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Liver Transplantation in the Era of Artificial Intelligence: Surgical Innovation, Risk Stratification, and Patient-centred Care

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Abstract: Liver transplantation continues to be the most effective and, in many cases, the only therapeutic recourse for individuals suffering from end-stage liver disease, select hepatocellular malignancies, and uncommon hepatic disorders. Alongside clinical advancements, artificial intelligence (AI) is increasingly being explored for its capacity to support clinical decision-making at all stages of the transplant continuum. In this narrative review, we synthesize recent advancements in liver transplantation and examine the expanding role of AI throughout the process. AI-driven technologies have demonstrated the ability to improve donor-recipient compatibility, evaluate graft function, interpret diagnostic images, and support post-surgical monitoring. Still, obstacles such as limited data availability, bias within algorithms, and unresolved ethical questions continue to pose challenges. At the same time, innovations like machine perfusion, synthetic grafts, and predictive models are helping refine surgical procedures and post-transplant care. Introducing AI into the transplant workflow may boost accuracy, fairness, and healthcare quality. A patient-centred approach that incorporates modern technology, mental health resources, and ethical responsibility will be essential for the future of liver transplantation.

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Introduction

Liver transplantation (LT) remains a well-established and life-saving intervention for individuals with end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), and acute liver failure (ALF). Over the past 20 years, changes in the global distribution of liver disease have influenced transplant eligibility criteria. In Western countries, nonalcoholic fatty liver disease (NAFLD) has become the leading cause of LT, whereas viral hepatitis continues to be the primary indication in parts of Asia, Africa, and South America (Cichoż-Lach et al., 2012; Safi et al., 2025). These epidemiological patterns highlight the need for region-specific transplant strategies tailored to local liver disease profiles.

Although significant progress has been made in surgical procedures and immunosuppressive treatments, several persistent challenges remain. These include a chronic shortage of donor organs, variability in patient outcomes after transplantation, and increasing complexity in selecting appropriate candidates. Moreover, non-medical factors such as frailty, psychological stress, and regret from living donors further complicate outcomes and are often insufficiently addressed in existing care models (Accardo et al., 2023; Hill et al., 2023).

At the same time, introducing artificial intelligence (AI) into clinical medicine creates new avenues for improving transplant success. AI tools, including machine learning algorithms, deep learning networks, and imaging-based platforms, have shown promise in enhancing diagnostic precision, improving donor-recipient compatibility, and monitoring patients postoperatively. These technologies can support decision-making, especially when traditional methods fall short (Balsano et al., 2023; Singhal et al., 2024; Zhang et al., 2024). Nevertheless, challenges such as limited data diversity, lack of algorithm transparency, and underdeveloped regulatory frameworks continue to hinder widespread implementation.

This review offers an in-depth overview of recent developments in liver transplantation, explicitly focusing on integrating AI into surgical and clinical practice. It explores updated transplant indications, advancements in surgical innovation, infection control strategies, and outcome monitoring. Furthermore, it examines ethical implications, translational hurdles, and future directions for research and practice in settings with varying healthcare resources.

From candidate selection to risk stratification: Foundations for AI-enhanced allocation

Patient selection for LT has evolved substantially in response to shifting disease burdens, expanded indications, and improved understanding of prognostic determinants (Battistella et al., 2024). Historically dominated by viral hepatitis and alcohol-related liver disease, the global LT landscape now reflects the increasing prevalence of NAFLD in Western populations. In contrast, hepatitis B and C

Table 1: Risk stratification models

Model name (Ref.)	Variables considered	Application phase	Predictive strength	Limitations
MELD (Chung et al., 2023)	Bilirubin, INR, creatinine	Pre	Good for short-term mortality	Does not account for functional status
MELD-Na (Chung et al., 2023)	Bilirubin, INR, creatinine, sodium	Pre	Improved over MELD; better for hyponatremia cases	Limited granularity in frail patients
APACHE IV (Hu et al., 2013; Hamilton et al., 2021; Matsushima et al., 2025)	Physiologic parameters, chronic health data	Post	High predictive accuracy in ICU settings	Complexity and data requirements
GEMA-AI (Gómez-Orellana et al., 2025)	Sociodemographics, clinical data	Pre	Superior to MELD-Na and MELD 3.0 for waitlist outcomes	Requires AI infrastructure and validation
Optimal Classification Trees (OCT) (Briceño et al., 2020)	Clinical, demographic, and functional data	Pre	Interpretable and customizable prediction models	Dependent on data quality and interpretability
Frailty tools (e.g., KPS) (Balogh et al., 2025)	Physical function, performance status	Pre and post	Predictive of long-term survival, especially post-transplant	KPS lacks granularity; validation needed for other tools

MELD – Model for End-Stage Liver Disease; MELD-Na – Model for End-Stage Liver Disease with sodium; APACHE IV – Acute Physiology and Chronic Health Evaluation IV; GEMA-AI – Generalizable Model for Early Allograft Dysfunction using Artificial Intelligence; KPS – Karnofsky Performance Status; AI – artificial intelligence; ICU – intensive care unit

predominate in Asia, Africa, and Latin America (Cichoż-Lach et al., 2012; Safi et al., 2025). These patterns necessitate region-specific approaches to transplant eligibility and health system planning.

Emerging data support the inclusion of patients with severe alcohol-associated hepatitis (AAH) under early transplant protocols, provided that stringent selection criteria are applied. Studies demonstrate that, despite increased infection risk, early LT in well-screened AAH patients yields favourable outcomes (Kulkarni et al., 2023). Similarly, rare indications such as metabolic liver disease and intrahepatic cholangiocarcinoma (iCCA) are increasingly considered in highly selected cases, often guided by neoadjuvant protocols or multidisciplinary consensus (Panayotova et al., 2021).

Risk stratification is central to transplantation decisions, influencing prioritisation of waitlist and post-transplant outcomes. The Model for End-Stage Liver Disease (MELD) score and its sodium-adjusted variant MELD-Na are widely used to estimate short-term mortality risk and allocate deceased donor organs (Chung et al., 2023). However, evidence suggests dynamic scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE IV) may offer superior predictive validity in orthotopic liver transplant intensive care settings (Hu et al., 2013; Hamilton et al., 2021; Matsushima et al., 2025). In particular, APACHE IV has shown enhanced accuracy in identifying candidates at risk for early postoperative mortality, with patients scoring within a MELD range of 15–25 exhibiting the lowest observed mortality in some cohorts (Hamilton et al., 2021).

Frailty has emerged as a critical, modifiable determinant of both pre-and post-transplant outcomes. Unlike biochemical indices, frailty reflects physiologic reserve and functional status, often providing greater prognostic utility in long-term survival than MELD alone (Balogh et al., 2025). The Karnofsky Performance Status (KPS), while widely used by the Organ Procurement and Transplantation Network (OPTN), remains a coarse surrogate, and efforts are ongoing to validate more granular tools tailored to LT populations.

Socioeconomic and geographic disparities also influence access to transplantation. Regional variation in organ procurement efficiency, insurance status, and healthcare infrastructure contributes to differences in MELD scores at listing, waitlist attrition, and time to transplant (Lentine et al., 2023; Yilma et al., 2023). These inequities emphasise the need for equity-informed allocation frameworks and risk models that incorporate social determinants of health. These evolving criteria reflect a broader shift toward individualised, multidimensional assessment of transplant candidates. As predictive analytics and AI-driven tools mature, they may further refine risk stratification by integrating clinical, functional, and sociodemographic data to guide patient selection (Table 1).

Artificial intelligence in liver transplantation

AI is emerging as a transformative force in liver transplantation, offering advanced analytical capabilities beyond traditional clinical judgment (Figure 1). AI applications enhance diagnostic accuracy, optimise organ allocation, and enable dynamic monitoring across the transplant continuum by integrating high-dimensional data from imaging, clinical records, and laboratory parameters. Although still in the early stages of clinical integration, these tools can augment decision-making and improve outcomes, particularly when implemented within structured, multidisciplinary frameworks.

Diagnostic enhancement

AI-enabled diagnostic platforms have demonstrated significant promise in detecting and characterising hepatocellular carcinoma (HCC). Machine learning

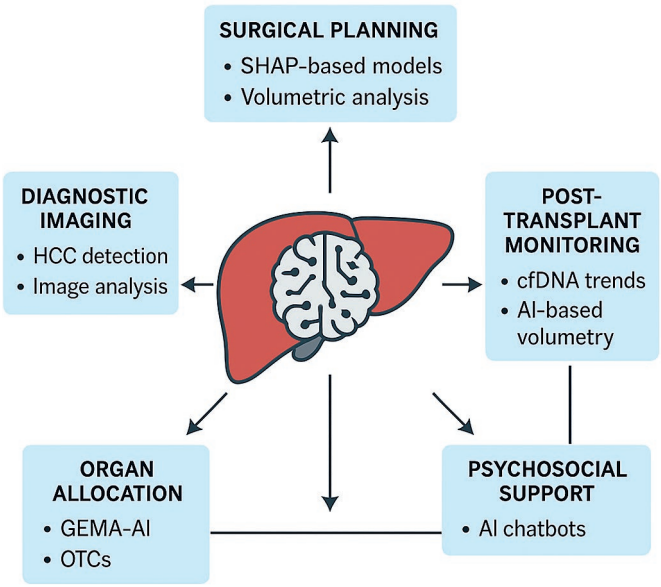

Figure 1: Framework of artificial intelligence (AI) applications across the liver transplantation. This figure presents a conceptual framework illustrating how AI is applied throughout the liver transplantation continuum. It highlights five key domains – diagnostic imaging, surgical planning, organ allocation, post-transplant monitoring, and psychosocial support – each supported by specific AI tools. These include machine learning for hepatocellular carcinoma (HCC) detection, SHapley Additive exPlanations (SHAP)-based surgical risk models, AI-enhanced volumetric analysis, predictive analytics for graft monitoring, and chatbot-assisted mental health support.

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algorithms applied to ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) have shown high sensitivity in identifying hepatic lesions and differentiating malignancies (Nishida and Kudo, 2022; Pomohaci et al., 2023). These tools can support earlier diagnosis, potentially expanding access to transplantation among patients with limited-stage HCC. Furthermore, radiomics and non-invasive image-based biomarkers may reduce dependence on histologic confirmation, minimising biopsy-associated risks (Malik et al., 2024).

Innovations such as LiverColor, a smartphone-integrated AI application, exemplify the growing accessibility of diagnostic technologies. Designed for use in low-resource settings, LiverColor leverages mobile camera input and machine learning models to estimate liver fat content, providing a scalable, cost-effective screening solution (Zsombor et al., 2023; Gómez-Gavara et al., 2024).

Surgical planning and organ allocation

In surgical planning, AI has been utilized to predict operative complexity and resource requirements. For example, explainable AI models using SHAP (SHapley Additive exPlanations) have been employed to assess the likelihood of conversion from laparoscopic to open surgery in segment 7 and 8 resections, offering real-time surgical risk profiling (Lopez-Lopez et al., 2024). AI-assisted tools also facilitate preoperative volumetric assessments to predict safe resection margins and reduce the incidence of post-hepatectomy liver failure (Kang et al., 2024).

Machine learning models are increasingly employed in organ allocation to supplement or refine existing scoring systems. The Gender-Equity Model for Allocation using Artificial Intelligence (GEMA-AI) has shown improved discrimination over MELD-Na and MELD 3.0 in predicting waitlist mortality and the likelihood of delisting due to clinical deterioration (Gómez-Orellana et al., 2025). Other AI frameworks, such as optimal classification trees (OCTs), provide interpretable, data-driven insights for prioritising recipients and guiding real-time donor-recipient matching (Briceño et al., 2020).

These innovations may also help to address persistent disparities in transplant access. Studies have demonstrated that sociodemographic factors – including race, insurance status, and educational attainment – significantly affect access to both deceased and living donor liver transplantation (Lentine et al., 2023).

Monitoring and post-transplant outcomes

AI applications in post-transplant care include predictive tools for rejection, infection, and graft dysfunction (Baciu et al., 2022). Remote monitoring systems, particularly in low-resource environments, are being developed to track vital signs, medication adherence, and immunologic markers, facilitating early intervention and reducing the burden of in-person follow-up (Nwankwo et al., 2024).

Donor-derived cell-free DNA (cfDNA) has emerged as a biomarker for early graft injury, and AI-assisted platforms may improve the interpretation of cfDNA trends and thresholds for intervention (Baumann et al., 2022; Jana et al., 2024). Similarly, AI-based liver volumetry significantly reduces analysis time while enhancing reproducibility, supporting consistent surveillance across centres (Machry et al., 2023). Quantitative assessment of hepatic steatosis through automated imaging platforms further improves graft acceptance criteria and risk stratification (Narayan et al., 2022).

Global and ethical considerations

Implementing AI in liver transplantation presents unique challenges, particularly in low- and middle-income countries (LMICs). Barriers include limited access to electronic health infrastructure, insufficient clinician training in AI technologies, and data scarcity (Kimiafar et al., 2023; Nakayama et al., 2023; Farhat et al., 2024; Krones and Walker, 2024). Moreover, AI models trained on datasets lacking population diversity may inadvertently perpetuate existing healthcare inequities (Liu et al., 2019; Mehrabi et al., 2021; Shipton and Vitale, 2024).

Robust data governance is essential. Regulatory frameworks such as the General Data Protection Regulation (GDPR) mandate transparency, data minimization, and informed consent in developing and deploying AI tools (Shabani and Marelli, 2019). Additionally, the adaptive nature of AI algorithms presents difficulties in achieving regulatory approval under current frameworks, necessitating updated guidelines from bodies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (Benjamens et al., 2020). As AI becomes increasingly embedded in transplant decision-making, its ethical and operational integration will require cross-disciplinary collaboration, continuous validation, and equitable access to technological infrastructure.

Surgical and technological innovations

Recent advances in surgical technique and perioperative management have redefined the technical boundaries of liver transplantation. Innovations such as minimally invasive procedures,

Table 2: Surgical and technological innovations

Innovation (Ref.)	Description	Clinical benefit	AI integration	Current limitations
Normothermic Machine Perfusion (NMP) (Bonaccorsi-Riani et al., 2024; Karageorgos et al., 2025; Safi et al., 2025)	*Ex vivo* organ preservation under near-physiologic conditions	Improves graft viability and assessment	Ongoing development for perfusion metric analysis	Expensive and technically demanding
Robotic liver transplantation (Matsushima et al., 2025)	Minimally invasive donor/recipient surgeries using robotic systems	Reduced blood loss, faster recovery	AI used in planning and simulation	High cost and technical skill requirement
Bioengineered liver grafts (Min et al., 2017; Khalil et al., 2023)	Liver constructs using stem cells and decellularized scaffolds	Potential long-term solution for organ shortage	AI used in design and optimization	Vascularization and immune tolerance challenges
AI-guided surgical risk models (Lopez-Lopez et al., 2024)	Explainable AI models for operative complexity prediction	Improves intra-operative planning and outcomes	Uses SHAP and machine learning algorithms	Limited availability and external validation needed
Hypothermic Oxygenated Perfusion (HOPE) (Safi et al., 2025)	Cold preservation technique with oxygenation to protect grafts	Reduces ischemia-reperfusion injury	AI models being tested for function prediction	Still under clinical evaluation

AI – artificial intelligence; SHAP – SHapley Additive exPlanations

machine perfusion systems, and bioengineered grafts are increasingly supported by AI-enhanced tools that refine surgical decision-making, expand donor utilisation and improve post-transplant outcomes. These technologies reflect a broader shift toward precision surgery and data-driven organ optimisation (Table 2).

Robotic and minimally invasive techniques

Robot-assisted and laparoscopic approaches are gaining acceptance in both donor and recipient surgeries, particularly in living donor liver transplantation (LDLT) (Liu et al., 2023). These techniques have demonstrated advantages in reducing intraoperative blood loss, enhancing visualisation, and shortening postoperative recovery times (Matsushima et al., 2025). AI-supported operative planning further strengthens these benefits by predicting technical complexity and intraoperative risk.

A multicentre study applying SHAP-based explainable AI models identified an increased risk of conversion to open surgery in segment 7 and 8 resections, especially in cases with high intraoperative blood loss or prolonged duration (Lopez-Lopez et al., 2024). Such tools may prove especially valuable in resource-constrained settings where optimising surgical outcomes and operative efficiency is paramount.

Bioengineered liver grafts

Developing bioengineered livers represents a long-term solution to the persistent donor organ shortage. These constructs rely on decellularized scaffolds and repopulation with induced pluripotent stem cells (iPSCs) or primary hepatocytes, aiming to replicate native liver architecture and function (Khalil et al., 2023). A key challenge remains the complete endothelialisation of the vascular network, which is essential for graft viability and host integration (Min et al., 2017).

Parallel clinical priorities include optimizing cardiovascular risk management in LT candidates. Multidisciplinary consensus recommends preoperative coronary revascularization for asymptomatic individuals with significant stenosis and initiation of guideline-directed medical therapy (GDMT) in high-risk patients. These strategies are increasingly considered in bioengineered graft trials (Pagano et al., 2024).

Machine perfusion and organ optimization

Normothermic machine perfusion (NMP) and hypothermic oxygenated machine perfusion (HOPE) represent transformative graft preservation and evaluation technologies. These techniques allow for *ex vivo* organ assessment under physiologic or hypothermic conditions, offering real-time data on hepatocellular function, bile production, and metabolic profiles (Bonaccorsi-Riani et al., 2024; Karageorgos et al., 2025; Safi et al., 2025).

NMP, in particular, has been instrumental in expanding the use of extended criteria and donation after circulatory death (DCD) grafts. AI-integrated perfusion systems are under development to interpret perfusion metrics and predict post-transplant outcomes, potentially guiding organ acceptance decisions more reliably than static parameters alone.

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Surgical risk allocation and ethical considerations

Concerns have been raised regarding the allocation of marginal or high-risk grafts, such as DCD livers, to recipients with increased vulnerability, including those with frailty or reduced physiologic reserve (Balogh et al., 2025). Several predictive models – such as the Liver Graft Assessment Following Transplantation (L-GrAFT) score and e-GLR index – are being evaluated to facilitate more accurate preoperative assessment and equitable graft allocation (Safi et al., 2025).

The GEMA-AI model has shown superior performance in short-term mortality prediction compared to MELD-based systems and may assist transplant centers in prioritizing candidates with the highest expected benefit (Gómez-Orellana et al., 2025). As AI tools become more integrated into clinical practice, ethical safeguards must accompany their application, ensuring transparency, equitable access, and the avoidance of implicit bias in recipient selection.

Infection risk and immunosuppression

Infectious complications remain among the most common and severe threats to graft and patient survival following liver transplantation. The interplay between immunosuppression, surgical stress, and nosocomial exposure contributes to a heightened risk, particularly in the early postoperative period. Advances in preoperative risk stratification, perioperative protocols, and AI-enabled predictive tools are reshaping infection prevention strategies and informing the next generation of immunosuppressive regimens.

Preoperative screening and risk factors

Pre-transplant screening protocols now routinely include assessment for cytomegalovirus (CMV), hepatitis viruses, and colonization with multidrug-resistant organisms (MDROs), given their established role in post-transplant infectious morbidity (Sun et al., 2024; Wu et al., 2024). Clinical risk factors such as diabetes mellitus, renal insufficiency, preoperative mechanical ventilation, and use of extracorporeal detoxification systems (e.g., MARS) have been independently associated with increased risk of postoperative respiratory failure (PRF) and sepsis (Huang et al., 2011). Early extubation strategies and personalized anesthetic approaches – such as epidural analgesia – have shortened ICU (intensive care unit) stays and reduced nosocomial infection rates (Aniskevich et al., 2023; Jeon et al., 2025). These findings support an integrated approach to perioperative care, combining infection prevention with enhanced recovery pathways.

Intraoperative and early postoperative control

Intraoperative contamination and early postoperative immunosuppression create a window of heightened susceptibility to infection. Adherence to strict aseptic techniques, appropriate perioperative antibiotic prophylaxis, and rapid extubation protocols are essential to infection control. AI-based predictive models have demonstrated potential in identifying high-risk patients preoperatively, facilitating earlier intervention, and targeted antimicrobial stewardship (Hohenreuther et al., 2025).

The increasing incorporation of immunotherapeutic agents into pre-transplant cancer management – such as checkpoint inhibitors and cytokine modulators – has introduced new complexities. While these agents may improve tumour control, their immunomodulatory effects pose potential risks in the peri-transplant period and require careful monitoring and prospective evaluation (Pettas et al., 2025).

Immunosuppressive regimens and metabolic complications

Contemporary immunosuppressive protocols often combine corticosteroids, calcineurin inhibitors (CNIs), antimetabolites, and mammalian target of rapamycin (mTOR) inhibitors, each associated with distinct metabolic and infectious risks. Corticosteroids contribute to insulin resistance and dyslipidemia. CNIs such as cyclosporine and tacrolimus are linked to hypertension and post-transplant diabetes mellitus (PTDM), with tacrolimus exhibiting a relatively favourable lipid profile (Gabrielli et al., 2024). mTOR inhibitors (e.g., everolimus, sirolimus) are associated with elevated triglyceride and LDL levels, although their antiproliferative effects may benefit selected oncology patients. Antimetabolites such as azathioprine and mycophenolate mofetil are metabolically neutral but insufficient for graft protection (Gabrielli et al., 2024).

Emerging approaches – including autologous cell-based bioengineered grafts – may reduce or eliminate the need for conventional immunosuppression in the future (Khalil et al., 2023). In the interim, AI-assisted risk stratification and pharmacogenomic profiling may support individualized immunosuppression strategies that balance graft tolerance with infection risk (Basuli and Roy, 2023).

Post-transplant outcomes and complications

While advances in surgical technique, perioperative management, and immunosuppression have improved

early survival after liver transplantation, long-term outcomes remain influenced by a complex interplay of graft-related, patient-specific, and systemic factors. The focus has progressively shifted toward preventing complications, enhancing functional recovery, and identifying recurrence risk, with AI-driven tools and biomarker platforms playing an increasingly prominent role in outcome surveillance.

Graft monitoring and biomarkers

Graft function assessment has traditionally relied on biochemical markers and imaging studies; however, these modalities often lack specificity and early predictive capacity. cfDNA has emerged as a promising biomarker for subclinical graft injury and acute rejection, allowing for earlier therapeutic intervention and potentially improved graft salvage (Baumann et al., 2022; Jana et al., 2024).

AI-assisted imaging analysis has demonstrated high accuracy in identifying steatosis, vascular abnormalities, and biliary complications, thereby reducing interobserver variability and enhancing diagnostic consistency (Narayan et al., 2022; Malik et al., 2024). Furthermore, AI-based liver volumetry has significantly improved the speed and reproducibility of graft size assessments, contributing to better surgical planning and postoperative monitoring (Machry et al., 2023).

One-year patient survival rates now exceed 85% in most transplant centers, with five-year graft survival approaching 75%, although variability persists depending on donor quality, cold ischemia time, and recipient comorbidities (Bolondi et al., 2016; Strauss et al., 2022; Olawade et al., 2025).

Morbidity and mortality predictors

Frailty, renal dysfunction, and infection are the most consistent predictors of early morbidity and mortality following liver transplantation. Notably, frailty has emerged as a time-dependent risk factor, increasingly predictive of outcomes beyond the immediate postoperative period, in contrast to the MELD score, whose predictive value diminishes after transplant (Balogh et al., 2025). KPS remains the only frailty-related tool incorporated by the OPTN, but it offers limited granularity for clinical decision-making.

Recent data suggest that the APACHE IV score outperforms MELD in predicting short-term mortality in critically ill transplant recipients, offering a more dynamic and physiologically comprehensive risk assessment (Hu et al., 2013; Hamilton et al., 2021; Matsushima et al., 2025). In high-risk populations such as early liver transplant recipients with AAH, elevated infection rates and healthcare utilization highlight the need for intensified post-discharge monitoring and resource planning (Kulkarni et al., 2023).

Recurrence and surveillance

Tumour recurrence, particularly after transplantation for HCC, remains a significant concern. Recent evidence suggests that late recurrence – occurring beyond two years post-transplant – may be more common than previously recognized, necessitating extended surveillance protocols (Garas et al., 2025).

Macrovascular invasion on explant histopathology is among the strongest predictors of recurrence and is increasingly integrated into selection criteria and prognostic models (Garas et al., 2025). AI-enhanced radiologic tools and dynamic risk scoring systems incorporating biomarkers such as alpha-fetoprotein (AFP) and glypican-3 (GPC3) offer opportunities for more refined recurrence prediction and post-transplant immunosuppression adjustment (Pettas et al., 2025). As transplant oncology continues to evolve, particularly in expanding criteria and immunotherapy integration, AI-based predictive analytics may support individualized surveillance strategies and facilitate earlier interventions in high-risk recipients.

Psychosocial outcomes and patient-centred care

Liver transplantation significantly improves life expectancy and physical function, yet psychosocial outcomes often lag behind biomedical recovery. Post-transplant quality of life (QoL) is influenced by factors such as immunosuppressive side effects, fatigue, anxiety, depression, and ICU-related psychological trauma. Integrating structured frailty assessment, early mental health intervention, and digital support tools is central to advancing a patient-centred approach in transplantation medicine.

Quality of life, frailty, and recovery

Although most transplant recipients report improved physical functioning, long-term recovery is frequently hindered by persistent fatigue, sleep disturbances, and affective symptoms. These challenges are exacerbated by chronic immunosuppression and its metabolic consequences, including diabetes, dyslipidemia, and weight gain (Gabrielli et al., 2024; Xi et al., 2025). Psychological distress – ranging from adjustment disorder to post-traumatic stress symptoms – is common, particularly in patients with prolonged ICU stays or preexisting psychiatric vulnerabilities (Sun et al., 2024).

Frailty plays a pivotal role in shaping recovery trajectories. Post-transplant mortality is significantly higher among frail recipients, and emerging evidence suggests that frailty becomes more predictive of outcomes over time, surpassing traditional markers

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such as the MELD score (Balogh et al., 2025). This underscores the value of incorporating prehabilitation strategies – nutritional optimization, physical conditioning, and cognitive support – into transplant pathways to mitigate adverse outcomes.

Enhanced recovery protocols that promote early extubation and ICU bypass in suitable patients have been associated with shorter hospital stays and improved psychological well-being (Aniskevich et al., 2023). Early identification of at-risk individuals and timely psychosocial intervention can reduce complications, improve adherence, and enhance long-term satisfaction.

Digital mental health tools and AI chatbots

Artificial intelligence has recently been explored to augment psychosocial support for transplant recipients. AI-powered chatbots, such as ChatGPT and similar platforms, have shown early promise in psychiatric inpatient settings, demonstrating improvements in self-reported quality of life and user satisfaction (Melo et al., 2024). In the transplant context, these tools may serve as adjuncts to traditional care by delivering personalized education, medication reminders, and psychological support (Garcia Valencia et al., 2023).

However, concerns regarding data privacy, lack of clinical oversight, and therapeutic misconception must be addressed. The perception that AI tools can replace human clinicians may compromise safety, particularly during crises (Khawaja and Bélisle-Pipon, 2023; Casu et al., 2024). Current guidelines recommend deploying such platforms under strict ethical frameworks, with oversight from qualified mental health professionals. Overall, enhancing psychosocial recovery requires a multidimensional strategy encompassing frailty mitigation, early mental health screening, and the ethical use of digital tools. These efforts are fundamental to improving survival and the lived experience of liver transplant recipients.

Challenges, gaps, and future directions

Despite substantial advances in surgical techniques, immunosuppressive therapy, and data-driven clinical tools, liver transplantation faces significant clinical, ethical, and technological challenges. Addressing these gaps is essential to improve long-term outcomes, reduce health disparities, and optimize the full potential of emerging innovations, particularly those involving AI.

Translational barriers to AI implementation

One of the foremost obstacles to the clinical integration of AI in transplantation is the limited availability of large, high-quality, and diverse datasets. Most current models are trained on retrospective, single-center data that may not generalize across populations, increasing the risk of algorithmic bias and poor external validity (Machry et al., 2023; Krones and Walker, 2024; Singhal et al., 2024). This issue is particularly acute in low- and middle-income countries (LMICs), where electronic health records are fragmented or absent, and AI literacy among clinicians is limited (Nakayama et al., 2023; Farhat et al., 2024; Krones and Walker, 2024).

Furthermore, many AI systems are "black boxes", offering limited interpretability and raising concerns regarding transparency and clinical accountability. Adaptive learning algorithms, which evolve based on new inputs, present additional challenges to current regulatory frameworks. Agencies such as the FDA and EMA are developing guidelines for such tools, but comprehensive regulatory infrastructure remains under development (Benjamens et al., 2020).

Data privacy and compliance with international standards such as the GDPR are essential to maintain patient trust and institutional integrity. Appropriate consent procedures must accompany the ethical deployment of AI tools, transparent disclosure of model limitations, and equitable representation of patient subgroups (Liu et al., 2019; Shabani and Marelli, 2019; Mehrabi et al., 2021).

Innovative frontiers and multidisciplinary integration

Integrating AI with other transformative technologies offers exciting possibilities as the field moves forward. AI-guided genome editing using CRISPR holds promise for tailoring immunologic compatibility and reducing reliance on long-term immunosuppression. AI models may assist in identifying immunogenic variants. At the same time, CRISPR-based techniques could be employed to modify relevant genetic loci in donor or recipient cells, though these applications remain largely theoretical (Dixit et al., 2024).

Open-access AI platforms and federated learning models could address equity concerns by enabling secure, decentralized training across multiple institutions (Ritoré et al., 2024). Such approaches may democratize access to transplant innovations, particularly in resource-limited settings (Machry et al., 2023). In parallel, cost-effective tools such as LiverColor for hepatic steatosis assessment or smartphone-based diagnostic platforms are expanding the reach of AI into underserved regions (Gómez-Gavara et al., 2024).

Additional clinical gaps include the need for validated frailty-specific scoring systems, improved utilization of marginal grafts, and refined strategies for long-term

surveillance and immunosuppression personalization. For example, phosphatidyl ethanol (PEth) has emerged as a reliable biomarker for alcohol use monitoring, particularly in recipients transplanted for alcohol-associated liver disease (Sharma et al., 2024). Similarly, tumour-specific markers such as AFP and GPC3, when integrated with AI-enhanced imaging, may improve transplant oncology outcomes (Pettas et al., 2025; Sha et al., 2025).

Disparities in access to deceased and living donor organs persist across demographic and socioeconomic strata, underscoring the need for policies that explicitly incorporate equity metrics into allocation algorithms (Strauss et al., 2022; Lentine et al., 2023). Moreover, structured psychological support for living donors remains inadequately addressed and warrants systematic implementation (Lee et al., 2025).

Advancing the next generation of transplant medicine will require cross-disciplinary collaboration among transplant surgeons, hepatologists, ethicists, data scientists, and policymakers. By aligning technical innovation with clinical pragmatism and ethical responsibility, the field is poised to redefine what is achievable in liver transplantation.

Conclusion

Liver transplantation continues evolving as a multidisciplinary endeavor integrating surgical precision, immunological management, and emerging technological advances. While considerable progress has been made in short- and intermediate-term survival, persistent challenges – including organ scarcity, post-transplant complications, and health disparities – highlight the need for ongoing innovation and systemic reform.

AI has emerged as a promising adjunct to traditional clinical decision-making, offering enhancements in diagnostic imaging, graft assessment, surgical planning, and postoperative surveillance. As these tools mature, their potential to improve risk stratification, personalize immunosuppression, and streamline organ allocation will depend on rigorous validation, equitable implementation, and ethical oversight.

Equally important is recognizing that patient-centred outcomes – such as quality of life, psychosocial recovery, and functional independence – are essential to defining transplant success. Addressing frailty, optimizing prehabilitation, and supporting post-transplant mental health must become integral components of comprehensive transplant care.

Future directions should focus on fostering cross-disciplinary collaboration, developing inclusive and representative datasets, and supporting scalable solutions applicable across diverse clinical and geographic contexts (Korylchuk et al., 2024). As liver transplantation enters the era of precision medicine, integrating ethical, technological, and clinical frameworks will be critical to ensuring that innovation translates into equitable and durable improvements in patient outcomes.

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Evaluating Adherence to the 2021 Surviving Sepsis Campaign Guidelines for Sepsis and Septic Shock Management in Intensive Care Units: A Prospective Observational Study

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Abstract: This study evaluated adherence to the 2021 Surviving Sepsis Campaign (SSC) guidelines for managing sepsis and septic shock in a tertiary intensive care unit (ICU), aiming to identify deviations from recommended practices and their clinical implications. A prospective observational study was conducted over six months in the ICU of an academic tertiary-care hospital. Patients aged 50–80 years with sepsis or septic shock were enrolled (n=138). Adherence to 17 SSC 2021 recommendations was assessed using structured case report forms and electronic medical records, and clinical parameters, therapeutic interventions, and outcomes were analysed to determine adherence rates and areas of nonadherence. Adherence was high for foundational resuscitative measures, including early administration of intravenous crystalloids (100%), maintenance of mean arterial pressure (MAP) ≥ 65 mm Hg (100%), and comprehensive medication reconciliation (100%). In contrast, adherence to the recommendation against using the Quick Sequential Organ Failure Assessment as a sole screening tool was 0%. Adherence was suboptimal for low-molecular-weight heparin as the preferred agent for venous thromboembolism prophylaxis (57.1%) and for lung-protective ventilation in acute respiratory distress syndrome (75%). ICU mortality was 16.7%, and the 30-day readmission rate was 23.9%. While adherence to core resuscitative components of the SSC guidelines was robust, important gaps persisted in diagnostic screening practices, thromboprophylaxis choice, and ventilatory strategies, highlighting actionable targets for quality improvement.

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Introduction

Sepsis and septic shock remain major causes of global morbidity and mortality. They arise from a dysregulated host response to infection that precipitates life-threatening organ dysfunction; in septic shock, profound circulatory and cellular-metabolic abnormalities necessitate vasopressors and are accompanied by elevated serum lactate (Liu et al., 2024). Globally, an estimated 48.9 million incident cases and 11 million deaths are attributed to sepsis each year – nearly 20% of all deaths (Rudd et al., 2020). Pathogenesis begins with activation of the innate immune system by pathogen- and damage-associated molecular signals, triggering systemic inflammation, endothelial injury, and subsequent immune suppression. This dysregulation drives multiorgan dysfunction and increases susceptibility to nosocomial infections (Jarczak et al., 2021).

Prompt recognition and early, bundle-based care are foundational. However, clinical features are nonspecific and overlap with other critical syndromes, contributing to delays – particularly among older adults and residents of long-term care facilities (Yoshikawa et al., 2019). The Sepsis-3 framework reconceptualised sepsis as infection complicated by organ dysfunction with increased mortality risk, aiming to improve diagnostic precision and reduce practice variability (Singer et al., 2016). Initial management centres on timely broad-spectrum antimicrobials, judicious intravenous fluids, vasopressors when indicated, and organ-supportive measures under evidence-based protocols such as the Surviving Sepsis Campaign (SSC). However, real-world implementation of SSC bundles remains uneven, with persistent gaps in time-to-antibiotics, fluid resuscitation volumes, and vasopressor practices (Dugar et al., 2020; Ranjit and Kissoon, 2021; Park et al., 2024). Even in well-resourced settings, adherence to key SSC elements is suboptimal, contributing to preventable morbidity and mortality (Levy et al., 2015).

Emerging approaches such as including biomarker-guided decision-making, individualised fluid strategies, and extracorporeal therapies show promise for improving early recognition and response, yet their uptake is limited by heterogeneous evidence, cost, and lack of standardised protocols (Kellum et al., 2016; Mehta et al., 2023; He et al., 2024). Against this backdrop, our prospective observational study aims to evaluate the clinical management of sepsis and septic shock in an intensive care unit, explicitly focusing on adherence to the 2021 SSC guidelines.

Aims and Objectives

Aim

To assess adherence with the 2021 Surviving Sepsis Campaign guidelines in treating sepsis and septic shock within intensive care unit (ICU) patients while pinpointing critical gaps in protocol adherence that impact patient outcomes.

Specific objectives

1) To measure the degree of alignment with key 2021 SSC recommendations concerning hemodynamic interventions, antimicrobial regimens, supplementary therapies, and supportive care among ICU patients diagnosed with sepsis or septic shock.
2) To examine clinical and treatment profiles, including fluid resuscitation approaches, vasopressor administration, ventilatory strategies, corticosteroid use, and venous thromboembolism (VTE) prevention, in the study cohort.

Methods

Study design and setting

This prospective observational study was conducted over six months in a tertiary-care academic hospital's ICU equipped with advanced monitoring and therapeutic capabilities.

Participants and eligibility

Patients aged 50–80 years admitted to the ICU with a clinical diagnosis of sepsis or septic shock were included. Restriction to 50–80 years reflects our ICU's local epidemiology: sepsis admissions. We initially screened using the quick Sequential Organ Failure Assessment (qSOFA) tool. We included if the diagnosis was confirmed by organ dysfunction consistent with the third international consensus definitions for sepsis and septic shock (Sepsis-3) and guideline-based clinical judgment.

Exclusion criteria were: age < 18 years, pregnancy or breastfeeding, advanced-stage organ dysfunction, receipt of palliative care, or incomplete medical records.

Sampling and sample size

Purposive sampling was used to enrol consecutive eligible patients during the study period. Assuming an ICU census of 210 patients over six months, a 5% margin of error, and a 95% confidence level target, the minimum sample size is 138.

Data collection and variables

Clinical and therapeutic data were collected prospectively using structured case report forms and

cross-verified with electronic medical records (EMRs). The following variables were recorded:

- Demographics: age, sex, and pre-existing comorbidities
- Clinical characteristics: qSOFA score, mean arterial pressure (MAP), blood glucose, and vital signs
- Therapeutic interventions: fluid resuscitation (type and volume), vasopressor use (agent and dose), antimicrobial therapy (agents, duration, and methicillin-resistant *Staphylococcus aureus* [MRSA] coverage), corticosteroid use (type and duration), and insulin administration
- Supportive care: mechanical ventilation, VTE prophylaxis, stress ulcer prophylaxis, and medication reconciliation
- Clinical outcomes: ICU length of stay, total hospital length of stay, duration of vasopressor support, achievement of MAP ≥ 65 mm Hg, complications, ICU mortality, and 30-day readmission

Guideline-adherence assessment

Seventeen Surviving Sepsis Campaign 2021 recommendations were preselected for adherence assessment based on: (1) direct measurability from EMRs or bedside documentation; (2) established clinical relevance to ICU management and patient-centred outcomes; (3) clear operational definitions enabling binary (yes/no) assessment; and (4) support from peer-reviewed literature, with a priori justifications (Supplementary Table 1).

Selected domains included:

- Hemodynamic management: initial MAP target, fluid choice, vasopressor selection, and escalation
- Antimicrobial stewardship: empirical MRSA coverage and removal of intravascular devices
- Adjunctive therapies: corticosteroids for refractory shock; low tidal-volume ventilation for acute respiratory distress syndrome (ARDS)
- Supportive care: VTE prophylaxis and stress ulcer prevention
- Monitoring and transitions: blood-glucose thresholds for insulin initiation; medication reconciliation at ICU and hospital discharge; and discharge summary documentation

Each recommendation was translated into a measurable binary variable. Adherence was coded as present when the specified practice was documented during the ICU stay or a contraindication was recorded; otherwise, it was coded as non-adherent. Data definitions followed SSC 2021 language and were adapted to local documentation practices to balance feasibility and clinical relevance.

Statistical analysis

Descriptive statistics summarised demographics, clinical characteristics, management strategies, and outcomes. Continuous variables were reported as means with standard deviations (SD) if the data were normally distributed; otherwise, medians and interquartile ranges were reported. Categorical variables as frequencies and percentages. All data were recorded in structured Excel spreadsheets and cross-validated against EMRs to ensure completeness and internal consistency.

Ethical considerations

The Institutional Ethics Committee approved the study (VIPT/IEC/Date: 24/09/2024; No. 119). Written informed consent was obtained from all participants or their legally authorised representatives. Data confidentiality was maintained, and all procedures adhered to the Declaration of Helsinki.

Table 1: Clinical parameters in sepsis and septic shock patients

Variable	Mean	SD
Age	65.68	8.59
qSOFA score	2.33	0.85
Vasopressor dose (mcg/kg/min)	0.92	2.14
Antibiotic duration (days)	9.16	2.67
Steroid duration (days)	3.61	3.35
Blood glucose (mg/dl)	203.78	78.17
Insulin dose (units)	4.72	4.07
ICU stay (days)	16.04	8.64
Hospital stay (days)	25.53	9.56

qSOFA – quick Sequential Organ Failure Assessment; ICU – intensive care unit; SD – standard deviation

Results

A total of 138 patients with sepsis or septic shock were enrolled over the study period. Descriptive statistics for continuous variables are summarised in Table 1. The mean age was 65.68 years (SD 8.59). The qSOFA score at presentation averaged 2.33 (SD 0.85). The mean ICU and hospital lengths of stay were 16.04 days (SD 8.64) and 25.53 days (SD 9.56), respectively. Mean blood glucose was elevated at 203.78 mg/dl (SD 78.17); insulin therapy was initiated when clinically indicated. The mean vasopressor dose was 0.92 µg/kg/min (SD 2.14). The median durations of antibiotic and corticosteroid therapy were 9.16 and 3.6 days, respectively.

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Table 2: Clinical and treatment characteristics of sepsis and septic shock patients

Variable	Category*	n (%)
Gender	male	72 (52.17%)
MAP	<65 mm Hg	122 (88.40%)
Comorbidities	yes	125 (90.58%)
Fluid type	crystalloid	138 (100.0%)
	colloids	16 (11.59%)
Vasopressin addition	yes	75 (54.35%)
MRSA coverage	yes	118 (85.51%)
Steroid use	yes	79 (57.25%)
BMI category	normal	55 (39.86%)
	overweight	35 (25.36%)
	obese	34 (24.64%)
	underweight	14 (10.14%)
Fluid volume (ml/kg)	30	132 (95.60%)
	500	11 (7.97%)
	25	6 (4.35%)
	1000	5 (3.62%)
Vasopressor used	Norepinephrine	111 (80.43%)
	Epinephrine	35 (25.36%)
	none	16 (11.59%)
	Dopamine	11 (7.97%)
Antibiotic used	Linezolid	13 (9.42%)
	Ceftriaxone	20 (14.50%)
	Piperacillin-Tazobactam	60 (43.48%)
	Vancomycin	105 (76.08%)
	Meropenem	45 (32.60%)
Steroid type	Hydrocortisone	60 (43.48%)
	none	59 (42.75%)
	Dexamethasone	15 (10.87%)
	Methylprednisolone	4 (2.90%)
Steroid dose (day doses)	none	59 (42.75%)
	200 mg/kg	60 (43.48%)
	6 mg	15 (10.87%)
	2 mg/kg	4 (2.90%)

*only "yes" and "higher frequency" responses are shown for dichotomous variables; MAP – mean arterial pressure; MRSA – methicillin-resistant *Staphylococcus aureus*; BMI – body mass index

Table 2 outlines the clinical and therapeutic characteristics of the cohort. Males comprised 52.2% of the cohort. Most patients (88.4%) presented with MAP < 65 mm Hg. Comorbidities were present in 90.6% of patients. Crystalloid resuscitation was universal, and vasopressin was added to catecholamine vasopressors in 54.3% of cases. Among antimicrobials, vancomycin (76.1%) and piperacillin-tazobactam (43.5%) were most frequently administered. Corticosteroids, predominantly hydrocortisone, were initiated in 57.3% of patients.

Table 3: Venous thromboembolism, prophylaxis, and medication safety practices in sepsis and septic shock patients

Variable	Category*	n (%)
Intravascular access devices used	yes	80 (57.98%)
GI bleeding risk	yes	39 (28.26%)
Stress ulcer prophylaxis	yes	67 (48.55%)
VTE prophylaxis	yes	91 (65.94%)
Medication reconciliation ICU	yes	116 (84.05%)
Medication reconciliation hospital	yes	138 (100.0%)
Medication discrepancies	yes	29 (21.01%)
Discharge summary provided	yes	123 (89.13%)
Mortality	deceased	23 (16.67%)
Readmission (30 days)	yes	33 (23.91%)
Complications	yes	63 (45.65%)
Prophylaxis type	PPI	43 (31.15%)
	H2 blockers	24 (17.39%)
	none	71 (51.45%)
VTE type	unfractionated heparin	39 (28.26%)
	LMWH	52 (37.68%)
	none	47 (34.06%)
VTE contraindications	none	91 (65.94%)
	bleeding risk	40 (28.99%)
	recent surgery	7 (5.07%)
Glucose monitoring frequency	every 6 hours	56 (40.58%)
	every 2 hours	48 (34.78%)
	every 4 hours	34 (24.64%)

*for dichotomous variables, only the category with the higher frequency (e.g., "yes" or "deceased") is shown; GI – gastro intestinal; ICU – intensive care unit; PPI – proton pump inhibitors; VTE – venous thromboembolism; LMWH – low-molecular-weight heparin; H2 – histamine 2

Medication safety and prophylactic practices are summarized in Table 3. Intravascular access devices were used in 58.0% of patients. Stress-ulcer prophylaxis and VTE prophylaxis were implemented in 48.6 and 65.9% of cases, respectively. When pharmacologic VTE prophylaxis was used, low-molecular-weight heparin (LMWH) was more common than unfractionated heparin (UFH). Medication reconciliation was documented for 84.1% of patients during the ICU stay and 100% at hospital discharge. Discharge summaries explicitly noting

Table 4: Adherence with 2021 Surviving Sepsis Campaign recommendations

S. No.	Recommendation*	Adherence – n/N (%)
1	Avoid qSOFA as sole screen	0/138 (0.0%)
2	Target MAP ≥ 65 mm Hg	122/122 (100.0%)
3	Empiric MRSA coverage	118/138 (85.5%)
4	Remove suspect IV access	60/80 (75.0%)
5	Use crystalloids first	138/138 (100.0%)
6	Albumin after large crystalloids	16/16 (100.0%)
7	Avoid starches	138/138 (100.0%)
8	Norepinephrine first-line	111/122 (91.0%)
9	Add vasopressin as needed	97/111 (87.4%)
10	Low tidal volume in ARDS	36/48 (75.0%)
11	IV corticosteroids in shock	79/100 (79.0%)
12	Stress ulcer prophylaxis	39/39 (100.0%)
13	VTE prophylaxis unless contraindicated	91/91 (100.0%)
14	Prefer LMWH over UFH	52/91 (57.1%)
15	Start insulin ≥ 180 mg/dl	78/78 (100.0%)
16	Reconcile ICU + discharge meds	138/138 (100.0%)
17	Document sepsis in discharge summary	123/138 (89.13%)

*recommendations abbreviated for brevity. Refer to supplementary material for full guideline descriptions; n – number of participants who were compliant with the recommendation; N – total number of participants for whom that recommendation was applicable; qSOFA – quick Sequential Organ Failure Assessment; MAP – mean arterial pressure; MRSA – methicillin-resistant *Staphylococcus aureus*; IV – intravenous; ARDS – Acute Respiratory Distress Syndrome; LMWH – low-molecular-weight heparin; UFH – unfractionated heparin; ICU – intensive care unit; S.No. – serial number

sepsis-related events were provided in 89.1% of cases. ICU mortality was 16.7%, and the 30-day readmission rate was 23.9%.

Adherence with the 2021 Surviving Sepsis Campaign guidelines is detailed in Table 4. Full adherence (100%) was achieved for early crystalloid administration, avoidance of starches, targeting MAP ≥ 65 mm Hg, applying insulin initiation thresholds as recommended, and completing medication reconciliation. Adherence varied for empiric methicillin-resistant *Staphylococcus aureus* (MRSA) coverage, early addition of vasopressin, low-tidal-volume ventilation, and corticosteroid use in shock. Among patients eligible for pharmacologic VTE prophylaxis, LMWH % preferred over UFH in 57.1%.

Discussion

In this evaluation of adherence to the 2021 SSC guidelines, compliance was high for core resuscitative measures, including early administration of crystalloids, maintenance of MAP ≥ 65 mm Hg, appropriate insulin initiation thresholds, avoidance of starch-based fluids, and thorough medication reconciliation. In contrast, several domains demonstrated suboptimal adoption. qSOFA was used as the sole screening tool in all cases, contrary to current guidance discouraging its standalone use. Guideline-concordant VTE prophylaxis favoured low-molecular-weight heparin over unfractionated heparin in only 57.1% of eligible patients. Implementation of lung-protective ventilation (LPV) in acute respiratory distress syndrome and corticosteroid therapy for vasopressor-dependent septic shock occurred in 75 and 79% of applicable cases, respectively. The observed ICU mortality of 16.7% and 30-day readmission rate of 23.9% provide clinical context and suggest that variability in diagnostic, prophylactic, and ventilatory practices may influence outcomes beyond initial hemodynamic management.

qSOFA, designed as a pragmatic bedside risk tool, continues to be used for initial screening, likely due to its simplicity and lack of laboratory requirements. However, the 2021 SSC discourages its use as a sole screening strategy because of limited sensitivity for early sepsis detection. Evidence indicates that only 24% of infected patients have qSOFA ≥ 2 (Oczkowski et al., 2022; Prescott and Ostermann, 2023), and while specificity is high (87–98%), sensitivity is low (26.9–53%) (Luo et al., 2019; Jamshed et al., 2023; Qiu et al., 2023). By comparison, SIRS maximises sensitivity (up to 98%) at the cost of specificity, whereas NEWS offers a more balanced diagnostic profile (Daga et al., 2021). Although requiring laboratory data, SOFA remains the strongest predictor of in-hospital mortality (sensitivity 89%, specificity 69%) (Qiu et al., 2023). Reliance on qSOFA alone risks delayed intervention; for example, nearly one-third of patients who progressed to pneumococcal septic shock were missed (Rein et al., 2020). Accordingly, qSOFA's role is best viewed as prognostic rather than diagnostic: patients with qSOFA ≥ 2 have substantially higher odds of 28-day mortality (OR [odds ratio] 6.9; 95% CI [confidence interval] 4.6–10.3) (Jamshed et al., 2023). A multimodal approach – combining clinical judgment with lactate, SOFA-based assessment, and early biomarkers – should replace qSOFA-only screening (Daga et al., 2021; Prescott and Ostermann, 2023).

LMWH is recommended by SSC and CHEST as the preferred pharmacologic prophylaxis in most critically ill patients due to predictable pharmacokinetics, lower risk of heparin-induced thrombocytopenia, minimal monitoring, and favourable cost-effectiveness (Wadhera and Piazza, 2014; Guarino et al., 2023; Patel and Varacallo, 2025). Meta-analytic data show

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reductions in pulmonary embolism and ICU length of stay, with fewer adverse events (Wadhera and Piazza, 2014). Despite these advantages and evidence supporting safety at prophylactic doses in moderate renal impairment (Crowther and Lim, 2015), LMWH utilisation remained modest (57.1%). Persistent concerns about bleeding, misconceptions regarding renal clearance, and acquisition-cost-driven protocols may explain the shortfall, even though downstream savings from fewer complications and readmissions are well documented (Wadhera and Piazza, 2014). Given the prothrombotic milieu of sepsis, protocolised LMWH use informed by validated risk models (Padua, IMPROVE) could reduce preventable events and resource use (Skeik and Westergard, 2020; Clapham and Roberts, 2023).

Robust evidence supports LPV (tidal volume ~ 6 ml/kg predicted body weight with plateau pressure targets) as a mortality-reducing strategy in ARDS; ARDSNet data demonstrated a ~ 9% absolute mortality reduction (Alhazzani et al., 2020). Nevertheless, real-world adherence remains inconsistent – reported as low as 13% under strict criteria – due to delayed ARDS recognition, default ventilator settings, and inter-provider variability (Ward et al., 2016). In this cohort, LPV use in 75% of eligible cases represents progress but leaves a sizable gap. Structured diagnostic pathways, ventilator order sets with default LPV parameters, and targeted education have been shown to improve fidelity (Knighton et al., 2020; Arrivé et al., 2021).

The SSC recommends 200 mg/day IV hydrocortisone in septic shock refractory to fluids and vasopressors (Garner et al., 2025). Randomised trials demonstrate reductions in time to shock resolution and duration of mechanical ventilation (Venkatesh et al., 2018) and, when combined with fludrocortisone, lower 90-day mortality and more vasopressor-free days (Annane et al., 2018). Implementation in 79% of eligible cases indicates reasonable uptake, yet gaps persist – often related to diagnostic uncertainty, concerns about hyperglycemia, immunosuppression, and secondary infection (Yerke et al., 2020). Evidence suggests benefits with early initiation (ideally within 3 hours of shock recognition) and that 200 mg/day, whether as divided boluses or continuous infusion, yields comparable efficacy (Alsulami et al., 2023). Algorithmic decision support linked to vasopressor dosing and lactate kinetics may standardise timing and monitoring.

Despite advances, case-fatality in septic shock remains 30–40% and correlates with poorer adherence to guideline bundles (Via et al., 2024). Observational analyses associate bundle completion, particularly the one-hour bundle, with reduced 28-day mortality (adjusted OR 0.44; 95% CI 0.25–0.78), and timely fluid resuscitation (>30 ml/kg within 3 hours) with lower in-hospital mortality (Piehl et al., 2025). The ICU mortality (16.7%) and 30-day readmission (23.9%) observed here are broadly consistent with prior registries (Walkey et al., 2018). Given that sepsis accounts for 12.2% of 30-day readmissions (Prescott and Angus, 2018), structured discharge planning, early follow-up, and VTE prophylaxis continuation where indicated are rational post-acute priorities.

Findings highlight concrete targets for quality improvement: (i) replace qSOFA-only screening with multimodal early-recognition pathways anchored by lactate and SOFA-based assessment; (ii) standardize LMWH-first VTE prophylaxis with embedded renal-dose and bleeding-risk safeguards; (iii) hard-wire LPV via default ventilator order sets and bedside prompts; and (iv) operationalize steroid initiation algorithms for vasopressor-dependent shock with predefined monitoring. Real-time electronic health record (EHR) prompts, multidisciplinary education, and audit-and-feedback cycles can help close these gaps.

This single-center, purposive-sample study lacked a control group, limiting causal inference and generalizability. EMR-based adherence measurement captured 17 SSC 2021 recommendations, potentially omitting relevant practices. Provider-level variables and precise intervention timing were not adjusted for and may confound associations between adherence and outcomes.

Conclusion

This study identifies persistent shortfalls in adherence to the 2021 Surviving Sepsis Campaign guidelines, most notably in early diagnostic screening, venous thromboembolism prophylaxis, lung-protective ventilation, and corticosteroid administration. Despite robust evidence and explicit recommendations, practice patterns remain inconsistent, indicating a need for system-level recalibration. Exclusive reliance on quick Sequential Organ Failure Assessment, underuse of low-molecular-weight heparin, and inconsistent delivery of LPV represent missed opportunities to optimise sepsis care. Future work should evaluate how bundle adherence affects long-term outcomes, including functional recovery and post-discharge morbidity. Multicenter, prospective studies with real-time data feedback and provider-level analyses are warranted to delineate persistent barriers. Integrating digital tools, audit-feedback cycles, and targeted education will be essential to improving adherence and, ultimately, clinical outcomes.

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How Does Capsular Distension Pain Manifest in Patients with Anterior Disc Dislocation with Reduction of Temporomandibular Joint?

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Abstract: Joint effusion (JE) refers to the presence of a pathological collection of fluid in the joint space, and JE is one of the symptoms of the inflammatory process in the temporomandibular joint (TMJ) and it is associated with the presence of TMJ pain. The authors of this study focused on the ultrasonographic evaluation of TMJ capsular distension, capsular width in patients with unilateral anterior disc dislocation. The cohort included 200 patients, 169 women and 31 men, with a mean age of 34.3 years (range 11–82 years). All patients were diagnosed with disc dislocation with reduction. 102 patients were completely pain free, 98 patients reported pain localized to the TMJ area. 28 patients perceived their pain as persistent in the last week before the examination, 70 patients perceived their pain as irregular. The results showed that capsular distension was demonstrably greater in patients with pain than in patients without pain. The increase in capsular distension is not affected by whether the pain is persistent or irregular. Capsular distension is enhanced in patients with TMJ palpation pain and painful dynamic testing. The authors confirm the use of ultrasonography as an ideal method for diagnosing JE. Also an association between the presence of JE and pain in patients with disc dislocation has been demonstrated. Painful lateral palpation and painful dynamic test are clinical signs of JE and thus signs of an intra articular inflammatory process in patients with TMJ pain.

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Introduction

Anterior temporomandibular joint (TMJ) disc dislocation is a pathological condition in which the disc is dislocated anteriorly, out of its physiological position. It becomes an obstacle to the movement of the articular head. There is a distinction between disc dislocation with reduction (when the articular head is under the dislocated disc, in its physiological position, during mouth opening) and disc dislocation without reduction (when the disc is permanently in front of the articular head and prevents movement of the head) (Laskin et al., 2006; Okeson, 2008).

Pain is not a typical symptom of anterior disc dislocation with reduction (DDwR) of TMJ. The typical symptoms are sound phenomena (clicking), asymmetry of jaw movement. Jaw movement is unrestricted. If pain is present, then its origin may be of extra-articular origin (myogenic pain) or of intra-articular origin. The cause of intra articular pain in disc dislocation lies in the traumatization of the ligament capsule, traumatization of the retrodiscal tissue, which leads to hyperemia of the tissues of the joint. The hyperemia results in the production of free radicals and cytokines, with the development of traumatic arthritis (Laskin et al., 2006; Okeson, 2008).

One of the signs of an inflammatory process in the joint is the presence of a pathological collection of fluid in the joint space, which is referred to as joint effusion (JE) (Manfredini et al., 2003; Bas et al., 2011). Magnetic resonance imaging (MRI) is the gold standard for imaging and diagnosis of JE (Kundu et al., 2013). However, it is a costly examination requiring special equipment. Complications for performing MRI are claustrophobia of the patient and presence of metals in the patient's body. Ultrasonography (US) can be used as an alternative in the imaging of TMJ effusion (Manfredini et al., 2003). US has been used for TMJ examination since the early 1990s, and compared to MRI, it is a method with significantly lower cost, easily performed in the physician's office, with minimal discomfort to the patient. Like MRI, US allows for static and dynamic examination of the TMJ (Nebeith and Speculand, 1991; Kundu et al., 2013; Almeida et al., 2018). Longitudinal and transverses scan, frequencies ranging 7.5–20 MHz, are most commonly used for TMJ diagnosis by US (Almeida et al., 2018). The major disadvantage of US is the quality of imaging requiring the experience of the physician in assessing the findings (Manfredini et al., 2003; Kundu et al., 2013). US assessment of disc position and quality is difficult and assessment of bone changes is only indicative (Manfredini et al., 2003; Kaya et al., 2010; Kundu et al., 2013).

The authors of this study focused on the evaluation of TMJ capsular distance, capsular width (measurement between the condylar laterosuperior surface and the articular surface) in patients with DDwR (Manfredini et al., 2003; Jank et al., 2005; Bas et al., 2011, Kim et al., 2021). They set several goals:

What is the difference of capsular distension in patients with TMJ pain and without pain?

What is the difference of capsular distension in patients with irregular and persistent TMJ pain?

What is the difference capsular distension in patients with and without palpatory TMJ pain?

What is the difference capsular distension in patients with and without a positive dynamic test?

Material and Methods

The study used the records of patients examined in a specialist outpatient clinic for TMJ disease to evaluate capsular distension. It was determined that the studied group would consist of 200 patients with anterior disc dislocation. In all these patients, US examination (Mindray DP-50, 7.5 MHz, Shenzen Mindray Bio-medical Electronics) was used to make the diagnosis, and the capsular width (measurement between the condylar laterosuperior surface and the articular surface) was recorded in all patients. The capsular widht value was measured not only on the side with disc dislocation but also on the side with physiological disc position. The data obtained was then the difference of capsular widht (CWD) of the two sides. This difference between the affected and unaffected side served as the JE value.

An X-ray (panoramic image) was performed in each patient to assess the bony changes of the TMJ structures.

Data from the examination record were used to determine whether or not the patient subjectively perceived TMJ pain, whether or not he subjectively rated his pain as constant or irregular (associated with jaw movement, mastication) in the last week before the examination. The patient's examination was also used to record whether pain was present on lateral TMJ palpation and whether TMJ pain was present on dynamic testing. The dynamic test entailed the patient performing mandibular movements (opening, closing, protrusion) with the examiner exercising a resistance against the direction of the movement.

Patients included in this study met the following criteria:

Including criteria: patients with unilateral TMJ involvement, according to clinical examination and according to ultrasound examination with a diagnosis of anterior disc displacement with reduction.

Excluding criteria: patients who presented changes in the shape of the articular head, socket and tuberosity (erosion, plating) on panoramic radiographs. Patients who had already undergone any TMJ therapy were not included. In addition, patients with endocrine, autoimmune disease, psychiatric therapy and patients who reported a history of facial skeletal trauma, higher stress load in the last year, bruxism were not included. Patients with palpatory pain of the masseter, neck and neck muscles were excluded.

The 200 patients included 169 females and 31 males (84.5:15.5%), with a mean age of 34.3 years (12–74 years). These were patients who were treated in the outpatient clinic for TMJ disorders between October 2022 and April 2023. 102 patients were completely pain free, 98 patients reported pain localized to the TMJ area. 28 patients perceived their pain in the last week before the examination as constant, 70 patients as irregular.

Statistical analysis
Liliefors test (based on Kolmogorov-Smirnov test) and Mann-Whitney test were used for statistical evaluation of the results.

Results

What is the difference of capsular distension in DDwR patients with and without pain?
98 patients (49%) perceived pain subjectively (regular and irregular). They were 86 females and 12 males, and the mean age was 36.1 years (14–74). The mean difference in capsular distension between TMJ on the affected and unaffected side was +0.41 mm in favour of the affected TMJ.

102 patients (51%) were without subjective pain perception. They were 83 women and 19 men, and the mean age was 32.4 years (range 12–62). The mean difference in capsular distension between the TMJ on the affected and unaffected side was +0.14 mm in favour of the affected TMJ.

Statistical evaluation
Liliefors test (Kolmogorov-Smirnov test): differences between patients with and without pain are statistically significant. Mann-Whitney $p<0.05$.

What is the difference of capsular distension in DDwR patients with irregular and persistent TMJ pain?
Of the 98 patients with pain, 70 patients reported their pain as irregular. They were 62 females and 7 males, with a mean age of 35.3 years (range 12–74). The mean difference in capsular distension between the affected and unaffected side was +0.41 mm in favour of the affected TMJ.

Twenty-eight patients perceived their pain as permanent. They were 24 women and 4 men, and the mean age was 38 years (range 22–64). The mean difference in capsular distension between the affected and unaffected side was +0.42 mm in favour of the affected TMJ.

Statistical evaluation
Liliefors test (Kolmogorov-Smirnov test): differences between patients with irregular and persistent TMJ pain were not statistically significant. Mann-Whitney $p>0.05$.

What is the difference in capsular distension in DDwR patients with and without TMJ palpation pain?
Palpation TMJ pain was noted in 22 patients (19 females, 3 males), with a mean age of 41.6 years (range 17–60). The mean difference in capsular distension between the affected and unaffected side was +0.5 mm in favour of the affected TMJ.

Palpation-free TMJ pain was noted in 178 patients (150 females, 28 males), and the mean age was 41.6 years (12–74). The mean difference in capsular distension between the affected and unaffected side was +0.24 mm in favour of the affected TMJ.

Statistical evaluation
Liliefors test (Kolmogorov-Smirnov test): differences between patients with and without TMJ palpation pain were statistically significant. Mann-Whitney $p<0.05$.

What is the difference in capsular distension in patients with and without a positive dynamic test?
Pain was present in 47 patients when the dynamic test was performed. They were 44 females and 3 males, the mean age was 39.6 years (16–74). The mean difference in capsular distension between the affected and unaffected side was +0.4 mm in favour of the affected TMJ.

No pain was elicited in 153 patients when the dynamic test was performed. They were 125 females and 28 males, and the mean age was 32.7 years (12–73). The mean difference in capsular distension between the affected and unaffected side was +0.23 mm in favour of the affected TMJ.

Statistical evaluation
Liliefors test (Kolmogorov-Smirnov test): differences between patients with and without a positive dynamic test were statistically significant. Mann-Whitney $p<0.05$.

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Discussion

Pain is not a typical symptom of disc dislocation with DDwR. Typical symptoms are sound phenomena (clicking), asymmetry of jaw movement. The cause of pain in disc dislocation can be extra articular (in the sense of myofascial pain) or intra articular. The origin of intra articular pain lies in the traumatization of the ligament capsule, traumatization of the retrodiscal tissue, leading to hyperemia of the tissues of the joint. As a consequence of hyperemia, free radicals and cytokines are produced, and traumatic arthritis develops (Laskin et al., 2006; Okeson, 2008). The inflammatory process in the joint may be accompanied by an increase in synovia, the presence of a pathological collection of fluid in the joint space. The presence of a pathological collection of fluid in the joint space is referred to as joint effusion (Manfredini et al., 2003; Bas et al., 2011; Kim et al., 2021).

The gold standard (if we disregard arthroscopy with direct visualization) for the assessment of inflammatory changes is MRI. JE can be recorded on MRI as a hyperintense signal within the articular space (Almeida et al., 2018). Another option for the diagnosis of JE is the use of US (Manfredini et al., 2003; Jank, et al., 2005; Bas et al., 2011; Almeida et al., 2018). The presence of inflammatory changes can be assessed by measuring the capsular width, which indicates the value between the condylar laterosuperior surface and the articular surface (Manfredini et al., 2003; Jank et al., 2005; Bas et al., 2011). Jank et al. (2005) reported an accuracy of US to detect of TMJ JE of up to 95%. Manfredini et al. (2003) presented a US value of capsular widht for JE above 2 mm. Bas et al. (2011) reported this value above 1.65 mm.

The use of US in the evaluation of JE means easier accessibility (the examination can be performed in a few minutes in the office), with significantly lower cost, and it is an examination without objective contraindications. Yet, the disadvantage of US is the subjective factor of interpretation of the results, which is related to the experience of the physician performing the US examination (Manfredini et al., 2003; Bas et al., 2011; Kundu et al., 2013; Severino et al., 2021). US has a number of limitations in the assessment of disc position and changes in joint head shape (Manfredini et al., 2003; Kaya et al., 2010; Kundu et al., 2013). However, for the assessment of JE, the use of US is comparable to the use of MRI (Nebeith and Speculand, 1991; Melis et al., 2007; Kundu et al., 2013; Almeida et al., 2018).

The results in the authors' work demonstrate that the presence of pain is related to the capsular widht value. By comparing the affected and unaffected joint, there was a statistically significant widening of the capsular widht in patients with TMJ pain than without pain. This is confirmed by the results of other authors who corroborate the association between increased intra-articular fluid and TMJ pain (Tanaka et al., 2002; Manfredini et al., 2003; Bas et al., 2011; Kim et al., 2021). The prevalence of JE in patients with TMJ pain is high, with Manfredini et al. (2003) reporting it to be 73–88%. Kim et al. (2021) evaluated capsular widht in patients with and without pain. The value of capsular widht in painful TMJs was 2.04 ± 0.52 mm, while in pain-free joints the value was 1.37 ± 0.36 mm. Bas et al. (2011) compared the mean capsular widht value with the mean pain value (visual analogue scale 0–10) in 91 patients with TMJ internal derangement. The mean pain value in patients with capsular widht up to 1.65 mm was 2.1, while in patients with capsular widht above 1.165 mm the pain value was 3.75. These values are consistent with the authors' results, with capsular distension being greater in patients with pain than in patients without pain. An interesting finding of the authors is that there was no statistically significant difference in the capsular widht value between patients with regular pain and patients with irregular pain.

Manfredini et al. (2003) confirmed the association of the presence of JE with clinical symptoms, pain on TMJ movement, pain on lateral and/or posterior TMJ palpation, and pain in the TMJ during dynamic tests. The authors' results support this finding. Pain during lateral TMJ palpation and during dynamic testing was associated with a statistically significantly higher capsular widht value than in patients with painless lateral palpation and painless dynamic testing.

Conclusion

The authors confirm the use of US as an ideal method for the diagnosis of JE. The authors' results demonstrate an association between the presence of JE and pain in patients with disc dislocation with reduction. Painful lateral palpation and painful dynamic test are associated with the presence of JE, confirming the fact that they are clinical indicators of an intra-articular inflammatory process.

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Aesthetic Chondrolaryngoplasty in Transgender Women

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Key words: Chondrolaryngoplasty – Thyroid cartilage – Transgender women

Abstract: A prominent thyroid cartilage is a typical male feature. Its reduction can achieve a female appearance of the neck in transgender women. The laryngeal prominence and notch area are gradually exposed as necessary under general anaesthesia, through an incision in the cervicomental angle. The cartilage is gradually reducing as planned. The wound is closed in layers. Chondrolaryngoplasty was done in 18 patients. No serious complications were observed in the patients. The aesthetic outcome was satisfactory in all patients. Chondrolaryngoplasty is well tolerated and effective procedure to reduce the thyroid cartilage and feminize the neck contour in transgender women.

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Introduction

Thyroid cartilage is part of the larynx. The male larynx and, in particular, the thyroid cartilage grows in puberty (Cohen et al., 2018). The cartilage is composed of the right and left lamina which are joined in the front and continue in the dorsolateral direction. The front angle of both laminae is approximately 90° in males and about 120° in females. A round edge – laryngeal prominence – is formed in the front where both laminae meet. In males, the larynx protrudes in the neck with its laryngeal prominence. The larynx does not protrude in females (Čihák, 2013). Aesthetic chondrolaryngoplasty is a surgical procedure that reduces the prominence of the thyroid cartilage (Cohen et al., 2018).

Chondrolaryngoplasty was first described by Wolfort and Parry (1975), and the technique was further specified by Wolfort et al. (1990). Conrad and Yoskovitch (2003) then Spiegel and Rodriguez (2008) used an endoscope and a needle, which they insert through the cartilage to visualize the location of the anterior commissure. Khafif et al. (2020) introduced computed tomography of neck and larynx into the preoperative examination to measure the distance between vocal cords and external thyroid cartilage.

The true vocal cords meet medially at the anterior commissure which attaches to the inside laminae of the thyroid cartilage in the midline, at approximately half way up the height of the cartilage (von Lanz and Wachsmuth, 1955; Conrad and Yoskovitch, 2003).

We present the group of 18 transgender women (male-to-female) with protruding thyroid cartilage. We also present our standard surgical procedure.

Patients and Method

Patients

Between January of 2016 and December of 2019, we performed chondrolaryngoplasty in 18 patients. The average age of these patients was 36 years (range, 25–51 years).

Technique

A horizontal incision, approximately 2 cm long, is made at the place of the natural crease in the area of the cervicomental angle, under general anaesthesia using endotracheal intubation. After dissection of the muscles and their lateral shifting, the perichondrium is cut; the perichondrium is then partially dissected from the outer and inner side of the cartilage. The laryngeal prominence and notch area are gradually exposed as necessary. A point at half height is marked. The cartilage is removed using a scalpel and a round diamond cutter to an extent that makes sure the vocal cords remain undamaged. Bleeding is carefully controlled with a bipolar cautery. The perichondrium is sutured using an absorbable material; the strap

Table 1: Clinical date

Patient	Age	Procedures at one time	Other procedures
1	38	chondrolaryngoplasty	
2	25	chondrolaryngoplasty	
3	47	chondrolaryngoplasty	
4	32	chondrolaryngoplasty	
5	39	chondrolaryngoplasty, genioplasty	rhinoplasty
6	42	chondrolaryngoplasty	
7	32	chondrolaryngoplasty, genioplasty	rhinoplasty, lip lift
8	33	chondrolaryngoplasty	rhinoplasty
9	31	chondrolaryngoplasty	
10	27	chondrolaryngoplasty, genioplasty, forehead contouring	rhinoplasty
11	51	chondrolaryngoplasty, genioplasty	
12	42	chondrolaryngoplasty	rhinoplasty, forehead contouring, genioplasty
13	35	chondrolaryngoplasty, genioplasty, mandibular angle reduction	rhinoplasty
14	32	chondrolaryngoplasty, genioplasty, mandibular angle reduction	rhinoplasty, forehead contouring
15	34	chondrolaryngoplasty, genioplasty	
16	45	chondrolaryngoplasty	
17	29	chondrolaryngoplasty	rhinoplasty, forehead contouring
18	36	chondrolaryngoplasty	

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muscles are reapproximated in the midline. The wound is closed in layers.

Antibiotics are administered in the perioperative period. A single intravenous corticosteroid dose is administered at the end of the procedure.

Results

Of the 18 patients, 8 patients had only chondrolaryngoplasty. Additional facial feminization surgery was done together with chondrolaryngoplasty in 7 cases. Additional facial surgery in the scope of feminization was done as a separate procedure in 3 cases (primarily only chondrolaryngoplasty). A total of 8 patients from this group underwent additional procedures (Table 1). No serious postoperative complications (characterised as changed voice) were observed in our patient group. The aesthetic outcome was satisfactory in all patients (Figure 1).

Discussion

A prominent thyroid cartilage is a typical male feature (Altman, 2012). Chondrolaryngoplasty is a safe and effective surgical procedure that can improve the neck appearance in transgender women (Lipschitz et al., 2017).

The extent of cartilage reduction is limited by the vocal cords attachment (Lipschitz et al., 2017). In connection with this procedure, it is necessary to balance aesthetic effect and function. With a conservative reduction, the patient may be dissatisfied after surgery; on the other hand, overresection can destabilize the anterior commissure tendo and change the voice (Cohen et al., 2018).

Wolfort et al. (1990) described that on the inside of laminae, the perichondrium and the thyrohyoid membrane are elevated to the level of the thyroepiglottic ligament.

As reported by Altman (2012), complication is rare. The risks of the surgery include a potential injury to the vocal cords and destabilization of the epiglottis (Altman, 2012). Injury to the anterior commissure can destabilize the vocal cords, thereby producing irreversible voice change (Spiegel and Rodriguez, 2008).

As found by Cohen et al. (2018) in connection with the thyreoepiglottic ligament based on intraoperative observation, the tracheal shave procedure does disrupt this attachment without reported postoperative dysphagia or aspiration.

Over the years, there have been increasing reports of the use of endoscopic visualisation of vocal cords and translaryngeal introduction of a needle to identify the level of anterior commissure, including presentation of results. The authors report a more radical and safe reduction and optimization of the results of the thyroid cartilage surgery in relation to this method (Spiegel and Rodriguez, 2008; Jazayeri et al., 2022; Vandenberg et al., 2023).

Chondrolaryngoplasty can be performed under local anesthesia (Altman, 2012) or local anesthesia with sedation (Spiegel and Rodriguez, 2008). Wolfort et al. (1990) described the surgery under general anesthesia using endotracheal intubation. Spiegel and Rodriguez (2008) under general anesthesia, used the laryngeal mask airway.

Surgery performed under general anesthesia using endotracheal intubation is preferred at our sites. The surgery is performed either separately or in combination with other feminization interventions. The cervicomental angle access localized in the crease

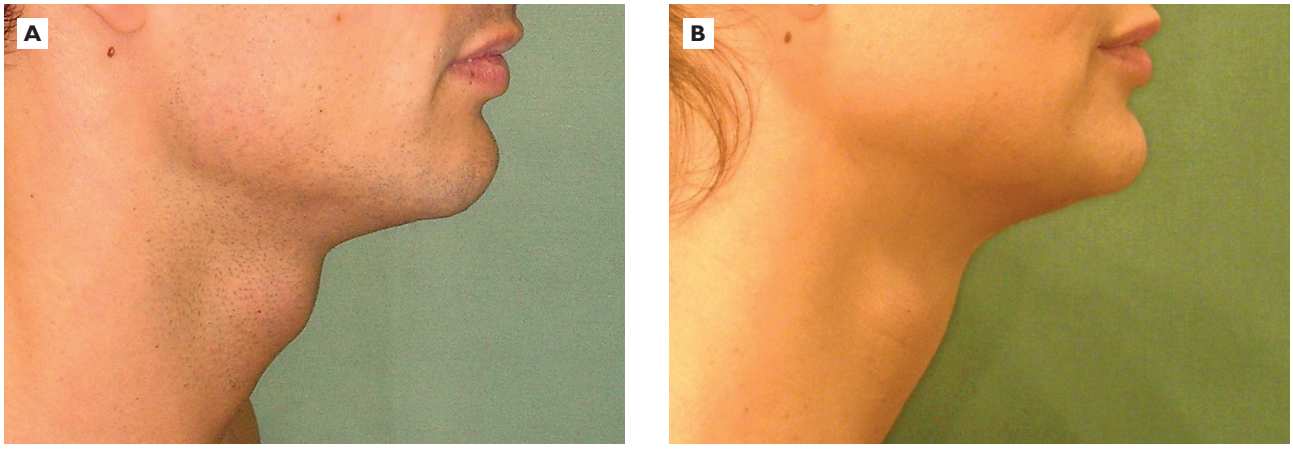

Figure 1: Result of chondrolaryngoplasty. A 32-year-old male-to-female: A) preoperative; B) 5-years postoperative. The patient also underwent a chin reduction.

is normally used. This approach provides a good view of the reduced part of the cartilage. The resulting scar is aesthetically satisfactory. A certain problem may be faced in cases, as reported by Cohen et al. (2018), where the angle is not as distinct and cannot hide the scar to a sufficient extent.

Ihnat et al. (2024) recommend locating the scar submentally, where it is less obvious. Khafif et al. (2020) recently described a novel technique for scarless chondrolaryngoplasty, transoral endoscopic vestibular approach and to report the results.

We did not observe any serious complications characterised as an injury to the vocal cords in our patients. Chondrolaryngoplasty can be performed alone or safely combined with other types of facial feminization surgery.

Conclusion

Aesthetic chondrolaryngoplasty is well tolerated and effective procedure to reduce the prominence of the thyroid cartilage. Patients should be aware that the extent of cartilage reduction is limited by anatomical structures and that the radicality of the procedure is limited, particularly with respect to voice preservation.

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Actual Problems of Osteoporosis and Osteopenia in Mountainous Regions of the Kyrgyz Republic

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Abstract: The aim of the study was to analyse the incidence of osteoporosis in mountainous regions of Kyrgyzstan, with special emphasis on the study of the influence of altitude on the incidence rate, as well as the identification of factors contributing to its development. For statistical analysis, aimed at assessing the relationship between altitude and the incidence of the disease, the Pearson correlation coefficient was applied. The survey reviewed data from five studies covering regions from altitudes ranging from 779 to 2,420 m above sea level. The incidence varied by region, gender and age group. The results showed no significant association between altitude and incidence of osteoporosis, but a trend towards lower prevalence was observed in high altitude areas, probably due to climatic conditions, physical activity and lifestyle. In addition to altitude, the study looked at other potential factors influencing the development of osteoporosis, including air pollution ($PM_{2.5}$, NO_2, NO_X), vitamin D levels and calcium intake. The results of the analysis of osteopenia showed that its incidence and frequency varied depending on age groups and region. In particular, in mountainous areas of Kyrgyzstan, there was a higher prevalence of osteopenia among older people, with the highest rates in urban and foothill regions. The practical significance lies in developing recommendations for osteoporosis prevention in mountainous Kyrgyzstan, improving diagnosis, treatment accessibility, and raising awareness of risk factors.

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Introduction

Osteopenia is a condition where bone density is reduced, but not to the level seen in osteoporosis. It is considered a precursor to osteoporosis, indicating an increased risk of developing the disease. The key difference is that osteoporosis leads to significant bone weakness, increasing the risk of fractures, while osteopenia is less severe and does not necessarily result in fractures. Osteoporosis is a systemic disease characterised by a decrease in bone mineral density (BMD) and impaired bone microstructure, resulting in increased fragility and fracture risk. Osteoporosis is not only a medical but also a socio-economic problem, contributing to the disability of the elderly population and increasing the burden on the health care system (Kashikova et al., 2024). The incidence of osteoporosis remains understudied in high mountainous areas, where chronic hypoxia, fluctuations in solar insolation and dietary patterns can significantly affect mineral metabolism. The absence of a national register, fragmented data, and limited access to diagnosis and prevention necessitate a comprehensive analysis of the impact of altitude on the prevalence of the disease in mountainous areas of Kyrgyzstan.

Bone tissue is constantly renewed through a remodelling process that is regulated by the balance between bone resorption by osteoclasts and bone formation by osteoblasts (Rowe et al., 2023; Latka et al., 2025). In osteoporosis, this balance is disturbed towards increased resorption or insufficient new bone formation. Osteoclast hyperactivity – increased bone resorption under the influence of parathyroid hormone, along with activation of receptor for nuclear factor kappa-B ligand and decreased osteoprotegerin levels. Osteoblast insufficiency – decreased differentiation and activity of osteoblasts due to hormone deficiency (estrogens, testosterone), vitamin D deficiency and chronic inflammation (Whitaker Elam, 2024).

Osteoporotic fractures are expected to increase by 68% by 2040 (Lewiecki et al., 2019). Femur fractures are considered one of the most dangerous among other fractures. About half of patients with this injury lose the ability to move independently, and mortality in women in the first year after fracture is 12–24%, compared to 33% in men (Zaheer and LeBoff, 2022). These findings support the importance of osteoporosis prevention and awareness of fracture risks in different age groups, especially among women over 70 years of age.

Primary osteoporosis is associated with aging and declining gender hormones, which deteriorates bone microstructure, decreases bone density, and increases fracture risk. Secondary osteoporosis is due to other diseases or their treatment (glucocorticoids [GCs], anti-epileptic drugs) and is more common in men (Lisiecka, 2024a, b). Predisposing factors include hyperparathyroidism, anorexia, malabsorption, hyperthyroidism, renal failure, Cushing's syndrome, prolonged immobility, secondary amenorrhoea, low weight, excessive exercise and hormone therapy. The risk increases with age, low weight, smoking, neurological disorders, early menopause, physical inactivity and after fractures (Lewiecki, 2024; Fathi, 2025). Patients with limited mobility, such as after spinal cord injuries, are particularly vulnerable (Porter and Varacallo, 2023).

There are many studies on osteoporosis that cover different aspects of the disease and risk factors, including the effects of altitude hypoxia, chronic diseases and genetic features. As a possible preventive approach of bone mass reduction Hao et al. (2023) proposed the application of pulsed electromagnetic fields (PEMF) to promote osteoblast activation and improve bone structure in rats exposed to hypobaric hypoxia.

The dynamics of fibrinogen during Ilizarov osteosynthesis was studied by Djumabekov et al. (2024). It was found that the fibrinogen level increases in high altitude conditions, indicating hypercoagulation and suppression of fibrinolysis. On day 21, the fibrinogen level reached 8.1 ± 0.3 g/l, which requires special attention during surgeries in such conditions. Among 395 people aged 50 years and above living in Madhesh region (Nepal), high risk of osteoporosis was found in 22.3% of participants. This risk was more common in women and underweight individuals. Chaudhary et al. (2024) also found that inadequate calcium intake was associated with an increased risk of osteoporosis.

Among residents of lowland Kyrgyzstan (Bishkek), reduced BMD was more common in patients with chronic obstructive pulmonary disease (COPD) and long-term glucocorticoid use (Asanbaeva et al., 2023). BMD was measured using dual-energy X-ray absorptiometry (DXA). Multiple logistic analysis revealed that COPD and GC intake were the most significant risk factors for osteoporosis.

In a study by Zhanybek Kyzy et al. (2023) studied bone composition in 800 Kyrgyz children of both genders aged 4–7 years. Anthropometric and bioimpedance analyses revealed individual variability in bone component content. In boys aged 4–7 years this indicator ranged from 3.24 to 6.02 kg, in girls – from 3.04 to 6.02 kg. The highest values of the bone component were observed in children with muscular somatotype, and the minimum values were observed in children with asthenoid and thoracic somatotypes. Boys of 4 and 7 years of age had higher values than girls of the same age.

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The studies included in this analysis were selected based on their relevance to the research topic, sample size, geographical coverage, and diagnostic methods. Relevance was ensured by focusing on studies specifically addressing osteoporosis and osteopenia in the Kyrgyz Republic and mountainous regions. Sample size was considered to ensure statistical robustness, with studies that included substantial participant numbers being prioritized. Geographical coverage was taken into account to provide a representative understanding of osteoporosis prevalence across different regions, including both mountainous and foothill areas. Diagnostic methods, such as ultrasound densitometry, were evaluated for consistency and reliability in measuring bone density. These criteria ensured that only studies with high methodological quality and pertinent data were included in the analysis.

This study will help to fill the lack of epidemiological data in the population of the Kyrgyz Republic, improve diagnosis, prevention and accessibility of treatment, and may become the basis for the development of national strategies to combat osteoporosis. The aim of this study was to assess the prevalence of osteoporosis in mountainous regions of the Kyrgyz Republic, to determine its relationship with altitude and to identify the key factors influencing the development of this disease. The tasks of the study included systematisation and analysis of data on the incidence of osteoporosis in mountainous regions of Kyrgyzstan, as well as comparison of the prevalence of the disease in different age and gender groups.

Material and Methods

For statistical analysis, data on the prevalence of osteoporosis in mountainous regions of the Kyrgyz Republic were collected on the basis of scientific publications and materials found in international databases. This approach allowed a comprehensive study of the influence of various factors on the development of osteoporosis. In addition, the study reviewed the literature on the peculiarities of mineral metabolism and bone tissue metabolism in people living in mountainous areas. Special attention was paid to the works devoted to the prevalence of osteoporosis and osteopenia among the population of Kyrgyzstan.

The studies of Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022) were considered. These studies examined various factors influencing the development of osteoporosis, including air pollution, vitamin D levels, and calcium intake, which may have an indirect effect on the incidence of the disease. The study analysed the general altitude ranges of the regions involved, with high-altitude areas ranging from 1,800 meters to over 3,000 meters above sea level, and lowland areas at approximately 800 meters. The altitude data were sourced from TessaDEM (2025, https://topographic-map.com).

To analyse the incidence of osteoporosis in mountainous areas of Kyrgyzstan, data were selected for regions with different altitudes: highland areas (Karakol city, located at an altitude of 1,801 meters; Naryn city, located at an altitude of 2,420 meters; At-Bashi village, located at 2,150 meters) and foothill areas (Bishkek city, at 848 meters; Osh city, at 1,068 meters; Jalal-Abad city, at 779 meters). The study period covers the years from 2019 to 2025. Data were analysed in different age groups: 18–39 years, 40–59 years, and 60 years and older.

For statistical processing of the data, the Pearson correlation coefficient was used to measure the degree of linear relationship between the altitude of the location of the region and the prevalence of osteoporosis. The correlation coefficient ranges from –1 (complete negative relationship) to +1 (complete positive relationship). Values close to 0 indicate no significant relationship between the variables. This method provided a way to objectively assess whether there was an association between terrain elevation and the incidence of osteoporosis, and to determine the influence of other factors such as age and gender.

The correlation coefficient was calculated separately for each age category, taking into account the incidence of osteoporosis and the altitude of the region. The association between altitude of the area and the prevalence of osteoporosis for men and women was also assessed to account for differences in the number of participants by sex in the studies.

Microsoft Excel software with the CORREL function was used to calculate the Pearson correlation coefficient, which allowed for an automated calculation of the linear relationship between variables. Regional heights and prevalence of osteoporosis in different age groups were entered into Tables, which allowed the calculation of correlation coefficients for each group separately. Additionally, the correlation between age, gender and incidence was analysed, which helped to identify groups at increased risk of osteoporosis.

The statistical significance of the results was assessed using GraphPad software's online calculator (P Value Calculator, 2025, https://www.graphpad.com/quickcalcs/pvalue1/), with the level of significance taken as $p<0.05$. This provided a strict statistical control and ensured the reliability of the findings. Using these methods, a more accurate and scientifically valid result was obtained to assess the effect of terrain

elevation on the prevalence of osteoporosis. Due to the limited availability of accurate elevation data for individual localities, average elevation values were used for the analyses. This could introduce errors into the data, especially in areas with pronounced elevation differences, which was also taken into account when interpreting the results obtained.

Results and Discussion

Review of osteoporosis research in the population of the Kyrgyz Republic

There is limited information on the incidence of osteoporosis in the Kyrgyz Republic. Based on the conducted work, five scientific studies on the prevalence of osteoporosis and osteopenia in the population of Kyrgyzstan were identified. Of these, studies by Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022) provided data on the regional affiliation of the studied groups (Table 1).

Karakol city (Issyk-Kul region), Naryn city (Naryn region) and At-Bashi villages (Naryn region), which are located in the higher mountainous areas of the country, can be attributed to the region with mountainous terrain. Foothill areas include Bishkek (Chui region), Osh and Jalal-Abad, which are located at the junction of mountains and lower areas.

Analyses of bone tissue status in mountainous regions of the Kyrgyz Republic have shown that the incidence of osteoporosis is lower in

Table 1: Research data on the prevalence of osteoporosis in mountainous regions of the Kyrgyz Republic

Author and date of the study	Tagaev (2022)	Tagaev et al. (2021)	Imanalieva (2020)	Imanalieva et al. (2019)	Mamatov et al. (2020)
Number of subjects	n=1,700	n=1,200	n=475	n=729	n=1,200
Age groups	60–74, 75–90 years	18–39, 40–59, >60 years	18–39, 40–59, >60 years	18–39, 40–59, >60 years	18–39, 40–59, 60–79 years
Gender (women/men, %)	51.8/48.2	51.7/48.3	61.3/38.7	64.9/35.1	57.6/42.4
Diagnostic method	ultrasound densitometry (heel bone)	ultrasound densitometry (heel bone)	ultrasound densitometry	ultrasound densitometry	ultrasound densitometry
Survey region	among patients of family medicine centres in Kyrgyzstan	Osh, Jalal-Abad	Karakol (Issyk-Kul region), as well as Naryn city and At-Bashi village (Naryn region)	Bishkek	Bishkek (Chui region), Karakol (Issyk-Kul region) and Naryn (Naryn region). Senior age groups – Chui region
Frequency of osteopenia (%)	60–74 – 43.5%, 75–90 – 36.5%, ≥60 years – 40.4%	Osh: 18–39 – 26%, 40–59 – 42.5%, >60 – 52.5%; Jalal-Abad: 18–39 – 25.5%, 40–59 – 44.6%, >60 – 60.7%	Karakol: 18–39 – 34.6%, 40–59 – 50.4%, >60 – 57.1%; Naryn and At-Bashi village: 18–39 – 30.3%, 40–59 – 54.8%, >60 – 77.4%	18–39 – 34.3%, 40–59 – 60%, >60 – 47.3%	18–39 – 38.9%, 40–59 – 60.2%, 60–79 – 50.2%
Frequency of osteoporosis (%)	60–74 – 31.1%, 75–90 – 45.5%, ≥60 years – 37.7%	Osh: 18–39 – 9%, 40–59 – 16.7%, >60 – 23.1%; Jalal-Abad: 18–39 – 6%, 40–59 – 21.2%, >60 – 28.7%	Karakol: 18–39 – 0.7%, 40–59 – 8%, >60 – 19.1%; Naryn and At-Bashi village: 18–39 – 1.1%, 40–59 – 7.1%, >60 – 9.7%	18–39 – 0.2%, 40–59 – 9.2%, >60 – 34.9%	18–39 – 5.5%, 40–59 – 8.9%, 60–79 – 40.3%
Range of overall osteoporosis prevalence (%)	18–39 years: 25.5–38.9 40–59 years: 42.5–60.2 ≥60 years: 40.4–77.4				
Range of overall osteoporosis prevalence (%)	18–39 years: 0.2–9 40–59 years: 7.1–21.2 ≥60 years: 9.7–34.9				

Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022)

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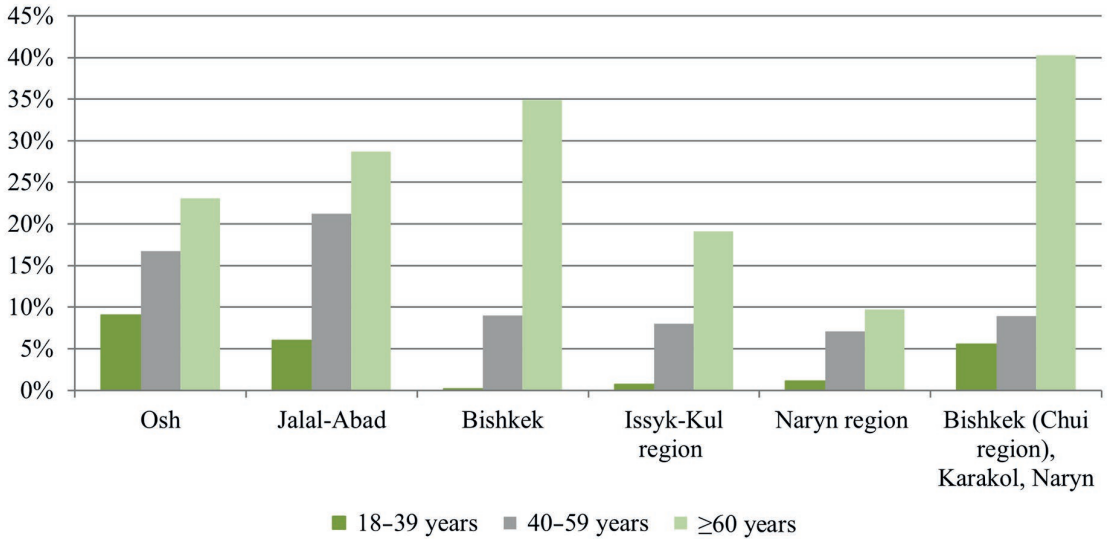

Figure 1: Frequency of osteoporosis in different regions of Kyrgyzstan by age groups.
Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022).

high-mountainous regions, such as Naryn and Issyk-Kul, which may be due to compensatory mechanisms caused by living in high-mountainous conditions (Figure 1).

The Issyk-Kul region is located in a mountainous area at an altitude of 2,471 metres (TessaDEM, 2025) and had the lowest incidence of osteoporosis among younger age groups. Among people older than ≥60 years of age, a relatively low incidence of the disease was recorded here compared to the foothill regions. This may indicate favourable climatic conditions, such as clean mountain air and sufficient sunlight, as well as lifestyle characteristics, including increased physical activity in these regions.

The Naryn city, located at an altitude of 2,420 meters (TessaDEM, 2025), which is part of the Naryn region (with an overall altitude of more than 3,060 meters), is characterised by low levels of osteoporosis among all age groups, especially the elderly. This may be due to the harsher climatic conditions, which may have favoured active physical activity in the daily lives of local residents, as well as possible environmental factors affecting health. At-Bashi village (Naryn region) is located at 2,150 metres above sea level (TessaDEM, 2025).

It is a high-altitude region, which makes it more susceptible to factors associated with osteoporosis risk, such as hypoxia and dietary patterns. Obviously, oxygen deficiency can significantly affect bone metabolism (Tulewicz-Marti et al., 2022). Studies indicating the effect of altitude on bone health are found in the scientific literature, but the results may be contradictory. The climatic conditions of Kyrgyzstan may have an additional impact on bone tissue regeneration processes. Factors that influence the healing of bone defects in high-altitude conditions include compensatory mechanisms for blood supply, such as vasoconstriction and increased levels of erythropoietin (EPO) and haemoglobin (Logvynenko et al., 2025).

Research by Chen et al. (2022) indicates that high sympathetic nervous system activity inhibits osteoblasts and stimulates osteoclast formation. Local acid-base compensation is accompanied by a decrease in pH, which hinders osteoblast differentiation and promotes osteoclast activation. Systemic compensation, characterised by a decrease in PaO_2 and an increase in $PaCO_2$, leads to an increase in pH, which in turn suppresses the proliferation of bone marrow precursor cells. It's worth noting that high-altitude conditions in this study were defined as altitudes above 2,500–3,000 metres above sea level.

In bone tissue, oxygen deficiency causes a reduction in osteoblast differentiation and activity, while simultaneously stimulating the maturation and function of osteoclasts (Łątka et al., 2024). Hypoxic conditions are associated with decreased bone formation and impaired mineralisation of the osteoblast matrix, which is explained by the suppression of osteoblast differentiation, largely through the Runx2, Sox9, Wnt, and PI3K/Akt signalling pathways (Usategui-Martín et al., 2022). Exposure to simulated very high altitude (5,500 m) causes significant changes in the skeletons of rodents. After 4 and 12 weeks of exposure to hypobaric hypoxia, Brent (2022) observed a 13–14% reduction in bone mineral density. This also supports the idea that oxygen deficiency is one of the factors that can trigger osteoporosis.

Table 2: Data for calculating the correlation coefficient by age groups

Region	Height (m)	Frequency of osteoporosis in the group		
		18–39 (%)	40–59 (%)	>60 (%)
Osh	1,068	9.0	16.7	23.1
Jalal-Abad	779	6.0	21.2	28.7
Bishkek	848	0.2	9.2	34.9
Karakol	1,801	0.7	8.0	19.1
Naryn and At-Bashi villages	2,420	1.1	7.1	9.7
Bishkek	848	5.5	8.9	40.3
Karakol	1,801	5.5	8.9	40.3
Naryn	2,420	5.5	8.9	40.3

Note: the repeated cities in Table (Bishkek, Karakol and Naryn) are due to the fact that the study by Mamatov et al. (2020) presented one common indicator for all three cities. Therefore, the same data are shown for these cities. Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022)

Therefore, altitude above sea level can have varying effects on bone tissue health. While the hypoxia that occurs at extremely high altitudes contributes to a decrease in bone mineral density, other factors predisposing to osteoporosis may be at play in relatively lower mountainous regions (Tulewicz-Marti et al., 2023; Logvynenko and Bursova, 2024). This is supported by epidemiological data from the Osh and Jalal-Abad regions (average altitude of Osh is around 1,068 metres, Jalal-Abad is approximately 779 metres) (TessaDEM, 2025), where the prevalence of the disease among people over 40 is higher than in high-altitude areas. The city of Bishkek, located at an altitude of about 848 metres (TessaDEM, 2025), is characterised by a high level of osteoporosis (34.9%) among people over 60. This may be related not only to altitude but also to the characteristics of urban lifestyles, diet, levels of physical activity, and other factors typical of large cities.

Literature data indicates that anthropogenic stress in densely populated urbanised areas leads to a significant increase in the concentrations of nitrogen dioxide (NO_2), nitrogen oxides (NO_X), and fine particulate matter ($PM_{2.5}$), which is due to emissions from road transport, industrial facilities, and slow dispersion rates of pollutants due to specific urban aerodynamics (Wang et al., 2022; Bikis, 2023). Air pollution increases the risk of osteoporosis and fractures.

Polluted air amplified the influence of genetic factors on the development of osteoporosis (Yu et al., 2023). The frequency of osteoporosis in the mountainous regions of Kyrgyzstan is lower, which may be related to adaptation mechanisms to high-altitude conditions, physical activity, and environmental factors, whereas in urban and pre-mountainous areas, the incidence is higher due to air pollution, a sedentary lifestyle, and other urban risks.

Relation of altitude to the incidence of osteoporosis

The results of the study indicate that there is no association between height and the incidence of osteoporosis in the age groups considered. The obtained correlation coefficient value for the 18 to 39-year group is close to zero (–0.255), indicating a very weak negative association between height and osteoporosis incidence in this age group. The p-value of 0.545 significantly exceeds the standard threshold of statistical significance of 0.05, indicating that this association is insignificant. Thus, it can be concluded that there is no statistically significant relationship between height and incidence of osteoporosis in the age group of 18–39 years (Table 2). For 40–59 years, the correlation coefficient was –0.581 indicating a moderately significant negative relationship between height and incidence of osteoporosis.

However, the p-value of 0.132 also does not reach the level of statistical significance, which means that this relationship is also not statistically significant. That is, although the correlation coefficient indicates some decrease in the incidence of osteoporosis with increasing altitude, this relationship is not statistically supported. The correlation coefficient for the population over 60 years of age also indicates a weak negative relationship between height and osteoporosis incidence (–0.273). However, the p-value of 0.513 is significantly higher than 0.05, which also indicates that there is no statistically significant relationship between these variables in the older age group.

Analysis of the data obtained did not reveal a statistically significant correlation between altitude and the incidence of osteoporosis in the studied age groups. However, other studies emphasise the possible influence of altitude on bone metabolism. For example, a cohort study by Zuo et al. (2022)

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Table 3: Data for calculating the correlation coefficient for men and women

Region	Height (m)	Men	Women
Jalal-Abad, Osh	923	13.1	22.3
Bishkek	848	19.3	19.6
Bishkek	848	12.8	15.5
Karakol	1,801	12.8	15.5
Naryn	2,420	12.8	15.5

Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022)

showed that living at high altitudes can negatively affect bone mineral density, increasing the risk of osteoporosis. The authors found an inverse relationship between altitude and quantitative ultrasound index of the heel bone (QUI) and also examined the influence of gut microbiota, including *Catenibacterium*, on bone health.

Short-chain fatty acid (SCFA) concentrations, associated with a lower risk of osteoporosis, were higher in residents of lowland regions. Other data indicate an association of higher altitude with better BMD scores in women with no physical activity habits (Takeda et al., 2015). These findings emphasise possible mechanisms of bone adaptation to high altitude conditions and provide a basis for further research on prevention.

The imbalance in gender representation across the studies can significantly affect the overall conclusions, especially since osteoporosis is more prevalent in women. In particular, women are more predisposed to the disease due to factors such as hormonal changes during menopause, which accelerate bone density loss. The differences in the proportions of men and women in the studies can introduce variability that may confound the relationship between altitude and osteoporosis prevalence.

For instance, in Table 3, the proportions of men and women vary considerably between regions. In some cases, such as in the Jalal-Abad and Osh regions, the proportion of women is significantly higher (22.3%) than men (13.1%), which could skew the results, as the higher female representation could amplify the observed prevalence of osteoporosis. Conversely, regions like Bishkek and Naryn show more balanced or even male-dominated proportions, which may yield different findings. Since four studies (Imanalieva et al., 2019; Mamatov et al., 2020; Tagaev et al., 2021; Tagaev, 2022) report data on osteoporosis separately for men and women, but the works by Mamatov et al. (2020) and Tagaev et al. (2021) provide generalized data for cities without specifying the level of morbidity, this inconsistency complicates the interpretation of results. The varying gender proportions in these studies might therefore obscure the true impact of altitude on osteoporosis, particularly if the risk factor for women is not adequately accounted for.

Data analysis shows a negative correlation between altitude of the area and the incidence of osteoporosis in men (–0.428) and women (–0.577), but the association is statistically insignificant ($p>0.05$). This indicates that there is no clear relationship between region height and incidence of osteoporosis in the study sample. The results show similar values of correlation coefficient with the results of all 5 studies,

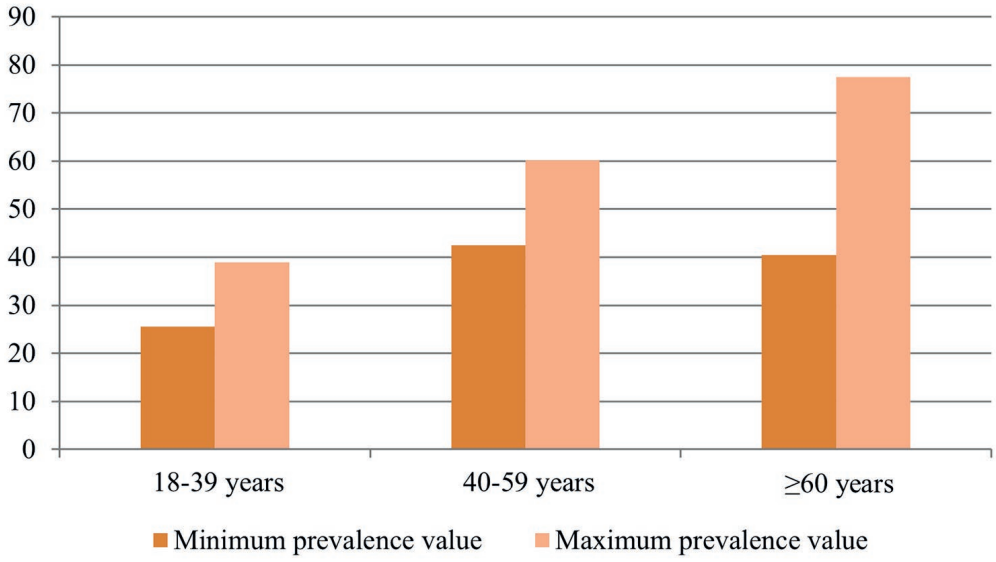

Figure 2: Range of osteopenia frequency values for each age group.
Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022).

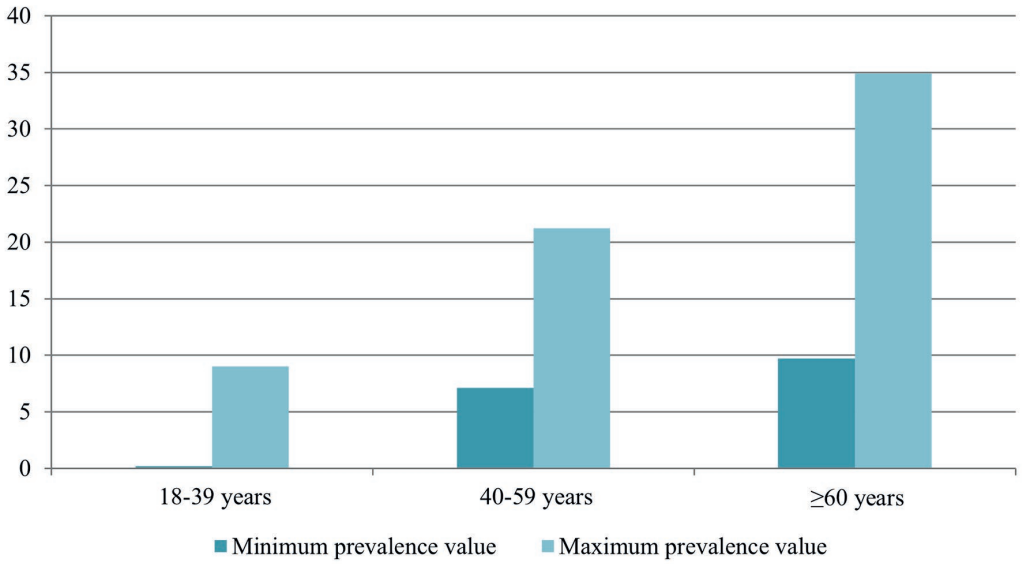

Figure 3: Variation in the incidence of osteoporosis among different age groups.
Source: compiled by the authors based on Imanalieva et al. (2019), Imanalieva (2020), Mamatov et al. (2020), Tagaev et al. (2021), Tagaev (2022).

indicating that the difference in gender ratio in these studies does not significantly affect the main results.

High rates of osteopenia (54.6%) and osteoporosis (9.6%) in postmenopausal Tibetan women were found by Zhong et al. (2023). The key risk factors were age, body mass index, height of residence and creatinine level. However, other findings were reported in a population in Sichuan Province, China, the incidence of osteopenia and osteoporosis decreased with increasing altitude, especially among women and middle-aged individuals (Yang et al., 2024). This study revealed an age-dependent prevalence of osteopenia and osteoporosis: their incidence increased in older age groups, confirming age as a key risk factor for the development of these conditions (Figures 2 and 3).

For osteoporosis, the correlation coefficient was 0.992, although the association was not statistically significant ($p=0.08$). The significant variation in the prevalence of osteoporosis (from 9.7 to 34.9 for the group over 60 years of age) may be due to differences in regional characteristics (Figure 3).

The relatively high rate of osteoporosis and osteopenia already at the age of 18–39 years (up to 38.9%) may indicate the presence of predisposing factors that require further study. This fact emphasises the need for early prevention and identification of factors contributing to bone mass loss, starting from childhood and adolescence. Optimal bone development in children and adolescents requires a balanced diet, physical activity and early correction of risk factors, including calcium deficiency and sedentary behaviour (Mora and Gilsanz, 2003; Berezenko et al., 2021). None of the five studies reviewed considered important determinants of osteoporosis such as nutrition, physical activity level and genetic factors. The lack of information on these indicators limits the possibility of comprehensive analyses and does not permit an assessment of their influence on the relationship between height and the incidence of osteoporosis.

Risk factors for osteoporosis in Kyrgyzstan: vitamin D, calcium and geographical features

Given the expected increase in the number of people with osteoporosis, the problem of vitamin D – 25(OH)D – deficiency becomes even more urgent, as this deficiency significantly affects bone health (Lewiecki et al., 2019). Vitamin D deficiency is a significant factor contributing to the deterioration of BMD, which is associated with impaired calcium metabolism and increased risk of osteoporosis.

According to Isupova and Isupov (2021), seasonal fluctuations of 25(OH)D levels have been detected in the blood serum of Kyrgyz residents. In spring its concentration is 41.7 ± 2.3 nmol/l (95% CI [confidence interval] 37.1–46.4), and in autumn – 50.0 ± 2.1 nmol/l (95% CI 45.9–54.2), indicating vitamin D deficiency. This confirms the need to develop comprehensive measures to prevent vitamin D deficiency at the national level.

Thus, despite the geographical location of the country and the duration of sunshine, vitamin D levels do not reach optimal health values. The representativeness of the sample for the entire population of Kyrgyzstan allows general conclusions to be drawn about the prevalence of vitamin D

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deficiency, but may smooth out regional differences. To identify specific factors affecting 25(OH)D levels in mountainous and lowland areas, additional stratification of the sample by geographical zone is required.

This approach will provide a more accurate identification of local characteristics that may influence vitamin D levels in Kyrgyzstan. Vitamin D deficiency remains a significant global problem with a high prevalence among populations in different regions and groups (Al-Maqtari e al., 2024). Despite some reduction in deficiency levels since 2010, it remains a serious health risk factor. According to Cui et al. (2023), women, high-latitude residents, and populations in low-income countries are particularly vulnerable to osteoporosis because hormonal changes, especially the decline in estrogen during menopause, accelerate bone loss in women, while high-latitude residents have limited sunlight exposure, reducing vitamin D synthesis essential for calcium absorption and bone mineralization. Populations in low-income countries are at higher risk due to limited access to healthcare, poor nutrition, and delayed diagnosis, all of which contribute to decreased bone density.

Altitude significantly affects the level of ultraviolet (UV) radiation reaching the earth's surface. The higher the terrain, the shorter the path that UV takes through the atmosphere, which favours more vitamin D synthesis in the skin (Antipikin et al., 2019). Wacker and Holick (2013) analysed vitamin D synthesis at different geographical locations: Agra (169 m), Kathmandu (1,400 m), and Everest base camp (5,300 m). Their results showed that pre-vitamin D formation was minimal in Agra in November, while at 5,300 m, it increased almost fivefold under the same latitudinal conditions. This emphasises the importance of considering altitude factors when investigating vitamin D levels in different regions, especially in high altitude areas.

Data on the frequency and amounts of dietary calcium intake among the Kyrgyz population, including milk and dairy products, are limited in the literature. Consumption of dairy products contributes to the bone health of the population, as milk is a major source of calcium and vitamins D and B12, which are essential for bone health (Ilesanmi-Oyelere and Kruger, 2020). Consumption of dairy products among children and adolescents in Kyrgyzstan remains insufficient: only 33.3% of respondents consume them daily, while 9.0% practically exclude them from their diet. In addition, less than a quarter of adolescents regularly include cheese and cottage cheese in their diets, which may reduce the intake of calcium and other important nutrients (Tolebaeva et al., 2021; Nabiyev et al., 2024). Dietary calcium and vitamin deficiencies are particularly critical for children and adolescents, as they can negatively affect bone development and predisposition to osteoporosis.

To better understand the influence of factors on bone health, it is important to consider the specific physiological state in mountainous regions, where living conditions can have a significant impact on mineral metabolism. In a study by Tashieva et al. (2024), 190 pregnant women from high mountainous regions of Kyrgyzstan (>2,500 m above sea level) and Osh city were examined. It was found that women living in the mountains for a long time have hypoestrogenaemia and compensatory hypocalcaemia, indicating an influence on the course of pregnancy and the process of childbirth. Animal experiments confirmed changes in bone tissue, indicating the development of osteopenia (Ilderbayev et al., 2021). Nutritional characteristics, including whey intake, have been found to influence calcium metabolism and hormonal status.

A significant decrease in bone mineral density in patients over 70 years of age was recorded by Amanalieva (2014). Women suffered from reduced BMD 2.8 times more often than men, especially those who underwent early menopause. More than 80% of patients were vitamin D deficient, and 93.7% with low levels of physical activity experienced a marked decrease in BMD. The greatest risk factor for osteoporosis was found to be low body mass index (BMI) and inadequate calcium intake (Nurgaziyev et al., 2024). These results emphasise the importance of monitoring calcium metabolism and hormonal status in women, especially those living in high altitude areas, as such changes may increase the risk of osteoporosis and fractures, including severe injuries like hip fractures.

Age and height increased the risk of major osteoporotic fractures, while weight had a protective effect in a study by Song et al. (2023). Clear differences by region in Canada in the incidence of low traumatic fractures, which did not always correlate with BMD, were found by Langsetmo et al. (2008). Fracture risk was found to be more dependent on complex factors including age, frequency of falls, previous fractures and vertebral deformity. This confirms that osteoporosis and its consequences are not only determined by BMD but also by other factors, emphasising the need for a multifactorial approach to risk assessment. According to a multifactorial analysis by Özmen et al. (2024), among postmenopausal women, the risk of osteoporosis was increased 2.46-fold in smokers, 3.78-fold in diabetic patients, and 6.23-fold in those with previous fractures. At the same time, increased BMI had a protective effect.

In Kyrgyzstan, osteoporosis is a growing problem associated with vitamin D deficiency and calcium deficiency in the diet. Seasonal variations in vitamin D and dietary patterns increase the risk of the disease. High altitude, hypoestrogenemia and hypocalcaemia in women also contribute to osteoporosis, which requires further attention. Age and level of physical activity play an important role in the development of the disease, emphasising the need for a comprehensive approach to prevention and treatment.

Thus, the presence of additional risk factors, such as high altitude, poses a challenge for the health care system to improve diagnosis and risk assessment of osteoporosis, as well as to develop recommendations for prevention aimed at reducing the incidence and preventing severe health consequences for the population.

A limitation of the study was the lack of data on individual regions, the small sample size, and the limited number of studies on the incidence of osteoporosis in Kyrgyzstan, which reduced the completeness of the information provided. The reviewed studies lacked information on the influence of nutrition, physical activity and genetic factors, which did not allow their role in the identified patterns to be taken into account. In two studies, gender was either not reported or was presented in a generalised form, which may have affected the accuracy of the results. The sample size should be increased to increase the power of the analyses. Expanding the geographical scope of the study to focus on the mechanisms of altitude exposure will provide more accurate, valid and meaningful data that will be important for the development of effective interventions to prevent and treat osteoporosis in the Kyrgyz Republic.

Conclusion

The review covers five scientific works investigating the prevalence of osteoporosis and osteopenia in Kyrgyzstan. The total number of study participants ranged from 475 to 1,700. In the age group 18–39 years, the incidence of osteopenia ranged from 25.5 to 38.9% and osteoporosis from 0.2 to 9%. For the 40–59 age group, these rates ranged from 42.5 to 60.2% for osteopenia and from 7.1 to 21.2% for osteoporosis. Over 60 years of age, the rates of osteopenia ranged from 40.4 to 77.4% and osteoporosis from 9.7 to 34.9%.

At the same time, studies demonstrated that in highland regions (Naryn and Issyk-Kul regions) the incidence of osteoporosis among the elderly is lower. In foothill regions such as Bishkek, Osh and Jalal-Abad, a higher incidence of osteoporosis was observed among people over 40 years of age. Age correlation with the prevalence of osteoporosis was found ($r=0.992$) but did not show statistical significance ($p=0.08$).

Analysis showed that the Pearson correlation coefficient between regional height and osteoporosis incidence was –0.255 (18–39 years), –0.581 (40–59 years) and –0.273 (≥60 years). The p-values obtained (0.545; 0.132; 0.513) did not reach statistical significance, indicating that there was no significant association between height and incidence of osteoporosis in the age groups studied. The study emphasises the importance of considering climatic and geographical factors in the prevalence of osteoporosis, noting that although altitude is not a major risk factor, it may have an indirect influence through environmental conditions and lifestyle.

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Non-Hodgkin's Lymphoma Mimicking Orbital Cellulitis: A Diagnostic Dilemma

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Abstract: We reported a rare case of disseminated diffuse large B-cell lymphoma (DLBCL) initially presenting as refractory orbital cellulitis in a 53-year-old male. The patient presented with acute periorbital swelling, pain, and restricted ocular motility, unresponsive to broad-spectrum antibiotics. Magnetic resonance imaging (MRI) revealed extensive sinusitis with a peripherally enhancing medial extraconal orbital mass and adjacent bony erosions. A prompt functional endoscopic sinus surgery and histopathology revealed a poorly differentiated malignant neoplasm. Immunohistochemistry confirmed DLBCL, non-germinal center B-cell subtype. Systemic evaluation with whole-body MRI and fluorodeoxyglucose-positron emission tomography demonstrated widespread dissemination involving the lungs, gastrointestinal tract, adrenal glands, and skeleton. The patient was initiated on required chemoimmunotherapy with central nervous system prophylaxis and remains under oncology follow-up. This case highlights the diagnostic challenge posed by orbital lymphoma mimicking infectious orbital cellulitis and underscores the need for early imaging and tissue diagnosis in culture-negative, non-resolving cases. A high index of suspicion and multidisciplinary collaboration are essential for timely diagnosis and effective management.

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Introduction

Orbital cellulitis is a serious ophthalmic emergency with potential for both vision and life-threatening complications, characterized by infectious and inflammatory involvement of the orbital soft tissues (American Academy of Ophthalmology: Basic and Clinical Science Course 2019–2020). The condition most commonly arises from contiguous spread of infection from adjacent periorbital structures such as the paranasal sinuses, facial skin, eyelids, lacrimal sac, or odontogenic sources. Additional etiologies include exogenous insults – such as trauma, retained foreign bodies, or iatrogenic introduction during surgical interventions – and hematogenous dissemination via septicemia or bacteremia with embolic phenomena. Less commonly, primary orbital infections, including endophthalmitis and dacryoadenitis, may serve as the nidus (Singh et al., 2018).

Although bacterial sinusitis remains the predominant cause, atypical and non-infectious etiologies must be carefully considered in cases with poor therapeutic response. Notably, masquerading neoplastic processes – including choroidal melanoma (Singh et al., 2018) and metastatic lesions from primary bronchogenic (Kumar and Issing, 2011) or urothelial carcinomas (Bobadilla-Romero et al., 2022) – have been documented and warrant inclusion in the differential diagnosis of refractory orbital cellulitis.

Case report

A 53-year-old male presented to the ophthalmology outpatient department with a 15-day history of acute-onset right side periorbital swelling (Figure 1)

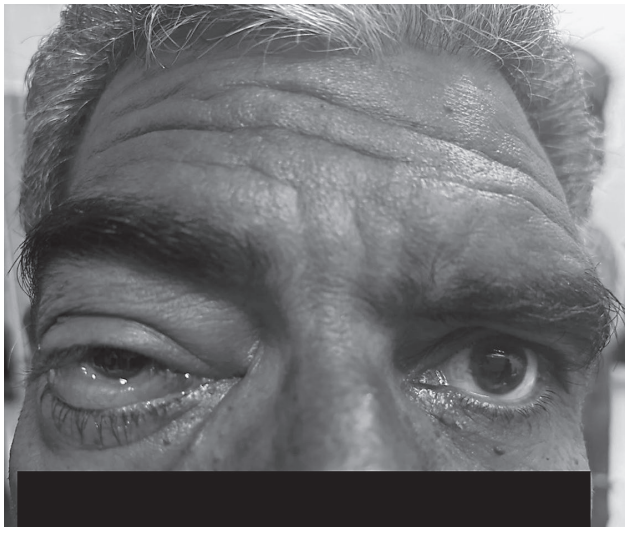

Figure 1: Presentation with right side periorbital swelling, lid swelling and conjunctival chemosis.

associated with pain, particularly aggravated by ocular movements. On clinical examination, best-corrected visual acuity (BCVA) in the right eye was 6/12 with an intraocular pressure of 14 mm Hg. Notable findings included mechanical ptosis, marked conjunctival congestion, severe chemosis, and gross restriction of extraocular movements in all directions (Figure 2). The pupillary reaction to light was preserved, and fundus evaluation was unremarkable. Ocular examination of left eye was normal. Based on the clinical features, a provisional diagnosis of right-sided orbital cellulitis was made. The patient was admitted and initiated on broad-spectrum intravenous antibiotics – ceftriaxone 1 g twice daily and metronidazole 400 mg thrice daily – after sending appropriate blood and urine samples for required investigations.

Despite appropriate medical therapy, the patient exhibited clinical deterioration, marked by worsening chemosis and pupillary involvement. Magnetic resonance imaging (MRI) of the brain, orbits, and paranasal sinuses demonstrated extensive mucosal thickening in the right maxillary, ethmoidal, and frontal sinuses with signal alterations along the maxillary floor, as well as a peripherally enhancing soft tissue lesion in the medial extraconal orbital space with suspected erosions of the lamina papyracea, orbital roof, and posterior maxillary wall. In light of these findings, the otorhinolaryngology team proceeded with functional endoscopic sinus surgery (FESS), during which representative tissue specimens were obtained for histopathological analysis. Given the radiological evidence of atypical enhancement and osseous destruction, a whole-body MRI was subsequently performed, revealing infiltrative lesions in the apical lung segments, humerus, radius, and multiple vertebral bodies – highly suggestive of systemic malignant dissemination.

Histopathological examination of tissue obtained via endoscopic debridement (including intra-orbital, paranasal, turbinate, and medial wall specimens) revealed a poorly differentiated malignant neoplasm composed of medium to large syncytial atypical cells arranged in diffuse sheets accompanied by dense lymphoplasmacytic infiltration. Special stains were negative for fungal or acid-fast organisms. The undifferentiated morphology gave the differentials suggestive of either nasopharyngeal carcinoma or non-Hodgkin lymphoma. Immunohistochemistry (IHC) demonstrated strong positivity for LCA, CD20, MUM1, BCL6, and BCL2, with negativity for CD3, CD30, CD10, and C-MYC, confirming a diagnosis of diffuse large B-cell lymphoma (DLBCL), non-germinal center B-cell (non-GCB) subtype.

A prompt referral to the oncology department with a whole-body fluorodeoxyglucose-positron

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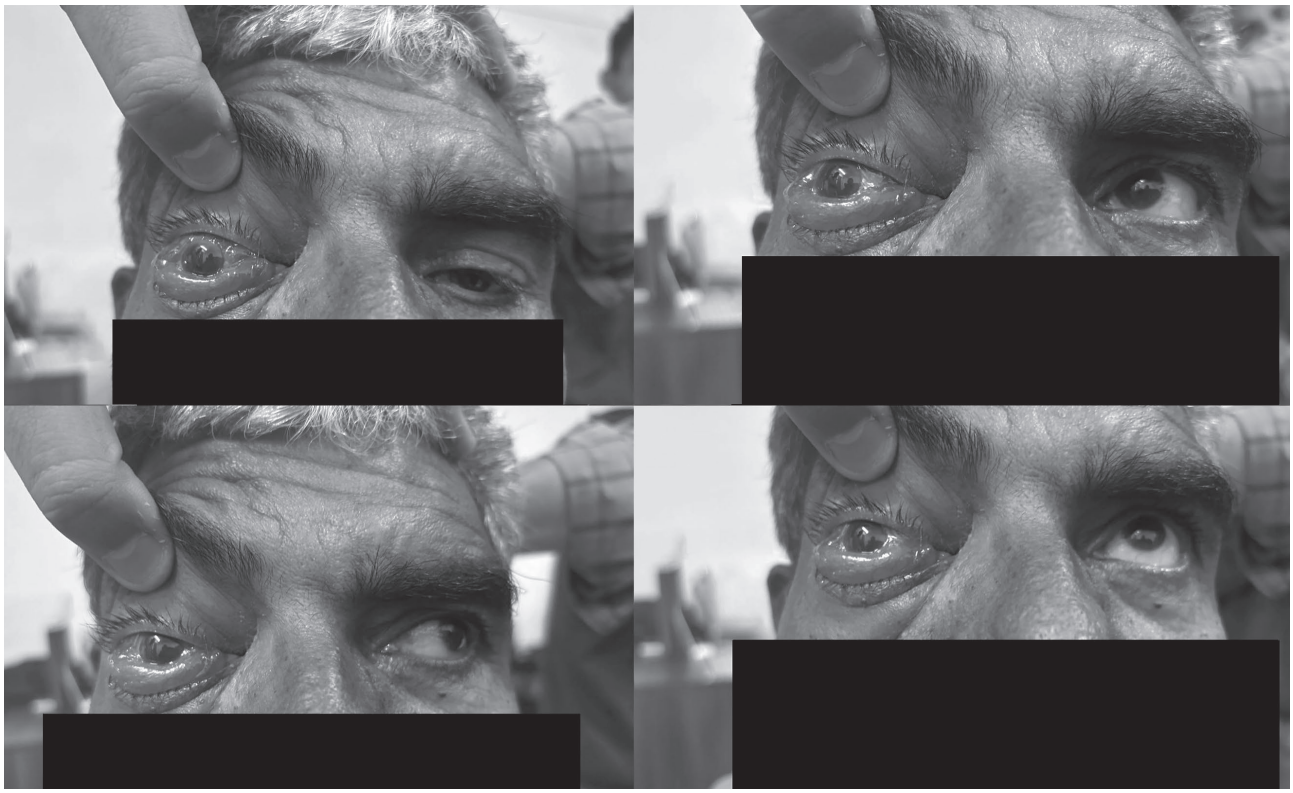

Figure 2: Restriction of extra-ocular movement in all gaze position.

emission tomography (FDG-PET) scan revealed a metabolically active mass involving the right orbit, paranasal sinuses, and adjacent naso-oropharyngeal structures, with intraconal extension and widespread lymphadenopathy. Systemic dissemination was evident, including pulmonary, gastrointestinal, peritoneal, adrenal, and osseous involvement – consistent with advanced hemato-lymphoid malignancy. A multidisciplinary tumour board recommended initiation of combination chemoimmunotherapy tailored to the diagnosis of high-grade B-cell lymphoma. The patient was started on the R-CHOP regimen, comprising Rituximab (600 mg), Cyclophosphamide (1,000 mg), Vincristine (2 mg), Doxorubicin (Adriamycin, 65 mg), and oral Prednisolone. Pegfilgrastim (6 mg subcutaneously) was administered for hematopoietic support, and intrathecal Methotrexate (1.5 mg) was included as prophylaxis against central nervous system involvement.

The patient successfully completed the prescribed chemotherapy cycles and is currently under maintenance surveillance, with ongoing follow-up at the oncology center.

Discussion

Non-Hodgkin lymphoma (NHL) represents a heterogeneous group of lymphoid malignancies derived from B, T, or NK cells, and is classified into indolent or aggressive subtypes. Risk factors include immunosuppression, chronic infections, and autoimmune conditions. Extranodal involvement – such as in the central nervous system, gastrointestinal tract, bone marrow, or orbit – is not uncommon. Diagnosis relies on histopathology, immunohistochemistry, and positron emission tomography-computed tomography (PET-CT) imaging, while treatment ranges from observation in indolent cases to systemic chemoimmunotherapy (e.g., R-CHOP) for aggressive forms. Prognosis is influenced by disease stage, age, lactate dehydrogenase levels, and extent of extranodal disease.

Although rare, orbital lymphoma can closely mimic the clinical features of orbital cellulitis, leading to diagnostic delays and suboptimal early management. Several case reports have illustrated this diagnostic pitfall. Ishak et al. (2024) described a 71-year-old woman with recurrent periorbital swelling, erythema, and progressive vision loss – initially misinterpreted as sphenoid meningioma or metastatic disease on imaging – who exhibited only transient improvement with intravenous antibiotics. Subsequent histopathological analysis confirmed high-grade B-cell lymphoma, underscoring the need for early consideration of neoplastic etiologies in atypical presentations (Ishak et al., 2024).

Other reports have documented cases of diffuse large B-cell lymphoma and small lymphocytic lymphoma presenting with classical features of orbital cellulitis but demonstrating poor or absent response to standard antimicrobial regimens, with final diagnosis established only after biopsy and immunohistochemical analysis (Mak et al., 2010; Chaurasiya et al., 2021). Extranodal NK/T-cell lymphomas have also been shown to present with clinical signs such as periorbital edema, erythema, and orbital soft tissue inflammation, closely resembling infectious etiologies and further compounding diagnostic challenges (Barkhuysen et al., 2008; Shah et al., 2017).

Scientific highlights

This case provides several important scientific insights into the management of orbital cellulitis. First, it demonstrates that refractory orbital cellulitis requires a high index of suspicion for underlying malignancy, especially in older patients. The role of MRI in identifying atypical patterns and guiding further diagnostic procedures is critical. Second, it emphasizes the importance of obtaining tissue for histopathological examination in cases with non-resolving clinical features. Finally, the addition of systemic steroids, while providing temporary relief, highlighted the aggressive nature of the underlying metastatic carcinoma, influencing our understanding of inflammatory responses in malignancy-related orbital cellulitis.

Conclusion

This case illustrates the importance of maintaining a broad differential diagnosis when managing cases of orbital cellulitis that do not respond to standard treatment. A multidisciplinary approach involving ophthalmology, radiology, otorhinolaryngology, and pathology was essential in reaching the correct diagnosis. Clinicians should be vigilant in recognizing atypical presentations and ensure timely investigation and referral in refractory cases of orbital cellulitis.

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Cytological Diagnosis of a Rare Case of Buccal Mucosa Squamous Cell Carcinoma with Malignant Pleural Effusion and Review of Literature

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Key words: Squamous cell carcinoma – Oral cavity – Malignant effusion – Pleura – Cytomorphology

Abstract: Oral squamous cell carcinoma (OSCC) is a major global health concern, especially in India, where it is one of the primary causes of cancer-related fatalities. OSCC is notorious for its propensity to spread to distal sites such as the lungs, bones, and liver, but malignant pleural effusions resulting from OSCC are extremely uncommon. This case report details an unusual presentation of OSCC in a 61-year-old male presenting with bilateral malignant pleural effusion from a primary buccal mucosa squamous cell carcinoma with no lung involvement. Through cytological analysis and immunocytochemistry, we confirm the diagnosis of metastatic squamous cell carcinoma, highlighting the significance of comprehensive diagnostic approaches.

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Introduction

Oral squamous cell carcinoma (OSCC), which accounts for more than 90 percent of all oral cavity malignant neoplasms, is the seventeenth most common cancer worldwide. It ranks third among the numerous cancer types that cause mortality in India, is the most prevalent cancer in men, and is the third most frequent cancer overall (Nethan et al., 2022). It is the most prevalent malignancy in developing nations, and its incidence is rising. In southeast Asia, the oral cavity is the most prevalent site for head and neck squamous cell carcinoma (SCC). The population's pervasive use of smokeless tobacco products, such as pan and supari, is the primary cause of such a high incidence. Oral cavity carcinomas rarely metastasize to distal organs (Singh and Sharma, 2017).

The lung is the most common distant location for metastasis, followed by the liver (Betka, 2001; Paul et al., 2023). However, pleural involvement by OSCC is extremely infrequent. Malignant effusions are often a symptom of disseminated malignancy and indicate the terminal phase of the disease. Serous effusions by OSCC are rare (Huang and Michael, 2014). There are extremely few accounts documenting pleural effusion brought on by metastasis from oral cavity cancer (Betka, 2001). The management and prognosis of oral cancer patients are greatly influenced by distant metastasis (Irani, 2016). Detection of metastatic cancer is crucial for staging and management of the patient as individuals exhibiting metastatic disease or advanced local recurrence have a dismal prognosis. No cytotoxic chemotherapy regimens have been found to enhance the longevity of the patients in the long haul (Shao and Hong, 2010). We report such an unusual case of distant metastasis of OSCC (buccal mucosa) presenting as a malignant pleural effusion diagnosed primarily on cytology.

Case report

A 61-year-old male, presented to emergency with history of cough, chest pain for two months along with acute onset of rapidly progressing shortness of breath for 1 week. On history, patient was found to be a diagnosed case of OSCC, buccal cavity five months back on punch biopsy. He was on palliation therapy due to its locally advanced disease. On general examination, patient was tachypneic (26–28 breaths/minute) with diminished breath sounds. Local examination revealed an ulceroproliferative lesion in the right buccal cavity involving the overlying skin (Figure 1A). Radiological investigations revealed bilateral pleural effusion. Pleural fluid was aspirated and sent for cytological examination. Grossly, the pleural fluid sample was hemorrhagic. Two air dried and two alcohol fixed

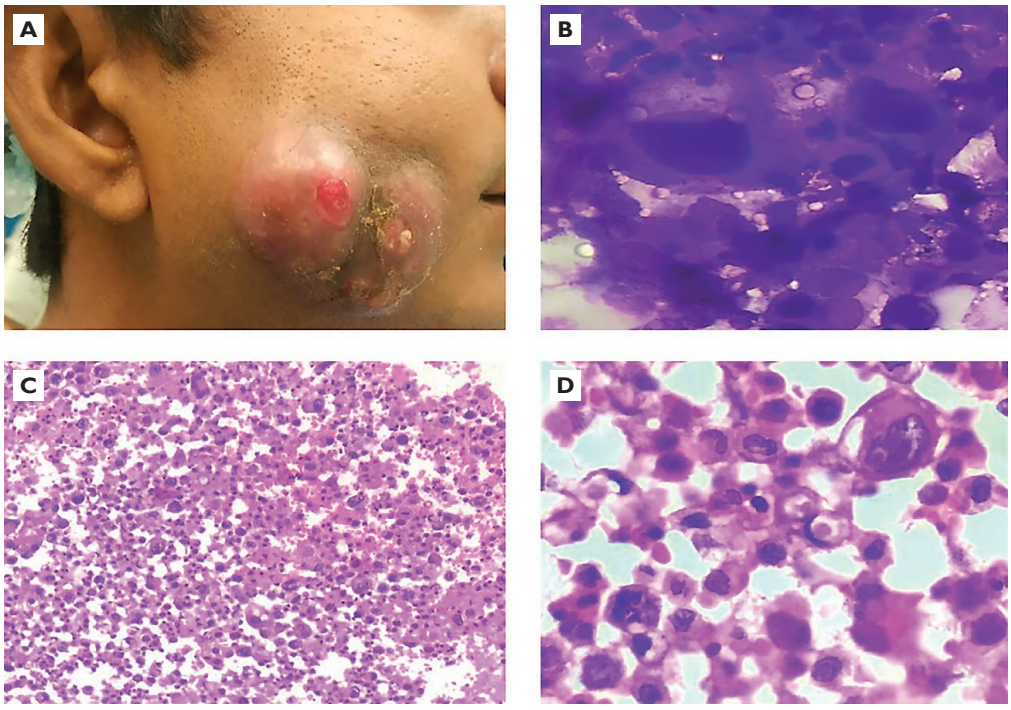

Figure 1: A) Clinical photograph of the patient with an ulceroproliferative lesion of the right buccal mucosa and extending to the right cheek. B) Cytospin smears from pleural fluid show scattered atypical cells among inflammatory cells (Giemsa, 400×). C) Cell block preparation showing discohesive tumour cells (haematoxylin and eosin [H and E], 200×). D) Atypical cells with bizarre nuclei on cell block (H and E, 400×).

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Papanicolaou smears were prepared from the cytospin deposits. Cell block preparation was also made from the aspirated material using 10% formalin as fixative and routine haematoxylin and eosin (H and E) stained sections were prepared from the paraffin embedded material.

The Giemsa stained smears were evaluated and showed presence of scattered single atypical cells amongst reactive mesothelial and inflammatory cells (Figure 1B). These atypical cells had high N:C ratio with large hyperchromatic nuclei, irregular nuclear membranes and moderate amount of cytoplasm. There were no three-dimensional cell clusters, signet ring cells, cytoplasmic vacuolations, "windows" between the cells, polygonal cells, anucleate cells, tadpole or fibre cells, squamous pearls were seen.

Cell block preparation showed discohesive singly lying tumour cells with moderate cytoplasm, pleomorphic and hyperchromatic nuclei amidst dense inflammatory background. Atypical cells with bizarre nuclei were also seen (Figure 1C and D). As the tumour cells were poorly differentiated, an initial immunocytochemistry panel of p63 and MUC5AC was done to rule out SCC, and adenocarcinoma respectively on cell block. In addition, Napsin A and TTF-1 was done to exclude any primary from the lung as the immunocytochemistry for MUC5AC was non-contributory. On immunocytochemistry, the tumour cells showed strong nuclear positivity for p63 and were negative for Napsin A and TTF-1 (Figure 2). Hence, on the basis of the patient's clinical history, morphological findings and immunocytochemistry, we conclusively determined that the patient had a metastatic SCC. Regrettably, the patient declined treatment after being informed of the dismal prognosis and was subsequently discharged. Unfortunately, he was lost to subsequent contact.

Discussion

The analysis of serous effusions, which are frequent specimens in cytopathology practice, provides a quick and precise way to identify metastatic illness (LePhong et al., 2017). Adenocarcinoma is the most prevalent malignant neoplasm found in serous effusions, followed by small cell carcinomas (14%), malignant mesotheliomas (8%), lymphoproliferative diseases (3.5%), and SCC (0.5–2.7%) (Cakir et al., 2011; Huang and Michael, 2014). The primary causes of malignant pleural effusions, which account for over 75% of cases, include lung, breast, ovary, and lymphoma malignancies. Even though SCC of the buccal cavity is common, malignant pleural effusions occur infrequently (Huang and Michael, 2014). It typically metastasizes to the lungs, bones, and liver after a protracted period of dormancy (Zbären and Lehmann, 1987).

Oral cancer with distant metastasis, which is uncommon, coincides with advanced stages of the disease, and is typically discovered after an interim dormant period (Betka, 2001).

The yield of exfoliative cytology from pleural effusion was greater than that of a biopsy, providing a diagnostic advantage over a biopsy (Paul et al., 2023). The most challenging aspect of assessing serous effusions is the extensive cytologic overlap between benign and reactive processes, as well as malignancies of diverse origins. Identification of metastatic SCC in pleural effusion is otherwise not difficult in patients who have a previous documented history of malignancy, in which the malignant effusion signifies disease progression (LePhong et al., 2017). However, when SCC is less distinct, the diagnosis might be difficult and error-prone. Due to its resemblance to other pathological effusions,

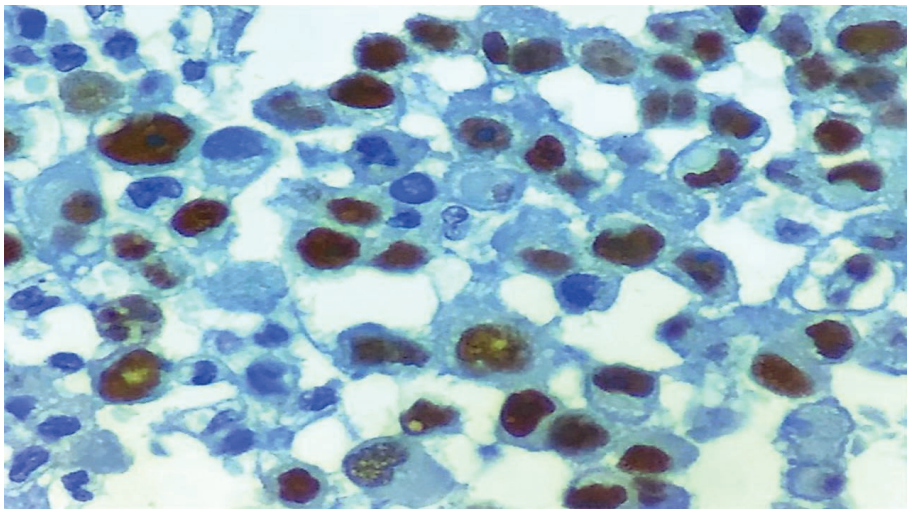

Figure 2: Immunocytochemistry on cell block showing strong nuclear positivity for p63 (400×).

the detection of metastatic moderately or poorly differentiated SCC in serous effusions offer a diagnostic difficulty (Huang and Michael, 2014). In serous effusions, adenocarcinoma and malignant mesothelioma are two frequent differential diagnoses for SCC (Huang and Michael, 2014; LePhong et al., 2017). Metastatic adenocarcinoma is the commonest imitator of poorly differentiated SCC due to the fact that both malignancies exhibit cell clusters and high nuclear atypia. However, morphologically poorly differentiated SCC cell clusters are two dimensional, more variable in size and have irregular borders, unlike the typical three-dimensional clusters with cytoplasmic vacuolations and signet ring cells in adenocarcinoma. In contrast to SCC, malignant mesothelioma cellular clusters show intercellular windows between the tumour cells and fuzzy borders attributable to the microvilli along with a low N/C ratio, relatively smooth nuclear contours and lesser nuclear hyperchromasia. Another diagnostic pitfall of SCC in pleural effusion is its coexistence with other primary malignancies like adenocarcinoma or urothelial carcinoma, the incidence of which is extremely low (Huang and Michael, 2014).

Table 1: Summary of previously reported cases of pleural metastasis from oral cavity SCC

Author	Age/ sex	Site of SCC	Radiological findings	Other metastasis	Cyto-morphology	Histomorphology	Follow-up
Ziaullah et al.[13] (2023)	61 Y/M	Left side buccal mucosa SCC	PET scan revealed a fluorodeoxy-glucose (FDG) avid uptake along the left pleura with a SUV max of 5.06 and massive pleural effusion.	Mediastinal lymphadeno-pathy. Thoracoscopy showed pleural deposits.	Negative for malignant cells	Frozen section from thoracoscopic pleural biopsy revealed infiltrating tumour cells arranged in nests with occasional keratin pearl formation suggestive of metastatic SCC deposits. Histo-pathology confirmed the diagnosis of metastatic SCC.	Expired four months later
Paul et al.[3] (2023)	54 Y/M	Right side buccal mucosa SCC extending into the left alveolus, gingivo-buccal sulcus and retromolar trigone	CT scan showed bilateral pleural effusion with no distinct mass or thickening was identified in the pleura and lung.	Absent	Metastatic squamous cell carcinoma (p40 positive cells)	Not performed	Not available
Wang et al.[14] (2017)	68 Y/F	Tongue SCC	Metastatic lesions were confirmed by neck or chest CT.	Neck and mediastinal lymph nodes, bone	NA	NA	Expired
	86 Y/F	Tongue SCC		Mediastinal lymph nodes			Expired
	67 Y/M	Tongue SCC		Lung			Expired
	68 Y/F	Floor of mouth SCC		Tiny lung nodules			Not expired
	64 Y/M	Tongue SCC		Lung nodules			Not expired
Ishikawa et al.[15] (1999)	74 Y/M	Right lower gingiva SCC	Presence of the pleural effusion and a well-circumscribed mass in the right hemithorax.	Absent	Not performed	On percutaneous biopsy found to have SCC of similar morphology.	Not available
Present case	61 Y/M	Right buccal mucosa	Bilateral pleural effusion	Absent	Metastatic SCC (p63 positive cells)	Not performed	Not available

The superscript numericals [13,3,14,15] are indexing mentioned in the references. Y – year; M – male; F – female; PET – positron emission tomography; SUV max – maximum standardized uptake value; NA – not available; SCC – squamous cell carcinoma; CT – computed tomography

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Immunocytochemical stains play a crucial role in distinguishing such differential diagnoses and establishing the diagnosis in such difficult cases as ours, in which the morphology is not particularly definitive.

In this case, immunocytochemical markers p63, Napsin A and TTF-1 were utilized to rule out alternative diagnoses. The tumour cells exhibited robust nuclear positivity for p63 but were negative for all other markers. This finding is in concordance with the previous literature, which showed that p63 is a potent nuclear stain that is expressed in 80–100% of SCC whereas it is scarcely expressed in adenocarcinoma or malignant mesothelioma making it a very useful confirmatory positive marker for diagnosing SCC (Huang and Michael, 2014; LePhong et al., 2017).

With negative expression of TTF-1 and Napsin A, metastatic adenocarcinoma from lung was also ruled out. In our case, we were aware of the history of a OSCC along with negative positron emission tomography (PET) scan for lung lesion. Therefore, the diagnosis necessitated the integration of the patient's clinical history, radiological findings, precise sample collection, and microscopic evaluation of cytology specimens. This comprehensive approach also involved utilizing immunocytochemistry on a cell block preparation to confirm the diagnosis. The patient declined treatment due to the dismal prognosis explained to him. Unfortunately, he was lost to follow up.

Pleural metastasis can be in the form of pleural effusion, pleural nodules, or nodular thickening of the pleura with enhancement, which can be seen on contrast computed tomography (Wang et al., 2017).

Pleural involvement is considered to be an extremely poor prognostic marker for survival and it does not always present with distant metastasis (Asciak and Rahman, 2018). Only a few cases have been reported in the literature (Table 1).

Conclusion

The rare occurrence of pleural involvement in metastatic OSCC is associated with a poorer prognosis. No cytotoxic chemotherapy regimen has been found to enhance the longevity of patients in such conditions. Identification of metastatic OSCC in pleural effusion is otherwise not difficult in patients with a documented history of malignancy, in which the malignant effusion signifies the progression of the disease.

In light of this, it is significantly more important for the pathologist to identify these uncommon cancers. In OSCC, malignant pleural effusion can be accurately detected using exfoliative cytology in conjunction with clinical information, imaging results, and cell block immunocytochemistry. To guarantee an accurate diagnosis, it is essential to integrate the clinical history with cytomorphological characteristics and an adequate immunocytochemistry panel.

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Chronotherapeutic Considerations in Immunotherapy: A Case of Durable Response in Metastatic Non-small Cell Lung Cancer

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Key words: Pembrolizumab – Circadian rhythms – Tumour progression – Neutrophil-to-lymphocyte ratio – Treatment timing

Abstract: Chronotherapy, the alignment of treatments with biological rhythms, has been explored in oncology, particularly for chemotherapy and targeted therapies, but its impact on immune checkpoint inhibitor (ICI) efficacy remains underexplored. This research aimed to examine the potential chronotherapeutic effects of morning ICI administration on the long-term response to pembrolizumab in metastatic non-small cell lung cancer (NSCLC), emphasising immune function stability via the neutrophil-to-lymphocyte ratio (NLR), and to assess the clinical significance of circadian synchronisation in immunotherapy. This study utilised a retrospective case study methodology, examining the treatment records and serial hematologic data of a patient with metastatic NSCLC. A patient diagnosed with metastatic NSCLC in 2019 showed a lasting full response to pembrolizumab for more than 6 years. A retrospective analysis revealed consistent morning ICI administration (08:00–11:00 h) and a stable NLR (2.16–3.66) during the treatment period. In addition, serial haematologic analysis showed a stable NLR, ranging between 2.16 and 3.66 throughout the treatment course. This immunological stability may reflect enhanced immune function aligned with early-day innate immune activity, particularly neutrophil and antigen-presenting cell priming, which is known to follow circadian patterns. Although specific molecular circadian markers were not examined, this case highlights a significant issue in current medical practice: there is almost no consistency in the timing of immunotherapy treatments. Taken together with emerging retrospective data, these findings underscore the need for prospective studies evaluating the influence of treatment timing on immunotherapy efficacy and durable immune surveillance in solid tumours.

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Introduction

Chronotherapy, the practice of aligning medical treatments with the body's circadian rhythms, has been extensively explored. This therapeutic approach represents a fundamental shift from the traditional "one-size-fits-all" dosing paradigm toward a more personalized, biologically-informed treatment strategy. That is, by timing drug administration to align with periods of optimal tolerance and efficacy, clinicians aim to enhance therapeutic benefit while simultaneously reducing toxicity – a dual objective that has become increasingly important as cancer treatments have grown more sophisticated and targeted (Fey et al., 2025). This chronotherapeutic method is especially pertinent for immunotherapy, as synchronising treatment with circadian rhythms may increase the immune system's capacity to prevent cancer. Immune checkpoint inhibitors (ICIs), including pembrolizumab, nivolumab, and atezolizumab, have profoundly altered cancer treatment paradigms, especially for conditions such as metastatic non-small cell lung cancer (NSCLC).

NSCLC is a predominant cause of cancer mortality worldwide, representing over 85% of all lung cancer cases (Xiao et al., 2023). The prevalence of NSCLC is elevated, with tobacco consumption being the primary risk factor. Recently, the growing acknowledgement of environmental contaminants, genetics, and occupational hazards as contributing factors has offered a more comprehensive epidemiological approach. The prognosis for NSCLC is frequently unfavourable due to a late-stage diagnosis, as the majority of patients come with metastatic illnesses. Although surgery, radiation, and chemotherapy have constituted conventional treatments, immunotherapy has transformed the therapeutic paradigm (Kaloshi et al., 2014; Latka et al., 2024). ICIs, including pembrolizumab, nivolumab, and atezolizumab, have demonstrated substantial survival advantages by strengthening the body's immunological response to tumour cells (Santry et al., 2024). Immunotherapy in NSCLC targets the programmed death-1 (PD-1) receptor or its ligand PD-L1, thereby blocking the tumour's capacity to avoid immune surveillance. The expanding significance of immunotherapy is particularly encouraging for patients with advanced or metastatic NSCLC, where survival prospects have historically been dismal with traditional therapies.

Circadian rhythms, governed by the body's internal clock, regulate numerous physiological functions, including sleep-wake cycles, hormone secretion, metabolism, and immune system function (Ding et al., 2024). These rhythms influence the immune system, causing immune cells like T-cells, macrophages, and dendritic cells to fluctuate in activity levels throughout the day. This temporal regulation boosts immune responses to infections and maintains homeostasis. Specifically, innate immune processes, including neutrophil migration and antigen-presenting cell priming, exhibit heightened efficacy during the early hours, which may elucidate the variations in immune responses correlated with the time of day (Chulenbayeva et al., 2018; Nurgaziyev et al., 2024). The circadian clock orchestrates the timing of cytokine production and immune cell trafficking, by optimising immune system activity during critical periods and facilitating rest during low-risk intervals. Comprehending these circadian fluctuations is essential for enhancing treatment options in immunotherapy, as misalignment between treatment and the body's circadian rhythms may result in inadequate responses or heightened side effects.

Clock genes, including BMAL1, PER2, and CRY1/2, serve as the molecular regulators of circadian rhythms. These genes form a transcriptional feedback loop that regulates the timing of biological activities. BMAL1 and CLOCK constitute a heterodimer that initiates the transcription of other clock genes, including PER and CRY proteins, which subsequently suppress the activity of BMAL1 and CLOCK to sustain rhythmic oscillations. These genes are expressed in diverse immune cells, and their expression affects immunological function. BMAL1 governs the metabolic reprogramming associated with T-cell activation, whereas PER2 influences the synthesis of inflammatory cytokines (Carbone et al., 2024). The CRY proteins facilitate the regulation of immune cell movement and the formation of immunological memory. Disruption of circadian rhythms, frequently caused by genetic abnormalities or environmental influences like shift work or jet lag, can compromise immune responses and facilitate the onset of illnesses, including cancer (Matiichuk et al., 2025). Moreover, understanding how these clock genes control the immune system may yield insights that optimise the timing of immunotherapy, potentially enhancing the effectiveness of treatments like ICIs.

The historical development of chronotherapy can be traced back to early observations in the 1970s and 1980s, when researchers first noted that the timing of chemotherapy administration could significantly impact both treatment outcomes and side effect profiles. Initial studies focused primarily on traditional cytotoxic agents, where the concept of therapeutic windows – periods during which normal tissues are least susceptible to damage while tumour cells remain vulnerable – became a cornerstone of treatment optimisation. Over time, this approach has evolved to encompass not only conventional chemotherapy but also oral agents and targeted therapies, reflecting

the growing understanding of how circadian biology influences drug metabolism, cellular repair mechanisms, and treatment response (Scheiermann et al., 2013; Mamontov et al., 2023).

The molecular machinery underlying these circadian immune rhythms involves several key clock genes, including Brain and Muscle ARNT-Like 1 (BMAL1), Period Circadian Regulator 2 (PER2), and the cryptochrome genes CRY1 and CRY2. These transcriptional regulators are known to modulate not only the amplitude and timing of immune responses but also the sensitivity of immune cells to various stimuli and their capacity for sustained activation. Research has demonstrated that BMAL1, for instance, plays a crucial role in regulating the metabolic reprogramming that occurs during T-cell activation, while PER2 influences the production of key inflammatory mediators. The CRY proteins, meanwhile, help coordinate the timing of immune cell migration and the establishment of immunological memory (Haspel et al., 2020; Karaboué et al., 2024). These biological mechanisms provide a strong theoretical foundation for the hypothesis that the timing of ICI administration could influence clinical outcomes.

The body's circadian cycles influence numerous fundamental biological systems, potentially enhancing the efficacy of morning drug delivery, particularly in immunotherapy (Al-Maqtari et al., 2024). Circadian rhythms regulate various immunological processes, determining the peak activity times of immune cells, including neutrophils, T-cells, and dendritic cells. Research shows that early in the day optimally prepares the immune system for increased activity, particularly for innate immune responses (Nagy et al., 2025). This includes the increased migration of neutrophils and the enhanced activity of antigen-presenting cells, which are crucial for beginning and maintaining immune responses against tumours. Administering drugs to align with peak immune responses may enhance the efficacy of ICIs such as pembrolizumab.

The circadian regulation of cytokine synthesis, with immune cell activity, plays a significant role. Cytokines, encompassing pro-inflammatory signals that activate immune cells, exhibit a predictable cycle, with production peaking at specific times of the day. Cytokine levels are elevated in the morning, rendering it an ideal period for treatment when immune cells exhibit heightened responsiveness. Administering ICIs at elevated cytokine levels may augment therapy efficacy, as it corresponds with the body's inherent immunological activation (Li et al., 2025).

Moreover, the study of how the time of day affects the body's metabolic processes, known as chronopharmacology, plays a significant role (Nagy et al., 2025). Drug metabolism, absorption, and elimination adhere to circadian rhythms. Enzymes responsible for medication metabolism typically exhibit heightened activity in the morning, perhaps leading to more effective digestion of immune checkpoint inhibitors and prolonged drug concentrations. This timing may also alleviate side effects by synchronising treatment with intervals when the immune system is better equipped to manage therapeutic medicines with fewer unexpected reactions.

However, to date, no prospective clinical trials have systematically evaluated the impact of circadian timing on ICI efficacy. Although retrospective studies and meta-analyses have begun to shed light on this relationship – particularly suggesting improved survival with morning administration in cancers such as melanoma and NSCLC – the data remain fragmented (Amiama-Roig et al., 2022; Wang et al., 2022a; Patel et al., 2024). Moreover, case-level evidence illustrating chronotherapeutic consistency is virtually absent from the literature.

The primary aim of this study was to document and analyse a real-world case of prolonged immunotherapy response in metastatic NSCLC with retrospective evaluation of treatment timing patterns and associated immunological parameters. This study's main hypothesis posits that timing the administration of ICIs with the body's circadian cycles may improve treatment efficacy and immunological responses in patients with metastatic NSCLC. The main objectives of the study were:

1) To assess the possible chronotherapeutic impact of morning ICI administration (between 08:00 and 11:00) on the long-term response to pembrolizumab in a real-world patient with metastatic NSCLC.
2) To examine the stability of immunological markers, specifically the neutrophil-to-lymphocyte ratio (NLR), as an indicator of systemic immune reactivity about treatment scheduling.
3) To delineate deficiencies in the existing chrono-immunotherapy literature and suggest avenues for additional investigation, particularly concerning circadian rhythms and the efficacy of immune checkpoint inhibitors in solid tumours.
4) To investigate the necessity for prospective trials assessing the impact of treatment scheduling on immunotherapy results and sustained immune surveillance.

Case report

A 58-year-old female initially presented in January 2019 with progressive dyspnoea, persistent dry cough,

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Table 1: Longitudinal laboratory monitoring of lymphocyte and granulocyte percentages in a patient with stage IV lung adenocarcinoma (2019–2025).

Time	18.04.2019 10:59	10.05.2019 09:26	14.05.2019 09:42	31.05.2019 09:37	13.06.2019 08:49	21.06.2019 08:41	11.07.2019 08:55	02.08.2019 09:37	23.08.2019 08:53	05.09.2019 08:40
Lym	26.8	30.1		23.2		29.4		61.9	60.7	
Gran	62.6	58.0		67.1		61.7		29.6	29.3	
Time	06.12.2019 09:10	06.12.2019 09:11	27.12.2019 10:44	08.01.2020 09:10	17.01.2020 11:08	05.02.2020 09:02	07.02.2020 11:45	07.02.2020 12:29	28.02.2020 09:17	05.03.2020 09:09
Lym	72.1	72.1	73.8	67.7	77.0	71.8	57.9		73.1	66.0
Gran	14.0	13.8	15.6	18.6	15.6	15.3	27.5		17.9	22.2
Time	31.07.2020 09:11	05.08.2020 11:51	21.08.2020 09:20	03.09.2020 09:23	11.09.2020 09:26	02.10.2020 11:59	26.10.2020 12:14	02.11.2020 09:11	16.11.2020 12:05	30.11.2020 11:38
Lym		72.0		62.0	65.8			67.6		65.8
Gran		19.4		25.6	21.2			20.6		23.4
Time	05.05.2021 11:45	05.05.2021 12:04	26.05.2021 10:48	04.06.2021 09:12	15.06.2021 10:44	05.07.2021 09:03	06.07.2021 10:36	27.07.2021 09:28	02.08.2021 09:31	17.08.2021 09:07
Lym				67.5				66.8		51.7
Gran				22.1				22.3		31.9
Time	30.11.2021 09:33	22.12.2021 12:38	06.01.2022 09:27	12.01.2022 12:26	03.02.2022 09:52	24.02.2022 09:04	17.03.2022 09:16	17.03.2022 09:17	07.04.2022 09:38	14.04.2022 09:58
Lym					64.6	58.4	58.1	59.5		58.2
Gran					22.1	27.8	27.4	27.3		28.7
Time	12.08.2022 09:40	02.09.2022 14:50	08.09.2022 10:56	23.09.2022 09:43	14.10.2022 09:43	14.10.2022 09:50	17.10.2022 15:50	08.11.2022 12:38	14.11.2022 09:34	29.11.2022 09:15
Lym	68.2	57.5	56.3	69.4	60.0	58.4			59.3	58.4
Gran										
Time	18.05.2023 09:35	01.06.2023 09:55	07.06.2023 09:43	29.06.2023 09:22	11.07.2023 11:26	20.07.2023 11:00	09.08.2023 11:15	09.08.2023 12:18	09.08.2023 12:19	09.08.2023 12:39
Lym	65.2	60.8	58.5	60.4	66.0	67.9	66.2	66.8		
Gran										
Time	14.03.2024 10:57	04.04.2024 09:47	25.04.2024 11:09	16.05.2024 10:00	06.06.2024 11:29	27.06.2024 11:10	25.07.2024 09:04	19.08.2024 08:56	22.08.2024 10:38	09.09.2024 09:47
Lym	64.6	59.4	57.7	60.8	67.4	61.9	61.4	60.2	63.0	68.5
Gran										

Source: compiled by the author

and general fatigue. A chest X-ray on January 31, 2019, revealed a suspicious mass in the right lung, prompting further evaluation. On February 27, 2019, a right pneumonectomy with mediastinal lymph node dissection was performed. Histopathological analysis confirmed a grade 3 poorly differentiated adenocarcinoma with acinar, papillary, and lepidic components infiltrating the parietal pleura and pericardium. The final staging was pT4 pN1 cM1a (stage IV).

Immunohistochemistry on March 29, 2019, demonstrated high PD-L1 expression (>50%) and negative status for EGFR and ALK mutations. A positron emission tomography/computed tomography (PET/CT) scan on April 15, 2019, revealed multiple bone metastases and abdominal lymph node involvement, confirming advanced disease. At treatment initiation, her ECOG performance status was 1. By the end of the first six months, clinical improvement was observed, and the patient was reassessed as ECOG 0, a status maintained throughout follow-up.

Following multidisciplinary tumour board discussion, first-line pembrolizumab monotherapy was initiated on April 22, 2019. A retrospective review of the hospital's pharmaceutical software revealed that all recorded infusions were consistently prepared and administered in the morning hours (08:00–11:00), with minimal deviations. This pattern was not based on a predefined chronotherapeutic strategy but rather emerged from routine hospital logistics. Even after checking for diseases and giving radiotherapy, the timing stayed the same, indicating an unintentional but ongoing match with the body's natural immune rhythms.

16.09.2019 08:23	17.09.2019 09:01	04.10.2019 09:13	04.10.2019 09:41	10.10.2019 12:32	15.10.2019 10:39	25.10.2019 09:00	07.11.2019 08:55	15.11.2019 08:50	26.11.2019 10:57
63.8			78.5			62.3		66.3	
26.7			15.5			27.0		22.8	
23.03.2020 08:52	02.04.2020 08:50	10.04.2020 10:40	07.05.2020 11:05	29.05.2020 10:49	04.06.2020 11:21	19.06.2020 09:42	19.06.2020 09:43	07.07.2020 11:08	10.07.2020 09:32
67.2		70.5	73.7			73.3		71.5	65.4
20.7		17.9	18.2			16.6		19.1	21.6
07.12.2020 13:11	29.12.2020 12:53	06.01.2021 09:50	15.01.2021 09:30	03.02.2021 09:50	26.02.2021 11:13	04.03.2021 10:58	19.03.2021 09:24	02.04.2021 09:33	14.04.2021 10:44
		63.6	59.6	56.0	69.4	63.0	63.4		
		23.3	25.7	28.2	19.2	21.5	26.1		
01.09.2021 09:37	03.09.2021 09:57	03.09.2021 09:58	03.09.2021 11:24	27.09.2021 09:41	27.09.2021 09:42	04.10.2021 11:54	19.10.2021 12:17	04.11.2021 09:52	09.11.2021 11:07
62.8									
23.6									
28.04.2022 09:49	12.05.2022 09:38	17.05.2022 10:57	09.06.2022 09:18	09.06.2022 09:19	27.06.2022 10:37	01.07.2022 10:58	07.07.2022 09:34	25.07.2022 09:14	03.08.2022 09:41
		55.9	56.8	57.3	70.2	65.1	64.4	60.2	64.3
		28.7	27.8	27.1					
20.12.2022 09:06	10.01.2023 09:22	31.01.2023 09:38	21.02.2023 09:33	28.02.2023 09:57	14.03.2023 09:24	28.03.2023 11:27	06.04.2023 08:33	27.04.2023 09:15	27.04.2023 09:16
55.0	63.1	66.7	50.7	56.9	58.8	67.0	60.0	60.4	61.0
31.08.2023 10:49	15.09.2023 09:40	21.09.2023 10:56	13.10.2023 09:24	06.11.2023 09:59	24.11.2023 10:55	15.12.2023 09:45	11.01.2024 09:53	01.02.2024 10:56	22.02.2024 08:25
66.4	62.1	66.6	58.3	52.0	66.5	62.7	63.1	66.0	62.9
27.09.2024 10:44	18.10.2024 09:35	08.11.2024 09:06	29.11.2024 09:43	20.12.2024 09:49	10.01.2025 11:37	31.01.2025 11:36	06.02.2025 10:53	21.02.2025 11:20	14.03.2025 10:59
66.5	66.5	64.7	60.5	67.5	70.7	65.9	63.8	72.3	69.1

In the context of treating patients with locally advanced or metastatic NSCLC, monitoring immunological status is of great importance as a prognostic and predictive factor (Labrecque and Cermakian, 2015). The NLR in peripheral blood has established itself as a reliable biomarker of systemic inflammatory response and overall immune reactivity, correlating with patient survival, especially in the context of immunotherapy.

Considering the chronobiological patterns of the immune system's functioning, the timing of immunotherapy administration may potentially affect the clinical efficacy of treatment through synchronisation with the circadian rhythms of immune cells. In the presented clinical case, the patient received the immune checkpoint inhibitor pembrolizumab at stable morning hours, providing a unique opportunity to study long-term changes in the cellular components of the blood (Catozzi et al., 2024).

To illustrate and analyse these dynamics, a retrospective compilation of data on the percentage of lymphocytes and granulocytes in the patient's blood serum was conducted over more than 6 years of treatment. Table 1 illustrates the time sequence of laboratory indicators, allowing visualisation of the stability of the immune profile and assessment of the potential impact of the regularity and timing of drug administration on the patient's immunological status. This approach opens perspectives for further research on chronotherapy in the field of immunotherapy for oncological diseases.

This heatmap illustrates the temporal dynamics of lymphocyte and granulocyte percentages in

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peripheral blood samples collected from a 58-year-old female patient with stage IV poorly differentiated lung adenocarcinoma (pT4 pN1 cM1a), who received continuous first-line immunotherapy with pembrolizumab. Data span from April 2019 to May 2025, covering 60 laboratory assessments. Notably, immune cell proportions remained within a stable physiological range throughout the observation period. The predominance of morning blood draws, coinciding with consistently timed ICI administration (08:00–11:00), allowed for an exploratory assessment of chronotherapeutic alignment.

High lymphocyte percentages (≥70%) and corresponding reductions in granulocytes were transiently observed during late 2019 and early 2020, suggesting possible reactive haematological shifts. However, the NLR calculations derived from these data remained consistently below the prognostically adverse threshold (>5), reinforcing the hypothesis of a sustained favourable immunological milieu under stable circadian treatment conditions. To explore the potential implications of this pattern, a retrospective analysis was conducted on serial haematological parameters, with a focus on the NLR, a surrogate marker of immune status (Mazzoccoli et al., 2020; Nelson et al., 2022; Mok et al., 2024). Sixty paired measurements were extracted from blood tests. The NLR values ranged from 2.16 to 3.66, remaining consistently below the prognostically unfavourable threshold (>5) and showing minimal variability. This immunological stability may reflect a favourable biological environment, possibly influenced by consistent ICI doses in the morning.

In October 2019, the patient received palliative radiotherapy to the Th1 vertebra. Pembrolizumab continued without interruption. Localised progression in July 2022 prompted radiotherapy at a mediastinal lymph node (25 Gy), while immunotherapy remained unchanged. In August 2024, a PET/CT scan showed that the lymph nodes in the chest area were still affected, which resulted in another round of radiotherapy (24 Gy) for that area. In the context of studying the immune status of patients or evaluating the function of the immune system, analysing long-term changes in the ratio of lymphocyte and granulocyte cell populations is of great importance. The percentage content of these cells in peripheral blood is an important biomarker of systemic immune reactivity, reflecting the balance between adaptive and innate immunity (Hergenhan et al., 2020; Ding et al., 2024; Quist et al., 2024).

In particular, the dynamics of these indicators allow assessment of the overall state of the immune response at different times, which can be useful in monitoring chronic processes or long-term treatment. Considering the chronobiological rhythms of the immune system's functioning, analysing changes in the cellular composition of blood over a long period opens up opportunities for studying the influence of circadian rhythms on immune indicators and their stability (Keller et al., 2009; Balachandran et al., 2023). Figure 1 illustrates a retrospective analysis of the percentage ratio of lymphocytes and granulocytes in the blood over a period of more than 6 years, enabling visualisation of trends and fluctuations in these cell populations.

Figure 1 shows the change in the percentage of lymphocytes (indicated in blue) and granulocytes (indicated in orange) in the blood over the period from 2019 to 2024. The X-axis represents the time scale in years, divided by observation dates, and the Y-axis represents the percentage ratio of the respective cells. Lymphocytes demonstrate an overall trend of fluctuations within approximately 50 to 80%,

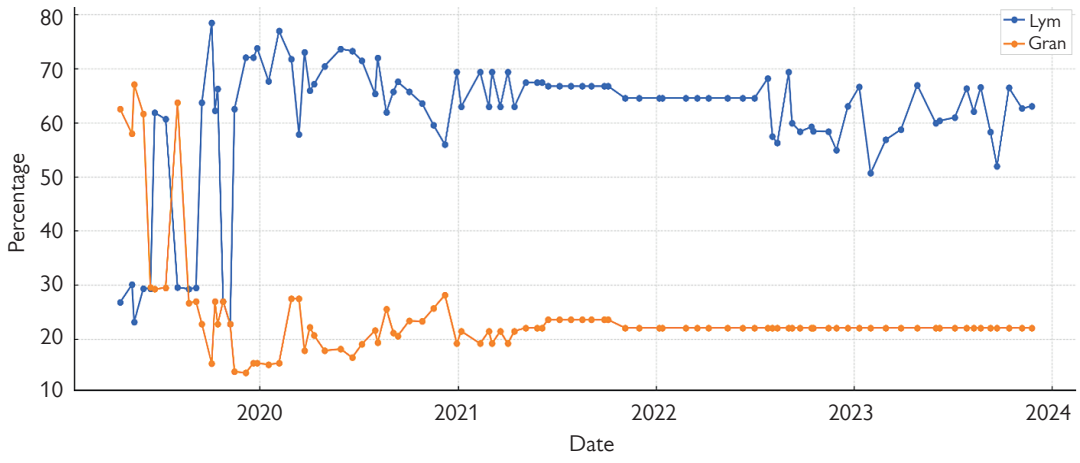

Figure 1: Dynamic changes in the percentage ratio of lymphocytes and granulocytes in the blood from 2019 to 2024. Source: compiled by the author.

stabilising at around 65–70% in the second half of the period. Granulocytes, on the other hand, initially have a high percentage (over 60%) but quickly decrease to around 20–30% and remain stable in subsequent years. The dynamics show an inverse relationship between the percentage of lymphocytes and granulocytes, which is typical for maintaining a balance in the number of different types of leukocytes in the blood.

An increase in lymphocytes is accompanied by a decrease in granulocytes, which may indicate adaptive changes in the immune system in response to various factors such as infections, inflammatory processes, or other changes in the body (Łątka et al., 2024). The stabilised indicators in the period after 2021 indicate a certain equilibrium in the cellular composition of the blood, which may be characteristic of the normal functioning of the immune system in the absence of acute pathological processes. Thus, this Figure 1 clearly demonstrates important features of the cellular immune response, which can be used for further analysis in medical and biological research.

Throughout her 6-year treatment journey, the patient received pembrolizumab infusions exclusively in the morning. Despite several tumour board evaluations, treatment adjustments, and progression events, the timing remained unchanged. Treatment compliance was excellent, with only two missed cycles (Cycle 74 and Cycle 84), both due to logistical reasons. As of March 2025, a total of 101 cycles of pembrolizumab have been completed, resulting in long-term disease control limited to localized progression, with no significant immune-related adverse events. In the context of studying the immune status of patients or evaluating the functioning of the immune system, analysing long-term changes in the ratio of lymphocytes and granulocytes is of great importance. The percentage content of these cells in peripheral blood is a significant biomarker of systemic immune reactivity, reflecting the balance between adaptive and innate immunity (Labrecque and Cermakian, 2015; Du and Holme, 2020).

In particular, the dynamics of these indicators allow assessment of the overall state of the immune response at different time intervals, which is useful for monitoring chronic processes or long-term treatment. Considering the chronobiological rhythms of the immune system's functioning, analysing changes in the cellular composition of blood over a long period opens up opportunities to study the influence of circadian rhythms on immune indicators and their stability. Figure 2 presents a retrospective analysis of the percentage ratio of lymphocytes (blue line) and granulocytes (orange line) in peripheral blood over a period exceeding 6 years, enabling visualisation of trends and fluctuations in these cell populations.

Figure 2 illustrates the changes in the percentage of lymphocytes (shown in blue) and granulocytes (shown in orange) in peripheral blood over a time span exceeding 6 years, from April 2019 to March 2025. The X-axis represents the chronological timeline divided by specific observation dates, while the Y-axis shows the percentage ratio of these two immune cell populations. Lymphocytes exhibit fluctuations generally ranging between approximately 50 and 80%, with a tendency to stabilise around 65–70% in the later stages of the observation period. In contrast, granulocytes start with a higher percentage, exceeding 60%, but rapidly decline to a range of about 15–30%, maintaining this relatively stable level throughout the subsequent years.

The graph clearly demonstrates an inverse relationship between the relative proportions

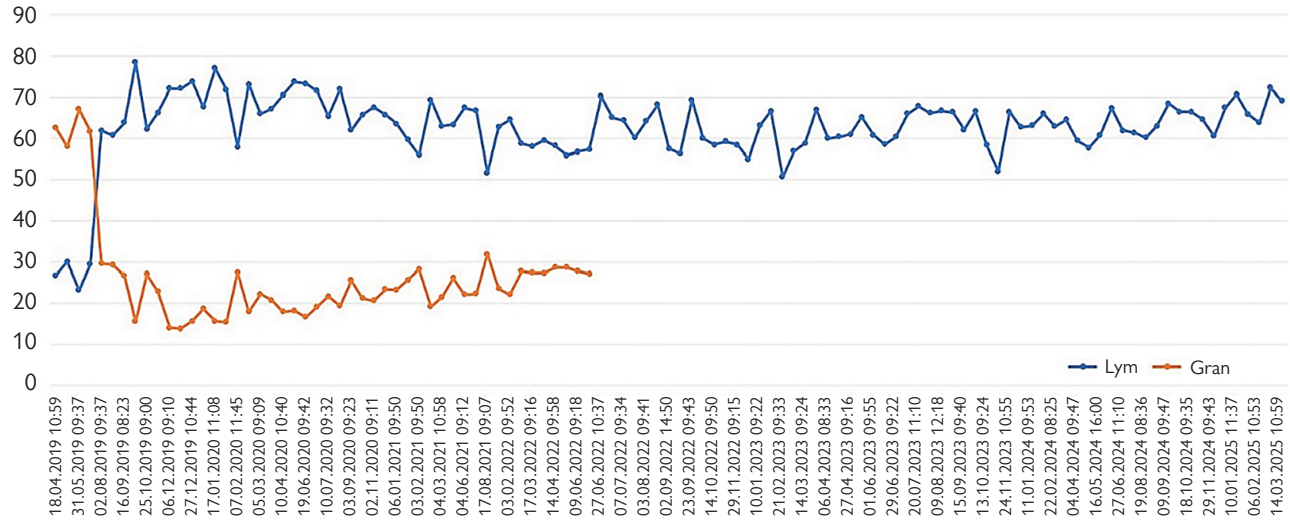

Figure 2: Dynamics of the percentage ratio of lymphocytes and granulocytes in peripheral blood over a long period.
Source: compiled by the author.

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of lymphocytes and granulocytes, reflecting the homeostatic balance typical of the immune system's cellular composition. This inverse dynamic suggests adaptive modulation of the immune response, possibly influenced by various internal and external factors such as infections, inflammation, or other physiological changes. The stabilisation of both lymphocyte and granulocyte percentages after approximately 2021 indicates a maintained equilibrium in the cellular makeup of the blood, which may correspond to normal immune function in the absence of acute pathological conditions. This Figure provides valuable insight into the long-term dynamics of key leukocyte populations, offering a basis for further immunological and clinical investigations.

A 58-year-old female with metastatic NSCLC undergoing pembrolizumab monotherapy offers important information regarding the possible influence of circadian rhythms on enhancing immunotherapy efficacy. Although there was no deliberate chronotherapeutic approach, the patient's treatment was regularly provided in the morning, aligning with natural peaks in immune system activity. Over 6 years of treatment, her haematological data exhibited stable immunological profiles, notably a consistently advantageous NLR, indicating a balanced immune response. Variations in lymphocyte and granulocyte populations suggested adaptive immune mechanisms, potentially enhanced by morning delivery. This case emphasises the advantages of synchronising immunotherapy with circadian rhythms, as the patient exhibited a beneficial immunological milieu with minimal side effects, underscoring the necessity for additional research into the impact of treatment timing on immune responses and long-term efficacy in cancer therapy.

Gaps in the current literature on chrono-immunotherapy

Even though more and more past studies and combined analyses indicate that when ICIs are given, they might affect results, there are still important gaps in the research that make it hard to apply these findings in practice. First, most published studies lack precise control over administration timing consistency. While several analyses stratify patients into "morning" and "afternoon" groups using fixed cut-offs (typically 11:30, 13:00, or 16:30), few account for whether this timing was maintained across treatment cycles. The possibility that inconsistent scheduling dilutes potential circadian effects has not been adequately addressed.

Second, the majority of available data comes from retrospective cohorts. Although the sample size is large, these studies are often affected by confounding variables – including performance status (PS), corticosteroid use, treatment line, or centre-specific logistics – that may influence both the timing of administration and outcomes. For instance, the scheduling of afternoon appointments may favour sicker patients or those receiving more aggressive supportive care, leading to bias. Although several studies attempt propensity score matching, the absence of random prospective trials continues to hamper definitive conclusions. Third, studies vary considerably in their biological depth. The mechanistic rationale behind chrono-immunotherapy often remains speculative. Only a few publications discuss the role of core circadian genes (such as BMAL1, PER2, or CRY1/2), immune cell trafficking rhythms, or cytokine dynamics. Also, there haven't been any human studies so far that have used direct signs of circadian function, like measuring gene activity or the cycles of melatonin and cortisol, to verify overall rhythmic alignment.

Fourth, in many studies, immune-related biomarkers such as NLR, PD-L1 expression levels, and tumour mutational burden are not uniformly reported or integrated into timing analyses. These parameters may interact with circadian factors and could help stratify patients more meaningfully. Fifth, only a minority of publications provide long-term follow-up data, particularly beyond 24 months. This makes it hard to understand how regular chrono-aligned dosing might affect ongoing immune monitoring, which is important for lasting responses, especially in NSCLC and melanoma.

Lastly, there is an evident gap in the literature regarding single-patient, high-resolution clinical observations – cases where timing was deliberately maintained, responses were thoroughly documented, and clinical confounders were minimised. Such cases may serve as valuable "probes" about the biological plausibility of chrono-immunotherapy, especially when randomised trials are still lacking. Given these limitations, there is a clear need for studies that carefully control the timing of treatments, utilize biomarkers for patient stratification, and monitor both clinical and biological factors longitudinally. Until such research is available, well-documented real-world cases may provide crucial insights into the clinical significance of circadian alignment in cancer immunotherapy.

Clinical observation and timing consistency

This case presents a compelling example of prolonged immunotherapy efficacy potentially influenced by treatment timing. A patient with metastatic NSCLC

has maintained a complete metabolic response for over 6 years under pembrolizumab monotherapy. A retrospective review revealed a consistently morning-aligned administration schedule (08:00–11:00), which, although unintentional, overlapped with known circadian peaks in innate immune activity, particularly neutrophil and antigen-presenting cell function, suggesting a possible chrono-immunological synergy.

To further investigate this observation, haematological parameters were analysed with particular attention to the NLR as a surrogate marker of systemic immune balance. Sixty NLR measurements demonstrated minimal fluctuation, with all values remaining below the prognostically unfavourable threshold (>5). This immunologic stability, coupled with sustained disease control and minimal toxicity, raises the hypothesis that consistent early-day dosing may enhance ICI efficacy by aligning with circadian immune rhythms.

While causality cannot be inferred from a single case, these findings resonate with the broader theoretical framework of chronobiology. Immune system processes – including T-cell activation, cytokine production, and antigen presentation – are governed by core circadian clock genes such as BMAL1, PER2, and CRY1/2 and follow well-established diurnal oscillations (Walker et al., 2021). Despite this, the integration of chronotherapy into immuno-oncology remains largely uncharted.

Retrospective studies and meta-analyses have recently begun to explore this link, suggesting improved survival with morning ICI administration in melanoma and NSCLC. However, substantial limitations persist in the current literature that restrict its translational potential.

Limitations in current evidence

First, most studies lack control over timing consistency – patients are typically categorised into "morning" and "afternoon" groups based on initial treatment times without documentation of whether this timing was maintained across treatment cycles. This procedure introduces variability that may obscure potential chrono-therapeutic effects. Second, the available evidence is predominantly retrospective in nature and susceptible to confounding factors such as performance status, corticosteroid use, treatment setting, and institutional scheduling preferences. These uncontrolled variables can significantly influence both treatment timing and outcomes.

Third, the mechanistic rationale behind chrono-immunotherapy remains largely speculative. Few studies incorporate direct molecular circadian markers, such as clock gene expression, melatonin or cortisol rhythms – to verify systemic rhythmic alignment. Moreover, immune-related biomarkers, like NLR, PD-L1 expression, or tumour mutational burden, are not uniformly analysed in relation to timing, further limiting their interpretability.

Fourth, long-term follow-up data are scarce. Most available studies report outcomes within 12–24 months, making it unclear how consistent, circadian-aligned dosing might contribute to sustained immune surveillance – an essential component of durable immunotherapy responses. Finally, the literature lacks high-resolution, single-patient reports with detailed timing data, immune marker tracking, and prolonged follow-up. These individual cases, although based on personal experiences, can offer helpful details about the potential of chrono-immunotherapy, especially since there are no planned studies.

Impact of chronotherapeutic strategies on immune checkpoint inhibitor efficacy and immune system responsiveness

The analysis of clinical data regarding the timing of ICI administration highlights not only the importance of considering dosing time but also expands the understanding of potential mechanisms underlying enhanced therapeutic efficacy with chronologically optimised administration.

Yeung et al. (2023) demonstrated that morning administration of ICIs in melanoma patients is associated with improved survival outcomes. This finding aligns with clinical observations where pembrolizumab infusions were consistently performed during morning hours, approximately between 08:00 and 11:00. Such temporal consistency in dosing may enhance immune responsiveness and contribute to sustained disease control without the emergence of significant immune-related adverse events. These results emphasise the role of circadian rhythms in the pharmacokinetics and pharmacodynamics of ICIs, potentially resulting in improved efficacy and safety profiles.

Lévi et al. (2023) highlighted significant differences between morning and evening dosing of ICIs, linking these differences to diurnal variations in immune system activity. Although deliberate chronotherapeutic strategies were not employed in the referenced clinical cases, the observed stability in administration time could have supported the maintenance of a favourable immunological milieu, thus potentiating the therapeutic effect. This observation corresponds with the concept that circadian rhythms regulate the expression of key immune molecules, including cytokines, chemokines,

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and receptors, suggesting that synchronising treatment timing with endogenous biological cycles may optimise treatment response (Kucherenko et al., 2019; Dyba and Berezenko, 2023).

Furthermore, Qian et al. (2021) provided additional evidence supporting the association between morning ICI administration and improved overall survival in melanoma patients. Their findings suggest the existence of critical temporal windows in which immune system activity peaks, and ICI administration during these intervals may more effectively stimulate antitumor immune responses. This accumulation of evidence strengthens the rationale for integrating temporal considerations into immunotherapy planning.

The foundational work by Cheng et al. (2022) offers valuable insights into the physiology of circadian synchronisation and its impact on pharmacological strategies, including immunotherapy. Morning administration of pembrolizumab may facilitate optimal interaction between the circadian system and immune mechanisms, enhancing T-cell activity, upregulating key cytokines, and reducing immunosuppressive factors. Such biological effects are crucial for achieving durable clinical responses in melanoma treatment (Montayeva et al., 2015, 2016). Additionally, contemporary chronopharmacological studies indicate that time of day influences not only drug pharmacokinetics but also the functional state of immune cells, such as lymphocytes and dendritic cells, which are essential for initiating and sustaining antitumor immunity (Dyba et al., 2024; Tutchenko et al., 2024). Circadian rhythms regulate immune cell trafficking, activation, and effector molecule production, directly impacting ICI efficacy. Maintaining consistent dosing times may thus help align therapy with peak immune responsiveness.

Johnson et al. (2022) discussed the long-term consequences of immunotherapy-related toxicity. The absence of significant immune-mediated adverse effects in this clinical context may be associated with the optimisation of drug administration timing. This observation aligns with Johnson and colleagues' emphasis on minimising toxicity during prolonged immunotherapy to improve patient outcomes. Boesch et al. (2023) investigated non-pharmacological interventions aimed at optimising cancer immunotherapy. Consistent morning administration of pembrolizumab can be considered such an intervention, potentially contributing to improved clinical outcomes. This finding corresponds with the conclusions of authors, who highlighted the importance of considering dosing time to enhance therapeutic efficacy.

Ortega-Campos et al. (2023) examined the interaction between circadian rhythm genes and cancer characteristics. Stable morning administration of pembrolizumab may support maintenance of a favourable immunological status, consistent with Ortega-Campos et al.'s (2023) conclusions regarding the critical role of circadian rhythm considerations in immunotherapy planning. Wang et al. (2022b) explored the role of dendritic cells in circadian antitumor immune responses. The observed stable morning dosing regimen likely contributes to sustaining an advantageous immune environment, in line with findings by Wang et al. (2022b) emphasising circadian rhythm alignment in immunotherapeutic strategies.

Thomas et al. (2023) discussed the gut microbiome as a potential biomarker for cancer immunotherapy. Maintaining a consistent morning dosing schedule of pembrolizumab may promote a beneficial immunological profile, which is in agreement with Thomas et al. (2023) recognition of circadian rhythm importance in immunotherapy design. Guillot et al. (2023) investigated manipulations of the gut and tumour microbiome to improve immunotherapy outcomes. Stable morning administration of pembrolizumab appears to support a favourable immune status, aligning with Guillot et al. (2023) findings on the significance of circadian rhythm considerations in the context of immunotherapy.

Chronotherapy may also reduce the incidence of immune-related adverse effects by modulating immune tolerance and inflammatory processes, both of which are under circadian control. Morning administration likely provides a more favourable balance between immune activation and immunopathology, consistent with observed reductions in severe adverse events (Missori et al., 2016). Collectively, these findings underscore the significance of incorporating dosing time into immunotherapy protocols and suggest promising avenues for further investigation in chrono-immunotherapy.

This study's findings indicate that synchronising ICI doses with the body's circadian cycles may enhance therapeutic success, especially in metastatic NSCLC. This might be clinically implemented by delivering ICIs throughout the early hours (between 08:00 and 11:00), a timeframe linked to enhanced innate immune activity, including elevated neutrophil and antigen-presenting cell functionality. Clinicians may consider using standardised morning dose regimens for patients undergoing immunotherapy to optimise therapeutic results. Moreover, the regular morning delivery could be integrated into clinical procedures, encouraging additional research into the ideal time of ICIs for various cancer types. Moreover, regular assessment of immune-related biomarkers, including the NLR, may facilitate the evaluation of the chronotherapeutic strategy's efficacy and inform subsequent treatment choices.

The stable NLR identified in this study indicates a balanced and advantageous immunological milieu, essential for successful cancer treatment. A continuously low NLR, as evidenced here (range from 2.16 to 3.66), correlates with enhanced immune reactivity and presumably decreased systemic inflammation, both of which facilitate superior treatment outcomes. The stability in NLR may indicate the alignment between circadian immunological rhythms and ICI treatment, thereby enhancing a more vigorous and enduring immune response. Nonetheless, it is crucial to acknowledge that additional factors, like the patient's overall health, concomitant therapies (e.g., radiation), and unique immunological attributes, may also affect NLR and treatment effectiveness.

Other studies have also suggested that the time of immunotherapy delivery, especially morning administration, may enhance clinical outcomes. Retrospective studies in melanoma and NSCLC indicate enhanced survival with morning ICI treatment, aligning with the results of this trial. Nevertheless, although our study underscores the relationship between timeliness and persistent immunological profiles, additional factors such as tumour burden, the specific medication administered, and patient characteristics may also influence the outcomes. Comparisons with research examining various circadian-based chronotherapeutic techniques might enhance the validation of the broader application of these findings. Future prospective trials that account for these characteristics will be crucial to validate the clinical significance of morning administration in immunotherapy. In light of these insights, it is proposed that future research prioritise prospective studies with stringent control of treatment timing, biomarker-based patient stratification, and incorporation of circadian molecular assessments. Until such trials are conducted, well-documented real-world cases may continue to offer critical insight into the therapeutic potential of chrono-immunotherapy.

Conclusion

This case highlights a potential association between the timing of immunotherapy administration and prolonged treatment response, raising a hypothesis that merits further investigation. The observed effect was not the result of a predefined chronotherapeutic strategy but rather an incidental finding, retrospectively derived from pharmacy records within routine clinical care. This observation underscores the current absence of formal frameworks guiding time-of-day considerations in immunotherapy protocols.

In addition to the consistent morning-aligned administration of pembrolizumab over more than 6 years, serial haematological analysis demonstrated a remarkably stable NLR, ranging from 2.16 to 3.66, without significant fluctuations or inflammatory peaks. This prolonged immunological equilibrium may reflect a chronobiologically favourable alignment between treatment timing and innate immune system activation.

At present, no large-scale retrospective or prospective studies have systematically examined the influence of circadian timing on immune checkpoint inhibitor efficacy. Case reports documenting such observations remain rare, and the field of chrono-immunotherapy is still in its infancy. Nevertheless, the established role of circadian biology in regulating immune function suggests that this relationship deserves formal exploration. Until robust evidence becomes available, this report serves as a hypothesis-generating observation – an early signal that biological timing may play a clinically relevant role in optimising long-term outcomes in cancer immunotherapy.

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Using Osstell to Monitor Primary Implant Stability: A Clinical Case Report

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Abstract: The increased demand for implants in the dental surgeon's clinical routine, methods and techniques have been created that involve non-invasive quantitative analysis, do not damage the bone-implant interface and objectively measure implant stability, such as resonance frequency analysis. The aim of this case report is to present a clinical case of a patient who came to the Dental School Clinic with a diagnosis of oblique root fracture with an indication for root extraction and immediate implant placement. The Osstell was used as another technique, in addition to the torque wrench, to measure the primary stability of the implant, which showed high stability, proving the importance of using the Osstell in the clinic.

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Introduction

Implant dentistry addresses the growing demand for both partial and complete tooth replacement through biologically based rehabilitation procedures, following the principles of osseointegration as described in the Brånemark protocol (Buser et al., 2000).

Successful treatment with implants is achieved through the process of osseointegration, which can be defined as a direct functional and structural connection between the bone and the implant surface (Branemark, 1983).

Implant stability, characterized by a clinical condition where there is no mobility (Meredith, 1998), and the ability to withstand lateral, rotational and axial loads (Oh and Kim, 2012), can be specified as primary and secondary. Primary stability, considered a fundamental factor for osseointegration, is dependent on the macroscopic characteristics of the implant, such as design and surface, including length, diameter, shape and thread types, as well as surgical technique, mechanical quality and local bone volume (Palarie et al., 2012). To guarantee the osseointegration process, implant stability must be analysed at different times. The ability to measure stability helps the implant dentist decide on the loading of an implant, allows the choice of protocol for each patient and provides adequate documentation for the case (Atsumi et al., 2007).

This analysis can be carried out using a device created by a company based in Gothenburg, Sweden, called Osstell, which monitors implant stability by measuring the resonance of a transducer attached to the implants at any stage of treatment and observation period (Hayashi et al., 2010). Studies have analysed resonance frequency analysis (RFA) in relation to its ability to measure implant stability and have confirmed its usefulness (Winkler et al., 2001). The aim of this study was to report the clinical case of a patient with a fractured root canal requiring extraction and immediate loading, in which Osstell was used to measure the primary stability of the implant friction during implant placement, the homogeneity of the implantation site, and implant factors such as shape conical or cylindrical, diameter, type of surface treatment, length, thread shape, presence of retentive grooves, and surface modifications can influence RFA and insertion torque values (Bannwart et al., 2024).

Case report

A 54-year-old female patient came to the Prosthodontics Postgraduate Clinic at the School of Dentistry with a diagnosis of root fracture of the upper right lateral incisor (Figure 1), which had already been rehabilitated with a cast metal core and full crown (Figure 2). Prior to the surgery to extract the remaining root canal and install the implant, the patient was asked to undergo panoramic complementary radiographic (Figure 3) and laboratory tests in order to assess whether her systemic condition was favourable for the surgical procedure (complete blood count, creatinine, glycemia, urea and coagulation time) (Bannwart et al., 2024).

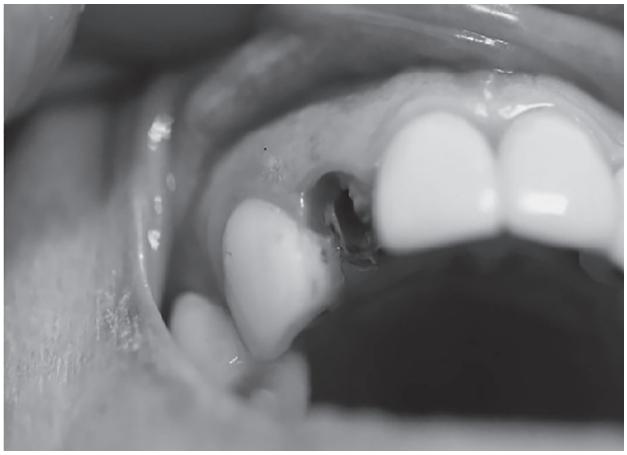

Figure 1: Intraoral clinical aspect showing alveolus with root remnant.

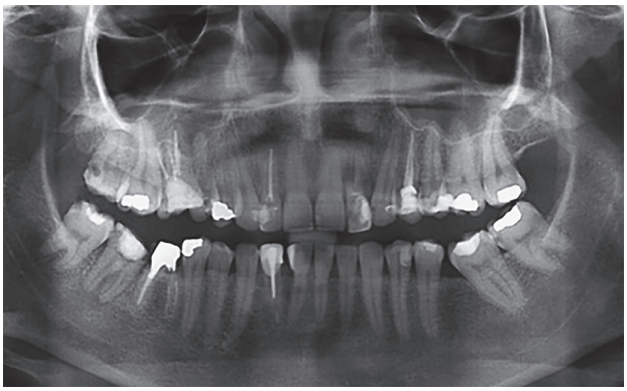

Figure 2: Cast metal core and full crown.

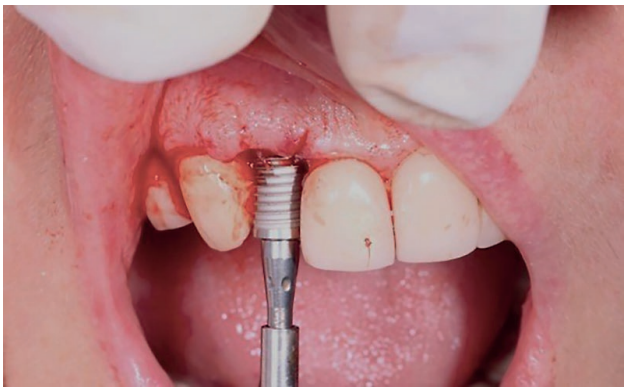

Figure 3: Panoramic radiograph after crown repositioning.

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Pre preparation

At the surgical stage, the patient's vital signs were checked blood pressure and heart rate, followed by antibiotic prophylaxis amoxicillin 1 g one hour before the procedure began.

In accordance with the appropriate biosafety standards, mouth antisepsis was performed, instructing the patient to rinse their mouth for 1 minute with 0.12% chlorhexidine antiseptic solution Periogard (Colgate, São Paulo, Brazil). The patient was then given an extra-mouth antisepsis using polyvinylpyrrolidone and iodine, 9% active iodine (PVPI), the operative field was affixed and infiltrative terminal anesthesia using mepivacaine Mepiadre 100, mepivacaine hydrochloride 2% with epinephrine 1:100,000, Dental Industry, RJ, Brazil (DFL) (Goiato et al., 2016; Bannwart et al., 2024).

Surgical phase

Local anesthesia was applied by infiltration with anesthetic together with vasoconstrictor. When necessary, after incision and syndesmotomy, the surgical bed was prepared by reaming with abundant irrigation with saline solution. A hexagonal Morse cone implant was installed. After completion of the surgical phase, the incised regions were sutured and medications were prescribed using the following protocol: antibiotic, amoxicillin 500 mg–1 gram 1 h before surgery followed postoperatively by one 500 mg tablet every 8 hours for 7 days 6; anti-inflammatory agent, nimesulide one 100 mg tablet 1 h before surgery followed postoperatively by one 150 mg tablet every 12 hours for 3 days (Goiato et al., 2016; Bannwart et al., 2024).

The root remnant had to be extracted and an immediate implant placed (Figure 4).

For the implant, staggered bone milling was carried out under sterile saline irrigation. With the surgical guide in place, the initial drilling was carried out. The pilot drill was used in the socket and then the 3 mm drill in depth. The progressive sequence of cutters followed the manufacturer's instructions according to the type of implant used.

Implant placement

After preparation, the hexagonal Morse cone implant 3.75×13 mm (CMH Biofit DSP Biomedical, Campo Largo, Brazil), implant conical connection for better primary stability in the extracted root region, preventing and preserving the crestal bone (Souza et al., 2021). The implant was installed 1 to 2 mm below the bone crest, favouring aesthetics, and the maximum implant insertion torque was recorded. Installation was carried out using a contra-angle reducer driven by an electric motor with torque control BLM 600 Plus (Driller, São Paulo, Brazil) and a ratchet wrench with a manual torque wrench, which showed a value of 40 N×cm.

Immediately after implant installation, the Osstell® Mentor (Goteborg, Sweden) was used as another technique in addition to the torque wrench, in order to measure the primary stability of the implant. The implant was coupled to a resonance frequency transducer device, SmartPeg™, specific to each type of screw. The Osstell® measuring rod was approached by starting to stimulate the SmartPeg™ by emitting magnetic pulses, causing it to resonate at specific frequencies depending on the implant's level of stability (Figure 5).

Once the insertion torque and implant stability quotient (ISQ) values had been obtained, which represented a high primary stability value, presented an accepted high stability range (ISQ > 70) (Alsaadi et al., 2007), another alternative treatment that could have been carried out was placing the implant with immediate loading, i.e. installing the prosthesis on the implant immediately after installing the implant. However, as this was a research project in which the

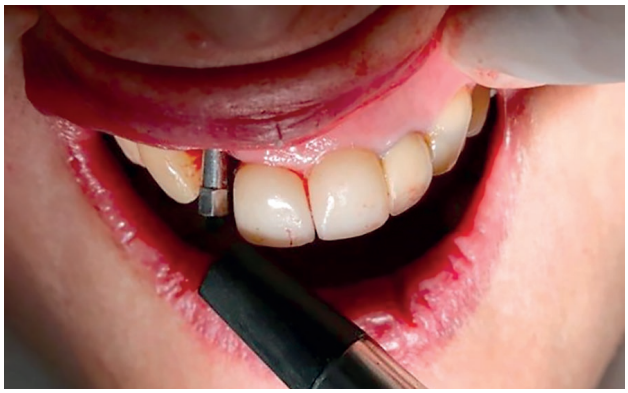

Figure 4: Trans-surgical implant placement immediately after root remnant removal.

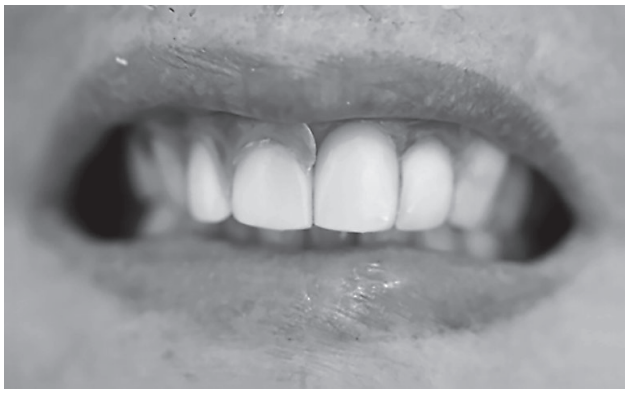

Figure 5: Measurement of primary implant stability using Osstell, immediately after implant placement.

focus was on measuring the stability of the implant immediately and six months after its installation, we opted to install the removable prosthesis, and finishing simple interrupted sutures were used with 4/0 nylons thread Procare, MedicoCoLtd.

Postoperative care

The patient was then rehabilitated with a temporary removable prosthesis until the implant had osseointegrated. In the post-operative period, the patient was instructed on the necessary post-operative care and medication with antibiotics amoxicillin, anti-inflammatories nimesulide and analgesics paracetamol in case of pain (Goiato et al., 2016; Bannwart et al., 2024).

Discussion

To ensure the osseointegration process, implant stability must be analysed at different times. The ability to measure stability helps the implant dentist decide on the loading of an implant, allows the choice of protocol for each patient and provides adequate documentation for the case (Atsumi et al., 2007).

The limitation of methods for verifying implant osseointegration, such as histological analysis, radiography and percussion tests due to their low degree of accuracy has led to the development of a non-invasive, clinically applicable diagnostic test which does not damage the bone-implant interface, is easy to use and reliable. In the resonance frequency analysis RFA method, a SmartPeg sensor is connected to the implant and then the tip of the device is held close to the sensor in the mesial, distal, buccal and lingual directions, while electromagnetic pulses are emitted. The description of RFA method and ISQ scale is repeated twice, which affects readability. RFA is a non-invasive way to evaluate implant stability. A SmartPeg™ is attached to the implant, and electromagnetic pulses are emitted from the Osstell device in various directions. The resonance frequency is then converted into ISQ value ranging from 1 to 100. According to the manufacturer, values above 70 indicate high stability, 60–69 medium stability, and below 60 low stability (Alsaadi et al., 2007).

No correlation was observed between insertion torque and ISQ, so we can say that they are independent methods that indicate two different characteristics of primary stability. The ISQ can indicate resistance to bending loads and the insertion torque can indicate resistance to shear forces (Souza et al., 2021).

The RFA technique provides clinically important information regarding the state of the bone-implant interface at any stage after implant placement. It can be used as an additional parameter for decision-making during treatment and all implant follow-up. Studies have analysed RFA in relation to its ability to measure implant stability and have affirmed its usefulness (Winkler et al., 2001).

Insertion torque values ranging from 30 to 40 N×cm represent good primary stability and are defined as limits for immediate loading (Souza et al., 2021).

In the study by Souza et al. (2021), 25 patients (average age 50 ± 9 years) received implants, most of which were placed in bone types I and III. One failure was reported in a type III bone site, while implants placed in type II bone showed successful osseointegration after six months.

In the resonance frequency analysis RFA method, a SmartPeg sensor is connected to the implant and then the tip of the device is held close to the sensor in the mesial, distal, buccal and lingual directions, while electromagnetic pulses are emitted. Subsequently, the resonance frequency values are automatically converted to a scale called ISQ and shown on the device's display, where the values range from 1 to 100. The device manufacturer states that ISQ greater than 70 represents high stability, ISQ between 60 and 69, medium stability and ISQ less than 60 is considered low stability. Therefore, the higher the ISQ, the greater the stability of the implant (Alsaadi et al., 2007).

No correlation was observed between insertion torque and ISQ, so we can say that they are independent methods that indicate two different characteristics of primary stability. The ISQ can indicate resistance to bending loads and the insertion torque can indicate resistance to shear forces (Choi et al., 2014; Souza et al., 2021).

Based on previously conducted studies, the RFA device has been widely used in clinical studies to assess implant stability, although it also has limitations due to the need for a specific transducer that is not available for all implant systems, in addition to difficulties in use in prostheses cemented with implants (Choi et al., 2014).

Implant design is essential to achieve stability. The external and superficial geometry of the screw is designed to promote a larger surface area of contact between bone and implant, which induces greater bone growth and load distribution, favouring superficial anchorage and offering resistance to insertion torques (Souza et al., 2021).

The advantage of using the Osstell device to analyse resonance frequency is that it can be measured at any stage of rehabilitation (Andreotti et al., 2017). In this way, it can be assessed at the time of implant installation, during the trans operative period, or even at the stage of prosthesis installation or after its

installation. The Osstell device allows implantologists to obtain clinically important and indispensable information about the stability of the bone-implant interface at any stage after implant placement.

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Plasma Cell Vulvitis (Zoon's Vulvitis): A Rare Case Report with Emphasis on Diagnostic Challenge

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Abstract: Plasma cell vulvitis (PCV), also referred to as Zoon's vulvitis, is a rare and chronic inflammatory condition of the vulva characterized by distinctive red, glistening patches with a subtle red-orange hue. The condition can be asymptomatic or present with symptoms such as discomfort, dyspareunia, and pruritus, often mimicking other vulvar mucosal disorders like lichen planus. Due to its rarity and the overlap of symptoms with more common vulvovaginal conditions, PCV is frequently underreported and misdiagnosed. The exact etiology of PCV remains unclear, with possible associations to herpes simplex virus (HSV) and abnormal immune responses being hypothesized. This manuscript presents a case of PCV in a 46-year-old female who presented with a red, glistening, focally ulcerated patch on the vulva.

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Introduction

Plasma cell vulvitis (PCV), also called Zoon's vulvitis, is an uncommon, chronic inflammatory condition of the vulva, marked by distinct red, glistening patches with a subtle red-orange tint (Goldstein et al., 2005; Damiani et al., 2017). The prevalence of PCV is not well-documented due to its rarity and likely under reporting, which can be attributed to the overlap of its symptoms with more common vulvo-vaginal disorders (Damiani et al., 2017). PCV can present as an asymptomatic lesion or cause symptoms such as discomfort, dyspareunia (pain during intercourse), and pruritus (itching), often resembling other vulvar mucosal conditions like lichen planus (Virgili et al., 2015).

The exact pathophysiology of PCV is not well understood. Some hypotheses suggest a possible link to herpes simplex virus (HSV), while others propose that it may result from an abnormal immune response (Morioka et al., 1988). This case report describes a rare occurrence of plasma cell vulvitis in a middle-aged woman, emphasizing the importance of biopsy for timely diagnosis and treatment. It highlights how patients presenting with well-defined red plaques and persistent vulvar discomfort should prompt consideration of PCV in the differential diagnosis.

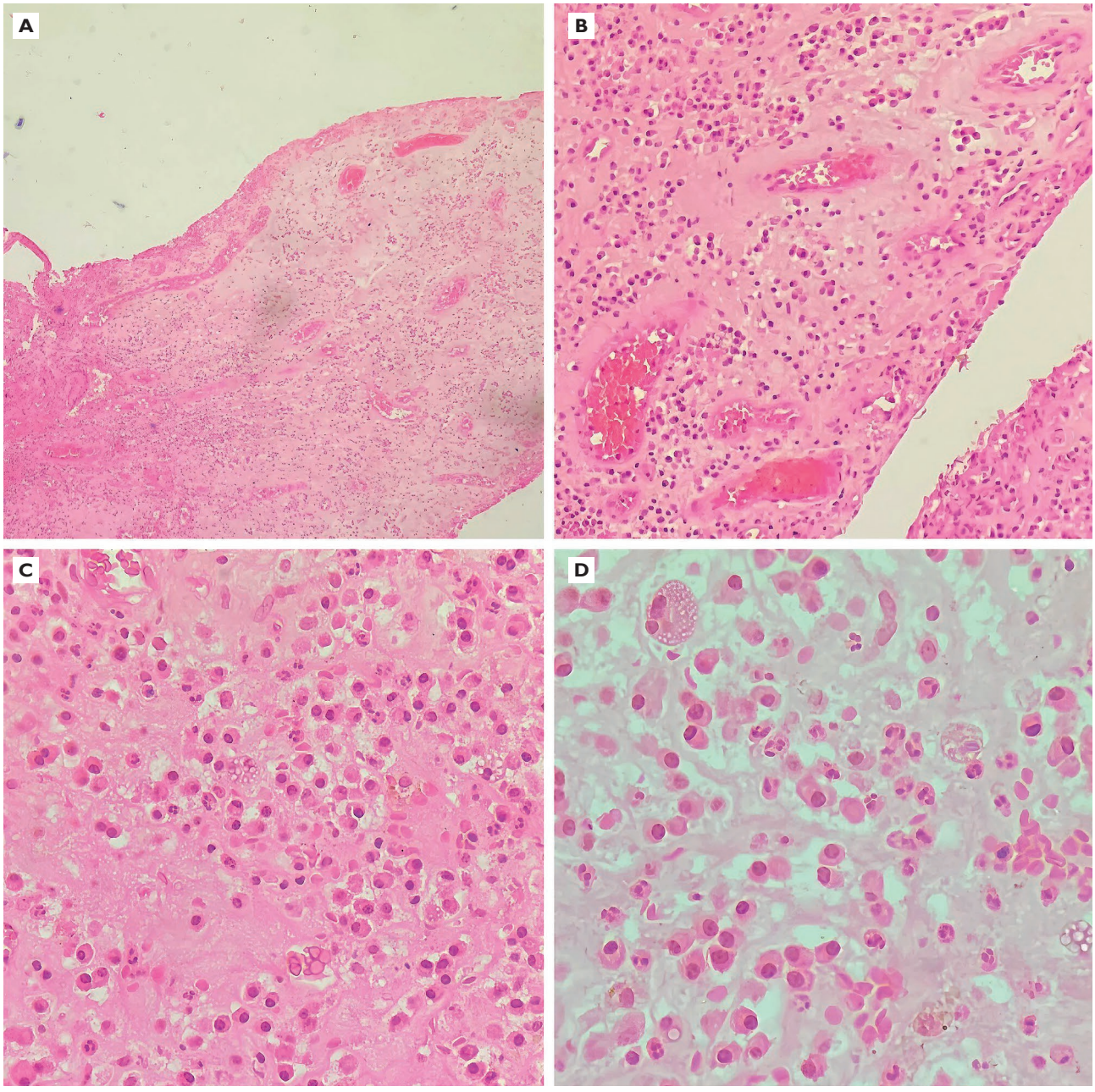

Figure 1: Histopathological features of plasma cell vulvitis. (A) Atrophic epidermis with focal ulceration (haematoxylin and eosin [H and E], 10×). (B) Subepithelial dense plasma cell infiltration with ectatic, congested vessels (H and E, 20×). (C and D) High-power view showing numerous plasma cells with eccentric nuclei and interspersed macrophages (H and E, 40×).

Case report

A 46-year-old female patient presented to the gynecology outpatient clinic with complaints of vulvar irritation, lower abdominal pain, and urinary incontinence for the past five months. She had a history of hysterectomy two years prior. There was no history of vaginal discharge, vulvar itching, allergic reactions, or medication use. Physical examination revealed a red, glistening, focally ulcerated patch on the vulva, measuring 1.5×2 cm in diameter. A biopsy was performed, and the specimen was sent for histopathological examination.

Histopathology revealed fragmented tissue lined by thin, atrophic epidermis with focal areas of ulceration. The underlying sub-epithelial stroma showed dense infiltration of plasma cells along with lymphocytes and histiocytes. Ectatic and congested small-caliber blood vessels were also noted (Figure 1). Based on these findings, a diagnosis of plasma cell vulvitis was made. The patient was prescribed topical steroids (2% hydrocortisone) and scheduled for follow-up.

Discussion

Zoon originally identified a chronic, benign inflammatory disorder of the penis and prepuce, histologically characterized by plasmacytic infiltration, which he termed balanitis plasmacellularis (Neri et al., 1995). In 1954, Garnier first described similar lesions in women as Zoon's vulvitis (Virgili et al., 2015).

PCV is indeed a rare condition, with an underreported prevalence likely due to its overlap with more common vulvovaginal disorders such as lichen planus, lichen simplex chronicus, and psoriasis, all contributing to its perceived rarity. Proper diagnosis typically requires a thorough medical history, physical examination, and often a biopsy to distinguish it from other similar conditions (Damiani et al., 2017).

The causes of PCV are still unclear. Due to its association with desquamative gingivitis, autoimmune polyglandular endocrine failure, and circulating antibodies, some researchers believe PCV may be linked to an autoimmune disorder (Doherty et al., 1993). Histopathologically, the hallmark of plasma cell vulvitis is a dense infiltrate of plasma cells in the subepithelial region. The overlying epithelium may show atrophy, hyperkeratosis, or parakeratosis. In addition to plasma cells, a mixed inflammatory infiltrate of lymphocytes and histiocytes may also be observed (Joshi, 1999).

Given the rarity of PCV, treatment strategies are often based on case reports, as incidence and management guidelines are poorly documented. Most case studies recommend topical steroids, although some describe the use of tacrolimus and other immunosuppressive therapies (Botros et al., 2006; Birx et al., 2010).

Conclusion

Owing mainly to its clinical similarity to more prevalent vulvovaginal dermatoses, PCV is still an uncommon, underdiagnosed, and sometimes misunderstood chronic inflammatory condition. This example emphasizes how crucial it is to take PCV into account while making a differential diagnosis for persistent vulvar lesions. Histopathological analysis is essential for making a conclusive diagnosis since it shows distinctive infiltrates that are rich in plasma cells. While the precise cause is still unknown, new data points to potential viral or autoimmune connections. Increased knowledge among pathologists and clinicians, along with timely biopsy and suitable therapy, can greatly enhance patient outcomes and avoid needless morbidity brought on by an inaccurate or delayed diagnosis.

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