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Comparative Effectiveness of Nonsteroidal Anti-inflammatory Drugs and Glucocorticoids in Managing Postoperative Pain Syndrome

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Abstract: The purpose of this study was to investigate the effectiveness of nonsteroidal anti-inflammatory drugs and glucocorticosteroids in reducing postoperative pain syndrome. For this purpose, information about postoperative pain syndrome was searched in PubMed, ResearchGate, Scopus, Web of Science, and Google Scholar databases for 2016–2024. Depending on the duration, it is classified into acute (up to 3 months) and chronic (3 months or more). Postoperative pain syndrome occurs due to tissue damage, the development of an inflammatory process, and a violation of nerve conduction. Risk factors include severe preoperative pain; mental disorders; anxiety; comorbidities; low income; lack of social support. Effective treatment of postoperative pain syndrome is the main factor for further recovery and a comfortable life of the patient. High-quality anaesthesia helps to cope with pain even at the acute stage and prevents chronicity of the process. Nonsteroidal anti-inflammatory drugs and glucocorticoids in multimodal anaesthesia provide optimal anaesthesia in the postoperative period. They have anti-inflammatory, analgesic, and antiemetic effects. Prevention includes the appointment of preventive multimodal anaesthesia, the selection of minimally invasive surgical access to reduce the area of tissue injury; psychological support of patients at all stages of treatment; the appointment of rehabilitation interventions in the acute period. It was concluded that for adequate anaesthesia of postoperative pain, it is necessary to use nonsteroidal anti-inflammatory drugs and glucocorticoids as part of multimodal anaesthesia, because when used independently, they have an insufficient analgesic effect.

Introduction

Postoperative pain syndrome is characterised by the appearance of pain in the postoperative period, provided that any other possible causes are excluded. This is a complex response to traumatic tissue and nerve damage during surgery. The syndrome was initially documented in 1999 and subsequently classified inside the International Classification of Diseases-11. Depending on the type and severity of surgery, the frequency of postoperative pain syndrome ranges from 7 to 80% (Viderman et al., 2023; Nuspekova et al., 2024). This leads to complete or partial disability of patients, sleep disorders, the development of a number of psychological problems, a decrease in the quality of life, and contributes to a high need for medical care, social, and economic costs. Postoperative pain increases the risk of further complications, prolongs the time of recovery and rehabilitation of patients. Acute postoperative pain is a normal body reaction in response to tissue and nerve damage (Navarro-Obeid et al., 2025). Nonetheless, inadequate therapy might lead to the onset of chronic postoperative pain, persisting for over 3 months. Therefore, it is important to immediately choose effective painkillers.

Pain perception is individual, depending on the pain threshold, mental state, and social context (Kaloshi et al., 2014; Efremov, 2025). A number of researchers have studied which surgical interventions increase the risk of postoperative pain syndrome. Thus, Kerimbayev et al. (2022), Viderman et al. (2023) and Nuspekova et al. (2024) noted that the main risk factors are breast removal, chest and pleural cavity opening operations, and amputations. The risk group for the syndrome includes young women; people with severe preoperative pain syndrome; preoperative opioid use; and the presence of severe mental disorders. Patients who have had isolated nerve damage are also at higher risk. When tissues are damaged due to surgery, changes occur in the somatosensory nervous system. The frequency and intensity of postoperative pain increase neuropathically. In patients after knee replacement who had severe postoperative pain for 1 month, the duration of the pain syndrome lasted up to 3 months.

The main problem is the lack of highly effective means of prevention and treatment of postoperative pain syndrome. Opioids quickly reduce severe pain, but their characteristic disadvantage is the development of tolerance and addiction. Stormholt et al. (2021), Hald and Møller (2024) and Zufferey et al. (2024) described those preventive measures include performing regional anaesthesia; performing epidural anaesthesia and paravertebral blockades

during operations on the chest cavity and chest; and performing spinal anaesthesia during caesarean section. Multimodal postoperative pain relief (i.e., simultaneous administration of several drugs with a synergistic effect), which acts on different mechanisms of pain response, is an effective method of postoperative pain relief (Missori et al., 2016; Sakaguchi et al., 2024). Treatment should be started with nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticosteroids, supplemented with opioids if necessary. Abdildin et al. (2023), Viderman et al. (2024) and Zhaksylyk et al. (2024) noted that the administration of ketamine, lidocaine, gabapentin, glucocorticoids, nonsteroidal anti-inflammatory drugs, and antidepressants during breast and chest surgery is important for pain management. Many researchers have already thoroughly investigated the effect of modern pharmacological drugs on the course and duration of postoperative pain syndrome.

The purpose of this study was to evaluate the importance of glucocorticoids and nonsteroidal anti-inflammatory drugs in reducing postoperative pain, regardless of the type of surgery performed. Tasks: to investigate and systematise the risk factors of postoperative pain syndrome; to describe the pathophysiology of postoperative pain syndrome; to analyse the main aspects of the intake, exchange, distribution, and conversion of nonsteroidal anti-inflammatory drugs and glucocorticoids; to describe the effect of these drugs on the patient's body; to investigate the effectiveness of NSAIDs and glucocorticoids in the occurrence of chronic postoperative pain syndrome as a result of performing common surgical interventions (caesarean section, thoracotomy, endoprosthetics, laparoscopic interventions, laparatomic interventions, spinal surgery).

Material and Methods

The first phase of the study from November 1 to November 30, 2024, was to perform a thorough structured systematic search for up-to-date information about postoperative pain syndrome, presented in the databases PubMed, ResearchGate, Scopus, Web of Science, and Google Scholar.

Throughout the investigation, all acquired papers were examined, emphasising material from peer-reviewed publications published between 2016 and 2024 in Polish, French, German, Spanish, and English. The necessary information was searched using a combined set of keywords: "postoperative pain syndrome", "acute pain", "chronic pain", "sensitisation", "nociception", "types of surgical

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interventions", "laparotomy", "laparoscopy", "joint replacement", "breast removal", "thoracotomy", "caesarean section", "amputations", "prevalence of postoperative pain syndrome", "risk factors for postoperative pain syndrome", "pathogenesis of postoperative pain syndrome", "treatment of postoperative pain syndrome", "diagnosis of postoperative pain syndrome", "prevention of postoperative pain syndrome", "mechanism of action of nonsteroidal anti-inflammatory drugs", "mechanism of action of glucocorticoids", "effect of anti-inflammatory drugs on chronic postoperative pain syndrome".

The search yielded 2,500 papers. They were thoroughly evaluated, processed, and analysed by titles, annotations, relevancy, publication dates, and case study evidence level. To find more information, relevant paper links were examined and their content analysed. Next, duplicate and non-time-related papers were deleted. After then, research papers were reviewed using inclusion/exclusion criteria. Non-inclusion papers were immediately removed. This analysis excluded old, unsubstantiated, and irrelevant information, animal study data, and minimally invasive procedures as lumbar puncture (Figure 1).

Chronic postoperative pain syndrome epidemiology, aetiology, risk factors, processes of development, clinical picture, diagnosis, management, and prevention were covered in this study. Included were papers on new methodologies for studying chronic postoperative pain syndrome without regard to gender, age, race, region of residence, social status, disease course, or severity. Nonsteroidal anti-inflammatory medications and glucocorticoids were studied for their basic mechanisms, pharmacokinetics, pharmacodynamics, indications, contraindications, and adverse effects. The effects of nonsteroidal anti-inflammatory medications and glucocorticoids on persistent postoperative pain syndrome after thoracotomy, arthroplasty, amputation, laparotomy, and caesarean section were discussed. As a result of a thorough systematic selection process, 50 relevant research papers were obtained that fully met the necessary selected criteria. To avoid errors, the selected information sources were re-evaluated, processed, and verified.

Results and Discussion

Risk factors and pathophysiology of postoperative pain

The pathophysiology of postoperative pain generally encompasses a confluence of various elements. The initial event is tissue injury, characterised by cell membrane rupture, the release of intracellular contents, and the initiation of the inflammatory
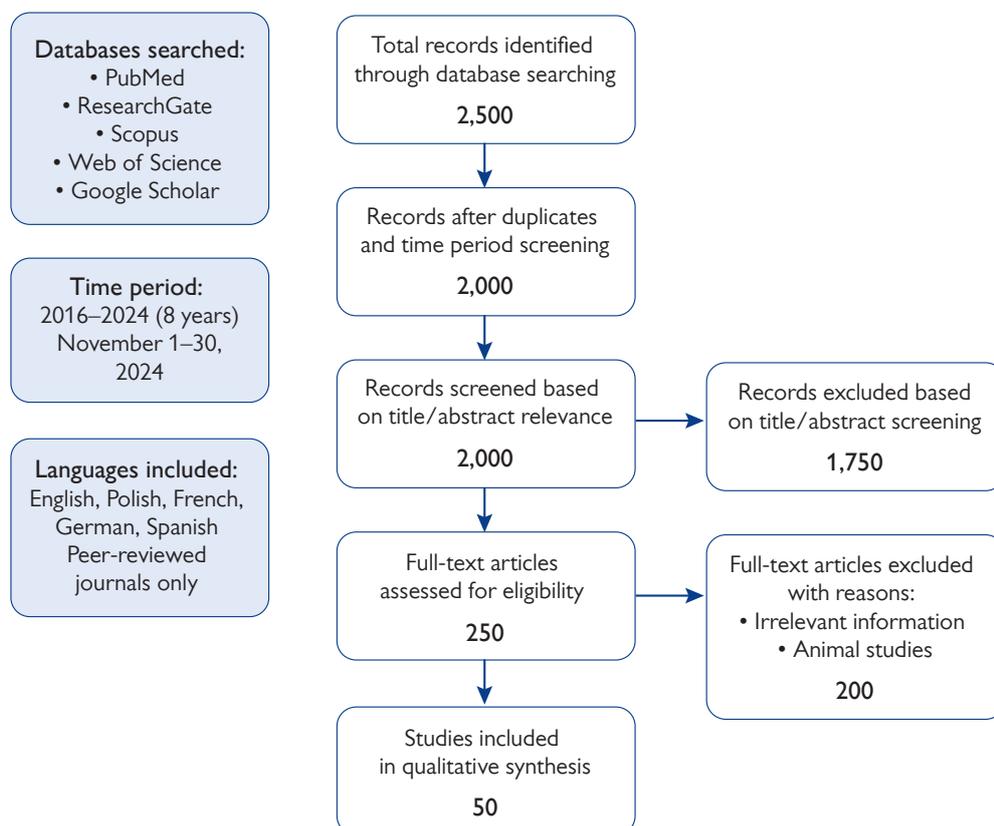

Databases searched:
• PubMed
• ResearchGate
• Scopus
• Web of Science
• Google Scholar

Time period:
2016–2024 (8 years)
November 1–30, 2024

Languages included:
English, Polish, French, German, Spanish
Peer-reviewed journals only

Total records identified through database searching
2,500

Records after duplicates and time period screening
2,000

Records screened based on title/abstract relevance
2,000

Records excluded based on title/abstract screening
1,750

Full-text articles assessed for eligibility
250

Full-text articles excluded with reasons:
• Irrelevant information
• Animal studies
200

Studies included in qualitative synthesis
50

Figure 1: Systematic review selection process.

Table 1: Risk factors for postoperative pain syndrome

Group	Representatives	Assessment scales
Psychological factors	Depressive disorders, anxiety, stress, fear of motor activity due to the risk of pain, sleep disorders, hypochondria, lack of effective psychological support.	Becks Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HADS), Patient Health Questionnaire (PHQ-8), Minnesota Multiphasic Personality Inventory (MMPI).
Factors associated with pain	Severe pain syndrome in the area of the postoperative wound; the presence of a pain syndrome of a different localisation unrelated to the underlying disease; pain sensitisation; neuropathic causes of pain.	Visual Analog Scale (VAS), Western Ontario and McMaster Universities Osteoarthritis Index (VOMAC), Oswestry Disability Index (ODI).
Health-related factors	Concomitant diseases, severe general condition; obesity; fibromyalgia; disability; preoperative opioid use.	Pain Self-Efficiency Questionnaire (PSEQ), Modified Somatic Perception Scale (MSPQ), Oswestry Disability Index (ODI).
Features of social life	Low level of education; lack of adequate social support; loneliness; low economic income.	Client Satisfaction Questionnaire (CSQ).
Demographic factors	Female, young age, African American race.	–

Source: compiled by the authors based on Aliyev and Asik (2023), Pergolizzi et al. (2023), Sydora et al. (2024)

response. Due to the release of inflammatory mediators (cytokines, bradykinin, prostaglandins [PG]), nociceptors – pain receptors – are activated. PG play a major role in the development of pain. They increase the sensitivity of nociceptors to stimuli; enhance the inflammatory response and transmission of pain impulses to the spinal cord and brain by activating cyclooxygenase-2 (COX-2). Bradykinin increases vascular permeability, and interleukins (IL-1, IL-6) stimulate nerve endings. The accumulation of inflammatory exudate causes mechanical pressure on the nerve endings. Platelet activation and the production of free radicals increase the inflammatory process and damage nearby tissues. Due to prolonged irritation of pain receptors, their activation threshold decreases and peripheral sensitisation develops. Then the central nervous system is activated and central sensitisation occurs. This process is characterised by changes in the structures of the brain and spinal cord (SC), which leads to increased sensitivity to pain impulses. Prolonged irritation of peripheral nerves activates N-methyl-D-aspartate (NMDA) receptors in the dorsal horns. This leads to a decrease in the pain threshold and the occurrence of hyperalgesia and/ or allodynia. Glial cells that secrete pro-inflammatory mediators are activated. Dysfunction of inhibitory pathways develops: there is an imbalance between excitatory and inhibitory neurotransmitters; the pain signal increases. In case of damage to nerve fibres, neuropathic pain occurs. Its signs include ectopic activity (the appearance of spontaneously active potentials at the site of damage); demyelination of the nerve (destruction of the myelin sheath, and the appearance of paresthesias). The autonomic nervous system affects the degree of pain expression in the postoperative period. When the sympathetic nerves are hyperactive, the pain increases by stimulating a-adrenergic receptors. An increase in the level of catecholamines leads to an increase in peripheral sensitisation. Reducing parasympathetic effects weakens anti-inflammatory defence mechanisms. Prolonged exposure to stress and/or sadness activates the limbic system, enhancing nociceptive pathway activity, while also inducing hormonal alterations characterised by elevated cortisol and epinephrine levels. With proper treatment of postoperative pain, it disappears at the stage of the acute process. However, with inefficiently selected analgesia, the condition is chronicled. It is characterised by long-term sensitisation; neuroplasticity (prolonged activation of central nervous system [CNS] structures contribute to the appearance of pathological nerve connections); the possibility of genetic predisposition. It is worth noting that if acute pain is a symptom, then chronic pain is already a disease.

In the course of the study, risk factors for postoperative pain syndrome were studied and classified (Table 1).

Psychological factors significantly impact postoperative pain outcomes. Conditions like depression and anxiety alter pain perception and coping abilities, while stress and fear of movement can increase pain sensitivity and delay recovery. Sleep disorders disrupt pain modulation and healing (Mirzakhmetova et al., 2024). Tools like the Beck Depression Inventory and Hospital Anxiety and Depression Scale help assess these factors. Pain-related factors include severe acute postoperative pain, pre-existing pain conditions, and pain sensitization, which can lead to chronic pain.

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Neuropathic pain from nerve damage adds complexity. Assessment tools like the Visual Analog Scale and Oswestry Disability Index quantify these factors. Health-related factors such as comorbid diseases, obesity, fibromyalgia, and preoperative opioid use affect pain outcomes through physiological and pharmacological mechanisms. These can be evaluated using the Pain Self-Efficacy Questionnaire and Modified Somatic Perception Scale. Social life factors, including education level, social support, isolation, and economic status, influence pain perception and recovery. Lower education and inadequate social support can lead to increased stress and poorer pain outcomes. The Client Satisfaction Questionnaire can assess these factors. Demographic factors like female sex, African American race, and young age influence pain susceptibility through biological and social mechanisms. These factors are important for risk stratification and personalized pain management planning. Understanding these multifactorial risk factors highlights the need for a biopsychosocial approach to postoperative pain management. Thus, to reduce the intensity of postoperative pain, it is necessary to provide adequate preoperative anaesthesia and provide high-quality psychological assistance at all stages of treatment.

Characteristic features of postoperative pain syndrome, depending on the type of operation performed

The intensity of postoperative pain syndrome is significantly influenced by the type of operation, the type of anaesthesia, and the time that has elapsed since the surgical intervention. This is confirmed by many researchers, in particular (Aliyev and Asik, 2023; Pergolizzi et al., 2023). Researchers indicated that patients reported the greatest intensity of pain 0–1 days after laparotomy gynecological interventions (Sydora et al., 2024). When using general endotracheal and subarachnoid anaesthesia, patients complained of more severe pain compared to intravenous anaesthesia. The intensity of postoperative pain is directly proportional to the time of the operation. The use of premedication moderately reduces pain. In particular, the use of gabapentin in the preoperative period effectively reduces postoperative pain and the need for opioids.

Caesarean section is accompanied by severe postoperative pain, which negatively affects the psychological state of the mother, slows down recovery and return to daily activity (Arapbaevna et al., 2021; Machado et al., 2024). This condition is often underestimated or treated insufficiently for fear of the negative effects of analgesics on a woman's milk quality. As a result of the conducted research, Zeng et al. (2016) found that prescribing systemic NSAIDs reduced the severity of pain, reduced the need for opioids, and their overall negative effects on the body. Khezri et al. (2018), when comparing the effectiveness of NSAIDs and opioids, found a better analgesic effect when taking NSAIDs. Intravenous administration of dexamethasone, in addition to the analgesic effect, provided an antiemetic effect. The intensity of postoperative pain due to caesarean section significantly depends on the choice of the method of anaesthesia of the operation and surgical technique (Sagindykova et al., 2017). Preoperative administration of a long-acting intrathecal opioid (morphine 100 mcg) is recommended. The least traumatic is the Joel-Cohen incision and non-closing of the peritoneum.

Surgical intervention for artificial replacement of the hip and knee joints is very traumatic; acute pain that occurs after surgery can last up to 2 days without relief. More than 50% of patients in the early postoperative period complain of severe pain; and 30% – moderate (Anger et al., 2021). High-quality anaesthesia after total endoprosthetics provides the possibility of early postoperative mobility, optimal functioning of the limb, and reduces the risk of a number of postoperative complications. For this purpose, the use of multimodal analgesia is recommended. Ge et al. (2023) note that parecoxib as part of multimodal anaesthesia reduces acute postoperative pain in patients with hip and knee prosthetics; reduces cumulative opioid use without increasing the risk of side effects. Dexamethasone is used as part of treatment; this remedy also has an antiemetic effect.

Performing laparoscopic cholecystectomy significantly reduced the severity of postoperative pain compared to laparotomy. However, 20–40% of patients have pain syndrome after surgery, and 4–7% have it permanent. This is explained by a significant sympathetic-adrenal response during this surgical intervention. The study by Cao et al. (2024) found that compared to placebo and paracetamol, preoperative use of nerve blockades, ibuprofen, morphine, and pregabalin reduced pain intensity 2 hours after laparoscopic cholecystectomy. Taking ibuprofen reduced the incidence of postoperative nausea and vomiting compared to placebo, gabapentin, and tramadol. However, Karaaslan et al. (2019) indicated that the mechanism of pain after cholecystectomy contains visceral and sensory components. This explains the lower analgesic effect of NSAIDs compared to pregabalin and gabapentin (since NSAIDs affect only inflammation and, accordingly, somatic pain).

10–40% of patients who underwent surgical treatment on the lumbar spine developed

postoperative pain syndrome with localisation in the back and legs in the postoperative period. Clinical signs included local pain, muscle spasms, numbness, and weakness. Pathogenesis includes a number of interrelated causes. Pathological compression of the spine accounts for up to 30% of the causes of chronic back pain. When the upper articular process is removed, the risk increases to 50%. Researchers Wang et al. (2021) note that inflammation of the spinal cord arachnoid membrane is also an important link in the pathogenesis of pain syndrome. Inflammatory mediators, in particular interleukin-8 and 6, prostaglandin E2 (PGE2) were found in postoperative drainage of patients. PGE2 causes the initial development of pain and subsequent sensitisation. Local pathophysiological processes due to intraoperative removal of the pulpous nucleus contribute to the development of pain syndrome. This is conditioned by the irritating effect of PGE2, cyclooxygenase 2, and nitric oxide on nearby nerve roots when the pulpous nucleus is exposed. Berta et al. (2017) indicate that inflammatory mediators enhance the regulation of N- and T-type calcium channels. This leads to sensitisation and hyperexcitability of dorsal root ganglion (DRG) neurons, which is associated with chronic pain and hypersensitivity. Central sensitisation of neurons in the posterior horn of the spinal cord is the main cause of chronic pain. This process is based on excessive stretching and compression of the dorsal horn, which leads to an increase in the amount of extracellular glutamate. Gliosis worsens chronic low back pain. Alshelh et al. (2022) confirmed that individuals with chronic low back pain exhibit elevated levels of brain translocator protein, a sign of glial activation. When examining spinal cord samples from patients, activation of astrocytes in the posterior horn of the spinal cord was detected.

Using a visually analogue scale (VAS), the patient can rate their pain from 0 (that is, nothing hurts at all) to 10 (the most severe pain). Postoperative pain is usually not limited only to the surgical site, but also includes local pain after performing spinal anaesthesia and injections, after tracheal intubation. The scale of clinical assessment of pain contains points regarding the change in pain, the effectiveness of its control, and the effect on sleep (Neumann-Podczaska et al., 2019; Tobis et al., 2020). Not all patients can correctly describe their symptoms, so appropriate assessment tools have been developed for them. For example, for people with dementia, pain in advanced dementia will be valid; for severe cognitive impairments – Dolopus-2, in intensive care – the Behavioural Pain Scale (BPS) (Aliyev and Asik, 2023; Pergolizzi et al., 2023). Information about the nature and origin of

pain (visceral, neuropathic, nociceptive) is important for effective treatment. The pain syndrome will differ based on the context of surgical therapy, whether it is scheduled or urgent. A differentiated approach to prescribing painkillers means selecting a drug based on the mechanism of pain occurrence, its characteristics, and individual characteristics of the patient. The main requirements for treatment are the need for the fastest and most complete anaesthesia; the use of drugs with proven effectiveness. The choice of adequate methods of analgesia should begin at the stage of planning the operation. For this purpose, preventive multimodal anaesthesia is used. This tactic involves blocking the pain sensation centre before surgery occurs, in order to suppress the sensitisation of the pain centre. Multimodal anaesthesia covers the use of drugs that act on different parts of the anatomical pain pathways (Figure 2). Wang et al. (2020) noted that the use of multimodal analgesia to reduce postoperative pain in liver donation reduced the need for opioids by 50%. It is advisable to combine drugs with different mechanisms of action, but synergistic effects to reduce the dosage and, accordingly, reduce the frequency of side effects. The combination of effective preoperative, intraoperative, and postoperative anaesthesia reduces the intensity of pain, the risk of postoperative bleeding, and reduces the need for anaesthetics. Multimodal anaesthesia is based on nonsteroidal anti-inflammatory drugs as the main group with a strong analgesic effect (Abushanab and Al-Badriyeh, 2021; Dieu et al., 2021; Jiang and Ye, 2022).

In the study by Chang et al. (2021) described the efficacy of NSAIDs as the main analgesics administered before, during, and after surgery. They inhibit cyclooxygenase-1 and cyclooxygenase-2 (COX-1 and COX-2), which regulates prostaglandin synthesis. The release of pro-inflammatory cytokines (interleukin-1
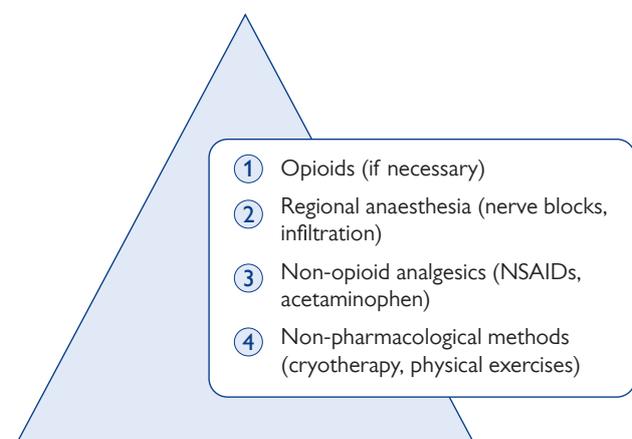

Figure 2: Components of multimodal anaesthesia.
Source: compiled by the authors based on Hobelmann and Huhn (2021), Wu et al. (2023).

1 Opioids (if necessary)
2 Regional anaesthesia (nerve blocks, infiltration)
3 Non-opioid analgesics (NSAIDs, acetaminophen)
4 Non-pharmacological methods (cryotherapy, physical exercises)

and tumour necrosis factor-alpha) slows down, white blood cell migration, phagocyte activation, and postoperative oedema decrease. Accordingly, due to the suppression of the inflammatory response, the activity and sensitisation of peripheral nociceptors is inhibited; the duration and intensity of pain decreases. Penetrating the blood-brain barrier, NSAIDs block COX-2 activity in the central nervous system, suppressing central sensitisation. It should be emphasised that central sensitisation underlies the development of chronic pain syndrome. That is, this group of drugs is a pathogenetic treatment for pain. The advantages are the absence of influence on consciousness, haemodynamics and respiratory rate, normalisation of reactions of the autonomic nervous system. Small and Laycock (2020) investigated that NSAID administration reduces the need for morphine in the postoperative period. However, this group of drugs has a number of side effects. Non-selective NSAIDs block COX-1 and inhibit thromboxane A2 (regulates platelet clotting). All NSAIDs are contraindicated in patients after coronary artery bypass grafting. But, if necessary, after cardiac operations, preference should be given to non-selective NSAIDs prescribed in the short term. With prolonged use, they inhibit the protective secretion of mucus bicarbonate in the gastric mucosa. Nonsteroidal anti-inflammatory drugs reduce glomerular pressure by narrowing their afferent arterioles; reduce creatinine clearance by 16 ml/min on the first day after surgery compared to placebo (Table 2). At the same time, there are no statistically significant differences in serum creatinine levels, urinary excretion, and cases of postoperative renal failure. Therefore, in individuals with normal renal function, controlled dosed administration of NSAIDs does not cause renal failure. This is also confirmed in a study by Chang et al. (2021), which states that the degree of nephrotoxicity directly depends on the level of kidney damage. NSAIDs affect the degree of healing of bones, tendons, and ligaments (in particular, selective COX-2 inhibitors).

Ketorolac is a highly effective analgesic; it quickly reduces peripheral sensitisation. The disadvantage is the high risk of adverse reactions from the gastrointestinal tract, in particular bleeding, so the drug should be prescribed for a short time together with proton pump inhibitors. Patients who were prescribed low doses of ketorolac (>30 mg) had a significantly lower risk of side effects. Compared to other analgesics (opioids, acetaminophen), taking ketorolac did not increase the risk of postoperative bleeding and, in particular, bleeding after knee replacement surgery.

Diclofenac is characterised by high anti-inflammatory activity; effectively reduces postoperative pain and inflammation (Latka et al., 2021, 2023). For inflammation caused by trauma, it reduces swelling and the recovery period of damaged joints, ligaments, tendons, and muscles.

The main advantage of ibuprofen, compared to representatives of its group of drugs, is a relatively low risk of side effects. Cao et al. (2024) noted that preoperative intravenous administration of ibuprofen reduces stress and inflammatory response by inhibiting the release of catecholamines, cortisol, and cytokines as a result of adult cholecystectomy. It was also reported that the use of this drug is safe in patients undergoing soft tissue surgery; it was noted that short-term administration of ibuprofen did not cause severe side effects, including gastrointestinal bleeding. However, it is worth noting that when ibuprofen was prescribed for a period of 2 weeks before hip surgery, the volume of perioperative blood loss increased. Therefore, NSAIDs are not recommended before surgery.

Celecoxib inhibits COX-2 synthesis. Due to its mechanism of action, it is a highly effective drug for controlling postoperative pain in patients at risk of gastrointestinal bleeding. The study described that administration of celecoxib after arthroscopic restoration of the rotator cuff increased the frequency of repeated ruptures compared to ibuprofen and tramadol (Chang et al., 2021). It is contraindicated in persons with disorders of the cardiovascular system.

Table 2: Classification of nonsteroidal anti-inflammatory drugs

Characteristics	Nonsteroidal anti-inflammatory drugs		
By selectivity	Non-selective COX-1 and COX-2 inhibitors (ibuprofen, diclofenac, ketorolac).	Selective COX-2 inhibitors (celecoxib).	Highly selective COX-2 inhibitors (lumiracoxib).
By duration of action	Short-acting (up to 6 hours): ibuprofen, ketorolac, diclofenac.	Medium duration (6–12 hours): naproxen, meloxicam.	Long-acting (more than 12 hours): piroxicam.
By pharmacological action	Drugs with mainly anti-inflammatory effects (diclofenac, indomethacin).	Drugs with mainly analgesic effects (ketorolac, aspirin).	Drugs with mainly antipyretic effects (ibuprofen, naproxen).

Source: compiled by the authors based on McQuay et al. (2016), Gasbjerg et al. (2022), Malik et al. (2024)

Inhibits water reabsorption in collecting tubes, preventing the action of antidiuretic hormone.

Parecoxib is an injectable selective COX-2 inhibitor. The mechanism of action is to reduce central sensitivity and inflammation of peripheral nociceptors. Preoperative administration of this drug significantly reduced postoperative cumulative opioid use and did not increase the risk of adverse reactions. It does not cause prolongation of bleeding time and does not disrupt the normal functioning of the gastric mucosa. It is an effective tool for orthopedic, obstetric, and general surgical interventions. When replacing joints, it performs a protective function, improves the immune response, and reduces the frequency of postoperative chills and delirium. When performing open liver resection, parecoxib was administered intravenously 40 mg half an hour before induction, and 40 mg every 12 hours for the first 2 days after surgery. Patients had lower VAS rates at rest after 2, 6, 12, and 24 hours and a lower need for fentanyl. Gau et al. (2023) described that administration of lidocaine and parecoxib after thyroidectomy provided adequate anaesthesia with minimal side effects (Hardman et al., 2021; Han et al., 2024).

Descetoprofen is structurally the active S(+)-enantiomer of ketoprofen. Due to this, there is no risk of side effects associated with the action of the R-enantiomer of ketoprofen. The incidence of gastrointestinal bleeding, nausea, and vomiting is significantly lower compared to representatives of the same pharmacological group. Inhibits cyclooxygenase, inhibits the conversion of arachidonic acid to cyclic ENDOPEROXIDES PGG2 and PGH2, which form prostaglandins PGE1, PGE2, PGF2a, PGD2, and prostacyclin PGI2 and thromboxanes (Tha2 and Thxv2). McQuay et al. (2016) indicated that the concomitant treatment of oral dexketoprofen 25 mg and tramadol 75 mg was more efficacious than the separate administration of both agents, particularly in the context of surgical intervention for total hip replacement.

Paracetamol belongs to analgesics-antipyretics, but is often prescribed in addition to NSAIDS as a component of multimodal anaesthesia. The mechanism of action is to block cyclooxygenase at the central level, affecting the pain centres and thermoregulation. With multimodal anaesthesia, this drug provides an opioid-sparing effect. McQuay et al. (2016) described a statistically significant reduction in morphine use with additional paracetamol administration. The intravenous injection of paracetamol correlates with a diminished occurrence of postoperative nausea and vomiting, attributed to enhanced pain management. Therefore, the use of paracetamol reduces pain and reduces dosages of other painkillers.

Glucocorticosteroids are synthetic or natural analogues of hormones that are produced by the adrenal cortex under physiological conditions. They are characterised by a pronounced anti-inflammatory, immunosuppressive, and metabolic effect. This group of pharmaceutical products is classified according to a number of characteristics (Table 3). The anti-inflammatory effect is due to inhibition of pro-inflammatory cytokines, induction of anti-inflammatory cytokines, decreased prostaglandin synthesis, and excitability of nerve cells (Mao et al., 2016; Silva et al., 2023; Han et al., 2024).

Methylprednisolone, compared to prednisone, has a more pronounced anti-inflammatory effect and retains less water and sodium. Reduces the number of immunoactive cells at the site of inflammation; reduces vasodilation; stabilises lysosomal membranes; inhibits phagocytosis; reduces prostaglandin production. Preoperative administration of methylprednisolone 125 mg reduced the severity of postoperative pain in the first 24 hours (Gupta et al.,

Table 3: Classification of glucocorticosteroids

Indicator	Glucocorticosteroids		
By origin	Natural (hydrocortisone).	Synthetic (prednisone, dexamethasone, betamethasone).	–
By activity spectrum	Glucocorticoid activity (predominant effect on the metabolism and conversion of proteins, fats, carbohydrates): prednisone.	Mineralocorticoid activity (predominant effect on water-electrolyte balance): hydrocortisone.	–
By action	Topical (topical use for skin and eye lesions): hydrocortisone.	Systemic (if necessary, effects on the entire body): prednisone, dexamethasone.	–
By duration of action	Short (up to 12 hours): hydrocortisone, cortisone.	Average (12–36 hours): prednisone.	Prolonged (>36 hours): dexamethasone.

Source: compiled by the authors based on Ross et al. (2021), Maloney et al. (2022), Huang et al. (2023)

2020; Arslan and Ünal Çevik, 2022; Ranjbari and Alimohammadi, 2024).

Prednisone is characterised by anti-inflammatory, immunosuppressive, and anti-allergic effects. The immunosuppressive effect is associated with inhibition of cytokine excretion from lymphocytes and macrophages (Shetty et al., 2020; Coşarcan et al., 2022; Vilai et al., 2023). The anti-inflammatory effect involves the suppression and release of inflammatory mediators by immunocompetent cells, reducing capillary permeability, and stabilising the membranes of mast cells. Anger et al. (2021) noted that prescribing 10 mg of prednisone perioperatively reduced VAS pain scores by 2 points, reduced the need for opioid prescribing in the first 24 hours, and improved acute recovery rates.

Dexamethasone has a pronounced anti-inflammatory, anti-allergic, and antipruritic effect (Lisiecka, 2024a). It affects all stages of the inflammatory process. It reduces the permeability of blood vessels, slows down the migration of white blood cells and phagocytes, the release of kinins, and the development of antibodies. Studies of intra-articular injections of glucocorticoids after total knee replacement revealed higher efficacy of the corticosteroid group compared to non-corticosteroids. This treatment reduced the severity of pain at rest and during movement. Two oral doses of dexamethasone as an adjunct to multimodal pain management with paracetamol, ibuprofen, and local infiltration analgesia reduced morphine intake and the severity of pain after knee replacement (Kerimbayev et al., 2022). Caution should be exercised when prescribing dexamethasone to people with diabetes mellitus, because their side effect is an increase in blood glucose.

Thus, the main advantages of NSAIDs in postoperative pain syndrome are effective suppression of inflammation, rapid reduction of pain, reduction of the need for opioid analgesics, and reduction of the duration of the rehabilitation period. Glucocorticoids are an effective component of multimodal anaesthesia, which, in addition to analgesic effect, have an antiemetic effect (Lisiecka, 2024b). The use of these groups of drugs in the preoperative and postoperative stages significantly reduced the postoperative need for opioid analgesics. It is necessary to consider the concomitant diseases of patients and their age, because nonsteroidal anti-inflammatory drugs and glucocorticoids have cardiotoxic, nephrotoxic, haepatotoxic effects. It is necessary to correctly choose the drug in accordance with the surgical treatment performed. Prevention includes the use of multimodal anaesthesia at the preoperative, intraoperative, and postoperative stages; selection of minimally invasive surgical access to reduce the area of tissue injury; psychological support and support of patients at all stages of treatment; appointment of rehabilitation interventions in the acute period.

In the postoperative period, NSAIDs and glucocorticosteroids are widely used to reduce pain and inflammation. However, their long-term use can lead to a number of serious complications. For example, NSAIDs can cause impaired renal function, which is manifested by decreased glomerular filtration rate and risk of acute renal failure. In addition, these drugs are often associated with gastrointestinal problems such as ulcers and bleeding due to their ability to reduce the production of protective mucus in the stomach. Cardiovascular risks are also increased with long-term use of NSAIDs, including an increased likelihood of myocardial infarction and stroke, especially in patients with a predisposition to cardiovascular disease. Glucocorticosteroids, in turn, can cause metabolic changes such as hyperglycaemia, weight gain and osteoporosis, which is particularly relevant in their long-term use. These drugs also contribute to increased blood pressure and increased risk of infections due to their immunosuppressive action. Thus, despite their efficacy in the short term, both NSAIDs and glucocorticosteroids require cautious use and careful monitoring during long-term use to minimise the risk of complications and ensure patient safety.

Conclusion

The effectiveness of nonsteroidal anti-inflammatory drugs and glucocorticosteroids in postoperative pain management has been conclusively established through extensive research across various surgical procedures. NSAIDs demonstrate superior analgesic efficacy by targeting cyclooxygenase pathways, thereby reducing prostaglandin synthesis and inflammatory responses while simultaneously addressing both peripheral and central sensitization mechanisms. Glucocorticosteroids complement this approach through their potent anti-inflammatory and antiemetic properties, contributing to comprehensive symptom control in the postoperative period.

The integration of these pharmaceutical agents within multimodal anaesthesia protocols represents the current gold standard for postoperative pain management. This approach capitalizes on synergistic effects while minimizing individual drug dosages and associated adverse reactions. The evidence consistently supports the opioid-sparing effects of NSAID and glucocorticosteroid combinations, which is particularly significant given the ongoing concerns regarding opioid dependence and tolerance.

However, the clinical application of these agents requires careful consideration of patient-specific factors and potential contraindications. The documented risks of gastrointestinal, cardiovascular, and renal complications with NSAIDs, alongside the metabolic and immunosuppressive effects of glucocorticosteroids, necessitate judicious prescribing practices and ongoing monitoring. The selection of specific agents within these drug classes should be tailored to individual patient profiles, surgical procedures, and risk-benefit assessments.

The implementation of preventive multimodal anaesthesia strategies, beginning in the preoperative period and extending through the entire perioperative continuum, represents a paradigm shift toward proactive rather than reactive pain management. This approach, combined with appropriate psychological support and minimally invasive surgical techniques where feasible, offers the greatest potential for preventing the transition from acute to chronic postoperative pain.

The limitations of the presented study are a small number of papers describing the independent analgesic effect of NSAIDs/glucocorticoids in the postoperative period, because they mainly investigate the analgesic effect of these drugs as part of multimodal anaesthesia. Future research should continue to refine optimal dosing regimens, timing of administration, and drug combinations while exploring novel therapeutic targets and delivery methods. The development of personalized pain management protocols based on individual risk stratification and genetic factors may further enhance outcomes while minimizing adverse effects.

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Evaluation of Glasgow Microenvironment Score in Colorectal Carcinoma and Its Association with Prognostic Markers

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Abstract: Colorectal carcinoma (CRC) ranks among the most prevalent cancers worldwide, contributing significantly to cancer-related mortality. Despite advancements in understanding CRC's pathophysiology, traditional staging systems like tumour, node, and metastasis (TNM) lack comprehensive prognostic indicators, particularly regarding tumour microenvironment and host-related factors. The Glasgow Microenvironment Score (GMS) integrates inflammatory cell infiltration and stromal percentage, offering a potentially more comprehensive prognostic tool. This study aims to evaluate GMS in CRC and its correlation with established clinicopathological prognostic markers and pathological tumour, node, and metastasis (pTNM) staging. A retrospective study involving 68 CRC patients who underwent curative surgery between January 2022 and March 2024. Haematoxylin and eosin-stained sections were assessed for inflammatory infiltration (Klintrup-Mäkinen score) and tumour stromal percentage, forming the GMS. Statistical analyses evaluated associations between GMS and clinicopathological markers, including lymphovascular invasion (LVI), perineural invasion (PNI), nodal status, and histological grading. The study found significant correlations between GMS and poor prognostic markers. High GMS was associated with increased LVI, PNI, and nodal involvement. GMS showed significant associations with LVI (p<0.0003), PNI (p<0.026), and nodal involvement (p<0.002). GMS serves as a robust prognostic indicator in CRC, correlating with key pathological features that influence patient outcomes. This scoring system could enhance traditional prognostic models, aiding in better stratification of CRC patients for therapeutic interventions.

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Introduction

Colorectal carcinoma (CRC) is one of the most prevalent cancers globally, ranking third in terms of frequency and being the third and fourth leading cause of cancer-related deaths in women and men, respectively (Siegel et al., 2014). The gut microbiota plays a crucial role in maintaining health, and disruptions in this balance, known as dysbiosis, can contribute to cancer development through chronic inflammation.

CRC has a high rate of morbidity and mortality unless detected early. Multiple clinicopathological parameters influence its progression and prognosis, including histological grade, stage, lymphovascular invasion (LVI), perineural invasion (PNI), and nodal metastasis. These elements are critical in assessing tumour biology and its aggressiveness (Poornakala and Prema, 2019).

Although there has been significant progress in understanding the pathophysiological mechanisms behind colorectal cancer (CRC), the tumour, node, and metastasis (TNM) staging system, which forms the foundation of clinical management, does not fully capture the factors influencing prognosis. One limitation of the TNM system is that it does not consider host-related factors, such as systemic inflammation or the local inflammatory response to the tumour (Dolan et al., 2017). A scoring method known as the Glasgow Microenvironment Score (GMS) was developed to address this. GMS evaluates the tumour microenvironment using haematoxylin and eosin (H and E)-stained slides, combining the assessment of inflammatory cell infiltration at the tumour's invasive margin (Klintrup-Mäkinen [KM] grade) with the tumour stromal percentage (TSP), which measures the amount of connective tissue in the tumour (Park et al., 2014, 2015; Nayak et al., 2018; Poornakala and Prema, 2019). A higher TSP is linked to a worse prognosis, including decreased overall survival (Freeman et al., 2013). The presence of peritumoral lymphocytes possesses anti-tumour activity and has also shown increased survival following immunotherapy (Roxburgh and McMillan, 2012). By combining these two critical parameters, the GMS provides enhanced prognostic value. The present study aims to evaluate the GMS score, followed by its association with known poor prognostic clinic-
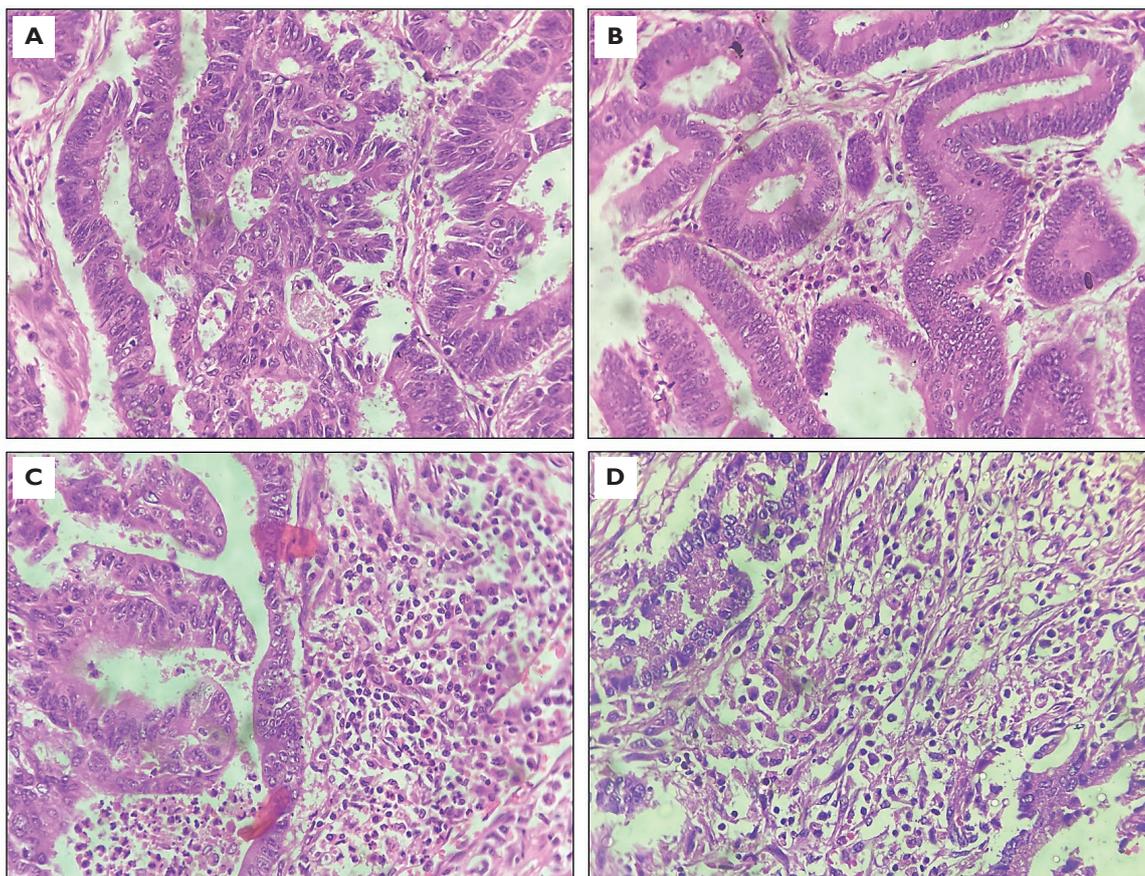

Figure 1: KM (Klintrup-Mäkinen) inflammation score. (A) KM score 0 showing no increase in lymphocytes. (B) KM score 1 shows only mild increase in lymphocytes. (C) KM score 2 shows band-like infiltrate of lymphocytes. (D) KM score 3 shows prominent lymphocytic infiltration along with tumour nest destruction (400×).

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pathological markers and pathological tumour, node, and metastasis (pTNM) staging.

Material and Methods

This was a retrospective study which included a total of 68 patients who underwent curative surgery for colorectal cancer between January 2022 to March 2024 in a tertiary care hospital. All the patients who received neo-adjuvant chemotherapy were excluded from the study. H and E-stained sections from the tumour were examined, and the scanner (4X lens) invasive tumour front or hot spot was identified. Lymphocytes surrounding the tumour cells were identified in the hot spot region and the invasive front of the tumour cells at the scanner (4X). The lymphocytes were counted as per the KM inflammation score at five high-power field. The score is assigned as follows: 0 = no increase in lymphocytes; 1 = only mild increase in lymphocytes; 2 = band-like infiltrate at invasive margin along with destruction of tumour nests; 3 = prominent destruction of tumour islands by inflammatory cells (Klintrup et al., 2005). Based on the above scoring, patients were graded as low (score 0/1) and high (2/3) (Figure 1). Using the same hot spot region stroma percentage is assessed in comparison to the tumour islands at 10× magnification. Stroma > 50% is considered to be high, and a stroma < 50% is classified as low, as done in previous studies (Figure 2). The GMS was calculated by combining these two parameters (Table 1).

The histological sections from the tumour were also assessed for lymphovascular invasion (LVI), perineural invasion (PNI), nodal involvement, extranodal extensions, serosal involvement, extent of tumour in the bowel wall and subsequently the pTNM staging.

Table 1: GMS classification

GMS score	KM score	Tumour stroma (%)
0	high (2 or 3)	–
1	low (0 or 1)	low (<50%)
2	low (0 or 1)	high (>50%)

GMS – Glasgow Microenvironment Score; KM – Klintrup-Mäkinen

Statistical analysis

The presentation of the categorical variables was done in the form of numbers and percentages (%). On the other hand, the quantitative data were presented as the means ± SD (standard deviation) and as median with 25th and 75th percentiles (interquartile range). The following statistical tests were applied to the results.

The association of the variables, which were qualitative in nature, were analysed using the chi-square test. If any cell had an expected value of less than 5, then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, v. 25.0.

For statistical significance, a p-value of less than 0.05 was considered statistically significant.

Result

The study population consisted of 68 individuals, comprising 38 males (55.88%) and 30 females (44.12%). Regarding the T-stage classification, 28 cases (41.18%) were T2, 26 cases (38.24%) were T3, 8 cases (11.76%) were T4, and 6 cases (8.82%) were T1. Nodal involvement was observed in 28 cases (41.18%), whereas node-negative cases were 40 (58.82%). The metastatic evaluation was not available due to the retrospective design.
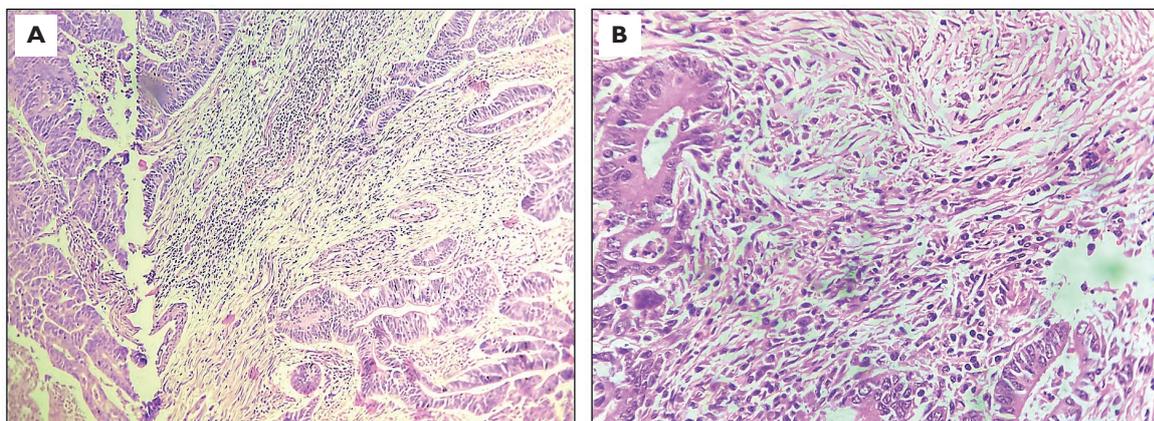

Figure 2: Assessment of stromal percentage. (A) <50% desmoplastic stroma. (B) >50% desmoplastic stroma (100×, 200×).

Table 2: Patient characteristics distribution

Patient characteristics		N (%)	Mean ± SD	Median (25th–75th percentile)	Range
Gender	Female	30 (44.12%)	–	–	–
	Male	38 (55.88%)			
T-stage	T1	6 (8.82%)	–	–	–
	T2	28 (41.18%)			
	T3	26 (38.23%)			
	T4	8 (11.76%)			
Nodal status	Negative	40 (58.82%)	–	–	–
	Positive	28 (41.18%)			
LVI	Negative	40 (58.82%)	–	–	–
	Positive	28 (41.18%)			
PNI	Negative	50 (73.53%)	–	–	–
	Positive	18 (26.47%)			
KM score	0	10 (14.70%)	–	–	–
	1	30 (44.11%)			
	2	24 (35.29%)			
	3	4 (05.88%)			
Tumour stroma ratio	Low	36 (52.94%)	–	–	–
	High	32 (47.05%)			
ENE	Negative	52 (76.47%)	–	–	–
	Positive	16 (23.53%)			
GMS score	0	28 (41.18%)	–	–	–
	1	10 (14.70%)			
	2	30 (44.11%)			
Histological grade	Well differentiated	22 (32.35%)	–	–	–
	Moderately differentiated	26 (38.24%)			
	Poorly differentiated	20 (29.41%)			
Age (years)		–	46.09 ± 13.3	45.5 (39.25–53.5)	15–75

SD – standard deviation; LVI – lymphovascular invasion; PNI – perineural invasion; KM – Klintrup-Mäkinen; ENE – extranodal extension; GMS – Glasgow Microenvironment Score

For pathological characteristics, LVI was negative in 40 cases (58.82%) and positive in 28 cases (41.18%). PNI was negative in 50 cases (73.53%) and positive in 18 cases (26.47%). KM scoring was performed as 0 in 10 cases (14.7%), 1 in 30 cases (44.11%), 2 in 24 cases (35.29%), and 3 in 4 cases (5.88%). High stroma was identified in 32 cases (47.06%), whereas low stroma was observed in 36 cases (52.94%). Extranodal extension (ENE) was absent in 52 cases (76.47%) and present in 16 cases (23.53%).

GMS system showed 30 cases (44.11%) had a score of 2, 10 cases (14.70%) had a score of 1, and 28 cases (41.18%) had a score of 0. Histological grading revealed that 26 cases (38.24%) were moderately differentiated, 22 cases (32.35%) were well differentiated, and 20 cases (29.41%) were poorly differentiated.

The mean age of the study subjects was 46.09 ± 13.3 years, with a median age of 45.5 years (interquartile range 39.25–53.5). Detailed information is provided in Table 2.

Statistical significance of GMS was also done for the clinic-pathological parameters, in which we observed nodal involvement, LVI, PNI, ENE, and histological grading to be statistically significant ($p<0.002$, <0.0003, <0.026, <0.045, <0.0001, respectively). A significantly higher number of patients with GMS 0 had an absence of LVI (100%), absence of PNI (100%), absence of ENE (100%), absence of nodal involvement (78.57%), and well-differentiated histological grade (71.42%) (Table 3).

Table 3: Association of patient characteristics with combined score

Patient characteristics		0 (n=28)	1 (n=10)	2 (n=30)	Total	p-value
Gender	Female	16 (57.14%)	2 (20.00%)	12 (40.00%)	30 (44.12%)	0.1760*
	Male	12 (42.85%)	8 (80.00%)	18 (60.00%)	38 (55.88%)	
Nodal status	Positive	22 (78.57%)	2 (20.00%)	4 (13.33%)	28 (41.18%)	0.0020*
	Negative	6 (21.42%)	8 (80.00%)	26 (86.66%)	40 (58.82%)	
T-stage	Low stage (T1–T2)	16 (57.14%)	4 (40.00%)	14 (46.66%)	34 (50.00%)	0.6340*
	High stage (T3–T4)	12 (42.85%)	6 (60.00%)	16 (53.33%)	34 (50.00%)	
LVI	Negative	28 (100%)	4 (40.00%)	8 (26.66%)	40 (58.82%)	0.0003*
	Positive	0 (0%)	6 (60.00%)	22 (73.33%)	28 (41.18%)	
PNI	Negative	28 (100%)	6 (60.00%)	16 (53.33%)	50 (73.53%)	0.0260*
	Positive	0 (0%)	4 (40.00%)	14 (46.66%)	18 (26.47%)	
ENE	Negative	28 (100%)	6 (60.00%)	18 (60.00%)	52 (76.47%)	0.0450*
	Positive	0 (0%)	4 (40.00%)	12 (40.00%)	16 (23.53%)	
Histological grade	Well differentiated	20 (71.42%)	0 (0.00%)	2 (06.66%)	22 (32.35%)	<0.0001*
	Moderately differentiated	6 (21.42%)	6 (60.00%)	14 (46.66%)	26 (38.24%)	
	Poorly differentiated	2 (07.14)	4 (40.00%)	14 (46.66%)	20 (29.41%)	
Age (years)		55.45 ± 11.33	44.95 ± 9.72	25.75 ± 8.85	46.09 ± 13.33	<0.0001**

*Fischer exact test; **One-way ANOVA; LVI – lymphovascular invasion; PNI – perineural invasion; ENE – extranodal extension

Discussion

The prognostic outcome in CRC depends on several factors, including the size of tumour, nodal status, LVI, PNI, histological grade, and molecular subtypes. The presence of peritumoral lymphocytes and tumour stroma ratio have been studied individually in the recent past. Both parameters, to some extent, showed their utility in determining prognosis and overall survival. Huijbers et al. (2013) in a trial observed that high stroma in CRC is a stage-independent marker. In their VICTOR trial, they found decreased survival in patients having higher stroma percentages. Interestingly, these patients did not show any benefit from 5-fluorouracil-based adjuvant chemotherapy.

The GMS provides a combined assessment of these parameters and can be used as an independent prognostic marker once validated in a larger cohort. Jakubowska et al. (2017) in their study observed that a weak or absent inflammatory cell infiltrate at the invasive front of the tumour is significantly associated with shorter disease-free survival.

Ahuja et al. (2023) also studied the utility of GMS in CRC patients, and they concluded that a lower GMS is a better prognostic marker. In the present study, we found 78.57% of the patients with low GMS had negative nodes, and a statistically significant association was observed with lymphovascular invasion. The observations were in line with Ahuja et al. (2023), who also found a positive correlation between LVI and GMS.

Out of 68 patients low tumour stroma ratio (TSR) was seen in 52.94% whereas high KM was seen in 53% of the cases. Ahuja et al. (2023) reported 54.05% of cases with low stroma and 45.95% of patients with high KM. Another study was conducted by Richards et al. (2012) in CRC patients to assess the peritumoral inflammatory infiltrate response on patient outcome. They observed that 48% of patients with low-grade inflammatory infiltrate showed poor survival when compared with the high-grade inflammatory infiltrate patients.

In our study, we also observed a statistically significant association of GMS with PNI and nodal involvement. The findings were concordant with Ahuja et al. (2023), in which they exhibited a positive correlation with PNI and lymph node metastasis (p=0.01, p=0.003). Alexander et al. (2021) studied the interaction of adjuvant therapy and GMS in their study, and they observed a significant interaction between chemotherapy type (p=0.01) and GMS. They also observed that disease-free survival was strengthened in patients receiving FOLFOX with a 5-year disease free survival (DFS) for GMS 0, 1 and 2 of 88, 62 and 54%, respectively.

GMS assessment is a simple, cost-effective method that can be incorporated into routine histopathological reporting. The role of tumour microenvironment has

been established in many solid tumours, however, combining different tumour microenvironment parameters further increases the efficacy when compared to individual entities. Our observations emphasize that GMS can be used as another prognostic tool while evaluating colorectal carcinoma patients. One of the limitations in our study was the lack of follow-up of our patients and their association with survival outcomes.

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PD-L1 Expression in Gliomas: A Potential Immunotherapeutic Target in High-grade Tumours

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Abstract: Gliomas are the most common primary tumours of the central nervous system, with glioblastoma (grade 4 glioma) being the most malignant form. Despite standard therapy, patient survival remains poor. Immune checkpoint blockade targeting the PD-1/PD-L1 axis has shown promise in other cancers, but its role in gliomas remains under investigation. This study evaluates PD-L1 expression in gliomas and its correlation with tumour grade. A total of 50 histologically confirmed glioma cases were studied. Tumours were graded according to WHO 2021 CNS classification, and immunohistochemistry (IHC) was performed using antibodies for IDH, ATRX, TP53, Ki67, and PD-L1. PD-L1 expression was scored using an immunoreactivity scale, and its association with tumour grade was analysed using ordinal regression. A p-value < 0.05 was considered statistically significant. Among the 50 gliomas, the majority were astrocytoma, IDH-mutant (54%) followed by glioblastoma, IDH-wild type (26%). Most tumours were grade 4 (44%), grade 2 (34%), or grade 3 (18%). PD-L1 expression was detected exclusively in grade 4 tumours, with 6 of 22 (27.27%) cases showing positive expression. No expression was noted in grade 1–3 tumours. The association between PD-L1 expression and tumour grade was statistically significant (p=0.007). PD-L1 expression is limited to high-grade (grade 4) gliomas, suggesting a role in immune evasion. These findings support the potential utility of PD-L1 as a biomarker to identify glioma patients who may benefit from anti-PD-1/PD-L1 immunotherapy.

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Introduction

Gliomas are the most common primary tumour of the central nervous system, comprising over 40–50% of primary brain tumours (Smith et al., 2022). In the United States (between 2012 and 2016), the overall incidence rate of all primary brain and other central nervous system (CNS) tumours was 23.41 per 100,000 of which 30.2% were malignant and 69.8% were non-malignant. Gliomas accounted for about 80.8% of the malignant tumours and about 25.5% of all the CNS tumours with the majority of them being formed by the glioblastoma (57.3%) (Ostrom et al., 2019).

Gliomas form a heterogeneous group of neoplasms with multiple histologic types and malignancy grades. Most gliomas, the diffuse gliomas, show extensive infiltration within the brain parenchyma. Diffuse gliomas were traditionally typed as astrocytic, oligodendroglial, or rare mixed oligodendroglial-astrocytic of World Health Organization (WHO) grade II (low grade), III (anaplastic), or IV (glioblastoma). Since many decades the histologic diagnosis formed a useful basis for the assessment of prognosis and therapeutic management of the glial tumours. But recently, molecular biomarkers have gained importance in providing both ancillary and defining diagnostic information. WHO 2021 classification, therefore, incorporates numerous molecular changes with clinicopathologic utility that are important for the most accurate classification of CNS tumours (Perry and Wesseling, 2016; Louis et al., 2021).

In the WHO 2021 classification, the adult-type diffuse gliomas, includes only three types: astrocytoma, IDH-mutant; oligodendroglioma, IDH-mutant and 1p/19q-codeleted; and glioblastoma, IDH-wild type.

All IDH-mutant diffuse astrocytic tumours are considered a single type (astrocytoma, IDH-mutant) and are then graded as CNS WHO grade 2, 3 and 4. For the diagnosis of glioblastoma, IDH-wild type, the fifth edition of WHO incorporates three genetic parameters – TERT promoter mutation, EGFR amplification or +7/–10 chromosome copy-number alteration (Brat et al., 2021).

An immunohistochemistry panel of IDH, ATRX, TP53 and Ki67 is used to confirm the diagnosis of gliomas and grade the tumour.

The conventional therapy for gliomas includes surgical intervention, chemotherapy and radiotherapy for low-grade gliomas, its median survival time in about 85% patients is nearly 5 years starting from the diagnosis, which reflects that the overall survival of glioma patients remains dismal. The most frequent but unfortunately the most malignant of all gliomas is the grade 4 glioma – glioblastoma (Wen and DeAngelis, 2007; Pouratian and Schiff, 2010; Schiff, 2011). It constitutes a universally lethal diagnosis and is characterized by highly aggressive behaviour and a high recurrence rate. Despite the conventional standard of care (surgery, chemotherapy and radiotherapy), glioblastoma is associated with a median survival of only 14.6 months and less than 10% of the treated patients are alive after 5 years of diagnosis (Stupp et al., 2009). In contrast to many other tumours, molecularly targeted therapies for glioblastoma (GBM) produced very limited advances in prolonging life expectancies of the patients, which can be attributable to the poor penetration of the blood brain barrier by therapeutic agents or the rapidly developing drug resistance (Schlageter et al., 1999; Ramirez et al., 2013).

Thus, there is a clinical need for new treatment strategies. In the past two decades, our understanding of pathology and the molecular details of cancer has improved. Basic research has provided scientific support towards immunotherapy as a potentially promising treatment approach (Preusser et al., 2011).

Programmed cell death-1(PD-1)/program death ligand 1(PD-L1) pathway is a classic immune checkpoint of a promising therapeutic approach. Programmed death ligand 1 (PD-L1) expression is upregulated in human tumour cell lines, which suggests that it has a close relationship with tumour growth and development. Several studies have focused on PD-L1 expression in many malignancies such as cancers of the breast, pancreas, lung, renal and stomach (Flies and Chen, 2007; Zou and Chen, 2008). However, the expression of PD-L1 on glioma cells has been documented recently (Berghoff et al., 2015; Heiland et al., 2017).

Immunotherapy targeting the PD-L1/PD-1 pathway has made a series of remarkable breakthroughs in the clinical treatment of a variety of cancers, showing response rates of 20–40%. Nivolumab, Pemrolizumab (anti-PD1 antibodies), Atezolizumab, Avelumab (anti-PD-L1 antibodies) are approved drugs in the treatment of melanoma, non-small cell lung carcinoma and some breast cancers (Gandini et al., 2016). This has led to the generation of increasing interest in the use of this therapy in the treatment of gliomas as well, particularly glioblastomas.

In our study, we have used PD-L1 monoclonal antibody immunohistochemically to study its expression in gliomas and also to compare its expression with varying grades of the tumour. If these gliomas are shown to express PD-L1, it will open avenues for cancer immunotherapy in these patients.

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Material and Methods

This cohort study included 50 histologically confirmed cases of gliomas. The haematoxylin and eosin sections were evaluated for the histological type and grade of the tumour. Immunohistochemistry for IDH, ATRX, TP53 and Ki67 was performed using their respective antibodies to confirm the diagnosis and grade the tumour.

Immunohistochemistry (IHC) for PD-L1 was performed and expression was assessed according to the immunoreactivity score (Table 1 [Di Bonito et al., 2016]). The association of this score with tumour grade was determined.

Data analysis was done using licensed SPSS software version 21.0. A p-value of < 0.05 was considered statistically significant. Ordinal regression analysis was used to evaluate the correlation of immunohistochemical marker (PD-L1) with the different grades of glioma.

Ethical approval

The study was done in accordance with the Helsinki Declaration. The study was approved by Institutional Ethics committee (IEC/VMMC/SJH/Thesis/2020-11/CC-241). Written informed consent was taken from all patients included in the study.

Results

50 histologically confirmed cases of gliomas were included in the study. In the majority (27 [54%]) of patients, diagnosis was astrocytoma, IDH-mutant type, followed by glioblastoma, IDH-wild type (13 [26%]) and oligodendroglioma, not otherwise specified (NOS) (8 [16%]). Pilocytic astrocytoma was diagnosed only in 2 out of 50 patients (4%). In 22 (44%) of patients, the tumour was grade 4, followed by grade 2 (17 [34%]) and grade 3 (9 [18%]).

Table 1: Scoring system for interpretation of immunohistochemistry for PD-L1

Extent of cell stained	Intensity of staining	Final score
0 (absence of membranous immunoreactivity or mild/moderate cytoplasmic positivity)	negative	0
1 (incomplete but moderate/intense membranous positivity, with/without cytoplasmic positivity, in ≥ 10% of tumour cells)	weak positive	1+
2 (complete and moderate/intense membranous positivity, with/without cytoplasmic positivity, in ≥ 10% of tumour)	strong positive	2++

PD-L1 score was assigned to every case based on the following immunoreactivity score
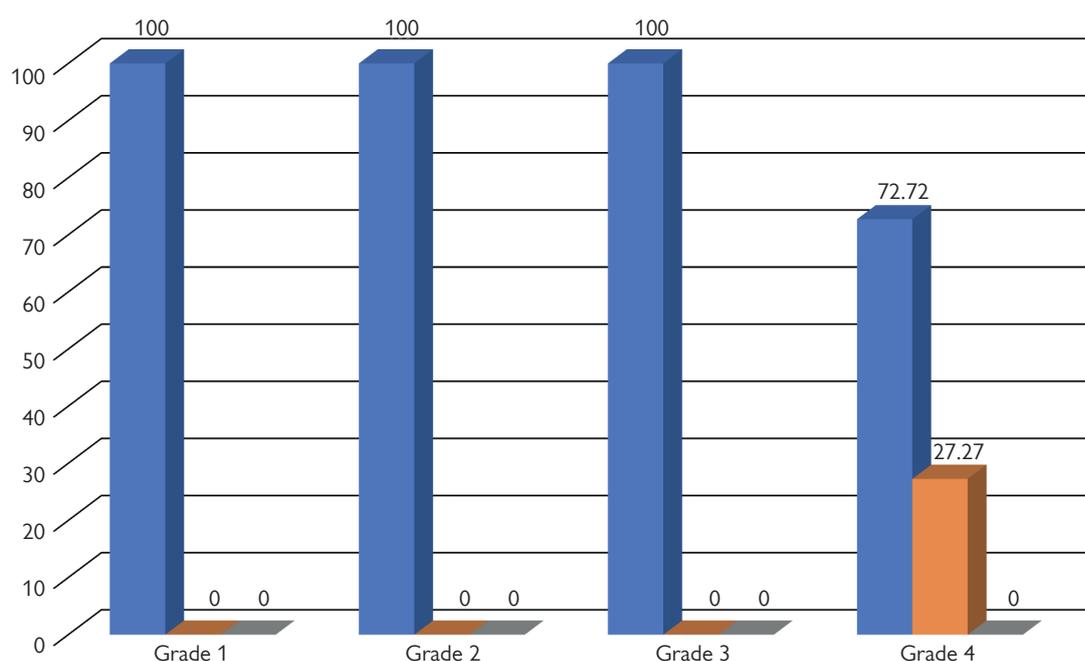

Figure 1: Expression of PD-L1 in the tumour in different grades.

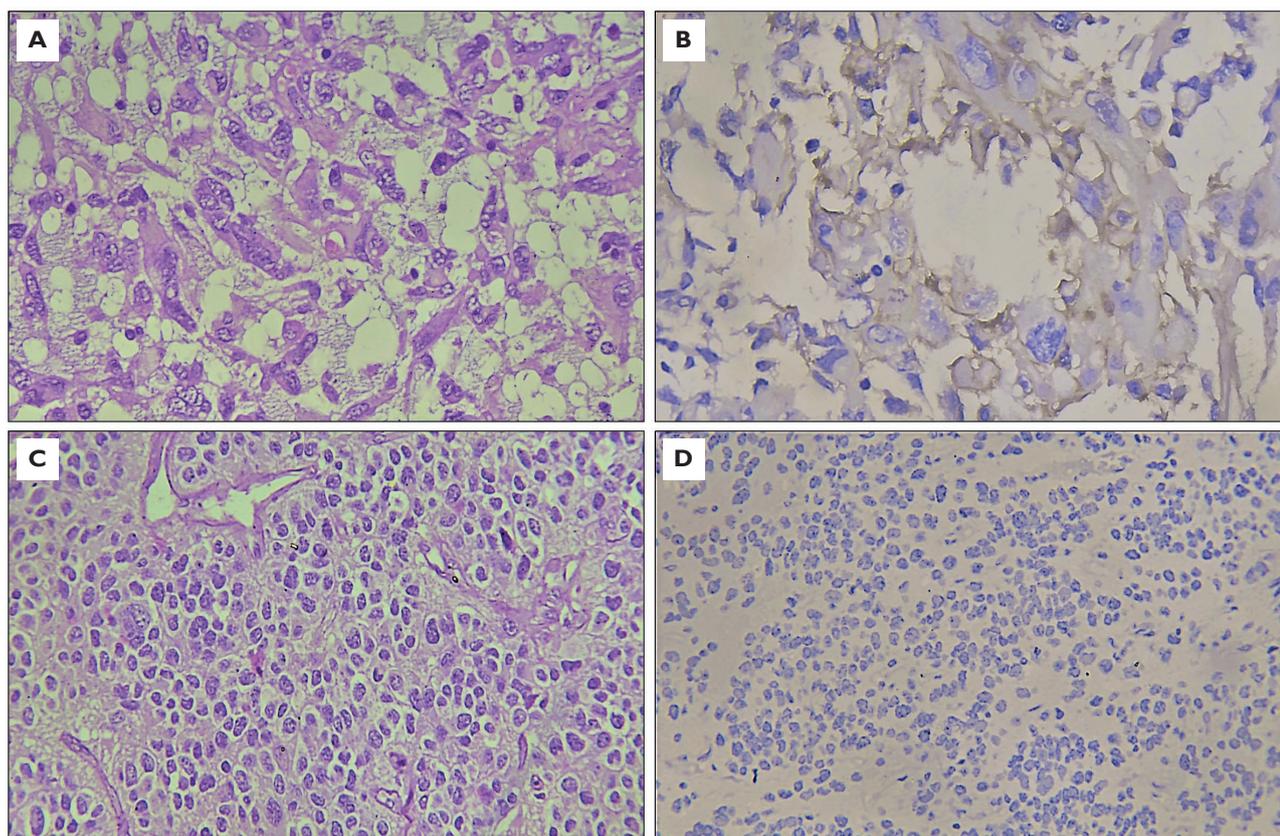PD-L1 Expression in Gliomas: A Potential Immunotherapeutic Target in High-grade Tumours

Figure 2: (A) Haematoxylin and eosin (H and E) stained section of grade 4 glioma (glioblastoma) in 100× magnification. (B) Immunohistochemistry (IHC) – positive expression of PD-L1 in tumour cells seen in a case of grade 4 glioma (glioblastoma) in 400× magnification. Membranous positivity of PD-L1 is seen in the tumour cells. (C) H and E stained section of grade 4 glioma (astrocytoma, IDH mutant) in 100× magnification. (D) IHC – negative expression of PD-L1 in tumour cells seen in a case of grade 4 glioma (astrocytoma, IDH mutant) in 100× magnification.

Table 2: Expression of PD-L1 in the tumour in different grades

WHO tumour grade	Score 0	Score 1	Score 2	Statistical significance (p-value)
Grade 1	02 (100%)	0 (0%)	0 (0%)	
Grade 2	17 (100%)	0 (0%)	0 (0%)	
Grade 3	9 (100%)	0 (0%)	0 (0%)	0.007*
Grade 4	16 (72.72%)	6 (27.27%)	0 (0%)	
Total	44	06	0	

*Fisher's exact test; WHO – World Health Organization

The tumour was grade 1 only in 2 out of 50 patients (4%). The mean value of age (years) of study subjects was 42.62 years with a standard deviation of 12.52. The male-to-female ratio was 2.1:1.

PD-L1 was not expressed in grade 1, grade 2 and grade 3 tumours. However, the expression of PD-L1 was observed in 6 (27.27%) of 22 cases of grade 4 tumour. P-value was found to be 0.007, which was statistically significant (p<0.05) (Figures 1 and 2, Table 2).

Discussion

The present study was designed to assess the immunohistochemical expression of PD-L1 in gliomas and to correlate its expression with the grade of the tumour. We aimed to find out if there was any association between the expression of PD-L1 and the grades of gliomas.

Among the 50 cases of gliomas included in our study, 6 cases (12%) expressed PD-L1. It was shown

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to have a statistically insignificant association (p-value = 0.007) between the expression of PD-L1 and the grade of the tumour (Table 2). However, the expression rate of PD-L1 in our study was much lower than the expression rates found in other studies. Shukla et al. (2021) in their study to analyse the expression of PD-L1 in adult diffuse gliomas in WHO grade II, III, and IV glioma found that PD-L1 was expressed in 33.3% (n=10/30) cases (20% [n=2]) grade II tumours, 30% [n=3] grade III tumours, and 50% [n=5] GBMs]. The p-value was found to be 0.013. Another study done by Zeng et al. (2016) found that the tumour cell PD-L1 expression rate was 51.1% (117/229) in all patients with gliomas. The PD-L1 expression rates were 49.2, 53.7 and 68.8% for grade II, III and IV samples, respectively. The difference in the expression rates of PD-L1 between the various studies could be attributed to the differences in the monoclonal antibody used and the scoring and interpretation of results. In the present study, none of the grade 1, grade 2 and grade 3 tumours expressed PD-L1. PD-L1 was found to be expressed in only 6 cases out of the 22 cases (27.27%) of grade 4 glioma (glioblastoma) (score 1). The expression of PD-L1 with the tumour grade was found to be statistically significant (p-value = 0.007). This result was found to be comparable to the previously conducted studies, which had also shown a statistically significant association between PD-L1 expression and the grades of glioma, with the grade 4 gliomas expressing higher scores of PD-L1 as compared to grade 2 and grade 3 gliomas. Our study suggested that the expression of PD-L1 is increased in the higher grade of the tumour (grade 4) in comparison to the lower grades of the tumour (grade 1, 2 and grade 3). Furthermore, in the study by Kumar et al. (2025) the majority of grade I and II gliomas showed no or low PD-L1 expression, whereas grade III and IV gliomas demonstrated increasing levels of moderate to strong expression. A statistically significant association was observed between PD-L1 expression and glioma grade (p=0.019), with higher expression correlating with higher tumour grade. They also reported a significant association between PD-L1 expression and tumour grade, with higher expression observed in grade III and IV gliomas compared to grade I and II tumours. Their findings further support the correlation between PD-L1 expression and increasing glioma aggressiveness.

The current study highlights the fact that the expression of PD-L1 increases with the grade of the tumour. A statistically significant association was observed between the expression of PD-L1 and the grade of the tumour. The expression of PD-L1 by the tumour could be used to identify those cases of glioma which could benefit from targeted chemotherapy using anti-PD-1/anti-PD-L1 monoclonal antibodies.

Conclusion

In our study, PD-L1 was expressed only by the high grade gliomas (grade 4).

This suggests that it could be one of the possible mechanisms of tumour evasion from host immunity. PD-L1 testing may be useful in identifying glioma patients who could benefit from targeted therapy.

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Changes in Cerebral Hemodynamics in Patients with Hypertension and Post-Covid

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Abstract: The study results are based on the data of examination of 73 patients with controlled hypertension of the II stage. The 1st study group consisted of patients with hypertension and history of Covid-19 infection (36 patients), the 2nd group – patients with hypertension was the control group. All patients were examined using ultrasound duplex scanning of head and neck vessels. The state of cerebrovascular reserve was studied according to the method of Lelyuk – the morphofunctional state of the middle cerebral artery in hypo- and hyperventilation. The vasomotor reactivity index was calculated. Statistical analysis methods were in accordance with generally accepted international standards. Thickening of the intimal media complex of the carotid arteries during ultrasound scanning of head and neck vessels was observed in 73 (100%) patients (intimal media complex more than 0.9 mm) in the area of maximum visual thickening. The vasomotor reactivity index in patients of the 1st study group was 35.4 (11.0; 49.2), in patients of the 2nd group – 46.7 (26.8; 76.4), which is a statistically significant difference, p=0.002, including the distribution of mean values and their descriptions in terms of the median and interquartile range Me (25%; 75%). Thus, patients with controlled hypertension and the history of Covid-19 infection were shown to have impaired cerebral blood flow, which was manifested by a decrease in the vasomotor reactivity index. When examining the main arteries of the head and neck, the vasomotor reactivity index should be determined to assess the state of cerebral hemodynamics and develop treatment measures.

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Introduction

The respiratory system is known to be at the forefront of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Regardless of its tropism to lung tissue, the SARS-CoV-2 virus attacks various organs and systems of the human body, including cardiovascular, neurocognitive, neurological, gastrointestinal, hepatic, metabolic and mental and resolve multi-organ dysfunction (McMichael et al., 2020). Concomitant illnesses will increase the risk of Covid-19 and increase mortality (Verity et al., 2020). Based on retrospective studies, approximately 50% of patients with Covid-19 have more than one comorbidity, and with severe infection, the number of such patients increases to 72% (Ruan et al., 2020). Database analysis of 5,700 patients with Covid-19 (mid-century 63 years), hospitalized in up to 12 hospitals in New York, showing that 88% of patients had one or more comorbidities: arterial hypertension (AH) increased 56.6% of patients have ischemic heart disease – in 11.1%, obesity – in 41.7% and diabetes – in 33.8% (Richardson et al., 2020). Among patients who died from Covid-19, comorbidity that worsened the prognosis was significantly more common (1.9 times). The presence of 2 concomitant diseases increased the risk of death by 9.5 times for patients with one disease. Viral infection can destabilize the cardiovascular system and increase the occurrence of new cardiovascular complications, which significantly increases the risk of death in Covid-19. In SARS-CoV-2-infected patients with concomitant cardiovascular diseases, mortality increased by 2.4 times (Guan et al., 2020a). Cardiovascular tissues or cells expressing angiotensin-converting enzyme 2 receptors (ACE-2 receptors) are potentially at risk of infection by SARS-CoV-2 (Zhang et al., 2020). In patients at high risk for developing cardiovascular disease (CVD), loss of ACE-2 due to receptor internalization caused by SARS-CoV-2, will worsen CVD. A decrease in the expression of ACE-2 receptors in the vascular wall contributes to the development of endothelial dysfunction and inflammation, especially with concomitant diseases such as atherosclerosis and diabetes (South et al., 2020). Factors associated with increased disease severity include comorbidities such as hypertension, diabetes, and coronary artery disease. Hypertension is one of the most important factors of poor prognosis in patients with Covid-19. The global prevalence of hypertension in 2019 among adults 30–79 years of age was 34% among men and 32% among women. Despite the high prevalence of hypertension, the level of awareness of existing hypertension, effective treatment and control of blood pressure was low in 2018–2019, and has worsened further during the Covid-19 pandemic (Guan et al., 2020b; Inciardi et al., 2020; Wang et al., 2020a; Wu and McGoogan, 2020; Wu et al., 2020; Zhou et al., 2020).

It is important to take into account possible functional and pathological disorders that are observed in patients who have had Covid:

- functional disorders of vital systems of the body can persist for a long time after the elimination of an acute infectious-inflammatory process and the resolution of viral pneumonia;
- functional and pathological disorders of varying severity can occur in patients with any course of Covid-19;
- patients with severe/extremely severe forms of Covid-19 experience the most pronounced negative changes due to the consequences of intensive care (intensive care aftereffects syndrome – ICU syndrome) and stay in the intensive care unit (ICU);
- consequences of staying in the ICU: forced immobilization (bed rest), polyneuromyopathy and polyneuropathy of critical illness, myopathy, post-intubation dysphagia, stiffness and contractures of the joints;
- with general muscle weakness, loss of muscle mass and muscle strength (peripheral muscle dysfunction), physical inactivity and decreased physical performance;
- weakness of the respiratory muscles, primarily muscle concussion, with the possible development of atrophy of the diaphragm, which leads to its dysfunction;
- dysfunction of the cardiovascular system, instability of hemodynamic parameters;
- risk of thrombosis and thromboembolism;
- insufficient control of cardiovascular risk factors;
- nutritional deficiency, violation of a nutritious and balanced diet;
- sleep and consciousness disorders (other cognitive disorders);
- psycho-emotional disorders (depression, anxiety disorders, which make up about 60% of all mental disorders) (Bubnova et al., 2020).

It is precisely because of the extensive damage to the body's systems that recommended instrumental and laboratory tests have long been known, such as:
- electrocardiography (ECG), according to indications – daily ECG monitoring;
- echocardiography (EchoCG);
- assessment of external respiration function using spirography;
- assessment of the SpO_2 level of blood oxygen saturation – pulse oximetry;

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- computed tomography (CT) scan data over time;
- clinical blood test with determination of the rate of erythrocyte subsidence, assessment of the number of platelets;
- coagulogram (international normalized ratio, activated partial thromboplastin time) and D-dimer level;
- biochemical blood test with determination of blood potassium and sodium levels, transaminases, total protein, albumin (if possible), C-reactive protein, glucose, creatinine with calculation of glomerular filtration rate using the CKD-EPI formula;
- general urine analysis and assessment of daily protein loss according to indications;
- to assess hypoxia tolerance, it is recommended to use Genchi and Stange functional tests;
- to assess exercise tolerance, a six-minute walk test with assessment of blood saturation dynamics during the test;
- cardiopulmonary loading testing on a treadmill or bicycle ergometer if necessary, preferably also with an assessment of the dynamics of blood saturation.

But the proposed methods for studying post-Covid patients are not sufficient to control the possible above-listed functional and pathological conditions that can develop after suffering from the corona virus. Namely, it is not enough to control the risks of damage from the cardiovascular system; as noted above, hypertension is the most significant risk factor for a negative prognosis. Therefore, in our study, we additionally conducted an ultrasound examination of the cerebrovascular reserve during transcranial Doppler sonography with the determination of the vasomotor reactivity index (VMRI) in patients with hypertension and post-Covid (Sonkaya et al., 2021).

The aim of the study
To determine the level of the brain's cerebral reserve for studying its state in patients with controlled hypertension and post-Covid.

Material and Methods

The study design was defined as an open, prospective, monocentric clinical trial in parallel groups of patients. The study results are based on the data of a comprehensive examination of 73 patients with controlled hypertension aged from 30 to 70 years (average age – 52.5 [8.4] years). The hypertension duration in the examined patients ranged from 5 to 23 years; the median was 10 (9–12) years. In 36 (49.3%) of the examined patients with hypertension had a history of Covid-19 infection, they constituted the 1st study group, the remaining

37 (50.7%) patients constituted the 2nd group – the control group. In the groups, patients were comparable in terms of gender, age, duration of hypertension and concomitant pathology. All the examinees underwent general clinical, instrumental, and laboratory diagnostics to verify the hypertension diagnosis and identify concomitant pathology.
A general clinical examination and instrumental and laboratory diagnostic methods were performed according to standard protocols for cardiac patients. Additional research methods were also performed: daily blood pressure monitoring, home and office ambulatory blood pressure monitoring, electrocardiography, sonography of the main arteries of the head and neck using ultrasound duplex scanning of the vessels of the head and neck. Using ultrasound duplex scanning of the vessels of the head and neck on the HDI-7 (Philips) device with a linear sensor with a frequency of 10–12 MHz and a sector sensor with a frequency of 2–4 MHz on the right and left anterior surfaces of the neck with the patient lying on his back, with the head turned 45° in the opposite direction from the artery being examined. The common, external carotid (ECA), internal carotid (ICA) and vertebral arteries were visualized on both sides using the standard technique. In all visualized arteries, including the ECA and ICA, the diameter of the specified vessels and such blood flow parameters as maximum systolic peak (Vps), maximum diastolic (Ved) blood flow velocity, resistance index (Ri), pulsatility index (Pi), peripheral resistance coefficient (systolic-diastolic ratio – S/D), as well as vascular elasticity were determined. In each study, the thickness of the intimal media complex (IMC) of the carotid arteries was determined (normal up to 0.9 mm) in the area of maximum visual thickening, and the quantitative and qualitative state of the ICA was assessed. The state of the cerebrovascular reserve (CVR) was studied by the morphofunctional state of the middle cerebral artery (MCA) in hypo- and hyperventilation tests according to the method of Lelyuk. First, a test was performed with holding the breath on exhalation for 20 s, after 5 min a test was performed with hyperventilation for 20 s with repeated registration of linear blood flow velocities (LBFV) in the middle cerebral artery. The vasomotor reactivity index was calculated using the formula:

$$VMRI = ([V_{apnea} - V_{hyper}]/V_0) \times 100\%$$

where: V_{apnea} is the average velocity of blood flow after holding the breath, V_0 is the initial average r velocity of blood flow, V_{hyper} is the average velocity.

The patients/participants provided written informed consent to participate in this study. The study was voluntary and anonymous, and only general data

was collected. Confidentiality of information was protected by depersonalizing participant identifiers. Statistical analysis, including the distribution of the average values and their description depending on the nature of the distribution (determined by the Shapiro-Wilk test) in the form of an arithmetic mean (M) and a 95% confidence interval (95% CI) with a normal distribution and the median and interquartile range Me (25%; 75%) – with asymmetric; calculation of relative values; assessment of the reliability of differences in the number of variables using the Mann-Whitney criterion; rank correlation analysis using the Spearman correlation coefficient (rs), using the additional STATISTICA program (version 6.1), serial number – AGAR 909E415822FA.

Results

The analysis of the obtained data showed that patients of both groups before inclusion in the study had hypertension of the with predominant damage to the heart, as a target organ, in the form of hypertrophy of the left ventricle (LV) of the heart, in 1 group there were 33 such patients (91.7%), in 2 group – 35 (94.6%). Patients with reduced LV ejection fraction (<50%) did not participate in the study. Also, the exclusion criteria were: myocarditis, as a complication

after Covid-19 and impaired repolarization in the myocardium of the left ventricle.

Patients with mild or moderate severity of Covid-19 and those who recovered more than 4 months ago took part in the study. The structure of concomitant pathology was as follows: coronary heart disease (class I–II functional class according to the Canadian classification) – 28.8% (21 patients), dyslipidemia – 79.5% (58 patients), chronic heart failure (class I and II according to NYHA) – 15.1% (11 patients), 71.2% (52 patients) were overweight or obese; chronic pyelonephritis – in 23.3% (17 patients), varicose disease of the lower extremities – in 5.5% (4 patients), manifestations of osteoarthritis of large and/or small joints – in 31.5% (23 patients), included in the study. Patients were given comprehensive information in a personal interview about the goals and points of action of drug treatment, the need for constant continuous intake of drugs. All patients were recommended a diet with a reduced content of animal fats, with an increased amount of fruits, vegetables, cereals, nuts and legumes, preference should be given to sea fish, dairy products with a low fat content or without them. Continuation of taking anticoagulants, vitamins, immunocorrectors prescribed earlier was not a reason for exclusion. Patients received complex treatment in accordance with approved national protocols for the underlying disease, personalized

Table 1: Echocardiographic data and sonographic characteristics of the middle cerebral artery and cerebrovascular reserve

Indicator (95% CI)	1st study group hypertension with Covid-19 (n=36)	2nd study group hypertension without Covid-19 (n=37)	Differences between groups (p)
LV hypertrophy, % patients	91.7	94.6	p>0.05
LVEF, %	67.0 (60.3–73.7)	69.0 (60.2–77.8)	p>0.05
Creatinine, µmol/l	102.5 (89.0–116.0)	97.8 (85.5–110.1)	p>0.05
LV wall thickness during diastole, cm	1.2 (0.6–1.8)	1.2 (0.8–1.6)	p>0.05
IMC, mm	1.1 (1.0–1.2)	1.0 (0.9–1.1)	p>0.05
Vps, cm/s	71.9 (66.4–77.4)	69.4 (59.6–79.2)	p>0.05
Ved, cm/s	30.2 (27.5–32.9)	29.5 (25.4–33.6)	p>0.05
Vmean, cm/s	48.4 (44.1–52.7)	47.6 (40.5–54.7)	p>0.05
Vps/Ved	2.4 (2.3–2.5)	2.3 (2.1–2.5)	p>0.05
TAMV, cm/s	46.3 (42.2–50.4)	48.6 (43.1–54.1)	p>0.05
Ri	0.5 (0.5–0.5)	0.6 (0.6–0.6)	p>0.05
Pi	0.8 (0.8–0.8)	0.8 (0.7–0.9)	p>0.05
VMRI, Me (25%; 75%)	35.4 (11.0; 49.2)	46.7 (26.8; 76.4)	p<0.05

Echocardiographic characteristics: LV – left ventricle; LVEF – left ventricle ejection fraction; sonographic characteristics: IMC – intima-media complex; Vps – peak systolic velocity; Ved – end diastolic velocity; Vmean – time-averaged mean velocity; Vps/Ved – systolic-diastolic velocity ratio; TAMV – time-averaged maximum velocity; Ri – resistance index; Pi – pulsatility index; VMRI – vasomotor reactivity index; Me – median and interquartile range; CI – confidence interval

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therapy according to indications: antihypertensive drugs (ACE inhibitors/sartans, slow Ca-channel blockers, diuretics), anti-ischemic drugs; lipid-lowering therapy; antiplatelet agents; therapy for comorbid pathology) (McEvoy et al., 2024). Patients received antihypertensive treatment prescribed earlier, which did not require correction due to adequate blood pressure control.

There was no significant difference between the groups in the LV ejection fraction (LVEF) (1 group – 67.0% [95% CI 60.3–73.7%], 2 group – 69.0 [95% CI 60.2–77.8%] and in the LV wall thickness during diastole: 1 group – 1.2 cm [95% CI 0.6–1.8 cm], 2 group – 1.2 cm [95% CI 0.8–1.6 cm]), which can be seen in Table 1.

The obtained data indicate that the blood flow velocity indices in the MCA in all groups of patients with hypertension were statistically comparable (p>0.05). Extracranial and transcranial main vessels in patients did not have significant changes in blood flow and autoregulation disorders.

Thickening of the intimal media complex of the carotid arteries during ultrasound duplex scanning of the vessels of the head and neck was observed in 73 (100%) patients (intimal media complex more than 0.9 mm) in the area of maximum visual thickening. The vasomotor reactivity index in patients of the 1st study group was 35.4 (11.0; 49.2), in patients of the 2nd group – 46.7 (26.8; 76.4), which is a statistically significant difference, p=0.002 (Figure 1).

Patients with a history of Covid-19 infection had a direct correlation between creatinine levels and LVEF (rs=0.80, p<0.001), which was not observed in patients without Covid-19. Of interest is the inverse correlation between creatinine levels and VMRI (rs=–0.60, p<0.001), where a reduction in creatinine
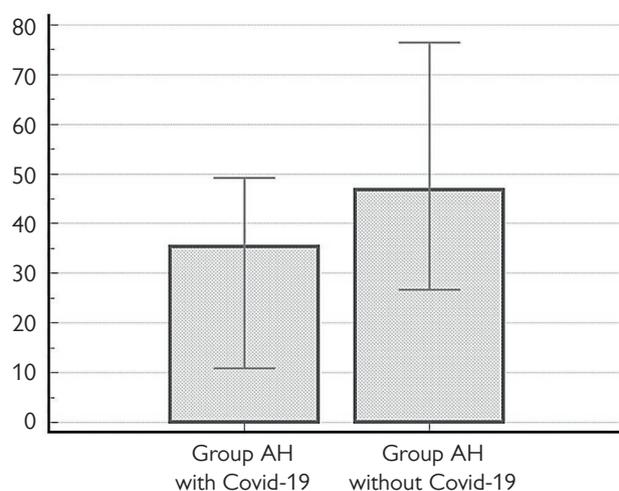
levels may be justified by the use of glucocorticoids in the treatment of Covid-19 (Wang et al., 2020b). This requires further study and scientific explanation in the future.

Discussion

One of the ways of implementing a negative impact on cerebral hemodynamics may be atherosclerotic and hypertensive vascular damage and deterioration of cerebral blood flow. That is why a study of the main arteries of the head and neck was conducted to determine the cerebrovascular reserve. The data obtained indicate that the blood flow velocity indicators in the middle cerebral artery in all groups of patients with arterial hypertension and hypertension with post-Covid were statistically comparable (p>0.05). Extracranial and intracranial main vessels did not have significant changes in cerebral blood flow and disturbances in autoregulation processes and significant structural differences. It is significant that all 73 (100%) patients with stage II hypertension had thickening of the intimamedia complex. Thickening of the IMC was independent of the presence or absence of Covid infection in the past. In the two study groups it was slightly higher than 0.9 mm, with an average of 1.0 to 1.1 mm. The results of the study revealed a significant (p<0.002) decrease in the VMRI in patients with hypertension and post-Covid (35.4 [11.0; 49.2]) as in patients with hypertension without post-Covid 46.7 ([26.8; 76.4]). The latter indicates a close relationship between the value of the VMRI and the presence of post-Covid in patients with hypertension; in patients with hypertension and post-Covid, there is a violation of cerebral blood flow, which was manifested in a decrease in the VMRI.

We understand the limitations of this study, associated with the small number of participants in the study groups, as well as the formation of special groups by age, gender, comorbid pathology and physiological characteristics, as well as treatment results. However, the results obtained allowed us to focus on the importance of studying the cerebrovascular reserve in patients with hypertension and post-Covid as an option for timely diagnosis and personalization of treatment along with adequate antihypertensive therapy.

Figure 1: The vasomotor reactivity index (VMRI) in patients, median and interquartile range Me (25%; 75%). AH – arterial hypertension.

Conclusion

Thus, hypertension and a history of COVID-19 disrupt adaptive changes in the cerebral vessels, which leads to increased stress on the vessel walls and impaired

protection of arterioles, capillaries and venules from potentially destructive fluctuations in blood pressure. An increase in basal cerebral blood velocity and a decrease in vasomotor reactivity rates in patients with Covid-19 can be considered as an indicator of dysfunction of cerebral hemodynamics in the central nervous system and this can be evaluated as a result of endothelial dysfunction. Autoregulation is a critical driver of both the structural and functional changes in cerebral blood flow caused by hypertension, but the pathogenic mechanisms remain poorly defined for the vital cerebrovascular regulatory mechanisms. The patients with controlled hypertension and a history of Covid-19 infection have impaired cerebral blood flow, which is manifested by a decrease in the VMRI. When examining the main arteries of the head and neck, the VMRI should be determined to assess the state of cerebral hemodynamics and develop treatment measures. Despite the disastrous consequences of hypertension and post-Covid disease, impaired cerebral blood flow, the state of the vascular bed and associated changes in brain tissue in patients with hypertension in clinical manifestations, the impact on quality of life, prognosis for vascular complications have not been sufficiently studied.

With regard to the diagnosis of early signs of brain damage and post-Covid in hypertension, as well as monitoring the effectiveness of medical rehabilitation, it is advisable to introduce the use of functional breathing tests with the determination of cerebrovascular reserve according to the vasomotor reactivity index in a sonographic study.

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Influence of Copper Tongue Scraper and Toothbrush on Morning Halitosis in Dentistry Students: A Brief Clinical Study

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Abstract: The objective was to evaluate the influence of two tongue cleaning methods (copper tongue scraper and toothbrush) on morning halitosis in dental students. Thirteen dental students were included. After training, the first participant took the halimeter home and used it for 6 days. On the first three days, halitosis was measured immediately after the participant woke up in the morning. The night before each of these first three days, before going to sleep, the participant cleaned their mouth with dental floss and a soft-bristled toothbrush. The individual's same soft-bristled toothbrush was also used to brush his tongue. Only one halitosis measurement was taken per day and the value was recorded each day (toothbrush group). On the fourth, fifth and sixth day, the same process was carried out, but the night before measuring halitosis, a copper tongue scraper was used to clean the participants' tongue. Only one halitosis measurement was taken per day and the value was recorded each day (tongue scraper group). Subsequently, for each participant, the highest halitosis value of the first three days (toothbrush group) was chosen, as well as the highest halitosis value of the last three days (tongue scraper group). The Wilcoxon test was used to compare the two groups (P<0.05). The halitosis value (median) in the toothbrush group was significantly higher than that in the tongue scraper group. Only the tongue scraper group showed a clinically acceptable halitosis value (imperceptible odour). Therefore, the copper tongue scraper is more recommended for cleaning the tongue.

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Introduction

In most patients, the origin of bad breath (also known as "halitosis") is related to the oral cavity due to materia alba, caries, tongue coating, dry mouth, poorly adapted dentures, or periodontal or systemic diseases (Pedrazzi et al., 2004; Acar et al., 2019; Souza et al., 2023). Among these factors, tongue coating is the main source of bad odour (Bosy et al., 1994; Seemann et al., 2001; Van Tornout et al., 2013), being formed by fungi, viruses, protozoa, bacteria, blood metabolites, desquamated epithelial cells, different kinds of food remnants, and leukocytes coming from periodontal pockets (Casemiro et al., 2008; Van Tornout et al., 2013; Jiang et al., 2023). The anaerobic bacteria present in the tongue coating are also responsible for the release of volatile sulfur compounds (VSCs), which cause bad breath, due to the degradation of organic substrates (Scully and Greenman, 2000; Seemann et al., 2001; Casemiro et al., 2008; Van Tornout et al., 2013; Jiang et al., 2023). Therefore, it is very important to remove tongue coating daily, as it is a normal phenomenon that occurs in individuals with and without periodontal disease (Van Tornout et al., 2013).

VSCs produced by microorganisms include hydrogen sulfide (H_2S), dimethyl sulfide: $(CH_3)_2S$, dimethyl disulfide ($C_2H_6S_2$), and methyl mercaptan (methanethiol, CH_3SH) (Seemann et al., 2001, Casemiro et al., 2008; Acar et al., 2019; Jiang et al., 2023). In addition to VSCs causing bad breath, which creates problems for interpersonal relationships and the psychological health of individuals (Lee et al., 2021), VSCs are toxic to periodontal tissues, which means that these compounds may play a role in the development of gingivitis and periodontitis (Ratcliff and Johnson, 1999; Seemann et al., 2001).

Saliva contains many antimicrobial agents such as lysozyme, lactoferrin and lactoperoxidase that protect teeth and oral mucosa against pathogenic microorganisms (Thie et al., 2002). During sleep, salivation is reduced, which consequently contributes to an increase in the number of microorganisms in the oral cavity, resulting in an increased risk of caries and bad breath (Marsh et al., 2016; Vila et al., 2019; Sotozono et al., 2021). Therefore, it is accepted that the mouth is cleaned before sleeping to help control microbial growth during the night, preventing oral diseases (Sotozono et al., 2021).

Regardless of brushing force, using a soft or medium toothbrush results in comparable teeth cleaning effectiveness (Tanner et al., 2023). However, toothbrushes with soft bristles are the most recommended for cleaning teeth, as they help prevent damage to the gum tissue (Romitti et al.,

2022). Because of this, it is common for patients to brush their teeth and tongue with a soft-bristled brush (Pedrazzi et al., 2004; Casemiro et al., 2008), although they can also use a scraper to clean their tongue (Seemann et al., 2001; Pedrazzi et al., 2004; Casemiro et al., 2008; Acar et al., 2019).

In 2025, a search on PubMed using the keywords "dentistry students and tongue scraper" or "tongue scraper and toothbrush" or "tongue scraper and toothbrush and halitosis" found no articles comparing tongue brushing with tongue scraping (using a copper tongue scraper), based on halitosis assessed by a halimeter, in dental students. Therefore, the objective of this study was to evaluate the influence of two tongue cleaning methods (copper tongue scraper and toothbrush) on morning halitosis in dental students.

Material and Methods

Ethics committee
This study was approved by the Ethics Committee for Human Research (No. 81690324.1.0000.5420) of the Araçatuba Dental School, São Paulo State University Júlio de Mesquita Filho (UNESP-FOA) and followed the recommendations of the Declaration of Helsinki (World Medical Association, 2013). All participants signed the free and informed consent form.

Thirteen (Pedrazzi et al., 2004) undergraduate dentistry students (UNESP-FOA) were included in this study according to the inclusion and exclusion criteria. All students included received a free copper tongue scraper (Yogateria, Ayurveda, Brazil).

Inclusion criteria
- Students in the 3rd or 4th year of the Dentistry course at the UNESP-FOA aged between 20 and 25 years old.
- Individuals classified as ASA (American Society of Anesthesiologists) I (Mayhew et al., 2019).
- Good oral health.
- Complete dentition and no malocclusion.
- Healthy sleep with 7 to 9 hours of sleep per night, as recommended by the National Sleep Foundation for young adults ages 18 to 25 (Hirshkowitz et al., 2015; Do, 2020).
- Those who clean their teeth with dental floss and a soft-bristled toothbrush and clean their tongue only with the soft bristles of the toothbrush.
- Those with toothbrushes in good condition.
- No previous orthodontic treatment, or orthodontic treatment completed at least 5 years ago and no use of permanent or removable retainers (Acar et al., 2019; Banjar et al., 2022).

Exclusion criteria

- Wearers of dental or maxillofacial prostheses (Casemiro et al., 2008; Acar et al., 2019; Souza et al., 2023).
- Pericoronitis, caries, gingivitis or periodontitis (Pedrazzi et al., 2004; Jiang et al., 2023).
- Those who already use tongue scrapers daily.
- Whitening treatment in progress or completed in less than 3 months.
- Fissured tongue.
- Smokers (Pedrazzi et al., 2004; Casemiro et al., 2008; Acar et al., 2019; Jiang et al., 2023).
- Pregnancy or lactation (Acar et al., 2019).
- Abusive consumption of alcoholic beverages (Acar et al., 2019; Jiang et al., 2023).
- Use of illicit drugs (Antoniazzi et al., 2017).
- Cancer (before, during and after cancer treatment) (Casemiro et al., 2008; Shen et al., 2024).
- Stomach or respiratory problems (Pedrazzi et al., 2004; Casemiro et al., 2008; Kinberg et al., 2010).
- Use of medications that reduce salivation such as fluoxetine (Casemiro et al., 2008; Miranda-Rius et al., 2015; Acar et al., 2019).
- Those who wear mouthguards while sleeping (D'Ercole et al., 2014).
- Antibiotics and mouthwashes used in the 3 months prior to sampling (Seemann et al., 2001; Casemiro et al., 2008; Acar et al., 2019).
- Oral surgery less than 6 months ago.

Halitosis test

Halitosis was measured using a portable halimeter (HC-312F Tanita Portable Fitscan Breath Checker, Tanita, USA) (Souza et al., 2023). This device assessed the quality of the volunteer's breathing using a semiconductor gas sensor that can measure the quantity of VSCs emitted by bacteria (Souza et al., 2023). The volunteers were instructed to blow into the device according to the manufacturer's recommendations. After the volunteer blew into the device, which should be 1 cm away from their mouth, the halimeter display showed the level of halitosis (0: no odour; 1: little odour; 2: moderate odour; 3: heavy odour; 4: strong odour; or 5: intense odour) (Souza et al., 2023).

Data collect

All participants used the same halimeter, therefore, before each of them used the device, the researcher (C.L.d.M.M.N.) trained the individual on how to use the halimeter. Students were instructed not to consume alcoholic beverages or use mouthwash on the days of halitosis measurement. The researcher also instructed each participant to use the same toothpaste

(Creme Dental Máxima Proteção Anticáries – Colgate, Brazil) during data collection days.

After training, the first participant took the halimeter home and used it for 6 days. On the first three days, halitosis was measured immediately after the participant woke up in the morning. The night before each of these first three days, before going to sleep, the participant cleaned their mouth with dental floss and a soft-bristled toothbrush. The individual's same soft-bristled toothbrush was also used to brush his or her tongue. Each participant was instructed to clean their tongue only with the toothbrush bristles, that is, they should not use the tongue scraper found on the back of the head of some toothbrushes (standardization of cleaning). Only one halitosis measurement was taken per day and the value was recorded each day (toothbrush group). On the fourth, fifth and sixth day, the same process was carried out, but the night before measuring halitosis, a copper tongue scraper (Yogateria, Ayurveda, Brazil) was used to clean the participant's tongue, instead of a toothbrush. Only one halitosis measurement was taken per day and the value was recorded each day (tongue scraper group). The volunteer then returned the halimeter to the examiner, who passed it to the second volunteer to perform the same protocol described above. This process was repeated until all thirteen volunteers had collected their halitosis data.

After six days, each participant collected 6 halitosis measurements. Subsequently, for each participant, the highest halitosis value of the first three days (toothbrush group) was chosen, as well as the highest halitosis value of the last three days (tongue scraper group).

Perception of tongue cleanliness

At the end of each participant's halitosis measurements, the operator asked the following question: "Between the toothbrush and the copper tongue scraper, which method generated the greatest perception of cleanliness for your tongue?"

Statistical analysis

Statistical analysis was conducted using the Jamovi software (Version 2.2.5.0, Jamovi Project, Australia). The Wilcoxon test was used to compare the two groups (toothbrush group and tongue scraper group) based on halitosis values ($P < 0.05$).

Results

Ten women and three men with an average age of 22 years participated in this study. Table 1 shows that the halitosis value (median) in the toothbrush group

Table 1: Comparison of halitosis values between the two groups

Groups	Halitosis value (median)	P-value
Toothbrush group	3	0.003*
Tongue scraper group	1	

Wilcoxon test (P<0.05); *represents a statistically significant difference

was significantly higher than that in the tongue scraper group.

The average halitosis value in the toothbrush group was approximately 3, while in the tongue scraper group it was approximately 1.

All participants reported that the greatest perception of cleanliness for their tongue was achieved with the copper tongue scraper.

Discussion

The halitosis value (median) in the toothbrush group was significantly higher than that in the tongue scraper group (Table 1). This theoretically happened for two reasons: 1) the metal scraper has greater resistance to bending than the soft bristles of a toothbrush, which prevented its metal arms from bending during tongue scraping. This factor, combined with the pointed surface of the metal scraper that came into contact with the tongue during cleaning, may have facilitated the application of the pressure necessary to remove the tongue coating. In this way, the copper tongue scraper generated enough friction with the tongue to completely remove the tongue coating, contributing to the reduction of microbial proliferation during sleep, which consequently reduced the release of VSCs. On the other hand, in the toothbrush group, the soft bristles of the toothbrush certainly did not generate enough friction with the tongue to completely remove the tongue coating, contributing to greater microbial proliferation during sleep that resulted in greater VSCs release (compared to the tongue scraper group); and 2) the copper tongue scraper may have cleaned a larger area of the tongue with each scraping action than the toothbrush bristles with each brushing action (Seemann et al., 2001). This may have made cleaning the tongue with the copper scraper easier, faster and more efficient, which may have prevented hygiene failures.

Clinically, halitosis values from 0 to 1 are clinically acceptable (imperceptible odour), while those from 2 to 5 are considered unacceptable (perceptible odour) (Souza et al., 2023). The toothbrush group

showed a clinically unacceptable halitosis value (i.e., median: 3), while the tongue scraper group showed a clinically acceptable value (i.e., median: 1) (Table 1). Furthermore, when obtaining the mean values of both groups, the same result was observed. Therefore, the copper tongue scraper was more efficient in reducing morning halitosis, which makes it the most clinically recommended method for cleaning the tongue.

Based on the level of halitosis measured by a halimeter, few studies have compared tongue brushing with tongue scraping (Seemann et al., 2001; Pedrazzi et al., 2004). Despite different methodologies, Seemann et al. (2001) and Pedrazzi et al. (2004) corroborate this study. Seemann et al. (2001) observed that the tongue scraper showed a significant reduction in halitosis compared to the toothbrush. Pedrazzi et al. (2004) noted that the plastic tongue scraper showed a 75% reduction in VSCs, while the toothbrush only achieved a 45% reduction in VSCs.

All participants (100%) reported that the greatest perception of cleanliness for their tongue was achieved with the copper tongue scraper. Dental schools should more strongly encourage the use of a copper tongue scraper as part of the daily oral hygiene of their dental students and patients. Thus, after students become dentists, they will recommend this method to their patients.

A limitation of this study is the absence of a group using a plastic tongue scraper.

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Accidental Environmental Hypothermia in a Nonagenarian Resulting in Cardiac Arrest

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Abstract: Accidental hypothermia after environmental exposure and/or impaired thermoregulation resulting in significant decrease in body temperature and cardiac arrest (CA) is linked to 1,500 deaths annually in the United States. Hypothermic CA treatment has specific presentation and clinical features. With appropriate treatment, its survival can reach 27–70%, contrasting ~ 10% in medical CA. Majority of accidental hypothermic CA survivors recover with favourable neurologic outcome. An integrated, dedicated multi-disciplinary team-approach is essential to maximize the chances of survival. We report on a 91-year-old female who was found outside and unresponsive in freezing temperatures. During transport, she required bag-and-mask ventilation. An esophageal temperature recorded 24.5 °C. Shortly after rapid sequence intubation, she developed CA. She was successfully resuscitated with chest compressions, epinephrine, atropine, and two defibrillations. Due to persistent hypothermia and bradycardia, she was rewarmed using extracorporeal membrane oxygenation. Perioperative transesophageal echocardiography showed normal cardiac function. She was extubated the next day. She remained stable for the rest of her hospital stay without focal neurological deficits on serial examinations. However, her post-arrest stay was complicated by acute delirium, likely from underlying dementia, with a waxing and waning level of consciousness, confusion, agitation and hallucinations. She was discharged on post-operative day 5. Her long-term recovery was complicated by repeated aspiration pneumonias, and gradual decline of her mental status due to Alzheimer's dementia. She died approximately two years later at the age of 93. Thus, full neurologic recovery remains possible after CA induced by severe hypothermia from environmental exposure, despite extreme age and frailty.

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Introduction

While the majority of out-of-hospital cardiac arrests (CA) are deemed to be of cardiac origin, other causes may play a role. Accidental hypothermia after environmental exposure and/or impaired thermoregulation resulting in significant decrease in body temperature and CA is linked to 1,500 deaths annually in the United States (Paal et al., 2022). Hypothermic CA has specific presentation and clinical features. Accordingly, its treatment should follow a protocol distinct from extracorporeal life support (ECLS) (Lott et al., 2021). With appropriate treatment, its survival can reach 27–70%, contrasting ~ 10% in medical CA from medical causes, as reported in major CA registries (Nishiyama et al., 2023). Of note, majority of accidental hypothermic CA survivors recover with a favourable neurologic outcome (Frei et al., 2019; Podsiadlo et al., 2021). Environmental exposure resulting in severe hypothermia in the prehospital setting, and the possibility of progression of hypothermia to CA must be promptly recognized and treated en route and throughout the continuum of care, to optimize the outcomes. An integrated, dedicated multi-disciplinary team-approach is essential to maximize the chances of survival with favourable outcome (Patterson et al., 2020).

We report on a case of a frail, elderly female, who experienced accidental environmental exposure eventually progressing to hypothermic CA in an urban setting. A written Health Insurance Portability and Accountability Act authorization has been obtained from the patient's family for the publication of this case report.

Case report

An unresponsive 91-year-old female was discovered lying on a sidewalk without any clothing in freezing temperatures. She exhibited agonal breathing at the scene. Physical examination revealed contusions and abrasions on her forearms and knees, consistent with crawling with mottled skin. Emergency Medical Service crew noted significant hypothermia and bradycardia, and initiated bag-valve-mask ventilation before transporting her to the emergency department (ED). On arrival to the ED, the patient remained unresponsive and hypothermic, with heart rate in the 30–40 beats/min range, systolic blood pressure ~ 60 mm Hg, Glasgow Coma Scale score of 3 and minimal spontaneous respiration. Unfortunately, no other history regarding her premorbid status was obtainable at the time of presentation.

In the ED, appropriate vascular access was established, and airway was secured using rapid-sequence intubation facilitated by etomidate and vecuronium. An esophageal temperature probe was placed, revealing a temperature of 24.5 °C. Rewarming was initiated with infusion of warm normal saline, and surface warming using warming blankets.

Shortly after, the patient developed ventricular fibrillation CA. Resuscitation efforts using Advanced Cardiac Life Support (ACLS) protocol were initiated. We administered chest compressions, epinephrine and atropine. Return of spontaneous circulation was achieved after two defibrillation attempts, although significant hypothermia and bradycardia remained.

At this point in time, given her level of hypothermia and cardiovascular instability, cardiothoracic surgery service was consulted for emergent ECLS management of active rewarming, according to our pre-established protocol. Upon acceptance, she was transported into the operating room. She was sedated and mechanically ventilated with ongoing neuromuscular blockade. Initial venous blood gas revealed mixed metabolic and respiratory acidosis with pH 7.24, $pvCO_2$ 54 mm Hg, pvO_2 29 mm Hg, HCO_3 22 mmol/l and base deficit −5 mmol/l. Lactate was 3.1 mmol/l. Electrolytes showed modest derangements that were subsequently corrected. Complete blood count showed anemia with hematocrit of 30, and markedly decreased platelet count of $68×10^9$/l, with functional collagen agonist platelet count of $16×10^9$/l. She was cannulated for extracorporeal membrane oxygenation (ECMO) via peripheral access using femoral artery and vein. Perioperative transesophageal echocardiography revealed small-size left ventricle with normal function, normal right ventricle size and function, trace mitral and tricuspid regurgitation, and borderline pulmonary hypertension. Transesophageal echocardiography confirmed favourable position of the venous ECMO venous cannula. After 86 minutes of ECMO-assisted rewarming, temperature of 37 °C was achieved, and she was successfully weaned from ECMO and decannulated in the operating room.

Considering her high risk of rearrest, the patient was transferred to the intensive care unit (ICU) where she remained monitored for the next two days. Subsequent evaluation after weaning from sedations and reversing neuromuscular blockade revealed a stable and awake patient with intact reflexes. She exhibited purposeful movements, although it was unclear if she was able to follow commands consistently. Thus, we continued target temperature management (TTM) for fever suppression. She met extubation criteria the day after her CA, and she was discharged from the ICU the next day. She remained stable for the rest of her hospital stay without any

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focal neurological deficits on serial examinations. However, her post-arrest stay was complicated by acute delirium, likely from underlying dementia, with a waxing and waning level of consciousness, confusion, agitation and hallucinations.

The patient was discharged to a dedicated nursing facility after a 5-day hospital stay. Per her family members at the time of discharge, she recovered fully to her previous mental and physical status without any new neurological deficits. She was seen two months post discharge for evaluation of a suspected hernia, which turned out to be a seroma after her ECMO cannulation. This was treated conservatively and resolved on its own.

Her long-term recovery was complicated by repeated aspiration pneumonias eventually necessitating placement of a PEG tube, atrial fibrillation, and gradual decline of her mental status due to Alzheimer's dementia. She died approximately two years after the accidental hypothermic CA at the age of 93.

Discussion

Accidental hypothermia is defined as an involuntary decrease of core body temperature below 35 °C (Lott et al., 2021) and can be further subdivided into mild (32–35 °C), moderate (28–32 °C), and severe (under 28 °C). Cardiac arrhythmia is uncommon above 32 °C, and most are seen below 30 °C. Patients > 65 years of age are at higher risk of arrhythmia between 30–32 °C (Lott et al., 2021). While severe hypothermia is often accompanied by bradycardia, hypotension, coagulopathy, and an increased risk of CA, it also offers unique protective benefits. A 1 °C decrease in core temperature reduces oxygen consumption by approximately 6%, meaning that at 30 °C, oxygen demand is decreased by about 50% (Mallet, 2002). This reduced metabolic rate protects the heart and the brain, and although the likelihood of CA is high, the odds of survival are greater than in normothermic patients (Paal et al., 2022). Similarly, accidental hypothermia has been shown to increase the odds of survival with a good neurological outcome five-fold compared to CA from cardiac causes (OR [odds ratio] 5.12, 95% CI [confidence interval] 2.98–8.80) (Takiguchi et al., 2024). However, these protective effects are only present if severe hypothermia develops before asphyxia or CA.

The gold standard for managing patients with severe hypothermia or hypothermic CA, as was the case in our patient, is rewarming with ECLS using cardiopulmonary bypass (CPB) or ECMO (Dow et al., 2019; Lott et al., 2021). ECMO is generally the preferred method due to its availability, reduced heparinization requirements, and the ability to provide extended support after reaching normothermia (Paal et al., 2022). Studies have also reported better outcomes with ECMO in hypothermic CA patients (Paal et al., 2022). Importantly, most ECLS protocols will restrict its use for situations when CA is witnessed, have immediate bystander cardiopulmonary resuscitation (CPR) and typically have an age restriction of < 65 to < 75 years of age (Richardson et al., 2021; Olson et al., 2022). These indications are based primarily on ECMO use in patients for heart failure and may be excessively restrictive in other CA scenarios which would still yield favourable outcome. The geospatial eligibility of CA patients for ECLS-capable and ECLS-ready programs also remain a limiting factor (Gottula et al., 2022, 2025).

In cases when ECLS capabilities are not readily available immediately after the CA event (especially in prehospital settings), continuous CPR is essential and should be initiated without delay. Mechanical CPR is generally preferred because it requires fewer people and facilitates other procedures. However, there are no data suggesting that mechanical CPR is associated with better outcomes (El-Menyar et al., 2024). One of the plausible explanations is that mechanical devices tend to become misplaced (e.g. over the left ventricular outflow tract) in a large proportion of cases (Teran et al., 2019).

Only when continuous CPR is not feasible should delayed or intermittent CPR be performed, with delays or interruptions of no more than 5 minutes without CPR (if the core temperature is between 20–28 °C or unknown) and no more than 10 minutes without CPR (if the core temperature is below 20 °C) in between at least 5 minutes of compressions (Gordon et al., 2015). Administration of resuscitative medications is generally not recommended in ACLS protocols, as their effect and metabolism is decreased, which might lead to possible overdose once rewarmed (Gordon et al., 2015). However, individual international guidelines differ on this controversial topic. For example, the American Heart Association guidelines state that it may be reasonable to consider administration of epinephrine along with rewarming during hypothermic CA (Panchal et al., 2020) albeit in prolonged interval of 6–10 min at temperatures > 30 °C (Lott et al., 2021). Atropine has been shown hemodynamically ineffective in hypothermic patients (Wüst et al., 1976) and not associated with improved outcomes in other CA populations (Greif et al., 2024).

Elderly patients are more susceptible to hypothermia due to various factors, such as reduced subcutaneous fat, decreased body water and muscle mass, impaired

thermoregulation, and limited mobility, as well as reduced autonomic and behavioural thermoregulatory responses (Szekely and Garai, 2018). While these age-related changes contribute to increased heat loss and decreased heat production, comorbidities and underlying medical conditions are the most significant risk factors and are closely associated with higher mortality in hypothermic elderly patients (Ballester and Harchelroad, 1999; Ranhoff, 2002). Although advanced age in general is considered a poor prognostic factor in accidental hypothermia (Morita et al., 2018; Okada et al., 2019; Takauji et al., 2021), it is not a contraindication to ECLS in patients experiencing CA in this setting (Swol et al., 2022). That said, increased age has been shown to significantly shorten the toleration of hypothermic CA before permanent neurological injury occurs (Svensson et al., 1993; Kaneko et al., 2015), which further emphasizes the critical need for high-quality, continuous CPR, and early consideration of ECLS in this population. Given the absence of advance directives at the time of presentation, we provided a full scope of resuscitative efforts spanning from pre-hospital setting, ED, anesthesia and perioperative care to critical care in the ICU. Post-resuscitative TTM is essential. In our patient, we chose to continue TTM with fever prevention. If she was not purposeful, we would have maintained TTM at 36 °C. Per family wishes, ICU care was not limited. Long-term recovery was significant for further progression of pre-existing Alzheimer's disease, and aspiration pneumonia. Despite these setbacks, the patient survived for two more years with an acceptable quality of life.

To the best of our knowledge, this is only the second reported case of a successful resuscitation with ECMO of a hypothermic arrest in a nonagenarian patient. Our case highlights that full neurologic recovery remains possible after CA induced by severe hypothermia from environmental exposure, even at extremes of age. This underscores the powerful protective effects of pre-arrest hypothermia and suggests that resuscitation efforts should be considered in such scenarios, regardless of advanced age and pre-existing frailty. An integrated team approach with ECLS capacities is pivotal in facilitating care for these patients.

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Primary Mucinous Bladder Adenocarcinoma

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Abstract: Mucinous adenocarcinoma, a rare subtype of primary bladder adenocarcinoma, accounts for approximately 20% of primary bladder adenocarcinomas and should be distinguished carefully from secondary adenocarcinomas of gastrointestinal origin. Herein, we report an unusual case of primary mucinous adenocarcinoma arising from a villous adenoma in a 52-year-old male presenting with urinary difficulties and recurrent bladder tumours. The patient had a significant medical history including right nephrectomy and left ureterolithotomy. Radiological and pathological evaluations revealed invasive mucinous adenocarcinoma. Surgical management included radical cystectomy, left nephroureterectomy, right ureterectomy, segmental rectal resection, and bilateral pelvic lymphadenectomy. This case emphasizes the complexity of diagnosis and management, highlighting the importance of distinguishing primary bladder mucinous adenocarcinoma from secondary gastrointestinal malignancies.

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Introduction

Bladder cancer is the 10th most common malignancy globally, with a significantly higher incidence in men than women. Urothelial carcinoma represents the majority of bladder cancers (90–95%), while adenocarcinomas constitute approximately 2%. Mucinous adenocarcinoma, a rare subtype of primary bladder adenocarcinoma (PBA), represents about 20% of adenocarcinomas (Tatli et al., 2012).

Adenocarcinomas of the bladder may be subclassified into three major categories: a) urachal adenocarcinoma, arising from the embryologic remnant at the bladder dome; b) non-urachal (pure) primary adenocarcinoma, which includes enteric, mucinous, signet-ring cell and mixed subtypes; and c) secondary adenocarcinoma, representing direct extension or metastasis from adjacent organs such as colon, prostate or gynecologic sites (Santos et al., 2015). The mucinous subtype is characterized by abundant extracellular mucin pools with clusters of neoplastic cells, often exhibiting columnar morphology and occasional signet-ring features.

Histologically, mucinous bladder adenocarcinoma demonstrates irregular glandular architecture floating in lakes of mucin, with tumour cells showing moderate-to-marked nuclear atypia and frequent mitoses. Immunohistochemically, primary mucinous adenocarcinoma typically co-expresses cytokeratin 7 (CK7) and cytokeratin 20 (CK20), with variable CDX2 positivity, whereas markers such as GATA3 and uroplakin are consistently negative, helping to exclude urothelial differentiation. By contrast, secondary colorectal adenocarcinomas invading the bladder often show strong CDX2 and nuclear β-catenin expression but lack CK7. Tuna (2018) recommend a panel including CK7, CK20, CDX2, β-catenin, and GATA3 to reliably discriminate primary bladder adenocarcinomas from metastases – critical given the therapeutic and prognostic implications.

Due to its rarity and overlapping morphology with metastatic lesions, primary mucinous bladder adenocarcinoma poses significant diagnostic challenges. Moreover, its propensity for aggressive local invasion – often involving periurethral or prostatic tissue – and occasional fistula formation further complicates management. Herein, we present an unusual and aggressive case of primary mucinous adenocarcinoma arising in a background of villous adenoma, with involvement of the prostatic urethra and development of a rectovesical fistula.

Case report

A 52-year-old man who had undergone right nephrectomy in 1989 for a nonfunctioning kidney secondary to severe vesicoureteral reflux presented on July 20, 2024, with a three-week history of gross hematuria, dysuria, urinary frequency, and two episodes of acute urinary retention. He had been on thrice-weekly hemodialysis for five years, maintaining approximately 200 ml of residual urine output per day. His medical history also included chronic left hydronephrosis – attributable to recurrent obstructive episodes over the past decade – hypertension controlled with amlodipine 10 mg and losartan 50 mg daily, and hyperlipidemia managed with atorvastatin 20 mg nightly.
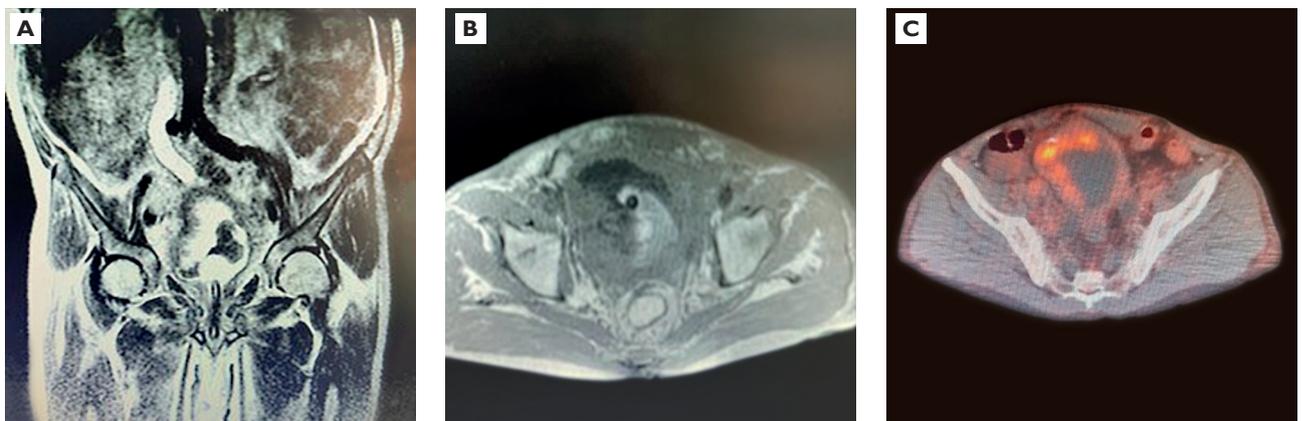

Figure 1(A and B): A mass configuration measuring approximately 4.2×1.6 cm, displaying a papillovillous appearance and disrupting the wall integrity, is observed in the right half of the bladder lumen. Amorphous signal void areas within the lumen are considered in favour of coagulum. Additionally, on the left side, starting from the 2 o'clock position to the 4 o'clock position, wall integrity is lost. An extravesical mass measuring approximately 5×3 cm, thought to be associated with the bladder wall, is detected in the left perivesical area. (C) A primary tumoral lesion with increased FDG-PET (fluorodeoxyglucose positron emission tomography) uptake and heterogeneous characteristics has been observed, appearing to invade the perivesical fatty plane, particularly on the left side, as well as the right and anterior walls of the bladder.

Four days after presentation, renal and bladder ultrasound demonstrated a large heterogeneous mass measuring 112×60×143 mm within the bladder and persistent grade 3 hydronephrosis of the left kidney. On August 2, 2024, pelvic magnetic resonance imaging (MRI) further characterized a 4.2×1.6 cm papillovillous lesion on the right bladder wall, accompanied by a separate 5×3 cm extravesical component extending from the 2 to 4 o'clock positions (Figure 1). The study revealed loss of bladder wall integrity, a fistulous tract toward the rectourethral space, and encasement of the left ureter as it traversed the mass.

For tissue diagnosis and partial debulking, the patient underwent transurethral resection of the bladder tumour (TURB) on October 18, 2024. Intraoperatively, gelatinous mucinous material and papillary foci were noted. Multiple biopsy samples were obtained from both the bladder mass and suspicious lesions in the prostatic urethra; two of these specimens lacked identifiable muscularis propria.

Staging investigations included an ^18F-FDG PET-CT on November 10, 2024, which showed heterogeneous uptake within the bladder lesion (SUVmax 8.4) and two pelvic lymph nodes (SUVmax 4.6) but no distant metastases. A colonoscopic examination performed on November 12, 2024, revealed no evidence of primary colorectal pathology, reinforcing the suspicion of a primary bladder tumour.

Definitive surgical management took place on January 06, 2025. The patient underwent an open radical cystoprostatectomy combined with left nephroureterectomy – electively performed because of the left kidney's chronic nonfunction and infection risk – and a low anterior resection of the rectum to address the rectourethral fistula. Urinary diversion was constructed with an end ileal conduit (Bricker) and right lower-quadrant stoma. His postoperative course was notable only for a mild paralytic ileus that resolved by postoperative day five, and he was discharged after a 14-day hospitalization.

Histopathologic examination of the en bloc specimen confirmed a moderately differentiated, intestinal-type mucinous adenocarcinoma infiltrating the bladder neck's muscularis propria and the prostatic urethra (pT4) (Figure 2). Two of twelve pelvic lymph nodes were positive (pN2). Immunohistochemistry showed strong CK20 and CK7 positivity, negative GATA3, and both nuclear and cytoplasmic β-catenin staining, supporting the diagnosis of primary mucinous adenocarcinoma of the bladder arising in a background of villous adenoma and effectively excluding colorectal or urachal origin. No adjuvant therapy was administered, and at six-month follow-up the patient remains free of recurrence.

Discussion

Primary adenocarcinomas of the bladder represent approximately 2% of all bladder malignancies. Mucinous adenocarcinoma is a histological subtype accounting for about 20% of primary bladder adenocarcinomas. Secondary adenocarcinomas, including metastases from colorectal and urachal adenocarcinomas, should be carefully excluded to ensure accurate diagnosis. Histologically, bladder adenocarcinomas are categorized into mucinous, enteric (colonic), signet-ring cell, and mixed types. Each subtype exhibits unique morphological and immunohistochemical features that can guide diagnosis and treatment decisions. It represents a relatively rare histopathological subtype of primary bladder cancer. Previous studies suggest a progression in the pathogenesis of primary mucinous adenocarcinoma, evolving sequentially from mucinous metaplasia
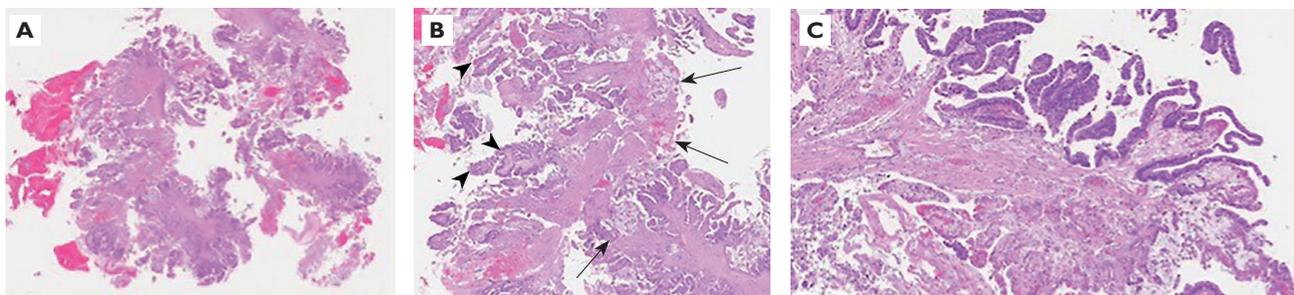

Figure 2(A): In the transurethral resection material, focal mucinous/colloid component containing intestinal-type well-differentiated adenocarcinoma and villous adenoma with high-grade dysplasia are observed together in the prostatic urethra. (B) The tumour infiltrates the muscularis propria bundles of the bladder neck. Intestinal-type well-differentiated adenocarcinoma (arrow) and villous adenoma with high-grade dysplasia (arrowhead). (C) An area of invasive mucinous adenocarcinoma showing continuity with the villous adenoma (upper part of the image) is observed together. (A) Haematoxylin and eosin staining, 40× magnification, (B) haematoxylin and eosin staining, 130× magnification, (C) haematoxylin and eosin staining, 400× magnification.

and mucinous adenoma into invasive mucinous adenocarcinoma (Di Lauro et al., 2013; Zhang et al., 2014).

Clinically, primary mucinous adenocarcinoma is characterized by aggressive behaviour and a high propensity for invasion and metastasis. At diagnosis, metastatic dissemination is reported in up to 40% of cases, primarily through lymphatic pathways, commonly involving iliac (internal, external, common) and obturator lymph nodes. Additionally, direct local invasion to adjacent structures such as the prostate and posterior urethra has been documented. More distant metastases, although less frequent, have also been reported in organs including the ovary, uterus, abdominal wall, colon, and penis (El-Ghobashy et al., 2009; Jo et al., 2011).

Our review of the literature highlights the exceptional rarity of urethral involvement by primary mucinous adenocarcinoma of the bladder, as illustrated by the current case. Clinical manifestations of primary mucinous adenocarcinoma are typically nonspecific and include suprapubic pain, hematuria, dysuria, and irritative voiding symptoms (Zaghloul et al., 2006).

The histogenesis of primary mucinous adenocarcinoma remains controversial, with two primary hypotheses proposed: origin from vestigial embryonic glandular remnants within the transitional epithelium, or glandular metaplasia arising from transitional epithelial cells.

Given the limited number of reported cases, well-established clinical and radiological characteristics remain undefined. Nevertheless, this case underscores the importance of meticulous ultrasonographic evaluation of the bladder and adjacent structures, particularly in patients presenting with atypical urinary symptoms, to facilitate timely diagnosis and treatment.

The mainstay of management for primary mucinous adenocarcinoma of the bladder involves surgical intervention, predominantly radical cystectomy with pelvic lymphadenectomy. Although the benefit of routine postoperative adjuvant therapy remains debatable, adherence to guideline-recommended chemotherapy protocols may offer therapeutic advantage. Moreover, diligent postoperative surveillance is imperative to detect early recurrence,

both local and distant, given the aggressive nature and metastatic potential of this malignancy.

Conclusion

This case highlights the importance of thorough histopathological and immunohistochemical evaluation in differentiating primary bladder mucinous adenocarcinoma from secondary gastrointestinal malignancies, especially in patients with complex urological histories and chronic renal disease. The presence of a rectovesical fistula and extensive local invasion underscores the tumour's aggressiveness. Comprehensive pathological and clinical assessment is crucial for accurate diagnosis and appropriate management.

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Jejunal Diverticulitis:
A Diagnostic and Therapeutic Overview

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Abstract: Jejunal diverticulitis is a rare and often underdiagnosed condition characterized by inflammation of jejunal diverticula, more commonly seen in elderly patients with comorbidities. While most cases remain asymptomatic and are incidentally discovered during imaging studies, some patients may present with nonspecific symptoms such as abdominal pain and discomfort. The diagnosis is challenging due to its low prevalence and non-specific clinical presentation, often mimicking other causes of acute abdomen like appendicitis or colonic diverticulitis. Computed tomography with intravenous contrast is considered the gold standard for identifying diverticula, associated inflammatory changes, and potential complications. Ultrasound can also aid in diagnosis in certain cases. Management depends on the clinical severity. Uncomplicated cases generally respond well to conservative treatment with antibiotics and supportive care, while complicated cases may require surgical intervention. Early recognition and appropriate management are essential to prevent severe complications, such as perforation, bleeding, or obstruction, and to improve patient outcomes.

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Introduction

Jejunal diverticulitis, characterized by inflammation of the diverticula, is a rare condition affecting between 0.02 and 4.6% of the population, and is more common in men. Although often asymptomatic, about 40% of cases may present with symptoms such as chronic pain or malabsorption (Cantão et al., 2016).

The diverticula in this case are false diverticula and are formed along the mesenteric border of the bowel. This diverticular formation is characterized by an area of fragility leading to herniation of the mucosa and submucosa. Additionally, factors such as alterations in peristalsis, intestinal dyskinesia, and high intraluminal segmental pressures are considered relevant to the development of jejunal diverticulitis (Alves et al., 2022).

Jejunal diverticulitis is rarely identified clinically but is often found incidentally during contrast studies of the gastrointestinal tract, such as gastrointestinal series, computed tomography (CT) enterography, magnetic resonance imaging, or endoscopy (Matli et al., 2022). In certain scenarios, complications such as digestive bleeding, perforation, intestinal obstruction, and associated inflammation may be observed (Alves et al., 2022).

Herein, we report the case of a 77-year-old female patient with persistent abdominal pain. Informed consent was obtained from the patient.

Case report

A 77-year-old woman presented with persistent abdominal pain that had not improved after one day of treatment with metoclopramide and dimethicone. She had a medical history of colonic diverticulitis, diabetes mellitus managed with insulin, hypertension controlled with hydrochlorothiazide and losartan, and Hashimoto's thyroiditis treated with levothyroxine. The patient reported eating grapes with seeds the previous day, which she believed might have triggered the symptoms.

On physical examination, her abdomen was soft, with localized tenderness in the left flank, but there were no signs of peritonitis. She appeared hemodynamically stable, with no signs of systemic infection. A CT scan of the abdomen revealed findings consistent with jejunal diverticulitis located in the left flank (Figure 1). Given the severity of her symptoms, intravenous antibiotic therapy with piperacillin and tazobactam was initiated. Within seven days, her symptoms had fully resolved, and she was discharged in stable condition. Upon discharge, she received dietary recommendations from a nutritionist, focusing on avoiding foods that could irritate her gastrointestinal system, and was referred for outpatient follow-up care.

Discussion

Jejunal diverticulosis is a rare condition characterized by the formation of multiple saccular mucosal herniations along the mesenteric border of the small intestine (Coulier et al., 2007; Alves et al., 2022). Although more common in the colon, small bowel diverticula, particularly in the jejunum, remain an uncommon but clinically relevant entity (Coulier et al., 2007).

The majority of cases are asymptomatic and incidentally identified during imaging studies performed for other reasons (Coulier et al., 2007). When symptomatic, patients may present with nonspecific
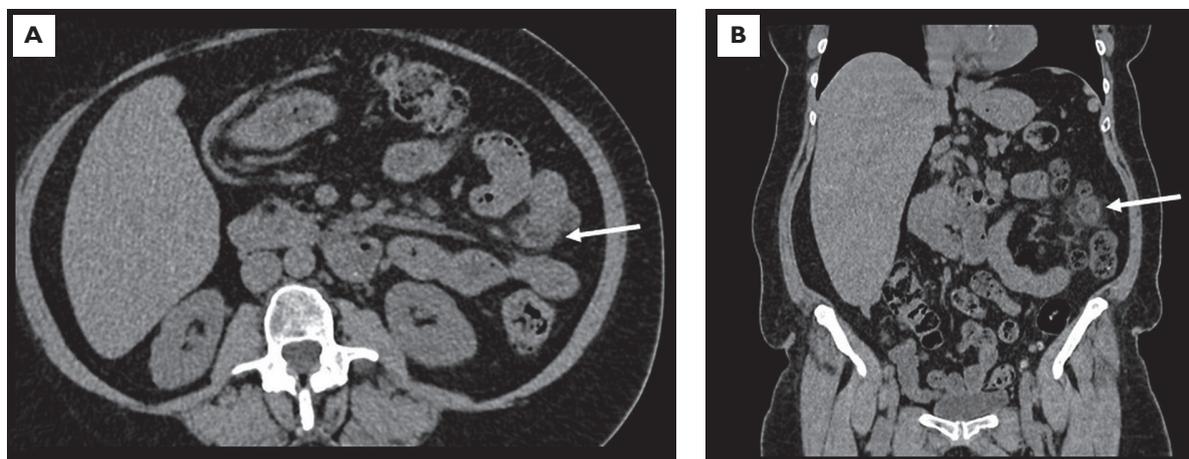

Figure 1: Non-contrast abdominal computed tomography in the axial section (A) and coronal section (B) showing a jejunal diverticulum with adjacent fat stranding, suggesting an inflammatory process.

abdominal complaints such as discomfort, bloating, or dyspepsia (Coulier et al., 2007). In some instances, acute complications like diverticulitis, hemorrhage, perforation, or intestinal obstruction may occur (Coulier et al., 2007).

The differential diagnosis of jejunal diverticulitis is broad, often including conditions like appendicitis, cholecystitis, colonic diverticulitis, neoplasms, and Crohn's disease (Cantão et al., 2016; Alves et al., 2022). Given the nonspecific clinical presentation, imaging plays a crucial role in diagnosis. Contrast-enhanced abdominal CT is considered the imaging modality of choice, allowing visualization of bowel wall thickening, surrounding fat stranding, and the presence of diverticula (Coulier et al., 2007; Alam et al., 2014). Ultrasound may serve as a useful adjunct, particularly when CT is contraindicated, though its diagnostic sensitivity is limited (Kelekis and Poletti, 2002).

Management depends on the severity and presence of complications. Hemodynamically stable patients with uncomplicated diverticulitis often respond well to conservative treatment with bowel rest and intravenous antibiotics (Harbi et al., 2017). Surgical intervention is reserved for patients with perforation, abscess formation, or clinical deterioration despite medical therapy (Harbi et al., 2017).

This case highlights the importance of considering jejunal diverticulitis in elderly patients with left-sided abdominal pain, particularly when imaging reveals focal small bowel inflammation.

Conclusion

Jejunal diverticulitis, although rare, should be included in the differential diagnosis of acute abdominal pain, especially in elderly patients with risk factors such as diverticular disease and comorbidities. Early imaging, particularly contrast-enhanced CT, plays a pivotal role in prompt diagnosis. In selected cases, conservative management with antibiotics can lead to full clinical recovery and prevent complications.

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A Novel Approach to Ultrasound-guided Out-of-plane Lumbar Plexus Block Using the Shamrock Technique: Technical Report

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Abstract: Lumbar plexus blockade can be performed using both the classical landmark technique and ultrasound guidance. Reports suggest that ultrasound-guided blockade may enhance the safety of the procedure. Various approaches can be utilized for ultrasound-guided lumbar plexus blockade, including the paravertebral paramedian transverse scan, the Shamrock approach, and Trident imaging. In these imaging methods, needle guidance can be accomplished using either an in-plane or out-of-plane technique. Each of these application methods has limitations concerning needle imaging and guidance. In this case report, we present the outcomes of five patients who underwent lumbar plexus blockade for hip fracture surgery using an out-of-plane approach with Shamrock imaging, which could serve as a viable alternative to other methods.

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Introduction

Intertrochanteric femur fractures are among the most common conditions requiring emergency orthopedic surgery (Lawrence et al., 2002). Spinal, epidural, or peripheral nerve blocks (such as lumbar plexus and sacral plexus blocks) are preferred because they offer better postoperative analgesia and faster recovery (Kirchmair et al., 2001; Beaupre et al., 2005). Over the years, various methods for performing lumbar plexus blockade have been developed, particularly with the increasing use of ultrasonography (Kirchmair et al., 2001; Sauter, 2013; Sato et al., 2018). However, in ultrasound imaging, the acoustic window may narrow due to reduced vertebral height, especially in elderly patients. This can hinder the visualization of both the needle and the ultrasound on the same axis. In this case series, we hypothesized that the out-of-plane technique might be more effective. Therefore, we present the results of lumbar plexus block applications using the out-of-plane approach in Shamrock imaging.

Case report

This case series included patients aged 18 to 90 years, classified as American Society of Anesthesiologists (ASA) risk classes I to III, who were determined to undergo femoral nailing surgery for intertrochanteric femoral neck fractures during preoperative evaluation (Table 1). Patients who agreed to participate in the study and had no local anesthetic allergy, bleeding disorder, mental status disorder and previous cerebrovascular disease were selected consecutively, and the block was applied.

Out-of-plane lumbar plexus blockage

After sedation with midazolam 1 mg and Fentanyl 25 mcg, and oxygen support with a mask, the patient was placed in the lateral decubitus position with the side to be blocked up. After appropriate site cleaning, a protective clothed Convex (2–5 mhz Esaote MyLab 30, Italy) ultrasound probe was placed in the abdominal flank in the cranial iliac crest in the transverse position. At the top, the abdominal wall muscles (ext. oblique, internal oblique and transversus abdominis muscle) were visualized (Sauter, 2013). Then, under the probe abdominal muscles, the psoas muscle in front of the transverse process of the L4 vertebra under the quadratus lumborum muscle and the erector spinae muscles forming the Shamrock image posteriorly were defined (Sauter, 2013) (Figure 1).

The lumbar plexus was observed as round-oval structures in the psoas muscle 2–3 cm anterior to the transverse process, 6–10 cm deep to the skin. A 100 mm, 21 G peripheral nerve block needle was inserted from the midpoint of the ultrasound probe, with an out-of-plane technique, at a 90-degree right angle. The needle was directed anatomically from the lateral abdomen to the medial side of the psoas muscle on the posterior axillary line. After reaching

Table 1: Patient characteristics and lumbar plexus block details

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	75.0	80.0	76.0	81.0	72.0
Weight (kg)	79.0	81.0	80.0	67.0	78.0
Height (cm)	173.0	167.0	161.0	155.0	158.0
BMI (kg/m^2)	26.4	29.0	30.9	27.9	31.2
Sex (males – M)/females – F)	M	M	F	F	F
ASA classification	III	III	III	III	III
Duration of surgery (min)	50.0	63.0	48.0	53.0	54.0
Ipsilateral epidural block	–	+	+	–	–
Onset of sensory block (min)	11.0	9.5	10.0	10.0	12.0
Onset of motor block (min)	14.0	13.0	13.0	12.0	12.5
Total sedative drug consumption in peropeative					
Midazolam (mg)	2	3	2	2	2
Fentanyl (mcg)	25	50	50	50	50
Mean arterial pressure (mm Hg)	77.7 ± 3.6	78.2 ± 3.6	79.5 ± 3.4	80.5 ± 3.4	80 ± 2.5
Block performance time (min)	8	9	8.5	9	10

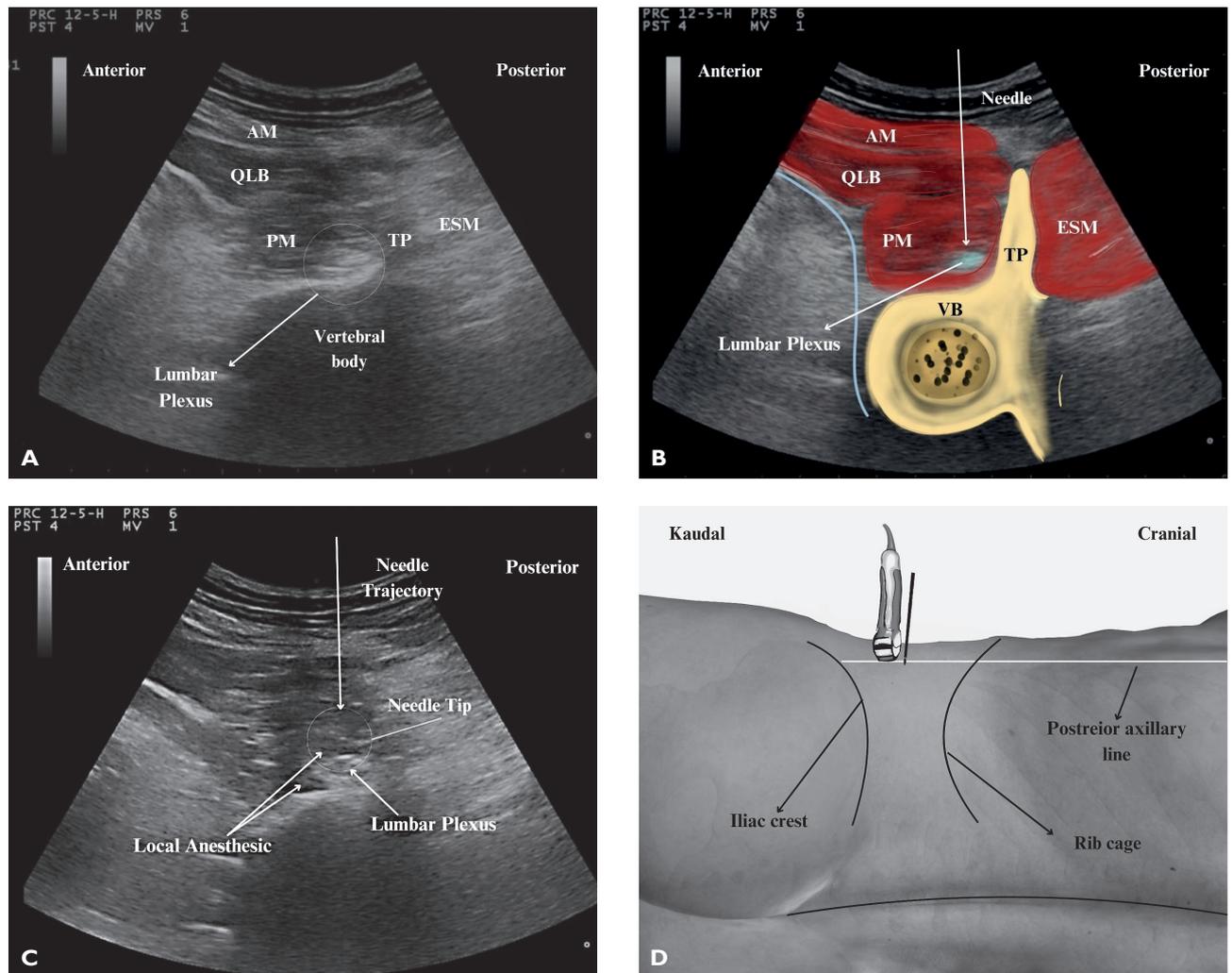BMI – body mass index; ASA – American Society of Anesthesiologists

Figure 1: (A) TP – transverse process; AM – abdominal muscle; ESM – erector spinal muscle; PM – psoas muscle; QLB – quadratus lumborum; white circle – lumbar plexus. (B) TP – transverse process; AM – abdominal muscle; ESM – erector spinal muscle; PM – psoas muscle; QLB – quadratus lumborum; VB – vertebral body; blue point – lumbar plexus. (C) Local anaesthetic distribution during injection; white circle – needle tip. (D) Figure showing the ultrasound probe and the entry site of the needle for an out of plane approach.

the injection site in the psoas muscle, the quadriceps muscle response was found with a peripheral nerve stimulator with a 0.3–0.4 mA 0.1 ms impulse and the location was confirmed (Figure 1). After confirming the appropriate site, 25 ml of 0.25% bupivacaine was injected with intermittent negative aspiration with a pressure transducer at a pressure < 15 psi (B-Smart™ Injection Pressure Monitor). Afterwards, ultrasound guided sacral plexus blockade was applied with 15 ml of 0.25% concentration of bupivacaine (Taboada et al., 2004).

The pinprick test for sensory block and the Bromage scale for motor block were used to assess the success of the procedure. These tests were repeated every five minutes after the procedure. If the desired level of sensory and motor block could not be achieved, it was considered a failed block and another procedure was planned. Tests were performed bilaterally to detect contralateral epidural spread. After the procedure,

surgery was started if the pinprick test was positive in the dermatomes of the femoral nerve, lateral femoral cutaneous nerve and obturator nerve, and the motor block score was 1 (unable to move against resistance) on the Bromage scale.

Discussion

In this case, a series of five patients underwent out-of-plane lumbar plexus blockade (LPB), which was successfully applied using Shamrock imaging. No complications were observed in the 24-hour follow-up of the patients included in the study.

With the identification of anatomical structures in the lumbar region using ultrasound, the course of the block needle as it passes through these structures during the block, its placement in the psoas muscle, and the spread of local anesthetic can be observed.

There are also variations for lumbar plexus (LP) visualization and block application using ultrasound. The main ones are the paramedian transverse oblique (transverse or articular process), the paramedian sagittal (trident view), and the Shamrock method (Karmakar et al., 2008, 2015; Sauter, 2013). Although ultrasound-guided LPB has advantages, the depth of the application area and bony structures may make imaging with ultrasound difficult. Today, the in-plane ultrasound-guided LPB method is widely used in short-axis imaging. In this method, it has been determined that the needle entry site is close to the midline, and bone structures can complicate the process by limiting the visibility of the needle. Sauter (2013) described an alternative approach known as the "Shamrock approach". This method provided a good visualization of the LP and surrounding structures. It is advantageous to define the lumbar plexus within the psoas muscle using the Shamrock method and to apply the needle from the exact location with the in-plane technique, employing the classical landmark method (Nielsen et al., 2018).

The technical difficulty with this approach lies in the challenges of imaging and orientation of the block needle due to the distance between the ultrasound scan area and the needle entry site. Aging and obesity can cause difficulties in imaging for all methods in which ultrasound-guided LPB is applied. Decreased fluid content in muscle tissue due to age may cause changes in echogenicity, and an increase in fat content in obesity may cause scattering of sound waves.

On the other hand, in-plane techniques may cause internal organ injuries in front of the psoas muscle if the needle tip is not fully visible or is not aligned along the axis (Eduardo et al., 2021). Due to the decrease in vertebral heights with age in Shamrock imaging, the distance between the iliac crest and the costal margin decreases, which causes difficulties in manipulating the ultrasound probe and providing visibility of the needle. Additionally, increased age-related echogenicity of the psoas muscle may make it challenging to confirm the intramuscular location of both the LP and the needle. The out-of-plane approach may shorten the procedure time and increase the success of the block in Shamrock imaging because the path to reach the lumbar plexus is away from the bony structures and requires a relatively shorter distance. In addition, the fact that the vertebral body is the target of the needle in the out-of-plane approach may reduce the risk of visceral injury and related complications.

Limitations

This method has certain disadvantages. While the needle tip is visible during the procedure, the overall visualization of the entire needle is not as effective as with the plane technique. The limitations of this study include a small sample size and an unclear understanding of the extent of epidural spread. Additionally, the risk of minor artery injury may be similar to that associated with other methods.

Conclusion

Shamrock imaging may benefit from an out-of-plane approach, especially in elderly patients. Large case series and randomized controlled trials may help determine this method's advantages and disadvantages.

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Mandibular Dislocation in a Patient Diagnosed with Bell's Palsy: A Case Report and Literature Review

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Abstract: Mandibular dislocation is a musculoskeletal disorder often associated with trauma and anatomical predispositions, which can result in severe pain and difficulty moving the mandible. Some conditions, such as Bell's palsy, can mimic signs and symptoms of mandibular dislocation, confusing some professionals during diagnosis. For this reason, a detailed anamnesis and clinical examination, combined with complementary tests such as computed tomography (CT) and magnetic resonance imaging (MRI), are necessary for a reliable diagnosis. The aim of this case report was to explore the management of mandibular dislocation, highlighting the importance of a detailed anamnesis and the use of complementary tests in the differential diagnosis of complications associated with temporomandibular disorders. Patient, 66-years-old, was referred to by her neurologist with a suspected relapse of Bell's palsy. After initial assessment, the suspicion was ruled out and a left-sided mandibular dislocation was hypothesized. A CT scan was requested, which confirmed the diagnosis. The treatment adopted was a maneuver to reposition the mandibular condyle in the articular fossa and the use of an anterior partial plate to stabilize mouth opening and closing. The patient received counselling therapy on more stable mandibular movement and was monitored to prevent recurrences. Confirmation of mandibular dislocation requires careful assessment, combined with complementary tests for an accurate diagnosis that excludes other conditions such as Bell's palsy. Conservative treatment, with reduction maneuvers, counselling therapy and the use of the Front Plateau, were effective in recovering mandibular function.

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Introduction

Temporomandibular disorders (TMD) are disturbances that can affect the temporomandibular joint (TMJ), the muscles of mastication and their adjacent structures (de Leeuw and Klasser, 2018; Melchior et al., 2019). They have a multifactorial etiology and may be associated with structural, neuromuscular, occlusal, psychological factors, parafunctional habits and trauma (Da-Cas et al., 2024). Among the main signs and symptoms related to TMD are pain on palpation, joint noises, headaches, otalgia, facial pain, muscle fatigue, spasms and mandibular deviations (List and Jensen, 2017).

Due to its multifactorial characteristics and complex diagnosis, the identification of TMD involves clinical examinations, such as muscle palpation, functional manipulation and, in some cases, it requires complementary tests such as computed tomography (CT) and magnetic resonance imaging (MRI) (Ferreira et al., 2016; Maulén-Yáñez et al., 2019; Małgorzata et al., 2020). MRI is the method of choice for visualizing changes involving the soft tissues of the TMJ. CT allows the visualization of articular bone structures in different planes, as well as their possible manipulation at different depths and three-dimensional reconstruction, indicated to precisely determine the location of bone components and their changes (Silveira et al., 2014).

Among TMD, mandibular dislocation can confuse some professionals, making it difficult to diagnose correctly. It is a condition that can be bilateral or unilateral, and as for its frequency, habitual or recurrent. Mandibular dislocation can occur when the condyle of the mandible extends beyond the articular eminence of the temporal bone, exceeding the articular eminence. Depending on which side it occurs on, it can be anterior, superior or lateral (Hillam and Isom, 2023). This dysfunction can occur because of atraumatic etiologies or trauma to the mandible. Factors leading to atraumatic dislocation can include anything that results in forced and excessive opening of the mandible, such as yawning, seizures or repeated chewing, as well as underlying anatomical causes, such as ligament laxity or connective tissue disorders (Cardoso et al., 2005; Liddell and Perez, 2015; Sharma et al., 2015).

Joints with a tendency to subluxation and/or dislocation itself can present a spontaneous manifestation, which occurs when the mouth is opened beyond its usual limit. In the case of subluxation, also referred to as hypermobility, this happens during a wide opening movement, where the condyle goes beyond the articular eminence. Clinically, it is possible to observe a "jump" of the mandibular condyle beyond the articular eminence, causing a depression in the preauricular region. Despite this, it is not a pathological condition, since in most cases the condyle returns to its original position when the mouth is closed (Okeson, 2013). In mandibular dislocation, the TMJ is forced beyond its maximum opening limit and the condyle exceeds the articular eminence in such a way that the depressors and elevators of the mandible are stimulated, making it difficult for the condyle to return to its original position. This can occur through the elevation of the mandible by the temporalis and masseter muscles before relaxation by the lateral pterygoid occurs (Okeson, 2013; Hillam and Isom, 2023).

This clinical situation can be underreported by some professionals, who may associate the clinical signs with other diseases such as Bell's palsy, a sudden and unilateral weakening of the facial nerve, which partially or totally affects one side of the face. Symptoms can include pain around the ear, facial numbness and altered sense of taste (Holland and Bernstein, 2014).

When the mandible dislocates, pain stimulates spasm or contraction of the masticatory muscles, which can cause the condyle to rise and lock anteriorly to the articular eminence (Cardoso et al., 2005). According to the literature, dislocations of more than 6 months usually require complicated surgical procedures such as condylectomy, myotomy and other methods to correct the occlusion and reduce the mandible to a normal relationship with the maxilla (Huang et al., 2011). As the time between the onset of dislocation and repositioning increases, the prognosis is less favourable (Wijmenga et al., 1986). In cases of subluxation and dislocation proper of the mandible, approaches can involve anything from manual reduction of the condyle to surgical procedures such as eminectomy (Cecílio, 2019). Failures of non-surgical methods are due to the resistance offered by spasm of the masticatory muscles, shortening and subsequent fibrosis of the temporal and pterygoid muscles, periarticular fibrosis, disc displacement and pseudoankylosis between the zygomatic arch and coronoid process (Debnath et al., 2006).

To avoid more invasive and irreversible treatments for the patient, non-invasive and reversible interventions are initially prioritized and, if they are not effective, more invasive procedures are used, aiming for the patient's functional, emotional and orthopedic balance (Almeida et al., 2016). Choosing the most appropriate course of action will depend on a detailed medical history, a well-constructed anamnesis and the help of complementary tests, when necessary (Reid and Greene, 2013). Therefore, the aim of this case report was to highlight the importance of a detailed anamnesis supported by complementary exams in the

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differential diagnosis of TMD in a patient referred with a diagnosis of Bell's palsy, exploring the management of the mandibular dislocation found.

Diagnostic methods for TMD

The diagnosis of TMD is a complex process that involves a detailed assessment of the clinical history, physical examination and, when necessary, complementary tests (Sassi et al., 2018). For a good diagnosis, a detailed anamnesis is of paramount importance, where the health professional collects information about the patient's symptoms, including the nature of the pain, its location, duration and factors that can aggravate or alleviate it (Okeson, 2019). In addition, it is important to identify factors that may be contributing to the dysfunction, such as parafunctional habits like bruxism, stress or a history of trauma (Chan et al., 2022).

During the clinical examination, it is essential to assess mandibular function, observing mandibular movements when opening and closing the mouth, as well as checking for the presence of clicks or crackles in the TMJ. Palpation of the masticatory muscles and the TMJ region is essential to detect areas of muscle tension or tenderness (Schiffman et al., 2014).

In addition to the physical examination, complementary tests are often necessary to confirm the diagnosis and assess the extent of dysfunction. CT is one of the most useful tools, as it allows the bony structure of the TMJ to be visualized in detail, which is important for detecting alterations such as a shallow articular eminence, which can predispose to dislocations, or anatomical deviations in the mandibular fossa (Talmaceanu et al., 2018). CT is also useful for assessing the presence of bone lesions and other joint alterations that may be associated with TMD (Dhabale and Bhowate, 2022).

Another widely used complementary test is MRI, which is very suitable for examining soft tissues associated with the TMJ, such as the articular disc, ligaments and masticatory muscles. According to Al-Saleh et al. (2016), MRI is extremely effective for assessing changes in the articular disc, which can be displaced or damaged in many cases of TMD, causing pain and compromising mandibular function. MRI can also identify inflammation in the soft tissues and the presence of altered anatomy that contributes to dysfunction (Balel et al., 2023).

Depending on the patient's condition, neurological examinations may be necessary, especially when there are symptoms that can be confused with other conditions, such as Bell's palsy, characterized by the inability to move the facial muscles. In these cases, the differential diagnosis between TMD and other neurological conditions, such as Bell's palsy, is made through the exclusion of neurological diseases and detailed analysis of joint and facial muscle function (Baugh et al., 2013).

Mandible dislocation

This condition occurs when the mandibular condyle dislocates from the mandibular fossa and can result in severe pain and the inability to close the mouth (Hillam and Isom, 2023). It can be caused by direct trauma, such as accidents or blows, or by an anatomical predisposition. Dislocation can be unilateral or bilateral, with the unilateral form being more common (Sharma et al., 2017).

The diagnostic hypothesis of mandibular dislocation can be raised from the clinical evaluation, based on mandibular movement (opening, closing, protrusion and laterality), which may be associated with severe pain (Hillam and Isom, 2023). Physical examination can reveal the abnormal position of the mandible, while complementary tests such as CT and MRI are used to confirm the diagnosis and assess the displacement of the condyle and joint changes (Okeson, 2019; Balel et al., 2023).

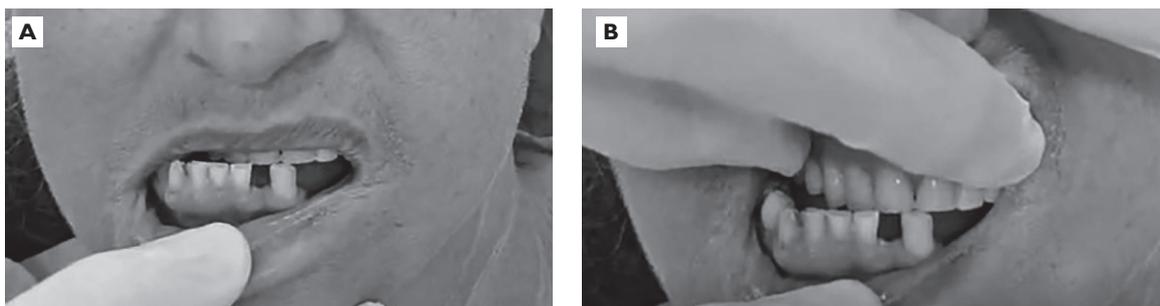Initial treatment usually involves reduction maneuvers, which reposition the mandible (Liddell

Figure 1: Initial appearance of the patient, revealing an anterior projection of the mandible (A) and deviation to the right side (B) even at rest.

and Perez, 2015). In recurrent or chronic cases, the use of devices such as full or partial occlusal splints, such as the Front Plateau, may be indicated to stabilize the condyle-joint relationship and prevent further dislocations (Okeson, 2019). If the maneuvers are not effective, surgical interventions such as eminectomy may be necessary to restore an anatomy compatible with a more stable joint function (Martins et al., 2014).

Case report

Study design
The case was conducted in a TMD School Clinic of the Department of Dentistry of a Federal University, by students of the Dentistry course under the supervision of two periodontics professors, one of whom was a TMD specialist and a professor in the area. In addition, the study followed the Helsinki Declaration of 1975, revised in 2013 (General Assembly of the World Medical Association, 2014), was approved by the Research Ethics Committee (7.263.258) and the patient signed an informed consent form. This case report was designed and written in accordance with the CARE Guidelines: Consensus-based Clinical Case Reporting Guideline Development (Gagnier et al., 2013).

Case description
Patient, 66-years-old female, living in a rural area, was referred to the University Clinic of Stomatology on June 26, 2024, by her neurologist, with a suspected recurrence of Bell's palsy diagnosed in January 2023. According to the patient, after the diagnosis, she underwent physiotherapy sessions with a slight improvement in her symptoms. Neurological examinations ruled out alterations in the spinal cord, spine and brain. The patient was systemically healthy.

The patient wore superior complete prostheses and had missing posterior inferior teeth on both sides. According to the patient's reports, she had received rehabilitative treatment for an inferior removable partial prosthesis (RPP), but due to the postural condition of her jaw she was unable to wear it.

When she was assessed by the stomatology team, no clinical signs compatible with Bell's palsy were found. The patient was therefore referred to the TMD clinic under the supervision of a specialist in the field. When mandibular movement tests (maximum opening, protrusion and laterality on both sides) and functional manipulation were carried out, the diagnostic hypothesis of left-sided mandibular dislocation was raised. Figure 1 shows the patient's initial facial appearance.

In this case, CT was requested to confirm the diagnosis. The CT scan revealed a change in the position of the mandibular condyle on the left during mouth opening (Figure 2A) and mouth closing, with no return to the articular fossa (Figure 2B), confirming mandibular dislocation. The right side showed no alteration, either during mouth opening (Figure 3A) or closed mouth (Figure 3B).

Treatment description

Jaw reduction maneuver
The bimanual method (Liddell and Perez, 2015) was used to reduce the mandibular dislocation identified on the left side. In this case, the patient was instructed to sit in a chair while the operator stood directly in front of the patient. The operator then positioned both thumbs in the region of the patient's respective inferior molars. As the posterior teeth were missing in this case, the external oblique ridge can be used as a reference, occupying the most posterior region
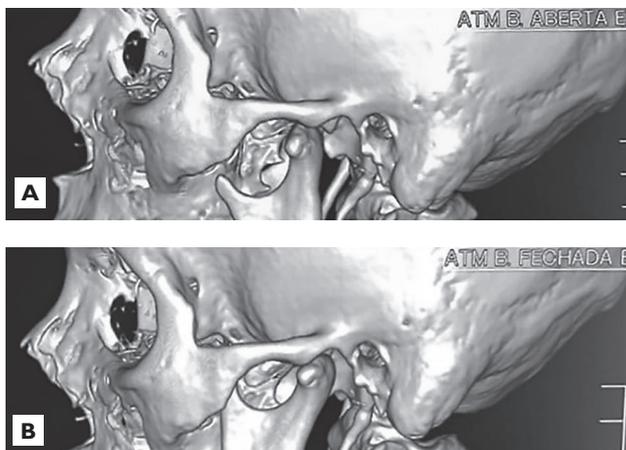

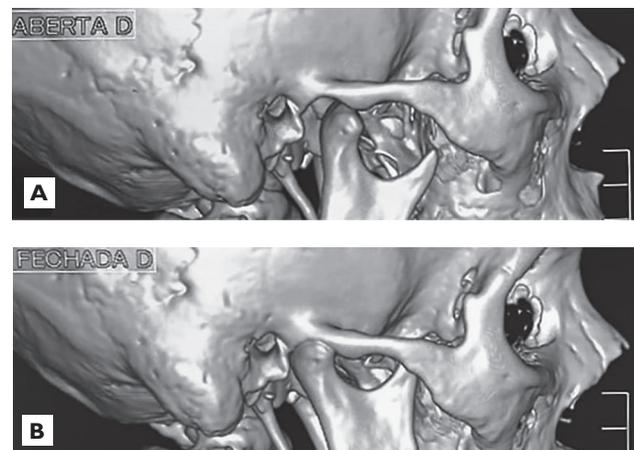*Figure 2: Computed tomography scan of the left side. (A) During mouth opening. (B) Mouth closed.*

Figure 3: Computed tomography scan of the right side. (A) During mouth opening. (B) Mouth closed.

possible. The thumbs can be wrapped in gauze for protection. The operator's other fingers were placed outside the mouth at the angle of the mandible to elevate the mandibular body and chin. Pressure was applied by the thumbs to push the mandible downwards and then backwards, keeping the mouth slightly open. In this case, the left side was pressed down and back more, as this was the side with the condyle trapped in front of the articular eminence. The aim was to release the condyle from the articular eminence and push the mandible back into the articular fossa of the temporal bone.

Counselling therapy for the patient

Due to the postural condition developed by the patient, counselling therapy was given to re-educate the mandibular posture during the opening and closing of the mouth. The aim of these exercises was to induce a more comfortable and stable mandibular position without pain (Simões et al., 2023). The guidelines adopted can be found in Table 1.

Adjustment of the inferior RPP

To provide the patient with complete rehabilitation treatment, attempts were made to adjust the inferior RPP during the appointments. However, due to the length of time the patient had not worn the prosthesis, it was not possible to achieve a satisfactory fit. In addition, the superior complete prostheses were also poorly adapted. The team therefore decided to refer the patient to the Integrated Clinic of the Department of Dentistry at the same institution to have new complete prostheses and an inferior RPP made.

Front Plateau manufacturing

To facilitate the patient's adaptation to the new mandibular position, a rigid occlusal splint with partial coverage was made, called a Front Plateau. In the case of this patient in particular, the Front Plateau involved the inferior anterior teeth (Gomes et al., 2018; Belchior et al., 2021; Leonan-Silva et al., 2025).

The following materials were used to make the Front Plateau: self-curing colourless acrylic resin liquid and powder, dosing cup, kit of cutters and polishing tips, carbon paper, Muller tweezers, No. 31 spatula, brush, paladon pot, water tank and procedure gloves.

After organizing the materials, the acrylic resin powder was mixed with the liquid in the paladon jar for manipulation. This was done until a homogeneous mixture was obtained. The paladon jar was then closed and we waited until the acrylic resin lost its shine and reached its plastic phase.

After isolating the patient's teeth and the operator's fingers with liquid petroleum jelly (to prevent the resin from sticking during manipulation), the resin was manipulated with the operator's fingers until it was shaped like a stick and adapted to the patient's inferior anterior teeth (33 to 43).

Table 1: Counselling therapy

1) Relax your jaw muscles	Try not to clench your teeth. Practice keeping your tongue on the roof of your mouth, behind your front teeth, your lips together and your teeth apart.
	Maintain good head, neck and back posture. This will help relax your jaw muscles.
	Avoid sleeping on your stomach or in other positions that strain your jaw and neck muscles.
2) Try not to open your mouth too widely	Avoid opening your mouth wide when yawning, avoid shouting and singing and avoid long sessions at the dentist.
	When yawning, place the palm of your hand under your chin to avoid opening it too much, keeping your tongue up.

Figure 4: Front Plateau after finishing and polishing.
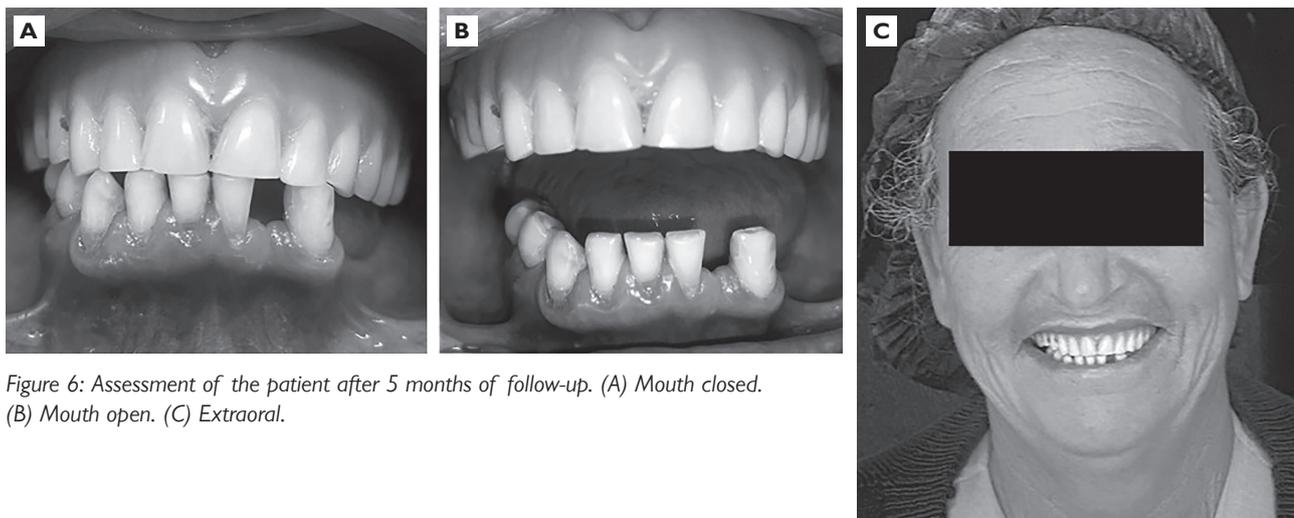

Figure 5: Patient assessment after 1 month.

Figure 6: Assessment of the patient after 5 months of follow-up. (A) Mouth closed. (B) Mouth open. (C) Extraoral.

The patient was instructed to always bite down with her tongue on the palate to ensure that the Front Plateau acted in centric relation. During the setting time, due to the acrylic resin heating up, the Front Plateau was removed from the patient's mouth and placed to rest in a tub of water. The material was then returned to the patient's mouth. After the setting time, occlusal adjustments were made, ensuring that all the anterior teeth were touching, and with a small step with slight marks on the antagonist teeth so that occlusion only occurred in that position.

At the end, the Front Plateau was finished and polished with a set of cutters and abrasive tips for delivery to the patient (Figure 4).

Patient follow-up

The patient has been followed up for 5 months, since the first assessment at the TMD Clinic and the interventions. After 1 month of using the Front Plateau and following the instructions, it was already possible to see a considerable improvement in the patient's mandibular posture (Figure 5).

The last appointment was made in November 2024, when it was possible to see a considerable improvement in the patient's initial condition (Figure 6A–C).

The need for restorative treatment was identified in teeth 42, 43, 44 and 45, so restorations in Vittra APS Unique monochromatic composite resin (FGM, Joinville, SC, Brazil) were made in teeth 42 (Class IV Distal), 43 (Class IV Mesial), 44 (Class II Distal), 45 (Class II Distal).

Subsequently, the patient will receive rehabilitative treatment with the manufacture of new: superior complete prostheses and a new inferior RPP. The treatment will be carried out by students in the Integrated Clinic of the Department of Dentistry under the supervision of teachers in prosthodontics.

Discussion

The patient in this study lives in a rural area in the Jequitinhonha Valley, located in the state of Minas Gerais in Brazil. Historically, the region has faced major challenges in terms of access to basic health services, especially specialized dental care (Bernardes, 2017; Andrade and Andrade, 2021). This contributes to late diagnosis and inadequate treatment of specific conditions, such as TMD. The scarcity of specialized professionals, the lack of health information, as well as restricted access to imaging tests such as CT and MRI in large urban centers, make it difficult to establish definitive diagnoses and specific treatment for each condition (Balel et al., 2023).

Detailed anamnesis is essential in the diagnosis of TMD (List and Jensen, 2017). Collecting data on medical history, such as previous episodes of mandibular dislocation or neurological diseases such as Bell's palsy, is fundamental to identifying risk factors and establishing an appropriate treatment plan. In the case of the patient in question, medical history ruled out possible neurological disorders resulting from the condition detected in 2023. In the literature, three cases of patients with confirmed Bell's palsy and TMD involvement were found, one of them with mandibular dislocation (Santos et al., 2009; Alfaya et al., 2012; Ascenço et al., 2012). However, in all cases, a sign was identified which is a differential of true Bell's palsy, namely the impossibility of voluntary eyelid closure on the paralyzed side (Hungria, 2000). This manifestation was not observed in the patient in question.

From then on, the diagnosis was directed towards the stomatognathic system and TMD. After assessing mandibular movement based on opening, closing, protrusion and laterality (Schiffman et al., 2014), signs and symptoms suggestive of mandibular dislocation were detected, such as difficulty closing the mouth, joint instability, muscle pain and the impossibility of performing functional movement (Hillam and Isom, 2023). These clinical findings are in line with other studies in which mandibular dislocation was confirmed (Man et al., 2011; Vasconcelos et al., 2014; Sharma et al., 2017).

Imaging tests play a fundamental role in confirming the diagnosis of mandibular dislocation and other TMDs. As discussed by Balel et al. (2023), CT and MRI are crucial for detailed visualization of the TMJ and surrounding tissues. With the CT scan, it was possible to obtain a conclusive diagnosis, revealing that the patient had a slightly shallow articular eminence, which made it easier for the mandibular condyle to escape from the mandibular fossa during the dislocation. CT is considered the imaging method of choice for assessing TMJ bone conditions and is superior to conventional radiography in visualizing structural lesions, even in cases without obvious bone lesions. The relevance of using CT was also highlighted by Talmaceanu et al. (2018), who state that CT allows detailed visualization of subtle anatomical features, such as the formation of the articular eminence, which may not be adequately detected by other imaging modalities.

The initial treatment of mandibular dislocation was carried out using the bimanual reduction maneuver, an effective conservative technique, especially in cases of acute dislocation (Liddell and Perez, 2015). Although the technique has proved effective in repositioning the mandible and relieving the pain associated with the dislocation, some authors report that, depending on the time and factors associated with the dislocation, such as those caused by macrotraumas, surgical interventions such as eminectomy and eminoplasty are necessary (Martins et al., 2014; Vasconcelos et al., 2014; Santos et al., 2022). Most cases reported were the result of car accidents and the condition had existed for at least 6 months. Another surgical approach also mentioned in the literature is the installation of mini bone plates, especially in cases of recurrent dislocation (Cardoso et al., 2005; Vasconcelos et al., 2009).

The use of auxiliary devices to stabilize the closing and opening arch after the reduction maneuver, such as occlusal splints, full and partial coverage, such as the Front Plateau, can be used (Okeson, 2019). Occlusal splints can be a good alternative for patients who have undergone treatment for chronic dislocations, as they allow the mandible to acquire an anatomically and physiologically correct position, stabilizing the temporomandibular joint and preventing recurrences (Al-Moraissi et al., 2020).

As noted in this report, a careful approach to cases of mandibular dislocation is necessary, because as described in the literature, minimally invasive treatment, such as the one adopted, is not always successful (Vasconcelos et al., 2014). In addition, it is essential to combine these approaches with counselling therapy on TMD and constant monitoring of the patient to assess the effectiveness of the treatment.

Conclusion

In this case, an anamnesis and detailed clinical examinations were essential in establishing the diagnostic hypothesis of mandibular dislocation and excluding recurrence of Bell's palsy. The use of CT was fundamental in confirming the diagnosis and establishing a specific treatment plan for the case. The bimanual mandibular dislocation reduction technique, followed using the Front Plateau and counselling therapy, contributed to greater mandibular stability, preventing recurrences of the condition. In addition, according to the patient's reports, there was a reduction in the pain that existed before treatment and an improvement in her self-esteem.

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