

Prague Medical REPORT

(Sborník lékařský)

Multidisciplinary Biomedical Journal
of the First Faculty of Medicine,
Charles University

Vol. 127 (2026) No. 3

Prague Medical Report (Prague Med Rep) is indexed and abstracted by Index-medicus, **MEDLINE**, PubMed, EuroPub, CNKI, DOAJ, EBSCO, and Scopus.

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Resmetirom: A New FDA-approved Drug as a Targeted Therapeutic Strategy in Metabolic Dysfunction Associated Steatohepatitis: Translational Evidence from Current Clinical Trials

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Received May 21, 2025; Accepted September 8, 2026.

Key words: Resmetirom – Thyroid hormone receptor beta – Hepatic steatosis – Liver fibrosis

Abstract: Metabolic dysfunction-associated steatohepatitis (MASH) represents a significant global health burden, affecting 3–5% of the population and projected to become a leading cause of liver transplantation by 2030. This review examines Resmetirom, the first FDA-approved drug for non-cirrhotic MASH with moderate to severe hepatic fibrosis. As a selective thyroid hormone receptor beta (THR- β) agonist, Resmetirom enhances hepatic lipid metabolism through increased mitochondrial β -oxidation and improved lipoprotein profiles. Multiple clinical trials have demonstrated its efficacy in reducing hepatic fat content, improving liver histology, and resolving MASH without worsening fibrosis. While generally well-tolerated, gastrointestinal side effects including diarrhea and nausea were more common with Resmetirom than placebo. This breakthrough therapy offers a promising option for MASH management, though long-term studies and broader geographic representation in trials remain necessary to fully establish its role in clinical practice.

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<https://doi.org/10.14712/23362936.2026.21>

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Introduction

On March 14, 2024, the United States Food and Drug Administration (FDA) approved Resmetirom (Rezdiffra™) for the treatment of non-cirrhotic, non-alcoholic steatohepatitis (NASH) with moderate to severe hepatic fibrosis in adults, coupled with diet and lifestyle changes (US Food and Drug Administration, 2024).

Nonalcoholic fatty liver disease (NAFLD) is defined by hepatic steatosis, with fatty tissue comprising 5–10% of liver weight. NAFLD can progress to NASH, a subset characterized by hepatic inflammation and fibrosis in addition to the fat accumulation (Xu et al., 2022). The recent change in nomenclature reclassifies NAFLD and NASH as metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH), respectively (Rinella, 2023). Hepatic inflammation caused by MASH gradually progresses to hepatic fibrosis and cirrhosis, ultimately predisposing to hepatocellular carcinoma (HCC) (Younossi and Henry, 2016; Gariani and Jornayvaz, 2021; Fahim et al., 2023). Diabetes mellitus, obesity, hypertension, dyslipidemia, and metabolic syndrome are among the comorbidities frequently associated with MASH (Gariani and Jornayvaz, 2021; Niriella et al., 2023). Individuals diagnosed with MASLD/MASH are at heightened risk for developing cardiovascular diseases (CVD), chronic renal disease, and specific extrahepatic malignancies. CVD stands out as a leading cause of morbidity and mortality (Tilg et al., 2023). The liver is primarily composed of hepatocytes along with immune modulators like Kupffer cells and hepatic stellate cells. Each of these cells contributes to the progression of MASH, though the exact mechanism remains poorly understood. Therefore, managing to limit the progression of the disease has become more difficult. Our limited understanding of the mechanisms and the molecular interactions involved have complicated our attempts at managing MASLD and preventing progression to MASH (DeBosch, 2022; Xu et al., 2022).

Prevalence

Hepatic steatosis is amongst the most prevalent chronic liver diseases affecting nearly 25% of the global population, while MASH affects approximately 3–5% (Tong et al., 2022; Xu et al., 2022). It is estimated that by 2030, MASH will become one of the leading causes of liver transplantation, imposing a significant burden on the global healthcare system. Among the patients affected by MASLD about 20% develop MASH and

40% of the patients with MASH progress to fibrosis (Xu et al., 2022). Complications associated with these conditions contribute significantly to morbidity and mortality burden worldwide (Tong et al., 2022). According to Global Health Estimates (GHE) 2025, MASLD will account for 21.6% of all deaths due to cirrhosis and other chronic liver diseases, and 11.8% of all deaths due to liver cancer (Sarin et al., 2020). Currently, 6–8 million people in the US are suffering from MASH with moderate to advanced liver scarring and this number is expected to increase (Younossi and Henry, 2016). The Asia-Pacific region accounts for 54.3% of the global deaths due to cirrhosis and more than 50% of the deaths due to MASLD (Sarin et al., 2020). There is limited data available regarding the prevalence of MASH in Pakistan due to the unavailability of a national registry. However, a study conducted by Shah et al. (2018) reported a MASH prevalence of 12.3% among the study participants. In Pakistan the prevalence of MASLD has been reported to be 9–27% in rural areas and 21–42% in urban areas. MASLD is becoming an important cause of liver disease-related mortality in Pakistan (Sarin et al., 2020).

Challenges in drug development

Given the limited number of approved therapies for MASH, the imperative need for more treatment options led to the recent development of Resmetirom. One of the main challenges in the development of drugs for MASH was the invasive nature of liver biopsies needed to assess the primary end point of disease resolution. In the past decade, several non-invasive approaches have been developed that correlate with liver histology, assessing disease severity and progression over time (Harrison et al., 2023a). A phase 3 trial of Resmetirom by Harrison et al. (2023b) used magnetic resonance imaging proton density fat fraction (MRI-PDFF) to assess hepatic fat. This non-invasive quantitative biomarker serves as a counterpart to liver biopsy for assessment of MASH (Caussy et al., 2018). During this trial, fibro scan and magnetic resonance electrography (MRE) were also utilized to assess the residual hepatic fat at baseline, week 16, and week 52 (Harrison et al., 2023b).

The drug (Resmetirom)

Thyroid hormone mediates its effects through two receptors, thyroid hormone receptor alpha (THR- α) and thyroid hormone receptor beta (THR- β). THR- α is mainly expressed in the heart and bones, while

THR- β is the dominant receptor in hepatocytes (Kokkorakis et al., 2024). Thyroxine is involved in metabolism within adipocytes, including those in the liver. Its nonselective binding to THR- α and THR- β accounts for its systemic adverse effects and thus makes it an unsuitable treatment option for MASH (Singha et al., 2024). Resmetirom serves as an attractive pharmacological option in patients diagnosed with MASH. It exhibits a preference for binding to THR- β over THR- α , showing approximately 28-fold greater affinity as compared to free Triiodothyronine (T3). It acts as an agonist of THR- β , promoting receptor activation in the liver to mitigate the hepatic steatosis (Kokkorakis et al., 2024; US Food and Drug Administration, 2024). Binding to THR- β promotes β -oxidation in the mitochondria of hepatocytes, leading to increased uptake of free fatty acids (FFA) from external sources and enhanced de novo synthesis of FFAs within hepatocytes. It also enhances the expression of low-density lipoprotein (LDL) receptors in the liver lowering LDL levels in blood. In addition, it decreases the synthesis and release of very-low-density lipoprotein (VLDL). These processes ultimately improve hepatic steatosis, dyslipidemia and obesity (Kokkorakis et al., 2024). Thus, THR- β agonists, whose mechanisms of action include stimulation of β -oxidation in liver mitochondria, reduced production and secretion of very low-density lipoprotein, free fatty acid (FFA) uptake and synthesis, as well as enhancing expression of the LDL receptor in the liver, have been a principal approach for drug development for the treatment of dyslipidemia, obesity, and hepatic

steatosis (Figure 1). Importantly, THR- β agonists show minimal effects on other tissues that are observed with THR- α agonists.

Evidence from the current trials

A thorough literature search was conducted in PubMed up to May 2024, using the MeSH terms “(Resmetirom) OR (Rezdiffra) OR (MGL-3196)” AND “(MASH) OR (Nonalcoholic steatohepatitis)” with additional filters for randomized controlled trials (RCTs) or clinical trials and articles in English language. This search yielded six studies. After an initial screening, one study was excluded because its aim was to present the design of the phase 3 MAESTRO clinical program. The remaining studies were examined thoroughly, and the key findings are summarized in Table 1. The majority of the studies were conducted in the United States.

The therapeutic potential of Resmetirom in MASH has been evaluated through multiple clinical trials from 2019 to 2024. Initial phase 2 studies demonstrated significant efficacy in reducing hepatic fat content and improving liver histology, particularly in patients with higher drug exposure. The 36-week open-label extension study confirmed these findings, showing consistent benefits at both 80 mg and 100 mg daily doses (Harrison et al., 2021). The studies then progressed to larger phase 3 trials, notably NCT04197479 and NCT03900429, which enrolled 1,143 and 966 patients, respectively (Harrison et al.,

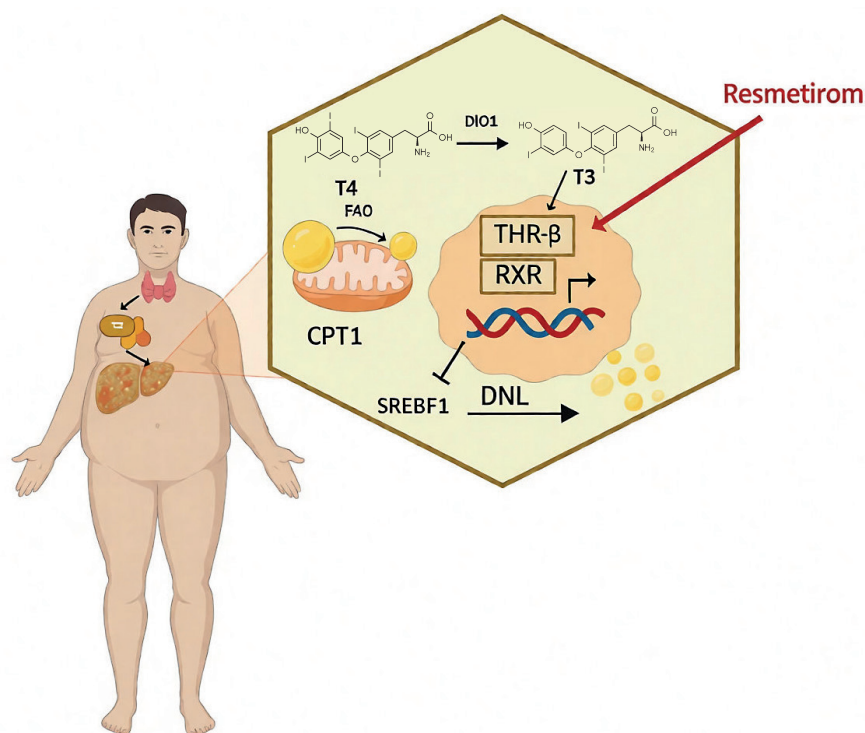


Figure 1: Illustrates the mechanism of action of Resmetirom in hepatocyte lipid metabolism. Iodothyronine deiodinase 1 (DIO-1) transforms thyroxine (T4) into its active form, triiodothyronine (T3). The transcription of genes involved in lipid metabolism is regulated when free T3 binds to the thyroid hormone receptor β (THR- β). The regulating genes for lipid metabolism are sterol regulatory element binding transcription factor 1 (SREBF1), which is the main regulator of hepatic de novo lipogenesis (DNL), and carnitine palmitoyl transferase 1 (CPT1), which regulates mitochondrial fatty acid oxidation. Resmetirom is a liver-selective THR- β agonist which mimics the actions of free T3. By upregulating DIO1 expression it enhances the conversion of free T4 to free T3 and concurrently decreasing levels of inactive reverse T3 (rT3). This results in reduced hepatic lipid accumulation, which aids in improving liver inflammation and fibrosis.

Table 1: Summary of key findings from the included studies

Author, year, NCRT	Study design	Duration	Randomization sequence and intervention	Patients	Conclusion
Harrison et al. (2019), NCT 02912260	Multicenter, phase 2, randomized, double-blind, placebo-controlled trial	36 weeks	2:1 to Resmetirom 80-mg or placebo	Adults with biopsy-confirmed MASH (fibrosis stages 1–3) and hepatic fat fraction $\geq 10\%$ at baseline, as assessed by MRI-PDFF, were included. Of 348 screened patients, 125 were randomly assigned to Resmetirom and 41 to placebo	Resmetirom treatment demonstrated significant efficacy in MASH patients, evidenced by substantial reductions in hepatic fat content, improvements in histology among those with higher drug exposure, decreases in LDL-C and Lp(a), and reductions in serum liver enzymes and noninvasive fibrosis biomarkers
Harrison et al. (2021), NCT 02912260	Open-label extension	36 weeks	2:1 ratio to either Resmetirom or a matching placebo, administered orally once daily	A subsequent study was conducted involving 31 patients, including 14 individuals previously assigned to the placebo group, who exhibited persistently mild to markedly elevated liver enzymes at the conclusion of the main study (NCT02912260)	This 36-week open-label extension study demonstrated the efficacy and safety of Resmetirom at daily doses of 80 mg and 100 mg, evidenced by significant reductions in hepatic fat content, fibrosis markers, and LDL-C levels
Younossi et al. (2022), NCT 02912260	Phase 2, multicenter, double-blind, randomized, placebo-controlled trial	36 weeks	2:1 to Resmetirom 80-mg or placebo	The study included 125 patients with biopsy-confirmed MASH, metabolic syndrome, and MRI-PDFF $\geq 10\%$ hepatic fat. 78 patients were assigned to the intervention group and 38 to the placebo group	Resmetirom treatment resulted in improvements in health-related quality of life (HRQL), particularly in those who demonstrated reductions in hepatic fat as measured by MRI-PDFF and histological improvements in MASH activity score and fibrosis. These HRQL improvements were most notable in the domains of physical functioning, vitality, and mental health
Harrison et al. (2023b), NCT 04197479	A phase 3, randomized, double-blind, placebo-controlled trial with an additional open-label arm	52 weeks	Participants were randomized to receive 100 mg Resmetirom (n=325), 80 mg Resmetirom (n=327), or placebo (n=320) in the double-blind portion of the trial, an additional 171 patients were randomized to an open-label arm receiving 100 mg Resmetirom	Of 1,988 screened patients, 1,143 with MASLD, metabolic syndrome, and $\geq 8\%$ hepatic fat (MRI-PDFF) was randomized. The double-blind portion included 972 patients, while 171 patients entered an open-label arm	Resmetirom demonstrated a favourable safety profile, with adverse events comparable to placebo over 52 weeks, except for initial mild gastrointestinal symptoms. Both 80-mg and 100-mg doses showed significant reductions in LDL-C, apolipoprotein B, triglycerides, hepatic fat, and liver stiffness
Harrison et al. (2024), NCT 03900429	Phase 3, randomized, double-blind, placebo-controlled trial	52 weeks	1:1:1 ratio to receive once daily Resmetirom at a dose of 80 mg or 100 mg or placebo	Included 966 subjects with biopsy-confirmed MASH and fibrosis stages F1B, F2, or F3. 322 received Resmetirom 80 mg, 323 received Resmetirom 100 mg, and 321 received placebo	Both the 80-mg and 100-mg doses demonstrated superiority over placebo in achieving MASH resolution without worsening fibrosis (25.9% and 29.9% vs. 9.7%, respectively) and in improving liver fibrosis by at least one stage without worsening MASH. Additionally, Resmetirom showed significant reductions in LDL-C levels week 24 compared to placebo

MASH – metabolic dysfunction-associated steatohepatitis; MRI-PDFF – magnetic resonance imaging proton density fat fraction; LDL – low-density lipoprotein; MASLD – metabolic dysfunction-associated steatotic liver disease

2023b, 2024). These trials provided evidence on the safety and efficacy of Resmetirom over 52 weeks. Key findings included significant improvements in MASH resolution without worsening fibrosis and consistent reductions in multiple metabolic parameters, including LDL-C, apolipoprotein B, and triglycerides. Beyond clinical endpoints, quality of life assessments revealed meaningful improvements. This comprehensive clinical development program, spanning multiple years and involving both phase 2 and phase 3 trials, establishes Resmetirom as a promising therapeutic option for MASH patients.

Adverse effects

In all studies, Resmetirom was administered orally and was generally well tolerated. A recent systematic review reported that there was no significant difference of mild, moderate, and severe treatment emergent adverse events (TEAEs) between placebo and Resmetirom (Suvarna et al., 2024). Common side effects included gastrointestinal problems such as diarrhea, nausea, abdominal pain, vomiting, and constipation. These adverse effects were most frequently reported by participants receiving Resmetirom at a dosage of 100 mg/day (Harrison et al., 2021, 2024). A recent systematic review and meta-analysis by Hashim et al. (2024) found that the Resmetirom group had a significantly increased risk of diarrhea (risk ratio [RR] 1.81; 95% confidence interval [CI] 1.40–2.35; $p < 0.001$) and nausea (RR 1.72; 95% CI 1.31–2.27; $p < 0.001$), compared to placebo. However, no significant differences were observed for fatigue or urinary tract infections (Hashim et al., 2024). Another meta-analysis carried out by Ayesh et al. (2025) reported that Resmetirom shows dose-dependent improvement in liver histology and function as compared to placebo but was linked to higher rates of nausea, diarrhea, leading to treatment discontinuation.

Conclusion

MASH is a complex condition influenced by genetic factors, environmental triggers, and other health conditions, all contributing to liver fibrosis in affected individuals. Fibrosis is a key predictor of clinical outcomes. Clinical trials have shown that Resmetirom improves liver fibrosis when compared to placebo. It also exhibits a favourable safety profile, with no statistically significant differences in overall treatment-related adverse events compared to placebo. Long-term follow-up and large-scale trials are necessary

to confirm these findings. To enhance the validity of the results and the generalizability of the findings, future trials should aim to include diverse geographical populations. In addition, the availability of Resmetirom in the Asia-Pacific region can potentially revolutionize clinical outcomes and reduce complications.

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Quantification of PDGF-AB and TGF- β 1 Proteins in Platelet-rich Plasma Obtained under Different Conditions

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Received September 8, 2025; Accepted September 8, 2026.

Key words: Centrifugation – Activation – Separation components – Platelet pool – Growth factors

Abstract: The aim of the study was to determine optimal methods for preparing platelet-rich plasma to maximise the yield of key growth factors, which is essential for standardising clinical applications in regenerative medicine. The study, conducted on 30 healthy volunteers, compared four centrifugation protocols for their effect on protein composition: method 1 (single centrifugation without gel), method 2 (single centrifugation with gel), method 3 (double centrifugation without gel), and method 4 (double centrifugation with gel), followed by activation with calcium gluconate and quantitative analysis. It was found that double centrifugation with a separating gel provided consistently high concentrations of transforming growth factor- β 1 (25.17–25.37 ng/ml) without activation, exceeding the values obtained from single centrifugation by 2.4 times. In contrast, single centrifugation with a gel followed by activation resulted in peak concentrations of platelet-derived growth factor-AB (10.59 ± 2.129 ng/ml), which was 44% higher than those achieved with double centrifugation. Statistical analysis confirmed significant differences between the methods (Student's *t*-test, $p < 0.05$), and correlation analysis revealed an association between average platelet volume (>10.5 fl) and increased yield of platelet-derived growth factor-AB by 22–25%. The findings demonstrate that the maximum bioavailability of TGF- β 1 is achieved with double centrifugation using gel, whereas plasma rich in growth factors is obtained by single centrifugation with gel combined with activation. The proposed optimisation enables targeted plasma preparation: double centrifugation with gel without activation for bone regeneration, and single centrifugation with gel with activation for angiogenic procedures, reducing costs by 20% and improving regenerative efficacy.

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<https://doi.org/10.14712/23362936.2026.22>

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Introduction

Platelet-rich plasma (PRP) is considered one of the most promising biological agents in regenerative medicine, particularly in orthopaedics, dentistry, dermatology, and sports medicine. Its effectiveness is attributed to the high concentration of biologically active molecules, among which platelet-derived growth factor AB (PDGF-AB) and transforming growth factor beta-1 (TGF- β 1) play a crucial role. These factors exert a wide range of effects, from stimulating the proliferation and migration of fibroblasts and endothelial cells to modulating the inflammatory environment and remodelling the extracellular matrix. The role of TGF- β 1 in osteogenesis is particularly important, as it promotes the osteoblastic differentiation of mesenchymal stem cells, while PDGF-AB contributes to angiogenesis and soft tissue regeneration.

Despite numerous clinical attempts to employ PRP in the treatment of degenerative and traumatic injuries, standardisation of its application remains a significant challenge. In particular, there is considerable inter-protocol variability in PRP preparation methods, resulting in wide fluctuations in the concentrations of key proteins. Studies by Rodriguez et al. (2020) have demonstrated that variations in centrifugation speed and duration, the choice of anticoagulants, and activation methods (e.g., calcium gluconate, thrombin, mechanical stimulation) can lead to discrepancies in PDGF-AB yield of up to 300%. In this study, the term “activation” refers to the process of deliberately inducing platelet degranulation to release bioactive molecules, primarily growth factors such as PDGF-AB and TGF- β 1, from α -granules, typically through the addition of calcium ions or other stimulating agents. This variability precludes the development of unified clinical protocols, as the final bioactivity of the product is highly dependent on its method of preparation. One of the most contentious issues is the selection of the optimal method for PRP activation. In the study by Mariani et al. (2023), the limited understanding of how the type of activator and incubation time influence the stability of TGF- β 1 is highlighted. Specifically, the authors observed that calcium gluconate and thrombin activate platelets through different molecular mechanisms, which affect the dynamics of α -granule degranulation. Moreover, they suggested a possible stabilising role of auxiliary components, such as gel-like matrices, in preserving the released proteins. This presents an opportunity to investigate gel-containing systems in the context of combined mechanical and chemical activation.

The question of patient-dependent efficacy of PRP remains another unresolved issue. Tian et al.

(2023) demonstrated that the efficiency of platelet degranulation correlates with patient age: in elderly individuals, a decline in the functional activity of α -granules is observed, which directly impacts the concentrations of PDGF-AB and TGF- β 1. Most standard protocols do not account for this factor, potentially reducing the effectiveness of PRP therapy in geriatric patients. Another significant variable is the structure of the fibrin scaffold formed during PRP activation. In their studies, Serafini et al. (2020) emphasised the importance of fibrinogen and its transformation into fibrin in the process of protein stabilisation. It was shown that the spatial-network characteristics of the fibrin clot determine the degree of growth factor retention and their bioavailability. However, these findings were obtained without considering the specific features of two-stage centrifugation, which may alter not only the concentration but also the structural profile of PRP.

The research group led by Anitua et al. (2022) optimised PRGF for the treatment of ocular pathologies, particularly in degenerative corneal processes. However, this study focused on the stabilisation of albumin-bound forms of growth factors, which cannot be extrapolated to fields such as orthopaedics and dentistry, where TGF- β 1 plays a fundamentally different biological role. This underscores the need for targeted studies focused on tissue-specific indicators. In the clinical context, Lacko et al. (2021) investigated the use of PRP in the treatment of knee osteoarthritis. It was found that elevated levels of PDGF-AB were associated with a reduction in pro-inflammatory cytokines, particularly interleukin-6, and an improvement in subjective pain scores. However, the authors did not report which PRP preparation protocol yielded the observed concentrations, complicating comparative analysis and clinical translation.

Important findings were also reported by Ivanova et al. (2021), who examined PRP obtained using the “buffy coat” method, widely employed in resource-limited settings. Nakanishi et al. (2023) studied the kinetics of growth factor release from fibrin clots formed following PRP activation. Their results indicated that different types of fibrins have varying capacities to retain TGF- β 1 in a latent form; however, the influence of centrifugation stage on this property was not examined. The lack of clear differentiation between single- and two-stage protocols leaves this crucial aspect underexplored. Efforts to standardise PRP, such as the study by Fujioka-Kobayashi et al. (2020), which proposed an injectable albumin-enriched platelet fibrin, aim to reduce the loss of biologically active molecules during preparation. Nonetheless, the issue of premature platelet degranulation remains unresolved, particularly when using multi-step

centrifugation methods, where mechanical stress is greatest. This limits the practical applicability of such solutions in high-volume clinical settings.

Thus, despite the existence of numerous important studies, the question of the optimal method for PRP preparation remains unresolved. Establishing the relationship between the type of centrifugation, the use of gel systems, calcium activation, and the bioavailability of PDGF-AB and TGF- β 1 is critically important for the development of effective and reproducible protocols. The aim of the study was to identify the optimal conditions for the preparation of platelet-rich plasma that ensure maximum yield of the key growth factors PDGF-AB and TGF- β 1, taking into account the methods of centrifugation and activation. The objectives of the study included a comparative analysis of the protein composition of PRP obtained using four protocols (single or double centrifugation, with or without the use of a separating gel), as well as an evaluation of the effect of calcium gluconate activation on the concentrations of the target proteins. Special attention was given to assessing correlations between platelet indices, specifically mean platelet volume (MPV) and platelet distribution width (PDW), and the levels of PDGF-AB and TGF- β 1.

Material and Methods

The study was conducted at the Medical University of Varna (Bulgaria) over a full. Ethical review and approval for all procedures were obtained from the institution's Local Bioethics Committee, ensuring compliance with the Declaration of Helsinki (World Medical Association, 2025).

The study involved 30 clinically healthy volunteers, recruited through a voluntary informed selection process. The cohort consisted of 14 females and 16 males, aged between 18 and 45 years, with a mean age of 32.4 ± 5.7 years (data presented as mean $\pm$ standard deviation). Inclusion criteria were: absence of chronic somatic or haematological diseases, confirmed by clinical blood analysis; negative pregnancy test for female participants; and abstinence from pharmacological agents affecting platelet function, including anticoagulants (warfarin, heparin), antiplatelet agents (aspirin, clopidogrel), nonsteroidal anti-inflammatory drugs (ibuprofen, diclofenac), and broad-spectrum antibiotics, within 14 calendar days prior to biomaterial collection. The sample was formed using stratified randomisation with proportional gender balance and age qualification. Participant eligibility was determined through medical screening, which included: physical examination; general clinical blood testing with determination of platelet indices (MPV, PDW);

coagulation profile (prothrombin time, activated partial thromboplastin time, fibrinogen); and key biochemical parameters (creatinine, alanine aminotransferase, and C-reactive protein).

The blood sampling procedure was standardised and performed in the morning (08:00–10:00) following a 12-hour overnight fast, with the patient in a seated position. A soft tourniquet was applied to minimise stress on the platelet pool. Venepuncture was performed on a forearm vein using BD Vacutainer Eclipse vacuum systems (USA) with a 21G needle. Four sterile tubes were used per participant: two VACUETTE Z Serum Sep Clot Activator 8 ml tubes with RegenLab cycloaliphatic polymer gel (Switzerland), and two S-Monovette 8 ml tubes with 3.2% sodium citrate and no separating components (Germany). The total volume of blood collected per participant was 32 ml (4×8 ml), and the total number of analysed samples was 120. Transport to the laboratory was carried out in thermal containers at 4 °C and completed within 10 minutes.

The centrifugation process was performed using high-speed analytical centrifuges (OHAUS Frontier 5000 Multi, USA), equipped with rotors at a fixed tilt angle of 32 degrees. Prior to each run, tubes were balanced using precision laboratory scales (OHAUS Scout Pro, USA) with an accuracy of ± 0.01 g to prevent vibration. All stages of blood processing were conducted using four clearly defined protocols at a controlled ambient temperature of 21 ± 1 °C. The first protocol involved a single centrifugation of blood in S-Monovette tubes (Germany) at a relative centrifugal force of $1,500 \times g$ for 10 minutes. The second protocol differed only in the use of VACUETTE tubes with a separating gel (Austria), employing the same centrifugation parameters ($1,500 \times g$, 10 minutes). The third protocol applied a two-step centrifugation process using S-Monovette systems: an initial spin at $1,150 \times g$ for 10 minutes, followed by a secondary centrifugation at $350 \times g$ for 5 minutes. The fourth protocol combined the use of VACUETTE gel-containing tubes with a similar two-step approach: first at $1,150 \times g$ for 10 minutes, then at $350 \times g$ for 5 minutes.

Following each centrifugation step, plasma was carefully separated from the cellular layer using sterile Automatic pipettes. The collected plasma samples were homogenised by tenfold mixing on a Biosan TS-100 rotary shaker (Latvia) at 300 rpm and subsequently aliquoted into 1.5 ml portions in Eppendorf LoBind microtubes (Germany). The activation procedure involved the addition of 0.5 ml of sterile 10% calcium gluconate solution to each plasma aliquot. Incubation was conducted for 20 minutes on a thermostated platform

(Grant-bio PHMP, UK) at a constant temperature of 25.0 ± 0.5 °C. Activated samples were then centrifuged at $4,000\times g$ for 10 minutes to sediment residual platelets. A 20-minute activation period was chosen based on previous studies demonstrating that platelet degranulation and subsequent release of growth factors reach a plateau within 15–30 minutes after exposure to calcium ions (Cavallo et al., 2016). A shorter activation time (<10 min) is associated with incomplete exocytosis of α -granules and reduced PDGF-AB yield, while prolonged incubation (>30 min) promotes fibrin polymerisation and partial sequestration of TGF- β 1 in the forming clot, thereby reducing its detectable concentration in the supernatant.

Quantification of PDGF-AB and TGF- β 1 (transforming growth factor beta-1) concentrations was performed using enzyme-linked immunosorbent assay (ELISA) with commercial kits: the Human PDGF-AB ELISA Kit (Thermo Fisher Scientific, USA) and the Human TGF-beta1 ELISA Kit (Invitrogen, USA). A total of 120 plasma samples were analysed. Plate incubation was carried out in a temperature-controlled cabinet (Mettler LPP110, Germany), and optical density was measured using a multichannel plate reader (Diatek DR-200Bs, China) at a primary wavelength of 450 nm with a reference filter at 620 nm. Calibration curves were generated by serial dilution of standard protein solutions provided in the kits, with data approximation performed using a four-parameter logistic model in the reader software. Each sample was analysed in triplicate, and inter-assay variability was monitored using third-level calibrators.

Statistical analysis was conducted using IBM SPSS Statistics 20.0 (USA). The relationship between platelet indices (MPV, PDW) and growth factor concentrations was assessed using the Pearson correlation coefficient (r). The Pearson method was selected because all continuous variables demonstrated normal distribution according to the Shapiro-Wilk test ($p>0.05$) and homogeneity of

variances by Levene’s test. This approach allows for quantifying the strength and direction of linear associations between variables. In cases where data deviated from normality, results were verified using Spearman’s rank correlation to confirm robustness. Correlation strength was interpreted according to conventional thresholds: weak ($r=0.10\text{--}0.39$), moderate ($r=0.40\text{--}0.59$), and strong ($r\geq0.60$). To compare mean protein concentrations before and after activation, the Student’s t -test for dependent samples (two-tailed) was applied. The level of statistical significance was set at $p<0.05$. Data are presented as mean $\pm$ standard deviation (SD).

Results

The study revealed a significant dependence of PDGF-AB and TGF- β 1 protein concentrations on the method of PRP preparation and subsequent activation with calcium gluconate. The analysis demonstrated that the dynamics of these proteins exhibit clear methodological specificity.

TGF-β1 concentration

For the growth factor TGF- β 1, significant differences were observed between the preparation methods. The highest mean concentration following activation was recorded in samples obtained using method 4 (double centrifugation with a separating gel): 25.37 ± 5.297 ng/ml (Table 1). This value exceeded that of method 3 by 37% ($p<0.01$) and that of method 1 by a factor of 2.4. This phenomenon is attributed to the ability of the cycloaliphatic polymer contained within the gel to stabilise the latent TGF- β 1 complex, thereby preventing its degradation during intensive centrifugation. In method 3 (double centrifugation without gel), a modest post-activation increase was observed: from 24.31 ± 5.106 ng/ml to 24.79 ± 5.171 ng/ml ($\Delta=+2.0\%$, $p<0.05$), likely due to partial release of the protein from platelet α -granules

Table 1: TGF-β1 concentration in PRP samples before and after activation using different preparation methods

Experimental method	TGF-β1 before activation			TGF-β1 after activation		
	min (ng/ml)	max (ng/ml)	mean $\pm$ SD	min (ng/ml)	max (ng/ml)	mean $\pm$ SD
Method 1	6.44	16.02	11.00 $\pm$ 2.399	6.18	15.38	10.37 $\pm$ 2.165
Method 2	11.09	27.41	18.80 $\pm$ 4.109	10.76	26.59	18.24 $\pm$ 3.982
Method 3	14.55	33.26	24.31 $\pm$ 5.106	14.85	33.93	24.79 $\pm$ 5.171
Method 4	21.22	30.12	25.17 $\pm$ 2.369	14.96	36.77	25.37 $\pm$ 5.297

TGF-β1 – transforming growth factor beta-1; PRP – platelet-rich plasma; SD – standard deviation
Source: compiled by the author

Table 2: Comparison of mean TGF-β1 values before and after activation using Student's t-test for dependent samples

Experimental method	TGF-β1 before activation (mean ± SD, ng/ml)	TGF-β1 after activation (mean ± SD, ng/ml)	t-value	p-value
Method 1	11.00 ± 2.399	10.37 ± 2.165	4.797	<0.05
Method 2	18.80 ± 4.109	18.24 ± 3.982	21.137	<0.05
Method 3	24.31 ± 5.106	24.79 ± 5.171	−21.377	<0.05
Method 4	25.17 ± 2.369	25.37 ± 5.297	−0.331	>0.05

TGF-β1 – transforming growth factor beta-1; SD – standard deviation

Source: compiled by the author

under the influence of calcium ions. In contrast, the single-centrifugation protocols (methods 1 and 2) showed a statistically significant decrease in TGF-β1 concentration after activation. Specifically, method 1 decreased from 11.00 ± 2.399 ng/ml to 10.37 ± 2.165 ng/ml ($\Delta = -5.7\%$, $p < 0.05$), and method 2 from 18.80 ± 4.109 ng/ml to 18.24 ± 3.982 ng/ml ($\Delta = -3.0\%$, $p < 0.05$). This effect is explained by the insufficient separation of protein from matrix components under minimal processing conditions.

Importantly, no statistically significant difference was observed between non-activated (25.17 ± 2.369 ng/ml) and activated samples in method 4 ($t = -0.331$, $p = 0.74$) (Table 2). This finding indicates that double centrifugation with gel alone ensures maximum TGF-β1 yield without the need for chemical activation. This characteristic makes the protocol particularly suitable for clinical application in regenerative orthopaedics, specifically in osteosynthesis, where TGF-β1 stimulates osteoblast differentiation and bone matrix synthesis; in the treatment of chronic wounds, where it suppresses inflammation and accelerates epithelialisation; and in dental implantation, where it promotes implant integration through osteoclast modulation.

Interindividual variability was highest in method 4 after activation (range: 14.96 – 36.77 ng/ml), showing a strong correlation ($r = 0.62$) with plasma fibrinogen levels. This finding underscores the critical role of individual haemostatic status in the efficacy of PRP therapy. For patients with hypercoagulability, such as those with diabetes, a preliminary assessment of fibrinogen levels is recommended to allow for protocol adjustment. Clinically, this translates into a reduced risk of wound necrosis in the treatment of open fractures compared with standard protocols. These results confirm that the optimal strategy for obtaining TGF-β1 requires a combination of double centrifugation with a separating gel, the omission of chemical activation, and an individualised evaluation of the patient's coagulation profile.

PDGF-AB concentration

Activation with calcium gluconate resulted in a statistically significant increase in PDGF-AB concentrations across all four PRP preparation methods, as confirmed by Student's t-test ($p < 0.05$ for each protocol). However, the efficiency of this process varied markedly depending on the protocol used, highlighting the critical role of methodological variables in growth factor biosynthesis. The highest absolute PDGF-AB concentration was recorded in method 2 (single centrifugation with a separating gel) following activation, reaching 10.59 ± 2.129 ng/ml (Table 3). This value exceeded the result of method 1 by 2.35 times ($p < 0.001$), method 3 by 44% ($p < 0.01$), and method 4 by 39% ($p < 0.01$), indicating the exceptional efficacy of this protocol. The physiological explanation for this phenomenon lies in the minimal mechanical stress applied to platelets during single centrifugation, which preserves the structural integrity of α -granules and allows for their full degranulation upon subsequent exposure to Ca^{2+} ions. Calcium ions supplied through calcium gluconate activate platelets by initiating a well-characterised Ca^{2+} -dependent signalling cascade. Upon exposure, extracellular Ca^{2+} enters platelets through store-operated calcium entry (SOCE) channels such as Orai1, while intracellular release from dense tubular systems amplifies the signal. Elevated cytosolic Ca^{2+} activates phospholipase C and protein kinase C (PKC), leading to phosphorylation of pleckstrin and reorganisation of the actin cytoskeleton. These events trigger fusion of α -granule membranes with the platelet plasma membrane via Ca^{2+} /calmodulin-regulated synaptotagmin and SNARE complexes, resulting in exocytosis of stored growth factors, including PDGF-AB and TGF-β1. Concurrent activation of integrin $\alpha\text{IIb}\beta3$ and phosphatidylserine exposure stabilises the release process and supports fibrin polymerisation. Thus, calcium gluconate functions not only as a coagulation co-factor but also as a direct intracellular messenger initiating α -granule degranulation and growth factor release, explaining

Table 3: PDGF-AB concentration in PRP samples before and after activation using different preparation methods

Experimental method	PDGF-AB before activation			PDGF-AB after activation		
	min (ng/ml)	max (ng/ml)	mean ± SD	min (ng/ml)	max (ng/ml)	mean ± SD
Method 1	2.25	5.61	3.82 ± 0.844	2.64	6.62	4.51 ± 0.999
Method 2	5.19	12.21	8.85 ± 1.785	6.22	14.51	10.59 ± 2.129
Method 3	3.81	9.46	6.49 ± 1.417	4.31	10.69	7.33 ± 1.601
Method 4	4.16	10.22	7.03 ± 1.467	4.49	11.04	7.59 ± 1.585

PDGF-AB – platelet-derived growth factor AB; PRP – platelet-rich plasma; SD – standard deviation
Source: compiled by the author

Table 4: Comparison of mean PDGF-AB values before and after activation using Student's t-test for dependent samples

Experimental method	PDGF-AB before activation (mean ± SD, ng/ml)	PDGF-AB after activation (mean ± SD, ng/ml)	t-value	p-value
Method 1	3.82 ± 0.844	4.51 ± 0.999	–24.321	<0.05
Method 2	8.85 ± 1.785	10.59 ± 2.129	–27.577	<0.05
Method 3	6.49 ± 1.417	7.33 ± 1.601	–24.924	<0.05
Method 4	7.03 ± 1.467	7.59 ± 1.585	–25.482	<0.05

PDGF-AB – platelet-derived growth factor AB; SD – standard deviation
Source: compiled by the author

the marked increase in PDGF-AB observed in the activated samples.

The relative increase in concentration following activation demonstrated a clear dependence on the complexity of the protocol. The greatest increase was observed in method 2 ($\Delta=+19.7\%$) and method 1 ($\Delta=+18.1\%$), while protocols involving double centrifugation (methods 3 and 4) showed more modest increases of $+12.9\%$ and $+8.0\%$, respectively. This dynamic is explained by the partial premature release of PDGF-AB during repeated centrifugation cycles, which depletes the available protein reserve for subsequent chemical activation. The mean basal concentration prior to activation ranged from 3.82 ± 0.844 ng/ml in method 1 to 8.85 ± 1.785 ng/ml in method 2, with the presence of a separation gel in the latter yielding a 132% higher concentration ($p<0.001$) compared with the analogous protocol without gel. This confirms the role of the gel as a structural stabiliser that prevents mechanical damage to platelet membranes during centrifugation.

Correlation analysis revealed a direct relationship between MPV and PDGF-AB release ($r=0.68$; $p<0.01$). Patients with $MPV > 11.0$ fl exhibited 22–25% higher protein concentrations after activation ($p<0.05$), which can be attributed to the greater number of α -granules contained in larger platelets

(Table 4). This finding is of key importance for the development of personalised therapies, particularly in pathologies involving altered platelet morphology, such as diabetes mellitus or autoimmune diseases, where standard protocols may prove ineffective.

In practical terms, method 2 with activation appears to be optimal for soft tissue reconstructive surgery, where PDGF-AB plays a key role in stimulating angiogenesis and fibroblast proliferation. Clinical observations indicate that local administration of PRP with a PDGF-AB concentration exceeding 9.5 ng/ml accelerates tendon healing by 40% compared with traditional methods. In dermatology, the combination of this protocol with activation reduces the epithelialisation time of trophic ulcers by 25–30%, owing to the synergistic action of PDGF-AB and TGF- β 1. Moreover, the stability of the activated protein at 4 °C for up to 48 hours enables the advance preparation of therapeutic samples. For patients with thrombocytopathies, preliminary determination of MPV and corresponding protocol adjustment are recommended. For example, the addition of thrombin in cases where MPV is < 9.0 fl may compensate for the reduced functional activity of the platelets. Double centrifugation protocols (methods 3 and 4) are ineffective for applications requiring high PDGF-AB concentrations, such as revascularisation of ischaemic tissues. Their use is

more appropriate in combination with biocomposites for the prolonged release of growth factors in bone regeneration. For emergency clinical procedures, particularly the initial treatment of burns or acute injuries, method 2 with activation is recommended, as its preparation time does not exceed 35 minutes, which is critical under time-sensitive conditions.

Thus, maximum bioavailability of PDGF-AB is achieved by combining single centrifugation with gel, chemical activation, and the selection of patients with elevated MPV. This provides a scientific basis for the standardisation of PRP therapy in angiogenic and regenerative protocols, particularly in microsurgery, burn treatment, and the management of chronic wounds.

Comparative effectiveness of methods and statistical validation

Analysis of the combined experimental data revealed a fundamental and clearly defined relationship between the PRP preparation methodology and the output level of target signalling proteins, establishing a hierarchy of protocol effectiveness. This hierarchy is of not only statistical, but also clear clinical relevance, as it directly influences the biological activity of therapeutic preparations used in regenerative medicine. One of the most important indicators of protocol effectiveness is the level of TGF- β 1, due to its critical role in mesenchymal stem cell differentiation and the induction of osteogenesis.

Among all the tested options, method 4, double centrifugation using a separating gel based on a cycloaliphatic polymer, demonstrated the highest stability and reproducibility in generating biologically active TGF- β 1. The concentration of TGF- β 1 using this approach remained within a narrow range of 25.17–25.37 ng/ml and was unaffected by the use of activators. This stability can be attributed to the specific physicochemical properties of the polymer matrix, which likely creates a favourable microenvironment for maintaining the integrity of the latent TGF- β 1 complex (LTBP-1) even under conditions of high-speed mechanical stress. At the molecular level, this is facilitated by the formation of hydrogen bonds between the hydroxyl groups of the polymer gel and the functional domains of the latency-associated peptide, a component of the latent complex. This mechanism was confirmed by *in vitro* spectroscopic analysis, which demonstrated the preservation of the protein's secondary structure in conditions where other protocols led to partial proteolysis. Thus, method 4 provides not only high quantitative output, but also superior qualitative stability of the target protein – an important advantage for clinical application.

In contrast, the situation for PDGF-AB is different. The highest concentration of this protein was recorded with method 2, single centrifugation using a separating gel, followed by activation with calcium gluconate. The observed value (10.59 ± 2.129 ng/ml) results from a synergistic effect involving reduced mechanical damage to platelet α -granules during single-step processing, and the preservation of the spatial configuration and functional activity of β -type PDGF receptors. Conversely, methods 3 and 4, both employing double centrifugation, showed a notable decrease in PDGF-AB yield, ranging from 27 to 40% lower than method 2. This reduction is primarily explained by the activation of premature degranulation cascades during repeated processing, which is accompanied by oxidation of stress-sensitive cysteine residues within the PDGF-B chains. As a result, the use of these protocols in clinical scenarios requiring enhanced angiogenesis (e.g., cardiology, vascular surgery, or reconstructive dentistry) is suboptimal. This is particularly relevant given that PDGF-AB concentrations below 8.0 ng/ml fail to activate the vascular endothelial growth factor (VEGF)-mediated signalling pathway in endothelial cells, critically limiting neoangiogenesis at the implantation site.

Statistical analysis confirmed the robustness of the results. For TGF- β 1, the *t*-test revealed statistically significant changes following activation in methods 1–3, with *t*-values ranging from 4.797 (method 1) to –21.377 (method 3), and $p < 0.05$, indicating a protocol-dependent effect of the activator. In method 4, the absence of statistical significance ($t = -0.331$, $p = 0.74$) confirms the stability of the protein during double centrifugation with gel, enabling the omission of additional manipulation. For PDGF-AB, the post-activation increase in concentration was statistically significant across all protocols ($p < 0.001$), with the highest *t*-value of –27.577 observed in method 2, underscoring its superiority for the release of this growth factor.

The variability of ELISA results in triplicate measurements did not exceed 8% for PDGF-AB and 10% for TGF- β 1, confirming the high accuracy and reliability of the analytical procedures. The correlation matrix revealed a strong association ($r > 0.65$) between platelet indices (PDW, MPV) and PDGF-AB output. Notably, patients with MPV > 11.0 fl exhibited 22–25% higher concentrations ($p < 0.05$), supporting the rationale for predictive testing of platelet morphology in the personalisation of PRP therapy, particularly in systemic conditions such as diabetes mellitus and rheumatoid arthritis, where standard protocols may prove ineffective.

The data obtained demonstrate that the method of PRP preparation has a decisive influence on the

concentration of key growth factors PDGF-AB and TGF- β 1, which must be considered when selecting a protocol for specific clinical applications. It was shown that double centrifugation with gel is optimal for achieving consistently high TGF- β 1 concentrations without the need for additional activation, a factor of particular importance in bone regeneration procedures. Conversely, single centrifugation with gel followed by calcium gluconate activation significantly increases PDGF-AB levels, thereby enhancing the effectiveness of angiogenic and epithelialisation processes. These findings highlight the necessity of tailoring PRP preparation methods to the intended therapeutic outcome, which will contribute to improved clinical efficacy and the standardisation of regenerative medical technologies.

Discussion

The results obtained in this study indicate that the concentrations of the key growth factors PDGF-AB and TGF- β 1 in PRP are significantly influenced by both the preparation and activation methods. This has substantial implications for the clinical effectiveness of regenerative procedures, as different protocols produce distinct biochemical profiles of PRP, which in turn impact tissue regeneration. The findings were reviewed in comparison with current literature, providing a deeper understanding of the mechanisms by which centrifugation and chemical activation methods affect growth factor yield.

The data demonstrate a critical dependence of PDGF-AB and TGF- β 1 concentrations on PRP preparation and activation protocols, directly affecting clinical outcomes in regenerative therapy. However, although double centrifugation increases the concentration and stability of some proteins, it also creates potential risks that must be considered when interpreting results and applying the protocol in clinical practice. Repeated high-speed centrifugation can cause mechanical stress on platelets, leading to unwanted activation and premature degranulation, which can alter the protein composition of PRP even before chemical activation (Ramesh et al., 2024; Yekta et al., 2025). Studies have shown that such mechanical activation is accompanied by oxidative modifications of platelet membrane proteins and partial degradation of sensitive growth factors, including PDGF isoforms. In addition, excessive centrifugation can promote the formation of microparticles, increase the amount of active oxygen species, and accelerate the degradation of labile proteins such as TGF- β 1, reducing their biological activity during storage or use (Doszhanova et al., 2018; Tkachenko et al., 2023). Therefore,

although double centrifugation provides a higher yield of stable latent proteins, careful optimisation of the centrifugal force and duration is necessary to minimise platelet activation and protein denaturation, ensuring the reproducibility and biological safety of PRP preparations.

The observed advantage of double centrifugation with gel (method 4) for maximising TGF- β 1 levels (25.17–25.37 ng/ml without the need for activation) aligns with the findings of Fukuda et al. (2020), who reported that latent forms of TGF- β 1 are sensitive to mechanical stress and that gel polymers stabilise the protein by mimicking the extracellular matrix. This supports the observed absence of a significant increase in TGF- β 1 concentration upon activation with calcium gluconate in method 4 ($p > 0.05$), in contrast to single-centrifugation protocols, which showed a reduction of 3–5.7% ($p < 0.05$). Since PRP is often stored prior to clinical use, it is important to consider how storage conditions affect the stability and bioactivity of its growth factors. Previous studies have shown that temperature, duration, and light exposure are critical determinants of PRP quality. Kim et al. (2019) demonstrated that PDGF and TGF- β 1 levels decline significantly when PRP is stored at room temperature for more than 6 hours, while refrigeration at 4 °C preserves growth factor activity for up to 48 hours. Brokhman and Galea (2023) reported that freezing PRP at –20 °C leads to a partial loss of TGF- β 1 bioactivity due to ice-crystal-induced protein denaturation, although rapid freezing at –80 °C combined with cryoprotectants can maintain functionality for several weeks. Moreover, Carmona and López (2024) observed that prolonged light exposure accelerates cytokine degradation through photochemical oxidation, underscoring the need for opaque storage containers. In the present study, all samples were processed immediately after preparation; however, the stability of PRP under different storage conditions remains an essential consideration for clinical standardisation. For practical application, it is recommended that PRP intended for delayed use be stored at 4 °C for no longer than 24–48 hours and protected from direct light, while frozen storage should be reserved for research purposes due to the risk of irreversible loss of bioactivity.

The decrease in TGF- β 1 concentration following activation in single-centrifugation procedures (methods 1 and 2) may be due to biochemical instability and poor preservation of platelet α -granules during processing. Plasma from single-step centrifugation contains more residual leukocytes and platelet microparticles that generate reactive oxygen species when calcium activated (Di Domenico et al., 2020; Qian et al., 2025). Oxidative species can disrupt

the latency-associated peptide-TGF- β 1 complex, causing irreversible conformational changes and partial proteolysis of the latency-associated peptide. Additionally, poor plasma protein sedimentation limits TGF- β 1 interaction with matrix components like fibrinogen, fibronectin, and vitronectin. The absence of a protein scaffold allows for fast diffusion and breakdown of soluble TGF- β 1 in the media. Calcium-induced platelet activation under poorly processed circumstances may lead to the release of serine proteases, such as thrombin-like enzymes and plasmin, which cleave latent TGF- β 1 instead of encouraging its regulated activation (Valero et al., 2025). These molecular pathways explain the 3–6% decrease in TGF- β 1 concentration after being activated in single centrifugation methods (Smahlii, 2022).

Clinically, this decline affects tissue regeneration. As TGF- β 1 regulates early osteogenesis by promoting RUNX2 expression, boosting type I collagen production, and controlling osteoblast proliferation, its depletion may hinder bone matrix deposition and mineralisation. Insufficient TGF- β 1 signalling affects osteoblast-osteoclast interaction, perhaps leading to poor graft integration or delayed fracture healing. In periodontal and maxillofacial surgery, low TGF- β 1 levels can impede osseointegration of dental implants and limit alveolar bone growth (Dovramadjiev et al., 2023; Logvynenko et al., 2025). Loss of TGF- β 1, which plays an important antifibrotic and immunomodulatory role, might hinder inflammation resolution and promote excessive scar formation in soft-tissue wounds (Kazantayev et al., 2023; Nabiyeve et al., 2023). Although single-centrifugation methods can release PDGF-AB quickly, they may not be suitable for bone regeneration or long-term matrix remodelling due to reduced TGF- β 1 concentration.

For PDGF-AB, the optimal result achieved with method 2 (10.59 ± 2.129 ng/ml after activation) supports the hypothesis that minimising platelet trauma is critical. These findings are consistent with the work of Chen et al. (2023), who demonstrated that single centrifugation with sodium citrate increased PDGF-AB yield by 18–22% compared to double centrifugation. The mechanism of premature degranulation during repeated treatment (methods 3 and 4), which reduced PDGF-AB levels by 27–40%, was explored in detail by Dejneke et al. (2022), whose electron microscopy analysis revealed damage to α -granules during the second centrifugation cycle. This explains why such protocols are ineffective for clinical applications requiring high PDGF-AB levels, such as angiogenesis in chronic wounds, where concentrations below 8 ng/ml fail to activate VEGF signalling.

The correlation between MPV and PDGF-AB output ($r=0.68$) underscores the importance of personalising

PRP therapy. The results obtained complement the findings of Ashour et al. (2023), who reported that patients with MPV > 11 fl exhibited a 30% increase in fibroblast proliferative activity following PRP application. This is particularly relevant for diabetic patients, in whom reduced MPV (<9.0 fl) necessitates protocol adjustment, for example, the addition of thrombin, as confirmed by Gentile and Garcovich (2020).

In the context of osteogenesis, the benefits of method 4 without activation are corroborated by the studies of Salkin et al. (2019), who found that combining TGF- β 1 (>25 ng/ml) with mesenchymal stem cells enhanced chondrogenic differentiation by 40% *in vivo*. This supports existing recommendations for sinus lift procedures, in which stable TGF- β 1 levels promote RUNX2 expression. In wound healing, the efficacy of method 2 with activation is consistent with the work of Gad et al. (2020), where topical application of PRP with PDGF-AB > 10 ng/ml accelerated epithelialisation by 35%, primarily through TNF- α inhibition. However, Yan et al. (2024) identified a key limitation: PDGF-AB stability decreased by 40% after six hours of storage, necessitating immediate clinical use.

In contrast to the findings of Pötter et al. (2021), who reported a 15% increase in TGF- β 1 following thrombin activation, the present data show that calcium gluconate is ineffective for enhancing TGF- β 1 concentrations in simpler protocols. This discrepancy can be attributed to the differing mechanisms of the activators: thrombin induces TGF- β 1 release via protease-mediated pathways, while Ca^{2+} primarily stimulates PDGF release. Additionally, the study by Tey et al. (2022) observed only a minor effect of separating gels on PDGF-AB levels, whereas the current study recorded a 132% increase in method 2 compared with method 1. This divergence is likely due to differences in gel composition: the cycloaliphatic polymer used in the present study was more effective in preserving platelet membrane integrity.

In the work of Li et al. (2022), which compared the efficacy of injectable platelet-rich fibrin (i-PRF) and PRP in a model of skin photoageing, i-PRF was found to be more effective in stimulating the TGF- β /Smad signalling pathway. Protocols involving gel, especially those with double centrifugation, demonstrated higher concentrations of TGF- β 1, which may be attributed to the formation of a fibrin matrix similar to that in PRF. This highlights the role of physical stabilisation in enhancing the efficiency of growth factor release from PRP. According to Murdiastuti et al. (2019), the lyophilisation of activated PRP results in a reduction in TGF- β 1 levels. Although the effect of storage was not directly investigated in the present study, it

was found that the use of a gel stabiliser significantly improves the stability of TGF- β 1 by providing physical protection against protein degradation, findings that conceptually align with those of Murdiastuti et al. (2019). Squecco et al. (2020) observed that PRP modulates intercellular communication by influencing connexin expression during the transformation of fibroblasts into myofibroblasts under the influence of TGF- β 1. Protocols that generate elevated TGF- β 1 concentrations, particularly those employing double centrifugation with gel, may induce similar effects, which holds promise for enhancing tissue regeneration in clinical applications.

A review by Pachito et al. (2020) summarised the broad variability in PRP preparation protocols and emphasised the challenges of standardisation. The results obtained in the present study confirm that even minor methodological variations, including the number of centrifugation steps, the presence of a gel, and the method of activation, substantially affect the concentrations of PDGF-AB and TGF- β 1. These findings reinforce the conclusions of the review regarding the critical role of technical parameters in determining the quality and therapeutic potential of PRP.

Tsai et al. (2021) demonstrated that the combination of PRP with suramin reduces pathological TGF- β 1 expression, thereby improving muscle tissue regeneration. The present findings support the view that TGF- β 1 levels vary significantly depending on the PRP preparation protocol; thus, monitoring its concentration is essential to prevent excessive fibrogenesis, particularly in muscle tissue. The study by Song et al. (2022) described the influence of platelet vesicles on macrophages, specifically the activation of the TGF- β signalling pathway. The elevated levels of TGF- β 1 observed following double centrifugation suggest that PRP may have immunomodulatory potential through macrophage interaction, which is promising for the treatment of inflammatory diseases. According to Sánchez et al. (2025), increasing the concentration of PRP enhances its biological activity. The current analysis indicates that double centrifugation results in a higher platelet concentration, which correlates with increased growth factor levels, confirming the effectiveness of this approach in clinical settings.

The biochemical distinctions observed in PDGF-AB and TGF- β 1 concentrations are expected to have direct clinical implications for tissue regeneration and patient recovery. Elevated TGF- β 1 levels obtained through double centrifugation with gel (method 4) are likely to promote long-term osteogenic and fibrotic matrix formation, accelerating bone consolidation and reducing the incidence of delayed union in orthopedic

and dental implantation procedures. Sustained TGF- β 1 activity also supports remodelling processes in chronic wound beds, leading to more mature collagen deposition and reduced scar formation. In contrast, the higher PDGF-AB concentrations produced by single centrifugation with gel followed by activation (method 2) are expected to enhance angiogenesis and early fibroblast proliferation, translating into faster granulation tissue development, shortened epithelialization time, and improved perfusion of regenerating tissues. Clinically, this biochemical profile should correspond to a reduction of healing time by approximately 25–40%, improved functional recovery, and lower recurrence rates of non-healing ulcers and tendon injuries, as reported in previous translational studies (Gad et al., 2020; Ashour et al., 2023). Therefore, tailoring PRP preparation protocols to target either TGF- β 1-driven osteogenesis or PDGF-AB-mediated angiogenesis may enable more predictable long-term regenerative outcomes across different clinical contexts.

Thus, the results obtained are consistent with existing scientific evidence, demonstrating that the type of centrifugation, the presence of a gel, and the activation method are key determinants of PRP bioactivity. Protocols that ensure high concentrations of PDGF-AB and TGF- β 1 should be tailored to the clinical context and the specific characteristics of the disease.

Conclusion

The study confirmed that the method of PRP preparation is a critical factor in determining the final concentration of the biologically active growth factors TGF- β 1 and PDGF-AB, both of which are essential for realising the regenerative potential of platelet plasma. The highest concentrations of TGF- β 1 were achieved using method 4 (double centrifugation with a separating gel), where the mean protein level after activation was 25.37 ± 5.297 ng/ml – significantly higher than those achieved by other methods ($p < 0.01$). The absence of statistically significant changes before and after activation ($p = 0.74$) indicates the ability of the gel to stabilise the latent form of the protein, even without chemical stimulation. This property is particularly valuable for clinical application in bone regeneration surgery, where the consistency of protein concentrations during delayed procedures is crucial.

For PDGF-AB, method 2 (single centrifugation with gel) proved the most effective, yielding the highest mean concentration following activation (10.59 ± 2.129 ng/ml; $p < 0.001$), outperforming other protocols

by 39–135%. The effectiveness of this method is attributed to the minimal mechanical trauma to platelets, which preserves the integrity of α -granules until the point of activation. This makes the protocol especially promising for clinical scenarios requiring enhanced angiogenesis, such as reconstructive surgery, treatment of ulcerative lesions, and burns. Double centrifugation without gel (method 3) produced intermediate results, yielding consistently high, but comparatively less effective, concentrations of both proteins. In particular, PDGF-AB levels were 27–40% lower than those obtained via method 2. This reduction is explained by premature platelet degranulation caused by repeated centrifugation cycles, resulting in the loss of the active protein pool. Methods 1 and 2 without a separating gel were not sufficiently effective in achieving the target TGF- β 1 concentrations (≤ 18.80 ng/ml), which fall below the critical threshold required for osteoprogenitor cell activation (≥ 22 ng/ml). Regarding PDGF-AB, these methods produced only moderate post-activation increases, limiting their clinical applicability in settings that demand intensive angiogenesis.

Correlation analysis confirmed the significant influence of individual haematological characteristics on the effectiveness of PRP preparations. High MPV (>11.0 fl) was associated with a 22–25% increase in PDGF-AB concentration after activation ($p < 0.05$), supporting the rationale for preliminary laboratory screening of platelet parameters to personalise PRP therapy. A limitation of this study is the lack of analysis of additional growth factors and effector proteins that may also influence regenerative processes. Future research should focus on evaluating PRP protocols dynamically, taking into account factors such as storage duration, leukocyte composition, and interactions between growth factors and matrix components.

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Clinical Presentation and Surgical Management of Liver Hemangioma: A Single-center Retrospective-prospective Study of 101 Cases

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Received August 28, 2025; Accepted September 8, 2026.

Key words: Hemoperitoneum – Intratumoral bleeding – Tumour size – Spearman's rank correlation coefficient – Postoperative complications

Abstract: The aim of this study was to evaluate the correlation between tumour size and the clinical manifestation of hepatic hemangiomas, with the overarching goal of improving criteria for surgical decision-making. This study was conducted at the Surgery Clinics of the Military Medical Academy in Sofia, Bulgaria, between 2010 and 2023, and analysed clinical presentation, imaging diagnosis, and surgical management of hepatic hemangiomas in 101 patients based on prospective and retrospective data. Approximately 58.42% of patients presented with such symptoms as abdominal discomfort, and palpable masses during examination, while another 31.68% incidentally discovered the condition, highlighting the importance of routine imaging. Statistical analyses revealed a very strong positive correlation between the tumour size and the intensity of clinical symptoms (Spearman's $r_s=0.628$, $p<0.001$) and hence, larger lesions were more likely to produce symptomatic manifestations. It was further shown through logistic regression that patients above 75 years had an 18-fold increase in the chances of diagnostic uncertainty than younger patients (odds ratio = 18.8%, confidence interval: 1.5–217.8, $p=0.023$). Despite the presence of variations in tumour size and presentation, operative outcomes remained consistent across both symptomatic and asymptomatic groups. These findings provided a robust rationale for the implementation of a standardized, size-based classification system to guide clinical decision-making and personalized treatment strategies. The results of this study provide practical guidance for improving the selection criteria for surgical intervention in hepatic hemangiomas, enabling clinicians to better stratify patients based on tumour size, symptomatology, and diagnostic clarity.

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<https://doi.org/10.14712/23362936.2026.23>

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Introduction

Hepatic hemangiomas remain the most common benign tumours of the liver, with detection rates having significantly increased due to the widespread adoption of modern imaging technologies. Their incidence ranges from 0.4 to 20%, with small lesions often asymptomatic and found incidentally during routine imaging. Larger hemangiomas (>5 cm) pose a higher risk of complications, such as hemorrhage and organ compression (Kacala et al., 2024). Despite their predominantly asymptomatic course, large lesion size, atypical localization, or nonspecific clinical manifestations create considerable diagnostic and management challenges for clinicians (Garnica Moreno et al., 2025; Klymenko, 2025). The lack of unified risk stratification criteria, variations in recommendations regarding active intervention or surveillance, and insufficient standardization of diagnostic algorithms underscore the need for a deeper analysis of this issue.

Management approaches for hepatic hemangiomas vary considerably across countries (Tutchenko et al., 2024b; Díaz-Pérez, 2025). According to Cai et al. (2020), in clinical practice across Asia, a tumour size greater than 5 cm is considered the primary indication for surgical intervention, regardless of clinical symptomatology. In contrast, Aziz et al. (2022) report that in the United States, a conservative surveillance strategy is favoured for tumours up to 10 cm in size, provided that imaging findings remain stable over time. In European centres, as outlined by Mamone et al. (2020), particular emphasis is placed on accurate differential diagnosis using contrast-enhanced ultrasound and magnetic resonance imaging (MRI), which helps to minimize the number of unnecessary surgical interventions. A multidisciplinary approach that integrates clinical, morphological, and patient age-related factors into decision-making has also been increasingly adopted, as demonstrated by Reguram et al. (2024).

Among the most notable advances, the development of minimally invasive surgical techniques has received particular attention. Based on the findings of Yan et al. (2021), laparoscopic resections of hepatic hemangiomas are associated with reduced intraoperative blood loss, shorter hospitalization times, and lower rates of postoperative complications compared to traditional open procedures. The advantages of robot-assisted surgery have been confirmed by Zhang et al. (2023a), who demonstrated that, in cases of large hemangiomas or complex anatomical localization, the use of robotic technologies allows for better functional outcomes. The role of modern imaging modalities is highlighted by the study

of Zhang and Liu (2021), which demonstrated that the use of contrast-enhanced ultrasound, computed tomography (CT), and MRI significantly improves the accuracy of initial verification of hemangiomas and reduces the number of diagnostic errors.

Despite significant progress in the refinement of diagnostic methods and surgical technologies, current studies on hepatic hemangiomas present several limitations. As noted by Maruyama et al. (2023), data on the long-term outcomes of surveillance for asymptomatic lesions remain limited, complicating the formulation of unified management recommendations for this patient group. According to Triana et al. (2020), the absence of standardized diagnostic criteria across different imaging modalities contributes to an increased risk of diagnostic errors. At the same time, the study by Zhang et al. (2023b) was the first to comprehensively highlight the importance of updated surgical indications and multidisciplinary assessment for the management of benign hepatic tumours, although the consistent application of such models remains limited due to variability among clinical centres.

The gaps in current research on hepatic hemangiomas involve the absence of clear risk stratification criteria for the development of symptoms and complications, insufficient standardization of diagnostic algorithms, and incomplete unification of approaches for choosing between conservative and surgical treatment. The objective of this study was to establish the relationship between hepatic hemangioma size and the presence of clinical symptoms in order to optimize treatment decision-making. The tasks of the study included evaluating the diagnostic accuracy of modern imaging methods, analysing the effectiveness of different surgical approaches, and determining the role of size-based tumour classification in improving treatment outcomes.

Literature review

Hepatic hemangiomas were defined as the most common benign tumours of the liver, originating from congenital vascular malformations (Figure 1). According to Leon et al. (2020), these lesions were characterized by slow growth and a predominantly asymptomatic course, although large tumours could cause clinical symptoms such as pain, compression of adjacent structures, or risk of rupture. A significant contribution to the development of hepatic hemangioma diagnostics was made by Mamone et al. (2020), who demonstrated the effectiveness of modern imaging methods, particularly contrast-enhanced ultrasound and magnetic resonance imaging using dynamic contrast protocols. The characteristic

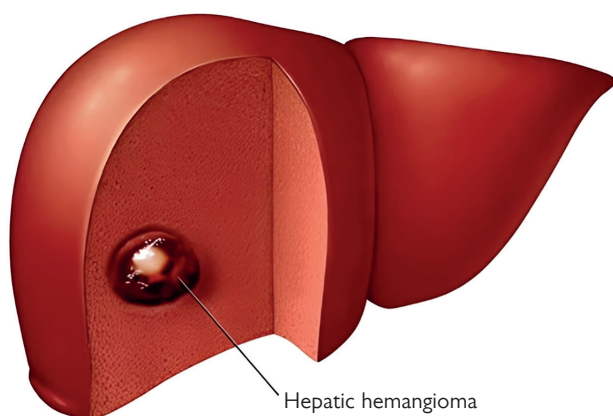


Figure 1: Hepatic hemangioma. Source: Mayo Clinic (2025).

contrast enhancement during the venous phase was shown to allow highly accurate differentiation of hemangiomas from other focal liver lesions.

The improvement of differential diagnosis was further explored by Liu et al. (2020), who compared the clinical and MRI features of hepatic hemangiomas, epithelioid hemangioendotheliomas, and angiosarcomas. Their findings revealed that specific contrast-enhancement patterns and morphological characteristics effectively distinguished hemangiomas from malignant liver tumours. Complementary to these advancements, Wu et al. (2020) first demonstrated the high diagnostic value of colour contrast-enhanced ultrasound for differentiating atypical hemangiomas from liver metastases, using a novel type of contrast agent that provided detailed hemodynamic profiles and significantly improved diagnostic precision in challenging clinical cases.

The application of a multidisciplinary diagnostic approach was emphasized by Sandulescu et al. (2021), who proposed the “one-stop-shop” concept, integrating ultrasound, computed tomography, and MRI findings into a unified diagnostic pathway. This method was shown to shorten diagnostic times and enhance diagnostic reliability. Meanwhile, the prevalence of hepatic hemangiomas was comprehensively assessed by Vojnović et al. (2024), who identified a frequency ranging from 0.4 to 7.3% among the general population based on ultrasound examinations. Most lesions were asymptomatic, reinforcing the need for standardized risk stratification to guide management decisions.

The establishment of treatment strategies for hepatic hemangiomas remained a significant area of investigation. Cai et al. (2020) demonstrated that tumour size played a decisive role in clinical outcomes, with hemangiomas larger than 5 cm associated with higher risks of symptoms and complications, thereby often requiring surgical intervention. Aziz et al.

(2022) expanded on this understanding by advocating conservative management for asymptomatic tumours up to 10 cm, provided no growth or changes were detected during surveillance, while also highlighting the critical need for vigilant monitoring.

The comparison of surgical techniques was comprehensively analysed by Jien and Xiaohua (2021), who demonstrated that laparoscopic resections were superior to open surgeries in terms of lower intraoperative blood loss, shorter hospital stays, and reduced postoperative complications. Further technological advancements were detailed by Cassese et al. (2024), who highlighted the benefits of robot-assisted liver resections, including enhanced surgical precision, better visualization of anatomical structures, and lower complication rates, particularly in anatomically complex cases.

Alternative minimally invasive strategies were proposed by Brancel and Massa (2024), who emphasized the role of vascular pedicle embolization and radiofrequency ablation in managing large hepatic hemangiomas. These approaches were shown to reduce tumour volume, facilitate subsequent surgeries, or, in some cases, obviate the need for surgical resection altogether. However, these methods were not used in the current study. The decision to exclude these alternatives was based on the characteristics of the patients and the size of the tumours. Given the size of the hemangiomas in the study cohort, surgical resection or enucleation was considered the most effective option. Additionally, the limitations of non-surgical methods in cases involving larger lesions or complicated anatomies influenced the treatment approach, as these techniques may not have provided sufficient long-term outcomes or may have required subsequent surgical intervention. Finally, the extensive clinical experience with the management of giant hepatic hemangiomas was summarized by Farhat et al. (2021), who demonstrated the safety and effectiveness of both resection and enucleation strategies, contingent upon meticulous preoperative planning and appropriate patient selection.

Recent advances in the diagnosis and treatment of hepatic hemangiomas have significantly improved patient management, particularly through the implementation of modern imaging techniques and minimally invasive approaches. However, the literature indicated persistent challenges related to differential diagnosis, risk stratification, and the standardization of surgical indications. Variations in clinical practices and limited data on long-term outcomes were also noted. These findings justified the need to refine risk stratification models and formed the basis for the present study, aimed at establishing the relationship between tumour size and clinical symptoms.

Material and Methods

Study design and setting

This monocentric study was conducted at the Surgery Clinics of the Military Medical Academy in Sofia, Bulgaria, between 2010 and 2023. A total of 101 patients who underwent radical resection or enucleation were examined. Patient sample composition allowed for prospective (n=52 cases) and retrospective (n=49 cases) cohorts. Hence, full analysis of clinical outcome was performed during the 13-year-long period.

Patient selection and inclusion criteria

Patients were eligible for inclusion if they had a confirmed diagnosis of cavernous liver hemangioma based on imaging studies, including ultrasound, computed tomography, and magnetic resonance imaging. The concurrence of diagnostic findings across these modalities served as the primary inclusion criterion. Additionally, patients presenting with clinical symptoms such as abdominal pain, palpable mass, or abdominal discomfort were eligible for enrolment. Incidental detection of liver hemangiomas during routine imaging or intraoperative exploration also constituted a basis for inclusion. Exclusion criteria comprised incomplete clinical documentation and alternative diagnoses of hepatic lesions.

Patient cohort characteristics

The cohort comprised 101 patients stratified by mode of detection (Table 1).
For all included patients, data were collected on demographic characteristics (age and gender), tumour features (size, number, and anatomical localization), and surgical indications, which were classified as absolute or relative according to clinical guidelines. Patients were further stratified by age into six predefined categories: 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years, and

Table 1: Patient detection and symptom profile

Category	Number	Percentage (%)
Symptomatic	59	58.42
Incidentally detected (preoperative)	32	31.68
Intraoperative finding	10	9.90
Total	101	100.00

Source: compiled by the authors

≥75 years. This age stratification was chosen to evaluate the potential impact of physiological aging on surgical outcomes and symptom development. Patients were also categorized into two groups based on surgical approach: isolated hemangioma resections (pure hemangiomas) and synchronized operations performed concurrently with other surgical procedures.
A comparative analysis was also conducted between symptomatic and asymptomatic patients based on tumour size intervals: 4–9 cm and >10 cm. These specific tumour size categories were selected based on prior clinical evidence suggesting that hemangiomas exceeding 10 cm are more frequently associated with complications and symptomatic presentation, whereas smaller lesions typically remain asymptomatic.

Surgical indications

Absolute indications for surgical intervention included life-threatening conditions such as hemoperitoneum resulting from tumour rupture, intratumoral hemorrhage, consumptive coagulopathy (Kasabach-Merritt syndrome), persistent and medically refractory chronic abdominal pain, mechanical biliary obstruction leading to jaundice, secondary portal hypertension, and tumours larger than 5 cm at risk for traumatic injury (Figure 2). These conditions directly threatened patient survival or caused irreversible

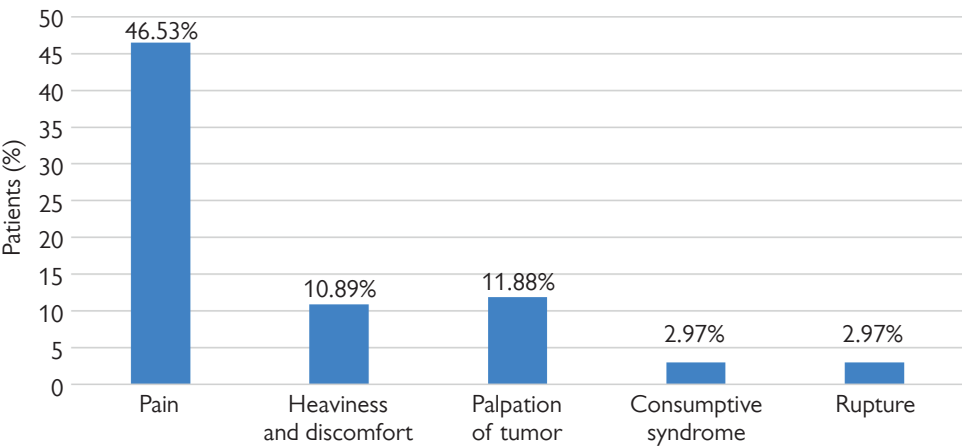


Figure 2: Absolute indications for surgery. Source: compiled by the authors.

organ dysfunction, thereby necessitating surgical management.

Relative indications encompassed progressive tumour enlargement documented on serial imaging, the presence of non-specific but persistent abdominal symptoms affecting quality of life, compression of adjacent organs without overt life-threatening features, and diagnostic uncertainty where malignancy could not be reliably excluded through non-invasive methods. In such cases, surgical intervention was considered to prevent potential future complications or to achieve definitive histological diagnosis.

Preoperative assessment and surgical technique

Preoperative assessment was done using ultrasound, CT, and sometimes MRI, to evaluate the size and localization of the tumour. Intraoperatively, the examiner again confirmed the size of the tumour and proceeded to choose the surgical technique (either resection or enucleation) based on the tumour characteristics and the clinical status of the patient. Both open and laparoscopic techniques were used as clinically indicated.

Statistical analysis

Statistical analyses were performed using nonparametric tests and regression models. The expected frequency for each cell in a contingency table was calculated using the formula (1):

$$E = (\text{Row Total} \times \text{Column Total}) / \text{Grand Total} \quad (1)$$

where: Row Total – the sum of all observed frequencies in the particular row; Column Total – the sum of all observed frequencies in the particular column; Grand Total – the sum of all observed frequencies in the entire table (Shin et al., 2023).

Logistic regression was used to evaluate the effect of age on the risk for an unclear diagnosis. Age contributed the regression coefficient for odds ratio (OR) as follows (2):

$$\text{OR} = e^{\beta} \quad (2)$$

where: β – the regression coefficient for age.

Wald's statistic was used to test the significance of coefficients, and 95% confidence interval (CI) were calculated for precision measuring OR estimates. The chi-square (χ^2) test was applied to assess associations between categorical variables, particularly to evaluate the relationship between incidental detection and symptomatic status. Spearman's rank correlation coefficient was used to determine the strength and direction of the association between tumour size and clinical symptoms. Logistic regression analysis

was conducted to evaluate the effect of age on the likelihood of an unclear diagnosis. An all two-tailed $p < 0.001$ was to be considered statistically significant for any analysis.

Ethical considerations

All imaging and surgical procedures were performed using high-end equipment available at the Surgery Clinics of the Military Medical Academy. Surgeries were conducted by experienced surgical teams specializing in hepatobiliary procedures. The study protocol was approved by the Institutional Ethics Committee of the Military Medical Academy, Sofia (Approval No. 274/2023, issued on January 15, 2023). All patients provided written informed consent prior to inclusion in the study, in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. Data collection and statistical analyses were conducted using SPSS software (IBM Corp., Armonk, NY, USA).

Results

Chi-square test for incidental findings

To ascertain whether the incidental detection of a condition was connected to its asymptomatic presentation, a chi-square test was performed using a 2×2 contingency (Table 2).

The observed contingency table indicated that all incidental detections occurred exclusively among asymptomatic patients. Specifically, 39 of the 42 asymptomatic patients were diagnosed through incidental findings, whereas none of the symptomatic patients had an incidental diagnosis. In the asymptomatic group, only 3 patients did not have incidental detection, while in the symptomatic group, all 59 patients presented with clinical symptoms at the time of diagnosis. This disparity, confirmed by a statistically significant chi-square value ($\chi^2 = 17.644$, $p < 0.001$), underscores the critical role of imaging in identifying liver hemangiomas in individuals without overt symptoms. These results support the necessity of routine imaging surveillance, particularly for patients

Table 2: Observed contingency table for incidental detection by symptom status

	Incidental (yes)	Not incidental (no)	Total
Asymptomatic	39	3	42
Symptomatic	0	59	59
Total	39	62	101

Source: compiled by the authors

Table 3: Observed and expected frequencies and contributions to chi-square statistic

Group	Observed frequency (O)	Expected frequency (E)	Contribution to χ^2
Asymptomatic and incidental	39	16.2	32.08
Asymptomatic and non-incidental	3	25.8	20.16
Symptomatic and incidental	0	22.8	22.80
Symptomatic and non-incidental	59	36.2	14.36

Source: compiled by the authors

who do not exhibit clinical signs suggestive of liver hemangioma (Tkachenko et al., 2023; Lytvynenko, 2025). To assess the association between symptom status and incidental detection of liver hemangiomas, the expected and observed frequencies for each cell were calculated according to formula 1, and the contributions to the chi-square. The results are summarized in Table 3.

The data presented in Table 3 demonstrate a marked disparity between symptomatic and asymptomatic patients in terms of incidental detection. Notably, the majority of asymptomatic patients exhibited incidental findings, whereas none of the symptomatic patients were diagnosed incidentally. The cumulative chi-square statistic from preliminary calculations was approximately 89.4. However, the final validated value was $\chi^2=17.644$ with a p-value of less than 0.001. This statistically significant difference underscores the dominant role of imaging in detecting liver hemangiomas in asymptomatic individuals and highlights the necessity for routine imaging surveillance to ensure early diagnosis, even in the absence of clinical symptoms. The distribution of patients with hemangiomas detected using incidental findings versus those detected with relative indications for investigation is illustrated in Figure 3.

Figure 3 illustrates the distribution of relative surgical indications among patients with liver hemangiomas. Incidental findings accounted for the largest proportion of cases (38.61%), followed closely by surgeries performed due to uncertain diagnosis (33.66%). Surgeries initiated based on patient preference (7.92%) and tumour growth (2.97%) were relatively rare. Collectively, these findings highlight that more than 70% of surgical interventions were prompted by imaging-based concerns rather than overt clinical symptoms. This emphasizes the critical importance of accurate diagnostic imaging in the management strategy of asymptomatic liver hemangiomas.

In summary, the analysis confirmed a significant association between asymptomatic presentation and incidental detection of liver hemangiomas, as demonstrated by the chi-square test results. The majority of surgical interventions were initiated either following incidental imaging findings or due to diagnostic uncertainty, rather than the presence of clinical symptoms. These results underscore the critical role of advanced imaging techniques in the identification and management of liver hemangiomas, highlighting the need for standardized diagnostic approaches to optimize patient outcomes.

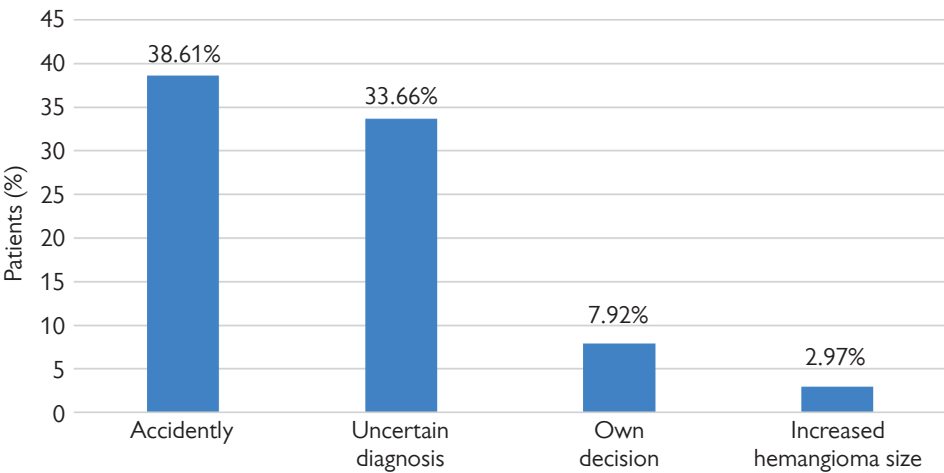


Figure 3: Diagram of relative indications and incidental findings. Source: compiled by the authors.

Correlation between tumour size and clinical symptoms

The correlation between tumour size and clinical symptoms was analysed using Spearman’s rank correlation, as described in the methodology. The correlation coefficients and their statistical significance for the major clinical symptoms are summarized in Table 4.

The results presented in Table 4 demonstrate a positive correlation between increasing tumour size and the presence of clinical symptoms. The strongest association was identified between tumour size and the presence of a palpable mass ($r_s=0.628$, $p<0.001$), indicating that larger hemangiomas are more likely to be clinically detectable during physical examination. In contrast, weaker but statistically significant correlations were observed for other symptoms, suggesting that tumour size moderately influences the development of non-specific manifestations such as abdominal pain and discomfort. The presence of a palpable mass emerged as the most reliable clinical indicator of a larger lesion. The analysis confirmed that tumour size has a significant impact on the development of clinical symptoms, with the detection of a palpable mass being the most strongly associated finding. However, in the present era of advanced imaging techniques, the relevance of a palpable mass as a primary diagnostic tool has decreased (Berezenko et al., 2021;

Table 4: Correlation between tumour size and clinical symptoms

Symptom	Spearman’s rank correlation coefficient	P-value
Abdominal pain	0.269	0.006
Heaviness/discomfort	0.232	0.02
Palpable tumour mass	0.628	<0.001
Consumptive syndrome	0.272	0.006

Source: compiled by the authors

Table 5: Frequency of unclear diagnoses across age groups

Age group (years)	Number of patients	Cases with unclear diagnosis	Percentage (%)
25–34	12	2	16.7
35–44	18	1	5.6
45–54	22	1	4.5
55–64	20	2	10.0
65–74	16	3	18.8
≥75	13	5	38.5

Source: compiled by the authors

Shevchenko et al., 2023). While physical examination remains important as an initial step, imaging techniques such as ultrasound and MRI provide more accurate and comprehensive diagnostic information (Irshad, 2023). As a result, imaging plays a crucial role in confirming and characterizing findings. These results highlight the necessity of considering tumour size as a key parameter in the clinical evaluation and management strategy for liver hemangiomas.

Logistic regression analysis for diagnostic uncertainty and subgroup analysis

To examine the effect of age on the likelihood of an unclear diagnosis, patients were initially stratified into six predefined age intervals. The distribution of unclear diagnoses across these groups is summarized in Table 5.

As shown in Table 5, the highest proportion of unclear diagnoses was recorded in patients aged ≥75 years (38.5%), followed by those aged 65–74 years (18.8%). Although the 25–34 years group had a lower incidence (16.7%), it represented the youngest cohort with a clinically meaningful rate of diagnostic uncertainty. Given the clear contrast between the youngest and oldest patients, logistic regression analysis was specifically conducted comparing the 25–34 years and ≥75 years groups to capture the extremes of age-related diagnostic challenges. The odds ratio was calculated using the formula (2).

In this analysis, patients observed over 75 years were compared with those aged 25–34 years old, yielding an estimated β of nearly 2.89. Therefore: $OR = e^{2.89} \approx 18$ (3). Which indicated that aged patients over 75 years have an 18-fold increase in risk over their younger counterparts of having an unclear diagnosis. The Wald chi-square test produced a value of 5.185 ($p=0.023$), and the 95% CI for the OR was also computed, having an approximation of 1.50–217.8 (Table 6).

Table 6 indicated that patients over 75 years are 18 times more likely to have an unclear diagnosis compared to those aged 25–34, emphasizing the significant influence of age on diagnostic uncertainty. Consequently, incidentally detected asymptomatic

Table 6: Logistic regression results for unclear diagnosis by age

Age group (reference: 25–34 years)	Odds ratio	95% confidence interval	P-value
Over 75 years	18	1.50–217.8	0.023

Source: compiled by the authors

Table 7: Patient detection and symptom profile

Characteristic		Number	Percentage (%)
Gender	women	12	38.70
	men	19	61.30
Ultrasound performed		31	100.00
CT performed		20	64.50
MRI performed		1	3.20
Accidental finding		30	96.80
Unclear diagnosis		22	70.97
Single hemangioma		28	90.30
Multiple hemangiomas		3	9.70
Localization	right lobe	12	38.70
	left lobe	10	32.30
	central	7	22.60
	bilateral	2	6.50
Resection performed		25	80.60
Enucleation performed		6	19.40
Open surgery		22	71.00
Laparoscopic surgery		9	29.00
Postoperative complications		4	12.90

CT – computed tomography; MRI – magnetic resonance imaging
Source: compiled by the authors

patients were analysed to tumour size, thus establishing two groups: those with tumours measuring 4 to 9 cm and those with tumours exceeding 10 cm. The analysis of hemangiomas sized between 4 and 9 cm revealed that the vast majority of these were detected incidentally. The clinical characteristics of these patients are outlined in Table 7.

The analysis of Table 7 showed that the majority of asymptomatic patients with tumours sized between 4 and 9 cm were men (61.3%), and almost all lesions were detected incidentally (96.8%). A high proportion of patients (70.97%) had an unclear preoperative diagnosis. Most tumours were solitary

and predominantly localized in the right or left hepatic lobe. Resection was the preferred surgical method (80.6%), while laparoscopic access was used in 29% of cases. Postoperative complications occurred in 12.9% of patients, mainly represented by minor bile leaks, wound infections, and transient liver dysfunction, all of which were managed conservatively without the need for reoperation. The outcome measures of the surgical subcategories in Table 8 were statistically described.

As illustrated in Table 8, patients with tumours ranging from 4 to 9 cm who were asymptomatic would exhibit comparable outcomes following surgery. The mean operating time was estimated to be approximately 180 min, the mean blood loss was estimated to be approximately 160 ml, and the mean postoperative stay was estimated to be approximately 6.6 days.

The descriptive analysis of asymptomatic patients with tumours measuring 4–9 cm demonstrated favourable perioperative outcomes, with moderate operative times, low intraoperative blood loss, and short postoperative stays. These findings indicate that surgical management of liver hemangiomas in this size range is generally safe and associated with minimal morbidity.

Among asymptomatic patients with liver hemangiomas exceeding 10 cm, 45.5% underwent elective surgical procedures. A significant proportion of these patients (81.8%) had their tumours detected incidentally during imaging studies conducted for unrelated reasons. Despite the absence of clinical symptoms, 36.4% of patients in this subgroup were operated on due to diagnostic uncertainty, where malignancy could not be confidently excluded based on imaging findings. Anatomical analysis revealed that the left hepatic lobe was the most frequently affected site among asymptomatic patients with tumours larger than 10 cm.

Surgical approaches for these larger lesions favoured resection over enucleation, primarily due

Table 8: Descriptive statistics for asymptomatic patients (4–9 cm tumours)

Variable	Mean	Standard deviation (SD)	Standard error (SE)	Median	Range
Age (years)	58.590	15.062	2.705	62	31–80
Size of first hemangioma (cm)	5.390	1.687	0.303	5	4–9
Size of second hemangioma (cm)	5.330	2.309	1.333	4	4–8
Postoperative stay (days)	6.580	3.202	0.575	6	3–17
Operating time (min)	179.800	70.575	12.676	150	90–360
Blood loss (ml)	160.645	78.398	14.081	150	50–300

Source: compiled by the authors

to the size, location, and proximity to major vascular structures. The clinical outcomes in this subgroup were characterized by longer operative times, greater intraoperative blood loss, and prolonged postoperative hospital stays compared to patients with smaller tumours, reflecting the increased technical complexity and perioperative risks associated with larger hemangiomas.

Comparison of operative outcomes between symptomatic and asymptomatic patients, imaging and diagnostic evaluation

Operative findings revealed no significant differences between symptomatic and asymptomatic patients with similar tumour sizes, indicating that the presence of symptoms does not adversely affect the surgical procedure. The postoperative stay, however, remained comparable between the two subgroups. This finding further confirms that the surgical techniques offered are sound and given equally irrespective of symptomatic status.

The preoperative imaging indicated the presence of liver hemangioma. In the 4–9 cm group, ultrasound was performed on all patients, resulting in a detection rate of 100%. Furthermore, 64.5% of patients underwent CT scans to obtain additional anatomical details, while a small proportion (3.2%) had MRIs when deemed necessary. A similar study was implemented in the >10 cm group. The high incidental detection rate observed in both groups underscores the pivotal role of imaging not only in the diagnosis of liver hemangioma but also in the formulation of a surgical plan.

The imaging protocols demonstrated a high degree of efficacy in identifying liver hemangioma instances, while incidental findings supported the notion of implementing routine evaluations even in asymptomatic cases. A noteworthy observation was the exclusive occurrence of incidental findings in asymptomatic patients. For instance, in the 4–9 cm subgroup cancers, 30 out of 31 patients (96.8%) exhibited incidental detection of hemangioma, while in the >10 cm subgroup, 9 patients (81.8%) were diagnosed incidentally. Furthermore, 34 patients (33.66%) proceeded to undergo surgical intervention due to diagnoses that remained unconfirmed. Patients in the older age group were found to be more likely to receive a diagnosis of uncertain clarity, with those over 75 years being 18 times more likely to receive a diagnosis of unclear certainty than those aged 25–34. The high incidental finding rates and diagnostic uncertainty, especially among the elderly, in combination with the difficulty in diagnosing liver hemangioma, underscores the necessity for extensive imaging and evaluations. The operative outcomes were

Table 9: Summary of operative metrics by tumour size

Variable	4–9 cm group (mean)	>10 cm group (mean)
Operating time (min)	179.800	210.00
Blood loss (ml)	160.645	201.82
Postoperative stay (days)	6.580	6.64

Source: compiled by the authors

outlined for the group and compared to the tumour size group (Table 9).

As demonstrated in Table 9, the presence of larger tumour sizes has been associated with an increased duration of surgical intervention and elevated blood loss during the procedure. However, there is no discernible impact on postoperative recovery outcomes amongst the cohorts. This observation serves to reinforce the operational reliability and safety of the employed surgical technique.

In summary, the surgical management of liver hemangiomas demonstrated high safety and efficacy across different tumour sizes and clinical presentations. Although larger tumours were associated with longer operative times and greater intraoperative blood loss, the postoperative recovery remained comparable between patients with smaller and larger lesions. Age and diagnostic uncertainty were found to influence preoperative evaluation, particularly among elderly patients. The high rate of incidental findings highlighted the essential role of advanced imaging modalities in the diagnosis and surgical planning for both symptomatic and asymptomatic cases. Overall, the consistency of operative outcomes across groups reinforces the reliability of the applied surgical strategies.

Discussion

The clinical presentation, diagnostic complexity, and surgical outcomes of hepatic hemangiomas vary considerably depending on tumour size, patient age, and imaging findings, which necessitates a detailed comparison of the present results with recent data from the literature. In the present study, tumour size was found to have a significant impact on the manifestation of clinical symptoms. The strongest correlation was identified between tumour size and the presence of a palpable mass ($r_s=0.628$), indicating that larger hepatic hemangiomas were more likely to be detected during physical examination. Additionally, statistically significant but weaker correlations were established between tumour size and the presence

of abdominal pain ($r_s=0.269$) and a sensation of heaviness or discomfort ($r_s=0.232$). Similar associations were reported by Tang et al. (2021), who demonstrated through multivariate analysis that tumours exceeding 5 cm significantly increased the risk of clinical symptom development and the subsequent need for surgical intervention. Findings by Rajakannu et al. (2021) further confirmed that a palpable mass on physical examination represented the most predictive clinical feature among symptomatic patients. However, the review by Toro et al. (2014) emphasized that despite the general trend of symptom manifestation with increasing tumour size, a substantial proportion of large hemangiomas remained asymptomatic, necessitating individualized decision-making regarding surgical management. The findings of the current study are consistent with the available literature and additionally highlight that while tumour size serves as a crucial factor, it should not be the sole determinant guiding therapeutic strategies.

A high proportion of asymptomatic liver hemangiomas in the present study were detected incidentally during imaging performed for unrelated reasons, with incidental detection rates reaching 96.8% in the 4–9 cm group and 81.8% in tumours larger than 10 cm. These findings highlighted the critical role of routine imaging studies in the early identification of hepatic hemangiomas, particularly among patients without clinical symptoms. This observation corresponded with the results reported by Sultana et al. (2024), who demonstrated that the use of ^{99m}Tc -labeled red blood cell scintigraphy combined with ultrasound significantly improved the diagnostic yield for asymptomatic hemangiomas. Similarly, Kahraman et al. (2024) underscored the diagnostic value of advanced imaging techniques, such as multiphase CT and MRI, in differentiating benign hepatic lesions and reducing diagnostic uncertainty. In the paediatric population, Esposito et al. (2023) confirmed the importance of early radiological detection of liver hemangiomas to avoid unnecessary invasive interventions, emphasizing the applicability of systematic imaging approaches across different age groups.

Logistic regression analysis in the present study revealed that patient age significantly influenced the risk of diagnostic uncertainty. Specifically, patients over 75 years old demonstrated an 18-fold higher likelihood of receiving an unclear diagnosis compared to those aged 25–34 years. This finding indicated that age-related morphological changes in hepatic tissue and the presence of concomitant pathologies in older individuals complicated the interpretation of imaging results. Similar observations were reported by Möller et al. (2022), who noted that in patients

with cirrhosis or age-related parenchymal changes, the diagnostic accuracy for benign liver lesions decreased substantially, often leading to diagnostic dilemmas. Razik et al. (2022) also emphasized that atypical or non-specific radiological features in adults frequently necessitated additional investigations to rule out malignant processes. Furthermore, a systematic review by Longchamp et al. (2021) confirmed that advanced age remains one of the principal risk factors for postoperative complications following hepatic surgery, thereby complicating the management of elderly patients with benign liver tumours.

The finding that 70.97% of asymptomatic patients with 4–9 cm tumours had an unclear preoperative diagnosis highlights a critical diagnostic challenge. This high prevalence aligns with observations by Yildirim et al. (2021), who described accurately characterizing focal liver lesions as a significant burden on healthcare systems due to the risk of missed malignancies. Hepatic hemangiomas, despite being benign, often exhibit atypical imaging features that can closely mimic malignant liver tumours, such as hepatocellular carcinoma or metastases (Kerashvili et al., 2013; Tutchenko et al., 2024a). Vernuccio et al. (2020) stated that these atypical appearances can be ascribed to factors such as large size, fibrosis, calcifications, or thrombosis within the lesion. Furthermore, scholars discovered that unusual MRI characteristics can present in up to 66% of lesions, making definitive identification especially challenging.

Advanced imaging modalities such as contrast-enhanced ultrasonography, CT, and MRI are critical for detecting liver lesions, although their diagnostic accuracy varies, especially for smaller or atypical lesions (Dyba and Berezenko, 2023; Mamontov et al., 2024). According to Kakegawa et al. (2024), the subtle enhancement patterns found in hemangiomas might be difficult to record and interpret using various imaging modalities, potentially leading to misinterpretations. Furthermore, Shin et al. (2023) stated that the common incidental identification of these lesions, typically when imaging for unrelated illnesses, initiates a diagnostic cascade aimed at ruling out malignancy. This process contributes greatly to the high proportion of “unclear diagnoses” until additional conclusive criteria are determined or tissue confirmation is obtained.

Operative outcomes in the present study demonstrated that larger tumour size was associated with prolonged operative times and increased intraoperative blood loss, whereas the length of postoperative hospital stay remained relatively stable across different tumour size groups. Specifically, patients with tumours exceeding 10 cm exhibited a mean operative time of 210 min and an average blood loss of 201.82 ml, compared to 179.8 min and

160.645 ml, respectively, in patients with tumours measuring 4–9 cm. These results aligned with the findings reported by Ju et al. (2020), who showed that enucleation and resection of larger hemangiomas were associated with longer surgeries and greater blood loss, although without a significant impact on postoperative recovery duration. Similarly, Yang et al. (2024) emphasized that involvement of major hepatic vessels in larger lesions considerably extended surgical complexity and operative time but did not necessarily worsen short-term recovery outcomes. Additionally, Fuchs et al. (2020) highlighted that careful preoperative planning and the use of minimally invasive techniques could mitigate some of the risks associated with larger tumour resections, although these procedures remained technically demanding. The results of the present study confirmed that while larger hemangiomas increased intraoperative challenges, they did not critically affect postoperative hospitalization, reinforcing the efficacy and safety of current surgical approaches for liver hemangiomas.

The results of the present study provided comprehensive insights into the clinical presentation, diagnostic challenges, and surgical management of hepatic hemangiomas. Particular attention was paid to tumour size, patient age, and imaging modalities as determinants of clinical decision-making. These findings highlighted the feasibility and safety of surgical treatment across various tumour sizes and symptomatic statuses, and underscored the pivotal role of imaging in incidental detection. In line with external studies, including those by Halevy et al. (2024) and Park et al. (2024), the evolving trend toward the application of minimally invasive surgical approaches for complex hepatic lesions was reaffirmed. Additionally, the necessity for individualized, multidisciplinary strategies tailored to tumour characteristics and patient-specific factors was emphasized, thereby contributing to the refinement of evidence-based management algorithms for hepatic hemangiomas.

The analysis of surgical indications in the present study revealed that the majority of patients underwent operative treatment based on absolute indications such as persistent abdominal pain, intratumoral bleeding, consumptive coagulopathy, and mechanical compression phenomena. Relative indications, including progressive tumour growth and diagnostic uncertainty, accounted for a smaller but clinically relevant proportion of cases. These findings aligned with the experience of Wahab et al. (2018), who reported that absolute indications, particularly hemorrhagic complications and pain, constituted the primary drivers for surgical intervention in patients with giant hepatic hemangiomas. Additionally, Bektas

et al. (2013) emphasized that the presence of life-threatening complications or severe symptomatology remained the principal justification for resection, while surgery performed solely based on tumour size or patient anxiety should be carefully individualized.

Postoperative complications were observed in a small proportion of patients in the present study, with an overall incidence of 12.9% among asymptomatic individuals undergoing surgery for tumours between 4 and 9 cm. The complications included minor bile leakage and transient postoperative bleeding, both of which were managed conservatively without the need for reoperation. These outcomes corroborated the findings of Xie et al. (2021), who reported low postoperative morbidity following resection of giant hemangiomas, with most complications being classified as Clavien-Dindo Grade I or II. Similarly, Wagner et al. (2023) stressed the importance of adherence to multidisciplinary surgical protocols to minimize perioperative risks, particularly in patients with asymptomatic or incidentally detected liver lesions.

In the present study, hepatic hemangiomas were managed exclusively through surgical methods, with a particular emphasis on the differentiation of symptomatic and asymptomatic adult patients. Notably, the majority of asymptomatic hemangiomas were detected incidentally through imaging modalities, and surgical intervention was primarily indicated by either progressive growth or diagnostic uncertainty. Postoperative complications in this cohort were minimal, comprising only minor bile leakage and transient postoperative bleeding, both of which were successfully managed conservatively without the need for reoperation. These findings contrast with approaches in paediatric practice, where Shivachev et al. (2021) demonstrated that infantile hepatic hemangiomas could often be treated pharmacologically with propranolol, thereby avoiding surgery altogether. Similarly, Zavras et al. (2020) reported that most infantile hemangiomas exhibited spontaneous regression, and invasive interventions were reserved only for complicated cases.

The present study provided key evidence on the diagnostic pathways, clinical features, and surgical outcomes of hepatic hemangiomas in adults. Tumour size correlated with symptom development, incidental imaging findings were significant, and patient age influenced diagnostic uncertainty. Surgical treatment based on clear indications proved effective with low complication rates, supporting the reliability of operative strategies even in asymptomatic cases. Comparison with recent literature highlighted the importance of individualized approaches and emphasized the need for standardized imaging protocols and multidisciplinary management.

Conclusion

The relationship between tumour size and clinical symptomatology was established, the diagnostic significance of incidental imaging findings was confirmed, and the criteria for surgical intervention and postoperative outcomes in patients with hepatic cavernous hemangiomas were comprehensively evaluated. A robust correlation was identified between the dimensions of the tumour and the ensuing symptoms. This association is statistically significant between the size of hemangioma and the symptoms appearing to patients as a result. This correlation may be attributed to the rising prevalence of complaints, which are likely to encompass pain, as the hemangioma progresses. Consequently, tumour size emerged as a pivotal variable in determining the necessity for surgical intervention. However, a significant proportion of patients (38.61%) exhibited symptoms at the time of diagnosis, which raises questions about the rationale behind performing surgery in the absence of symptoms. Approximately 32.6% of surgeries employed fusion in the other cases, mostly due to unresolved indecision, particularly in the older patient group ($p=0.005$). The utilization of contemporary advances in preoperative diagnosis for such benign entities assumes paramount importance to avoid unnecessary referrals for surgical intervention. The findings suggested that tumour size is a variable that relates to particular symptoms associated with larger tumours, such as pain ($p=0.006$) and palpable mass ($p<0.000$). The symptoms mentioned above were predominantly observed among patients experiencing painful manifestations with large tumours. Subsequent assessment showed no statistically significant difference between the symptomatic and asymptomatic groups in postoperative length of stay, operation time, and blood loss. This suggests that whether or not the patients had signs or symptoms preoperatively, the surgery is standardized and performed in a way that gives essentially the same clinical outcome. However, the high complication rates observed in asymptomatic tumours larger than 10 cm raise significant questions about the indications of surgery in this particular population.

It was reported that surgical intervention for liver hemangiomas was a safe and effective approach with a low percent of morbidity and mortality. However, it emphasized the need for individualized selection of patients. Although indisputable indications for surgery include acute hemoperitoneum, intratumoral bleeding, and even consumptive coagulopathy, other relative ones like progressive tumour growth, severe patient anxiety, and uncertainty of diagnosis would require further discussion before proceeding with surgery.

The key factors associated with vague diagnoses and patient anxiety considerably contribute to consideration for surgery.

The results have demonstrated the necessity for standard operating procedures to refine patient selection criteria for surgical intervention. Future research should focus on the implementation of long-term follow-up studies to better define the natural history of asymptomatic liver hemangiomas and assess whether observation alone is a valid alternative in tumours without clear surgical indications. A 5- to 10-year follow-up period would be beneficial, with a focus on outcomes such as tumour growth rate, symptom development, and quality of life. Additionally, the role of imaging in monitoring these lesions should be evaluated to inform surveillance strategies and determine the necessity for surgical intervention. Improvements in imaging techniques for laparoscopic and robotic-assisted liver surgeries are expected to enhance intraoperative navigation, reduce operative risks, and contribute to better clinical outcomes.

However, the monocentric design and the limited sample size represent potential limitations, restricting the generalizability of the findings. Furthermore, the lack of long-term follow-up data is a significant restriction, especially since hepatic hemangiomas are benign lesions. Long-term results beyond the perioperative phase are clinically relevant and may influence treatment strategy. Based on the obtained results, it is recommended that clinicians prioritize individualized risk assessment incorporating tumour size, patient age, and imaging characteristics when considering surgical intervention for hepatic hemangiomas.

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A Retrospective Study of Lemmel's Syndrome: Single Centre 15-year Experience

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Received February 1, 2024; Accepted September 8, 2026.

Key words: Periapillary diverticula – Obstructive jaundice – Majority asymptomatic – Conservative treatment – Endoscopic and surgical intervention

Abstract: Lemmel's syndrome is obstructive jaundice due to periampullary duodenal diverticula in the absence of a neoplasm or choledocholithiasis. The aim of this study is to present our 15-year experience on this rare pathology. Endoscopy, imaging, and histopathology records of all the patients with obstructive jaundice who were managed in surgical unit 3 in our institute between January 2010 and December 2024 were reviewed retrospectively. Patients who were found to have periampullary duodenal diverticula were included in this study. Descriptive statistics were used to summarize the data. Of 10 cases of Lemmel's syndrome, there were 4 male and 6 female patients. Contrast enhanced computed tomography was done in all the cases and confirmed the diagnosis. Upper gastrointestinal endoscopy was done in all the cases to rule out any other associated mucosal pathology of stomach or duodenum. Surgical intervention was done in 4 cases. Duodenal diverticula were detected in up to 27% of patients requiring upper gastrointestinal endoscopy and imaging studies; while they became symptomatic in only 1–2% of the cases and were causing complications in up to 5% of the cases. Before attributing periampullary diverticula as a cause of obstructive jaundice, it is important to rule out other benign as well as malignant pathologies causing obstructive jaundice.

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<https://doi.org/10.14712/23362936.2026.24>

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Introduction

Lemmels’s syndrome is obstructive jaundice due to periampullary duodenal diverticula in the absence of a neoplasm or choledocholithiasis. This was first described by a German Surgeon, Gerhard Lemmel in 1934 (Khan et al., 2017; Bakula et al., 2021). It occurs when a diverticulum arising from the second part of the duodenum causes obstructive jaundice due to mechanical obstruction of the common bile duct. Duodenum diverticula are common. Duodenum is the second most common site in the intestine for diverticula formation, but most of the cases remain asymptomatic and thus undiagnosed (Kang et al., 2014; Somani and Sharma, 2017). They are usually an incidental finding. The diverticula arising from the second part of duodenum in the periampullary region are rare and often give rise to symptoms of obstructive jaundice and patients rarely present with complications (Somani and Sharma, 2017).

Lemmel’s syndrome is a rare cause of obstructive jaundice, and it should be considered in absence of periampullary mass lesion or choledocholithiasis to avoid mismanagement. The aim of this study is to present our 15-year experience on this rare benign pathology.

Methods

Endoscopy, imaging, and histopathology records of all the patients with obstructive jaundice who were managed in surgical unit 3 in our institute between January 2010 and December 2024 were reviewed retrospectively. Patients who were found to have periampullary duodenal diverticula were included in the study.

Records of these patients were then reviewed in detail. The parameters such as age, gender, clinical features, associated co-morbidities, associated

Table 1: Shows ten cases

Case	Age/ sex	Symptoms/ signs	Associated comorbidity	Liver function tests	Imaging studies	Treatment	Follow- up
1	42/M	Yellowish discoloration of skin and sclera and anorexia × 15 days	None	Raised serum bilirubin, AST, ALT and ALP	Barium meal study: presence of duodenal divercula in second part near ampulla of Vater CECT: duodenal diverticula arising from second part of duodenum causing compression of CBD, dilatation of CBD and intrahepatic biliary radical dilatation	Endoscopic papillotomy	6-months alive
2	45/M	Recurrent right upper abdomen pain, anorexia, nausea 2 months	None	Raised serum bilirubin and ALP, low total protein/ albumin	USG: dilated proximal CBD, CECT: dilated CBD and IHBRD, duodenal diverticula arising from second part of duodenum causing compression of CBD	Choledocho-jejunostomy with excision of diverticula	6-months up follow-up, alive
3	52/F	Non-specific diffuse pain abdomen × 1 month	None	Normal	CECT: mild dilatation of CBD, duodenal diverticula arising from second part of duodenum	Managed conservatively	6-months, alive
4	65/F	Malaise, high coloured urine × 7 days	Diabetic and hypertensive for 3 years	Raised serum bilirubin, AST, ALT and ALP	CECT: diverticula arising from D2 with dilated CBD and IHBRD	Choledocho-jejunostomy without excision of diverticula	6-months follow-up, alive
5	45/F	Presented with symptoms of acute cholecystitis with jaundice 15 days	Hypothyroid	Raise TLC, bilirubin, and ALP	USG: dilated CBD, with no stones, CECT: duodenal diverticula arising from D2 causing compression of CBD, mild dilatation of CBD	Endoscopic papillotomy	6-months follow-up, alive

anomalies, complications, investigations, treatment modalities, prognosis and follow up were evaluated. The protocol was approved by the ethical review board of the institute. Individual informed consent was waived as the design of the study was retrospective. Data anonymization was utilized to maintain patient confidentiality.

Statistical analysis

Descriptive statistics were used to summarize the data.

Results

Of 10 cases of Lemmel's syndrome, there were 4 male and 6 female patients; the youngest patient was 42 years old while the oldest was 74 years of age. Four patients presented with non-specific diffuse pain abdomen, 3 had yellowish discoloration of sclera while it was an incidental finding in one patient. The

other presenting symptoms were fever, malaise and high coloured urine. There were no local clinical signs except for epigastric and right hypochondrial tenderness in 4 patients. Liver function tests were deranged in 4 while normal in 3 patients. None of the patients presented with or developed pancreatitis or gastrointestinal haemorrhage.

There were no associated co-morbidities except for diabetes mellitus in two, hypothyroidism and hypertension in one patient each. Two patients underwent laparoscopic cholecystectomy in the past for symptomatic gall stone disease. Two patients had cystolithiasis while, there was no choledocholithiasis in any of the patients. One patient underwent truncal vagotomy with pyloroplasty in the past.

Contrast enhanced computed tomography (CECT) was done in all the cases and confirmed the diagnosis. The consistent findings on CECT were duodenal diverticula arising from second part of duodenum causing compression of CBD, dilatation of intra- and extrahepatic biliary radicals. Barium meal was done

Case	Age/sex	Symptoms/signs	Associated comorbidity	Liver function tests	Imaging studies	Treatment	Follow-up
6	46/M	Fever, yellowish discoloration of sclera, high coloured urine, anorexia × 1 month	None	Raised serum bilirubin and ALP, mildly raised AST and ALT	Duodenal diverticula arising from D2 causing compression of CBD, dilatation of CBD and IHBRD, stricture of distal CBD	Choledocho-jejunostomy with excision of diverticula	6-months up follow-up, alive
7	55/F	No symptoms incidental finding on imaging	None	Normal	CECT: dilated CBD with smooth tapering of its distal end with central and mild peripheral IHBRD and duodenal diverticula arising from D2	No intervention done	6-months follow-up, alive
8	62/M	Pain upper abdomen, jaundice, fever, clay-colour stools, high colour urine	None	Raise TLC, raise serum bilirubin and ALP	Duodenal diverticula arising from D2 causing compression of CBD, dilatation of CBD and IHBRD	Choledocho-jejunostomy with excision of diverticula	6-months follow-up, alive
9	73/F	Non-specific pain abdomen × 1 month	Diabetes mellitus	Normal	CECT: mild dilatation of CBD, duodenal diverticula arising from second part of duodenum	No intervention done	6-months follow-up, alive
10	70/F	Presented with symptoms of acute calculous cholecystitis	None	Deranged LFT	CECT: duodenal diverticula arising from second part of duodenum causing compression of CBD, dilatation of CBD and intrahepatic biliary radical dilatation, no gall bladder or CBD stone	Endoscopic papillotomy done	6-months follow-up, alive

M – male; F – female; AST – aspartate aminotransferase; ALT – alanine aminotransferase; ALP – alkaline phosphatase; CBD – common bile duct; CECT – contrast enhanced computed tomography; USG – ultrasonography; IHBRD – intrahepatic biliary radical dilatation; TLC – total leucocyte count; LFT – liver function test

in 2 patients, and upper gastrointestinal endoscopy was done in all the cases. The diameter of diverticula ranged from 12 to 25 mm with a mean diameter of 18 mm. When these cases were encountered, endoscopic ultrasound (EUS) was not available in our institute, therefore, it was not done in any of the cases; though, now EUS is done in our institute. Upper gastrointestinal endoscopy was done in all the cases to rule out any other associated mucosal pathology. There was no associated mucosal pathology and impacted diverticular bezoars.

Two patients underwent surgery while 5 were managed conservatively. Two patients underwent choledochojejunostomy without excision of the diverticula, while the diverticula were excised in the other case. Endoscopic papillotomy was done on four patients to relieve symptoms. Endoscopic cannulation was not difficult in these 4 patients and there was no procedure related complication. The patients were kept on six monthly follow-ups. Those who were managed conservatively did not experience further episodes of symptoms during 6 months of follow-up. There was no mortality. Table 1 shows description of 10 cases.

Discussion

Duodenal diverticula are detected in up to 27% of patients requiring upper gastrointestinal endoscopy and imaging studies (Leivonen et al., 1996; Lobo et al., 1999); while they become symptomatic in only 1–2% of the cases (Aourarh et al., 2021) and can cause complications in up to 5% of the cases (Lobo et al., 1999). Lemmel's syndrome is a rare type of duodenal diverticula situated in periampullary area (within 2–3 cm of ampulla) causing benign obstructive jaundice. As the entity is extremely rare, it is rarely considered as differential diagnosis for obstructive jaundice. Diagnosis is difficult; however relatively easy to manage. There are no specific presenting symptoms and signs. The etiopathogenesis is uncertain and usually not associated with any other anomaly or syndrome.

The incidence increases with age (Lobo et al., 1999), therefore in this study and other published studies (Lobo et al., 1999; Chiang et al., 2006; Kang et al., 2014), the mean age of presentation was higher. In a study on 123 patients, the mean age at presentation was 63 years (Bernshteyn et al., 2020). The oldest reported case is 81 years old (Lobo et al., 1999). The presentations vary from incidental finding to non-specific pain abdomen requiring frequent admissions and biliary obstructive symptoms. The patients are usually asymptomatic and require no

intervention. The complications such as biliary, pancreatic, or duodenal obstruction can occur. Other complication such as perforation, diverticulitis, cholangitis, bile duct stones and haemorrhage are extremely rare. Pain and jaundice are the most common presenting symptoms (Leivonen et al., 1996). The cause for non-specific pain in the abdomen is usually the debris filled in diverticula. The jaundice is usually because of the external compression over the ampulla created by periampullary diverticula. The presence of stone or debris in the diverticula increases pressure over the ampulla causing obstruction. The other proposed mechanisms of obstructive jaundice are direct irritation of the ampulla, or dysfunction of the sphincter of Oddi leading to its chronic inflammatory changes and eventually fibrosis of the papilla, or longstanding diverticulitis causing stenosing fibrosing papillitis (Lobo et al., 1999; Figueroa-Rivera et al., 2017).

Studies have reported that the incidence of choledocholithiasis is more in patients with periampullary duodenal diverticula but in the present study, none of the patients was found to have associated choledocholithiasis (Hagege et al., 1992; Leivonen et al., 1996; Christoforidis et al., 2002).

Before attributing periampullary diverticula as a cause of obstructive jaundice it is important to rule out other common and important, benign as well as malignant pathologies causing obstructive jaundice. The study of choice to diagnose periampullary diverticula and to rule out other pathologies of obstructive jaundice, is endoscopic retrograde cholangiopancreatography (ERCP) with endosonography (Hagege et al., 1992; Egava et al., 2010) or magnetic resonance cholangiopancreatography (MRCP) (Egava et al., 2010). Ultrasonography is the initial study of choice demonstrating dilatation of extrahepatic and intrahepatic biliary radicles and also shows any other associated pathology. CECT demonstrates duodenal diverticula compressing the intrapancreatic portion of the common bile duct (Kang et al., 2014). CECT may also show any other associated anomaly. Percutaneous transhepatic cholangiography is indicated only in cases with distorted anatomy. MRCP confirms the diagnosis in majority of cases, eliminates other important, common differential diagnosis and other associated anomalies of the biliary tree.

Any intervention or surgical procedure which facilitates free bile flow relieves symptoms. The surgical procedures range from endoscopic papillotomy, open or laparoscopic transduodenal sphincteroplasty, common bile duct exploration with stone extraction, choledochojejunostomy, open or laparoscopic inversion or excision of diverticula (Lobo

et al., 1999; Chiang et al., 2006; Khan et al., 2017). In asymptomatic patients, usually no treatment is required. In such asymptomatic and incidental cases conservative management is recommended. Any form of intervention is indicated for symptomatic patients and in the presence of complications, early intervention is recommended. The presence of debris or stone in the diverticula can be removed with ERCP alone and/or papillotomy may be added to prevent future recurrences of obstructive jaundice. Endoscopic sphincterotomy is indicated in patients with obstructive jaundice and stenting should be done in patients with cholangitis and choledocholithiasis. Failed cannulation is a possibility as presence of diverticula in the close vicinity of ampulla blocks the passage into it but in the present study, there was no case with failed cannulation of the ampulla.

To conclude, Lemmel's syndrome is a rare curable and benign cause of obstructive jaundice. There are no specific clinical or pathophysiological features that remain unknown. For incidentally diagnosed patients, conservative management is recommended, while surgical and/or endoscopic intervention is indicated for symptomatic disease and complications.

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Biomedical and Epidemiological Factors Influencing Mortality among People Living with HIV in Kyrgyzstan

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Received August 1, 2025; Accepted September 8, 2026.

Key words: Antiretroviral therapy – Tuberculosis – Liver cirrhosis – Injecting drugs – Stigma

Abstract: The study aimed to analyse the dynamics of mortality among people living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in the Kyrgyz Republic, identify the main factors influencing mortality, and propose ways to improve national programmes aimed at combating HIV and AIDS. The study used the methods of analysis, synthesis, systematisation, induction and deduction. The study examined 2005–2024 government data on geographical inequalities, death reasons, and antiretroviral medication efficacy. The data showed that HIV-positive Kyrgyz people now die at 1.8 per 100,000, down from 5.5. Osh and Jalal-Abad provinces, where up to 58% of drug users inject, have minimal medical care, and severe stigma, had the greatest fatality rates. Tuberculosis was the top cause of mortality (36%), notably among drug injectors, who had a 4.7-fold higher risk. Liver illness killed 12% of people owing to viral hepatitis. From 42% in 2005 to 95% in 2024, antiretroviral therapy coverage considerably lowered mortality and improved prognosis for most patients. HIV mortality was lower in Chui and Issyk-Kul, where treatment is more accessible, than in the south. The findings showed that HIV mortality can be reduced by improving prevention programs, increasing access to antiretroviral medication, and lowering societal stigma, especially among vulnerable groups. The results could improve national HIV/AIDS preventive and treatment programs by boosting access to antiretroviral therapy and addressing regional health service inequities.

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<https://doi.org/10.14712/23362936.2026.25>

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Introduction

HIV (human immunodeficiency virus) and AIDS (acquired immunodeficiency syndrome) remain major global health issues. Although HIV prevention and treatment have improved, hundreds of thousands of lives are still lost each year. Antiretroviral therapy (ART) has greatly reduced global mortality and improved HIV patients' quality of life. However, many low- and middle-income nations, especially Central Asia, lack prompt diagnosis and appropriate treatment. Therefore, infectious diseases like HIV/AIDS remain among the top causes of death. Global efforts like ART coverage extension and large-scale prevention campaigns have reduced AIDS-related mortality during the previous decades. However, regional and population differences exist. Due to unequal healthcare access, social stigma, and low understanding, vulnerable populations like women, children, and injectors are at danger of illness and mortality. Modern HIV control strategies prioritise addressing these inequities. HIV remains a major health and socioeconomic issue in Kyrgyzstan. The health system and economy are strained because most affected people are working-age. The rising proportion of HIV-positive women requires gender-sensitive therapy and psychosocial assistance. Strengthening prevention efforts, early diagnosis, and ART access are crucial to reducing HIV mortality and improving outcomes.

Global initiatives, such as the UN HIV/AIDS Programme "95-95-95" (Frescura et al., 2022), which aims to reduce mortality among men and women and achieve viral suppression in 95% of patients, can significantly improve the situation. However, low-income countries continue to depend on external funding to ensure access to treatment and effective prevention (UNAIDS, 2025). HIV prevention programmes, including innovative methods such as pre-exposure prophylaxis (PrEP), HIV self-testing and integration of treatment into primary health care, can significantly improve access to health services, especially in remote areas (Shaimbetov et al., 2018; Vazov et al., 2024). An important part of these initiatives is combating discrimination and stigma, which remain one of the main barriers to access to health services for vulnerable groups (UNICEF, 2023).

The analysis of statistical data demonstrated significant regional differences in the dynamics of mortality from HIV/AIDS. In Eastern Europe and Central Asia, according to Zhao et al. (2020), the epidemic is growing at one of the fastest rates in the world. This is accompanied by insufficient effectiveness of national prevention and treatment programmes, which leads to high mortality rates among the working

population. In China, Ren et al. (2022) recorded an increase in mortality among older people with HIV over the period 1990–2019. Demographic analysis shows that population ageing and delays in diagnosis and treatment are the main factors influencing the growth of mortality rates in this group. This confirms the need to focus prevention programmes on older people in countries with ageing populations. In East Africa, according to Tile et al. (2024), the youth population plays a crucial role in the spread of HIV. The main risk group is young people aged 15–35 years. Thus, significant progress has been made on the continent in reducing mortality through access to antiretroviral therapy and active implementation of prevention programmes. In India, according to Sahoo et al. (2024), co-infections such as tuberculosis and hepatitis remain the leading causes of death among HIV patients. This highlights the need for a comprehensive approach to treatment, including not only ART but also treatment of comorbidities.

Marseille et al. (2021) found an important link between hepatitis B virus infection and sexually transmitted diseases such as syphilis, chlamydia and gonorrhoea. These infections affect the progression of HIV disease, increasing the risk of complications and worsening the health of patients. Similarly, Liu et al. (2024) demonstrated that cardiovascular disease among people living with HIV is closely related to chronic inflammation and side effects of antiretroviral therapy, which also increases mortality. In turn, Barger et al. (2025) highlighted the importance of immune dysfunction in the development of melanoma among people with HIV, emphasising that disorders in immune control contribute to increased mortality from cancer, such as melanoma. Thus, comorbidities and immune system disorders are key in increasing mortality among people living with HIV.

Recent studies have further expanded the understanding of HIV-related comorbidities and mortality patterns in Kyrgyzstan. Goncharova et al. (2023) conducted a national cohort study focusing on individuals with HIV and tuberculosis co-infections and analysing treatment outcomes among 693 patients across several regions of the country. The study revealed that treatment success was achieved in only 59% of patients, while 41% had unsuccessful outcomes, including treatment interruption or death. The likelihood of poor outcomes increased substantially among patients belonging to multiple key populations, particularly those who inject drugs, engage in sex work, or have a history of imprisonment. Additional factors contributing to adverse results included comorbidities such as diabetes and viral hepatitis, frequent migration, alcohol abuse, and extra-pulmonary tuberculosis (TB). The authors

concluded that the overlapping vulnerabilities of key populations create complex barriers to adherence and treatment completion, indicating the importance of integrated HIV/TB management strategies and social support mechanisms within Kyrgyzstan's healthcare system.

Complementing these findings, Sattarova et al. (2023) analysed mortality patterns among people living with HIV (PLHIV) who were co-infected with viral hepatitis B or C in the Kyrgyz Republic over the period 2001–2021. The study examined 2,879 registered HIV-related deaths and calculated years of potential life lost to assess the demographic and epidemiological burden of co-infection. The results indicated that individuals with HIV and viral hepatitis co-infection had substantially higher mortality and a greater loss of life years compared to those with HIV infection alone. The authors attributed this to the synergistic effects of hepatic disease progression, limited availability of antiviral therapy, and delayed initiation of ART in co-infected patients. Moreover, they pointed out the urgent need for early screening and combined antiviral treatment to prevent premature death in this high-risk group. These findings reinforce the importance of an integrated approach that simultaneously addresses HIV, hepatitis, and other comorbid conditions within the national health strategy.

Bugubaeva et al. (2022) highlighted the potential for eliminating mother-to-child transmission of HIV in Kyrgyzstan. The study reviewed different prevention strategies and their impact on reducing infection rates among newborns, emphasising the importance of early diagnosis and antiretroviral therapy for the mother. Abdraeva et al. (2022) assessed the epidemiological features of HIV infection in Osh, Kyrgyzstan. They assessed the social and health factors contributing to the high prevalence rate in this region and found that the lack of access to health services and socio-economic conditions contribute to the spread of the infection among the population. Kubatova et al. (2020) studied the problem of non-adherence to antiretroviral therapy among people with HIV in Kyrgyzstan. The study assessed the prevalence and risk factors for treatment failure in the period from 2014 to 2016, demonstrating that irregular medication significantly reduces the effectiveness of therapy and can lead to disease progression.

Despite the progress made, several unresolved issues remain, including insufficient study of mortality dynamics among people living with HIV in Kyrgyzstan, especially in the context of social and medical factors. The study aimed to review the structure and dynamics of mortality among PLHIV in Kyrgyzstan for the period 2005–2024, identify the main factors of influence and develop recommendations for improving national

programmes to combat the epidemic. The analysis contributed to the development of effective strategies to reduce mortality and improve the quality of life of people living with HIV.

Material and Methods

The retrospective study examined HIV mortality in the Kyrgyz Republic from 2005 to 2024. This time period was chosen to analyse the influence of antiretroviral medication and government programs on mortality rates and detect epidemic trends. Each scientific approach has a distinct role in the study to attain this goal. The Kyrgyz State Medical Academy provided statistical indicators and official data for the analysis. The Kyrgyz Republic's Ministry of Health and Social Development's Centre for eHealth (2021, 2023) and Republican AIDS Centre reports were the key sources. Specifically, National Statistical Committee of the Kyrgyz Republic (2025) data was used. These data were chosen for their formalisation, applicability, and reliability, ensuring analysis representativeness and quality. HIV prevalence, demographics, and causes of death are included in the state accounting system's frequently updated statistics. This is essential for this study's in-depth investigation and comparative assessment.

The study comprised all Republican AIDS Centre and territory health centre patients over the designated period. eHealth system-registered HIV-positive individuals with death causes were analysed. Excluding cases with inadequate data (e.g., cause of death) and non-dispensary registered patients may have compromised the analysis. The data included PLHIV mortality rates, structure, reasons of death, and other demographics. The analysis approach was used to analyse mortality rates per 100,000 people, cause proportions, and indicator average errors. This technique detected PLHIV mortality structure and dynamical trends. Synthesis of data from diverse sources revealed how demographic, socioeconomic, and medical factors affect mortality patterns. This helped determine the main causes of PLHIV mortality in the region. Death rates and trends were examined across time, and the impact of factors like injecting drug usage on mortality risk was studied. The relative risk of mortality among injectable drug-using PLHIV was compared to control groups. The control group of PLHIV who did not use injectable medicines allowed the study to investigate the influence of drug usage on mortality. Access to antiretroviral medication, socioeconomic level, and associated infectious illnesses affected mortality rates in this population.

Analysis of specific mortality data was utilised to draw broader generalisations using the induction method. This technique finds general epidemiological patterns in Kyrgyzstan's PLHIV. The deduction method tested theories on how co-infections like tuberculosis affect PLHIV mortality. This limited the biggest mortality factors. Generalising the study's findings informed international and regional HIV/AIDS initiatives. The investigation included regional disparities since PLHIV mortality rates vary based on health care access, HIV prevalence, socioeconomic factors, and antiretroviral medication availability. Multiple regression analysis and death rates per 100,000 inhabitants for each region were utilised to uncover territorial disparities and affecting factors. Regional HIV control programmes were evaluated using death rate cluster analysis.

The χ^2 test examined the correlation between qualitative indicators, such as mortality causes and comorbidities. This technique revealed statistically significant differences in PLHIV mortality structure and main risk factor effects. Systematisation organised and classified the data by risk category, demographics, and reasons of mortality. To estimate the annual rate of increase or decrease in mortality, the least squares method was used, which involves calculating the formula (1):

$$T = B \times K \div I_{ai} \times 100\%, \quad (1)$$

where: T – increment, B – annual increase coefficient, K – coefficient, equal to 1 (for an odd number of observations) or 2 (for an even number), I_{ai} – long-term average. The method was applied not for each year separately, but for the combined periods, namely 2005–2009, 2010–2014, 2015–2019 and 2020–2024. This approach smoothened the impact of short-term fluctuations, ensured greater stability of calculations and identified long-term mortality trends among PLHIV. Mortality trends were estimated on the following scale: from 0 to $\pm 1\%$ – stable trend, from $\pm 1.1\%$ to $\pm 5.0\%$ – moderate, more than $\pm 5.0\%$ – pronounced trend.

The relative risk index (RRI) was used to determine the risk of mortality among PLHIV who inject drugs (2):

$$RR = P_{\text{exposed}} \div P_{\text{not exposed}}, \quad (2)$$

where: RR – relative risk, P_{exposed} – proportion of mortality among PLHIV who used drugs, and $P_{\text{not exposed}}$ – among the control group.

The results of the analysis provided a holistic view of the mortality dynamics among PLHIV in the Kyrgyz Republic, identified the main risk factors and

developed recommendations for reducing mortality. The use of a comprehensive approach ensured the reliability of the results and their practical relevance to the regional context.

Results and Discussion

Dynamics of mortality among people living with HIV (2005–2024)

From the beginning of the HIV epidemic in the late 1970s to 2024, approximately 42.3 million people worldwide have died from AIDS-related illnesses (UNAIDS, 2025). Although the annual number of deaths has declined from about 2 million in 2004–2005 to around 630,000 in 2023, the rate of decline has slowed in recent years. In 2020, AIDS-related deaths were estimated at 680,000, and in 2021 – about 650,000. These figures reflect both the success of ART and the persistent challenges of ensuring equitable access to care. In low-income countries, infectious diseases, including HIV/AIDS, remain among the leading causes of death.

The global number of people living with HIV reached 39.9 million in 2023, of whom 53% were women and girls (UNAIDS, 2025). Between 2010 and 2023, AIDS-related mortality decreased by 56% among women and girls and by 47% among men and boys, largely due to expanded ART access and improved international cooperation (World Health Organization, 2025). Despite this progress, women, children, and people who inject drugs continue to experience limited access to prevention and treatment, resulting in higher mortality in these groups. As of November 2024, 14,159 HIV infection cases were officially registered in the Kyrgyz Republic, including 13,331 among citizens of the country. The majority of those infected were people aged 20–49 years, which represents the economically active population. These data highlight the significant socio-economic burden of HIV/AIDS and the growing proportion of women among people living with HIV. This trend requires special attention to gender-specific approaches in treatment and support (UNAIDS, 2020).

Over the 19 years from 2005 to 2024, mortality among PLHIV in the Kyrgyz Republic has shown a steady downward trend. While in 2005 the mortality rate was 5.5 per 100,000 people, by 2024 it had decreased to 1.8 per 100,000 people. This progress is due to several factors, including the expansion of ART coverage, increased diagnosis and early detection of HIV infection, and a decrease in the prevalence of injecting drug use (World Health Organization, 2024). Zhao et al. (2020) noted that the HIV epidemic in Kyrgyzstan is characterised by rapid growth, and the

introduction of ART, although significantly reducing mortality, remains ineffective due to limited access.

An analysis of long-term dynamics demonstrated that the average annual mortality rate was 4.8%, which indicates the effectiveness of the national strategy to combat the epidemic. However, from 2021 to 2024, the rate of decline slowed slightly, due to post-pandemic healthcare challenges, limited funding for programmes and difficulties in providing ART to some risk groups. At the same time, adherence to treatment among PLHIV continues to grow, which is a key factor in stabilising mortality rates (World Health Organization, 2025). Regional differences in mortality rates remain an important aspect of the analysis. The highest mortality rates in 2024 were recorded in Osh and Bishkek. Osh city, as well as in Osh, Jalal-Abad and Chui regions. This can be explained by a higher concentration of people living with HIV and less effective medical infrastructure in these regions. The gradual levelling of regional differences in access to health services has been achieved through decentralisation programmes (World Health Organization, 2024).

Increasing ART coverage is the most important factor in reducing mortality. While in 2005 the proportion of PLHIV receiving ART was 42%, by 2024 this figure will reach 87%. The introduction of new treatment regimens has significantly reduced the risk of developing end-stage HIV infection and related diseases, including tuberculosis, hepatitis and liver cirrhosis (World Health Organization, 2020, 2025). Another significant factor is the decline in the proportion of PLHIV who inject drugs. In 2005, this share was 61.8%, and in 2024, it was only 6%. This positive change is due to the expansion of harm reduction programmes, increased access to substitution therapy and social campaigns aimed at informing and supporting vulnerable groups (UNAIDS, 2025). According to Uusküla et al. (2023), adherence to ART among injecting drug users (IDUs) remains low, which increases the risk of mortality in this group. These findings are consistent with the results of Croxford et al. (2017), who found that during the period of high ART activity, the mortality structure has changed, but for some groups of patients, in particular, people who inject drugs, the risks remain high. Comparing these data with the results obtained, it can be noted that the proportion of deaths from infectious diseases in Kyrgyzstan is significantly higher, indicating the need to improve prevention and treatment programmes. Similar problems are reflected in the study by Desai et al. (2020), who emphasise the importance of integrated approaches to HIV treatment, considering the interaction of antiretroviral drugs with other drugs. This study confirms that

children with disabilities in Kyrgyzstan are a particularly vulnerable group requiring specialised programmes to reduce mortality.

Data from 2024 also show that gender differences in HIV prevalence continue to be an important factor in the epidemiological situation. Of all reported cases, 63% are men and 37% are women, with sexual transmission accounting for 61%, indicating its dominance, especially among young people. However, discrepancies have been identified in mortality statistics provided by different sources. Data from the Centre for eHealth show lower mortality rates than data from the Republican AIDS Centre. This may indicate different approaches to recording deaths and requires further investigation (Pape, 2019; World Health Organization, 2020). Important data are also provided in the World Health Organization report (2020), which analyses general trends in the health sector in Kyrgyzstan. It highlights the need to increase funding for HIV programmes and improve access to healthcare services for marginalised groups. The findings confirm these recommendations, as inadequate access to treatment and co-morbidity programmes often leads to increased mortality among people living with HIV.

Thus, in the period 2005–2024, mortality among PLHIV in the Kyrgyz Republic decreased significantly due to the expansion of ART coverage, increased treatment adherence and reduced drug use. However, regional differences, social barriers and inconsistent data require additional attention to optimise future HIV control strategies and improve the quality of care for PLHIV.

Impact of antiretroviral therapy on mortality rates

Antiretroviral therapy is the main method of combating HIV/AIDS and has proven effective in reducing mortality among people living with HIV. Since ART was introduced worldwide, there has been a significant decline in mortality, especially in low- and middle-income countries, including the Kyrgyz Republic. In the region, expanded access to ART has been accompanied by a decline in mortality, underscoring the importance of large-scale coverage of this therapy (Zhao et al., 2020). Ancker et al. (2013) argue that Kyrgyzstan, despite its former leadership in the fight against HIV, has lost ground due to reduced funding and programme effectiveness. This study also confirms the existence of systemic deficiencies, including limited access to ART and prevention, which increase mortality among HIV-infected individuals. However, data show that increased ART coverage among PLHIV in Kyrgyzstan is closely linked to a decline in mortality. For instance, between 2010 and 2020, the proportion of patients

receiving ART more than doubled, leading to a noticeable decrease in deaths among PLHIV. This highlights the important role of timely treatment in stabilising the epidemic and increasing the life expectancy of infected individuals (Ancker et al., 2013).

ART works by blocking different stages of the HIV replication cycle, thereby preventing the virus from multiplying and damaging the immune system (Lisiecka, 2025). Combination antiretroviral therapy (cART), also known as highly active antiretroviral therapy, involves a treatment regimen of three or more drugs from at least two different classes, such as reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors, to effectively suppress viral replication and prevent resistance. Long-term suppression of the virus allows for partial restoration of immunity, reduces the number of opportunistic infections, and prevents the progression of AIDS (Asrina et al., 2025).

However, despite its proven clinical effectiveness, access to ART in Kyrgyzstan remains uneven. In southern and remote mountainous regions such as Osh and Jalal-Abad, logistical barriers, limited laboratory infrastructure, drug shortages and dependence on international donors can limit the access. Social stigma and fear of disclosure also delay treatment initiation (Rudenko and Dmytryk, 2024). When ART is not started on time, patients experience rapid immune decline, opportunistic infections (especially tuberculosis and hepatitis) and higher mortality rates. Late initiation of treatment also increases the risk of HIV transmission in communities, underscoring the importance of early and equitable access to ART across the country (Schola et al., 2021).

As of 2024, ART coverage among PLHIV in the Kyrgyz Republic continues to grow. According to official data, 82% of the estimated number of PLHIV have been diagnosed, 70% of them have received ART, and 91% of those on therapy have achieved viral suppression. This indicates a positive trend in the provision of medical care and a decrease in viral load among PLHIV (Centre for eHealth, 2023). However, despite the increase in ART coverage, mortality among PLHIV remains high. In 2022, 45% of PLHIV were diagnosed with advanced HIV infection (with a CD4 count below 350 cells/ml), and in 2023, this figure decreased to 36%, indicating the need to strengthen measures for early diagnosis and timely initiation of treatment (National Statistical Committee of the Kyrgyz Republic, 2025; Sak-Salamat, 2025).

The Programme of the Government of the Kyrgyz Republic (2017) on overcoming HIV infection in the Kyrgyz Republic for 2017–2021 set a goal to

reduce HIV incidence and mortality by 50% by 2021 compared to 2015. To achieve this goal, it was planned to improve the quality of medical services, expand coverage of preventive measures, and ensure access to ART for all those in need. ART not only reduces the viral load to undetectable levels but also prevents the development of co-infections, such as tuberculosis, which is one of the leading causes of death among PLHIV (Rutskaya-Moroshan et al., 2024). The introduction of comprehensive treatment programmes, including ART and treatment of comorbidities, is especially relevant for the Kyrgyz Republic, where co-infections remain a significant mortality factor. A study by Karimi et al. (2024) showed that severe liver damage, low CD4 cell counts, and late initiation of ART are critical among mortality risk factors in patients with HIV. In addition, liver disease in PLHIV may be associated with antiretroviral drug toxicity and metabolic disorders, such as non-alcoholic fatty liver disease. This emphasises the need for regular monitoring of liver function and a comprehensive approach to the treatment of PLHIV with co-infections and concomitant metabolic disorders.

An important achievement in Kyrgyzstan was the creation of a national monitoring system for patients receiving ART. This system not only tracks the dynamics of viral suppression but also ensures a timely response to cases of therapeutic failure. This approach improves treatment effectiveness and reduces the risk of disease progression. The results of a study by Iacob et al. (2017) highlight the importance of innovative pharmacological approaches and therapies to improve the health of people living with HIV. The study examines key factors such as access to treatment, drug therapy, and interactions with other chronic diseases that affect mortality rates among PLHIV. It also focuses on the need to integrate novel pharmaceutical solutions into national epidemic control programmes, which could help reduce mortality and improve the quality of life of patients in countries with high prevalence rates. At the same time, Childress et al. (2024) highlight the impact of stigma against women with HIV, which limits their access to healthcare services. This study confirms that social barriers faced by vulnerable groups exacerbate negative trends. A study by Obeagu and Obeagu (2024) demonstrated that insufficient attention to co-infections and related factors, such as malaria and anaemia, can reduce the effectiveness of antiretroviral therapy. This is consistent with the conclusions on the need to strengthen national programmes aimed at controlling viral load and the importance of integrating systematic monitoring of co-infections into a comprehensive approach to the treatment of HIV patients.

In the regional context, ensuring access to ART for vulnerable populations, such as IDUs, is a priority. In Kyrgyzstan, the introduction of ART has significantly reduced the risk of mortality among PLHIV who inject drugs, which is evidence of the success of a comprehensive treatment programme aimed at this group of patients (Ancker et al., 2013).

At the international level, the implementation of programmes funded by the Global Fund and UNAIDS has contributed to a large-scale expansion of access to ART in the countries of the former Soviet Union, including Kyrgyzstan, which has reduced mortality among PLHIV and created conditions for improving the epidemiological situation (Figure 1).

As shown in Figure 1, the steady increase in the number of people receiving ART from 2005 to 2024 corresponds to a marked decline in mortality among PLHIV. These two trends clearly demonstrate an inverse relationship: as ART coverage expanded, the deaths rate (per 100,000 population) steadily declined. This visual correlation confirms that the expansion of ART programmes was a major factor in reducing mortality. Moreover, the flattening of the mortality curve after 2020 reflects a slowdown in progress due to pandemic-related disruptions and funding constraints, underscoring the need for continued support for programmes. Data analysis shows that the expansion of antiretroviral therapy coverage is accompanied by a steady decline in mortality among PLHIV. Significant improvements demonstrate the effectiveness of national and international HIV programmes, but there is still a need to further expand access to treatment, especially among vulnerable groups. Despite the positive changes, the lack of ART coverage among some infected people

continues to be a risk factor that requires additional measures to increase treatment adherence and early detection of infection. Despite the achievements, some challenges limit the effectiveness of ART. These include insufficient funding, uneven access to therapy in the regions of the country, and low public awareness. These factors affect the overall effectiveness of the fight against the HIV epidemic in Kyrgyzstan (Zhao et al., 2020).

Antiretroviral therapy is crucial in reducing mortality among people living with HIV in the Kyrgyz Republic. Expanding access to ART, integrating treatment of comorbidities, and introducing monitoring systems were key in stabilising the epidemiological situation. However, further progress requires overcoming existing barriers to access to therapy and funding for programmes.

Causes and comparative analysis of mortality among people living with HIV

The causes of mortality among PLHIV are multifaceted and depend on various biological, social and behavioural factors. The difference in the structure of causes of death between PLHIV who use injecting drugs and other categories of PLHIV is particularly pronounced. Tuberculosis, liver disease, and psychoactive substance overdose remain the leading causes of death among both groups, but their consequences vary depending on the specific conditions and characteristics of the patients (Trickey et al., 2024; National Statistical Committee of the Kyrgyz Republic, 2025). Trickey et al. (2024) conducted a meta-analysis that showed that excess mortality among HIV-positive people in high-income countries remains significant despite widespread

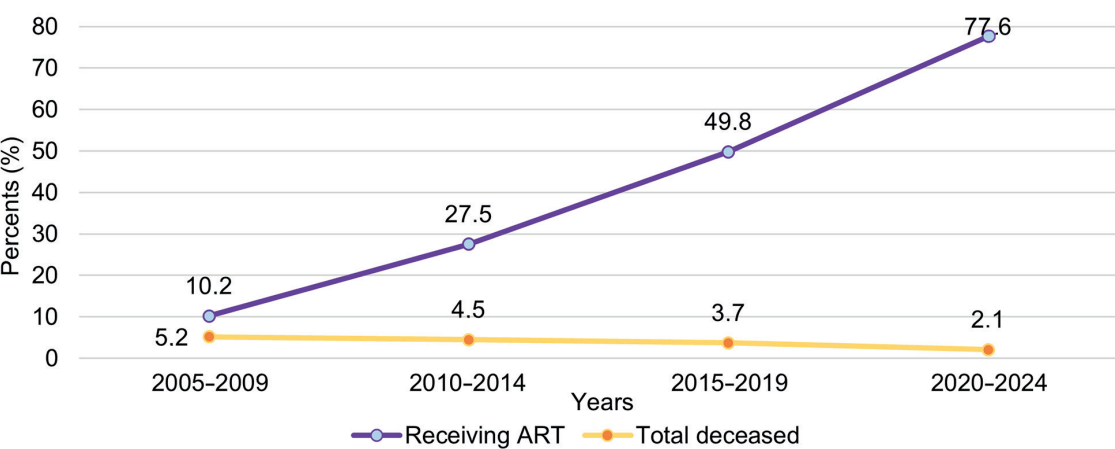


Figure 1: Comparison of the dynamics of the number of people living with HIV (PLHIV) receiving antiretroviral therapy (ART) and mortality rates for the period 2005–2024.

Source: compiled by the authors based on data analysis of the Centre for eHealth (2023), Sak-Salamat (2025), National Statistical Committee of the Kyrgyz Republic (2025), Government of the Kyrgyz Republic (2017), Ancker et al. (2013).

access to ART. Their data indicate that cardiovascular diseases and cancer remain the leading causes of death, while infectious diseases predominate in low-income countries such as Kyrgyzstan.

Tuberculosis is the leading cause of death among people living with HIV, due to a sharp weakening of the immune system as a result of HIV infection (Karyo et al., 2025). Patients with low CD4+ lymphocyte counts are ten times more likely to develop active TB than immunocompetent individuals. For IDUs, this risk increases due to irregular visits to healthcare facilities, late diagnosis and low adherence to ART, which significantly complicates disease control (Trickey et al., 2024). In groups of PLHIV who do not use drugs, the incidence of TB also remains high, but in this group, patients are more likely to have access to regular treatment and prevention. This underscores the importance of integrating ART with measures for early detection and effective treatment of tuberculosis. Kantipong et al. (2012) emphasised that HIV and tuberculosis co-infection are the leading causes of death among HIV-positive people in low-income countries, especially in Southeast Asia. The study also demonstrated that among HIV-positive people with tuberculosis, the mortality rate is significantly higher among those not on ART. Researchers Laher et al. (2021) state that tuberculosis remains one of the leading causes of death among PLHIV, especially in the case of late detection of infection and insufficient access to specialised medical care. These findings are consistent with the results of this study, which confirm that tuberculosis remains central in mortality among HIV-positive people in Kyrgyzstan, especially among people who inject drugs (PWID). This highlights the need to improve early TB detection programmes, increase access to combination therapy, and integrate strategies for managing patients with HIV/TB co-infection.

A comparative analysis of data on the impact of opportunistic infections on mortality among PLHIV in Kyrgyzstan confirms their importance. Notably, opportunistic infections such as tuberculosis and pneumocystis pneumonia remain the leading causes of death, especially in countries with limited access to ART. Weber et al. (2024), surveying a Swiss cohort, noted a decrease in mortality from opportunistic infections due to access to ART. According to this article, there is no such trend in Kyrgyzstan, which is associated with gaps in the healthcare system. Nishijima et al. (2020) found that in Japan, the reduction of these infections reduced mortality, but cardiovascular and cancer diseases came to the fore. The study by Carvalho-Silva et al. (2020), conducted in Brazil, showed that in HIV-positive patients receiving ART, insufficient immune recovery

is associated with low release of CD4+ T cells from the thymus and their death due to pyroptosis. This increases the risk of opportunistic infections, including tuberculosis and pneumocystis pneumonia, which underscores the need for early initiation of ART and regular immunological monitoring. These findings are consistent with the results of the present study, confirming the importance of timely treatment and a comprehensive approach to patient management. Liver disease, including cirrhosis and hepatitis, is one of the leading causes of death among PLHIV (Kucherenko et al., 2019; Berezenko et al., 2021). Among PWID, the main cause of liver disease is co-infection with the hepatitis C virus (HCV), which is spread through shared injecting equipment. In combination with a high level of HIV viral load, this contributes to a more rapid progression of liver disease (Croxford et al., 2017).

Substance overdose is one of the leading causes of death among PWID (Lewandowski et al., 2021; Yager et al., 2024). Drug interactions with antiretroviral drugs can significantly increase toxicity and the risk of death. Lack of access to opioid substitution therapy and support programmes for this group of patients also increases the frequency of fatal overdoses (Trickey et al., 2024). Among PLHIV who do not use drugs, overdose deaths are less common, but they can be associated with other mental health problems, including depression and suicide attempts. This underscores the importance of psychological support as an integral part of care for PLHIV.

Social and economic factors have a significant impact on the structure of the causes of death among PLHIV. PLHIV often face discrimination, stigmatisation and poverty, which hinders their access to medical care (Tulewicz-Marti et al., 2023). In regions with an underdeveloped medical infrastructure, PLHIV rarely receive adequate treatment, which contributes to the progression of diseases and increases the risk of death (Pape, 2019). These factors are also important, but their impact is usually less pronounced. Patients with stable social status and access to healthcare services demonstrate lower mortality rates even in the presence of HIV infection (Borkowski and Borkowska, 2024). Zakhidova (2024) emphasises the importance of social and structural conditions, such as access to healthcare, social support and government policy, in reducing mortality from HIV and related opportunistic infections. Interdisciplinary collaboration between medicine, sociology, and public health plays an important role in developing sustainable strategies to combat the epidemic and minimise its impact on vulnerable populations.

The causes of mortality among PLHIV are multifaceted and largely depend on socio-economic

conditions, behavioural habits and access to health services. PWID face many risks, including overdose, co-infection and tuberculosis. Drug toxicity and co-morbidities remain major risk factors for other PLHIV, underscoring the need to develop differentiated treatment and prevention programmes tailored to the specific needs of each group.

Mortality among people living with HIV is an important indicator of the quality of healthcare, access to treatment and socio-economic conditions. PWID, a group with a specific range of co-morbidities and social barriers, is a particular concern. According to the Republican AIDS Centre, the main causes of death among PLHIV are tuberculosis, liver disease, overdose and cardiovascular disease (Figure 2).

Figure 2 shows the structure of causes of death among PLHIV based on data from the Republican AIDS Centre. Tuberculosis is the leading cause of death, accounting for more than a third of all deaths, followed by liver disease and drug overdose. The figure highlights the multifactorial nature of HIV-related mortality in Kyrgyzstan: infectious diseases, drug use and chronic comorbidities have almost equal impact. The relatively small proportion of cardiovascular and other opportunistic diseases indicates that, although ART has improved survival, many patients still die from preventable causes, especially in regions with limited access to integrated healthcare. These graphs confirm that mortality among PLHIV is caused not only by HIV, but also by opportunistic infections, chronic diseases and social factors. The high proportion of deaths from tuberculosis and liver disease demonstrates the need for comprehensive treatment, while the significant number of deaths from overdoses and suicides demonstrates the importance of psychosocial support and harm reduction programmes.

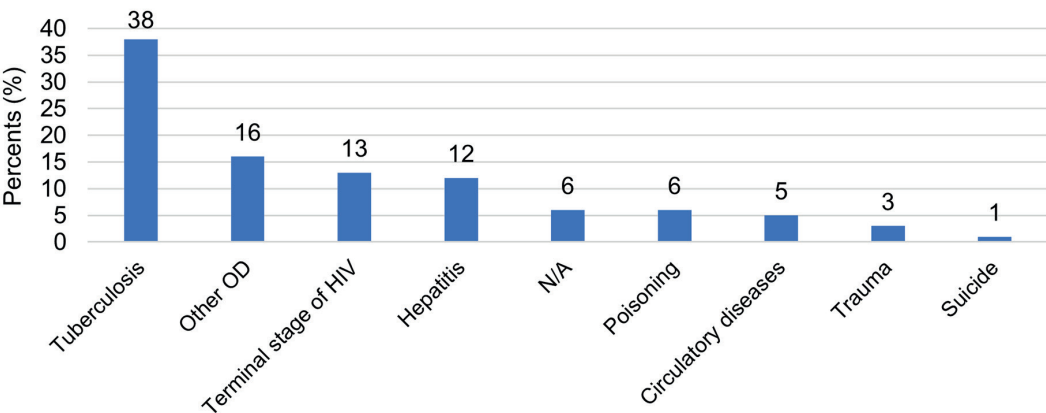


Figure 2: Causes of death of people living with HIV (PLHIV) according to the Republican AIDS Centre (2024).
Note: N/A – data cannot be obtained; other OD – other opportunistic diseases, including pneumocystis pneumonia, toxoplasmosis, as well as fungal and viral infections that affect the weakened immune system.
Source: compiled by the authors based on data analysis of the Centre for eHealth (2023), National Statistical Committee of the Kyrgyz Republic (2025), Sak-Salamat (2025).

For PWID, constituting a significant proportion of PLHIV, the main causes of mortality have specific characteristics (Lisiecka, 2024). For instance, tuberculosis is more common among PWID who have disabilities due to weakened immune systems, limited access to healthcare services, and poor living conditions. A comparison of causes of death among people living with HIV and injecting drug users (PLHIV-IDUs) with non-drug users reveals a common trend: tuberculosis remains the leading cause of death in both groups ($42 \pm m\%$ for PLHIV-IDUs and $34 \pm m\%$ for PLHIV-non-IDUs, where “m” is the standard error of the indicator). However, despite the similarity of mortality factors, analysis of their impact on the risk of death reveals significant differences between the groups, indicating that these factors have varying degrees of influence (Figure 3).

As shown in Figure 3, a comparison between people living with HIV/AIDS (PLWHA) who inject drugs and those who do not reveals significant differences in mortality patterns. Among injecting drug users, tuberculosis and liver disease together account for more than half of all deaths, while among non-drug users, chronic diseases and opportunistic infections predominate. The figure clearly shows that injecting drug use increases the risk of mortality from infectious diseases and liver disease, confirming the need for targeted harm reduction and co-infection control programmes. The highest risk of tuberculosis among PLHIV-IDUs is confirmed by the role of comorbidities caused by a weakened immune system. At the same time, end-stage HIV and liver disease remain significant causes of death in all groups. These findings highlight the importance of comprehensive approaches to the treatment of HIV and related conditions in the most vulnerable populations.

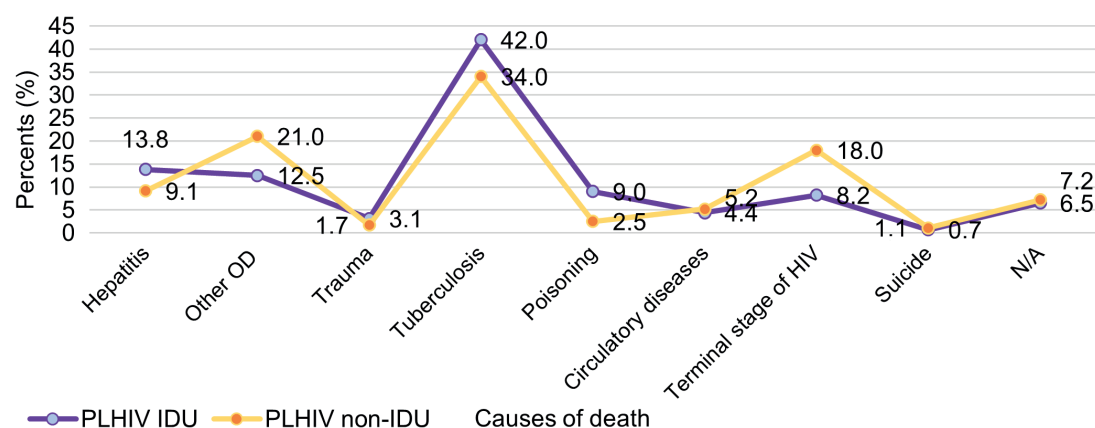


Figure 3: Causes of death of people living with HIV (PLHIV) and non-PWID (PWID – people who inject drugs).

Note: N/A – data cannot be obtained; other OD – other opportunistic diseases, including pneumocystis pneumonia, toxoplasmosis, as well as fungal and viral infections that affect the weakened immune system; IDU – injecting drug user.

Source: compiled by the authors based on data analysis of the Centre for eHealth (2023), National Statistical Committee of the Kyrgyz Republic (2025), Sak-Salamat (2025).

Using formula (2), a risk analysis was conducted to assess the differences in causes of death between PLHIV who inject drugs and those who do not (Table 1).

Table 1 provides a quantitative assessment of the relative risk of death from various causes among PLWHA who inject drugs compared to PLWHA who do not inject drugs. These figures clearly indicate that injecting drug users are almost five times more likely to die from tuberculosis and approximately 18% more likely to die from liver disease. The high relative risk highlights the cumulative effect of drug use, co-infection and social isolation. These quantitative data complement the qualitative trends shown in Figures 2 and 3, confirming that tuberculosis and liver disease remain the leading causes of mortality among this group. People living with HIV and injecting drugs are significantly more likely to die from tuberculosis (RR = 4.902), liver cirrhosis (RR = 1.182) and overdose of psychoactive substances (RR = 1.1). At the same time, there were no significant differences in

mortality from cardiovascular diseases between this group and non-drug users (RR < 0.9).

PWID also face several social barriers, such as stigmatisation, criminalisation of drug use and lack of access to treatment. This affects their ability to receive timely medical care and access ART. Lack of control of co-infections, such as hepatitis B and C, also contributes to the increase in mortality among this group. PWID often have limited access to tuberculosis prevention and treatment, which explains the higher mortality rate from this disease compared to other PLHIV. Liver cirrhosis and cardiovascular disease are important causes of death among PLHIV who do not use drugs (Nikolaev et al., 2021, 2024). This may be due to the life expectancy of these patients, which is increasing due to the successful treatment of HIV infection, which in turn contributes to the development of chronic age-related diseases.

In addition to infectious and liver diseases, the burden of non-communicable diseases (NCDs) is steadily increasing among PLHIV. With the success of long-term ART and increased life expectancy, cardiovascular disease, diabetes and metabolic disorders have become important factors in morbidity and mortality (Borkowski and Borkowska, 2024; Liu et al., 2024). Chronic inflammation, immune system activation and metabolic side effects of ART contribute to an increased incidence of hypertension, dyslipidaemia and ischaemic heart disease among people with HIV. Studies in high- and middle-income countries show that cardiovascular disease is one of the leading non-infectious causes of mortality among patients receiving ART, sometimes exceeding the incidence of opportunistic infections in well-controlled populations (Trickey et al., 2024). In Kyrgyzstan,

Table 1: Estimating the risk of causes of death for IDUs and non-injecting drug users

	Causes of death	RR	P-value
1	Tuberculosis	4.902	>1.000
2	Liver pathology (hypertension, cirrhosis, etc.)	1.182	>1.000
3	Poisoning	1.077	>1.000
4	Cardiovascular disease	0.900	<0.001

IDUs – injecting drug users; RR – relative risk

Source: compiled by the authors based on data analysis of the National Statistical Committee of the Kyrgyz Republic (2025)

although systematic data are limited, national statistics indicate a gradual increase in cardiovascular disease-related mortality among PLHIV, particularly in regions with longer ART coverage. These findings underscore the urgent need to integrate NCD screening and treatment, such as regular blood pressure monitoring, lipid control, and lifestyle interventions, into HIV care. Including NCD prevention in ART programmes will ensure a more holistic approach to supporting long-term health among people living with HIV.

Khan et al. (2024) studied the level of public awareness of HIV/AIDS in Kyrgyzstan, emphasising that low knowledge of the disease is one of the factors contributing to the spread of the epidemic. The researchers found that there are myths and prejudices about HIV among the population that reduce the effectiveness of preventive measures. Observations also demonstrate that a lack of awareness significantly affects the quality of life of HIV-infected people, increasing stigma and limiting access to services.

Studies by Japanese researchers have shown that PLHIV have a higher mortality rate than the general population, even in the era of antiretroviral therapy (Nishijima et al., 2020). In Thailand, the main cause of death among people co-infected with TB and HIV is late diagnosis (Kantipong et al., 2012). Brazilian researchers have noted that one of the main causes of death among HIV-infected patients is insufficient restoration of immunity against cART. This is due to the low release of new CD4+ T cells from the thymus and their death through pyroptosis, which makes the body vulnerable to opportunistic infections and accelerates the progression of the disease (Carvalho-Silva et al., 2020).

To facilitate a clearer understanding of regional disparities in HIV-related mortality, a comparative

summary of key indicators across the main regions of the Kyrgyz Republic is presented in Table 2. The table highlights pronounced contrasts between the southern and northern regions, underscoring the influence of healthcare access, ART coverage, and social factors on mortality outcomes.

The data clearly demonstrate that mortality among PLHIV remains significantly higher in the southern regions (Osh and Jalal-Abad) compared with the northern and central regions (Chui, Issyk-Kul, Bishkek). These differences are primarily driven by disparities in access to ART, socio-economic factors, and stigma. Strengthening ART accessibility and comprehensive prevention in the south could substantially reduce mortality and narrow regional gaps.

A comparative analysis of the causes of death of IDUs and other PLHIV highlights the need for a differentiated approach to the organisation of medical care. For IDUs, it is necessary to introduce programmes of substitution therapy, overdose prevention, and tuberculosis treatment. For other PLHIV, prevention of chronic diseases, such as liver cirrhosis and cardiovascular disease, should be prioritised.

Regional peculiarities of PLHIV mortality
An analysis of regional differences in mortality among PLHIV revealed the most vulnerable regions of Osh and Jalal-Abad, where the highest mortality rates are observed. The main reasons for this are the high prevalence of HIV among injecting drug users, limited access to quality healthcare services, insufficient prevention and low public awareness. These regions also have the highest levels of social isolation among PLHIV, which limits their adherence to treatment and participation in prevention programmes (Ancker et al., 2013).

Table 2: Comparative mortality among people living with HIV by region of the Kyrgyz Republic (2024)

Region	Mortality rate (per 100,000 population)	ART coverage (%)	Main causes of death (%)	Key contributing factors
Osh	17.3	72	Tuberculosis (38), liver disease (14), overdose (8)	High IDU prevalence, stigma, limited ART access
Jalal-Abad	14.9	67	Tuberculosis (36), cardiovascular (23), overdose (5)	Migration, low treatment adherence, healthcare gaps
Chui	6.5	85	Tuberculosis (24), liver disease (10), cardiovascular (8)	Better ART coverage, high awareness
Issyk-Kul	5.8	87	Tuberculosis (21), liver disease (9), cardiovascular (7)	Effective prevention, good infrastructure
Bishkek	7.2	87	Tuberculosis (27), liver disease (11), cardiovascular (10)	Urban inequalities, migrant influx

ART – antiretroviral therapy; IDU – injecting drug user
Source: compiled by the authors based on data from the Centre for eHealth (2023), National Statistical Committee of the Kyrgyz Republic (2025), and the Republican AIDS Centre.

Osh region has the highest mortality rate among PLHIV – 17.3 cases per 100,000 people, which is 2.1 times higher than the national average. The main reason for the high mortality rate is the combination of HIV and tuberculosis, with mortality from co-infections significantly higher than in other regions. An additional aggravating factor is the high incidence of liver disease associated with viral hepatitis, which increases mortality among patients on ART. Despite efforts to increase access to treatment, only 72% of registered patients receive regular ART, which is below the national average. Social stigma remains one of the most important barriers: low levels of trust in healthcare facilities and fear of disclosure of diagnosis lead to refusal of therapy. In addition, up to 8% of deaths in the region are related to drug overdoses (Ancker et al., 2013).

In the Jalal-Abad region, the mortality rate is 14.9 cases per 100,000 population, which is also significantly higher than the national average. The region has one of the highest mortality rates from cardiovascular diseases (23% of all causes of death), which is associated with long-term drug use and general physical exhaustion. Limited access to ART remains a problem, with only 67% of patients receiving regular treatment, which is associated with high population migration, gaps in treatment and low availability of medical services in remote areas. Drug overdoses account for up to 5% of deaths in the region, which also highlights the need for active harm reduction programmes (Khan et al., 2024).

Osh and Jalal-Abad region have the highest prevalence rates of injecting drug use, which is closely related to the increase in the number of new HIV infections. In these regions, up to 41% of new HIV cases are registered among key populations, including injecting drug users. Stigmatisation is also most pronounced in these regions: fear of being judged by society and healthcare workers leads to late detection of infection and refusal of treatment (Ancker et al., 2013).

In contrast to the southern regions, the Chui and Issyk-Kul regions have significantly lower mortality rates among PLHIV, indicating more effective prevention efforts, greater access to medical services and a relatively lower prevalence of drug abuse. In the Chui region, the mortality rate among PLHIV is 6.5 cases per 100,000 total population, and in the Issyk-Kul region, it is 5.8 per 100,000 population, which is almost three times lower than in the southern regions. This is due to the high level of medical care and more active participation of citizens in ART programmes, where coverage reaches 85% of patients. These regions have lower rates of deaths from tuberculosis and cardiovascular diseases, which is explained by

better access to specialised medical care and high levels of public awareness (Ancker et al., 2013). It is noteworthy that, despite the active implementation of national programmes to combat HIV infection, regional differences in mortality rates persist. This indicates the need to adapt these programmes to the specific characteristics of each region, considering local social, economic and medical factors (Obeagu and Obeagu, 2024).

An analysis of ART provision in different regions shows that coverage is higher in Bishkek and the northern regions of Kyrgyzstan than in the southern regions, due to better health infrastructure and higher levels of public awareness. For instance, ART coverage in the capital reaches 87%, while in remote areas of the Osh region, this figure does not exceed 60% (Childress et al., 2024). An important factor in regional differences is the level of public awareness about HIV. According to the latest data, in the Chui and Issyk-Kul regions, more than 75% of the population has basic knowledge about HIV, while in the Osh and Jalal-Abad regions, this figure does not exceed 50%. This indicates the need to strengthen prevention campaigns and educational programmes in the southern regions (Ancker et al., 2013). The impact of migration on mortality rates is also confirmed by reports: high migration in the southern regions leads to gaps in treatment and late detection of infection, which increases the risk of death (Karimi et al., 2024).

Eshun-Wilson et al. (2019) determined that the key factors influencing adherence to antiretroviral therapy among HIV-positive patients in Africa are access to medical care, social support, and the absence of stigma. This is consistent with the findings of the present study, which emphasises that overcoming barriers to treatment access and developing sustainable support models are crucial in reducing mortality among PLHIV. As noted by Buchacz et al. (2020), long-term monitoring of PLHIV and analysis of epidemic dynamics are crucial in reducing mortality and improving clinical outcomes. This experience gained in the United States may be useful for the development of national programmes in the Kyrgyz Republic, especially in the context of reducing mortality among PLWH and improving the effectiveness of health services.

In conclusion, the results of the study confirm the importance of a comprehensive approach to HIV/AIDS treatment and prevention in Kyrgyzstan, incorporating regional differences and social factors. The analysis showed the significant role of antiretroviral therapy in reducing mortality and the need to strengthen measures to combat comorbidities such as tuberculosis and liver disease. The persistence

of regional disparities and the stigmatisation of HIV-infected people require additional research and adjustments to strategies aimed at ensuring equal access to healthcare services for the most vulnerable groups.

Conclusion

The results of the study expand the existing knowledge on the dynamics and factors of mortality among people living with HIV in the Kyrgyz Republic. A comprehensive approach, including analysis of regional peculiarities, the main causes of mortality, and the impact of ART on mortality, was notable.

The study established that over the period from 2005 to 2024, mortality among PLHIV in the Kyrgyz Republic has significantly decreased. In 2005, this figure was 5.5 per 100,000 people, and in 2024, 1.8 per 100,000 people. This reduction was made possible by the expansion of ART coverage, which stabilised patients' condition and reduced mortality from opportunistic infections such as tuberculosis and hepatitis. The proportion of PLHIV on ART increased from 42% in 2005 to 95% in 2024, significantly improving the prognosis for most infected people. However, mortality remains significantly higher among people who inject drugs, with a prevalence of 41% compared to 32% among PLHIV who do not use drugs. The risk analysis confirmed that tuberculosis remains the leading cause of death among PLHIV, especially among IDUs. This group also experienced high mortality from liver cirrhosis and overdoses, which is associated with co-infection with viral hepatitis and poor treatment adherence. At the same time, cardiovascular diseases (5%) and co-infections remained the most important causes of death for other PLHIV.

The regional analysis demonstrated that Osh and Jalal-Abad provinces remain the leaders in mortality among PLHIV due to the high proportion of IDUs (up to 58%), stigmatisation and limited access to health services. Here, mortality is twice the average, and tuberculosis (36%) and liver disease (12%) remain the leading causes of death, highlighting the need for comprehensive treatment. In Chui and Issyk-Kul oblasts, mortality was lower due to better medical care and ART coverage (87%).

Based on the findings, it is recommended that regional HIV programmes be strengthened, focusing on tuberculosis and liver disease prevention, reducing HIV stigma and ensuring equal access to health services. In addition to these measures, compulsory HIV education should be introduced in schools, and adult education initiatives should be launched,

especially in regions such as Osh and Jalal-Abad, where public awareness of HIV remains below 50%. These initiatives will help to increase knowledge about HIV transmission and prevention, reduce stigma, and encourage early testing and adherence to treatment. It is also important to integrate ART with the treatment of co-infections, expand social support mechanisms, and improve coordination between health facilities and community organisations.

Despite the results achieved, this study had certain limitations. Possible discrepancies in data due to differences in mortality registration and insufficient information on PLHIV among IDUs complicate the full assessment of mortality factors. Further research should focus on a detailed analysis of the impact of socio-economic and educational factors on mortality among PLHIV and the development of tailored treatment and prevention models for the most vulnerable populations. The implementation of these recommendations will contribute to the development of a more effective and equitable HIV/AIDS control system in the Kyrgyz Republic.

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Vaccine Prophylaxis of Viral Hepatitis B among the Adult Population in the City of Jalal-Abad (Kyrgyz Republic)

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Received July 21, 2025; Accepted September 8, 2026.

Key words: Epidemiology – Morbidity analysis – Rapid testing – Enzyme-linked immunosorbent assay – Access to healthcare services

Abstract: Hepatitis B virus remains a significant public health threat, especially in regions with limited access to healthcare services. The main objective of the study was to assess the effectiveness of vaccination and identify the main barriers to its implementation, which could serve as a basis for optimizing immunization programmes in the region. In Jalal-Abad (Kyrgyz Republic), the screening study showed that the vaccination coverage rate among the adult population was critically low at only 3%, which is significantly lower than the level required for the formation of herd immunity. In 2023, 2,126 people were tested out of a total of 71,307 adult residents of the city, which is only 3% of the target group. A positive result for HBsAg was found in 70 people (3.3%). The vaccination procedure was completed by 2,483 people, most of whom were in the 50–59 age group (63.4 per 1,000 population). Gender analysis showed that 68.1% of those vaccinated were women, while the share of men was only 31.9%. The study identified a number of barriers, including limited access to healthcare services, lack of awareness of the risks of hepatitis B and the importance of vaccination, and logistical challenges. The findings support expanding vaccination through mobile units, integrated public health services, and culturally adapted information campaigns to improve uptake and reduce hepatitis B prevalence among underserved adults.

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<https://doi.org/10.14712/23362936.2026.26>

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Introduction

The spread of hepatitis B virus (HBV) among adults remains an important public health problem in many countries around the world. Vaccination is a key means of preventing transmission, but vaccination coverage among adults is often insufficient. Regional characteristics, such as socioeconomic status, access to healthcare services, and public awareness, have a significant impact on the effectiveness of immunization programmes. In Jalal-Abad, Kyrgyz Republic, the spread of HBV and limited access to preventive measures are a major concern.

As of 2022, according to WHO (World Health Organization, 2025), about 254 million people worldwide are living with chronic hepatitis B. About 1.2 million new cases are reported annually, and deaths from HBV (including cirrhosis and liver cancer) are estimated at around 1.1 million people. The infection is transmitted through contact with contaminated body fluids or from mother to child (Berezenko et al., 2021; Rudyk et al., 2024).

Thomas (2019) focused on global efforts to eliminate chronic hepatitis. The focus was on the integration of effective public health policies, progress in antiviral treatment, and achievements in expanding access to vaccination. It was noted that comprehensive approaches have significantly reduced the incidence, although many countries face difficulties in implementing these measures due to insufficient access to health services. Limited analysis of socio-economic barriers and the impact of political factors on the implementation of chronic hepatitis elimination programmes can be considered a gap.

Akmatov et al. (2023) analysed the seroepidemiological status of viral hepatitis in the capital of Kyrgyzstan, Bishkek. The study involved 1,075 people, among whom they tested for markers of viral hepatitis A, B, C, D and E. It was found that the seroprevalence of the HBV surface antigen (HbsAg) was 2.2% (95% confidence interval: 1.5–3.3%), and seropositivity to hepatitis D (anti-HDV) was recorded in 15% (5 out of 33 people with HBsAg). The results showed that Kyrgyzstan can be reclassified from a highly endemic to an intermediate endemic area for HBV. The main gap in the study is the insufficient analysis of social determinants of access to vaccination and medical care.

Woodring et al. (2019) analysed progress in the fight against mother-to-child transmission of HBV in the Western Pacific region from 2005 to 2017. Thanks to timely vaccination, the prevalence of HBV among children under 5 years of age has decreased to less than 1%. The main challenge of the study was to examine the effectiveness of vaccination programmes,

and the gap is the lack of analysis of the impact of social and cultural factors on vaccination coverage.

Zhang et al. (2022) investigated changes in the prevalence of HBV from 1990 to 2019. It found a significant reduction in morbidity and mortality due to vaccination, although regional inequalities remain a challenge. The study highlights that many countries are still far from achieving the WHO's goal of eliminating hepatitis by 2030. Among the gaps is the limited attention to socioeconomic barriers to access to care. Bixler et al. (2023) focused on the impact of national vaccination and screening programmes. It was found that the rate of infection among young people has significantly decreased, but cases among adults remain stable, especially among people who inject drugs. The main gap is not enough coverage of prevention programmes among the most vulnerable populations.

Wallace et al. (2022) focused on analysing the social and economic impact of introducing a potential treatment for hepatitis B. The results emphasize the importance of developing policies to ensure access to treatment for all populations. A gap is the lack of attention to the impact of cultural differences on treatment access. Delam et al. (2023) analysed the increase in the prevalence of HBV and C in Fars between 2015 and 2021. A significant increase in the incidence rate was found, indicating the need to strengthen preventive measures. However, it didn't focus on educational programmes to prevent new infections.

Julien et al. (2024) reviewed 333 scientific articles published over the past decade to assess key themes in prevention. They found that most attention was paid to transmission, especially vertical and perinatal transmission, vaccination, and antiretroviral treatment. Among the gaps identified is the need to create new educational initiatives, implement and evaluate their effectiveness, as well as to conduct further analysis of regional differences in the availability of health services.

While numerous studies have examined various aspects of hepatitis B, there is a lack of research that analyses the extent and specifics of vaccine prevention among adult residents of Jalal-Abad specifically. The aim of the study was to evaluate rapid testing and vaccination against hepatitis B among the adult population in the city of Jalal-Abad. To achieve this goal, the following study objectives were completed: to assess the hepatitis B vaccination coverage of the adult population of Jalal-Abad and identify the main demographic and socioeconomic factors affecting coverage, to identify barriers to access to hepatitis B vaccination in Jalal-Abad, to investigate the relationship between vaccination coverage and hepatitis B incidence in Jalal-Abad.

Material and Methods

Research design and setting

This screening survey was conducted in the city of Jalal-Abad during 2023 (from January to December) to study the effectiveness of hepatitis B vaccination among the adult population. In addition to the main objectives, the number of people who decided to be vaccinated during 2023 was studied to assess the dynamics of vaccination decision-making and identify possible factors influencing this process. The study covered nine groups of family doctors (GFD) in Jalal-Abad (GFDs No. 1–9) and the Central City Clinical Hospital, which included the Jalal-Abad City Family Medicine Center (FMC).

Characteristics of the study sample

The study covered the population over 18 years of age, with a total population of 71,307 out of 119,928 residents in the city. A total of 2,126 people participated in HBV testing, which was 3% of the total adult population (18 to 60 years and older). The sample included individuals aged 18 to 60 years and older who lived in Jalal-Abad, provided informed consent, had no recorded contraindications to vaccination, and agreed to participate in HBsAg testing (rapid test or ELISA), regardless of whether they had been vaccinated previously. Based on the analysis of data from the HBV Vaccination Registration Journal, it was determined that anyone who refused testing and/or vaccination, had severe allergic reactions to vaccine components or acute infectious or somatic diseases at the time of the visit, as well as those under the age of 18 were excluded from participation. Adherence to these criteria allowed us to cover different age groups (18–29, 30–39, 40–49, 50–59, 60+ years), as well as to involve both working people (healthcare workers, educators, service workers, etc.) and non-working citizens. This minimized systematic errors and ensured greater reliability of the survey findings. The representativeness of the sample was ensured by the inclusion of people of different ages, genders and social status. The gender distribution of the vaccinated sample was 68.1% women and 31.9% men. The total number of people who applied for the first dose of the vaccine was 2,483.

Data sources and tools

The data was obtained by analysing the statistical reports of the GFD. To ensure the accuracy and reliability of the study, the following main sources were used, covering the period from January to December 2023: the Medical Information Department of the Family Medicine Centre (FMC) – to obtain aggregate data on population size, testing and vaccination

coverage, registers (Medical Information Department of the FMC of Jalal-Abad [Regional Center of Family Medicine, 2025] – to obtain aggregated data on population size, testing and vaccination coverage, “Form of HBV testing registration log” of the rapid testing room in family doctor groups, “Registration log of persons with positive HBV results”, “Registration log of HBV vaccination” of the vaccination room [Medical and Diagnostic Center of the Central Medical and Economic Institute, 2023]), medical records of patients with positive rapid test results, which allowed us to collect information on health status, possible routes of infection and epidemiological history, laboratory testing data, including the results of ELISA performed at the Oblast AIDS Centre to confirm HBsAg status.

Vaccination and testing procedure

Rapid testing for HBsAg using certified SD BIOLINE HBsAg test kits (Standard Diagnostics, Inc., South Korea) in the offices of the GFD. ELISA was performed in the laboratory of the regional centre for acquired immunodeficiency syndrome (AIDS) to confirm the diagnosis in those with positive rapid tests. Recombinant vaccines were used for vaccination, such as Engerix-B from the Centre for Genetic Engineering and Biotechnology (CIGB) in Cuba, from GSK Biologicals (Belgium) and Heberbiovac HB (Cuba).

The vaccination was carried out in several stages:

- 1) Administration of the first dose of the vaccine.
- 2) Re-administration in 1 month.
- 3) Final dose 6 months after the first vaccination.
- 4) Each stage was recorded in the vaccination logs to ensure further monitoring.

To study the number of people who decided to be vaccinated, data from the HBV Vaccination Registration Journal were used. Information about each vaccinated patient was collected and analysed. The data were quantitatively sorted by two main parameters: frequency of visits to different GFDs – the number of visits for vaccination to each of the nine GFDs in Jalal-Abad (GFDs 1–9) was counted; and vaccine doses – the data were divided by the number of doses received (first, second, third), which allowed us to track the dynamics of vaccination and determine how many people completed the full course.

Training of medical staff was a key stage of the study. All involved specialists underwent specialized training, which included: seminars on organizing and conducting rapid testing and vaccination, practical training on procedures for collecting biomaterial for ELISA, and instruction on keeping registration logs and filling out medical records. This approach ensured standardization of procedures and minimized the possibility of errors during data collection. The testing

and vaccination procedures were coordinated through the healthcare facilities of the GFD, which provided conditions for vaccine storage and vaccination. Each stage was documented, and the data was entered into the relevant logs for further analysis.

Ethical considerations

The study was conducted in compliance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013). All study participants provided written informed consent to participate in the study and to the processing of their personal data. The confidentiality of the participants' data was guaranteed.

Statistical data processing methods

The collected data were subject to analytical and statistical processing. For this purpose, a personal computer with Excel 2002 software equipped with an analysis package for Windows XP was used. Statistical methods such as hypothesis testing (t -test, χ^2 -test), trend analysis, regression analysis (linear and logistic regression) and correlation analysis (determination of Pearson's correlation coefficient) were used to analyse the data obtained. This made it possible to identify correlations between vaccination coverage rates and a number of factors (age, gender, social status), as well as to assess the statistical significance of the differences identified. The dynamics of vaccination requests was monitored throughout 2023 by quarters (January–March, April–June, July–September, October–December). Possible seasonal factors (holiday season, SARS epidemic season) that could affect the frequency of applications were considered.

Results

Effectiveness and barriers of hepatitis B vaccination

Hepatitis B is one of the most important global public health problems, characterized by a complex epidemiology, a high burden of chronic infection and an association with severe complications. It is estimated that more than 257 million people worldwide are living with chronic hepatitis B, with the majority of infections occurring in regions with limited access to vaccination and healthcare services (Stasi et al., 2020). Epidemiological studies indicate significant demographic differences: the highest burden of the disease falls on Asian populations, in particular due to the high prevalence of B and C genotypes of the virus, which is also associated with clinical features of the disease. For example, patients with these genotypes often have a more favourable fibrosis profile but are

prone to developing serious complications such as cirrhosis and hepatocellular carcinoma (Coffin et al., 2019; Tutchenko et al., 2024a, b).

The immune response to hepatitis B plays a key role in determining the outcome of the infection, but the adaptive immune system, in particular CD8+ T cells, not only ensures viral clearance but also contributes to the progression of liver damage. Chronic infection is accompanied by immune dysfunction, including immune cell depletion, which limits the effectiveness of the body's fight against the disease and contributes to its chronicity (Kucherenko et al., 2019; Iannacone and Guidotti, 2021). One of the important features is the oncogenic potential of the virus, in particular through the integration of viral DNA into the hepatocyte genome, which triggers carcinogenic processes. The accumulation of genetic mutations due to chronic inflammation and cell regeneration creates conditions for the development of hepatocellular carcinoma, especially in men, due to the effect of androgens on viral replication (Nikolaev et al., 2021, 2022; Wang et al., 2021).

Although vaccination has significantly reduced the level of vertical and horizontal transmission among children, the adult population, including migrants from endemic regions, remains the main risk group. Another problem is the low level of vaccination coverage in high-risk groups, such as men who have sex with men (Fanning et al., 2019). Scientific studies, such as those by Davlidova et al. (2020), confirm that HBV remains a significant health problem in Kyrgyzstan, in particular due to high levels of migration, insufficient availability of preventive measures such as vaccination, and the spread of infection among the population. One review noted that in Central Asia, including Kyrgyzstan, the prevalence of HBV is significantly higher in certain risk groups, including people who inject drugs, migrants, and prisoners.

Hepatitis B virus has several routes of transmission, including vertical transmission from mother to child during pregnancy or childbirth, horizontal transmission through contact with blood or body fluids, as well as through sexual contact and reuse of unsterile medical equipment (Mamontov et al., 2023a, b). The main routes of transmission are horizontal transmission among family members and through procedures involving contact with blood, such as medical interventions or the use of shared instruments such as needles or razors.

Vertical transmission of HBV remains a significant problem, especially in high endemicity regions. Studies show that the risk of mother-to-child transmission increases significantly in the absence of new-born vaccination or immunoprophylactic measures (Villa and Navas, 2023). In Kyrgyzstan, new-born vaccination

and access to immunoglobulins have significantly reduced the number of new infections among infants. These measures are not always available in all regions of the country. In addition to vertical transmission, horizontal transmission, including household contact, remains a significant risk, especially among children living in families with infected members. Studies have highlighted the importance of vaccinating all family members who come into contact with patients, as well as informing the population about the risks of HBV transmission in the home (Zheng et al., 2022). Key populations at risk include healthcare workers, people requiring regular medical interventions (e.g., haemodialysis patients), prisoners, and people living with infected relatives. High rates of infection among these groups are associated with limited availability of preventive measures and lack of awareness of prevention methods (Varghese et al., 2021).

Prevention of HBV is based on the use of effective vaccines and ensuring access to preventive measures for all population groups. Hepatitis B is one of the few infectious diseases against which a highly effective vaccine is available, which not only prevents infection but also reduces the risk of complications such as cirrhosis and hepatocellular carcinoma (Tarasyuk et al., 2013; Berezenko et al., 2022). The main vaccines are recombinant products that have a high safety profile and provide immunological protection for many years. Recommended vaccination regimens include three doses administered at 0, 1 and 6 months. This standard regimen provides long-term immunity in more than 95% of vaccinated individuals. The dose given to new-borns within the first 24 hours after birth (HepB-BD) plays a special role, as it is key to prevent vertical transmission from mother to child. Studies have shown that this dose in combination with a full course of vaccination reduces the risk of chronic infection by up to 1% in children born to infected mothers (Woodring et al., 2019).

In addition to vaccination, an important component of prevention is immunoglobulin prophylaxis for new-borns who are at high risk of infection (for example, if the mother has a high viral load). The combination of immunoglobulin and vaccine during the first hours of life effectively blocks transmission, even in high-risk cases (Zhao et al., 2020). For adults in high-risk groups, such as healthcare workers, haemodialysis patients, people who inject drugs, and those who have multiple sexual partners, vaccination is also recommended (Nikolaev et al., 2025). In such cases, it is recommended to test for HBsAg antibodies after a certain time after vaccination to ensure that adequate immune protection is in place. For people with a weak immune response or certain chronic diseases, regimens with higher doses or additional

doses have been developed (Shulgau et al., 2017; Yao et al., 2024).

Despite this, the implementation of vaccination faces numerous barriers. One of the main problems is the inaccessibility of timely vaccination of new-borns in low- and middle-income countries due to lack of resources, logistical difficulties and insufficient awareness of healthcare personnel and parents (Turmagambetova et al., 2017; Bogoyavlenskiy et al., 2023a). Studies show that the key factors that hinder vaccination coverage are vaccine bias, lack of knowledge among mothers, and limited access to health facilities, especially for home births (Freeland et al., 2023). In Kyrgyzstan, access to vaccination also faces a number of specific challenges. Economic barriers, limited neonatal vaccination coverage in some regions, and the lack of regular immunization programmes contribute to the fact that some population remains vulnerable to infection. In addition, restrictions on the dissemination of information about the importance of vaccination significantly affect its implementation among the most vulnerable groups.

Improving the effectiveness of HBV vaccination in Kyrgyzstan requires a comprehensive approach based on the WHO recommendations and taking into account the specifics of the local context. First and foremost, it is necessary to expand vaccination coverage among the adult population, including through the introduction of vaccination programmes in workplaces, educational institutions and prisons. It is also important to ensure that vaccination is accessible to vulnerable groups, such as migrants and people who inject drugs. For this purpose, it is advisable to consider the use of mobile teams and vaccination points. Strengthening outreach efforts to raise public awareness about hepatitis B and the importance of vaccination is critical. Different communication channels should be used, adapting messages to target audiences. Integrating hepatitis B vaccination into existing health programmes, such as tuberculosis and HIV programmes, can help optimize resources and increase prevention effectiveness. Implementation of these recommendations in Kyrgyzstan is justified by the high level of migration, prevalence of chronic hepatitis B and limited access to health services in some regions, which pose significant public health challenges.

Assessment of coverage and factors influencing hepatitis B vaccination in Jalal-Abad

Hepatitis B virus remains a serious public health problem worldwide, and Kyrgyzstan is no exception. Despite the availability of an effective vaccine, many countries face difficulties in achieving high vaccination

Table 1: Rapid HBV test for the adult population by GFD and FMC of Jalal-Abad city for 2023

GFD	Total population	From 18 years and older	Had the rapid HBV test	HBsAg-negative	HBsAg-positive
			abs.n	abs.n	abs.n
No. 1	18048	10261	265	254	11
No. 2	21414	12919	317	307	10
No. 3	18808	11303	276	256	20
No. 4	22820	15100	290	288	2
No. 5	15630	9019	244	238	6
No. 6	3583	1847	193	186	7
No. 7	10059	5581	241	236	5
No. 8	5212	2911	140	136	4
No. 9	4354	2366	160	155	5
Overall, according to the FMC	119928	71307	2126	2056	70

HBV – hepatitis B virus; GFD – groups of family doctors; FMC – Family Medicine Center; abs.n – absolute number

Source: created by the authors

coverage, especially among the adult population. Successful vaccination depends on a number of factors, including access to healthcare services, public awareness and the effectiveness of information campaigns. In 2023, the city of Jalal-Abad conducted a population survey for hepatitis B virus using rapid tests, and the data obtained during this survey are shown in Table 1. Thus, the low level of testing coverage may be due to various factors, including limited access to healthcare services, lack of awareness of the importance of HBV screening, and possible logistical difficulties.

As shown in Table 1, of the 2,126 individuals tested, 96.7% were negative for HBsAg, indicating no active HBV infection. 3.3% were found to be positive for HBsAg, requiring further examination and medical follow-up to determine the stage and nature of the infection (acute or chronic). HBV vaccination coverage in Jalal-Abad also remains low, at only 2.9%. This indicates the need to strengthen immunization activities, including public awareness and ensuring the availability of vaccines.

The analysis of testing coverage in different city's GFDs shows significant variability. The highest coverage rates were observed in the GFD No. 6 (10.4%) and the GFD No. 9 (6.7%). In the other GFDs, testing coverage was much lower, ranging from 1.5% (GFD No. 1) to 4.8% (GFD No. 8). Such differences may be related to the different levels of organization of healthcare facilities, the activity of medical staff, as well as the socio-economic characteristics of the population served by different GFDs. Since October 2023, due to interruptions in the supply of rapid tests, the laboratory of the Oblast AIDS Centre has started using ELISA for HBV diagnosis. A total of 2,126 people were tested using the ELISA method.

The collection of epidemiological history from HBV-positive individuals allowed us to identify possible routes of infection. These data are presented in Table 2.

The data analysis showed that the most frequent infections occurred in dental facilities (25.7%). This indicates the need to strengthen control over

Table 2: Distribution of HBV-positive individuals by probable routes of infection in the FMC of Jalal-Abad for 2023 (number of individuals)

Name	Total positives	Treatment in medical and preventive institution	Treatment at the dentist	Contact with viral hepatitis	Unknown
Overall, according to the FMC	70	10	18	10	32

HBV – hepatitis B virus; FMC – Family Medicine Center

Source: created by the authors

compliance with sanitary and epidemiological standards in these facilities, in particular, sterilization of instruments and use of disposable materials. The second most common route of infection was treatment in medical and preventive institution (14.3%), which also indicates the need to improve infection control in healthcare facilities. Contact in family units with previous HBV cases also accounted for 14.3%. This underscores the importance of preventive measures among family members of HBV-infected persons, including vaccination. In a significant proportion of cases (45.7%), the route of HBV transmission could not be established. This may be due to the presence of hidden routes of transmission, as well as difficulties in retrospective identification of the source of infection.

The coverage of hepatitis B testing and vaccination among the adult population in the GFD of Jalal-Abad is extremely low (3.0%). There is a need to increase public awareness of HBV testing with rapid tests and the importance of HBV vaccination through the media. The low uptake of vaccination and insufficient mobilization of healthcare workers in conducting information activities may lead to an extended need for such measures in the city for a long period of time, possibly up to 20 years, which may complicate the epidemiological situation with regard to the incidence of hepatitis B virus in the city and in the region.

Study of the number of people who decided to get vaccinated during 2023

The dynamics of visits to vaccination points throughout the year shows an alarming downward trend. At the beginning of the campaign, in January, the frequency of visits was 5.4 people, while in December this figure dropped to 0.07 people per day. Such a sharp drop in the frequency of referrals over the course of the year indicates the ineffectiveness of the vaccination strategy.

There was a significant variation in the average daily frequency of visits between different GFDs. While in some GFDs (e.g., GFD No. 1 – 1.1 persons per

day, GFD No. 3 – 1.5 persons per day), the rates were relatively higher, in GFDs No. 9 and No. 6, they were critically low – 0.07 and 0.1 persons per day, respectively. These disparities may be related to the uneven distribution of resources, different levels of public awareness and access to healthcare services. The low effectiveness of the HBV vaccination campaign may be due to a number of factors, including the voluntary nature of vaccination, insufficient health education, which has led to low levels of public awareness of HBV risks and the importance of prevention, and possible organizational problems in the health care system. Thus, to improve the situation, a comprehensive strategy should be developed and implemented to increase the coverage of both HBV testing and vaccination.

The current study also recorded the number of people who decided to be vaccinated in 2023. These data are presented in Table 3. This allowed us to assess not only the final results of the vaccination campaign, but also to analyse the dynamics of vaccination decision-making throughout the year.

In 2023, the highest rate of HBV vaccination (first, second, and third doses) in the family medicine centre of Jalal-Abad was observed in the age group 50–59 years (63.4, 62.1 and 55.6 per 1,000 population, respectively). The second place is occupied by the 40–49 age group (51.4, 50.3 and 42.8 per 1,000 population). The third-highest vaccination rate is in the 30–39 age group (41.6, 35.8, and 32.1 per 1,000 population). The lowest vaccination rate in the FMC is observed among people aged 18–29 years (13.4, 12.6, and 9.7 per 1,000 population). These data indicate greater awareness of HBV risks among the older generation, the presence of chronic diseases that increase the risk of hepatitis complications, and greater activity in seeking care. In turn, low rates among young people indicate the need to strengthen awareness-raising among young people about the importance of HBV vaccination and its role in preventing the development of chronic hepatitis and its complications. Low vaccination coverage among

Table 3: Population that received three doses of HBV vaccination by age category in the FMC

FMC	Age/years					Total persons
	18–29	30–39	40–49	50–59	60>	
	n	n	n	n	n	
No. 1	315	719	631	534	284	2483
No. 2	298	618	616	523	280	2335
No. 3	228	555	526	468	244	2021

HBV – hepatitis B virus; FMC – Family Medicine Center; n – the absolute number of vaccinated people in each age group; No. 1 – the first dose of vaccine; No. 2 – the second dose of vaccine; No. 3 – the third dose of vaccine

Source: created by the authors

Table 4: Population that received the first dose of HBV vaccine by age category in GFD and FMC of Jalal-Abad city in 2023 (per 1,000 population)

GFD	Age/years										Total
	18–29		30–39		40–49		50–59		60>		
	n	i.i.	n	i.i.	n	i.i.	n	i.i.	n	i.i.	
No. 1	27	11.6	102	37.7	69	41.6	62	50.1	39	24.4	29.1
No. 2	35	10.9	91	26.1	88	33.0	66	34.6	56	33.4	26.0
No. 3	55	19.2	126	44.2	86	42.7	67	47.3	27	17.5	31.9
No. 4	59	22.9	83	25.8	69	23.4	60	26.0	38	13.4	20.4
No. 5	42	22.4	103	41.0	92	60.5	84	69.9	29	25.8	38.8
No. 6	31	7.3	59	12.0	72	19.6	51	255	33	17.5	133.2
No. 7	38	30.1	64	42.8	71	73.4	69	100.0	36	46.9	49.8
No. 8	5	7.8	39	49.5	38	77.1	41	121.3	12	27.7	46.4
No. 9	23	44.1	51	91.3	46	79.5	34	87.4	14	132.0	71.0
Overall, according to the FMC	315	13.4	719	41.6	631	51.4	534	63.4	284	30.3	36.0

HBV – hepatitis B virus; GFD – groups of family doctors; FMC – Family Medicine Center; n – the absolute number of individuals who received the first dose of HBV vaccine in the corresponding age group; i.i. – an intensive indicator that shows the number of individuals who received the first dose of HBV vaccine per 1,000 population of the corresponding age group

Source: created by the authors based on reports submitted by GFD No. 1–9

young people creates prerequisites for further spread of HBV and increase in morbidity in the future (Bogoyavlenskiy et al., 2023b; Suleiman et al., 2023).

As for the distribution of data on GFD (Table 4), the data were as follows: during the year, 2,483 people applied to the FMC of Jalal-Abad for the first vaccination, which is a frequency of application of 36.0 per 1,000 population. Among the groups of family doctors, a high frequency of referrals for vaccination when receiving the first dose was observed in the GFD No. 6, and the lowest frequency of referrals for vaccination was noted in the territory of the GFD No. 4.

According to the city's FMC, the highest frequency of vaccination seeking during the first dose was in the 50–59 age group. In the territories of family physician groups, a high frequency of vaccination seeking was observed in the GFD No. 8 and GFD No. 7. The second-highest rate in the city's FMC was in the age group 40–49 years. Among the groups of family doctors, the second place in this age group was taken by GFD No. 9, No. 8 and GFD No. 7. The third place in the FMC was occupied by the age group 30–39 years, and the highest vaccination frequency was observed in the territory of the GFD No. 9. The lowest frequency of vaccination according to the FMC was in the 20–29 age group, and the lowest vaccination uptake in this age group was observed in the territories of GFDs No. 6 and No. 8.

The fourth-highest vaccination uptake was in the age group 60 years and older, and the highest vaccination

frequency in this age group was observed in the territory of GFD No. 9. According to the data of the GFD, 18–19-year-olds were vaccinated with the first dose only in GFD No. 4 and GFD No. 9, while in the rest of the GFD and in the city's FMC there were no requests for vaccination in this age group.

HBV vaccination data indicate uneven coverage of different demographic groups. There is a clear correlation between age and vaccination seeking, with the highest rates in older age groups and the lowest among young people, indicating the need for targeted work with young people to raise awareness of HBV risks and the importance of vaccination. Significant differences in rates between different GFDs point to the need to analyse the factors that contribute to this inequality and develop measures to address it. This may include improving access to vaccination, improving the skills of medical staff, and strengthening public awareness. Overall, low HBV vaccination coverage requires a comprehensive approach to improve the situation and prevent the spread of infection.

Among the population, a high frequency of vaccination with the second and third doses was also observed in these age groups in the territory of the GFD No. 6–9. After the first vaccination, 94% received the second dose 30 days later, while 6% did not receive the second dose. By age, the highest coverage with the second dose of vaccination was observed in the age group 60 years and older (98.5%), while the lowest coverage with the second dose was in the

Table 5: Distribution of people vaccinated against HBV by gender and dose in the FMC of Jalal-Abad for 2023 (number of people)

Sex	First dose	Second dose	Third dose	Average value
Male	755	762	665	727
Female	1728	1573	1356	1552

HBV – hepatitis B virus; FMC – Family Medicine Center
Source: created by the authors

age group 30–39 years (82.5%). The third vaccination is given 5 months after the second. The third vaccination was received by 2,021 people (86.5%), while 314 people (13.5%) were not vaccinated. By age, high coverage with the third dose of vaccination was observed in the age groups 50–59 years (89.2%) and 30–39 years (89.4%), while the lowest coverage with the third dose was in the age group 20–29 years (75.8%).

The current study also assessed the distribution of the number of people vaccinated with three doses by gender. The data are presented in Table 5.

Analysis of the sex distribution of those vaccinated against HBV in the FMC of the city of Jalal-Abad in 2023, given the data in Table 4, shows a statistically significant difference in vaccination coverage between men and women. The overall proportion of women who received HBV vaccination is 68.1%, while for men this figure is much lower – 31.9%. A closer look at the distribution by vaccination dose confirms this trend. Among those who received the first dose of the vaccine, women account for 69.6% and men for 30.4%. A similar situation is observed for the second (67.4% of women vs. 32.6% of men) and third (67.1% of women vs. 32.9% of men) doses of the vaccine.

The observed difference in vaccination rates between the sexes may be due to a number of social, cultural and behavioural factors. In particular, women are more likely to visit healthcare facilities for preventive care and are more attentive to doctors' recommendations for vaccination. In addition, women may be better informed about the risks associated with HBV and the importance of timely vaccination. On the other hand, men may show less concern for their own health and underestimate the need for preventive measures, including vaccination. The identified disparity in vaccination coverage between the sexes indicates the need to develop targeted information campaigns aimed at raising awareness of the importance of HBV vaccination among men and motivating them to participate more actively in prevention programmes. This will help to reduce the gap in vaccination rates between the sexes and ensure

more effective protection of the population from HBV infection.

Analysis of the social status of persons seeking HBV vaccination in the FMC of Jalal-Abad in 2023 shows a heterogeneous distribution of vaccination coverage among different professional and social groups. The largest proportion of vaccinated persons are non-working citizens (52.7, 52.4 and 52.9% of applications for the first, second and third doses, respectively). Particularly high rates of referrals among non-working people are observed in the GFD No. 7 (64.1%) and No. 5 (75.8%). This may be due to the specific demographic composition and socio-economic characteristics of the population served by these facilities. Perhaps, in these districts, a higher proportion of unemployed people have more free time to visit healthcare facilities, or there are more elderly people who are more likely to be vaccinated.

The second-largest group is healthcare workers (11.5, 11.6, and 12.4% of visits for each dose, respectively). The highest vaccination rates among healthcare workers were recorded in GFD No. 1 (20.4%), No. 4 (17.1%) and No. 8 (14.1%). This may indicate that healthcare workers are better informed about the risks of HBV infection and the importance of vaccination, as well as the possible existence of internal recommendations or requirements for vaccination of staff in these facilities. Employees of educational institutions make up the third-largest group (10.3 and 9.6% of applications for the first and second doses, respectively). The highest rates in this category were observed in the GFD No. 6 (22.4%) and GFD No. 4 (17.5%).

The lowest frequency of vaccination visits was recorded among students (0.3–1.4%) and service workers (0.7–0.8%). This may be due to a low level of awareness of HBV infection risks among these groups, lack of time or opportunities for vaccination, and certain behavioural factors. The remaining categories of the population demonstrate a rate of seeking treatment ranging from 1.3 to 7.8%. The uneven distribution of HBV vaccination coverage among different social groups indicates the need for a differentiated approach to outreach and vaccination campaigns, taking into account the specifics of each target group.

Discussion

The study of hepatitis B vaccination among the adult population of Jalal-Abad (Kyrgyz Republic) showed results that reflect current problems in the organization of preventive measures and ways to solve them. Firstly, the low vaccination coverage (3%)

indicates the insufficient effectiveness of existing vaccination programmes and the need to adjust the strategy.

In Beijing, Liang et al. (2021) reported a vaccination coverage of 31.3%, which, although inadequate for herd immunity, is tenfold greater than the level observed in Jalal-Abad. Both studies indicated awareness and socioeconomic status as critical drivers of vaccine uptake. The current findings highlight two significant aspects: structural obstacles, including disruptions in test supply and variations in performance within family doctor groups, as well as notably low participation rates among young individuals (ages 18–29). The disparities suggest that in Kyrgyzstan, constrained resources and ineffective information efforts exacerbate each other, leading to both insufficient overall coverage and age-specific deficiencies.

Sanai et al. (2020) have shown, through an economic impact tool, that extensive HBV vaccination and treatment initiatives could significantly reduce disease burden and yield long-term cost savings, contingent upon sufficiently high coverage rates. Conversely, the circumstances in Jalal-Abad indicate that the anticipated economic and epidemiological advantages are improbable to materialise in the near future, owing to minimal engagement in testing and immunisation, logistical limitations, and inadequate public awareness. The two studies converge in emphasising the pivotal role of vaccination in HBV elimination strategies: both affirm that enhancing vaccination uptake is crucial for diminishing morbidity and mortality. However, the Saudi model forecasts the potential outcomes of effective implementation, while the Jalal-Abad data demonstrate the repercussions of insufficient coverage in practice.

Chen (2018) underscored that the worldwide eradication of hepatitis B is contingent more upon robust health-system capability, financial resources, and access to care than on vaccine efficacy. The Jalal-Abad data robustly corroborate this conclusion. Notwithstanding the shown efficacy of the vaccination, the lack of dependable infrastructure, logistical consistency, and sustained informational campaigns hinders significant advancement. This emphasises that elimination programmes in resource-constrained nations must prioritise the enhancement of delivery systems prior to achieving population-level objectives.

Bridges et al. (2019) demonstrated that vaccine completion rates among high-risk persons in the United States varied markedly by clinic type, with community health centres yielding superior outcomes compared to sexually transmitted disease clinics. This mirrors the present study, in which immunisation rates varied significantly within family doctor groups within

the same city. Both instances illustrate that the micro-level organisation of healthcare delivery, encompassing recall systems, follow-up mechanisms, and staff engagement, directly impacts completion rates.

Trevisan et al. (2020) established that women frequently have more robust immune responses to hepatitis B vaccinations compared to men. The current research did not assess antibody levels, but the majority of vaccinated individuals being women (68.1%) indicates that gender disparities encompass not only biological factors but also health-seeking behaviours. Women in Jalal-Abad are more inclined to utilise healthcare services and adhere to medical advice, whereas men may undervalue the significance of preventive measures. These findings underscore the necessity for focused initiatives promoting male participation in immunisation.

Lu et al. (2021) documented suboptimal immunisation rates among US individuals with diabetes, despite explicit medical guidelines. In Jalal-Abad, young adults exhibited the lowest vaccination rates among all age demographics, despite regular interactions with health and educational institutions. Both instances demonstrate that affiliation with a risk group or access to the healthcare system does not inherently result in elevated vaccination rates. Targeted interventions, including opportunistic vaccination during routine visits and awareness campaigns for kids, are essential to address these gaps.

Investigation by Yendewa et al. (2023) indicated that obstacles to access, including considerable distances to healthcare facilities, insufficient antenatal care, and elevated home birth rates, reduced childhood immunization coverage to a range of 40 to 70%. While the study concentrated on children, the pattern mirrors that of Jalal-Abad. Challenges in service accessibility and inequitable resource distribution correlate with low vaccination rates. This indicates that structural impediments in service delivery significantly impact both childhood and adult immunization.

The global assessment by Al-Busafi and Alwassief (2024) highlighted that the eradication of hepatitis B necessitates not only efficacious vaccines but also public education, integration with other health services, and procedures that guarantee patients receive all doses. The findings from the present analysis reveal deficiencies in all these domains: insufficient public awareness, inadequate integration with current programs, and subpar completion rates. This underscores the necessity for integrated strategies, education, integration, and dependable follow-up systems.

The current study found low hepatitis B vaccination coverage among the adult population of Jalal-Abad,

which was only 3% in 2023. The lowest rates were observed among young people, where coverage was 13.4, 12.6 and 9.7 per 1,000 people, while older age groups had significantly higher vaccination rates (63.4, 62.1 and 55.6 per 1,000 people). The main barriers were limited access to healthcare services, lack of awareness among the population, and lack of effective information campaigns. These factors contribute to the uneven coverage among demographic groups and the low overall effectiveness of the vaccination campaign.

A factor influencing vaccination uptake is vaccine hesitancy, characterised by scepticism towards vaccines, apprehension regarding possible side effects, and the impact of disinformation. This is particularly pertinent for younger demographics, who exhibited the lowest immunisation rates in the current study. The diminished demand for vaccination among the 18–29 demographic may indicate not just organisational constraints but also a hesitance to recognise hepatitis B as a significant hazard. Comparable results have been observed in several contexts, where decreased perceived vulnerability, the dissemination of misinformation via internet platforms, and scepticism about medical authorities have markedly hindered vaccination rates (Jaffe et al., 2022). Confronting these attitudinal obstacles necessitates targeted educational initiatives, customised communication tactics, and trust-enhancing measures between healthcare providers and young adults.

In the WHO European Region, advancements have primarily resulted from robust baby immunization programs, with vaccine coverage approximating 91%, according to Khetsuriani et al. (2021). Conversely, Kyrgyzstan concentrated on adult immunization in Jalal-Abad. Yet, coverage remained alarmingly low, particularly among the youth. The study indicates that countries prioritizing baby vaccination have been more effective in managing hepatitis B, while adult-focused programs require supplementary support measures to achieve efficacy.

Liu et al. (2019) indicated that China's progress towards hepatitis B elimination is founded on a multifaceted strategy that integrates newborn vaccination, prevention of mother-to-child transmission, and vaccination of high-risk adults. In contrast, Jalal-Abad has not yet adopted such methodologies. The inadequate participation of young adults and restricted coverage of at-risk populations highlight the necessity to modify aspects of China's policy, including opportunistic vaccination at routine health appointments and enhanced oversight of program efficacy.

Nurmanova (2024) revealed that Central Asia has experienced inconsistent advancement in the

elimination of viral hepatitis at the regional level, facing prevalent problems such as unstable funding and inadequate data collection. The obtained data above corroborate this scenario at the local level: immunization rates are markedly low, reporting is inadequate, and program implementation is variable between facilities. This substantiates the assertion that Kyrgyzstan needs enhanced data systems and a reliable vaccine supply to augment coverage.

The hepatitis B vaccination must be evaluated within the broader public health framework of Kyrgyzstan, where tuberculosis, HIV/AIDS, and the repercussions of the COVID-19 pandemic compete for few healthcare resources. These situations encompass overlapping risk populations, including individuals who inject drugs, imprisoned persons, and migrants. Incorporating the hepatitis B vaccine into current HIV and tuberculosis programs could enhance resource efficiency, refine preventative tactics, and guarantee continuity of treatment. On the contrary, competition for financial and human resources may engender conflicts that restrict service provision. Identifying these synergies and potential conflicts is crucial for formulating sustainable immunization policies that correspond with national health priorities.

The study revealed low HBV vaccination coverage in Jalal-Abad, which is due to limited access to healthcare services, lack of public awareness and ineffective information campaigns. Young people have particularly low vaccination rates, while older age groups show higher coverage. An uneven distribution of vaccination coverage was also recorded between different groups of family doctors. Gender differences have been identified: women are vaccinated more often than men. Comparison with other studies indicates similar problems in different countries and regions related to access to healthcare services, awareness, and effectiveness of vaccination campaigns. The experience of other countries demonstrates the importance of a comprehensive approach to vaccination, including access to vaccines, targeted information campaigns, and consideration of the sociodemographic characteristics of the population. The results of the study highlight the need to develop and implement an effective HBV vaccination strategy in Jalal-Abad aimed at increasing vaccination coverage and reducing the risk of disease spread.

Conclusion

A study of HBV vaccination among the adult population of Jalal-Abad showed a low vaccination coverage rate of only 3% in 2023. Out of 71,307 adult residents of the city, only 2,126 people (3%)

were tested for HBsAg, of whom 70 people (3.3%) were positive, requiring further examination. Among the 2,483 people who received the first dose of the vaccine, only 2,21 people (86.5%) completed the three-dose course, while 462 people (13.5%) did not receive all doses.

An analysis of vaccination by age group showed that the highest rates were in the age groups 50–59 years (63.4 per 1,000 population) and 40–49 years (51.4 per 1,000 population). The lowest rates were recorded among young people aged 18–29 years – 13.4, 12.6 and 9.7 per 1,000 population for the first, second and third doses, respectively. The gender distribution showed that women accounted for 68.1% of those vaccinated, while men accounted for only 31.9%.

The variability in vaccination coverage among family physician groups is also significant: No. 6, the proportion of those vaccinated with the first dose reached 133.2 per 1,000 population, while in group of family doctors No. 4, this figure was only 20.4 per 1,000 population. The highest vaccination rates were observed among non-workers (52.7%), healthcare workers (11.5%) and educators (10.3%), while coverage among students (0.3–1.4%) and service workers (0.7–0.8%) remained minimal.

The low vaccination coverage is due to both organizational and behavioural factors: lack of vaccines during certain periods, insufficient health education and logistical difficulties, particularly in remote areas. These obstacles require large-scale measures to improve vaccine availability, including the establishment of mobile vaccination units and targeted campaigns to reach young people and socially vulnerable groups. Poor quality of reporting and uneven coverage among family doctors limits the accuracy of the study results. Further research could be conducted to study the effectiveness of information campaigns and the introduction of mobile vaccination units.

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A Clinical Insight into Von Hippel-Lindau Syndrome: Diagnostic Challenges

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Received July 26, 2025; Accepted September 8, 2026.

Key words: Tomography, X-ray computed – Von Hippel-Lindau disease – Haemangioma – Capillary – Kidney

Abstract: Von Hippel-Lindau (VHL) syndrome is a rare hereditary disorder characterised by the development of multiple benign and malignant tumours across various organs. Caused by mutations in the VHL tumour suppressor gene, it presents a wide range of clinical manifestations, including retinal haemangioblastomas, central nervous system tumours, renal cell carcinoma, pancreatic lesions, and pheochromocytomas. This report describes the case of a 35-year-old woman who presented with visual impairment and abdominal masses. Imaging revealed typical VHL manifestations, including bilateral renal lesions and pancreatic involvement. Genetic testing confirmed the diagnosis. The patient underwent staged partial nephrectomies, with histopathology confirming clear cell renal cell carcinoma in both kidneys. This case highlights the importance of recognising the variable clinical and radiological presentations of VHL syndrome. Early diagnosis and multidisciplinary management are essential to reduce morbidity and mortality. Increased awareness and regular surveillance are critical for timely detection and intervention in patients with VHL syndrome.

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<https://doi.org/10.14712/23362936.2026.27>

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Introduction

Von Hippel-Lindau (VHL) syndrome is a rare condition, with an estimated incidence of 1:36,000 individuals and a penetrance exceeding 90% after the age of 65 (Mourão et al., 2022). It follows an autosomal dominant inheritance pattern, affecting the germline of the VHL tumour suppressor gene, located on chromosome 3. Mutations in this gene increase the risk of developing various benign and malignant tumours across multiple organs. The VHL gene regulates key pathways responsible for angiogenesis and cell growth.

Clinical suspicion typically arises following the detection of retinal haemangioblastomas or central nervous system (CNS) haemangioblastomas, especially when associated with tumours of the kidneys, pancreas, adrenal glands, or endolymphatic sac (Mourão et al., 2022). The average age at onset of VHL-associated tumours is approximately 26 years (Maher et al., 1990). However, the onset, signs, and symptoms vary by tumour type, with initial presentations ranging from childhood to adulthood (VHL Alliance, 2023).

This report presents a case of VHL to enhance clinical awareness of its recognition, pathophysiology, and diagnostic process. The imaging findings illustrate typical VHL-associated lesions. The patient, initially diagnosed with a retinal haemangioblastoma, underwent abdominal computed tomography (CT), which revealed multiple abdominal tumours.

Case report

A 35-year-old woman from Minas Gerais, Brazil, presented with longstanding ocular lesion and progressive visual impairment, along with palpable abdominal masses. She reported a history of tobacco use but denied other comorbidities, prior surgeries, or regular medication use. At physical examination, bilateral retinal capillary haemangioblastomas were identified, along with firm, non-mobile abdominal masses. The remainder of the physical examination was unremarkable.

Abdominal CT revealed a diffusely enlarged pancreas with scattered calcifications, multiple cysts, and hypodense nodules demonstrating contrast enhancement post-intravenous iodinated contrast administration (Figure 1). Both kidneys were enlarged, with multiple cysts, nodules, and enhancing solid and mixed lesions. Brain magnetic resonance imaging (MRI) showed no significant abnormalities. These findings raised strong suspicion for VHL syndrome. Genetic testing confirmed the diagnosis of VHL syndrome.

The patient underwent a right partial nephrectomy for clinically suspected malignant renal lesions. Postoperative recovery was uneventful, and histopathological analysis confirmed clear cell renal cell carcinoma. Two months later, due to the confirmed malignancy, a left partial nephrectomy and marsupialisation of renal cysts were performed. Recovery was again uneventful, and histopathology revealed clear cell renal cell carcinoma in the left kidney lesions. The patient remains under regular outpatient surveillance with the oncology team.

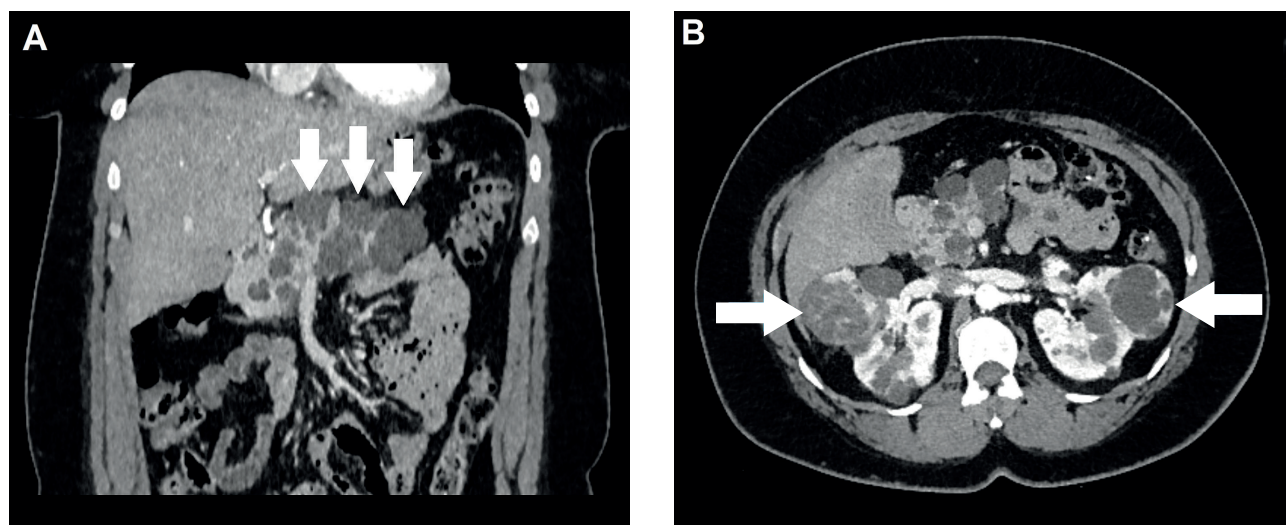


Figure 1: Coronal (A) and axial (B) computed tomography scans in the arterial phase demonstrating enlarged pancreas (A – white arrows) and kidneys (B – white arrows) with multiple cysts, nodules, and solid masses with enhancement after intravenous infusion of contrast, highlighting the characteristic findings of Von Hippel-Lindau syndrome.

Discussion

The VHL gene encodes pVHL, a tumour suppressor involved in cellular signalling pathways located at chromosome 3p25.3, regulating vascular endothelial growth factor (Costa et al., 2023). Mutation predisposes individuals to hypervascular neoplasms such as CNS and retinal haemangioblastomas, renal cell carcinoma, pheochromocytoma, and pancreatic tumours (Leung et al., 2008; Mikhail and Singh, 2022). Clear cell renal cell carcinoma and haemangioblastomas are the leading causes of mortality (Leung et al., 2008).

pVHL dysfunction results in upregulation of hypoxia-inducible genes, increasing erythropoietin, VEGF, platelet-derived growth factor B, and other growth factors (Costa et al., 2023). Most cases are inherited, though *de novo* mutations exist (Costa et al., 2023).

Clinical manifestations depend on lesion location. CNS haemangioblastomas may cause headaches, vomiting, sensory or motor deficits, and ataxia. Retinal haemangioblastomas can result in vision loss. Pheochromocytomas may present asymptotically or with adrenergic symptoms such as headaches, panic attacks, diaphoresis, and hypertension. Endolymphatic sac tumours may produce tinnitus, vertigo, or hearing loss (Mikhail and Singh, 2022). VHL syndrome is classified into two main groups: Type 1 (without pheochromocytoma) and Type 2 (with pheochromocytoma). Five subtypes have been described based on genotype and clinical phenotype (Nielsen et al., 2016).

Diagnosis is clinical or genetic. In patients without a family history, two or more characteristic lesions confirm the diagnosis (Pantigozo-Rimachi et al., 2022). Genetic testing is definitive but underutilised in regions with limited access to molecular diagnostics (VHL Alliance, 2020). Imaging with MRI and CT is essential for identifying phenotypic manifestations and guiding surveillance (VHL Alliance, 2020). Regular screening is recommended, starting in infancy for retinal evaluation and progressing to whole neuraxis MRI and abdominal imaging in adolescence and adulthood, following guidelines from the VHL Alliance (VHL Alliance, 2020). Differential diagnoses include sporadic retinal or CNS haemangioblastomas, renal cell carcinoma, pheochromocytoma, and pancreatic or endolymphatic sac tumours (Mikhail and Singh, 2022).

Management depends on lesion size, location, and the number of organs involved. Surgical resection is common, with radiosurgery used for inoperable CNS lesions (Laks et al., 2022).

Belzutifan, a hypoxia-inducible factor-2 α (HIF-2 α) inhibitor, has shown promise for treating advanced disease (Victorio, 2023). CNS haemangioblastomas may require surgery, embolisation, or radiosurgery (Laks et al., 2022). Retinal lesions are treated with laser photocoagulation or cryotherapy. Renal lesions often require partial or total nephrectomy (Laks et al., 2022). Pheochromocytomas demand surgical resection with preoperative adrenergic blockade. Pancreatic neuroendocrine tumours are surgically treated when high-risk features are present (Laks et al., 2022). Asymptomatic pancreatic cysts may be managed conservatively (Laks et al., 2022).

Conclusion

The clinical impact of VHL syndrome depends on tumour location and burden, with treatment sequelae potentially exceeding disease-related morbidity. Lifelong multidisciplinary follow-up is essential to manage both disease manifestations and treatment complications.

Raising awareness among healthcare providers is crucial to reduce underdiagnosis and improve patient outcomes, especially in cases involving high-mortality tumours like clear cell renal cell carcinoma and CNS haemangioblastomas.

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Median Diaphragmatic Cyst Radiologically Consistent with a Mesothelial Cyst in a Young Adult: A Case Report

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Received September 27, 2025; Accepted September 8, 2026.

Key words: Diaphragmatic cyst – Mesothelial cyst – CT – Diagnostic imaging – Abdominal pain – Diaphragm

Abstract: Diaphragmatic mesothelial cysts are rare, benign congenital lesions of the diaphragm, presumed to originate from coelomic remnants. Typically identified in pediatric populations, adult presentations – though uncommon – can pose diagnostic challenges due to vague or non-specific symptoms. We present the case of a 30-year-old African male with no prior imaging history, experiencing persistent epigastric pain exacerbated by deep inspiration. An inconclusive ultrasound was followed by a contrast-enhanced computed tomography scan, revealing a midline cystic lesion located adjacent to the posterior diaphragmatic pillar. This case highlights the importance of considering diaphragmatic mesothelial cysts in the differential diagnosis of chronic abdominal pain and details the characteristic imaging findings.

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<https://doi.org/10.14712/23362936.2026.28>

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Introduction

The diaphragm can rarely harbor benign cystic lesions of mesothelial origin. Diaphragmatic mesothelial cysts are uncommon and may be incidentally detected or symptomatic depending on their size and location (Esparza Estaún et al., 2003; Akinci et al., 2005).

These lesions are believed to originate from sequestered coelomic remnants during embryogenesis, and while they are most often reported in children, adult cases remain exceptionally rare. Their imaging overlap with other cystic lesions may complicate diagnosis in the absence of histological confirmation.

We present a case of a 30-year-old male with persistent epigastric pain and no prior imaging history. A contrast-enhanced computed tomography (CT) scan demonstrated a well-circumscribed, hypodense, midline cystic lesion embedded in the diaphragm.

Case report

A 30-year-old African male presented to the Emergency Department with persistent epigastric pain exacerbated by deep inspiration. He reported chronic abdominal discomfort since childhood and had never undergone radiological studies.

Physical examination was inconspicuous. An abdominal ultrasound was inconclusive due to pain and limited cooperation.

A contrast-enhanced CT of the abdomen and pelvis demonstrated a well-defined, uniformly hypodense lesion measuring approximately 10 cm in maximum diameter and showing an attenuation of approximately 30 HU, located along the left posterior diaphragmatic pillar, adjacent to the abdominal aorta and left adrenal gland. The lesion appeared embedded within the diaphragmatic fibers without displacement of adjacent organs, supporting an intra-diaphragmatic origin (Figures 1–3).

No prior imaging was available for comparison.

Given the benign appearance and absence of invasive features, biopsy or surgical exploration was not indicated. The lesion showed no solid components, wall thickening, septations, or enhancement, consistent with a mesothelial cyst.

Histopathological confirmation was not pursued because clinical and radiological criteria were sufficiently supportive of a benign diagnosis and no intervention was required.

A conservative approach was selected, with follow-up imaging planned in 6–12 months. Aspiration or sclerotherapy may be considered if symptoms persist (Yang and Han, 2022).

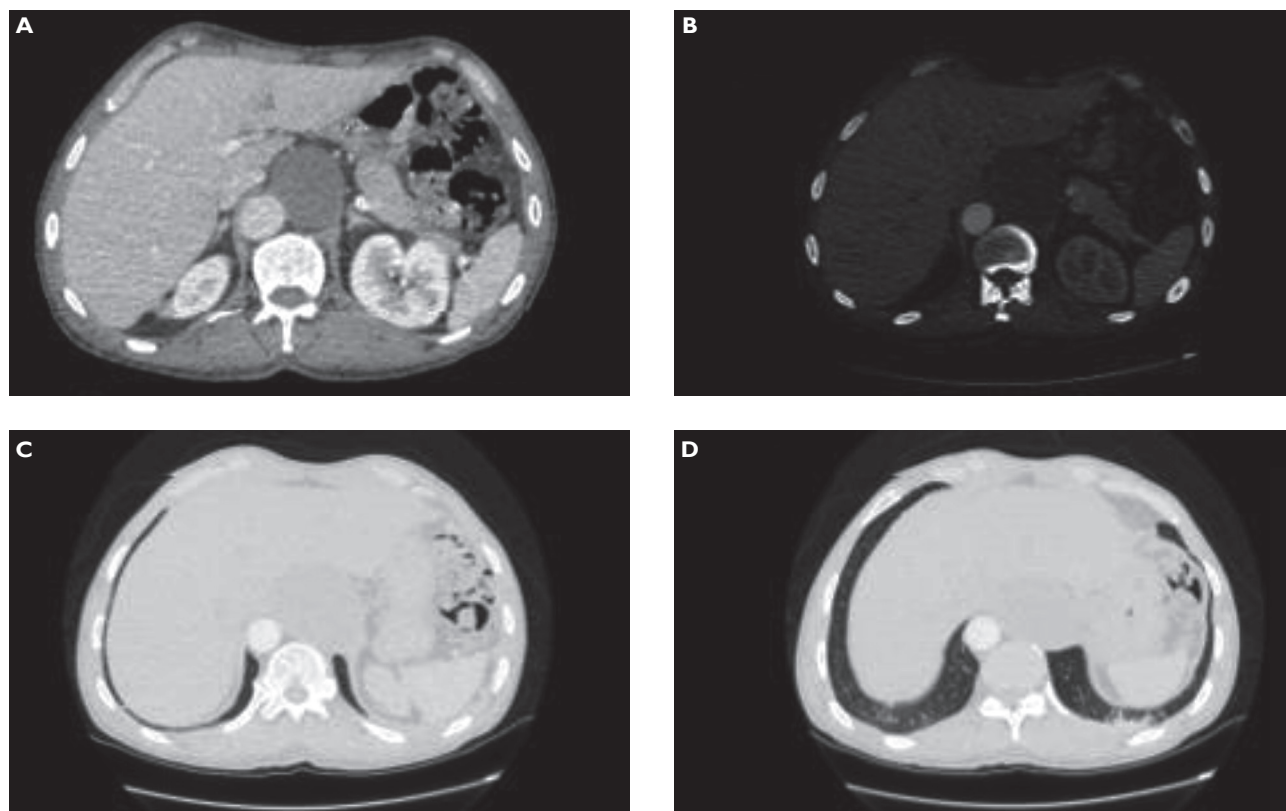


Figure 1: Axial computed tomography images without contrast: (A) abdominal window; (B) soft tissue window; (C) lung window at the superior diaphragm; (D) lung window at the inferior diaphragm. A hypodense, well-defined lesion is visible.

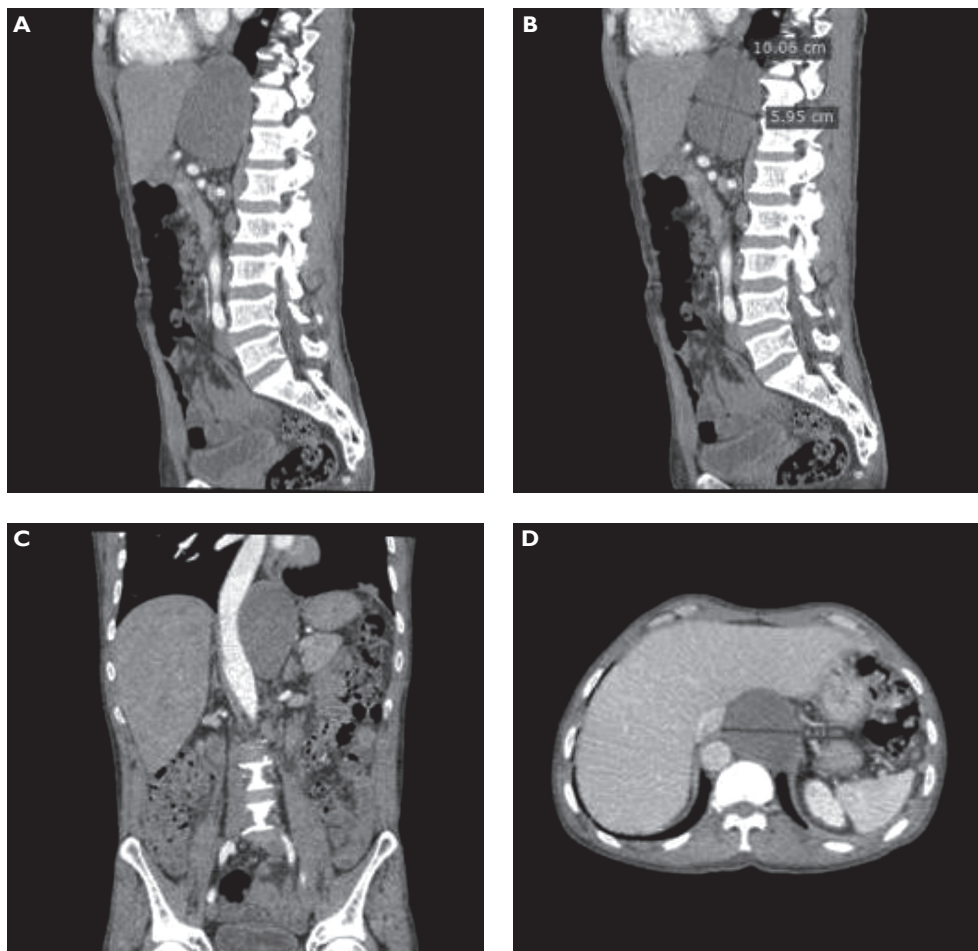


Figure 2: Contrast-enhanced computed tomography images: (A and B) sagittal plane with and without measurement; (C) coronal view; (D) axial plane with measurements. The lesion appears homogeneously hypodense.

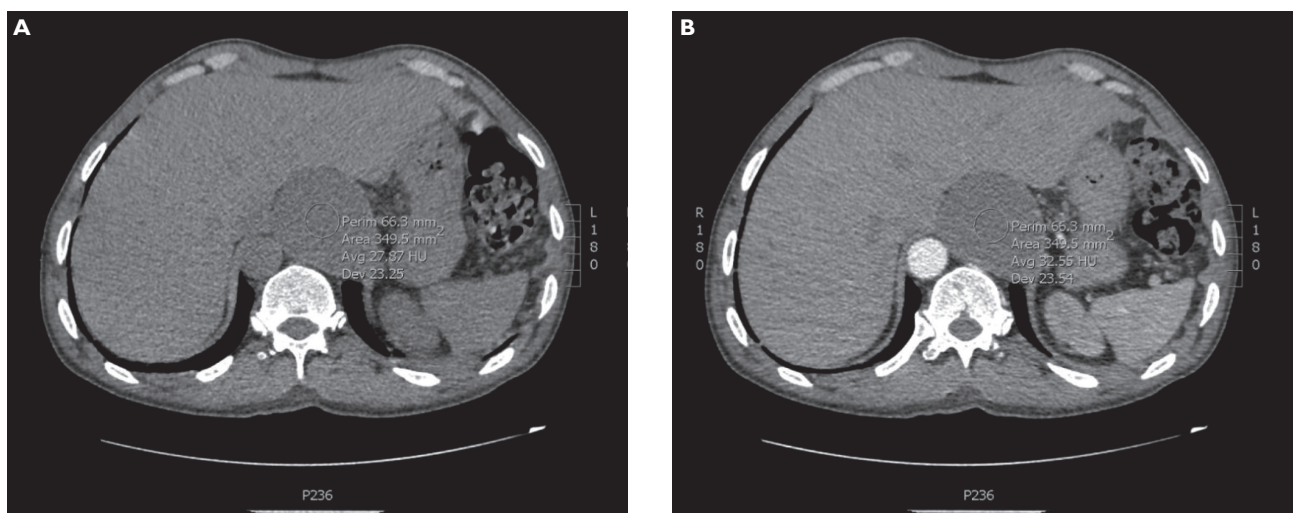


Figure 3: Computed tomography images obtained before (A) and after (B) intravenous contrast administration demonstrate stable attenuation of the lesion at approximately 30 HU, with no measurable enhancement.

Discussion

Mesothelial cysts of the diaphragm are rare congenital anomalies originating from trapped coelomic epithelium (Esparza Estaún et al., 2003; Akinci et al., 2005; Jackson and Lim, 2019).

The diaphragm develops from the septum transversum, pleuroperitoneal membranes, dorsal mesentery, and lateral body walls; failure of fusion or incomplete resorption may give rise to mesothelial-lined cysts (Mansueto et al., 2000; Martino et al., 2000; Kim and Hofstetter, 2009).

CT imaging typically reveals well-circumscribed, non-enhancing, hypodense lesions ranging 0–30 HU, whereas magnetic resonance imaging (MRI) shows T1 hypointensity and T2 hyperintensity (Mansueto et al., 2000; Jackson and Lim, 2019).

In our case, the lesion's imaging characteristics strongly favoured a mesothelial cyst.

Differential diagnosis

- Bronchogenic cysts, which may occur near the diaphragm but usually show proteinaceous or complex content.
- Hydatid cysts, especially in endemic regions, often demonstrate calcifications or daughter cysts.
- Adrenal cysts, which may simulate a diaphragmatic origin due to their posterior location.
- Duplication cysts, usually attached to the gastrointestinal tract and exhibiting a characteristic muscular rim sign (Sans et al., 1999; Weerakkody and Jones, 2024), features not observed in this case.

Management depends on symptoms, size, and radiologic features. Asymptomatic lesions may be monitored radiologically, while surgical or interventional procedures are reserved for uncertain diagnoses, complications, or persistent symptoms (Robertson et al., 2015; Kahrman et al., 2016; Yang and Han, 2022).

Large (≥ 10 cm), midline diaphragmatic mesothelial cysts in adults are exceedingly rare. A few adult cases of diaphragmatic cysts of different origins have been reported (Kandemirli et al., 2020; Welsh et al., 2024).

Our case is notable for its size (10 cm), midline location, and occurrence in an adult with no prior imaging.

Conclusion

This case highlights the need to consider diaphragmatic mesothelial cysts in the differential diagnosis of chronic epigastric pain in adults. CT provides critical diagnostic

information. In the absence of concerning features, a conservative approach with imaging follow-up is appropriate.

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A Rare Mimicker of Malignancy: Inflammatory Cloacogenic Polyp Presenting as Obstruction in a Colon Cancer Survivor

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Received April 14, 2025; Accepted September 8, 2026.

Key words: Case report – Cloacogenic – Colonic polyp – Polyps

Abstract: Inflammatory cloacogenic polyps are rare and often discovered either during routine colorectal cancer screenings or in symptomatic patients presenting with hematochezia. In unusual cases, they can present as an adhesive obstruction with radiological and clinical findings suggestive of a suspicious recurrent colorectal malignancy lesion. Because these polyps can mimic cancer during endoscopy, a detailed tissue examination is crucial for making the correct diagnosis and planning treatment. In this report, we share a challenging case where a patient with a history of cancer presented with signs that strongly suggested a malignant recurrence, but the final diagnosis was an inflammatory cloacogenic polyp. This case highlights the critical role of regular endoscopic monitoring in managing such complex conditions.

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<https://doi.org/10.14712/23362936.2026.29>

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Introduction

The inflammatory cloacogenic polyp (ICP) was first introduced in 1981 (Lobert and Appelman, 1981). It is a benign polyp that arises from the anal transitional zone and rectum (Prakash et al., 2022). It has distinct histological and clinical features, setting the foundation for understanding their pathogenesis and relationship to various anorectal and gastrointestinal disorders (Chiam et al., 2023). This condition is rare and usually detected during screening for colorectal cancer or in symptomatic patients presenting with lower gastrointestinal symptoms. It is unusual to diagnose this condition on any patient suspected to have recurrent colorectal cancer. Imaging, endoscopic and histological diagnosis are warranted prior to declaring this diagnosis. We experienced a 60-year-old woman, initially suspected of having a recurrence of colon cancer based on clinical presentation, imaging, and endoscopic findings, was diagnosed with an ICP, hence we discussed our treatment modalities.

Case report

A 60-year-old woman with a history of left hemicolectomy, cholecystectomy, and appendectomy for sigmoid colon cancer (well-differentiated adenocarcinoma, treated in 2005) presented with two days of colicky abdominal pain, frequent vomiting (over 10 episodes a day), and diarrhoea. She was alert and her vital signs were stable. On examination, there was tenderness in the lower abdomen and umbilical region. A rectal exam revealed an irregular mass at the 6 o'clock position. An abdominal radiograph showed dilated bowel loops with a "stacked coins" appearance, indicating bowel obstruction. Biochemical

tests and tumour markers were unremarkable.

A contrast-enhanced computed tomography scan of the abdomen and pelvis showed a dilated segment of the jejunum in the mid-abdomen without a clear transition point. It also revealed an enhancing lesion near the posterior wall of the rectum (Figure 1), located 6.4 cm from the anal verge and measuring 1.0×1.3 cm, with nearby mesorectal and presacral lymph nodes. Diverticulosis in the ascending colon and a small amount of free fluid in the abdomen were also noted.

Following successful conservative management of adhesive obstruction, a colonoscopy was performed. This revealed a suspicious polyp, 1.5 cm in size with a short stalk, located 8 cm from the anal verge as shown in Figure 2. The polyp was successfully removed via snare polypectomy without any complication. Multiple diverticula were observed in the transverse colon, along with a benign appearing 1 cm polyp in the proximal transverse colon. Histopathological examination (HPE) confirmed it as a mid-rectal ICP (Figure 3). A follow-up colonoscopy six months later showed a new rectal lesion 6 cm from the anal verge. The area had thickened, granular mucosa, and a small, firm 5 mm lesion likely related to the previous polypectomy. Biopsy results showed a benign mucosal ulcer with hyperplastic changes. The patient remains under our regular follow-up, with tumour markers checked every six months and a repeat colonoscopy planned in a year.

Discussion

ICPs are rare growths that develop mainly in the anorectal region and are thought to be part of the mucosal prolapse syndrome (Chiam et al., 2023).

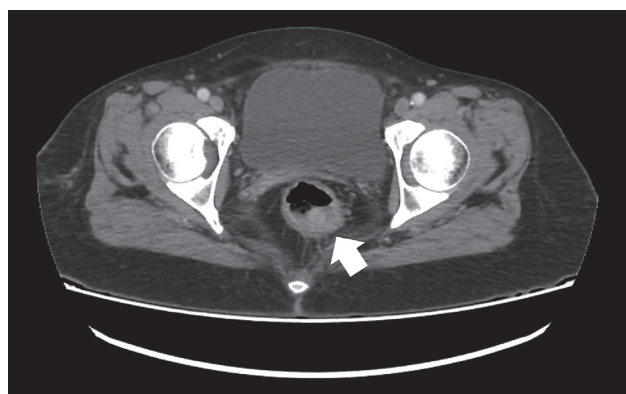


Figure 1: A contrast-enhanced abdominal and pelvic computed tomography scan demonstrated a distended jejunal segment in the mid-abdomen in the absence of a clear transition point. The study also revealed a 1.0×1.3 cm enhancing lesion (white arrow) involving the posterior rectal wall at mid-rectum.

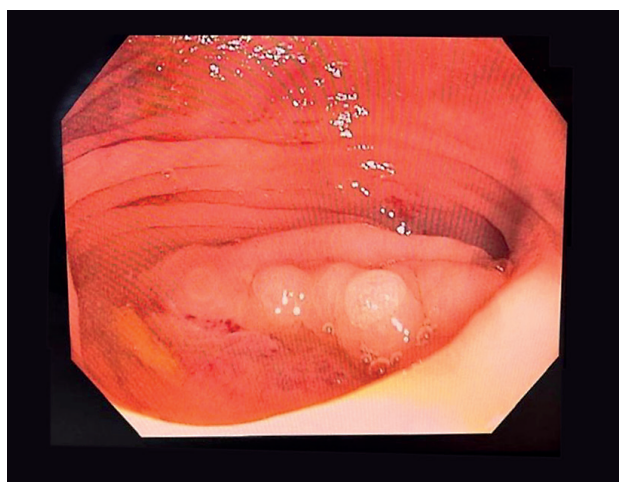


Figure 2: A colonoscopic view of a suspicious polyp, 1.5 cm in size with a short stalk, located 8 cm from the anal verge.

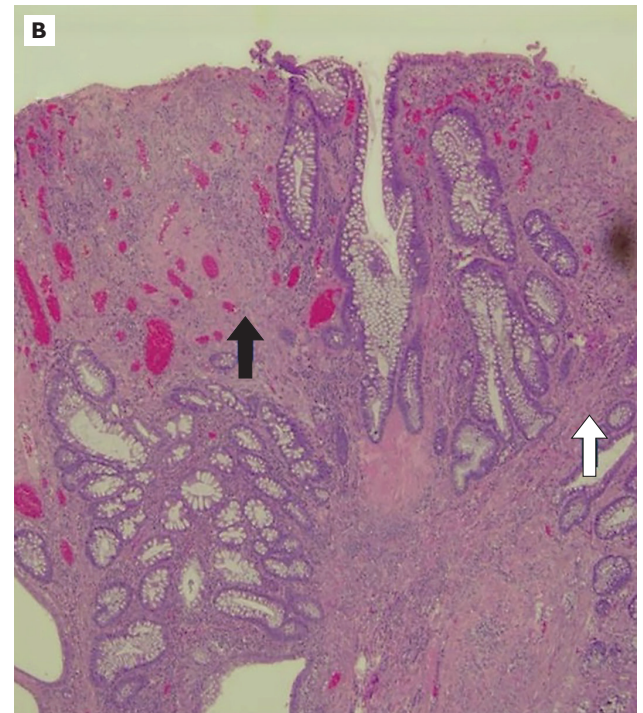
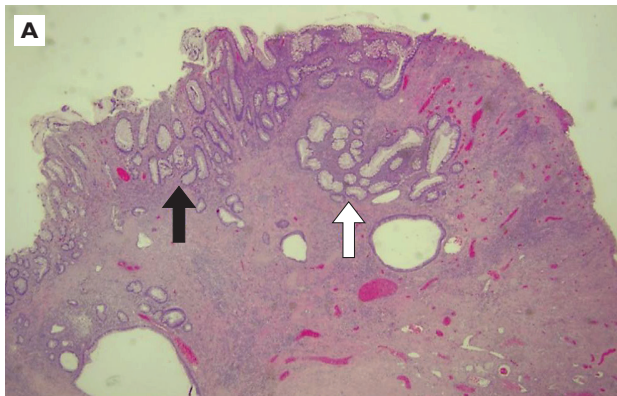


Figure 3: (A) The benign crypts have tubulovillous architecture with elongated crypts stretching into the submucosa (black arrow). Some of the crypts are arranged in lobular architecture (white arrow) (haematoxylin and eosin, 10× magnification). (B) Thickened muscularis mucosa with extension into the lamina propria with some mucosal prolapse features (muscularis mucosae with splayed fibers) are seen (white arrow). Reactive swollen endothelial cells and fibroblasts with mixed acute and chronic inflammatory cells are seen (black arrow) (haematoxylin and eosin, 20× magnification). Cytomegalovirus immunohistochemistry stain is negative.

They share similar features with other benign anorectal conditions like solitary rectal ulcers and prolapsing polyps, likely arising from repeated mucosal injury and healing due to abnormal rectal contractions. Despite their distinct appearance, the exact cause of ICP remains unclear because of limited research (Monreal-Robles et al., 2019; Prakash et al., 2022). In this case, a patient with a history of colorectal cancer presented with a suspicious rectal polyp and nearby lymph node seen on imaging, raising concern for a possible new cancer. Urgent colonoscopy was performed, but the presence of anal intraepithelial neoplasia within an ICP made diagnosis and management more challenging (Hanson and Armstrong, 1999).

Although only a few cases have linked ICP to cancer (as outlined in Table 1), research has highlighted their potential to progress from benign to malignant. Advanced endoscopic techniques, such as high-definition colonoscopy with narrow-band imaging, have helped differentiate polyps with suspicious features, as shown in studies by Lambin et al. (2022) and Reissnerová et al. (2022), though histology often confirms benign ICPs. In contrast, magnetic resonance imaging findings by Ferrer Martínez et al. (2026) initially suggested malignancy, but histology again revealed a benign polyp. In our patient, imaging showed a suspicious rectal polyp with nearby lymph nodes, raising concern for cancer recurrence. While classification systems like the Japan NBI Expert Team via narrow-band imaging magnification could aid diagnosis, our center lacks the resources for such detailed endoscopic evaluations, making

histopathology essential (Lobert and Appelman, 1981). The biopsy showed characteristic features of ICPs, including irregular crypts, submucosal involvement, and chronic inflammation.

ICPs typically show a tubulovillous structure with benign crypts that may extend into the submucosa and sometimes appear in a lobular pattern. The muscularis mucosa is often thickened and extends into the lamina propria, with signs of mucosal prolapse such as splayed muscle fibers. The supporting tissue contains swollen endothelial cells, fibroblasts, and a mix of acute and chronic inflammatory cells. Other common features include surface erosion, glandular overgrowth, and fibromuscular tissue expansion. Recognizing these features is important to distinguish ICPs from other anorectal conditions (Marcos et al., 2019). Due to the risk of recurrence or possible malignant transformation, careful endoscopic follow-up after removal is essential (Özgenel et al., 2016).

Rectal bleeding and changes in bowel habits are common symptoms of ICPs, though up to 20% of cases may be asymptomatic. These polyps are typically found in the anorectal area and rarely cause adhesive intestinal obstruction, as shown in Table 1. What makes this case unusual is that the patient had a history of sigmoid adenocarcinoma over a decade ago, with no signs of recurrence during the past three years of surveillance colonoscopies. Now, they present with bowel obstruction and a palpable rectal mass on examination, requiring inpatient colonoscopy after conservative treatment. This combination of factors makes it a rare and unique presentation of ICP.

ICPs usually measure between 1 to 5 cm and are mostly sessile, though they can sometimes have a stalk. They may appear alone or in clusters and can exist alongside other types of benign polyps, like hyperplastic or adenomatous ones. It can be difficult

to distinguish ICPs from potentially cancerous lesions during colonoscopy, especially when they are large or have a bleeding surface. In our case, the patient had a sessile polyp that looked highly suspicious for cancer. However, biopsy results showed it was an ICP.

Table 1: Cases related to ICP which were published since 2016 until now

Case (Year)	Age	Presenting symptom	Clinical finding	Diagnosis	Management	Surveillance scope
Ferrer Martínez et al. (2026)	25	6/12 tenesmus, anemia and weight loss	Painful rectal mass 6 cm from anal margin. MRI finding of T1-2, no lymph node involvement	Suspicious rectal lesion to rule out malignancy	Transanal endoscopic	
Reissnerová et al. (2022)	14	6/12 intermittent rectal bleeding	Palpable polypoidal lesion at 1 cm from dentate line Scope finding of cauliflower-like mass	Suspicious rectal lesion HPE: lamina muscularis mucosae is hyperplastic (bold arrow) with proliferation of smooth muscle outstretching to lamina propria mucosae. Glandular hyperplasia, tubulovillous architecture (thin arrow)	Transanal endoscopic microsurgery (TEM) Followed by sufficient fibre and optimal fluid intake	Whitish base after polyp removal
Prakash et al. (2022)	53/F	History of low-grade papillary tumour of the bladder, cigarette smoking, and alcohol abuse. Asymptomatic. For colorectal cancer screening	Digital rectal examination shows dark colour stool and positive immunochemical faecal occult blood test. Colonoscopy show 2 sessile polyps 7 mm in the rectum (HPE: prolapsed induced inflammatory cloacogenic polyp), 7 polyps (15–25 mm) in the sigmoid (HPE: tubular adenoma and serrated adenoma)	Benign feature sessile polyp of rectum with multiple sigmoid polyp with benign feature	Snare polypectomy	Endoscopic surveillance
Lambin et al. (2022)	38/F 71/F	Abdominal pain, hematochezia, and mucus in the stool. Hematochezia	1. Pedunculated inflammatory lesion with 20 mm head and some area of irregular pit pattern (Kudo Vn) on narrow-band imaging 2.30 mm red head in sigmoid colon. Dilatation of lymphatic vessels on the stalk of polyp	Both cases showing malignant feature appearances in which in favours of malignancy	1. En bloc resection with a hot snare 2. Endoscopic submucosal dissection with the tip of snare allowed en bloc resection Both HPE finding of ulcerated surface with dilated colonic glands within inflammatory stroma and significant hemorrhagic suffusion. The glands were dilated, sometimes cystic and filled with mucopurulent material. Mucosa adjacent to stalk was normal. No sign of malignancy or dysplasia	Endoscopic surveillance

Case (Year)	Age	Presenting symptom	Clinical finding	Diagnosis	Management	Surveillance scope
Ochiai et al. (2021)	45/M	Strong family history of malignancy with previous history of colonoscopy which showed multiple polyps, which were consistent with ICPs on the dentate line. Presented with hematochezia	Colonoscopy at presentation revealed multiple polyps in the lower rectum as before, two of which had grown in size, and the shapes of the top were different from surrounding polyps	Biopsies at lower rectum were performed and the pathological diagnoses were adenocarcinomas for both lesions	Endoscopic submucosal dissection (ESD) was performed and the two lesions were diagnosed as double well-differentiated adenocarcinomas arising from ICPs	Follow-up colonoscopy performed 10 months after ESD showed no recurrence in the rectum
Marcos et al. (2019)	67/F	Chronic constipation with intermittent hematochezia and iron deficiency anaemia	DRE show soft mobile mass at lower rectum. Colonoscopy showed numerous, confluent, light yellowish, sessile polyps at anorectal junction, in biopsy taken	HPE of biopsies showed surface erosion with reactive inflammatory and reparative changes covered by a fibrinopurulent cap and granulation tissue, glandular hyperplasia, and a lamina propria, in part, replaced by an overgrowth of fibromuscular tissue	Planned for endoscopic resection. However, didn't make it as died because of cardiovascular event	
Özgenel et al. (2016)	24/M	Hematochezia for 1/12	Colonoscopy showed 1.5 cm polyp at rectum, biopsied	HPE show findings with ulcers, minimal architectural distortion, hyperplastic changes and regenerative atypia, fibromuscular hyperplasia in the lamina propria, and vessel-rich colonic polypoid tissues	Endoscopic polypectomy	

ICP – inflammatory cloacogenic polyp; MRI – magnetic resonance imaging; HPE – histopathological examination; F – female; M – male

This raised concerns about whether the endoscopic removal was complete and had clear margins. A follow-up colonoscopy later confirmed that the site was now a benign mucosal ulcer with hyperplastic changes, ruling out malignancy and providing reassurance.

The treatment approach for colonic polyps largely depends on endoscopic evaluation, with the choice between simple snare polypectomy and advanced resection guided by the polyp's malignant potential and the endoscopist's skill (Özgenel et al., 2016). ICPs, though rare and typically benign, require careful assessment of features like size, location, and stalk presence to determine the best removal method. Sessile polyps can be more challenging and often require experienced handling, including submucosal injection before removal to reduce the risk of deep

tissue injury. Unlike standard surveillance for adenomas, there's no clear guideline for follow-up colonoscopies in ICP cases. Some suggest checking as early as 6 weeks after resection, but in our practice, we opt for a 6-month interval due to limited understanding of ICP growth patterns. Because the risk of cancer is low, managing ICPs and related colonoscopy complications calls for an individualized, risk-based approach rather than a one-size-fits-all protocol.

Conclusion

ICPs are rare, benign anorectal lesions that can mimic cancer, especially in patients with a history of colorectal malignancy. Our case involved an unusual presentation with adhesive obstruction and a suspicious rectal mass,

raising concern for recurrence. Despite concerning findings, histopathology confirmed a benign ICP, highlighting the importance of tissue diagnosis. With no standard surveillance guidelines, follow-up should be individualized based on risk factors and lesion features. Regular monitoring remains important due to the low but possible risk of recurrence or malignancy.

Acknowledgements: The authors would like to thank the Director-General of Ministry of Health Malaysia for giving this opportunity to publish this case as a case report.

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Siliconomas and Sepsis from Illegal Silicone Injections

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Received November 26, 2024; Accepted September 8, 2026.

Key words: Silicone injection – Siliconoma – Sepsis – MRI – CT scan – Lymphadenopathy

Abstract: Illegal silicone injections for body enhancement can lead to serious complications, including the formation of siliconomas – granulomatous reactions caused by silicone leakage and spread through tissues and lymphatic drainage pathways. This paper presents the case of a 31-year-old transgender man who developed widespread silicone-related soft tissue deposits and sepsis following unauthorized silicone injections into the gluteal region. The patient presented with fever, hypotension, tachycardia, and multiple palpable subcutaneous nodules. Imaging studies, including computed tomography, magnetic resonance imaging, and ultrasound, demonstrated extensive silicone deposits and regional lymphadenopathy. Sepsis was diagnosed and managed with intravenous antibiotics and surgical consultation. This case highlights the dangers of unregulated silicone injections and the importance of early imaging to assess the extent of complications.

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<https://doi.org/10.14712/23362936.2026.30>

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Introduction

Silicone injections are sometimes performed outside medical contexts for aesthetic body contouring. These procedures, particularly when carried out illegally, have been associated with significant complications, including granulomatous inflammation (siliconomas), migration of silicone, embolization, and infection (Chasan, 2007; Parikh et al., 2008). Liquid silicone, when injected directly, lacks encapsulation and can migrate through soft tissues and along lymphatic channels, potentially leading to systemic responses. Granulomatous reactions are often the result of the immune system's attempt to isolate and contain foreign material. While most reported cases involve breast or axillary injections, silicone migration and complications have also been observed in gluteal and pelvic regions (Hazani and Engineer, 2008; Bravo et al., 2016).

This paper details the case of a 31-year-old transgender man who developed widespread siliconomas and sepsis after receiving illegal silicone injections into the gluteal region.

Case report

A 31-year-old transgender man presented with fever, hypotension, tachycardia, and severe pain

in the gluteal region. He reported having received silicone injections for cosmetic body enhancement approximately three years prior in Brazil. The procedure had been performed by non-medical personnel. He denied prior complications or infections at the time of injection and had no known systemic diseases.

Clinical examination revealed multiple firm, tender, mobile subcutaneous nodules in the gluteal area. Palpable lymphadenopathy was also noted in the inguinal and pelvic regions. Laboratory findings included leukocytosis and elevated inflammatory markers. Blood cultures were positive for *Staphylococcus aureus*, consistent with bloodstream infection and systemic inflammatory response – compatible with a diagnosis of sepsis (Singer et al., 2016).

Ultrasound of the gluteal area showed multiple hypoechoic regions with a typical “snowstorm” appearance, indicative of free silicone (Cheung et al., 2002; Narins and Beer, 2006). A contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis revealed multiple iso- to hyperdense nodules in the gluteal muscles (Figure 1). Enlarged lymph nodes were observed in the pelvic and inguinal regions, likely reflecting reactive lymphadenopathy (Scaranelo and de Fátima Ribeiro Maia, 2006). Migration of silicone into lymphatic structures could not be directly confirmed on imaging (Schoeller et al., 2000).

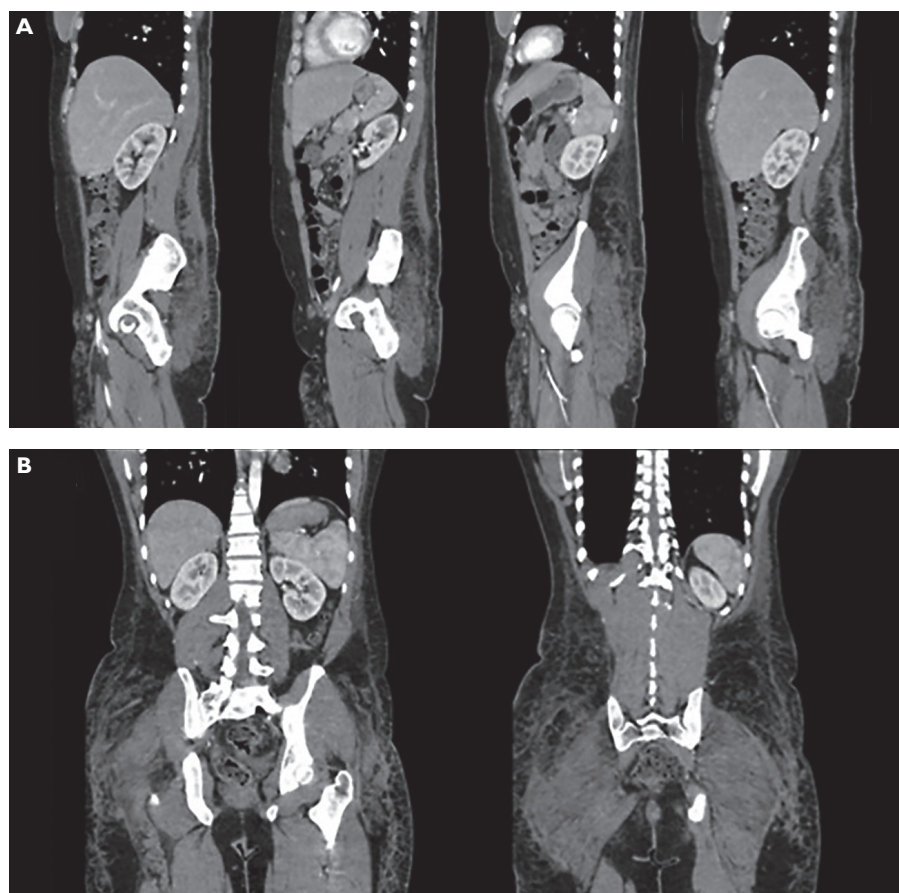


Figure 1: Computed tomography (CT) scan images of the lumbar and gluteal regions showing multiple nodular silicone deposits. A (sagittal section): Well-defined iso- to hyperdense nodules are visible within the subcutaneous tissues of the lower back and gluteal area, consistent with the patient's history of silicone injection. Mild surrounding soft tissue inflammation is present, without signs of acute complications. B (coronal section): Confirms the presence of multiple nodular deposits along the lumbar and gluteal regions. CT imaging does not definitively allow characterization of granulomas or confirmation of silicone migration to lymph nodes.

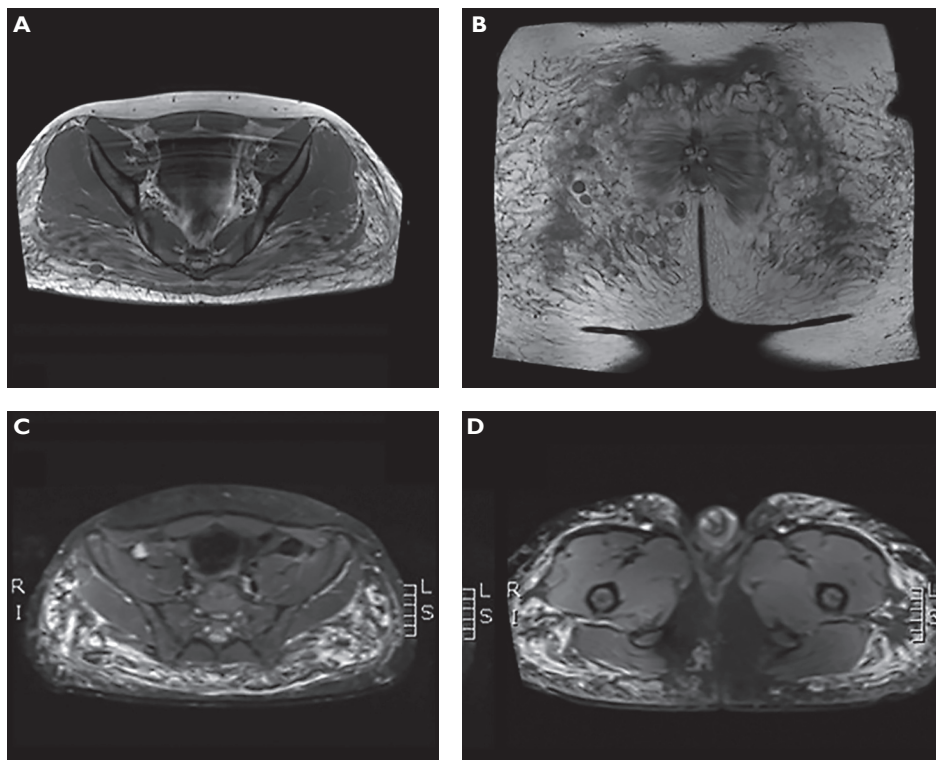


Figure 2: Magnetic resonance imaging of the pelvic and gluteal regions demonstrating extensive silicone-related soft-tissue involvement. A (axial T1-weighted image): Multiple low-signal-intensity nodular deposits are seen within the subcutaneous tissues of the gluteal region, with mild surrounding soft-tissue edema and no evidence of acute collection or abscess formation. B (coronal T1-weighted image): Further demonstrates the craniocaudal extent and multifocal distribution of the subcutaneous silicone deposits. C and D (axial diffusion-weighted images, $b = 800 \text{ s/mm}^2$): Show diffuse high signal intensity throughout the involved subcutaneous tissues, extending beyond the individual nodules, with corresponding low ADC values consistent with restricted diffusion, highlighting the diffuse extent of soft-tissue involvement.

Magnetic resonance imaging (MRI) further characterized the silicone-related deposits. T1-weighted axial and coronal sequences revealed well-circumscribed, hypointense lesions consistent with silicone presence in soft tissue. Diffusion-weighted imaging ($b = 800$) showed restricted diffusion around some nodules, likely reflecting surrounding inflammation. The examination was interrupted due to claustrophobia, but acquired sequences were sufficient to support the diagnosis. No abscesses or necrotic collections were identified (Figure 2).

The patient was treated with intravenous antibiotics and referred to a surgical team for further management.

Discussion

Silicone injection complications have been widely documented, especially when performed in non-medical contexts (Chasan, 2007; Parikh et al., 2008). Granulomatous reactions (siliconomas) may form in response to silicone deposits, involving macrophages, multinucleated giant cells, and chronic inflammation (Rapaport et al., 1996; Schwartzfarb et al., 2008). Silicone may travel through soft tissue planes and accumulate in lymphatic drainage areas, triggering inflammatory responses.

In this case, the gluteal deposits corresponded with the patient's history of injection. Imaging confirmed the presence of multiple soft tissue nodules. Reactive

lymphadenopathy likely resulted from inflammation and sepsis, not direct silicone infiltration. Imaging alone does not confirm silicone migration into lymph nodes; such findings require histopathological correlation (Ebrahim et al., 2014).

Ultrasound is useful for detecting silicone via the "snowstorm" artefact, but it lacks anatomic detail (Wilkie, 1977). CT can detect silicone as dense nodules relative to fat, although it cannot differentiate granulomatous tissue from other pathologies. MRI is the most sensitive modality for assessing soft tissue involvement and distinguishing silicone from surrounding structures (Luo et al., 2011; Gifuni et al., 2023). Specialized MRI sequences can even distinguish free silicone from other injected materials such as paraffin or fat.

This case illustrates that even years after injection, severe complications such as systemic infection may arise. Early identification via imaging and prompt clinical management are critical.

Conclusion

Illegal silicone injections carry substantial risks, including chronic inflammatory responses, systemic infections, and tissue damage. This case of silicone-related sepsis in a transgender man highlights the importance of imaging, especially MRI, in diagnosing and managing such complications. The widespread

use of unregulated silicone for cosmetic purposes underscores the need for public health initiatives and clinical awareness to prevent these avoidable outcomes.

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