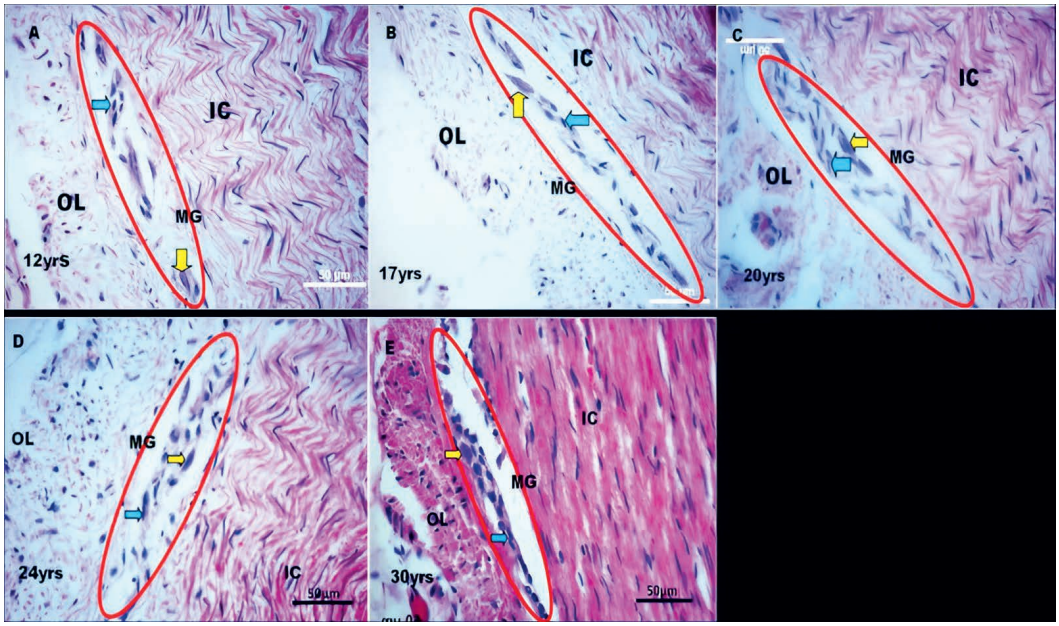

Fig. 1 Photomicrographs (40×) of Hematoxylin and Eosin-stained transverse sections of the human transverse colon from individuals aged 12 years (A), 17 years (B), 20 years (C), 24 years (D), and 30 years (E). Myenteric ganglia (MG) (red circle) are located between the inner circular (IC) and outer longitudinal (OL) muscle layers. Myenteric neurons (yellow arrows) and enteric glial cells (EGCs) (cyan arrows) are identifiable within the ganglia. Scale bar: 50 µm.

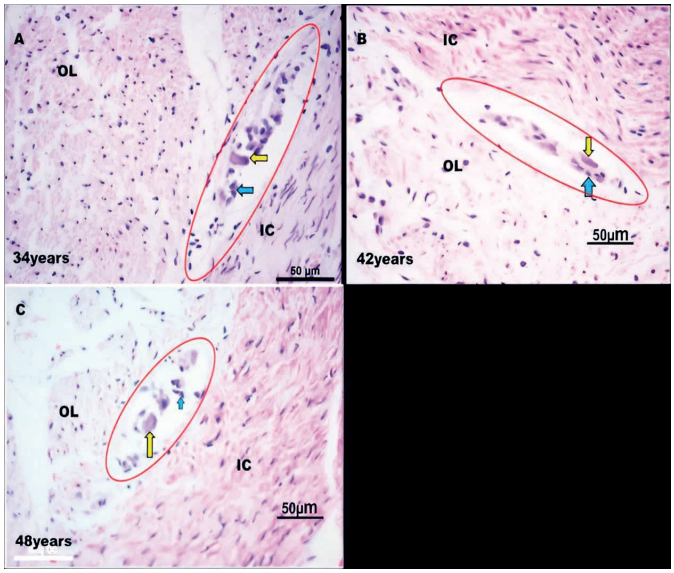

Fig. 2 Photomicrographs (40×) of Hematoxylin and Eosin-stained transverse sections from individuals aged 34 years (A), 42 years (B), and 48 years (C). Myenteric ganglia (MG) (red circle) and their organization within the muscle layers are shown. Myenteric neurons (yellow arrows) and EGCs (cyan arrows) are labelled. Scale bar: 50 µm.

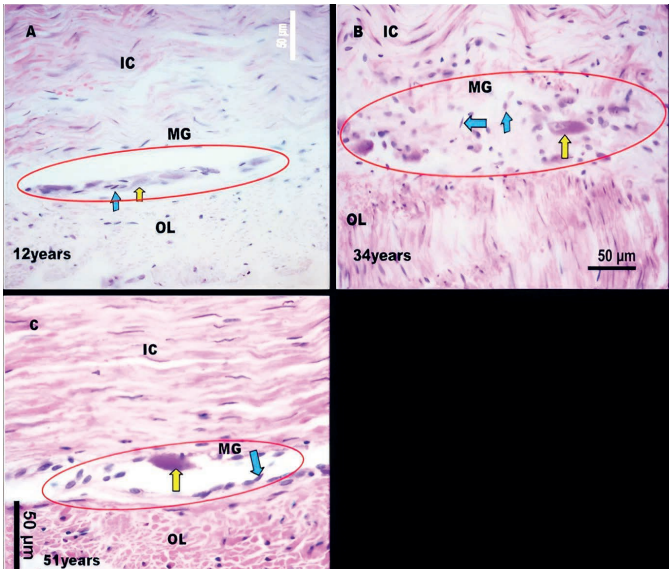

Fig. 3 Photomicrographs (40×) of Hematoxylin and Eosin-stained transverse sections from individuals aged 12 years (A), 34 years (B), and 51 years (C). Myenteric neurons (yellow arrows) and EGCs (cyan arrows) are labelled to illustrate their distribution within the myenteric ganglia (MG). Scale bar: 50 µm.

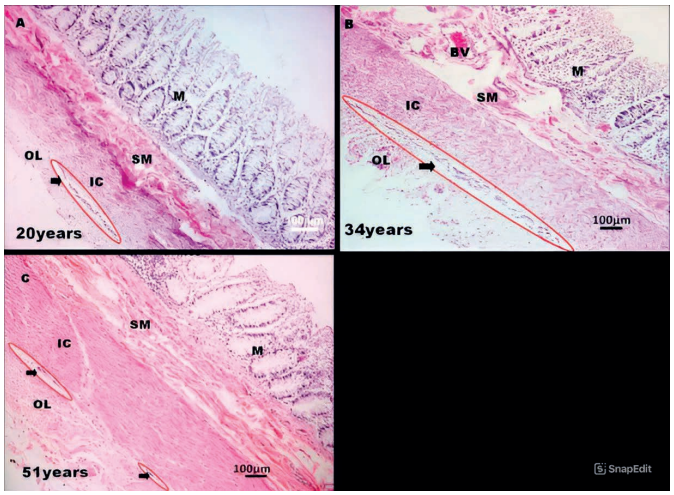

Fig. 4 Photomicrographs (10×) of Hematoxylin and Eosin-stained sections from individuals aged 20 years (A), 34 years (B), and 51 years (C). Myenteric ganglia (MG) (black arrowheads) are shown in relation to surrounding layers including mucosa (M), submucosa (SM), inner circular (IC), and outer longitudinal (OL) muscle layers. Scale bar: 100 µm.

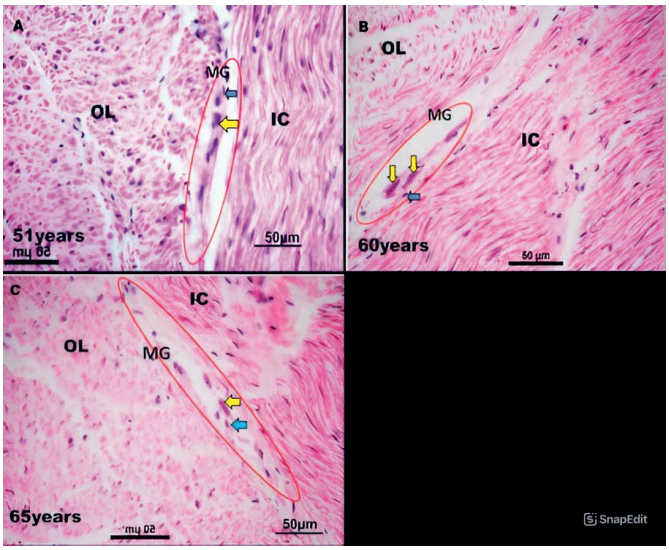

Fig. 5 Photomicrographs (40×) of Hematoxylin and Eosin-stained sections from individuals aged 51 years (A), 60 years (B), and 65 years (C). Myenteric ganglia (MG), myenteric neurons (yellow arrows), and EGCs (cyan arrows) are labelled. Scale bar: 50 µm.

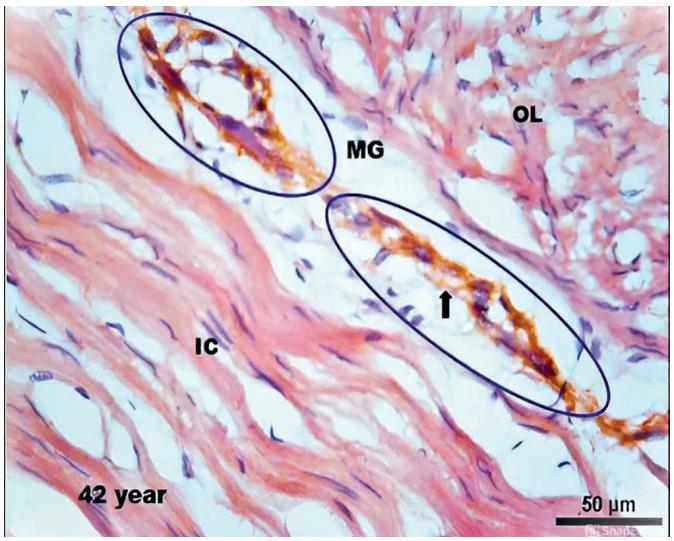

Fig. 6 Photomicrograph (40×) of GFAP-immunostained transverse section from a 42-year-old. Enteric glial cells (EGCs) and their processes (arrowheads) are visualized within myenteric ganglia (MG). IC – inner circular muscle; OL – outer longitudinal muscle. Scale bar: 50 µm.

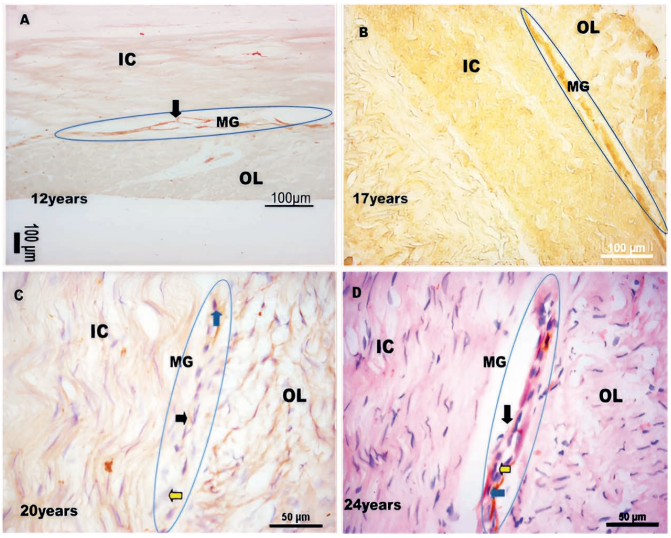

Fig. 7 Photomicrographs of GFAP-immunostained transverse sections from individuals aged 12 years (A), 17 years (B), 20 years (C), and 24 years (D). Neurons (yellow arrows), EGCs (cyan arrows), and their processes (black arrowheads) are shown in myenteric ganglia (MG). Scale bars: 100 µm (A, B) – 20×; 50 µm (C, D) – 40×. IC – inner circular muscle; OL – outer longitudinal muscle.

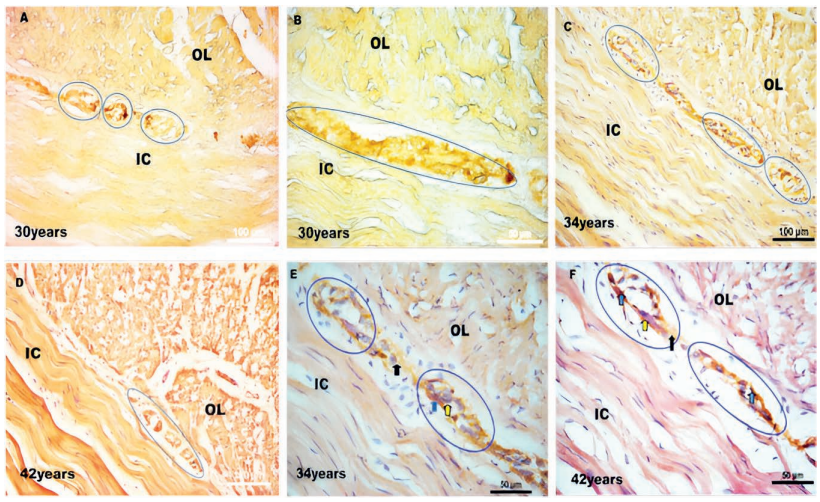

Fig. 8 Photomicrographs of GFAP-immunostained transverse sections from individuals aged 20 years (A), 30 years (B), 34 years (C), 42 years (D), 48 years (E), and 51 years (F). Myenteric ganglia (MG), neurons (yellow arrows), EGCs (cyan arrows), and EGC processes (black arrowheads) are labelled. Scale bars: 100 µm (A) – 20×; 100 µm (C, D) – 10×; 50 µm (B, E, F) – 40×.

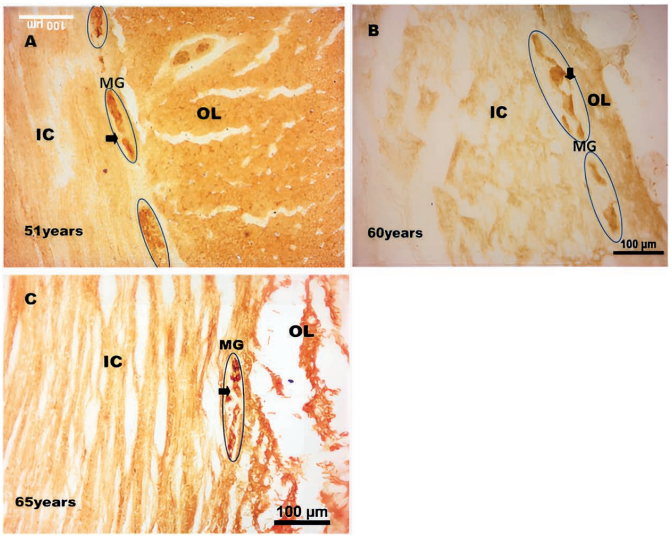

Fig. 9 Photomicrographs (20×) of GFAP-immunostained transverse sections from individuals aged 51 years (A), 60 years (B), and 65 years (C). Myenteric ganglia (blue ovals) and EGC processes (black arrowheads) are labelled. Scale bar: 100 µm.

MORPHOMETRIC EVALUATION

For quantitative analysis, the samples were divided into two groups:

Group 1 Young age (12–34 years, n = 6) and Group 2 Middle-aged (42–65 years, and n = 5).

There was a decrease in GFAP-positive EGCs (both in expression of counts per ganglionic area and per ganglion) in the transverse colon of the middle-aged group. The difference in the count of EGCs per ganglion and the mean count of EGCs per mm² of ganglionic area was significant (p =< 0.05). The mean count of EGCs per MG was 12.5 ± 1.9 and 8.2 ± 1.7 in the young age and middle-aged group, respectively (p = 0.002) (Figure 10). The mean count of EGCs per mm² of ganglionic area was 7.5 ± 1.6 and 1.4 ± 0.2 in the young age and middle-aged group, respectively. (p =< 0.0001) (Figure 11).

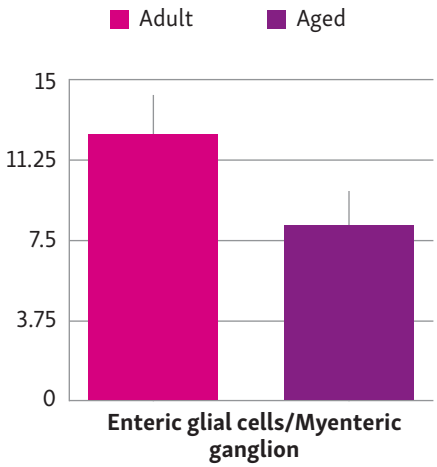

Fig. 10 Graph showing the mean number of GFAP-positive enteric glial cells (EGCs) per myenteric ganglion in **Group 1 (Adults, 12–34 years, n = 6)** and **Group 2 (Middle-aged, 42–65 years, n = 5)**. The mean EGC count per ganglion was **12.5 ± 1.9** in Group 1 and **8.2 ± 1.7** in Group 2, demonstrating a significant decrease in the middle-aged group (**p = 0.002**).
Data are presented as **mean ± SD**.

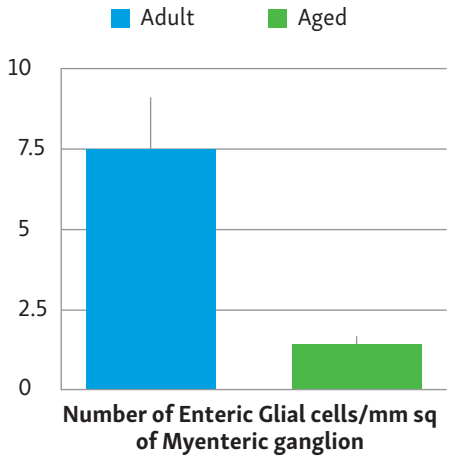

Fig. 11 Graph showing the mean density of GFAP-positive enteric glial cells (EGCs) per mm² of myenteric ganglionic area in **Group 1 (Young, n = 6)** and **Group 2 (Middle-aged, n = 5)**. The mean EGC density was **7.5 ± 1.6 cells/mm²** in Group 1 and **1.4 ± 0.2 cells/mm²** in Group 2. This difference was statistically significant (**p < 0.0001**). Data are shown as **mean ± SD**.

The myenteric fraction per inner circular muscle was significantly greater that is 0.4 ± 0.1 in group 1 Young age (<40yrs) and it was 0.2 ± 0.11 in group 2, Middle-aged (≥40yrs) (p = 0.01) (Figure 12). The number of EGCs increases with age from 12–34 yr and reduces with middle age onwards that is 42 yrs onwards (Figure 13).

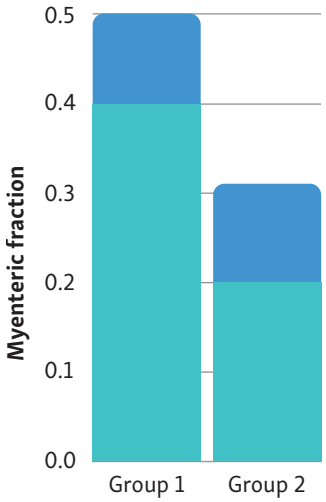

Fig. 12 Graph showing the myenteric fraction per inner circular muscle layer in **Group 1 (Young <40 years, n = 6)** and **Group 2 (Middle-aged ≥40 years, n = 5)**. The myenteric fraction was significantly greater in Group 1 (**0.4 ± 0.1**) compared with Group 2 (**0.2 ± 0.11**), with **p = 0.01**. Values are presented as **mean ± SD**.

DISCUSSION

Age-related changes in EGCs in the human colon are of significant interest to researchers globally. Although numerous studies have been conducted on animal models, there is limited and less significant data available for human specimens. To the best of our knowledge, this is the first study examining the morphological changes of EGCs in the human transverse colon (TC) within the Indian population. The aim of this study is to investigate whether

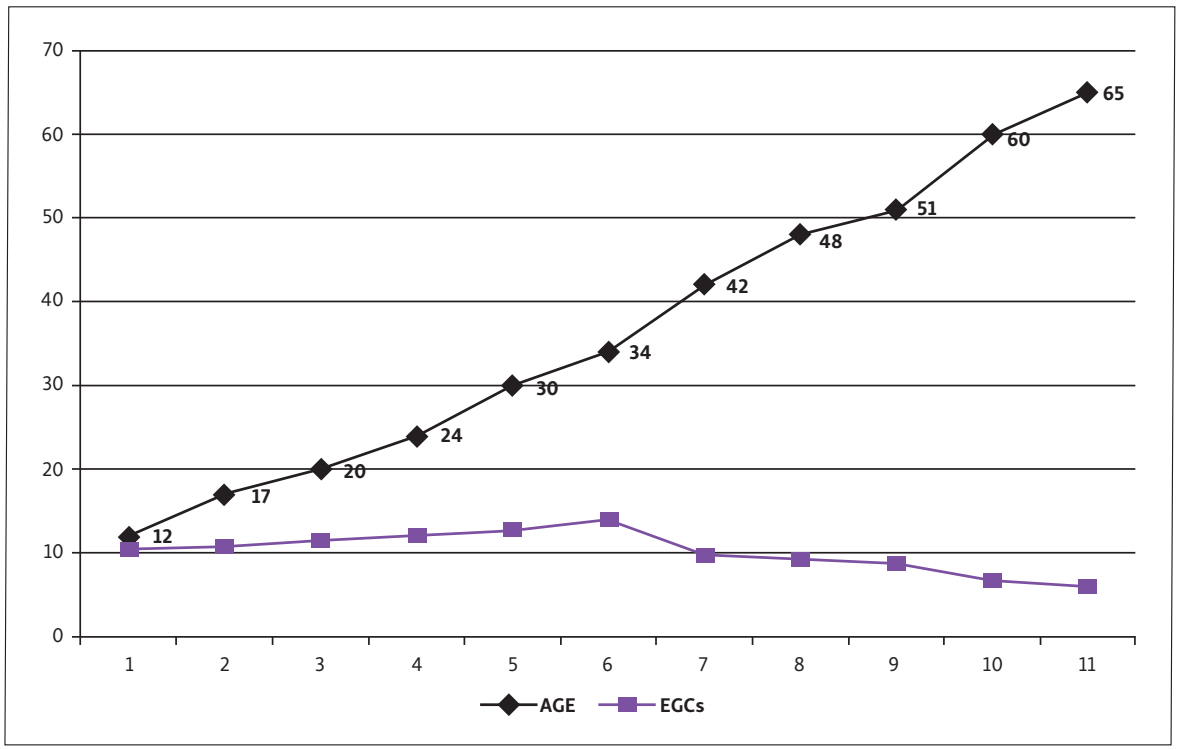

Fig. 13 Graph showing the distribution of GFAP-positive enteric glial cells (EGCs) across the full age range (12–65 years; total n = 11). Each point represents an individual measurement. The data demonstrate an **increase in EGC counts from 12 to 34 years**, followed by a **reduction beginning at 42 years and continuing through 65 years**.

EGCs in the human transverse colon undergo morphological changes with age.

Morphological changes in the MG of the human TC at various ages were observed in the present study. Similar to findings in old guinea pigs, which reported separation of MG and less densely packed myenteric neurons (27), the current study also observed that MG appeared separated from 42 years onwards, with maximum spacing at 65 years of age. Neurons were found to be less densely packed starting at 42 years. Additionally, a reduction in the size of MG was noted in middle-aged individuals, which was more evident in whole-mount preparations and H&E staining. An increase in the myenteric fraction was observed from 12 to 34 years, while a decrease was noted from 42 to 65 years. These observations are consistent with previous studies, which also reported a reduction in the size of MG with age in the ileum of guinea pigs (28). The observed gaps and spacing within MGs in the human colon are attributed to stretching effects from gut growth, with changes in MG shape occurring due to peristalsis and gut movements (29).

This study examined age-related morphological changes in myenteric neurons and EGCs of the human TC, noting alterations in size, shape, and distribution. Previous research has documented age-related loss of enteric neurons in the human esophagus, with evidence of reduced peristaltic contractions in the lower esophagus of the middle-aged (30). The population of enteric neurons in humans begins to decline at an early age, with decreases in submucosal and myenteric plexuses reported as early as the fourth year (31). In this study, a significant reduction in the number of myenteric neurons was observed in middle-aged individuals 40 years and older (Group 2) compared to those under 40 years (Group 1). A reduction in myenteric neurons was noted from 42 years onwards. Previous research has also reported a loss of cholinergic neurons in ageing rats (32). Additionally, the number of neurons can be influenced by diet, microbiota, and calorie intake. Gut growth may cause apparent reductions in neuron density due to a dilution effect. Furthermore, reduced motility can lead to fewer bowel movements and subsequent loss of myenteric neurons. Observed spaces within and between myenteric ganglia support the idea of neuron loss (33). Hippocrates observed that intestinal function slows with age. Contemporary research shows that age-related changes in the ENS can influence GI function. Conditions such as diarrhea and fecal incontinence (34), irritable bowel syndrome (35), and gastroesophageal reflux disease (36) are commonly seen in middle-aged and older adults and can significantly impact their quality of life and independence.

In the present study, myenteric neurons were found to be smaller in individuals under 42 years of age and increased in size with age, with larger neurons observed in those above 42 years. This increase in neuron size with age is consistent with observations in older rats (32). The shape of myenteric neurons in the present study varied, with neurons appearing irregular, spherical, or oval, and some exhibiting a horny profile. Similar horny profiles have been noted in myenteric neurons of ageing animals (27). In middle-aged individuals (above 42 years), some large myenteric neurons with smooth profiles were observed at the edges of MG, and some extra ganglionic neurons were noted within the myenteric plexus. Previous studies have also reported peripherally located myenteric

neurons in humans and extra-ganglionic neurons in the ileum of ageing guinea pigs (37).

Human EGCs in the ENS express GFAP, a protein associated with glial intermediate filaments (38). This study observed a decline in EGCs starting from age 42, correlating with a loss of myenteric neurons. Previous research on rats has shown significant EGC loss in various intestinal regions at ages 5–6 months and 26 months, except the rectum (39). This age-related reduction may indicate deficits in neural stem cells or mechanisms regulating their differentiation into glial cells, potentially due to increased apoptosis. In this study, EGC loss was notably greater in individuals aged 40 years and older. Additionally, EGCs, which have numerous processes, were observed to decrease with age, consistent with findings from previous studies (37). Previous research has shown that Sox-10-, S100-, and GFAP-IR EGC expression is present in the human colon and varies with age and colonic location. Therefore, in the myenteric and CM of the old person, there is a decrease in the density of S100-IR EGCs, but this reduction is not followed by a loss of Sox10-IR EGCs in the MP. The absence of GFAP expression in the middle-aged samples would suggest that EGCs do not become activated as people age. Findings from prior work in the human descending colon demonstrate that ageing induces selective alterations in enteric glial subpopulations rather than a uniform loss of glial cells. Sox10-positive enteric glia, representing the total glial pool, were largely preserved in both myenteric and submucosal plexuses of older individuals, indicating that chronological age alone does not cause widespread depletion of glial cell bodies. In contrast, S100-positive glia showed a marked reduction in density, particularly within the myenteric plexus and circular muscle, suggesting a specific vulnerability or phenotypic shift of this subset with advancing age. These authors also reported region-dependent changes in additional markers, such as GFAP, consistent with a remodelling of glial phenotype and distribution across the colonic wall. Notably, the absence of GFAP expression in the middle-aged group in our study further suggests that enteric glia may not undergo GFAP-associated activation during normal ageing. Together, these observations support the presence of significant heterogeneity within human EGC populations, reflected in the variable expression of Sox10, S100, and GFAP, and indicate that while the fundamental glial scaffold is maintained, ageing drives marker-specific and region-specific adaptations that may alter glial support for neurons, smooth muscle, and overall gut homeostasis (40).

Immunocytochemical studies have revealed that neurodegeneration and a decline in EGCs begin after age 40. This loss is significant because it is associated with various GI disorders, including fecal incontinence and constipation, which heavily impact quality of life and healthcare costs in the middle-aged. The reduction in EGCs with age might suggest a deficit in neural stem cells or issues with their differentiation into EGCs, potentially due to increased apoptotic activity. However, the study has several limitations: it involved a small sample size per age group, lacked information on dietary conditions of the deceased, and did not differentiate between types of EGCs. Additionally, the study did not explore sex-related differences between males and females. Using whole-mount preparations (41) might have offered more detailed insights. Furthermore, the absence of a pan-EGC biomarker remains a significant challenge in ageing research. We acknowledge that the interpretation of glial cell shape is limited by the use of paraffin-embedded transverse sections, as sectioning angle can influence apparent morphology. Lastly, inclusion of individuals <18 years may introduce developmental variability and represents a limitation of the study.

CONCLUSION

This study outlines age-related morphological variations of enteric glial cells (EGCs) in the myenteric plexus of the human colon, influenced by gut growth and responses to dietary and environmental changes. The number of myenteric neurons and EGCs appeared to decrease with increasing age. The decreased GFAP expression and morphometric changes observed in middle-aged samples (Group 2) may suggest that enteric glial cells are less activated or functionally impaired with advanced age. These findings are valuable for clinicians, surgeons, and scientists in enhancing the understanding of functional bowel disorders in geriatric age groups.

AUTHOR CONTRIBUTIONS

AA and SS[1] contributed substantially to the conception and design of the study. AA, AV and SR contributed substantially to the acquisition of data. AA, VD, AV, SR, SS[2] and SS[1] made substantial contributions to the analysis and interpretation of data. AA and SS[1] drafted the manuscript. AA, VD AV, SR, SS[2] and SS[1] critically revised the manuscript for important intellectual content. All the authors approved the final version submitted for publication and took responsibility for statements made in the published article.

CONFLICTS OF INTEREST STATEMENT

None of the authors has any potential or actual conflicts of interest concerning the published article to disclose.

DATA SHARING STATEMENT

All data generated or analyzed during the present study are included in this published article.

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Health Literacy: Key to Self-Care in Diabetes & Hypertension

Mahycol Reynner Harold Bravo-Ramirez[1,*], Danis Yanet Castillo-Esquivel[2]

ABSTRACT

Introduction: Health literacy is a fundamental tool for improving patients self-care, so this study evaluated the association between health literacy and self-care in patients with hypertension and type 2 diabetes mellitus.

Method: Cross-sectional observational study of 200 patients at Hospital Florencia de Mora (June–November 2024), using the Health Literacy Survey Questionnaire (HLS-Q12), Diabetes Self-Management Questionnaire, and Self-Care of Hypertension Inventory. Parametric tests (t-test, ANOVA) and multivariate analyses were applied.

Results: The sample included 47.5% patients with hypertension, 39.5% with diabetes, and 13% with both conditions, mean age 67.54 years (±8.82), female predominance (58.5%). Health literacy demonstrated a moderate correlation with self-care in patients with hypertension ($r = 0.648$; $p < 0.001$) and weak but significant correlation in patients with diabetes ($r = 0.274$; $p < 0.001$). Multivariate analyses revealed that health literacy was associated with 42% of self-care variance in patients with hypertension ($\beta = 0.927$; 95% CI: 0.729–1.125; $p < 0.001$), while in patients with diabetes, together with sex factor, it was associated with 10.6% of variance ($\beta = 0.117$; 95% CI: 0.027–0.207; $p = 0.011$).

Conclusion: Health literacy shows a stronger association with self-care hypertension's patients than in patients with diabetes, suggesting the need for differentiated strategies to improve self-care in both populations.

KEYWORDS

health literacy; self-care in patients with diabetes; self-care in patients with hypertension

AUTHOR AFFILIATIONS

[1] Facultad de Ciencias Médicas, Universidad César Vallejo, Trujillo, Peru
[2] Facultad de Humanidades, Universidad Privada del Norte, Lima, Peru
* Corresponding author: Facultad de Ciencias Médicas, Universidad César Vallejo, Trujillo, Peru; mbravor11@ucvvirtual.edu.pe

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INTRODUCTION

Health literacy has emerged as a topic of growing importance in the field of public health as a fundamental component in the management of chronic, non-communicable diseases, particularly arterial hypertension and type 2 diabetes mellitus. These pathologies represent a significant challenge for global health systems, with a prevalence of 18.6 million cases of arterial hypertension and 476.6 million in patients with diabetes diagnosed up to 2021 (1, 2).

In the Peruvian context, statistics show that approximately 10% of the population suffers from hypertension and 5.9% from diabetes mellitus. However, adherence rates to treatment are worryingly low, reaching only 61.2% in patients with hypertension and 64.4% in patients with diabetes (2, 3). This situation underscores the imperative need to understand the factors that influence the effective management of these chronic conditions.

Health literacy, conceptualized by Sorensen as the ability of individuals to access, understand, evaluate and apply health information, has become a crucial determinant in health-related decision making (4). This concept, first introduced by Simonds in the 1970s, has evolved significantly to become a central element of modern health care (5, 6).

Sorensen's model establishes four essential competencies that are fundamental to health literacy: accessing, understanding, valuing and applying health information. These competencies are directly intertwined with three critical dimensions: health care, disease prevention and health promotion (4). The interaction between these competencies and dimensions defines the individual's ability to effectively manage his or her health.

On the other hand, self-care, recognized as a vital element since the 19th century, has been theorized by Riegel through his Middle Range Theory, which identifies three fundamental dimensions: maintenance, monitoring and management of self-care (7). This theory emphasizes the importance of factors such as previous experience, motivation, cultural beliefs and access to medical care in the process of self-care.

In the specific context of type 2 diabetes mellitus, self-care requires a multifaceted approach that encompasses four main dimensions according to Schmitt: glucose management, dietary control, physical activity and the use of medical care (8). Each of these dimensions contributes significantly to effective disease control and prevention of complications.

For patients with hypertension, Dickson's model, based on Riegel's theory, establishes three critical dimensions: self-care maintenance, self-care management, and confidence in self-care (9, 10). This theoretical framework emphasizes the importance of self-efficacy and adaptive capacity in the effective management of hypertension.

A thorough understanding of the relationship between health literacy and self-care in patients with hypertension and diabetes mellitus is essential for the development of effective interventions to improve health outcomes. This research aims to explore how different levels of health literacy influence self-care practices, considering the multiple dimensions and competencies involved in both constructs, with the ultimate goal of optimizing management and control strategies for these prevalent chronic diseases.

MATERIALS AND METHODS

An observational, cross-sectional study was conducted at Hospital Florencia de Mora, a public secondary-level hospital in Trujillo, Peru, serving predominantly low to middle-income patients from urban and peri-urban areas. From June to November 2024, consecutive patients attending outpatient consultations for hypertension and/or diabetes management were invited to participate. Of 370 eligible patients approached, 200 agreed to participate (response rate: 54%). The non-randomized convenience sampling was conducted during regular clinic hours across different days of the week to enhance representativeness. All participants provided prior informed consent after receiving detailed information about the study objectives and procedures.

Likewise, the information collected on sociodemographic variables as well as on health literacy and self-care was carried out in person by means of an anonymous questionnaire, respecting confidentiality and patient well-being, excluding incomplete answers and those who did not wish to participate.

Patients were included if they had a confirmed diagnosis of arterial hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) and/or type 2 diabetes mellitus (fasting glucose ≥126 mg/dL or HbA1c ≥6.5%) documented in their medical records, with at least 6 months since diagnosis. Patients with both conditions (n = 26, 13% of the sample) were analysed separately in each disease group according to their specific management needs. Exclusion criteria included cognitive impairment that would prevent understanding the questionnaires, severe complications requiring hospitalization, and pregnancy.

Health literacy was measured using the HLS-Q12 Health Literacy Questionnaire, an abbreviated version derived from the original HLS-EU-Q47 (European Health Literacy Questionnaire). This instrument consists of 12 items assessed on a 4-point Likert scale ranging from 1 (very difficult) to 4 (very easy) and assesses health literacy in three conceptual areas: healthcare, disease prevention and health promotion, with four items per area. The theoretical score range extends from 12 to 48 points, with higher scores indicating higher levels of health literacy and a greater ability to access, understand and apply health information for better self-care and better health decision-making. For this study, the Spanish version validated by Muñoz-Villaverde et al. (2024) was used, which demonstrated strong psychometric properties with a Cronbach's alpha of 0.88 and a McDonald's omega of 0.91; however, no specific cultural adaptation for the Peruvian context was documented. The questionnaire showed good internal consistency in the validation sample, with an interpretation of the scores that follows the original framework: lower scores (12–24 points) indicate significant difficulties in managing health information, average scores (25–36 points) demonstrate moderate health literacy with some

limitations, and the highest scores (37–48 points) show a high capacity for autonomous health management (11).

The Diabetes Self-Management Questionnaire (DSMQ), developed at the Research Institute of the Diabetes Academy in Mergentheim, Germany, was employed to assess self-care behaviors in diabetic patients. This instrument comprises 16 items evaluating four subscales: Glucose Management (5 items), Dietary Control (4 items), Physical Activity (3 items), and Health-Care Use (3 items), plus one additional item assessing overall self-care that contributes only to the Sum Scale. Each item is rated on a 4-point Likert scale ranging from 0 (does not apply to me) to 3 (applies to me very much), with responses converted such that higher scores indicate more effective self-care behaviors. Scale scores are calculated as sums of item scores and transformed to a 0–10 range (raw score/theoretical maximum score × 10), where a score of 10 represents optimal self-care. In practical terms, higher subscale scores reflect better diabetes management practices: superior blood glucose monitoring and medication adherence (Glucose Management), healthier dietary choices facilitating glycemic control (Dietary Control), regular physical activity (Physical Activity), and consistent adherence to medical appointments (Health-Care Use). The original validation by Schmitt et al. (2013) demonstrated robust psychometric properties with excellent internal consistency (Cronbach's alpha = 0.84 for the Sum Scale; subscales ranging from 0.60 to 0.77) and significant correlations with HbA1c values. For this study, the Spanish version was utilized; however, no specific cultural adaptation for the Peruvian context has been documented (8).

Finally, to measure self-care in patients with hypertension, the Self-Care of Hypertension Inventory version 2.0 (SC-HI v.2.0) was employed, originally developed by Dickson et al. (2017). This instrument comprises three independent scales: self-care maintenance (11 items), self-care management (6 items), and self-care confidence (6 items). The Colombian Spanish version validated by Herrera et al. (2021) was used, which demonstrated adequate psychometric properties with Cronbach's alpha coefficients of 0.64 for maintenance, 0.70 for management, and 0.86 for confidence. For the present study, no additional cultural adaptation was required for the Peruvian population. Each scale is scored separately and standardized from 0 to 100 using the following formula: [(obtained score – minimum possible score) × 100] / (maximum possible score – minimum possible score). Higher scores indicate better self-care behaviors, with scores of 70 or above generally considered adequate self-care. In practical terms, higher maintenance scores reflect consistent adherence to health-promoting behaviors and treatment regimens, higher management scores indicate effective recognition and response to elevated blood pressure, and higher confidence scores demonstrate greater self-efficacy in performing self-care activities (10).

Data analyses was performed using SPSS (Statistical Package for Social Sciences) for Windows, version 24.0, employing descriptive statistics such as means and standard deviations (SD) for quantitative variables, while frequencies and percentages were used for qualitative variables. The Kolmogorov-Smirnov normality test confirmed the normal distribution of all continuous variables ($p > 0.05$). Comparative analyses included t-tests for independent samples to examine differences by gender and one-way ANOVA to assess differences between educational levels (primary, secondary, and higher education). Pearson's correlation coefficients were calculated to assess the relationships between health literacy, age, gender, educational level, and self-care outcomes in both patient groups. Separate multivariate regression models were constructed for diabetic and patients with hypertension, with unstandardised beta coefficients (β) and 95% confidence intervals (CI) to indicate the magnitude and direction of associations. For diabetic patients, the final model included health literacy and gender as independent variables, while age and educational level were excluded due to non-significant correlations ($p > 0.05$). In patients with hypertension, health literacy was introduced as the only associated variable, as other sociodemographic variables did not show significant associations with self-care outcomes. Model fit was assessed using the coefficient of determination (R^2), which represents the proportion of variance in self-care explained by the predictive variables. A significance level of $p < 0.05$ was set for all statistical tests.

This study was approved by the Ethics Committee of Hospital Florencia de Mora with Approval number: 1794-2024-1734. All participants provided written informed consent prior to their inclusion in the study. Participation was entirely voluntary, and participants were informed of their right to withdraw at any time without consequences. Confidentiality and anonymity of all data were strictly maintained throughout the study, with all information stored securely and accessible only to the research team. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

As shown in Table 1, a demographic composition of 200 participants between in patients with diabetes and hypertension was revealed, the latter standing out with 54%, with an average age of 67.54 years (±8.82), predominantly female (58.5%), while it was evident that the educational level was mostly high school level (85.5%).

In Table 2, the results show the mean scores of the sociodemographic variables, emphasizing that there is a significant difference in self-care in diabetic patients according to sex ($t = 2.25$; $p = 0.03$), highlighting women ($\bar{x} = 21.51$; SD ± 3.105) over men ($\bar{x} = 20.82$; SD ± 3.642), while in patients with hypertension the opposite is true. In the level of education, the outstanding means were at the elementary school level both in self-care in diabetic ($\bar{x} = 21.38$; SD ± 3.739) and in patients with hypertension ($\bar{x} = 71.91$; SD ± 10.634), but when evaluating differences by ANOVA it did not show significance in relation to the other levels.

For diabetic patients, glucose management presented a mean of 7.5 (±2.153), while physical activity showed the lowest value, with 2.9 (±1.628). In patients with hypertension, the maintenance dimension registered the highest

Tab. 1 Sociodemographic variables, health literacy scores and self-care in patients with hypertension and diabetes.

Sociodemographic variables	N	%	$\bar{x}$ ± SD
Sex			
Male	83	41.5	
Female	117	58.5	
Morbidity			
Hypertension	108	54	
Diabetes	92	46	
Level of education			
Elementary	21	10.5	
Secondary	171	85.5	
Higher	8	4	
Age			67.54 ± 8.82
Health Literacy			30.8 ± 7.431
Self-care in patients with diabetes			**21.2 ± 3.330**
Glucose management			7.5 ± 2.153
Dietary control			5.6 ± 1.319
Physical activity			2.9 ± 1.628
Self-care in patient with diabetes			5.0 ± 1.233
Self-care in patients with hypertension			**70.8 ± 11.022**
Maintenance			30.2 ± 6.492
Management			19.4 ± 3.618
Confidence			21.2 ± 3.224

N: number of participants; SD: standard deviation.

Tab. 2 Comparison of means between sociodemographic variables and health literacy with self-care in patients with hypertension and diabetes with their dimensions.

Variables	**Patients with diabetes**		**Patients with hypertension**	
	Mean ± SD	"t" test / ANOVA (p-value)	Mean ± SD	"t" test / ANOVA (p-value)
Total self-care score	21.20 ± 3.33	–	70.80 ± 11.02	–
Sex				
Male	20.82 ± 3.64	2.25† (0.03)*	67.94 ± 12.80	2.43† (0.67)
Female	21.51 ± 3.11		72.85 ± 9.20	
Education level		0.50† (0.61)		0.57† (0.57)
Elementary	21.38 ± 3.74		71.91 ± 10.63	
Secondary	21.29 ± 3.34		70.93 ± 11.13	
Higher	19.33 ± 1.53		64.33 ± 9.61	
Health Literacy	"r" coeficcient	p-value	"r" coeficcient	p-value
Total self-care	0.274	<0.001**	0.648	<0.001**
GM / M	0.27	0.01*	0.61	<0.001**
DC / G	0.16	0.11	0.52	<0.001**
PA / C	-0.11	0.11	0.41	<0.001**
Medical care	0.24	0.01*	–	–

* p < 0.05; ** p < 0.001; † ANOVA F-test and "t" test; GM = glucose management, DC = dietary control, PA = physical activity, MC = medical care (Self-care in patients with diabetes); M = maintenance, G = management; C = confidence (Self-care in patients with hypertension). Prior to the multivariate study, correlation was performed in Table 3, which identified health literacy for both and sex with self-care in diabetic patients, which were added to the regression model.

Tab. 3 Correlation of sociodemographic variables, health literacy and self-care in patients with diabetes and hypertension.

	Health literacy	Age	Sex	Level of education
Self-care in patients with diabetes	0.274**	-0.062	0.217*	-0.061
Self-care in patients with hypertension	0.648**	0.004	0.039	-0.070

* Correlation is significant at the 0.05 level (bilateral).
** Correlation is significant at the 0.01 level (bilateral).

mean of 30.2 (±6.492), with confidence showing comparable values of 21.2 (±3.224). Regarding the relationship between health literacy and self-care, a moderate positive correlation was observed in patients with hypertension ($r = 0.648$; $p < 0.001$), indicating that approximately 42% of the variance in self-care could be attributed to health literacy levels. This moderate association was consistently observed across all self-care dimensions in this group. In contrast, diabetic patients exhibited a weak but statistically significant correlation ($r = 0.274$; $p < 0.001$), suggesting that health literacy accounted for only 7.5% of the variance in overall self-care. Among the specific dimensions in patients with diabetes, weak correlations were found with glucose management ($r = 0.27$; $p = 0.01$) and medical care ($r = 0.24$; $p = 0.01$), while dietary control and physical activity showed no significant associations.

Consequently, the multivariate analyses in Table 4, in relation to self-care in in patient with diabetes, sex and health literacy, explains 10.6% of its variance, the latter standing out between both, showing that for each time that health literacy increases, self-care increases by 0.117 times (95% CI: 0.027–0.207; $p = 0.011$). In addition, women will have 1.196 points higher than men in self-care in patients with diabetes. On the other hand, when performing linear regression, regarding self-care in patients with hypertension, 42% of the variance was explained by health literacy (β=0.927 [95% CI: 0.729–1.125; $p < 0.001$]).

DISCUSSION

This study provided information related to the association between health literacy and self-care in both diseases with a predominance of hypertension. Self-care in diabetic patients was associated with health literacy, which showed the strongest association among the variables studied (β = 0.117 [95% CI, 0.027–0.207; $p = 0.011$]). This finding is similar to the studies by Butayeva et al. (12) and Su Hyun et al. (13), where health literacy is considered as a tool in which patients can actively participate, thus generating greater self-care, despite the fact that there are studies in South America that refute this (14). On the other hand, a slight relationship was shown with medical care and glucose control, which is reinforced by several studies (12, 15–17), while dietary control and physical activity were not correlated. This is due to the fact that in our country 24.1% of people over 15 years of age have obesity and 37.2% are overweight, while 61.3% have excess weight, being reinforced by the low score obtained ($\bar{x} = 2.9$; SD ± 1.628), suggesting a potential area for intervention by the health system (18).

To address these deficiencies in dietary control and physical activity, targeted health literacy interventions could prove beneficial. Evidence demonstrates that interventions addressing low health literacy – including structured patient education programs, self-care training sessions, and comprehensive disease management strategies – are effective in improving diabetes outcomes (19). Specifically, nurse-led educational programs incorporating visual aids, problem-solving exercises, and teach-back techniques have shown statistically significant improvements in health-promoting behaviors, including medication adherence, dietary management, and complication prevention among patients with diabetes (20). Such interventions could directly address the observed gaps in physical activity and dietary control dimensions identified in this study.

Another of the variables that showed association in the regression model was the female sex (β = –1.196 [95% CI, –2.47–0.037; $p = 0.045$]) standing out with a better assessment compared to men, which is similar to the study by Abdulaziz et al. (21) (β= 0.20 [95% CI, 0.10–0.96; $p = 0.015$]). This is explained by the fact that women by nature generally normalize seeking medical help, while male stereotypes encourage resistance to vulnerability. On the other hand, the study by Okoye et al. (22), where in addition to reporting that women have a lower literacy rating, presents 2.96 times more risk of poor self-care (β = 2.96 [95% CI, 0.70–5.11; $p = 0.140$]). In addition to mentioning that also in the mean a significant difference between

Tab. 4 Multivariate analyses of health literacy, sex, and self-care in patients with diabetes and hypertension.

	Self-care in patients with diabetes					Self-care in patients with hypertension				
	β	β Standard	CI 95%	p-value	R^2	β	β Standard	CI 95%	p-value	R^2
Health literacy	0.117	0.245	0.027–0.207	0.011*	0.106	0.927	0.648	0.729–1.125	0.000**	0.42
Sex[a]	-1.196	-0.177	-2.47–0.037	0.045*		–	–	–	–	–

* Correlation is significant at the 0.05 level (bilateral).
** Correlation is significant at the 0.01 level (bilateral).
[a] Sex: Female = 0; Male = 1.

both sexes was evidenced (t = 2.25; p = 0.03) with women again predominating with higher scores, despite the fact that in other countries such as Nigeria (22) and Iran (23) males had higher scores, due to the social characterization marked in those places.

On the other hand, self-care in patients with diabetes did not correlate with sociodemographic variables such as age, being comparable to the study by Hussein et al. (15), and objected to by others (23–25). This is due to the different pathophysiological alterations such as cognitive alterations, visual impairment, peripheral neuropathy and psychological wear and tear resulting from the chronic disease, which significantly limit the capacity for self-care, in addition to the average age in our study ($\bar{x}$ = 67.54; SD ± 8.82). In the same way, the level of education did not show significance in the results, despite the fact that the highest score was given by patients at the primary level followed by secondary level, in contrast to other studies where the highest score was given by patients at the higher level (22, 23). This is due to the fact that most of the participants were over 60 years of age, where, taking into account the sociocultural level in our environment in past years, in addition to the deficit and economic crisis of the country at that time, hindered the completion of their studies at school, which is currently reflected in our sample represented with 96% between primary and secondary level.

With regard to the self-care in patients with hypertension, literacy showed a stronger association (R2 = 0.42; β = 0.927 [95% CI, 0.729–1.125; p = 0.000]), being analogous to the study by Davirshpour et al. (26) (β = 0.639 [95% CI, 0.276–0.410; p = 0.000]) and to that of other studies (27, 28). Similarly, a moderate correlation was revealed between the two (r = 0.648; p = 0.000); similar to that of Spriprachot et al. (29) (r = 0.858; p = 0.000). This is due to the fact that timely knowledge of the disease improves the actions in patients with hypertension.

It is worth mentioning that, in contrast to diabetic patients, literacy shows significant correlations with the dimensions of self-care in patients with hypertension, in addition to being associated with a greater proportion of their variance. This inequity is due to the fact that hypertensive older adults achieve better self-care compared to diabetic patients due to the less complex nature of their therapeutic regimen, since the management of arterial hypertension differs greatly from that of diabetes mellitus because blood pressure control is performed by non-invasive devices such as digital blood pressure monitors, which are harmless to the patient, unlike diabetes, which requires digital punctures or invasive tests for its control. Similarly, the burden of disease management varies between conditions, with hypertension presenting fewer lifestyle disruptions compared to diabetes. While the patients with hypertension primarily require medication adherence and periodic blood pressure monitoring, diabetic patients face more complex self-management demands including glucose monitoring, dietary control, physical activity, and medical care as identified by Xie et al. (30). This complexity is reflected in the multiple behavioral dimensions required for diabetes self-care, whereas hypertension management does not necessitate extensive meal planning in social settings or continuous invasive monitoring, resulting in reduced social stigma and enhanced disease acceptance.

CONCLUSION

Health literacy showed significant associations with self-care in both in patients with hypertension and diabetes, although with different magnitudes of association. In patients with hypertension, health literacy was associated with 42% of the variance in self-care, showing significant correlations with all its dimensions, suggesting a stronger and more consistent relationship. In diabetic patients, health literacy, together with gender, was associated with 10.6% of the variance in self-care, where women showed better levels of self-care than men. The results suggest the need to develop differentiated strategies to improve self-care in both populations, considering that health literacy, although important, shows limited association as a single factor with adequate self-care, especially in diabetic patients, where other factors not identified in this study could have a significant influence.

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“A Paralyzing Snack”: An Endocrine Cause of Paralysis

Ferdinando Rombola[1,*], Marianna Rodolico[2]

ABSTRACT

A case of a young Caucasian man presenting to the Emergency Department (ED) with lower limb weakness, anxiety, and sweating is described. Clinical and laboratory evaluations revealed severe hypokalemia (1.4 mmol/L) associated with thyrotoxicosis, leading to a diagnosis of Thyrotoxic Periodic Paralysis (TPP). After initial improvement following potassium infusion, the patient experienced symptom exacerbation. Further investigation linked the recurrence to excessive carbohydrate intake from vending machine snacks. TPP, a complication of hyperthyroidism, is extremely rare in Western countries but must be promptly recognized due to its potential life-threatening complications.

KEYWORDS

thyrotoxic periodic paralysis; thyrotoxicosis; hypokalemia; paralysis; hyperthyroidism

AUTHOR AFFILIATIONS

[1] Internal Medicine, Vibo Valentia Hospital, Italy
[2] Emergency Medicine, Vibo Valentia Hospital, Italy
* Corresponding author: Internal Medicine, Vibo Valentia Hospital, ASP VV, Piazza Fleming, 1 – 89900 Vibo Valentia, Italy; rombolaf@libero.it

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INTRODUCTION

Thyrotoxic Periodic Paralysis (TPP) is a rare neurological disorder characterized by muscle paralysis, hypokalemia, and hyperthyroidism. It primarily affects Asian males, but is far less common in non-Asian populations. This makes the disease little known in Western countries, where it is uncommon, thus making it potentially dangerous if not diagnosed early. A peculiarity of this clinical case is that TPP represents the initial presentation of hyperthyroidism.

TIMELINE

2023-06-05
Onset of symptoms.
2023-06-07
Hospital admission.
2023-06-07
Neurological evaluation, cranial CT scan, ECG, EMG, laboratory tests.
2023-06-07
Initial diagnosis of hypokalemic paralysis and initiation of potassium infusion therapy.
2023-06-08
Diagnosis of thyrotoxic periodic paralysis. Therapy with methimazole.
2023-06-10
Recurrence of neurological symptoms, with marked asthenia and low potassium levels, after consumption of a carbohydrate-rich snack.
2023-06-14
Discharge in good health.
2023-07-10
After about a month from discharge, the patient is in good health and continues therapy with methimazole.

NARRATIVE

A 31-year-old Caucasian man presented to the ED with a sudden onset of lower limb weakness upon awakening. His medical history included arterial hypertension managed with bisoprolol 1.25 mg daily. He denied any trauma, alcohol, tobacco, or drug use, or other medications. On physical examination, the patient appeared anxious with mildly warm, sweating skin. Vital signs showed a heart rate of 106 bpm, blood pressure of 120/70 mmHg, and tympanic temperature of 37.2 °C. Neurological evaluation revealed flaccid weakness and absent tendon reflexes in the lower limbs, while the rest of the neurological exam was unremarkable. Electrocardiogram (ECG) showed sinus tachycardia, incomplete right bundle branch block, and nonspecific ventricular repolarization abnormalities. The patient was admitted for further evaluation, including laboratory tests and a cranial CT scan, which was unremarkable. An Electromyography was scheduled. Laboratory findings revealed significant hypokalemia (1.4 mmol/L) and hypophosphatemia (0.5 mg/dL), aldosterone 19.0 ng/dL, renin (ortho) 21.5 IU/mL, blood gas analysis: pH 7.47, PaO2 91 mmHg, PaCO2 47 mmHg, HCO3 28.2 mEq/L, K+ 1.2 mmol/L. Intravenous potassium chloride was administered at 20 mEq/hour. A thorough review of personal and family history revealed no prior neurological conditions. Weakness improved on the first day as serum potassium levels gradually increased. A careful family and personal history helped exclude, in the differential diagnosis, Familial Hypokalemic Periodic Paralysis (HypoPP), secondary hypokalemia-related paralysis (absence of vomiting and diarrhea, excluding diuretic abuse, and normal aldosterone values), and Guillain-Barré syndrome due to the normal EMG picture and the lack of the characteristic evolutionary progression. However, anxiety, warm sweating, and tachycardia persisted, prompting evaluation of thyroid function. Thyroid function tests showed FT3 7.77 pg/mL, FT4 2.45 ng/dL, and TSH 0.004 µIU/mL, TRAb 18.4 IU/L, AbTG 380 IU/mL; TPOAb 450 IU/mL (Tab. 1). Thyroid ultrasound revealed diffuse thyroid enlargement with hypoechogenicity and no nodules. Antithyroid therapy with methimazole 30 mg/day and propranolol 120 mg/day was initiated. By the third day, the patient experienced an unexpected recurrence of neurological symptoms, with marked asthenia and a drop in serum potassium levels to 2.8 mmol/L. Investigation revealed excessive consumption of carbohydrate-rich snacks and chocolate from a vending machine the previous evening. Potassium chloride infusion resolved the symptoms. Subsequent oral glucose tolerance testing and insulin levels were normal (insulin 14µU/mL). The patient was discharged on the seventh day in good health and remains asymptomatic on methimazole therapy.

Tab. 1 Thyroid function tests.

Test name	Normal range
Potassium	3.5–5.0 mmol/L
Phosphorum	2.5–4.5 mg/dL
FT3	2.0–4.4 pg/mL
FT4	0.7–1.9 ng/dL
TSH	0.4–4.0 µIU/mL
Aldosterone	3.0–30 ng/dL
Renin	4.4–46.1 IU/mL ortho
TRAb	<1.75 IU/L
AbTG	<20 IU/mL
TPOAb	<34 IU/mL
Insulin	2–25 µU/mL

DISCUSSION

Thyrotoxic Periodic Paralysis (TPP) is a rare neurological disorder characterized by muscle paralysis, hypokalemia, and hyperthyroidism. It primarily affects Asian males, with a prevalence of approximately 2%, but is far less common in non-Asian populations, with an incidence of 0.1–0.2% (1–3). Western physicians are often unfamiliar with TPP, which can lead to potential mismanagement and serious consequences (3). Although hyperthyroidism more commonly affects women, TPP predominantly occurs in men, with a male-to-female ratio of 20:1. The peak age of onset is between 20 and 40 years. All forms of hyperthyroidism can be associated with TPP, including

Graves' disease, toxic multinodular goiter, Plummer's disease, thyroiditis, TSH-secreting pituitary adenomas, and iatrogenic thyrotoxicosis. In TPP patients, there is a significant increase in Na+/K+ ATPase activity in skeletal muscle, driven by thyroid hormones. This occurs through both transcriptional activation of the Na+/K+ ATPase gene and direct receptor-mediated effects (4). Hyperadrenergic states in thyrotoxicosis further stimulate the Na+/K+ ATPase via cyclic AMP, causing potassium to shift intracellularly (5). Hypokalemia in TPP results from altered potassium distribution rather than total body potassium depletion (6, 7). Carbohydrate loads, such as in this case, precipitate TPP episodes by increasing insulin levels, which enhance Na+/K+ ATPase activity and intracellular potassium uptake (8). Other triggers include trauma, cold exposure, menstruation, emotional stress, and infections (2). Genetic predisposition also plays a role; mutations in the Kir2.6 potassium channel gene have been identified in some TPP cases (9, 10). A functional loss of Kir2.6, combined with Na+/K+ ATPase hyperactivity, leads to sarcolemmal depolarization, sodium channel inactivation, and muscle inexcitability (11). Neurological symptoms in TPP range from mild proximal weakness, usually affecting the lower limbs, to flaccid tetraplegia. Paralysis is typically symmetrical, sparing bulbar, respiratory, and ocular muscles, though severe cases with such involvement have been reported (12, 13). Thyrotoxicosis symptoms may be absent, and TPP can be the initial manifestation, as seen here (14, 15). Differentiating TPP from thyrotoxic myopathy, which causes persistent weakness, is crucial. Unlike thyrotoxic myopathy, TPP is reversible with potassium correction, and neuromuscular symptoms do not persist outside of attacks (16). Potentially fatal complications include cardiac arrhythmias related to hypokalemia and hyperthyroidism, such as sinus tachycardia, atrioventricular block, and ventricular fibrillation (17–19). Acute TPP management involves intravenous potassium chloride to normalize plasma potassium levels. However, since hypokalemia in TPP results from redistribution rather than depletion, potassium supplementation must be cautious to avoid rebound hyperkalemia, which occurs in approximately 40% of patients, particularly with doses greater than 90 mEq/24 hours (20). Rebound hyperkalemia can cause life-threatening arrhythmias and must be promptly recognized and treated (21, 22). Long-term treatment involves controlling hyperthyroidism with antithyroid medications (methimazole), nonselective β-blockers (propranolol), or definitive therapy with radioiodine or thyroidectomy.

CONCLUSION

Therefore, though rare in Western countries, TPP requires early recognition and prompt treatment to prevent severe complications. Education on this condition is essential for timely diagnosis and appropriate management.

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