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Plasma levels of quinolinic acid and kynurenic acid in patients with major mental illnesses

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Abstract. Clarifying antipsychotic effects on kynurenine-pathway metabolites may improve understanding of their role in major mental illnesses. Therefore, this study aimed to assess plasma quinolinic and kynurenic acid levels in patients with major mental illnesses. 85 adults comprising 55 treatment-experienced patients with major mental illnesses; schizophrenia, bipolar and depression, and 30 controls were enrolled into this study. The plasma levels of quinolinic acid and kynurenic acid were determined using Enzyme Linked Immunosorbent Assay. Plasma quinolinic acid level was significantly lower in patients with major mental illnesses (14.52 (7.16-48.24) mg/mL) compared with the controls (157.79 (68.64-464.05) mg/mL). In contrast, plasma kynurenic acid level was higher in patients with major mental illnesses (243.96 (210.65-283.05) μmol/L) compared with the controls (215.36 (185.67-243.65) μmol/L). After stratification into groups, patients with schizophrenia (22.86 (7.62-53.14) mg/mL), bipolar (15.34 (8.37-48.21) mg/mL)

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and depression (6.18 (2.66-43.05) mg/mL) had significantly lower quinolinic acid levels compared with the controls (157.79 (68.64-464.05) mg/mL). However, kynurenic acid levels were only significantly elevated in patients with schizophrenia (247.0 (208.34-290.22 μmol/L) and bipolar (243.20 (212.85-291.12) μmol/L) compared with the controls (215.36 (185.67-243.65) μmol/L). The plasma levels of quinolinic acid and kynurenic acid did not differ significantly among patients with schizophrenia, bipolar disorder, and depression. Treated patients with major mental illnesses exhibited a kynurenine metabolite profile indicative of reduced neurotoxicity and enhanced neuroprotection. These metabolites may serve as potential biomarkers for monitoring treatment effects

Keywords: antipsychotics; inflammation; tryptophan metabolism; mental health disorders; neuroprotection

Introduction

Major mental illnesses (MMI), including schizophrenia, bipolar disorder, and depression, are complex and heterogeneous conditions with substantial personal, social and economic burdens worldwide. Aetiology extends beyond neurotransmitter as it involves abnormalities in hypothalamic-pituitary-adrenal axis regulation, alongside epigenetic modifications, neuroinflammatory processes, and altered kynurenine pathway metabolism. Adequate understanding of the biological pathways that integrate these systems is clinically essential for improving diagnosis, monitoring treatment response, and advancing personalised therapy. Among these pathways, alterations in tryptophan metabolism and downstream neuroactive metabolites continue to gain growing attention as possible contributors to symptom progression and therapeutic outcomes.

Inflammation has been shown to play a significant role in the clinical progression of neuropsychiatric disorders. Elevated levels of proinflammatory cytokines, inflammatory mediators, acute phase proteins, cell sensors, and adhesion molecules were found in a study by K.S. Akinlade *et al.* [1] in the blood and cerebrospinal fluid of patients with MMI. The kynurenine pathway is a biological interface linking immune activation to neurochemical and behavioural disturbances in psychiatric disorders as the pathway generates multiple neuroactive metabolites. Approximately 95-99% of tryptophan is metabolized through the kynurenine pathway, while the remainder is used for protein synthesis or converted into serotonin and melatonin [2]. Several studies have examined alterations in kynurenine pathway metabolites in schizophrenia. M. Marković *et al.* [3] assessed plasma levels of tryptophan, kynurenine, and kynurenic acid (KA) during both the acute and remission phases of schizophrenia. Their findings showed that kynurenine and KA were consistently reduced in affected individuals, regardless of disease stage, antipsychotic therapy, episode number, or illness duration. In a related study, C. Kuuskmäe *et al.* [4] evaluated kynurenine pathway dynamics in schizophrenia spectrum disorders and similarly reported decreased KA and quinolinic acid (QA), noting that antipsychotic treatment diminished the magnitude of pathway alterations over time.

M. Li *et al.* [5] analysed serum and urine kynurenine metabolites in drug-naïve patients with first-episode schizophrenia and observed an elevated QA/KA ratio, indicating a shift toward neurotoxic dominance alongside reduced concentrations of neuroprotective metabolites. In patients with depression, Y. Pan *et al.* [6] examined the association between cognitive deficits and kynurenine-pathway metabolites in individuals with depression. They reported reduced plasma concentrations of kynurenine and QA, alongside a marked increase in KA, when compared with healthy controls. In a related study, R. Colle *et al.* [7] also found decreased circulating levels of kynurenine, KA, and picolinic acid in depressed patients, and further noted that KA levels rose significantly after treatment with antidepressant medications.

K. Hebbrecht *et al.* [8] investigated how alterations in the kynurenine pathway relate to cognitive performance across various mood states in individuals with bipolar disorder. Their findings showed that plasma KA concentrations were markedly reduced in patients compared with healthy controls, and lower KA levels correlated with poorer overall cognitive outcomes. More recently, E. Yavuz Ataşlar & K. Altınbaş [9] assessed the predictive value of circadian rhythm markers and tryptophan-kynurenine pathway indices in bipolar disorder. They found that both patients with bipolar disorder and their siblings exhibited an increased kynurenine/tryptophan ratio. In a study investigating if individual catabolites could serve as diagnostic biomarkers, M. Brum *et al.* [10] reported that plasma concentrations of tryptophan, kynurenine, KA, and QA were reduced in the overall patient cohort (schizophrenia, bipolar disorder and depression) compared with healthy controls, and that the pattern was largely driven by differences observed in individuals with bipolar disorder. They however, did not observe any significant difference among the specific diagnostic groups.

Findings across studies have been inconsistent, particularly regarding KA and QA concentrations, due to factors like study populations, ethnicity, diagnostic thresholds, medication exposure, and methodologies. Few studies have explored these metabolites in African populations, despite evidence that genetic, environmental, dietary, and treatment factors may affect immune-metabolic pathways. Given the differences in antipsychotic responses across populations, there is a need for population-specific investigations. Despite the clinical burden of mental illnesses in Nigeria, data on kynurenine-pathway metabolites during antipsychotic therapy remain limited. The purpose of this study was to assess alterations in specific metabolites of the kynurenine pathway in patients with major mental disorders receiving treatment, in order to address this knowledge gap.

Materials and Methods

This study was conducted in full compliance with the ethical principles of the Declaration of Helsinki [11]. The study was conducted at the University of Ibadan and approved by the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee (UI/EC/23/0456) signed on 05 August 2024. Written informed consent was obtained from all the study participants, and for individuals with impaired decision-making capacity, assent was secured from appropriate relatives or guardians. The study was conducted between August 2024 and January 2025. This study enrolled 85 participants, comprising 33 patients with schizophrenia, 12 with bipolar disorder, 10 with depression, and 30 apparently healthy controls. Considering the sex of the study participants, there were 15 males and 15 females among the controls, while the MMI group had 28 males and 27 females. Patients were recruited from the Psychiatry Department of the University College Hospital, Ibadan, and New World Specialist Hospital, Molete, Ibadan, Nigeria. Control participants were recruited from the Ibadan metropolis and were certified to be free of psychiatric disorders by a Consultant Psychiatrist.

Diagnoses of schizophrenia, bipolar disorder, and depression were established using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [12]. Exclusion criteria included current substance abuse or dependence, autoimmune disorders or steroid therapy, diabetes mellitus, and severe or unstable medical conditions. A short structured questionnaire was used to obtain information on demography and clinical history. The questions included age of the participant at the time of enrollment, sex (male or female), highest level of education attained, marital status (single, married, separated/divorced, widowed), employment status (employed, unemployed, student, retired), duration of illness since initial diagnosis (in years), family history of psychiatric disorders particularly first-degree relatives, current medications and duration of treatment, including antipsychotics, mood stabilizers, and antidepressants, history of substance abuse, and history of comorbid medical conditions, including autoimmune disorders, diabetes mellitus, or other chronic illnesses. Therefater, venous blood samples (5 mL) was collected from each study participant into heparin-containing sample bottles and plasma was obtained as appropriate. The plasma samples were thereafter, stored at -20°C until analysed. Plasma levels of KA and QA were determined using sandwich ELISA following the manufacturer's instruction (Melsin Medical Co., China).

Data were analysed using the Statistical Package for Social Sciences version 27.0 and Graphpad version 9.0 software package. Normal distribution of the data was assessed using Shapiro-Wilk test and Kolmogorov-Smirnov test. Differences in the mean values of age was determined using the Student's t-test, while the Kruskal-Wallis H and Man Whitney *U* tests were used to determine the differences in the median values of each variable between the groups. Chi-square was used to determine association between sex and various cohorts. Thereafter, a rank-based one-way analysis of covariance was conducted to compare the different groups on the dependent variable, adjusting for age as a covariate. The dependent variable was rank-transformed due to violations of normality assumptions. The correlation between the variables was assessed using Spearman's Rho correlation. P-values below 0.05 (2-tailed) were regarded as statistically significant. The results are presented as mean ± standard deviation, median (interquartile range), and in box plots, where applicable.

It is important to note that the statistical power of this study was limited by the small and unequal sample sizes in some diagnostic subgroups. This reduces the ability to detect small to moderate effect sizes and may affect the stability of variance estimates. Also, the absence of baseline QA and KA levels and medication history prevent causal inference regarding the effects of antipsychotic therapy on selected metabolites of the kynurenine pathway. Therefore, findings from this study should be interpreted as preliminary and require validation in larger, well-powered longitudinal studies involving drug-naive cohorts.

Results and Discussion

The mean ages of the patients with MMI and controls were 36.38 ± 11.65 years and 29.40 ± 7.41 years, respectively. There was significant difference between the mean ages of MMI compared with the controls (p = 0.001). There was no significant association between the sex and the study cohorts (p = 0.936). As shown in Table 1, plasma QA level was significantly lower in patients with MMI compared with the controls. In contrast, the plasma KA level was significantly higher in patients with MMI compared with the controls. Similarly, the median KA/QA ratio was significantly higher in MMI group compared with the controls.

Table 1. Age, sex and plasma levels of QA and KA in patients with MMI and control

Parameters	MMI (n = 55)	Controls (n = 30)	p-value
Age (years)	36.38 ± 11.65	29.40 ± 7.41	0.001*
Sex Male Female	28 (50.9%) 27 (49.1%)	15 (50.0%) 15 (50.0%)	0.936†
QA (mg/mL)	14.52 (7.16-48.24)	157.79 (68.64-464.05)	0.000*
KA (μmol/L)	243.96 (210.65-283.05)	215.36 (185.67-243.65)	0.004*

Continued Table 3

Parameters	MMI (n = 55)	Controls (n = 30)	p-value
KA/QA ratio	17.51 (5.46-44.21)	1.38 (0.25-2.47)	0.000*

Note: *significant at $p < 0.05$; †p-value from chi-square
Source: compiled by the authors

Since age was significantly different between the two groups, a rank-based analysis of covariance was performed to assess group differences in plasma QA, KA, and the KA/QA ratio in MMI group compared with the controls while adjusting for age. For QA, KA and KA/QA ratio, the overall models were statistically significant ($p = 0.000$, $p = 0.010$ and $p = 0.000$, respectively). As shown in Table 2, QA ranks differed significantly in patients with MMI and controls, after age adjustment. A similar pattern was observed for KA and KA/QA ratio. However, age showed insignificant independent associations with QA, KA and KA/QA ratio. Across all analyses, Bonferroni-adjusted pairwise comparisons revealed significant differences in QA, KA and KA/QA ratio between the two groups.

Table 2. Age-adjusted differences in the parameters in the study participants

Outcome variable	Source of variation	F (df = 1.82)	p-value	Partial η^2
QA rank	Diagnostic group	69.375	0.000*	0.458
	Age (covariate)	1.469	0.229	0.018
KA rank	Diagnostic group	7.255	0.009*	0.081
	Age (covariate)	0.428	0.515	0.005
KA/QA ratio rank	Diagnostic group	71.542	0.000*	0.466
	Age (covariate)	2.273	0.135	0.027

Note: *significant at $p < 0.05$. Rank-based Analysis of Covariance was used because QA and KA were non-normally distributed. Diagnostic groups included MMI and controls
Source: compiled by the authors

As shown in Figure 1, the plasma levels of QA were significantly lower in patients with schizophrenia, bipolar disorder and depression compared to controls (p-values; <0.0001, <0.0001, and <0.0001, respectively). In contrast, plasma KA levels were significantly higher in patients with schizophrenia, and bipolar compared to controls (p-values; 0.0030 and 0.0296, respectively) but the level was similar in patients with depression and the controls. Similarly, the ratio of KA to QA was significantly higher in patients with schizophrenia, bipolar and depression compared to controls (p-values; <0.0001, <0.0001, and <0.0001, respectively).

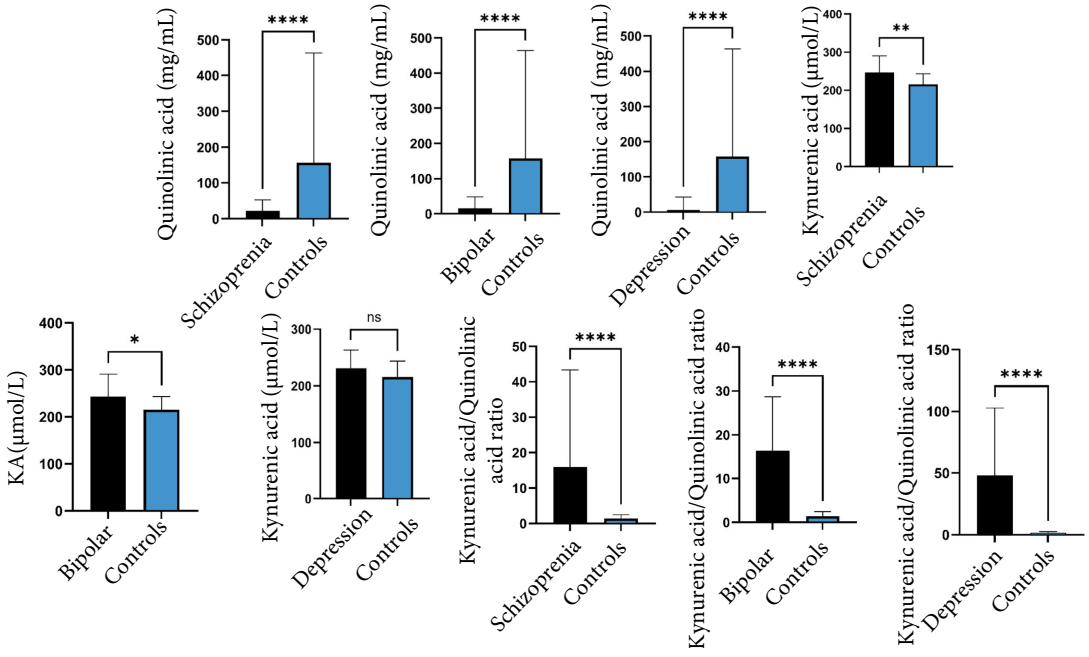

Figure 1. Plasma levels of QA, KA and KA/QA ratio in patients
Source: compiled by the authors

Table 3 presented the plasma concentrations of KA and QA in patients with schizophrenia, bipolar disorder, and depression. While significant age differences were observed between the three groups, the plasma levels of QA, KA, and the KA/QA ratio were comparable across all groups.

Since age was significantly different among the patients groups, a rank-based analysis of covariance was performed to assess group differences in plasma QA, KA, and the KA/QA ratio while adjusting for age. As shown in Table 4, after age adjustment, QA ranks did not differ significantly among patients with schizophrenia, bipolar disorder, and depression ($F(2.51) = 0.573$, $p = 0.568$). A similar pattern was observed for KA. For the KA/QA ratio, the overall model was statistically significant; however, the diagnostic group effect remained non-significant, while age showed a significant independent association with the ratio ($p = 0.006$). Across all analyses, Bonferroni-adjusted pairwise comparisons revealed no significant differences between diagnostic groups.

Table 3. Age, sex and plasma levels of QA and KA in patients with MMI and control

Parameters	Schizophrenia	Bipolar	Depression	p-value
Age (years)	40.42 ± 11.43	30.08 ± 10.93	30.60 ± 7.29	0.000*
Sex Male Female	 17 (51.5%) 16 (48.5%)	 5 (41.7%) 7 (58.3%)	 6 (60.0%) 4 (40.0%)	0.689†
QA (mg/mL)	22.86 (7.62-53.14)	15.34 (8.37-48.21)	6.18 (2.66-43.05)	0.422
KA (μmol/L)	247.0 (208.34-290.22)	243.20 (212.85-291.12)	230.76 (182.06-263.46)	0.448
KA/QA ratio	15.99 (6.41-43.38)	16.47 (4.38-28.71)	48.03 (3.45-102.67)	0.482

Note: *significant at $p < 0.05$, †p-value from chi-square
Source: compiled by the authors

Table 4. Age-adjusted differences in the parameters in schizophrenia, bipolar disorder, and depression patients

Outcome variable	Source of variation	F (df = 2.51)	p-value	Partial η^2
QA rank	Diagnostic group	0.573	0.568	0.022
	Age (covariate)	3.784	0.057	0.069
KA rank	Diagnostic group	0.641	0.531	0.025
	Age (covariate)	0.277	0.601	0.005
KA/QA ratio rank	Diagnostic group	1.324	0.275	0.049
	Age (covariate)	8.294	0.006*	0.140

Note: *significant at $p < 0.05$. Rank-based Analysis of Covariance was used because QUIN and KYNA were non-normally distributed. Diagnostic groups included schizophrenia, bipolar disorder, and depression
Source: compiled by the authors

Correlations between plasma QA and KA levels in patients with MMI and controls are shown in Table 5. Plasma QA level had no significant correlation with plasma KA level in patients with MMI and controls.

Table 5. Correlation between plasma levels of QA and KA in patients with MMI and controls

Parameters	MMI		Controls	
	r-value	p-value	r-value	p-value
QA vs KA	0.179	0.191	0.162	0.391

Source: compiled by the authors

The pathophysiology of schizophrenia, bipolar disorder, and depression encompasses various levels of neuroimmune interactions, from the hypothalamic-pituitary-adrenal axis to elevated pro-inflammatory cytokines that interfere with neuroplasticity, neurogenesis, and the regulation of neurotransmission in different brain regions. Considering the complex crosstalk between neurotransmitter systems, neuroplasticity, and immune function, the kynurenine pathway represents a promising target for investigation [13]. QA, a known N-methyl-D-aspartate receptor agonist, is a known neurotoxic metabolite implicated in neuroinflammatory processes in MMIs such as major depressive disorder [14]. In this study, it was observed that plasma QA levels were significantly lower in MMI patients compared to healthy controls, even after adjusting for age. Although this observation supported the report of K. Skorobogatov *et al.* [15]

which showed that serum QA level was significantly lower in combined patients with schizophrenia and bipolar disorder compared to controls, it contrasts with other studies that linked elevated QA level to heightened neuroinflammation and excitotoxicity in patients with MMI [16]. These discrepancies could be due to the heterogeneity in patient characteristics, particularly the use of antipsychotic medications. In this study, all the MMI patients were on antipsychotic treatment at the time of sample collection, although medication type, dosage, or treatment duration could not be standardised or controlled for due to limited clinical documentation. S.R. Patlola *et al.* [17] reported that certain antipsychotics such as risperidone, an atypical antipsychotics, downregulate interleukin-6 and tumour necrosis factor-alpha levels in patients with chronic schizophrenia. They also reported that the duration of illness influences the extent of cytokine alteration. This antipsychotic-associated modulation of inflammatory pathways may impact kynurenine metabolism. While antipsychotic therapy may play a role, the absence of baseline QA levels precludes definitive conclusions about causality as other factors such as illness chronicity, nutritional status, or immune function may also play important roles. Taken this together with the unexpectedly elevated QA levels observed in the control group, these findings underscore the need for large population prospective studies that will explore the influence of diet, systemic inflammation, and assay variability on metabolites of the kynurenine pathway in patients with MMI.

Changes in peripheral metabolites of the kynurenine pathway, as reported by M. Brum *et al.* [10], are phase-specific and specific to disorders in patients with major depressive disorder, schizophrenia, and bipolar disorder. In this study, even after adjusting for age, the plasma levels of QA were insignificantly different in patients with schizophrenia, bipolar and depression. This observation corroborates the report of F. Cathomas *et al.* [18] which showed that the levels of QA in patients with schizophrenia and depression are similar. Observation from this study could indicate that the pattern of change in QA level in patients with MMI on antipsychotics is similar irrespective of the illness. KA, an endogenous antagonist of N-methyl-D-aspartate and α-7 nicotinic receptors, was found to be significantly elevated in MMI patients particularly, those with schizophrenia and bipolar disorder compared to controls. These observations are consistent with the results of a study by A. Trepci *et al.* [19], which reported elevated cerebrospinal fluid levels in these disorders. A.M. Myint *et al.* [20] reported an upward trend in KA after six weeks of antipsychotic therapy, which may reflect a shift in the kynurenine pathway toward neuroprotection. While observation from this study is consistent with the possibility of such a shift, the lack of baseline or drug-naïve comparisons limits the strength of this inference. A study by F. Cathomas *et al.* [18] reported that plasma KA levels in patients with schizophrenia and depression were similar. Similar trend was observed in this study as the plasma levels of KA were insignificantly different in patients with schizophrenia, bipolar disorder and depression. This observation further supports the earlier suggestion that the pattern of change in kynurenine metabolites during antipsychotics therapy is similar irrespective of the illness.

While KA levels were elevated and QA levels reduced in MMI patients relative to controls, were observed a significantly higher KA/QA ratio across all patient subgroups compared to controls. The KYNA/QUIN ratio has been proposed as a neuroprotective index, largely reflecting the balance between excitotoxic and neuroprotective arms of the kynurenine pathway [14]. Previous reports on KA/QA ratio in patients with MMI are inconsistent. B.E. Wurfel *et al.* [21] reported decreased KA/QA ratio in bipolar disorder and depression, while W. Marx *et al.* [22] observed no significant differences in schizophrenia. This variability may stem from differences in sample types, analytical methods, clinical status, and treatment exposure. The absence of significant differences in the KA/QA ratio, similar to the patterns observed for QA and KA levels, across schizophrenia, bipolar disorder, and depression groups further suggest a shared metabolic profile in treated patients with MMI.

In summary, drug-experienced patients with MMI exhibited significantly lower plasma QA levels and higher KA levels compared with healthy controls, resulting in a markedly increased KA/QA ratio, even after adjusting for age. These alterations were consistent across schizophrenia, bipolar disorder, and depression, with no significant differences among diagnostic subgroups. The findings suggest a shift in kynurenine pathway metabolism towards reduced neurotoxicity and enhanced neuroprotection in drug-experienced patients.

Conclusions

This study demonstrated that age-adjusted plasma QA levels were markedly lower in patients with MMIs than in controls (median 14.52 (7.16-48.24) vs 157.79 (68.64-464.05) mg/mL; $F(1.82) = 69.375$, $p < 0.001$, partial $\eta^2 = 0.458$). In contrast, plasma KA levels were significantly higher in patients with MMI (243.96 (210.65-283.05) vs 215.36 (185.67-243.65) μmol/L; $F(1.82) = 7.255$, $p = 0.009$), resulting in a substantially elevated KA/QA ratio (17.51 (5.46-44.21) vs 1.38 (0.25-2.47); $F(1.82) = 71.542$, $p < 0.001$). Subgroup analyses showed that patients with schizophrenia, bipolar disorder, and depression all exhibited significantly reduced QA levels and increased KA/QA ratio compared with controls, while age-adjusted differences in the parameters and their ratio were not significant among the three diagnostic categories. These observations suggested a shared kynurenine metabolic profile across MMI in drug-experienced patients. Furthermore, plasma QA and KA levels were not significantly correlated in either the patients or controls, indicating independent regulation of these metabolites. Overall, the observed pattern of reduced QA, elevated KA, and increased KA/QA ratio is indicative of a shift towards reduced excitotoxicity and enhanced neuroprotection in treated MMI patients, potentially reflecting the immunomodulatory and anti-inflammatory effects of antipsychotic

therapy. These metabolites, particularly the KA/QA ratio, may therefore serve as candidate peripheral biomarkers for monitoring treatment response in patients with MMI. Future research prioritising large-scale, longitudinal studies incorporating drug-naïve patients, standardised medication data, and baseline measurements are suggested to clarify causal relationships. Additionally, integrating dietary, inflammatory, and genetic factors will be essential for a more comprehensive understanding of the dynamics of the kynurenine pathway in MMI.

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Conflict of Interest

The authors have no competing interests to declare.

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Рівень хінолінової кислоти та кінуренової кислоти в плазмі крові пацієнтів з важкими психічними захворюваннями

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Анотація. З'ясування впливу антипсихотичних препаратів на метаболіти кінуренінового шляху може покращити розуміння їхньої ролі у розвитку основних психічних захворювань. Тому метою цього дослідження було оцінити рівні хінолінової та кінуренової кислот у плазмі крові пацієнтів з основними психічними захворюваннями. У дослідженні взяли участь 85 дорослих, серед яких 55 пацієнтів з основними психічними захворюваннями (шизофренія, біполярний розлад та депресія), які раніше проходили лікування, та 30 осіб з контрольної групи. Рівень хінолінової кислоти та кінуренової кислоти в плазмі крові визначали за допомогою імуноферментного аналізу. Рівень хінолінової кислоти в плазмі крові був значно нижчим у пацієнтів з тяжкими психічними захворюваннями (14,52 (7,16-48,24) мг/мл) порівняно з контрольною групою (157,79 (68,64-464,05) мг/мл). Натомість рівень кінуренової кислоти в плазмі був вищим у пацієнтів з тяжкими психічними захворюваннями (243,96 (210,65-283,05) μмоль/л) порівняно з контрольною групою (215,36 (185,67-243,65) μмоль/л). Після стратифікації на групи пацієнти зі шизофренією (22,86 (7,62-53,14) мг/мл), біполярним розладом (15,34 (8,37-48,21) мг/мл) та депресією (6,18 (2,66-43,05) мг/мл) мали значно нижчий рівень хінолінової кислоти порівняно з контрольною групою (157,79 (68,64-464,05) мг/мл). Однак рівень кінуренової кислоти був значно підвищений лише у пацієнтів із шизофренією (247,0 (208,34-290,22 μмоль/л) та біполярним розладом (243,20 (212,85-291,12) μмоль/л) порівняно з контрольною групою (215,36 (185,67-243,65) μмоль/л). Рівень хінолінової та кінуренової кислот не відрізнявся істотно у пацієнтів із шизофренією, біполярним розладом та депресією. Пацієнти, які лікувалися від серйозних психічних захворювань, мали профіль метаболітів кінуреніну, що вказував на зниження нейротоксичності та посилення нейропротекції. Ці метаболіти можуть слугувати потенційними біомаркерами для моніторингу ефектів лікування

Ключові слова: антипсихотики; запалення; метаболізм триптофану; розлади психічного здоров'я; нейропротекція

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Cardiopulmonary responses to neurophysiological facilitation of respiration in mechanically ventilated ICU patients

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Abstract. Mechanical ventilation is essential in acute illness but may lead to complications such as atelectasis and monotonous breathing, which physiotherapists help counter by using neurophysiological facilitation techniques to enhance the respiratory function of unconscious and sedated patients. By exploring neurophysiological facilitation techniques, the study aimed to evaluate the immediate effects of perioral pressure and intercostal stretch on cardiopulmonary parameters in mechanically ventilated patients at the University of Benin Teaching Hospital. A randomised crossover experimental design was used, involving ten patients (5 males, 5 females; mean age 66.2 ± 8.5 years) who were haemodynamically stable but unconscious and ventilated. Cardiopulmonary variables including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, oxygen saturation, and mean arterial pressure were measured before and after each neurophysiological facilitation techniques intervention using a standardised protocol. The results showed that perioral pressure significantly improved diastolic blood pressure (77.10 ± 9.01 to 79.30 ± 10.34 mmHg, $p = 0.005$), respiratory rate (26.40 ± 6.08 to 28.30 ± 6.60 breaths/min, $p = 0.014$), and mean arterial pressure (92.70 ± 10.70 to 94.00 ± 10.06 mmHg, $p = 0.022$). Intercostal stretch significantly increased respiratory rate (26.8 ± 6.07 to 28.2 ± 6.07 breaths/min, $p < 0.001$), while changes in systolic pressure, heart rate, and oxygen saturation were not statistically significant ($p > 0.05$). Gender did not influence the magnitude of changes in any cardiopulmonary parameter. The study established that neurophysiological facilitation techniques elicited beneficial acute effects on respiratory rate and haemodynamic parameters in mechanically

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ventilated patients and highlighted neurophysiological facilitation techniques as a practical adjunct to respiratory physiotherapy for improved cardiopulmonary stability in critically ill patients

Keywords: haemodynamic parameters; perioral pressure; intercostal stretch; respiratory therapy intervention; intensive care physiotherapy

Introduction

The respiratory care of unconscious patients in the intensive care unit (ICU) is particularly complex due to their inability to perform optimal voluntary respiratory activities, which leads to shallow breathing, atelectasis, reduced chest expansion, and monotonous breathing. This predisposes them to complications such as atelectasis, inefficient gas exchange, and secretion retention. Mechanical ventilation remains a vital supportive treatment for patients with acute respiratory failure, sedation, or compromised consciousness; however, prolonged use of a mechanical ventilator can result in respiratory muscle atrophy, reduced lung compliance, ventilation-induced lung injury, and altered haemodynamics. These challenges underscore the need for adjunct physiotherapeutic techniques to preserve respiratory function, maintain ventilation efficiency, and minimise complications in ventilated patients.

Researchers are working to improve respiratory mechanics, gas exchange, and treatment outcomes for patients on mechanical ventilation. The study by S. Das *et al.* [1] investigated the effect of intercostal stretch in combination with standard chest physical therapy in mechanically ventilated patients. They found significant improvements in arterial oxygen partial pressure (PaO_2) and significant reductions in arterial carbon dioxide partial pressure ($PaCO_2$), with the intervention group showing greater effect than control. In the scoping review by J.A. Carabalí-Rivera *et al.* [2], respiratory muscle training protocols (threshold load training at 40-50% maximal inspiratory pressure, twice daily, 30 repetitions) were reported to improve inspiratory muscle strength and enhance weaning success. In a systematic review by D. Mankad *et al.* [3], combining intercostal stretch and anterior basal lift techniques in neurophysiological facilitation of respiration, vertebral pressure, and perioral pressure techniques were collectively found to effectively improve haemodynamic (heart rate (HR), blood pressure) and pulmonary parameters (tidal volume, lung compliance, respiratory rate (RR), and peripheral oxygen saturation (SpO_2)) in mechanically ventilated patients.

In the research by K.N. Chowdhury [4], narrative review highlighted that intercostal stretch technique produced consistent improvements in chest expansion, diaphragm excursion, and intra-thoracic lung volume across various pulmonary conditions, including among patients with chronic respiratory disease and in ICU settings. S. Tong *et al.* [5] found that diaphragmatic stimulation significantly reduced the duration of patients on mechanical ventilation, improved maximal inspiratory pressure, and increased the proportion of patients who were successfully weaned. Furthermore, the study by T. Bassi *et al.* [6] on restoring Brain Connectivity by Phrenic Nerve Stimulation, the addition of phrenic nerve stimulation in deeply sedated ventilated patients with acute respiratory distress syndrome increased cortical connectivity in frontal-temporal-parietal cortices, suggesting neural benefits that may extend beyond gas exchange alone. F. Azimi *et al.* [7] compared two physiotherapy techniques (lung squeezing versus chest vibration/percussion) in mechanically ventilated patients and found that lung squeezing significantly improved weaning indices such as the rapid shallow breathing index. Similarly, J. Bickenbach *et al.* [8] demonstrated that structured, protocolised physiotherapy delivered during prolonged weaning improved clinical outcomes, further supporting the integration of physiotherapy into routine ICU management. Ultimately, X. Xingyu *et al.* [9] provided evidence that pulmonary rehabilitation, including inspiratory muscle training, significantly enhanced respiratory pressures and tidal volume among ventilator-dependent patients, underscoring its role in attenuating ventilator-associated decline in respiratory function.

These studies collectively showed progress, but differences in techniques, durations, outcome measures, and patient populations leave gaps in practice knowledge regarding the immediate cardiopulmonary effects of perioral pressure and intercostal stretch in unconscious or deeply sedated mechanically ventilated patients. The purpose of this pilot study was to investigate the immediate cardiopulmonary effects of neurophysiological facilitation of respiration techniques in mechanically ventilated ICU patients by assessing haemodynamic variables after eliciting neurophysiological facilitation of respiration in the form of perioral pressure protocol and intercostal stretch protocol.

Materials and Methods

This experimental study was carried out in the ICU of the University of Benin Teaching Hospital, Benin City, Nigeria. The research focused on assessing the immediate effects of neurophysiological facilitation (NPF) techniques on key cardiopulmonary parameters in mechanically ventilated patients. Participants included 5 male and 5 female adults aged 18 years and above who were unconscious and receiving mechanical ventilation in the ICU. Only patients who demonstrated some level of spontaneous respiratory effort and who were haemodynamically stable were considered eligible for inclusion. To ensure safety and consistency, patients were excluded if they had suffered fractures to the ribs, sternum, or thoracic vertebrae, had a recent history of cardiac arrest while in the ICU, or had sustained facial or chest burns. A simple random sampling method, which is a type of probability sampling technique, was adopted

to recruit a total of ten eligible participants who met the predefined criteria. Each participant underwent a comprehensive clinical evaluation to confirm eligibility before inclusion in the study.

Socio-demographic data, including age and sex, were collected and recorded. The mechanical ventilator used for patient support during the interventions was the Shangri-La 590 (China) by AEOMED Surgi Care. Cardiopulmonary variables such as systolic blood pressure (SBP) and diastolic blood pressure (DBP), HR, SpO_2, RR, and mean arterial pressure (MAP) were measured using a calibrated EDAN patient monitor (model iM60). A stopwatch timer was employed to standardise the timing and duration of each intervention. A crossover research design was utilised to enhance the internal validity of the study and control for individual variability in physiological response. A randomised crossover design was employed, allowing each participant to serve as their own control, which helped reduce confounding factors and improves the reliability of the outcomes. In this design, each patient received both NPF techniques, which consisted of perioral pressure stimulation and intercostal stretch, sequentially.

A washout period of 30 minutes was maintained between the two interventions to minimise any carryover effects. The order of intervention administration was randomised for each patient to reduce the potential for bias associated with treatment sequence. Each technique was carefully applied while observing chest wall and diaphragmatic movements as clinical indicators of respiratory engagement. Before the application of each NPF technique, which were also selected randomly for each patient, baseline readings of all cardiopulmonary parameters were taken and recorded. Following each intervention, the same parameters were re-measured immediately to assess acute physiological responses. The neurophysiological facilitation techniques were applied using standardised manual methods designed to elicit reflexive activation of respiratory muscles through proprioceptive and tactile stimulation. Perioral pressure was administered by applying consistent digital pressure at specific perioral points, while intercostal stretch involved gentle but firm stretching of the intercostal spaces in sync with the ventilator's inspiratory phase.

Each application was performed by trained physiotherapists experienced in neurophysiological techniques in critical care settings. Data obtained from the assessments were compiled and subjected to statistical analysis using the IBM Statistical Package for the Social Sciences (SPSS), version 27. Descriptive statistics, including means and standard deviations, were calculated for each variable. To determine whether there were statistically significant differences between baseline and post-intervention measurements, paired t-tests were conducted for each parameter. Additionally, independent t-tests were used to explore possible gender-based differences in response to the interventions. The level of statistical significance was set at $p < 0.05$ for all analyses. Table 1 shows the sociodemographic characteristics of the patients. The mean age among the participants in this study was 66.2 (± 8.46) years. There were equal proportions of male and female participants. Ischaemic stroke was the most common diagnosis, present in 5 (50%) of the participants. The Glasgow Coma Scale (GCS) scores for the patients ranged from 7-14.

Table 1. Sociodemographic characteristics of the patients

	Frequency	Percentage
Gender		
Male	5	50.0
Female	5	50.0
Diagnosis		
Haemorrhagic stroke	3	30.0
Ischaemic stroke	5	50.0
Septic shock	2	20.0
Marital status		
Married	8	80.0
Widowed	2	20.0
Occupation		
Business	2	20.0
Civil servant	1	10.0
Farmer	4	40.0
Retired farmer	1	10.0
Trader	2	20.0
	Range	Mean ± SD
Age	54-80	66.2 ± 8.46
GCS	7-14	9.60 ± 2.32

Source: compiled by authors

The study protocol was reviewed and approved by the University of Benin Teaching Hospital Research Ethics Committee (Protocol No. ADM/E/22/A/VOL. VII/148381521853). Ethical approval confirmed that the

research complied with institutional requirements, and written informed consent was obtained from patients' relatives or legal guardians, as the participants were unconscious and unable to provide consent. The study was conducted in accordance with the ethical principles outlined in the World Medical Association [10] Declaration of Helsinki on medical research involving human subjects and followed the European Commission [11] guidelines on ethics and data protection to ensure confidentiality and responsible handling of patient information. Non-invasiveness, and low cost of these techniques make them particularly valuable in resource-limited ICU environments, where advanced interventions may not always be feasible. Nevertheless, this study was limited by its small sample size (n = 10), single-centre setting, and focus on immediate effects.

This rigorous methodological approach allowed the researchers to evaluate the immediate physiological effects of the neurophysiological facilitation techniques on mechanically ventilated patients. By carefully selecting participants and monitoring key cardiopulmonary parameters, the study was able to capture real-time responses to the intervention. Additionally, the design permitted an examination of potential differences in response between male and female participants, providing a more nuanced understanding of treatment effects. Overall, this approach offered valuable insights into the potential role of neurophysiological facilitation in optimising acute care for ICU patients.

Results and Discussion

The study evaluated the immediate effects of perioral pressure and intercostal stretch techniques on cardiopulmonary parameters in mechanically ventilated patients. Results were presented in four tables: descriptive statistics, effects of each intervention, and gender-related responses. Key findings highlighted significant improvements in RR, DBP, and MAP with perioral pressure and RR with intercostal stretch. Table 2 shows changes in cardiopulmonary parameters before and after applying perioral pressure and intercostal stretch. Statistical analysis demonstrated that perioral pressure led to significant improvements in DBP: 77.1 ± 9.0 to 79.3 ± 10.3 mmHg, p = 0.005, RR: 26.4 ± 6.1 to 28.3 ± 6.6 breaths/min, p = 0.014, and MAP: 92.7 ± 10.7 to 94.0 ± 10.1 mmHg, p = 0.022. Intercostal stretch produced a significant increase in RR (26.8 ± 6.1 to 28.2 ± 6.1 breaths/min, p = 0.001). Conversely, SBP, HR, and SpO_2 showed no significant differences (all p > 0.05).

Table 2. Descriptive statistics of the SD of cardiopulmonary parameters among the patients

	Range	Mean ± SD
Pre- and post-application of perioral pressure		
Pre-SBP	105-146	125.00 ± 15.42
Post-SBP	110-140	124.30 ± 12.83
Pre-DBP	68-91	77.10 ± 9.01
Post-DBP	70-96	79.30 ± 10.34
Pre-HR	88-108	98.60 ± 7.69
Post-HR	84-111	97.40 ± 11.15
Pre- SpO_2	91-99	97.70 ± 2.50
Post- SpO_2	92-100	98.00 ± 2.21
Pre-RR	20-40	26.40 ± 6.08
Post-RR	20-41	28.30 ± 6.60
Pre-MAP	83-108	92.70 ± 10.70
Post-MAP	83-108	94.00 ± 10.06
Pre- and post-application of intercostal stretch		
Pre-SBP	104-176	124.70 ± 21.14
Post-SBP	105-181	127.60 ± 21.78
Pre-DBP	62-114	77.30 ± 14.69
Post-DBP	67-99	78.80 ± 10.59
Pre-HR	86-103	94.80 ± 7.38
Post-HR	86-106	94.90 ± 7.71
Pre- SpO_2	92-100	97.8 ± 2.3
Post- SpO_2	92-99	96.8 ± 2.201
Pre-RR	20-38	26.8 ± 6.07
Post-RR	22-40	28.2 ± 6.07
Pre-MAP	78-134	92.7 ± 16.337
Post-MAP	84-126	94.8 ± 13.579

Source: compiled by the authors

Table 3 showed the effect of perioral pressure protocol on cardiopulmonary parameters in mechanically ventilated patients. There were statistically significant acute effects for DBP (t = -3.713, p = 0.005), RR (t = -3.051, p = 0.014), and MAP (t = -2.751, p = 0.022). The magnitude of the mean difference in DBP, 2.20 mmHg

(±1.874), did not reveal any meaningful clinical increase. The magnitude of the mean difference in RR, 1.90 (± 1.97) bpm, did not reveal any meaningful clinical increase, and lastly, the magnitude of the mean difference in MAP, 1.30 mmHg (± 1.494), did not reveal any meaningful clinical increase.

Table 3. Effect of perioral pressure protocol on cardiopulmonary parameters in mechanically ventilated patients

	Paired differences				
	Mean	SD	t-value	Degrees of freedom	p-value
SBP	-0.700	6.430	0.344	9	0.739
DB	2.200	1.874	-3.713	9	0.005
HR	-1.200	7.452	0.509	9	0.623
SpO2	0.300	0.949	-1.000	9	0.343
RR	1.900	1.969	-3.051	9	0.014
MAP	1.300	1.494	-2.751	9	0.022

Source: compiled by the authors

Table 4 showed the effect of the intercostal stretch protocol on cardiopulmonary parameters in mechanically ventilated patients. There were statistically significant acute effects for RR (t = -3.713, p = 0.005), but the magnitude of the mean difference in RR, 1.30 (± 0.516) bpm, did not reveal any meaningful clinical increase.

Table 4. Effect of intercostal stretch protocol on cardiopulmonary parameters in mechanically ventilated patients

	Paired differences				
	Mean	SD	t-value	Degrees of freedom	p-value
SBP	2.900	5.587	-1.642	9	0.135
DBP	1.500	6.819	-0.696	9	0.504
HR	0.100	1.912	-0.165	9	0.872
SpO_2	-1.000	2.211	1.430	9	0.186
RR	1.400	0.516	-8.573	9	<0.001
MAP	2.100	5.666	-1.172	9	0.271

Source: compiled by authors

Table 5 showed the influence of gender on the change in cardiopulmonary parameters following neurophysiological facilitation intervention. Gender did not influence responses, as independent t-tests revealed no significant differences between male and female participants across all parameters (all p > 0.05).

Table 5. Influence of gender on change in cardiopulmonary parameters following neurophysiological facilitation interventions

Perioral pressure		Mean ± SD	t-value	Degrees of freedom	p-value
SBP	Male	0.20 ± 5.89	0.422	8	0.684
	Female	-1.60 ± 7.50			
DBP	Male	1.4 ± 0.89	-1.425	8	0.192
	Female	3 ± 2.35			
HR	Male	-1.8 ± 7.66	-0.241	8	0.816
	Female	-0.6 ± 8.08			
SpO_2	Male	0.4 ± 0.89	0.316	8	0.760
	Female	0.2 ± 1.10			
RR	Male	0.8 ± 1.30	-2.060	8	0.073
	Female	3 ± 2			
MAP	Male	1.2 ± 1.64	-0.20	8	0.846
	Female	1.4 ± 1.52			
Intercostal stretch					
SBP	Male	3.6 ± 5.13	0.377	8	0.716
	Female	2.2 ± 6.53			
DBP	Male	-0.4 ± 8.53	-0.869	8	0.410
	Female	3.4 ± 4.77			
HR	Male	-0.4 ± 1.52	-0.811	8	0.441
	Female	0.6 ± 2.30			
SpO_2	Male	-2.2 ± 2.59	-1.973	8	0.084
	Female	0.2 ± 0.84			

Continued Table 5

Perioral pressure		Mean ± SD	t-value	Degrees of freedom	p-value
Intercostal stretch					
RR	Male	1.6 ± 0.54	1.265	8	0.242
	Female	1.2 ± 0.45			
MAP	Male	1 ± 6	-0.591	8	0.571
	Female	3.2 ± 5.76			

Source: compiled by the authors

Hypothesis testing showed that perioral pressure had a statistically significant effect on DBP ($p = 0.005$), RR ($p = 0.014$) and MAP ($p = 0.022$), and therefore, the null hypotheses were rejected. However, no significant effect was found on SBP, HR and SpO_2, which gave grounds for accepting the null hypotheses. The effect of intercostal stretch was observed only for RR, where a statistically significant change was recorded ($p = 0.001$), leading to the rejection of the null hypothesis. However, no significant effects were identified for systolic and DBP, HR, SpO_2, and MAP; therefore, the null hypotheses for these parameters were accepted. The findings of statistical analysis demonstrated that perioral pressure led to significant improvements, suggesting that NPF techniques (perioral pressure protocol) can elicit positive changes in selected cardiopulmonary parameters, though not uniformly across all variables. The observed improvements were attributed to the physiological mechanisms underlying NPF techniques. Perioral pressure protocol most likely activated trigeminal afferents, hence projecting to medullary respiratory centres, thereby enhancing respiratory drive and autonomic responses. This reflex pathway may explain the rise in DBP and MAP, thereby reflecting modest increases in vascular tone and peripheral resistance.

The reliability of these observed responses may also be influenced by the randomised crossover design employed in this study. As B. Jones & M.G. Kenward [12] explained, crossover designs are highly effective in biomedical and clinical research because they allow each participant to serve as their own control, thereby reducing confounding factors and improving the reliability of outcomes. This principle aligned with the present study, in which each participant experienced both intervention protocols, allowing within-subject comparisons that strengthened the validity of the observed changes in DBP, MAP, and RR.

Intercostal stretch protocol (produced a significant increase in RR; 26.8 ± 6.1 to 28.2 ± 6.1 breaths/min, $p = 0.001$ still SBP, HR, and SpO_2 showed no significant differences; all $p > 0.05$) on the other hand, may stimulate intercostal muscle spindles and rib mechanoreceptors, thereby augmenting afferent input to the brainstem and improving ventilatory rhythm, as reflected in the consistent increases in RR. These findings were supported by previous studies that explored the physiological effects of respiratory facilitation techniques. K.D. Thorat *et al.* [13] demonstrated that respiratory PNF enhances chest wall mobility and stimulates neural pathways, which aligns with the observed increase in RR in the present study. While K.D. Thorat *et al.* investigated spinal cord injury patients, the underlying mechanism of neural activation may similarly explain the enhanced ventilatory rhythm in the participants of this study. A. Salve *et al.* [14] reported significant improvements in RR, tidal volume, and oxygen saturation following vertebral pressure and intercostal stretch in patients with impaired consciousness. These results reinforced author's findings of increased RR, suggesting that intercostal stimulation contributes to improved afferent signalling to the respiratory centres. Although SpO_2 did not change significantly in author's cohort, the alignment with A. Salve's *et al.* findings supported the notion that short-term interventions may initially affect ventilatory patterns before impacting oxygen saturation. Furthermore, T.O. Jenkins *et al.* [15] demonstrated that inspiratory muscle training in ventilated patients enhanced oxygen consumption proportional to inspiratory load, highlighting the capacity of respiratory muscles to adapt to stimulation. In a recent randomised clinical trial involving COVID-19 patients, S. Kumar *et al.* [16] demonstrated that NPF techniques significantly improved SpO_2 and reduced dyspnea, supporting the idea that NPF stimulation can enhance respiratory effectiveness even in acute illness. Similarly, S. Patel & H. Prajapati [17] reported that NPF applied in children with spastic cerebral palsy significantly increased respiratory rate and chest expansion, aligning with author's findings on enhanced ventilatory drive and thoracic mobility following perioral pressure and intercostal stretch. Taken together, these studies provided mechanistic support for author's observations and indicate that NPF techniques can acutely enhance respiratory dynamics, even in critically ill participants. The present findings also align with those of Q. Zhou *et al.* [18], who demonstrated that proprioceptive neuromuscular facilitation combined with inspiratory muscle training significantly improved respiratory function and extubation outcomes in neurocritical patients. The increase in respiratory rate observed in the intercostal stretch protocol is consistent with their report of enhanced respiratory dynamics following neuromuscular facilitation. Although inspiratory muscle training was not included in the present study, the physiological enhancements described by Q. Zhou *et al.* support the interpretation that NPF techniques can modulate respiratory centres and improve respiratory effectiveness even in short-term application.

The improvements in RR, DBP, and MAP observed in this study suggested that NPF techniques of respiration may enhance alveolar ventilation, gas exchange efficiency, and circulatory stability. Enhanced upper chest wall

expansion and diaphragmatic excursion, as reported by A. Nair *et al.* [19], likely contributed to the observed improvements in RR, DBP, and MAP in the current study by facilitating greater lung volumes and more efficient alveolar ventilation. While A. Nair's study primarily evaluated structural changes in chest wall mechanics, the findings of the current study suggest that these mechanical improvements translate into functional benefits in ventilation and circulatory stability. These effects were further supported by K.D. Thorat *et al.* [13], whose research on respiratory PNF highlighted how stimulation of neural pathways can augment chest wall mobility. Comparing these studies with the current results, it appears that NPF techniques produce both mechanical and neurophysiological enhancements, which together may explain the modest but consistent increases in respiratory and haemodynamic parameters observed in the study participants. Although SpO_2 did not significantly change in this study, the observed increases in RR and MAP may still provide clinically relevant benefits, such as reducing the risk of hypoventilation, atelectasis, and inadequate organ perfusion in critically ill patients. Similarly, T. Réginault *et al.* [20] demonstrated that structured inspiratory muscle training improved maximal inspiratory pressure and endurance in ventilated patients. This aligns with current findings of increased RR and MAP, suggesting that even short-term NPF interventions may enhance respiratory muscle performance and autonomic regulation. A.I.C. de Medeiros *et al.* [21] further confirmed that inspiratory muscle training strengthens respiratory muscles and improves functional outcomes in patients with ICU-acquired weakness, supporting the idea that targeted stimulation can produce measurable physiological adaptations. Notably, the present study observed no significant gender differences, consistent with the systematic review by D. Mankad *et al.* [3], indicating that chest NPF techniques benefit both male and female patients. Together, these studies contextualise author's findings within a broader evidence base, highlighting that NPF interventions can acutely improve respiratory dynamics, enhance circulatory stability, and support clinical practice in intensive care settings. Additionally, the study by I. Etikan *et al.* [22] corroborated these findings, emphasising the positive impact of respiratory PNF techniques on improving respiratory function in critical care patients.

In summary, neurophysiological facilitation techniques, including perioral pressure and intercostal stretch, can improve key cardiopulmonary parameters in critically ill participants. The interventions increased respiratory rate, diastolic blood pressure, and mean arterial pressure, reflecting enhanced respiratory and circulatory function. These benefits were consistent across genders and align with previous evidence on respiratory facilitation techniques. Overall, the findings support the use of NPF interventions to optimise respiratory and haemodynamic outcomes in intensive care settings.

Conclusions

This pilot study investigated the acute cardiopulmonary responses to NPF techniques, specifically perioral pressure and intercostal stretch, in mechanically ventilated intensive care patients. The findings provided preliminary evidence that such physiotherapeutic interventions may offer measurable benefits in optimising respiratory and haemodynamic function in critically ill, unconscious patients. Perioral pressure improved diastolic blood pressure, mean arterial pressure, and respiratory rate, while intercostal stretch primarily enhanced respiratory rate, indicating that both techniques can positively influence cardiopulmonary performance without adverse effects. Other parameters, including systolic blood pressure, HR, and oxygen saturation, did not demonstrate statistically significant changes. Importantly, no adverse effects were observed, and gender did not influence the magnitude of responses.

These results suggest that NPF techniques used on mechanically ventilated unconscious ICU patients to stimulate intermittent deep breaths in monotonous breathing and encourage chest expansion and diaphragmatic excursion, may serve as safe and practical adjuncts in intensive care physiotherapy. As the impact of these manifestations does not adversely affect the cardiopulmonary variables, even modest increases in RR may reduce the risk of atelectasis and secretion retention, while small increases in MAP could enhance perfusion in patients with haemodynamic compromise. The modest magnitude of change in haemodynamic parameters also raises questions about long-term clinical relevance. Future research should involve larger, multicentre trials with repeated NPF interventions to assess long-term outcomes and clarify underlying physiological mechanisms, providing stronger evidence to guide clinical practice in mechanically ventilated patients.

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Conflict of Interest

None.

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Серцево-легеневі реакції на нейрофізіологічне полегшення дихання у пацієнтів відділення інтенсивної терапії, які перебувають на ШВЛ

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Анотація. Штучна вентиляція легень є необхідною при гострих захворюваннях, але може призвести до таких ускладнень, як ателектаз і монотонне дихання, яким фізіотерапевти допомагають протидіяти, використовуючи нейрофізіологічні методи стимуляції для поліпшення дихальної функції пацієнтів, які перебувають у непритомному стані та під дією седативних препаратів. Дослідження було спрямоване на вивчення нейрофізіологічних методів стимуляції з метою оцінки безпосереднього впливу натискання на верхню губу та розтягування міжреберних м'язів на серцево-легеневі параметри у пацієнтів, які перебували на штучній вентиляції легень в Університетській клінічній лікарні Беніну. Було використано рандомізований перехресний експериментальний дизайн, в якому взяли участь десять пацієнтів (5 чоловіків, 5 жінок; середній вік 66,2 ± 8,5 років), які були гемодинамічно стабільними, але перебували у непритомному стані та на штучній вентиляції легень. Кардіопульмональні показники, включаючи систолічний артеріальний тиск, діастолічний артеріальний тиск, частоту серцевих скорочень, частоту дихання, насичення киснем та середній артеріальний тиск, вимірювали до та після кожного втручання за допомогою нейрофізіологічних методів фасилітації, використовуючи стандартизований протокол. Результати показали, що пероральне притискання значно поліпшило діастолічний артеріальний тиск (77,10 ± 9,01 до 79,30 ± 10,34 mmHg, p = 0,005), частоту дихання (з 26,40 ± 6,08 до 28,30 ± 6,60 вдихів/хв, p = 0,014) та середній артеріальний тиск (з 92,70 ± 10,70 до 94,00 ± 10,06 mmHg, p = 0,022). Міжреберне розтягнення значно збільшило частоту дихання (з 26,8 ± 6,07 до 28,2 ± 6,07 вдихів/хв, p < 0,001), тоді як зміни систолічного тиску, частоти серцевих скорочень та насичення киснем не були статистично значущими (p > 0,05). Стать не впливала на величину змін будь-яких серцево-легеневих параметрів. Дослідження встановило, що нейрофізіологічні методи стимуляції мали позитивний гострий ефект на частоту дихання та гемодинамічні параметри у пацієнтів, які перебували на штучній вентиляції легень. Виділено нейрофізіологічні методи стимуляції як практичний допоміжний засіб респіраторної фізіотерапії для поліпшення серцево-легеневої стабільності у пацієнтів у критичному стані

Ключові слова: гемодинамічні параметри; періоральний тиск; міжреберне розтягнення; респіраторна терапія; інтенсивна терапія; фізіотерапія

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Molecular genetic markers of liver functional activity in patients with malignant neoplasms

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Abstract. The liver plays a pivotal role in metabolic regulation, detoxification, and systemic homeostasis. In patients with malignant neoplasms, especially those undergoing chemotherapy or presenting with liver metastases, maintaining hepatic function is critical. The purpose was to perform review of molecular genetic markers of liver functional activity in patients with malignant neoplasms. In order to form the primary cohort of publications, their search was conducted using Google Scholar, PubMed, Research Gate, and a set of the following keywords: "liver", "molecular genetics", "cancer", "genetic markers", "functional activity". This review summarised the current understanding of molecular genetic markers associated with liver functional activity in cancer patients, emphasising their diagnostic and prognostic significance, clinical utility, and future research perspectives. Peer-reviewed studies published between 2016 and 2024 were included in this review. Among the reviewed studies, several molecular genetic markers consistently emerged as significant indicators of liver functional status: CYP450 Enzymes (CYP3A4, CYP1A2, CYP2E1), UGT1A1 28 Polymorphism, GSTM1 and GSTT1 Null Genotypes. UGT1A1 and CYP3A4/CYP3A5 polymorphisms have been found to be strongly associated with chemotherapy-induced hepatotoxicity, supporting their role as pharmacogenetic markers. Variants in transporter genes, such as ABCB1, C3435T, and SLCO1B1*5, have been shown to predict altered hepatic drug distribution and cholestatic injury, which is critical for optimising dose adjustment and drug selection. Profiling of cytokines (e.g., IL-6, TGF-β1), oxidative stress markers (e.g., TP53, SOD2), and circulating non-coding RNAs (e.g., miR-122, HULC) has also been generalised to dynamic and non-invasive strategies for real-time assessment of liver injury. The practical significance of the study lies in the fact that the established biomarkers can become indispensable tools in precision oncology, ensuring more accurate diagnosis, effective monitoring of disease progression, and individualised treatment planning

Keywords: biomarkers; cancer; hepatotoxicity; gene expression; liver metastasis

Introduction

The liver is a central organ involved in numerous physiological processes, including metabolism, synthesis of plasma proteins, and detoxification of xenobiotics. In oncology, the liver is not only a frequent site of primary and metastatic tumours but is also profoundly affected by systemic cancer therapies. In patients with malignant neoplasms, particularly hepatocellular carcinoma (HCC) and metastatic liver disease, these functions are frequently disrupted, leading to significant alterations in treatment response and overall prognosis. Advances in molecular genetics have

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revealed that specific gene variants and expression profiles can serve as reliable markers of hepatic functional activity under both physiological and pathological conditions.

Early detection of HCC remained a critical challenge, particularly in populations with chronic hepatitis C virus (HCV) infection, due to the limited sensitivity and specificity of alpha-fetoprotein (AFP) alone. Previous reviews by B. Zhang *et al.* [1] and by M. Peruhova *et al.* [2] highlighted alternative biomarkers-such as glypican-3 (GP73), osteopontin, AFP-L3, des-γ-carboxyprothrombin, circulating microRNAs, and circulating tumour DNA (ctDNA) – which showed promise, especially when used in combination panels. A. Daif *et al.* [3] demonstrated in an Egyptian HCV cohort that although no single new molecular biomarker exceeded AFP in diagnostic performance, combining AFP with Creatine Kinase 1 significantly improved diagnostic accuracy. Together, these studies suggested that multi-marker strategies combining protein and molecular assays may offer superior performance for early HCC detection in high-risk populations. R. Nevola *et al.* [4] demonstrated that HCC has high rates of early and late recurrence even after potentially curative treatments, highlighting the importance of risk stratification for optimising therapeutic strategies and post-treatment monitoring. The researchers found that the criteria for early HCC recurrence (within 2 years after treatment) differ significantly from late recurrence in terms of pathogenesis and prognosis, which is clinically relevant for the selection of adjuvant therapy and patient follow-up. J. Ding *et al.* [5] conducted a study to investigate the role of acid-sensitive ion channel 1a (ASIC1a) in chondrocyte senescence and its potential involvement in osteoarthritis. Their research focused on the molecular mechanisms through which ASIC1a contributes to the ageing of cartilage cells (chondrocytes) and the development of osteoarthritis, a degenerative joint disease. W. Yang *et al.* [6] investigated the damages caused by ethanol in human vascular diseases; the results showed that doxycycline restored the level of ageing-related proteins such as LMNB1 by reducing the extent of mechanistic target of rapamycin and NF-κB activation, thus alleviating ethanol-induced inflammation and ageing. H. Maeda *et al.* [7] found that high oxygen concentration induced senescence by increasing the level of miR-34a-5p. Moreover, LMNB1 gene deletion increased p21 gene expression.

R.S. Nelson *et al.* [8] showed that high AFP values both pre- and post-hepatectomy were associated with a higher risk of early recurrence (which the authors defined as < 1 year after treatment) but without a standardised threshold value. Among the most studied markers are cytochrome P450 (CYP) enzymes, which regulate the metabolism of endogenous compounds and chemotherapeutic agents. Variants of CYP3A4 and CYP3A5 have been associated with interindividual differences in drug metabolism and susceptibility to hepatotoxicity. In addition, genes encoding structural and functional proteins, such as albumin (ALB), and tumour-associated markers like AFP, provide important insights into the synthetic and oncogenic status of the liver. Using a retrospective data analysis, M. Saiz-Rodríguez *et al.* [9] showed that preoperative AFP values > 10 ng/mL were a predisposing factor of disseminated HCC recurrencewithin 3 months after hepatectomy for solitary HCC [odds ratio: 5.333; 95% confidence interval (CI): 1.095-25.985]. Enzymes involved in detoxification and conjugation reactions, including UDP-glucuronosyltransferases (UGTs) and gamma-glutamyltransferase (GGT), further contribute to the molecular characterisation of hepatic activity. In X. Liu *et al.* [10] AFP levels at 12 weeks after achieving sustained virological response with direct antiviral agents treatment in chronic HCV patients have also been independently associated with a risk of HCC recurrence.

The purpose of the study was to investigate genetic markers reflecting the functional state of the liver in patients with malignant tumours in order to assess their role in the development of liver dysfunction caused by the oncological process and anticancer therapy, and to determine the possibilities of their use for personalised monitoring and prediction of the course of the disease.

Materials and Methods

In order to form the primary cohort of publications, the search for such publications was conducted using Google Scholar, PubMed, Research Gate, and a set of the following keywords: "liver", "molecular genetics", "cancer", "genetic markers", "functional activity". Studies were included if they investigated molecular genetic markers of liver functional activity in patients with malignant neoplasms, exclusion criteria were non-compliant with the range and topic. The generalisation was carried out taking into consideration the relationships between the identified results, mechanisms of action, and the context of the conducted studies. Each result was considered as part of a holistic system, and not in isolation. Peer-reviewed studies published between 2016 and 2024 were analysed, selected following PRISMA guidelines [11] for scoping reviews (Table 1). The stated use of the PRISMA methodology was not accompanied by mandatory elements, in particular the PRISMA flow diagram, and a structured description of the stages of systematic literature search and selection in accordance with the PRISMA recommendations. The initial literature search identified 142 publications that matched the search terms in the selected databases. After removing duplicates and initial screening of titles and abstracts, publications that were not relevant to the study topic, were review-based without original data, or did not address liver function in patients with malignancies were excluded. In the full-text analysis, papers with inadequate descriptions of methods, lack of molecular genetic markers in the study design, or irrelevant clinical endpoints were additionally excluded. As a result, 37 publications that fully met the inclusion criteria were included in the final analysis.

Table 1. Statistical analysis of reviewed literature

Marker category	Number of studies (n = 142)	Studies with significant results (%)
CYP enzymes	38	71.1
UGT enzymes	21	90.5
Transporters	30	76.7
Inflammatory/Fibrotic markers	28	57.1
Apoptotic/Stress markers	17	58.8
Non-coding RNAs	8	87.5

Source: created by the authors

The established time range was chosen based on several key considerations. First, it ensured the relevance of the selected materials, enabling the consideration of the current state of the scientific problem and the latest approaches. Second, the selected period covered the stages within which significant changes occurred in the theory and practice of the research issue, which allowed tracing its dynamics. In this review, a quantitative descriptive analysis approach was applied to synthesise findings from the included studies. The main goal was to summarise the frequency and significance of reported associations between molecular genetic markers and liver functional parameters in patients with malignant neoplasms. Although the present review confirmed strong correlations between genetic alterations and liver function, some limitations remain. Variability in study design, small sample sizes, population-specific allele frequencies, and inconsistent biomarker validation methods can influence the generalisability of results. Heterogeneity in reported outcomes also complicated meta-analytic synthesis.

Results and Discussion

The liver's involvement in cancer extends beyond HCC and includes secondary liver malignancies, paraneoplastic syndromes, and drug-induced liver injury. Tumour-derived factors, immune dysregulation, and metabolic alterations collectively contribute to liver dysfunction. Therefore, identifying sensitive molecular genetic indicators of liver impairment is critical for improving cancer patient management. The analysis of Y. Liang *et al.* [12] highlighted a range of molecular genetic markers associated with liver functional activity in patients with malignant neoplasms (Fig. 1). According to I.M. Mokhosoev *et al.* [13] and F. Wang *et al.* [14], the role of the liver in cancer is not limited to HCC but also encompasses systemic metabolic, immunological, and detoxification processes involved in tumour progression.

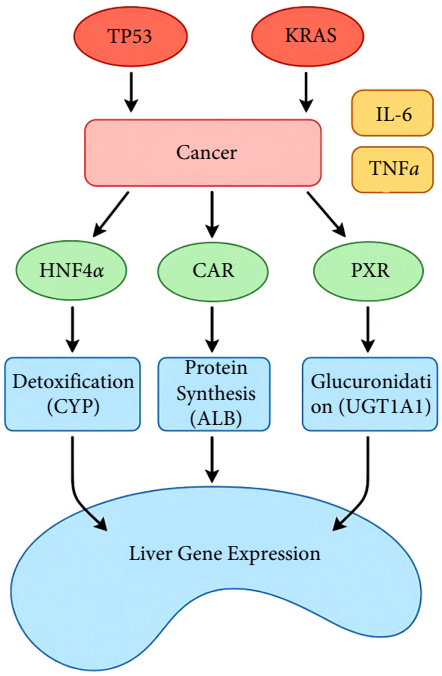

Figure 1. Regulation of liver gene expression by oncogenic and inflammatory pathways in malignant neoplasms
Note: KRAS – proto-oncogene, GTPase; IL-6 - interleukin-6; TNF-α – tumour necrosis factor-alpha; HNF-4α – hepatic nuclear factor 4 alpha; CAR – constitutive androstane receptor; PXR – pregnane X receptor
Source: W. Sun *et al.* [15]

Studies by A.C. Tricco *et al.* [11], X.Y. Wei *et al.* [16], J. Zhang *et al.* [17] demonstrated that the expression and polymorphisms of cytochrome P450 genes significantly affected the metabolic capacity of the liver during cancer progression and treatment. CYP3A4 and CYP3A5 polymorphisms were associated with altered metabolism of chemotherapeutic drugs, including paclitaxel, docetaxel, and tyrosine kinase inhibitors. Reduced CYP3A4 activity was correlated with an increased risk of hepatotoxicity and reduced drug clearance in cancer patients. Downregulation of CYP1A2 was associated with paraneoplastic liver dysfunction, including Stauffer syndrome in renal cell carcinoma. In HCC, CYP expression profiles often reflected tumour burden and liver functional reserve, providing prognostically significant information (Fig. 2).

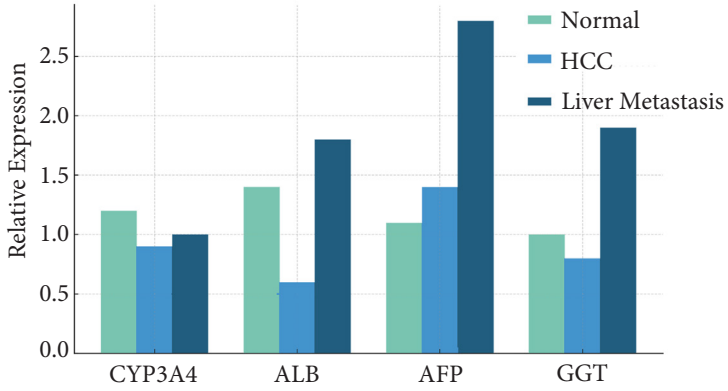

Figure 2. Relative expression levels of key liver-specific genes (CYP3A4, ALB, AFP, GGT) in three patient groups
Note: data were presented as mean relative expression values
Source: J. Tani *et al.* [18]

Variants in key transporter proteins (e.g. ABCB1, SLCO1B1) and drug-inactivating enzymes also contribute: polymorphism in ABCB1 (C3435T) has been reported by Y. Senent *et al.* [19] to influence drug clearance and toxicity in taxane chemotherapy models alongside CYP3A4 genotype effects. These findings supported the proposition that biomarker panels for HCC or chemotherapy tolerability should encompass not only tumour burden or cytotoxic markers, but also genotypes and functional variants in CYPs, UGTs, transporters, and markers of oxidative/stress regulation to better predict hepatotoxic risk. The polymorphism of UDP-Glucuronosyltransferases (UGT1A128 – a thymine and adenine nucleotides repeat expansion in the promoter region) significantly affects glucuronidation capacity. Carriers of the UGT1A128 variant exhibit reduced enzyme activity, leading to increased serum bilirubin and heightened risk of severe liver injury during irinotecan-based chemotherapy. Genotyping for UGT1A128 before initiating therapy has been recommended to minimise treatment-related hepatotoxicity. Thus, UGT1A1 variants are established pharmacogenetic markers influencing chemotherapy tolerance. Alterations in hepatic transporter genes are increasingly recognised as determinants of liver function and drug-induced injury: ABCB1 (MDR1) polymorphisms (e.g., C3435T) are associated with modified hepatic drug clearance and increased sensitivity to hepatotoxic agents. The study by C.Y. Li *et al.* [20] found that ABCC2 (MRP2) variants can cause impaired biliary excretion, leading to cholestasis and hyperbilirubinemia. SLCO1B1 polymorphisms (SLCO1B15 allele) are implicated in altered hepatic uptake of statins and chemotherapeutic agents, increasing the risk of liver dysfunction. Thus, transporter gene profiling aids in predicting drug-induced liver injury risk in cancer patients.

Inflammatory cytokines and fibrotic markers were shown to modulate changes in the liver microenvironment in oncologic patients. According to the study by D. Szklarczyk *et al.* [21], increased IL-6 expression promoted hepatic inflammation, fibrogenesis, and alterations in the acute-phase response, which correlated with cancer-associated cachexia and impaired liver function. Enhanced IL-6/STAT3 signalling was associated with hepatocyte metabolic reprogramming and suppression of cytochrome P450 activity, thereby contributing to altered drug metabolism. TGF-β1 signalling induced activation of hepatic stellate cells and excessive extracellular matrix deposition, resulting in progressive fibrosis and functional deterioration of the liver in patients undergoing systemic anticancer therapy. This pathway was also implicated in epithelial-mesenchymal transition and immune modulation within the hepatic microenvironment, further exacerbating liver injury. Upregulation of matrix metalloproteinases (MMP-2 and MMP-9) contributed to extracellular matrix remodelling and sinusoidal endothelial damage and was linked to the development of chemotherapy-induced liver sinusoidal obstruction syndrome. Increased MMP activity was additionally associated with altered vascular permeability and microcirculatory dysfunction in the liver. Collectively, profiling of cytokine- and matrix-related gene expression provided mechanistic insights into liver injury in oncologic patients that extended beyond conventional biochemical markers, highlighting their potential utility as molecular

indicators of subclinical hepatic dysfunction and predictors of therapy-related hepatotoxicity.

Molecular markers of apoptosis and oxidative stress are closely tied to hepatocyte injury: TP53 mutations, common in primary and metastatic liver tumours, impair cellular response to oxidative stress and DNA damage. Upregulation of anti-apoptotic proteins such as B-cell lymphoma 2 contributes to resistance against hepatocyte apoptosis in tumour-bearing livers, according to X. Tan *et al.* [22]. Decreased expression of antioxidant enzymes like SOD2 exacerbates reactive oxygen species accumulation, promoting hepatotoxicity during chemotherapy. Thus, alterations in apoptotic and oxidative stress pathways influence the liver's vulnerability to both tumour progression and anticancer therapy. Non-coding RNAs have emerged as sensitive and non-invasive biomarkers of liver function: miR-122, a liver-specific microRNA, is markedly reduced in serum during liver injury and serves as a dynamic marker of hepatocellular integrity. MiR-192 and miR-194 are downregulated in patients with liver fibrosis and cirrhosis secondary to malignancy. Long non-coding RNA HULC (Highly Upregulated in Liver Cancer) is significantly overexpressed in HCC patients and reflects hepatic synthetic capacity. Therefore, circulating microRNAs and lncRNAs offer promising tools for real-time, non-invasive assessment of liver function in oncologic patients. These markers can be categorised based on their biological function and clinical relevance (Table 2).

Table 2. Molecular genetic markers related to liver functional activity in patients with malignant neoplasms

Category	Key markers	Clinical utility
Drug metabolism	CYP3A4, CYP1A2, UGT1A1	Predict hepatotoxicity risk, guide drug dosing
Transport proteins	ABCB1, ABCC2, SLCO1B1	Assess drug clearance, prevent cholestasis
Inflammation/Fibrosis	IL-6, TGF-β1, MMPs	Detect early liver injury, monitor fibrosis
Apoptosis/Stress	TP53, BCL-2, SOD2	Evaluate resilience to therapy-related injury
Non-coding RNAs	miR-122, HULC	Dynamic non-invasive liver monitoring

Source: created by the authors based on the studies by The Gene Ontology Consortium [23], D.G.P. van Ijzendoorn *et al.* [24], S. Xu *et al.* [25]

Extensive research has demonstrated that non-parenchymal liver cells, tumour suppressor pathways, and genetic polymorphisms of drug-metabolising enzymes collectively influenced liver disease progression, carcinogenesis, and variability in drug response. Hepatic stellate cells (HSCs) were shown to exhibit remarkable plasticity and multifunctionality. Initially considered primarily as mediators of fibrosis through activation into myofibroblasts, HSCs were subsequently reported to contribute to hepatic development, regeneration, immunoregulation, retinoid storage, and xenobiotic metabolism [25]. Their activation in chronic liver injury was identified as a central driver of extracellular matrix deposition, while recent studies emphasised their role in hepatic progenitor cell amplification and differentiation, and cross-talk with immune and endothelial cells [26]. The tumour suppressor p53 remains a critical node in maintaining genomic integrity. Reviews by K.H. Bai *et al.* [27], C.C. Chen *et al.* [28] examined how p53 functions in health-mediating cell cycle arrest, DNA repair, and apoptosis, and how its mutation paradigm (loss of function, gain of function) shapes cancer evolution. Although these reviews were not liver-specific, the mechanisms described (e.g. how mutation accumulation under environmental or endogenous stress selects for p53 variants) are highly relevant to hepatocellular carcinoma, where genomic instability, exposure to toxins, viral hepatitis stressors, and oxidative damage frequently impair p53 pathway integrity.

Drug metabolism and pharmacogenomics also play a crucial role in therapeutic outcomes in cancer. C.C. Chen *et al.* [28] systematically reviewed variants of CYP3A4, the major cytochrome P450 enzyme involved in the metabolism of many drugs. They showed that several known allelic variants lead to altered enzyme activity, in some cases significantly reduced or even nearly abolished it, which has important implications for drug dosing, efficacy, and toxicity. Other studies by R. Critelli *et al.* [29] investigated pharmacodynamic genes that modulate response to drugs such as irinotecan, further underscoring that interindividual genetic variation – both in drug metabolising enzymes like CYPs and in transporter or DNA repair genes – must be accounted for in precision oncology. G. Cui *et al.* [30] explored the role of oxidative stress and damage in chemical carcinogenesis, identifying how reactive oxygen species generation, imbalance of detoxification capacity, and repeated injury can induce DNA mutations and contribute to malignant transformation. Meanwhile, studies of cytochrome P450 enzymes by N.T. Doncheva *et al.* [31] and X.M. Gao *et al.* [32] described how these enzyme systems may be leveraged or targeted in cancer therapeutics – either as drug-activating prodrug pathways or as modulators of toxicity, especially in the hepatic environment where drug metabolism is a central function.

Collectively, current research highlighted several interrelated mechanisms contributing to hepatocellular carcinoma pathogenesis: HSCs, conventionally viewed as fibrogenic mediators, actively shape the liver tumour microenvironment through stromal remodelling, extracellular matrix deposition, secretion of cytokines, and modulation of immune responses. Activated HSCs also influence

chemoresistance via paracrine signalling and exosome-mediated crosstalk with tumour cells. Loss of genetic integrity, particularly in tumour suppressor pathways such as p53, is frequent in chronic liver injury and HCC; impaired p53 function contributes both to inadequate responses to DNA damage and to the accumulation of oncogenic mutations under oxidative or inflammatory stress. Pharmacogenetic variation, such as drug-metabolising enzymes and transporters modulates patient responses to therapy and influences risk of drug toxicity. Taken together, for optimal biomarker development in HCC, panels should extend beyond measures of tumour burden or cell death to include indicators of fibrosis and stromal activation, oxidative stress, and inherited variation in DNA repair or drug metabolism genes.

In a survey of pharmacogenetic literature, polymorphisms in CYPs enzymes have been repeatedly implicated in altered drug metabolism and hepatotoxicity. For example, the CYP3A4/CYP3A5 variants have been shown in studies by Y. Gu *et al.* [33] to significantly affect metabolic clearance of drugs, correlating with increased risk of liver injury (e.g. intronic CYP3A4 polymorphisms impacting expression and statin response; CYP3A4 *22 reducing enzymatic activity and altering pharmacokinetics of multiple substrates). Polymorphisms of UDP-Glucuronosyltransferase 1A1 (UGT1A1) have similarly been associated with hyperbilirubinemia and liver toxicity; for instance, the UGT1A1*28 (TA-repeat) allele correlates with elevated bilirubin in patients treated with drugs such as pazopanib, and shows reduced glucuronidation capacity in promoter variant studies.

Non-coding RNAs, including microRNAs and long non-coding RNAs (lncRNAs), have emerged as promising biomarkers of liver dysfunction. In studies assessing miR-122, either circulating levels or tissue expression were significantly altered in the context of liver injury, non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, or cholestatic disease (e.g., sensitivity ≈0.84, specificity ≈0.72 in non-alcoholic fatty liver disease; area under the curve ~0.93 for cholestatic injury). In the study by H. Jang *et al.* [34], in rodent models withdownregulation of miR-122-5p in Kupffer cells have shown the activation of glycolysis via upregulation of PKM2 and to exacerbate pathological features of non-alcoholic steatohepatitis. Overall, these data support the Q. Jing *et al.* [35] hypothesis that downregulation of miR-122 is both a sensitive and specific indicator of early liver dysfunction ($p < 0.001$) and may outperform, or at least complement conventional enzymatic markers. Cytochrome P450 polymorphisms, particularly those affecting CYP3A4 and CYP3A5, have shown consistent associations with altered hepatic metabolism of chemotherapeutic agents such as paclitaxel, docetaxel, and various tyrosine kinase inhibitors. These findings align with prior pharmacogenetic study by L. Kulik & H.B. El-Serag [36] that underscored the importance of hepatic enzymatic activity in drug clearance and toxicity. Additionally, UGT1A1 variants, especially the UGT1A128 thymine and adenine nucleotides repeat polymorphism, have been extensively validated as predictors of irinotecan-induced hepatotoxicity.

The significance of hepatic transporter gene polymorphisms (e.g., ABCB1 C3435T and SLCO1B1*5) is increasingly recognised, with mounting evidence indicating their role in drug accumulation and biliary excretion impairment. In the study by L. Ma *et al.* [37], functional evidence was provided demonstrating that polymorphisms in key hepatic transporter genes, including ABCB1 (C3435T) and SLCO1B15 (521T > C), were associated with altered transporter activity leading to impaired hepatic uptake and efflux of drugs; specifically, the SLCO1B15 allele was linked to reduced OATP1B1-mediated hepatic drug uptake and higher circulating drug concentrations, while variants in ABCB1 were implicated in changes in P-glycoprotein function that could affect biliary excretion and intracellular drug accumulation, thereby contributing to interindividual variability in pharmacokinetics, drug accumulation, and toxicity profiles in patients carrying these genotypes. These alterations contribute not only to dose-limiting hepatotoxicity but also to inter-individual variability in therapeutic efficacy. Notably, the ABC family transporters are also implicated in multidrug resistance in tumours, further reinforcing the relevance of transporter profiling in clinical oncology. In the context of the tumour microenvironment, inflammatory mediators such as IL-6 and TGF-β1 are key modulators of hepatic fibrosis, systemic inflammation, and liver function deterioration. Their upregulation in cancer patients often reflects both direct hepatic involvement and paraneoplastic effects. Matrix remodelling enzymes (MMP-2 and MMP-9) additionally mediate hepatic structural changes during systemic therapy, including sinusoidal obstruction syndrome, which remains a major complication of certain chemotherapeutic regimens.

Molecular signatures of apoptosis and oxidative stress, including TP53 mutations and altered expression of BCL-2 and SOD2, are common in primary and secondary liver tumours. These factors contribute to hepatocyte vulnerability and impaired regenerative capacity, particularly in the context of systemic oxidative injury. Meanwhile, non-coding RNAs, such as miR-122, miR-192, and HULC, provide a sensitive, minimally invasive means of detecting liver dysfunction, and the studies analysed have confirmed their prognostic and diagnostic utility in liver oncology. Overall, the cumulative evidence supported the incorporation of molecular genetic markers into routine oncological assessment to improve the prediction, prevention, and management of liver dysfunction, especially in patients undergoing hepatotoxic chemotherapy or presenting with hepatic comorbidities.

Conclusions

Molecular genetic markers hold significant potential for enhancing the evaluation of liver functional activity in patients with malignant neoplasms. It was proved that their integration into clinical practice could revolutionise risk assessment, treatment planning, and monitoring by

enabling a personalised approach to oncology care. The review showed genetic variations in cytochrome P450 enzymes, glucuronosyltransferases, transporter proteins, inflammatory mediators, apoptotic regulators, and non-coding RNAs provide valuable insights into inter-individual differences in liver metabolism, drug toxicity susceptibility, and treatment outcomes. UGT1A1 and CYP3A4/CYP3A5 polymorphisms demonstrated robust associations with chemotherapy-induced hepatotoxicity, supporting their role as pharmacogenetic markers. Transporter gene variants such as ABCB1 C3435T and SLCO1B1*5 have been shown to predict altered hepatic drug disposition and cholestatic injury, which is critical in optimising dose adjustments and drug selection. Moreover, the profiling of cytokines (e.g., IL-6, TGF-β1), oxidative stress indicators (e.g., TP53, SOD2), and circulating non-coding RNAs (e.g., miR-122, HULC) offers dynamic and non-invasive strategies for assessing liver injury in real time. The review also showed that profiling cytokines (IL-6, TGF-β1), oxidative stress markers (TP53, SOD2), and circulating non-coding RNAs (miR-122, HULC) provided dynamic and non-invasive strategies for real-time assessment of liver injury. Moreover, it was demonstrated that combining multiple biomarkers enhanced the predictive accuracy of liver dysfunction risk assessment. Future research should focus on the development of combined biomarker panels and composite risk scores to enable personalised monitoring and optimise treatment strategies for patients with malignant neoplasms.

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Conflict of Interest
None.

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Молекулярно-генетичні маркери функціональної активності печінки у пацієнтів зі злоякісними новоутвореннями

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Анотація. Печінка відіграє ключову роль у метаболічній регуляції, детоксикації та системному гомеостазі. У пацієнтів зі злоякісними новоутвореннями, особливо тих, хто проходить хіміотерапію або має метастази в печінці, підтримка функції печінки є критично важливою. Метою роботи було провести огляд молекулярно-генетичних маркерів функціональної активності печінки у пацієнтів зі злоякісними новоутвореннями. Для формування первинної когорти публікацій їх пошук проводився за допомогою Google Scholar, PubMed, Research Gate та набору наступних ключових слів: «печінка», «молекулярна генетика», «рак», «генетичні маркери», «функціональна активність». Цей огляд підсумував сучасне розуміння молекулярно-генетичних маркерів, пов'язаних з функціональною активністю печінки у онкологічних хворих, підкреслюючи їх діагностичне та прогностичне значення, клінічну корисність та перспективи майбутніх досліджень. До цього огляду включено рецензовані дослідження, опубліковані між 2016 і 2024 роками. Серед розглянутих досліджень кілька молекулярно-генетичних маркерів послідовно виявилися значущими показниками функціонального стану печінки: ферменти CYP450 (CYP3A4, CYP1A2, CYP2E1), поліморфізм UGT1A128, нульові генотипи GSTM1 та GSTT1. Було встановлено, що поліморфізми UGT1A1 та CYP3A4/CYP3A5 мають сильний зв'язок з гепатотоксичністю, індукованою хіміотерапією, що підтвердило їхню роль як фармакогенетичних маркерів. Було показано, що варіанти генів-транспортерів, такі як ABCB1 C3435T та SLCO1B1*5, прогнозують змінений розподіл ліків у печінці та холестатичне пошкодження, що є критично важливим для оптимізації корекції дози та вибору препаратів. Також було узагальнено профілювання цитокінів (наприклад, IL-6, TGF-β1), індикаторів оксидативного стресу (наприклад, TP53, SOD2) та циркулюючих некодуючих РНК (наприклад, miR-122, HULC) на динамічні та неінвазивні стратегії для оцінки пошкодження печінки в режимі реального часу. Практична цінність дослідження полягає в тому, що встановлені біомаркери можуть стати незамінними інструментами в прецизійній онкології, забезпечуючи точнішу діагностику, ефективний моніторинг прогресування захворювання та індивідуальне планування лікування

Ключові слова: біомаркери; рак; гепатотоксичність; експресія генів; метастази

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Comparative efficacy of regenerative therapies for β-cell preservation in diabetes mellitus: A meta-analysis

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Abstract. Diabetes mellitus, which is associated with progressive loss of pancreatic β-cells, leading to insulin deficiency and hyperglycaemia, is of global health concern. Regenerative therapies, including stem cell therapies, have potential to address β-cell depletion and improve diabetes outcomes. The objective of this review was to compare the efficacy of stem cell-based regenerative therapies for the management of patients with both type 1 and type 2 diabetes mellitus. In carrying out this review, PubMed, ClinicalTrials.gov, and Google Scholar were the primary databases consulted. The analysis of 9 studies, including 5 randomised controlled trials and 4 non-randomised studies, revealed modest improvements in C-peptide levels, particularly in patients with type 2 diabetes mellitus, with a mean difference of 0.09 (95% confidence

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interval: -0.03, 0.21; p-value = 0.13), suggesting some benefit for β-cell preservation. However, the therapies did not show improvements in glycated haemoglobin levels, an increase in glycated haemoglobin level was observed, with a mean difference of 0.71 (95% confidence interval: 0.27, 1.15; p-value = 0.002), indicating worsening of glucose control, particularly in patients with type 2 diabetes mellitus. Although stem cell therapies show promise for β-cell preservation, such interventions do not appear to improve glycaemic control. This research has significant implications for clinicians involved in diabetes care, particularly those exploring regenerative treatments for type 1 and type 2 diabetes mellitus, and it underscores the necessity for personalised therapeutic strategies that account for the distinct pathophysiological mechanisms in these types of diabetes

Keywords: stem cell therapy; regenerative medicine; C-peptide levels; HbA1C levels; glycaemic control

Introduction

Diabetes mellitus (DM) is a global health challenge, largely due to the progressive loss of insulin-producing beta cells. Both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are marked by beta-cell dysfunction, which contributes to chronic hyperglycaemia and severe complications. While current treatments focus primarily on managing blood glucose levels, these treatments do not address the underlying loss of beta cells. This limitation underscores the need for disease-modifying therapies, such as regenerative stem cell therapies, which aim to restore or preserve beta-cell function. The latest studies suggest that stem cell approaches, including mesenchymal stem cells (MSCs), show promise in regenerating beta cells and enhancing glycaemic control.

For example, as noted in the study by S.P. Chin *et al.* [1], umbilical cord mesenchymal stem cells, particularly those derived from umbilical cord blood, have shown promise in improving beta-cell function and glycaemic control, and it was concluded that it is safe for patients with T2DM and is associated with overall health outcomes, with improvement in metabolic indices such as liver and renal profile and systemic subclinical inflammation. Similarly, M. Izadi *et al.* [2] and S. Gao *et al.* [3] have noted the potential of MSCs to enhance endogenous beta-cell regeneration through the differentiation into insulin-producing cells or by supporting existing beta cells. In addition, in the study by T.W. Reichman *et al.* [4], islet-derived stem cells have been investigated for the role in beta-cell preservation and regeneration, and an increase in C-peptide levels (a marker of insulin secretion) in T1DM was reported. In a study by W. Wei *et al.* [5], bone marrow-derived mononuclear cells (BM-MNCs) were investigated for the ability to enhance beta-cell mass and improve glycaemic control in T2DM. The results demonstrated a significant reduction in Haemoglobin A1c (HbA1c) levels and improved insulin secretion in patients, suggesting that BM-MNC therapy may help restore beta-cell function by reducing inflammation and promoting beta-cell regeneration. This study highlighted the potential of BM-MNCs in addressing the metabolic dysfunction in T2DM, though challenges related to long-term efficacy and scalability remain.

Similarly, in a systematic review and meta-analysis conducted by I.G. Pires *et al.* [6], the clinical efficacy of stem cell therapies for T1DM and T2DM was assessed by comparing laboratory parameters, including fasting blood glucose, HbA1c, and C-peptide levels, before and after treatment. The study included 38 original articles with 647 control cases and 654 treated patients, with follow-up periods ranging from three to twelve months. The analysis revealed that stem cell therapies significantly reduced the need for insulin and improved fasting blood glucose and HbA1c levels in both T1DM and T2DM patients. Furthermore, a significant increase in C-peptide levels, a marker of beta-cell function, was observed in most patients. Notably, bone marrow-derived hematopoietic stem cell therapy produced better results compared to conventional treatments like semaglutide. Although the benefits were more pronounced in T1DM, stem cell therapies still showed potential in improving insulin resistance and metabolic parameters in T2DM patients, suggesting a promising avenue for further research and clinical application.

Despite the promising potential of stem cell therapies for managing diabetes, several challenges persist, particularly regarding immune rejection and long-term safety. D.B. Zuo *et al.* [7] emphasised that stem cell therapies have significant immunomodulatory capabilities, yet immune rejection remains a critical hurdle, especially in T1DM. MSCs have been shown to possess immune-regulatory properties that could counter autoimmune attacks against β-cells in T1DM. However, even with advancements such as CRISPR-edited human leukocyte antigen knockouts, the risk of immune rejection is not entirely mitigated, underscoring the need for more refined immune modulation techniques. In T2DM, which is often associated with insulin resistance and metabolic stress, stem cell therapies face additional challenges. M. Zarei *et al.* [8] highlighted the dual challenge of insulin resistance and β-cell dysfunction in T2DM, making it more difficult for regenerated β-cells to function optimally without addressing the metabolic underlying factors. The study noted that while stem cell therapies like MSCs can help rejuvenate pancreatic function, the effectiveness is limited unless these metabolic stressors are concurrently managed. This supports the need for combination therapies that integrate stem cell-based interventions with lifestyle modifications or pharmacological treatments aimed at reducing insulin resistance.

Further studies by A.M. Mouzzam *et al.* [9] revealed that stem cell therapies hold significant potential in reversing T1DM by regenerating insulin-producing β-cells. However, the authors also pointed out that immune rejection

remains a significant barrier, as even autologous stem cell treatments may not prevent the autoimmune destruction of newly created β-cells. The study thus emphasised the importance of developing personalised therapies tailored to the immunological profiles of individual patients. This would help improve the success rates of these therapies and avoid the issue of immune rejection. In addressing the challenges of long-term safety and scalability, B. Gieroba *et al.* [10] discussed the potential complications of stem cell therapies, including tumorigenicity and the difficulty of ensuring consistent outcomes across diverse patient populations. The study focused on the clinical challenges of translating stem cell-based treatments into large-scale applications. Thereby suggesting that overcoming these barriers may require advancements in stem cell engineering, such as the use of encapsulation technologies or the development of more controlled differentiation protocols to prevent the formation of unwanted cell types, such as those contributing to tumours.

Additionally, S.M. Nameghi [11] emphasised the need for personalised approaches to stem cell therapies, and the findings from the research demonstrated that targeting the unique metabolic and immunological challenges in each patient, especially those with T2DM, is crucial for improving the efficacy of stem cell treatments. Personalised medicine could be integrated with stem cell therapies to account for individual genetic predispositions and responses to metabolic stress, thereby enhancing the therapeutic outcomes and minimising adverse effects. Finally, A. Hassanein & S. Akhtar [12] explored the challenges related to scalability and the complex nature of diabetes management, stressing that while stem cell therapies show promise, there is still a lack of sufficient comparative studies that evaluate the long-term effects of these therapies across various patient groups. The researchers argued that future research should focus on conducting large-scale, long-term clinical trials that assess both the efficacy and safety of stem cell-based interventions in diverse patient populations to improve clinical decision-making and direct future funding toward promising areas.

Based on this, the present review aimed to compare the efficacy of the adoption of regenerative therapies (stem cell therapies) for the preservation of β-cells in T1DM and T2DM by considering C-peptide levels and HbA1c levels as outcome measures.

Materials and Methods

This study followed the guidelines for meta-analysis outlined in the analysis by M.J. Page *et al.* [13]. To address the goal, the PICO framework was employed [14]. The Population (P) for this study included human patients diagnosed with T1DM or T2DM. The Intervention (I) was regenerative therapy through stem cell approaches. The Comparison (C) was made between patients receiving stem cell therapy and untreated patients or those receiving conventional treatments. The Outcome (O) variables of interest were C-peptide levels, HbA1c, insulin requirements, and fasting plasma glucose levels. The inclusion criteria considered were original research articles, including randomised controlled trials and non-randomised studies, published in English between 2020 and 2025 that involved human subjects, specifically individuals diagnosed with T1DM or T2DM. The therapy under investigation had to be stem cell-based. Furthermore, to be eligible, studies needed to report on either HbA1c levels or C-peptide. The excluded studies were those that were not published in English, those involving animal subjects, reviews, conference proceedings, or those where full-text access was unavailable. A comprehensive search was carried out in PubMed, ClinicalTrials.gov, and Google Scholar from 30 November 2025 to 3 December 2025. In searching the databases, a combination of keywords relating to diabetes mellitus, such as diabetes mellitus, hyperglycaemia, and those relating to stem cell therapies were employed. The search results were refined with the application of Boolean operators "AND" and "OR" [15]. MeSH terms were also applied in searching PubMed, which is the only database that features such terms [16]. The compiled search terms and filters applied for each database (such as year of publication, English language, and human participants) were represented in Table 1.

Table 1. Studies search strategy

Database	Search term	Search yield	Filters applied	Yield following application of filters
ClinicalTrials.gov	(diabetes mellitus OR hyperglycaemia) AND (C-peptide Levels OR HbA1c Levels) AND (stem cells OR progenitor cells OR hematopoietic stem cells OR bone marrow-hematopoietic stem cells OR mesenchymal stem cells OR bone marrow-mesenchymal stem cells OR bone marrow mononuclear cells OR umbilical cord blood OR umbilical cord-mesenchymal stem cells OR placenta-derived mesenchymal stem cells OR insulin-secreting-adipose-derived mesenchymal stem cells)	89	nil	
Google Scholar	(diabetes mellitus OR hyperglycaemia) AND (stem cells OR progenitor cells OR hematopoietic stem cells OR bone marrow-hematopoietic stem cells OR mesenchymal stem cells OR bone marrow-mesenchymal stem cells OR bone marrow mononuclear cells OR umbilical cord blood OR umbilical cord-mesenchymal stem cells OR placenta-derived mesenchymal stem cells OR insulin-secreting adipose-derived mesenchymal stem cells)	204	2020-2025	69

Continued Table 1

Database	Search term	Search yield	Filters applied	Yield following application of filters
PubMed	("diabetes mellitus"[Title/Abstract] OR "hyperglycaemia"[Title/Abstract]) AND ("stem cells"[Title/Abstract] OR "progenitor cells"[Title/Abstract] OR "hematopoietic stem cells"[Title/Abstract] OR "bone marrow hematopoietic stem cells"[Title/Abstract] OR "mesenchymal stem cells"[Title/Abstract] OR "bone marrow mesenchymal stem cells"[Title/Abstract] OR "bone marrow mononuclear cells"[Title/Abstract] OR "umbilical cord blood"[Title/Abstract] OR "umbilical cord mesenchymal stem cells"[Title/Abstract] OR "placenta derived mesenchymal stem cells"[Title/Abstract] OR (("insulin"[Supplementary Concept] OR "insulin"[All Fields] OR "insulin"[MeSH Terms] OR "insulin s"[All Fields] OR "insuline"[All Fields] OR "insulinic"[All Fields] OR "insulinisation"[All Fields] OR "insulinised"[All Fields] OR "insulins"[MeSH Terms] OR "insulins"[All Fields]) AND "derived mesenchymal stem cells"[Title/Abstract]))	3,044	2020-2025, Free full text, Clinical Trial, Multicentre Study, Observational Study, Randomised Controlled Trial, English, Humans	16

Source: compiled by the authors

Following a systematic search in PubMed, Google Scholar, and ClinicalTrials.gov, 3,403 records were retrieved. After applying appropriate filters, 240 articles remained, then 8 duplicates were removed, 177 were removed during title and abstract screening, and the full text of 12 articles was not retrieved. The full text of the remaining 43 articles was subjected to a detailed eligibility assessment, after which 34 articles were excluded that did not meet the inclusion criteria, and the remaining 9 articles were included in the analysis in this review. The literature selection process was illustrated in the PRISMA flow diagram, as shown in Figure 1.

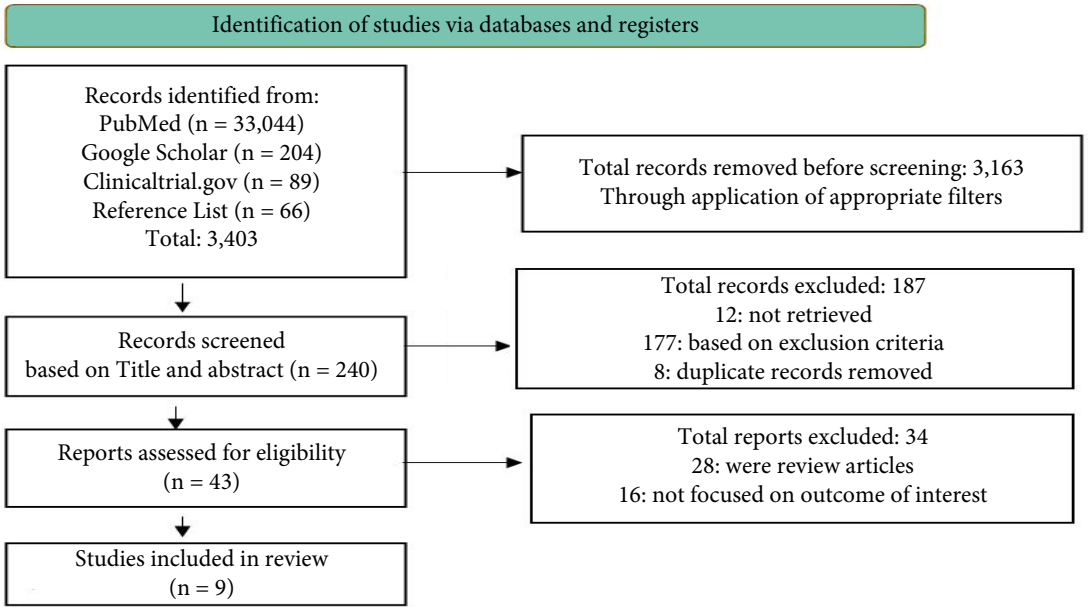

Figure 1. PRISMA flow diagram

Source: compiled by the authors

After retrieving the relevant studies, the data extraction was conducted independently by two researchers, and discrepancies were resolved through discussion. Key data extracted from the studies included information relating to study details, patient demographics, regimen, and laboratory parameters for diabetes (HbA1c and C-peptide) at baseline and during the follow-up period. To assess the quality of the included studies, the Revised Cochrane risk-of-bias tool for randomised trials Version 22 was employed for the randomised controlled trials [17] and the ROBINS-I tool for non-randomised studies [18]. The included studies in this review comprised a total of 9 studies, of which 5 were randomised controlled trials, and 4 were non-randomised studies, with 3 focusing on T1DM, 7 on T2DM, and 3 out of the 9 studies did not feature a control group. The included studies were conducted

in different countries of the world, including China (5), Iran (2), Sweden (1), and Malaysia (1). A total of 694 participants were featured in all the studies; the mean age of patients varied from 10.27 years to 61.5 years, with T1DM patients typically younger than T2DM patients. However, there was a significant difference in the duration of the disease before therapy. The T1DM patients had shorter histories compared to those with T2DM; this is due to the distinct characteristics of both conditions. All regimens involved stem cell therapies administered at varying doses, ranging from 1×10^6 to 200 million cells per dose. The mode of administration recorded was intravenous (IV) and intra-arterial pancreatic infusion (IAPI). Follow-up periods varied, with the majority of studies reporting 12 months, although some extended to as long as 96 months. This variation in study characteristics underscores the diverse approaches used to assess regenerative therapies and the potential for β-cell preservation in diabetes. Table 2 summarised the characteristics of the included studies in this review. Thus, this review analysed 9 studies (5 randomised controlled trials (RCT), 4 non-randomised) involving 710 participants with T1DM and T2DM, evaluating stem cell therapies with varying doses, administration routes, and follow-up periods.

Table 2. Characteristics of included studies

Study	Country	Study design	Type of DM	Number of patients TG / CG	Mean age of participants (years)	History of disease	Regimen	Mean regimen dose	Mode of injection	Mean follow-up (months)
M. Izadi *et al.* [2]	IR	RCT	T1DM	TG = 11; CG = 10	TG=10.27 CG=11.5	Newly diagnosed (<6 weeks)	BM-MSCs	1×10^6 cells/kg	IV	12
P.O. Carlsson *et al.* [19]	SE	RCT	T1DM	TG = 9; CG = 5	TG=31 CG=31	Newly diagnosed (<2 years)	UC-MSCs	200 mln cells	IV	12
Z. Wu *et al.* [20]	CN	RCT	T2DM	57(29 in MSC + MC and 28 in MC-only group)/ 29 in CG)	Dual MSC + MC group = 52.8; MC-only group = 53.2; CG = 54.6	≥ 3 and ≤ 15 years	MSC and MC	1×10^6 cells/kg	IV and IAPI	96
L. Zang *et al.* [21]	CN	RCT	T2DM	TG = 45; CG = 46	TG = 50; CG = 50.45	< 20 years	UC-MSCs	1×10^6 cells/kg	IV	12
L. Zang *et al.* [22]	CN	RCT	T2DM	TG = 37; CG = 36	TG = 50.97; CG = 50.53	< 20 years	UC-MSCs	1×10^6 cells/kg	IV Infusion	12
S.P. Chin *et al.* [1]	MS	ROS	T2DM	218 in 6 mo. FUG and 83 in 12 mo. FUG, no CG	61.5	Not reported	UC-MSCs	$50–100\times10^6$	IV Infusion	6 in 6 FUG and 12 in 12 FUG
J. Lu *et al.* [23]	CN	Open-label, parallel-arm, non-randomised prospective study	T1DM	TG=27; CG=26	TG=22.4; CG=27.4	Not reported	UC-MSCs	1×10^6 cells/kg	IV Infusion	12
R. Raoufinia *et al.* [24]	IR	Open-label, single-arm pilot clinical trial	T2DM	11 participants; no CG	20-65	≥ 10 years	UC-MSCs	1×10^8 cells/kg	IV Infusion	2
X.F. Lian *et al.* [25]	CN	Single-arm, open-label, exploratory clinical trial	T2DM	16 participants; no CG	52.5	10.06 ± 5.74 years	UC-MSCs	1×10^6 cells/kg	IV Infusion	3

Note: BM-MSCs – bone marrow-mesenchymal stem cells, UC-MSCs – umbilical cord-mesenchymal stem cells, MC – mononuclear stem cell; TG – Treatment Group; CG – Control Group; FUG – Follow-Up Group; ROS – Retrospective observational study; IR – Iran; SE – Sweden; CN – China; MS – Malaysia
Source: compiled by the authors

Based on the quality assessment of the included studies, among the five randomised controlled trials, the majority demonstrated low risk of bias across most domains except for M. Izadi *et al.* [2], where concerns regarding missing outcome data were noted due to participant dropout, which could influence the robustness of the findings. For the four non-randomised studies, moderate risks were identified in the works by S.P. Chin *et al.* [1], J. Lu *et al.* [23] and R. Raoufinia *et al.* [24], due to potential confounding factors and unclear adjustments, which could lead to over- or underestimation of the treatment effects. These biases, particularly related to missing data and confounding, may lead to misleading conclusions, potentially exaggerating the efficacy of stem cell therapies in β-cell preservation or misrepresenting the true impact of these therapies on diabetes management.

The software used for the meta-analysis was Review Manager version 5.4.1. The effect estimates from the included studies were pooled by adopting a random-effects model, inverse variance, and mean difference (MD) of C-peptide and HbA1C levels at baseline and after therapy were used for comparison. The use of random-effects modelling in this analysis is beneficial in that it accounts for heterogeneity among studies. Analyses of subgroups were carried out according to the type of stem cell therapy and the type of diabetes. To test the robustness of the finding, sensitivity analyses were conducted by excluding one study at a time in the analysis to observe the effect on the overall pooled estimate. This specific type of sensitivity analysis was conducted to assess whether the exclusion of any single study would significantly alter the pooled results. However, several limitations must be considered when interpreting the results from this study. The significant heterogeneity across studies, particularly in terms of the stem cell types used, dosage, administration routes, and follow-up durations, may have contributed to the variability in outcomes. Additionally, the relatively small sample sizes and short follow-up periods in many of the included studies limit the generalisability of the findings. Moreover, while this meta-analysis provides a pooled estimate of the effects of stem cell therapies on C-peptide and HbA1c levels, it does not account for other important factors such as quality of life, adverse events, and cost-effectiveness, which are critical for evaluating the feasibility of widespread clinical implementation.

Results and Discussion

C-peptide levels are closely linked to β-cell preservation in diabetes. C-peptide, an insulin byproduct, is a biomarker for β-cell activity. Research indicates that higher C-peptide levels enhance β-cell function and reduce diabetes complications [26]. Conversely, low C-peptide levels cause glucose fluctuations, acute hypoglycaemia, and HbA1c. According to previous studies, C-peptide levels predict β-cell function in T2DM. Therefore, C-peptide levels serve as a measure of the effectiveness of treatments aimed at maintaining β-cell activity in diabetes management [27]. For T1DM, as shown in Figure 2, the pooled effect size across studies showed a mean difference (MD) of 0.04 (95% CI: -0.09, 0.18). The p-value associated with this effect is 0.51, which indicates that the observed minimal improvement in C-peptide levels is not statistically significant. This suggests that stem cell therapies, while showing a slight trend towards increasing C-peptide levels, do not provide strong enough evidence to support a meaningful impact on β-cell function in T1DM. The subgroup analysis for different types of stem cells, such as BM-MSC and UC-MSC, also did not reveal significant heterogeneity, reinforcing the conclusion that the impact of stem cell therapies on C-peptide levels in T1DM is inconclusive.

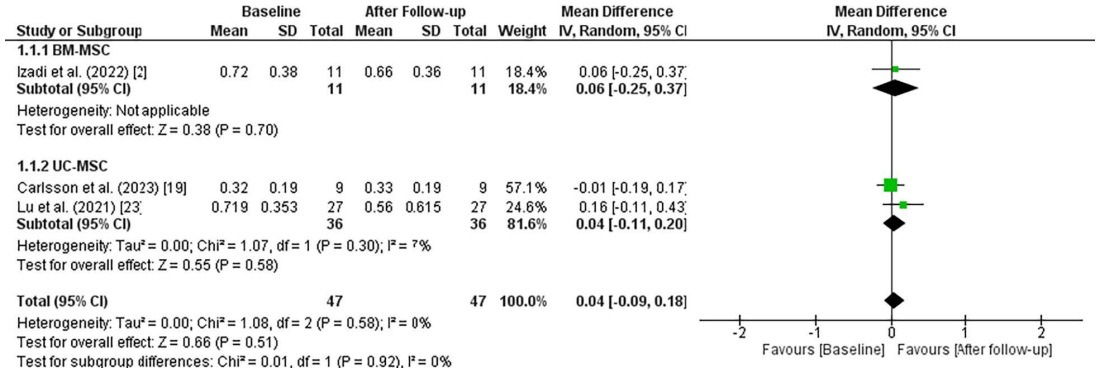

Figure 2. Forest plot for fasting C-peptide levels (ng/mL) in T1DM individuals from baseline to follow-up
Source: created by the authors

In contrast, the results for T2DM, as shown in Figure 3, presented more favourable insights. The pooled effect for T2DM across studies showed a mean difference (MD) of 0.09 (95% CI: -0.03, 0.21). The p-value for this pooled effect is 0.13, indicating a non-significant, modest improvement in C-peptide levels following stem cell therapy. This suggests that stem cell therapies are more effective in enhancing β-cell regeneration or function in T2DM patients compared to T1DM. Subgroup analysis for T2DM, including therapies such as BM-MSC+MC, MC, and UC-MSCs, demonstrated some variability in outcomes, but the overall trend points toward a positive effect on C-peptide levels, though the effect remains modest.

When comparing the pooled effects for T1DM and T2DM, it is evident that stem cell therapies yield more consistent but modest effects in T2DM patients. The p-value of 0.13 for T2DM suggests a more pronounced effect compared to the p-value of 0.51 for T1DM, highlighting the more substantial response to stem cell therapies in T2DM. This difference may be attributed to the distinct pathophysiological mechanisms of β-cell loss in both types of diabetes. T1DM, characterised by autoimmune-mediated destruction of β-cells, presents more challenges for regeneration, whereas T2DM, driven by metabolic stress, may be more responsive to therapies targeting the rejuvenation of existing β-cells. While both T1DM and T2DM show some potential for improvement in C-peptide levels with stem cell therapies, the effects are more pronounced in T2DM. This highlights the need for personalised regenerative approaches tailored to the specific pathophysiological mechanisms

of β-cell dysfunction in each form of diabetes. Further research with larger sample sizes and standardised protocols is needed to fully evaluate the long-term efficacy and safety of stem cell-based therapies for β-cell preservation.

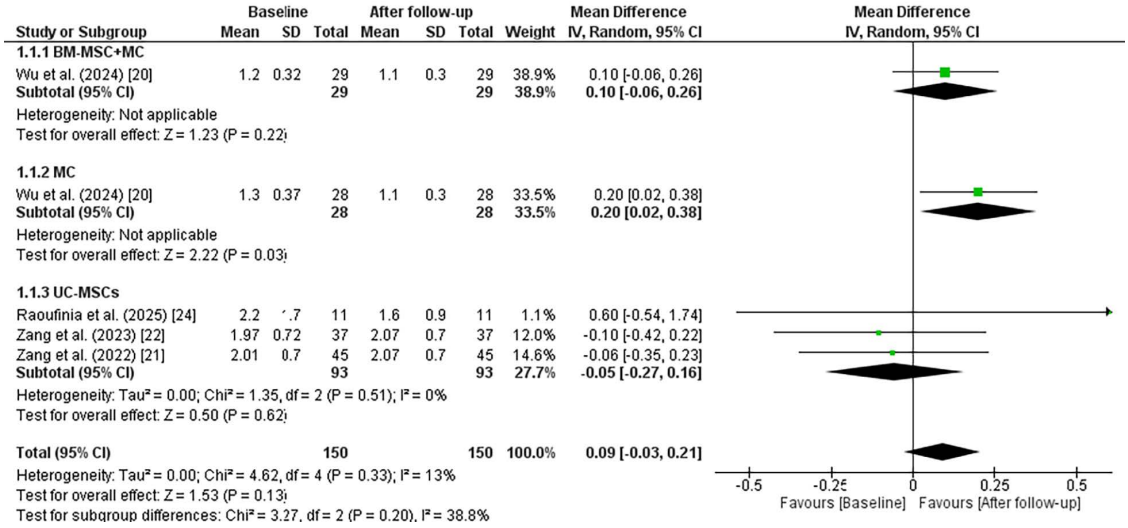

Figure 3. Forest plot for fasting C-peptide levels (ng/mL) in T2DM individuals from baseline to follow-up
Source: created by the authors

HbA1c levels significantly affect β-cell preservation in diabetes. Insulin production decreases with low β-cell activity, leading to hyperglycaemia and high HbA1c levels. Research links high HbA1c levels to impaired β-cell function and diabetes consequences. Conversely, lower HbA1c levels improve β-cell function and glycaemic control. Monitoring HbA1c levels can indicate β-cell function and the effectiveness of therapies to maintain it. Maintaining β-cell activity is crucial for diabetes management, and HbA1c readings can assess treatment effectiveness [28, 29].

For T1DM, according to Figure 4, the total pooled effect across studies showed a mean difference (MD) of 0.78 (95% CI: -0.32, 1.89), with a p-value of 0.16. This indicates that stem cell therapies investigated have a non-significant increase in HbA1c levels, suggesting a potential worsening of glucose control. The wide confidence interval (CI) and the high p-value suggest that any change in HbA1c is modest and likely due to random variation. The subgroup analysis for BM-MSC and UC-MSC therapies revealed some variability in the outcomes, but overall, the results do not support a clear, consistent benefit of stem cell therapies in lowering HbA1c in T1DM patients.

In contrast, the results for T2DM in Figure 5 showed a statistically significant increase in HbA1c levels, with a mean difference (MD) of 0.71 (95% CI: 0.27, 1.15) and a p-value of 0.002. This suggests that stem cell therapies are associated with a worsening of glucose control in T2DM patients, contrary to the expected outcome (i.e., a worsening of glucose control in T2DM patients rather than improvement). The subgroup analysis showed variability in outcomes with effect size in the MC group, derived from Z. Wu *et al.* [20] showing -0.10, which indicates a decrease in HbA1c levels, which is not statistically significant. However, the overall result indicates a need for further investigation into the effects of stem cell therapies on HbA1c levels in T2DM.

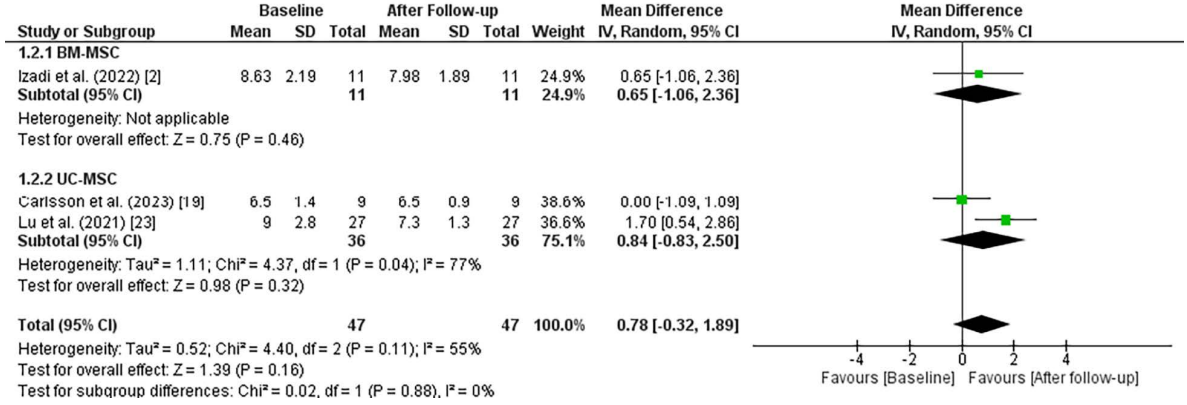

Figure 4. Forest plot for HbA1c levels (%) in T1DM individuals from baseline to follow-up
Source: created by the authors

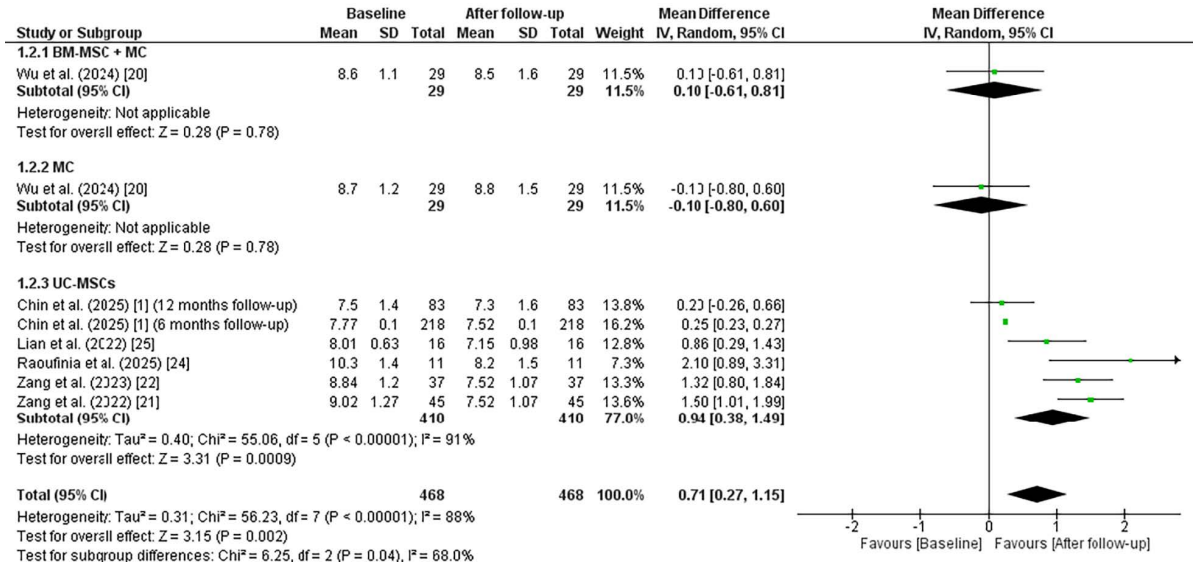

Figure 5. Forest plot for HbA1c levels (%) in T2DM individuals from baseline to follow-up
Source: created by the authors

Therefore, in T1DM, stem cell therapies showed no significant effect on HbA1c levels, indicating only modest changes that are likely due to random variation. For T2DM, stem cell therapies were associated with a significant increase in HbA1c, suggesting a potential worsening of glucose control, and further research is needed to better understand these effects. The findings of this study provide insights into the efficacy of stem cell therapies in preserving β-cell function in T1DM and T2DM. The results indicated that in terms of C-peptide levels, stem cell therapies have limited benefits in T1DM compared to T2DM, with minimal improvement in C-peptide levels, indicating some benefit in β-cell preservation. On the other hand, a non-significant increase in HbA1c levels was observed in T1DM, and a significant increase in HbA1c levels was observed in T2DM, suggesting a potential worsening of glucose control. These findings suggest that stem cell therapies may offer a modest benefit in preserving β-cell function due to an increase in c-peptide levels, particularly in T2DM patients, but do not appear to have a beneficial impact on HbA1c levels in either T1DM or T2DM.

The use of stem cell-based therapies, particularly MSCs, for diabetes management has been explored in various meta-analysis studies. For example, Q. Wu *et al.* [30] conducted a meta-analysis on the efficacy of stem cell transplantation for T1DM and found that MSC therapy could reduce insulin requirements and improve C-peptide levels, although the improvement was not statistically significant. This is consistent with the results of the current study, which observed a slight improvement in C-peptide levels in patients with T1DM, which is also not statistically significant. However, in contrast, Q. Wu *et al.* found that MSC therapy significantly decreased HbA1c levels, whereas in this study, an increase in HbA1c levels was recorded. This decrease in HbA1c was also reported in the study by J. He *et al.* [31], in which MSC therapy was also investigated, and according to the report for fasting C-peptide levels, no significant increase in fasting C-peptide levels was recorded as well. Similarly, S.Y. Sun *et al.* [32] reported a significant improvement in C-peptide levels in T1DM patients following MSC therapy, supporting the idea that stem cells may help regenerate insulin-producing β-cells. However, S.Y. Sun *et al.* also reported a significant decrease in HbA1c levels in RCTs, but with high heterogeneity. This suggests that while there may be some improvement in glycaemic control, it is not consistent across all studies, and the effect size is uncertain. Moreover, according to findings of M. Kashbour *et al.* [33], significant reductions in HbA1c levels in T2DM patients treated with MSCs were also reported.

A potential explanation for the variation in HbA1c level outcomes recorded in studies such as those of Q. Wu *et al.* [30], J. He *et al.* [31], and S.Y. Sun *et al.* [32] compared with the findings in this study may be attributed to differences in sample sizes, cell source, and injection protocols across studies as well as the comparator arms included in the meta-analysis. In addition, it is worth noting that in these studies, comparisons were made between treatment groups and control groups, whereas in this study, comparison was made with baseline outcomes in treatment groups and the outcomes in treatment groups recorded at the end of varying follow-up periods across studies. Moreover, changes in HbA1c did not consistently align with modest changes in fasting C-peptide, suggesting that β-cell preservation may not translate directly into improved glycaemic control [34].

Nevertheless, a critical consideration in interpreting findings is the differences in pathophysiology between T1DM and T2DM, which likely contribute to the varied responses observed in stem cell therapies. T1DM is characterised by autoimmune destruction of β-cells, so it is essential to manage the immune system to avoid the

rejection of newly transplanted or regenerated β-cells, as the autoimmune destruction of these cells is the primary factor contributing to this condition. It is essential that these cells are safeguarded through the application of immunosuppressive techniques [35]. Conversely, the immunological dysregulation inherent in T1DM presents specific challenges, as the immune system may persist in targeting newly formed β-cells even after the creation. This holds particularly true in circumstances where immunosuppressive treatment fails to meet adequate levels. The successful outcome of these therapies hinges on achieving a balance between promoting β-cell regeneration and managing the immune response [36].

On the other hand, T2DM is marked by insulin resistance and β-cell dysfunction, which arise from chronic metabolic stress [37]. The findings of this study suggest that therapies utilising stem cells show a limited enhancement in C-peptide levels, implying that regenerated β-cells still face metabolic challenges in T2DM. The presence of insulin resistance in T2DM could potentially reduce the effectiveness of stem cell-based therapies, as noted by N. Yang *et al.* [38]. This holds particularly true when the underlying metabolic issues, such as hyperglycaemia, obesity, and chronic inflammation, are not simultaneously addressed. The therapeutic effects of regenerated β-cells may be constrained, as the operational efficiency could be compromised if the upstream variables remain unaddressed [39]. Moreover, the long-term safety profile of stem cell therapy remains to be determined, especially concerning the risks of cancer development or unintended differentiation of stem cells [40].

It is crucial to highlight that while stem cell therapies may hold promise for success, there are several potential risks involved, necessitating a careful approach. The variability in the outcomes of different regimens represents a significant concern. The effectiveness of these therapies is influenced by various factors, such as the quality of the stem cells, the delivery method employed, and the standard of care administered post-transplant. Furthermore, the source of stem cells – whether derived from autologous or allogeneic donors – may significantly affect both the efficacy and safety of the treatment, as allogeneic transplants carry an inherent risk of immune rejection, while autologous approaches may be limited by the quality of the patient's own cells. The variety of outcomes reported in the trials included in this meta-analysis highlighted the lack of standardisation in clinical protocols, which complicates the ability to compare results across different studies.

Conclusions

The pooled effect of fasting C-peptide levels showed a slight, non-significant improvement in T1DM patients, with an MD of 0.04 (95% CI: -0.09, 0.18; p = 0.51), suggesting no substantial impact on β-cell regeneration or preservation. In contrast, T2DM patients exhibited a modest, though still non-significant, improvement in C-peptide levels (MD = 0.09, 95% CI: -0.03, 0.21; p = 0.13), pointing to some potential for stem cell therapy in enhancing β-cell function in this population. This suggests that stem cell therapies may be more effective in T2DM patients, where metabolic stress is the primary factor affecting β-cell function. However, contrary to expectations, an increase in HbA1c levels was observed in both T1DM and T2DM patients, indicating a worsening of glucose control, particularly in T2DM, with a statistically significant mean difference of 0.71 (95% CI: 0.27, 1.15; p = 0.002). This suggests that while stem cell therapies may offer some benefits in preserving β-cell activity, such therapies do not result in better glycaemic control and may potentially exacerbate metabolic issues. These findings underscored the complexity of using stem cell therapies for diabetes management, especially in cases where insulin resistance or autoimmune destruction significantly impairs β-cell function.

The results of this meta-analysis were influenced by several biases, including missing data and confounding variables, which could distort the actual effectiveness of stem cell therapies. Moreover, the variability in study designs, stem cell types, and follow-up durations further complicates the interpretation of results. Therefore, stem cell-based regenerative therapies show modest promise for β-cell preservation in T2DM, but further research is required to evaluate the long-term efficacy, safety, and impact on overall diabetes management. Future studies should aim to standardise protocols, include larger sample sizes, and incorporate more comprehensive outcome measures, including quality of life and adverse events, to better inform clinical decision-making. Additionally, personalised approaches that account for the distinct pathophysiological mechanisms of T1DM and T2DM could enhance the therapeutic potential of stem cell therapies, offering more tailored and effective treatments for patients suffering from these chronic conditions. The need for rigorous, long-term clinical trials remains essential to better inform clinical decision-making and optimise the integration of regenerative therapies into mainstream diabetes management.

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Conflict of Interest

None.

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Порівняльна ефективність регенеративних методів лікування для збереження β-клітин при цукровому діабеті: метааналіз

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Анотація. Цукровий діабет, який пов'язаний з прогресуючою втратою β-клітин підшлункової залози, що призводить до дефіциту інсуліну та гіперглікемії, є глобальною проблемою охорони здоров'я. Регенеративні методи лікування, включаючи терапію стовбуровими клітинами мають потенціал для вирішення проблеми виснаження β-клітин та поліпшення результатів лікування діабету. Метою цього огляду було порівняння ефективності регенеративних методів лікування на основі стовбурових клітин для лікування пацієнтів з цукровим діабетом 1 та 2 типу. При проведенні цього огляду основними базами даних для звернення були PubMed, ClinicalTrials.gov та Google Scholar. Аналіз 9 досліджень, включаючи 5 рандомізованих контрольованих випробувань та 4 нерандомізованих дослідження, виявив помірне поліпшення рівнів С-пептиду, особливо у пацієнтів з цукровим діабетом 2 типу, із середньою різницею 0,09 (95 % довірчий інтервал: -0,03, 0,21; р-значення = 0,13), що свідчить про певну користь для збереження β-клітин. Однак терапія не показала поліпшення рівня глікованого гемоглобіну, спостерігалося підвищення рівня глікованого гемоглобіну із середньою різницею 0,71 (95 % довірчий інтервал: 0,27, 1,15; р-значення = 0,002), що вказує на погіршення контролю глюкози, особливо у пацієнтів з цукровим діабетом 2 типу. Хоча терапія стовбуровими клітинами є перспективною для збереження β-клітин, було виявлено, що вона не покращує глікемічний контроль. Це дослідження має важливе значення для клініцистів, які займаються лікуванням діабету, особливо тих, хто досліджує регенеративні методи лікування 1 та 2 типів цукрового діабету, і підкреслює необхідність індивідуалізованих терапевтичних стратегій, що враховують особливості патофізіологічних механізмів цих типів діабету

Ключові слова: терапія стовбуровими клітинами; регенеративна медицина; рівні С-пептиду; рівні HbA1C; контроль глікемії

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Evaluation of anorectal fistula using an MRI fistulogram and its correlation with intraoperative findings

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Abstract. Despite magnetic resonance imaging being the preferred modality for the preoperative assessment of *fistula-in-ano*, evidence from direct MRI-intraoperative correlation remains essential to confirm that internal openings, secondary tracts, and abscesses are accurately mapped, thereby preventing missed disease and recurrence. This study aimed to evaluate the correlation between magnetic resonance imaging findings and intraoperative observations in patients with anorectal fistulas. This prospective study was conducted at Al Amin Medical College and Hospital, including 50 patients with clinically suspected or previously diagnosed perianal fistula who underwent magnetic resonance imaging on a 1.5 Tesla scanner using T1-, T2-, short inversion recovery, and diffusion-weighted imaging sequences. Findings were analysed for fistula classification, tract location, internal openings, abscesses, and contrast enhancement. Surgical exploration findings were compared with magnetic resonance imaging results to assess correlation. The most affected age

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groups were 31-50 years, with a male predominance (66%). Intersphincteric (42%) and transsphincteric (36%) fistulas were the most common. Magnetic resonance imaging showed single internal and external openings in 86% of patients. Associated abscesses were detected in 20%, and contrast enhancement was noted in 46%. Magnetic resonance imaging demonstrated 100% sensitivity and specificity for internal openings, 90% sensitivity for abscesses, and 76.5% sensitivity for secondary tracts. Magnetic resonance imaging findings correlated with intraoperative findings in 86% of cases. Magnetic resonance imaging is a highly effective tool for evaluating *fistula-in-ano*, showing strong concordance with surgical findings. Its routine use can significantly enhance surgical planning and reduce recurrence rates

Keywords: preoperative imaging; surgical correlation; perianal fistula; perianal abscess; internal opening

Introduction

The relevance of this study arises from the high prevalence of *fistula-in-ano* and the complexity of its surgical management. Achieving a lasting result requires complete removal of the primary tract and secondary branches while preserving the function of the anal sphincter, which remains a clinical challenge. Standard examination often underestimates the complexity of the fistula, especially in cases of recurrence or deep extension. This increases the risk of persistence and repeat interventions. Therefore, improving preoperative diagnosis and accurate mapping of fistula tracts is critical for optimising surgical management and reducing the incidence of complications. Magnetic resonance imaging (MRI) has been increasingly refined as the principal imaging tool for perianal fistulas, supported by studies evaluating the added value of functional sequences, protocol optimisation, and comparisons with operative findings.

In the study by D.K. Boruah *et al.* [1], diffusion-weighted imaging (DWI) was investigated as an adjunct to conventional MRI for perianal fistula assessment. The authors emphasised that combining diffusion information with standard anatomical sequences can improve confidence in detecting inflammatory components and distinguishing active disease from less active tracts, supporting an approach in which DWI complements high-resolution T2-weighted imaging rather than replacing it. In the study by L. Soydan [2], DWI and apparent diffusion coefficient measurements were explored for assessing fistula "activity". This study highlighted the clinical value of functional imaging in characterising inflammatory burden, suggesting that diffusion metrics may help stratify disease activity when morphology alone is insufficient, which is particularly relevant when determining the timing of surgery or evaluating suspected persistent inflammation after treatment.

Protocol refinement has also focused on post-contrast imaging and the advantages of modern 3D acquisitions in complex disease. In the study by K.V. Abdulla *et al.* [3], contrastenhanced 3D T1-weighted sequences were compared with conventional 2D postcontrast imaging for perianal fistula evaluation. Their research demonstrated that 3D techniques can enhance the visualisation of surgically critical targets such as internal openings and ramifications, and highlighted the practical importance of acquisition efficiency and image conspicuity when assessing complex branching anatomy. In the study by A.H. Madany *et al.* [4], MRI was presented as central to defining fistula relationships to the sphincter complex, demonstrating its role in outlining extensions and identifying associated sepsis that may not be evident clinically. This study also highlighted a recurring problem in practice: even when MRI is performed, variability in reporting structure and completeness may limit its translation into consistent surgical decision-making across institutions.

A closely related area of investigation is the evaluation of perianal sepsis, especially abscesses that influence the urgency and extent of surgical intervention. In the study by P. Aggarwal *et al.* [5], DWI was assessed for detecting and characterising perianal abscesses, with comparison to contrast-enhanced MRI. This line of research supports the notion that diffusion-based approaches can be clinically useful for evaluating sepsis and may be particularly relevant when gadolinium administration is undesirable, while also emphasising the need to ensure that subtle secondary extensions are not missed when protocols are simplified. In the study by N.P. Narsingh *et al.* [6], preoperative MRI findings were compared with intraoperative observations in patients with anorectal fistula. Large-cohort studies have further examined how different MRI sequence combinations perform in depicting fistula characteristics and surgically relevant landmarks. In the study by Q. Tao *et al.* [7], multi-phase contrast-enhanced fat-suppressed 3D T1-weighted imaging (VIBE-based) was compared with fat-suppressed T2-weighted imaging combined with DWI in anal fistula evaluation. This research illustrates a continuing unresolved issue: the optimal balance between contrastenhanced anatomical detail and diffusion-based assessment, and whether specific sequence strategies can consistently improve the depiction of internal openings and secondary tracts across readers and institutions.

Technique innovation has also been explored to improve tract conspicuity and accessibility in different practice settings. In the study by U.K. Basavaraju *et al.* [8], magnetic resonance fistulography using percutaneous instillation of aqueous jelly was described as a method to enhance tract delineation. This approach highlights ongoing efforts to improve the visualisation of fine tracts and openings, but it also raises practical questions about standardisation, reproducibility, and comparative benefit compared with optimised conventional MRI protocols. Finally, comparative modality studies continue to inform diagnostic pathways. In the study by A.Ö. Cantürk *et al.* [9], contrast-enhanced endoanal ultrasound was compared with MRI for preoperative fistula mapping. Such research supports the concept

of complementary imaging, with ultrasound offering targeted evaluation in selected contexts, while MRI provides broader multiplanar mapping; however, it also underscores a persistent gap: how to choose the most efficient and accurate preoperative strategy across varied resource environments while maintaining reliable detection of internal openings, secondary tracts, and occult sepsis.

Taken together, recent literature establishes MRI as the primary modality for the preoperative evaluation of *fistula-in-ano*, while also revealing unresolved issues such as variability in detecting secondary extensions, heterogeneity in protocol selection (contrastenhanced versus diffusion-centred strategies), and the need for local validation of MRI reporting against operative findings using standardised classifications and clearly defined anatomical endpoints. Therefore, this study was conducted to evaluate MRI fistulogram findings in anorectal fistula, focusing on fistula classification, tract course, internal opening localisation, secondary extensions, and associated abscesses, and to compare these findings with intraoperative observations.

Materials and Methods

This prospective cohort study was conducted in the Department of Radiodiagnosis, Al-Ameen Medical College and Hospital, Vijayapura (Bijapur), Karnataka, India, over a two-year period from 2023 to 2025. The study protocol was finalised before participant recruitment. Ethical approval was obtained from the Institutional/Local Ethics Committee of Al-Ameen Medical College and Hospital (IEC Approval No.: IEC/AMMC/2023/045, dated 11 April 2023). Written informed consent was obtained from all participants prior to enrolment. The study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki [10]. Reporting and methodological transparency were aligned with internationally accepted guidance for observational studies [11].

A total of 50 consecutive patients aged ≥18 years who were clinically suspected or previously diagnosed with a perianal fistula were included. Patients were excluded if they had any non-MRI-compatible implants or devices, significant claustrophobia/MRI-related anxiety, or did not complete follow-up required for surgical correlation. Each participant underwent a standardised clinical assessment including history taking, physical examination (including local perianal examination), and baseline laboratory investigations as per institutional practice. MRI was performed on a 1.5 Tesla scanner using a four-channel phased-array body coil. Imaging planes were planned with reference to the anal canal axis to optimise depiction of the sphincter complex and fistula course. The protocol included axial T1-weighted imaging, coronal T2-weighted imaging, short tau inversion recovery (STIR) imaging, and DWI acquired using b-values of 0, 500, 1,000, and 1,500 s/mm^2. In cases where presacral or higher extension was suspected clinically or on initial images, additional sagittal T1-weighted sequences were obtained. Intravenous gadolinium contrast and endorectal coils were not used in this study. The MRI protocol used for fistulography is presented in Table 1. Disease severity was categorised using the St James's University Hospital MRI grading system [12].

Table 1. MRI protocol used for fistulography

MRI sequences	Non-contrast scans		Non-contrast fatsuppressed scans		Contrast-enhanced fatsuppressed scans
	T1W FSE	T2W FSE	FS T1W FSE	FS T2W FSE	FS T1W FSE with 3D reconstruction
Imaging plane	Axial and coronal	Sagittal, axial, coronal	Axial and coronal	Sagittal, axial, coronal	Sagittal, axial, coronal
TR/ TE (ms)	633 / 11	5,040 / 113	766 / 11	6,320 / 116	500 / 11
FOV	345 × 345	346 × 346	347 × 347	347 × 347	300 × 300
Section thickness (mm)	6 mm	6 mm	6 mm	6 mm	6 mm
Matrix	512*512	512*512	512*512	512*512	512*512

Note: FSE – fast spin echo; T1W/T2W – T1-weighted/T2-weighted; FS – fat suppressed; TR – repetition time; TE – echo time; FOV – field of view
Source: compiled by authors

All MRI examinations were interpreted by a radiologist experienced in pelvic MRI. The radiologist documented the fistula type and classification (based on its relationship to the sphincter complex), the location of the internal opening (including its position relative to the anal canal), and the presence of secondary tracts/ramifications and abscesses/collections. Imaging features suggestive of active inflammation were assessed using STIR signal and diffusion restriction patterns. Findings were recorded in a structured format to facilitate comparison with operative findings. Surgical intervention was performed in most cases within one week following MRI, with a median interval of one day between imaging and surgery. Intraoperative findings were documented by the operating surgeon, in-

cluding the fistula course, internal opening site, presence of secondary tracts, and associated abscesses. MRI findings were compared with intraoperative observations (reference standard) to assess diagnostic concordance for internal opening localisation, secondary tract detection, and abscess identification. Data were entered into Microsoft Excel and analysed using IBM SPSS Statistics (Version 26). Continuous variables were summarised using the mean and standard deviation or range, where appropriate, while categorical variables were presented as frequencies and percentages. Associations between categorical variables were evaluated using the chi-squared test. A p-value < 0.05 was considered statistically significant, whereas $p < 0.001$ was considered highly significant where applicable.

Results

A total of 50 patients with clinically suspected or previously diagnosed *fistula-in-ano* were evaluated using MRI fistulography, and imaging findings were correlated with intraoperative observations whenever surgery was performed. The cohort demonstrated a typical epidemiological profile for *fistula-in-ano*, with a predominance in mid-adulthood and a higher frequency in males. However, beyond demographic patterns, the results highlighted a clinically important finding: patients diagnosed with clinically uncomplicated disease based on initial clinical examination may in fact have more extensive lesions, abscesses, or secondary branches. In this context, MRI plays a key role in preoperative detection.

The age distribution showed a clear concentration in the middle decades of life. Patients aged 31-40 years (34%) and 41-50 years (32%) together comprised nearly two-thirds of the cohort, indicating that the disease burden peaked in the third to fifth decades. Fewer patients were observed at the extremes of age (<30 years and >60 years), implying relatively lower disease occurrence in younger and older groups. This distribution is relevant because mid-adulthood is often associated with delayed presentation after recurrent perianal sepsis, increasing the likelihood of tract maturation, branching, or occult collections that benefit from detailed imaging. A male predominance was observed (66% male, 34% female). While this confirms that *fistula-in-ano* was more frequent among men in this cohort, subsequent analyses showed that sex did not significantly influence key MRI indicators such as contrast enhancement or grade distribution. Thus, sex appeared more reflective of disease occurrence than of disease activity or complexity in those affected.

Clinical inspection showed that single internal and external openings were present in 86% of patients, implying that most patients presented with a single dominant pathway rather than multiple external exits. This finding can create an impression of clinically uncomplicated disease; however, MRI grading demonstrates that a substantial proportion already exhibit transsphincteric or more complex patterns, reinforcing the need for imaging even when clinical examination suggests a straightforward tract. The distribution of openings and the predominance of single openings are illustrated in Figure 1, which supports the observation that most cases did not present with multiple cutaneous exit points.

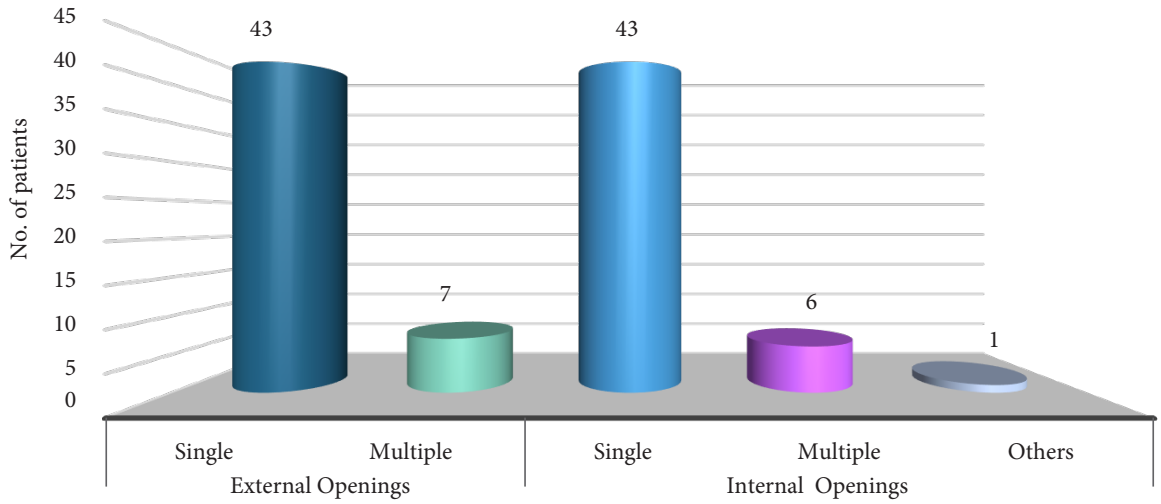

Figure 1. Distribution of fistula openings

Source: compiled by authors

The location of external openings demonstrated a strong posterior tendency. Most external openings were located at the 4-6 o'clock positions (58.1%), indicating posterior quadrant predominance (Fig. 2). This pattern is clinically meaningful because posterior tracts may extend deeply and curve around sphincteric planes, and they may be associated with concealed sepsis that is not readily apparent on digital rectal examination. Although multiple openings were infrequent, they tended to occur in association with more advanced disease, consistent with the clinical concept that multiple external openings frequently represent branching, chronicity, or recurrent sepsis rather than early uncomplicated fistula.

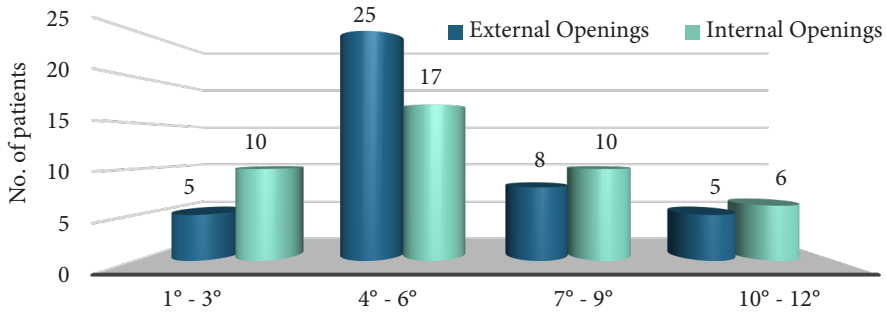

Figure 2. Clock-face distribution of fistula openings

Source: compiled by authors

Regarding tract anatomy, intersphincteric fistulas were the most common subtype (42%), confirming that the intersphincteric plane remains the dominant route of spread in many patients. From an operative standpoint, intersphincteric disease is often amenable to sphincteraparing techniques, and MRI mapping helps define tract location, height, and internal opening position. However, the cohort also included a considerable proportion of tracts extending beyond the intersphincteric plane, indicating that a meaningful fraction of patients already had transsphincteric or higher-grade disease. This mixture of simple and complex patterns underscores why reliance on clinical impression alone can result in underestimation of disease extent. MRI detected associated abscesses in 20% of patients (Fig. 3). This is a key clinical finding because undrained abscesses and missed septic foci are major contributors to persistent symptoms and postoperative recurrence. Abscess detection on MRI therefore provides direct, actionable information for operative planning, prompting careful drainage and exploration for related extensions.

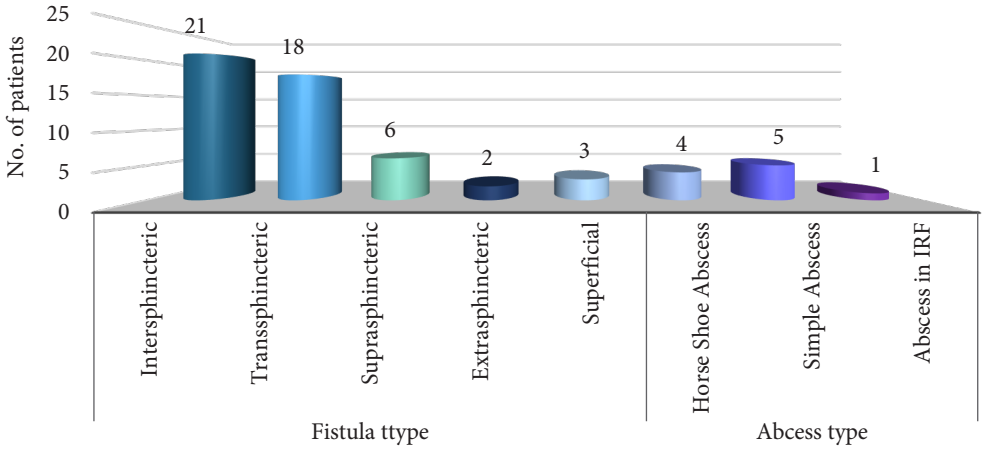

Figure 3. Types of fistula tracts and associated abscesses on MRI

Source: compiled by authors

Inflammatory activity was assessed using contrast enhancement, which was present in 46% of cases and absent in 54%. Enhancement is clinically relevant because it often reflects active inflammation or granulation tissue and may signal ongoing disease activity rather than inactive fibrotic tracts. The demographic breakdown of enhancement showed a statistically significant association between age and enhancement (p = 0.0456, Table 2). The 31-40-year group demonstrated the highest relative proportion of enhancing disease, suggesting that patients in this age band were more likely to present with active inflammatory fistulas rather than quiescent chronic tracts. In contrast, older age groups showed relatively more non-enhancing disease, which may reflect chronic fibrosis or less active inflammation. Importantly, no significant sex-based difference in enhancement was found (p = 0.9141, Table 2), reinforcing that inflammatory activity on MRI was not dependent on sex within this cohort.

Table 2. Contrast enhancement findings by demographics

Demographics		Present (n, %)	Absent (n, %)	p-value
Sex	Male	15 (30.0)	18 (36.0)	X = 0.1163
	Female	8 (16.0)	9 (18.0)	p = 0.9141

Continued Table 2

Demographics		Present (n, %)	Absent (n, %)	p-value
Age	<30	2 (4.0)	4 (8.0)	X = 9.709 **p = 0.0456***
	31-40	13 (26.0)	4 (8.0)	
	41-50	5 (10.0)	11 (22.0)	
	51-60	2 (4.0)	5 (10.0)	
	>60	1 (2.0)	3 (6.0)	

Note: *p < 0.05 was considered statistically significant. The chi-squared test was used to assess the association between demographic variables and contrast enhancement findings
Source: compiled by authors

Disease severity was categorised using the St James's University Hospital MRI grading system [12]. Grade I (34%) and Grade III (26%) were the most prevalent grades (Table 3). This distribution is clinically important: Grade I reflects uncomplicated intersphincteric disease, whereas Grade III reflects transsphincteric involvement, representing a step-up in anatomical complexity and potential surgical risk. The relatively high proportion of Grade III cases indicates that a substantial subset of patients had fistulas that traverse sphincteric structures, making accurate mapping essential to avoid iatrogenic sphincter injury and to plan appropriate sphincter-preserving approaches.

Table 3. MRI classification of fistula tracts (St James's classification)

Grade	Frequency (n = 50)	Percentage (%)
I	17	34.0
II	9	18.0
III	13	26.0
IV	7	14.0
V	4	8.0

Source: compiled by authors

No statistically significant association was found between St James's grade and age (p = 0.4347) or between grade and sex (p = 0.3006) (Table 4). In other words, neither age group nor sex reliably predicted fistula complexity on MRI. This is clinically relevant because it supports the use of MRI across all demographic categories rather than limiting imaging to selected groups. In contrast, a strong association between grade and contrast enhancement was identified (p < 0.0001). This finding indicates that more complex fistulas were more likely to demonstrate enhancement, aligning with the concept that advanced disease often carries a greater inflammatory burden, larger tract volume, recurrent infection, and more frequent secondary sepsis.

Table 4. Correlation of St James's grade with sex, contrast enhancement, and age

Grade	Male (n, %)	Female (n, %)	Present (n, %)	Absent (n, %)	<30 (n, %)	31-40 (n, %)	41-50 (n, %)	51-60 (n, %)	>60 (n, %)
	Sex		Contrast		Age				
I	11 (22.0)	6 (12.0)	2 (4.0)	15 (30.0)	2 (4.0)	3 (6.0)	7 (14.0)	3 (6.0)	2 (4.0)
II	4 (8.0)	5 (10.0)	8 (16.0)	1 (2.0)	0 (0.0)	5 (10.0)	2 (4.0)	1 (2.0)	1 (2.0)
III	10 (20.0)	3 (6.0)	3 (6.0)	10 (20.0)	3 (6.0)	2 (4.0)	6 (12.0)	1 (2.0)	1 (2.0)
IV	4 (8.0)	3 (6.0)	7 (14.0)	0 (0.0)	0 (0.0)	5 (10.0)	1 (2.0)	1 (2.0)	0 (0.0)
V	4 (8.0)	0 (0.0)	3 (6.0)	1 (2.0)	0 (0.0)	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)
p-value	X = 4.873; p = 0.3006		X = 27.01; p < 0.0001*		X = 16.26; p = 0.4347				

Note: *p < 0.05 was considered statistically significant
Source: compiled by authors

Complexity-related features increased with grade. Among Grade II-V fistulas, 20% had associated abscesses and 26% demonstrated secondary tracts (Table 5). The absence of abscesses in Grade I cases supports the interpretation that uncomplicated intersphincteric fistulas are less likely to harbour established sepsis, whereas higher grades require careful evaluation for collections. Secondary tracts were most frequently seen in Grade III fistulas, suggesting that once the tract extends transsphincterically, the opportunity for lateral or superior extension increases, making Grade III an important "transition" category between simple and complex disease.

Table 5. Correlation of fistula severity with abscess and tract presence

Grade	Abscess present (n, %)	Secondary tract present (n, %)
I	0 (0.0)	2 (4.0)
II	2 (4.0)	3 (6.0)
III	3 (6.0)	4 (8.0)
IV	3 (6.0)	2 (4.0)
V	2 (4.0)	2 (4.0)

Source: compiled by authors

MRI demonstrated 100% sensitivity and 100% specificity for detecting internal openings, which indicates their reliable identification without false-positive results. This is of great practical importance, since an undetected internal opening is the main cause of recurrence. For abscesses, MRI showed 90% sensitivity and 100% specificity (Table 6), indicating high reliability of the method and a low rate of missed collections. For secondary tracts, the sensitivity was 76.5% with a specificity of 100%: the branches detected by MRI were reliable, but some small or intermittently patent secondary tracts could only be identified intraoperatively, which emphasises the complementary role of surgical exploration. Although ideal values (100%) are rare, they are possible in the absence of misclassification, especially with small samples. At the same time, 95% confidence intervals remain wide, particularly for specificity, due to the limited number of true negative cases (e.g. 7 TN), which necessitates cautious generalisation of the results despite the high observed efficacy.

Table 6. Diagnostic accuracy of MRI for fistula evaluation

Feature	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Secondary tracts	13	0	4	33	76.5	100.0	100.0	89.2
Abscess detection	9	0	1	40	90.0	100.0	100.0	97.6
Internal openings	43	0	0	7	100.0	100.0	100.0	100.0

Note: TP – true positive; FP – false positive; FN – false negative; TN – true negative
Source: compiled by authors

Grade-wise concordance between MRI and surgery remained strong (Table 7), indicating that MRI grading generally aligned well with operative findings across the severity spectrum. Minor reductions in specificity at certain grades likely reflected borderline interpretative findings or the inherent difficulty of distinguishing subtle extensions in early disease, whereas more complex grades tended to show clearer imaging patterns and strong surgical agreement.

Table 7. MRI and surgical concordance by fistula grade

Grade	MRI detected (n, %)	Surgical concordant (n, %)	Not operated (n, %)	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)
I	17 (34.0)	13 (26.0)	1 (2.0)	13	4	0	33	100	89.2
II	9 (18.0)	9 (18.0)	0 (0.0)	9	0	0	41	100	100
III	13 (26.0)	12 (24.0)	1 (2.0)	12	1	0	37	100	97.4
IV	7 (14.0)	7 (14.0)	0 (0.0)	7	0	0	43	100	100
V	4 (8.0)	3 (6.0)	1 (2.0)	3	1	0	45	100	97.8

Note: TP – true positive; FP – false positive; FN – false negative; TN – true negative
Source: compiled by authors

In this cohort, *fistula-in-ano* predominantly affected middle-aged adults and occurred more frequently in males. While many patients appeared to have single-opening disease, MRI demonstrated a meaningful burden of higher-grade fistulas, abscesses, and secondary extensions that could alter surgical strategy. Contrast enhancement was significantly related to age and strongly associated with higher MRI grades, supporting its value as a marker of active and complex disease. Overall, MRI fistulography showed excellent performance for internal opening identification and abscess detection and provided reliable preoperative mapping to guide surgery and reduce the risk of missed disease.

Discussion

Fistula-in-ano is anatomically heterogeneous, ranging from simple intersphincteric tracts to complex disease with secondary extensions, horseshoe components, supralevator spread, and abscess formation. Because recurrence is most commonly driven by failure to identify the true internal opening and occult secondary pathways, preoperative delineation of fistula anatomy is essential for selecting an

appropriate operative approach and for minimising avoidable sphincter injury. Although clinical examination and examination under anaesthesia remain important, these approaches may under-recognise deep intersphincteric extensions, high transsphincteric tracts, or small collections – particularly in recurrent or scarred disease – thereby creating a rationale for MRI-based mapping.

MRI is currently regarded as the most informative imaging modality for perianal fistulas because it depicts the sphincter complex and fistulous tracts with high soft-tissue contrast in multiple planes. This aligns with the observations of G.N. Buchanan *et al*. [13] and I.J. Beckingham *et al.* [14], who emphasised MRI's ability to define tract course, internal openings, and associated inflammation in a manner that is directly actionable for surgeons. MRI also supports the planning of sphincter-sparing strategies by clarifying the relationship of the tract to the internal and external sphincters, which is often difficult to establish confidently with clinical assessment alone. The present findings, showing substantial agreement between MRI and operative assessment for key anatomical targets, therefore align with the expected global trend rather than diverging from it. The clinically decisive advantage of MRI lies in revealing disease elements that change surgical management, including secondary tracts, horseshoe extensions, and abscesses. High concordance for these components has been reported in large operative-correlation cohorts. For example, D. Vo *et al*. [15] documented very high agreement between MRI and intraoperative findings across a large patient series, with particularly strong performance for internal opening localisation and abscess detection. The present study similarly demonstrated meaningful MRI-operative alignment for these endpoints, supporting the concept that MRI functions as a "surgical roadmap" rather than merely a diagnostic test. In addition, the distribution of occult disease elements detected in the present cohort is comparable to findings from regional cohorts. H.R. Jat *et al.* [16] reported similar frequencies of secondary tracts and abscesses in a 50-patient study, supporting the reproducibility of MRI-based detection in routine practice settings.

At the same time, some performance differences relative to the larger literature warrant explanation to provide a balanced interpretation. Secondary tract sensitivity in the present cohort was lower than in some high-volume studies, including those of D. Vo *et al*. [15] and prospective series discussed by P. Garg *et al*. [17]. Several factors could account for this discrepancy without contradicting MRI's overall utility. First, patient mix strongly influences secondary tract prevalence and detectability; cohorts enriched with recurrent disease or highercomplexity fistulas tend to yield higher rates of ramifications and therefore may report higher apparent detection, while more typical mixed outpatient cohorts may include fewer complex branches. Second, MRI protocol design affects conspicuity: studies that routinely incorporate contrast-enhanced fat-suppressed T1-weighted sequences, 3D acquisitions, or tailored high-resolution approaches may better depict fine ramifications than conventional noncontrast protocols. This is consistent with observations by I.J. Beckingham *et al.* [14], who noted that contrast can help distinguish active inflammation from fibrosis, and with later study by B.A. Kumar *et al.* [18], who reported improved depiction of specific complex features using enhanced sequences. Third, sample size may contribute; smaller cohorts inherently produce wider variability in sensitivity estimates compared with multi-hundred-patient datasets, making modest differences plausible even when imaging quality is high. The potential incremental value of diffusion-based techniques in improving tract conspicuity has also been highlighted. S.M. Abd-Elwahab *et al*. [19] reported improved diagnostic performance when MR fistulography was combined with DWI, supporting the view that advanced sequences may be particularly helpful for subtle secondary branches or complex inflammatory disease.

The present article also supported the practical value of structured MRI-based grading for standardised communication. The St James's University Hospital MRI classification [12] is widely used because it summarises sphincter involvement and the presence of complications in a manner that is useful for surgical planning. H. Sarda *et al.* [20] reported strong agreement between St James's grading and operative assessment, particularly in higher grades where clinical evaluation is least reliable, while B.A. Kumar *et al.* [18] similarly reported statistically significant MRI-surgical correlation in complex fistulas. The observed agreement in the present cohort reinforces the utility of structured classification for aligning radiological description with operative decision-making. However, discrepancies may still occur in advanced disease, where fibrosis, oedema, and postoperative scarring can obscure subtle branches or where operative assessment may underestimate deep extensions that are better appreciated on multiplanar imaging. These limitations highlight the need for structured reporting and systematic surgical exploration rather than suggesting any fundamental weakness of MRI.

Comparative evidence also clarified why MRI is consistently preferred over alternative modalities for complex disease. Studies by S.M. Hussain *et al*. [21] and A.G. Maier *et al*. [22] have reported MRI superiority over endoanal ultrasound for defining the full tract course, sphincter relationships, and deep extensions, while N. Tripathi *et al.* [23] noted that conventional fistulography may miss internal openings and ramifications, limiting its usefulness in surgical planning. Reports such as S.S. Patil & R.S. Tathode [24] further emphasised that MRI-guided mapping can assist in selecting the appropriate operative pathway in higher-grade fistulas, especially where abscess drainage or identification of hidden extensions alters the surgical plan. Together, this body of studies supports the interpretation that MRI's advantage lies not only in detection but also in reproducible anatomical mapping across planes and compartments. Methodological considerations must also be acknowledged when interpreting concordance. Single-radiologist interpretation may introduce observer bias, and

lack of surgeon blinding to MRI findings may inflate agreement because operative exploration can be guided by preoperative imaging. These limitations have been recognised in operative-correlation designs, including those discussed by D. Vo *et al.* [15] and H. Sarda *et al.* [20]. Additionally, timing between imaging and surgery can affect detection of collections if sepsis evolves between assessments, particularly for small abscesses. Such factors help explain why concordance rates vary across studies even when MRI is widely accepted as the most informative modality.

Thus, MRI provides dependable preoperative anatomical mapping for *fistula-in-ano*, with strong alignment to operative findings for primary tract characterisation and internal opening localisation. Differences from some larger or contrast-enhanced series were most apparent in secondary tract depiction and can be reasonably attributed to protocol differences, case mix, and study design rather than to inconsistency with the broader evidence base. These findings support the continued routine use of MRI for operative planning and underscore the value of standardised MRI protocols and structured reporting. A clear implication is that optimising sequence selection – particularly through selective incorporation of advanced diffusion-based or contrast-enhanced techniques where appropriate – and improving reporting consistency may further enhance detection of subtle secondary extensions and small collections, thereby strengthening surgical precision and reducing recurrence risk.

Conclusions

In this prospective cohort study of 50 patients with clinically suspected or previously diagnosed *fistula-in-ano*, MRI fistulogram provided accurate preoperative delineation of fistula anatomy. Analysis showed that intersphincteric fistulas were the most common subtype (42%). It was demonstrated that most patients presented with a single dominant pathway, as single internal and external openings were identified in 86% of cases; however, MRI identified additional surgically relevant complexity in a subset of patients, including associated abscesses (20%) and secondary tracts, which can directly influence operative strategy. MRI-surgical correlation was available in 43 patients (86%), and MRI demonstrated high diagnostic accuracy for the most critical surgical endpoint: internal opening localisation showed 100% sensitivity and 100% specificity. It was also found that abscess detection showed 90% sensitivity and 100% specificity, supporting MRI's value in identifying sepsis requiring targeted drainage. For secondary tracts, MRI demonstrated 76.5% sensitivity and 100% specificity, indicating high reliability when secondary extensions were detected, while also emphasising that very small or intermittently patent branches may still be revealed intraoperatively. Further research should focus on larger multicentre cohorts with standardised reporting and blinded image interpretation to validate diagnostic performance across different settings. Comparative evaluation of optimised MRI protocols, including diffusion-weighted and contrast-enhanced sequences, is warranted to determine whether secondary tract detection and grading accuracy can be further improved, particularly in complex and recurrent fistulas.

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Conflict of Interest

The authors declare that there are no conflicts of interest related to this study.

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Оцінка аноректальної фістули за допомогою МРТ-фістулограми та її корекція з урахуванням інтраопераційних даних

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Анотація. Незважаючи на те, що магнітно-резонансна томографія є кращим методом для передопераційної оцінки анальної фістули, дані прямої магнітно-резонансної томографії та інтраопераційної кореляції залишаються необхідними для підтвердження точного відображення внутрішніх отворів, вторинних проходів та абсцесів, щоб запобігти несвоєчасній діагностиці та рецидиву. Метою цього дослідження було оцінити кореляцію між результатами магнітно-резонансної томографії та інтраопераційними спостереженнями у пацієнтів з аноректальними фістулами. Це проспективне дослідження було проведено в Медичному коледжі та лікарні Аль-Амін з 50 пацієнтами з клінічно підозрюваною або раніше діагностованою періанальною фістулою, яким було проведено магнітно-резонансну томографію на сканері 1,5 Тесла з використанням послідовностей T1, T2, короткого відновлення інверсії та дифузійно-зваженої візуалізації. Результати були проаналізовані з метою класифікації фістул, визначення місця розташування тракту, внутрішніх отворів, абсцесів та контрастного підсилення. Результати хірургічного дослідження були порівняні з результатами магнітно-резонансної томографії для встановлення кореляції. Найбільш ураженими віковими групами були 31-50 років, з переважанням чоловіків (66 %). Найбільш поширеними були міжсфінктерні (42 %) та транссфінктерні (36 %) фістули. Магнітно-резонансна томографія показала поодинокі внутрішні та зовнішні отвори у 86 % пацієнтів. Супутні абсцеси були виявлені у 20 %, а контрастне підсилення було відзначено у 46 %. Магнітно-резонансна томографія продемонструвала 100 % чутливість і специфічність для внутрішніх отворів, 90 % чутливість для абсцесів і 76,5 % для вторинних проходів. Результати магнітно-резонансної томографії корелювали з інтраопераційними результатами в 86 % випадків. Магнітно-резонансна томографія є високоефективним інструментом для оцінки анальних фістул, демонструючи високу узгодженість з хірургічними результатами. Її регулярне використання може значно поліпшити планування хірургічного втручання та зменшити частоту рецидивів

Ключові слова: передопераційна візуалізація; хірургічна кореляція; періанальна фістула; періанальний абсцес; внутрішній отвір

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Dynamics of left ventricular ejection fraction changes after surgical correction of mitral regurgitation

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Abstract. Mitral regurgitation is among the most prevalent disorders of the cardiac valvular apparatus and leads to chronic volume overload, left ventricular dilatation, and adverse ventricular remodelling. Despite the proven efficacy of contemporary surgical techniques for correcting mitral regurgitation, early recovery of left ventricular systolic function and the tempo of reverse remodelling remain clinically important. The aim of this study was to assess early postoperative changes in left ventricular systolic function and to analyse the dynamics of ejection fraction as a marker of the effectiveness of surgical correction of mitral regurgitation. The study enrolled 40 patients with grade III-IV mitral regurgitation who underwent either mitral valve repair (45%) or mitral valve replacement (55%). Transthoracic echocardiography was performed three times – preoperatively and at 1 and 3 months after surgery. Ejection fraction was calculated using the biplane Simpson method in accordance with ASE/EACVI recommendations. Statistical analysis was performed using built-in Microsoft Excel tools with computation of means, standard deviations, and percentage changes. Preoperatively,

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mean ejection fraction was 48.2%. At 1 month, it increased to 51.7%, and at 3 months to 54.9%, consistent with early reverse remodelling. The most pronounced improvement was observed in patients with a baseline ejection fraction <50% (increase of 8-10%). Mitral valve repair was associated with more favourable early dynamics than replacement (7-9% vs 5-6%). Overall, 75% of patients demonstrated a positive trajectory as early as one month postoperatively. Surgical correction of mitral regurgitation is associated with a substantial early improvement in left ventricular systolic function. Ejection fraction dynamics within the first 1-3 postoperative months represent an important prognostic tool, enabling assessment of procedural efficacy, the rate of reverse remodelling, and optimisation of subsequent patient management

Keywords: reverse remodelling; echocardiography; systolic function; annuloplasty; valve replacement; postoperative recovery; myocardial contractility

Introduction

Mitral regurgitation remains one of the leading drivers of chronic left ventricular volume overload and progressive cardiac remodelling, ultimately resulting in symptomatic heart failure and an increased risk of adverse clinical outcomes. As emphasised in contemporary international guidelines by A. Vahanian *et al.* [1] and C.M. Otto *et al.* [2], timely, anatomically guided intervention is critical to prevent irreversible myocardial injury and to improve long-term prognosis. In routine clinical practice, many patients present only once functional limitations have developed – corresponding to New York Heart Association (NYHA) functional class II-III – when symptoms may still be moderate, yet structural remodelling is already established and may constrain postoperative recovery, as noted by P.A. Heidenreich *et al.* [3].

Accurate assessment of mitral regurgitation severity, mechanism, and remodelling phenotype is fundamental to therapeutic decision-making. Current recommendations advocate an integrated approach based on quantitative and qualitative echocardiographic parameters, supplemented, when necessary, by other imaging modalities. This is highlighted in the guidelines by A. Vahanian *et al.* [1], C.M. Otto *et al.* [2], and the imaging recommendations of P. Lancellotti *et al.* [4], who emphasised that disease trajectory and response to intervention depend not only on the degree of regurgitation but also on the adaptation of the myocardium and cardiac chambers to chronic loading.

Secondary mitral regurgitation is closely intertwined with the pathophysiology of heart failure: left ventricular dilatation, papillary muscle displacement, and remodelling of the fibrous annulus sustain regurgitation and perpetuate a vicious cycle of progressive dysfunction. A joint European statement by A.J.S. Coats *et al.* [5] underscores that management should be stepwise – optimisation of guideline-directed heart failure therapy, meticulous clinical and imaging reassessment, and timely multidisciplinary Heart Team discussion to determine whether surgical or transcatheter intervention is likely to deliver durable benefit. Importantly, the anticipated clinical effect depends on the ability to interrupt maladaptive remodelling and to initiate reverse remodelling once regurgitation is reduced.

Growing evidence consistently indicates that baseline myocardial status and the extent of remodelling influence outcomes and must be considered when interpreting early postoperative functional changes. Current heart failure guidelines emphasise that baseline left ventricular dysfunction and structural remodelling substantially influence prognosis and should be taken into account when interpreting treatment response in patients with secondary mitral regurgitation [3].

In addition, studies by G. Benfari *et al.* [7] and Joung *et al.* [8] indicate that variability in baseline left ventricular function, remodelling severity, and postoperative recovery patterns further contribute to heterogeneity in clinical outcomes after correction of mitral regurgitation. Trial-level comparisons show that patient selection and baseline remodelling substantially affect outcomes, as reflected by differences between populations enrolled in major transcatheter mitral repair studies, as reported by B. Iung *et al.* [9] and D. Messika-Zeitoun *et al.* [10].

Taken together, contemporary data confirm that the clinical benefit of mitral valve interventions is closely linked to the degree of reverse remodelling achieved after correction of regurgitation. However, available evidence remains insufficiently systematised regarding the rate and characteristics of ejection fraction recovery during the first three months after mitral valve surgery, particularly across different baseline remodelling phenotypes. This gap provides a clear rationale for targeted investigation of early postoperative changes in left ventricular systolic function as potential markers of effective correction and myocardial recovery. The aim of this study was to assess early postoperative changes in left ventricular systolic function and to analyse the dynamics of ejection fraction as a marker of the effectiveness of surgical correction of mitral regurgitation.

Literature Review

Guidance from the European Association of Cardiovascular Imaging, as presented by P. Lancellotti *et al.* [4], further highlights that standardised multimodality imaging improves reproducibility and enables a meaningful evaluation of remodelling dynamics before and after intervention. This is particularly relevant because postoperative changes in chamber size and systolic performance reflect both recovery of contractile function and alterations in loading conditions following elimination of regurgitant volume. Large imaging analyses in patients with heart failure and reduced ejection fraction, such as those conducted by G. Benfari *et al.* [7], also demonstrate that both grading and clinical consequences of functional mitral regurgitation differ across

phenotypes, underscoring the need for individualised interpretation of remodelling and function. Evidence from contemporary clinical studies suggests that differences in baseline left ventricular systolic function and remodelling status may help explain heterogeneous responses to mitral valve intervention and divergent trajectories of reverse remodelling [8]. Post hoc analyses, in particular, underscore that the degree of left ventricular remodelling modifies clinical benefit, suggesting that marked dilatation and limited myocardial reserve may attenuate functional recovery even when regurgitation is effectively reduced, as shown by D. Messika-Zeitoun *et al.* [10]. Moreover, previous surgical series have shown that baseline ventricular status and the extent of structural myocardial adaptation are important modifiers of postoperative recovery and may influence the magnitude of functional improvement after intervention [11].

Long-term follow-up from transcatheter correction trials demonstrates that sustained reduction of secondary mitral regurgitation can translate into durable clinical benefit in appropriately selected patients. Three-year outcomes confirm further reductions in heart failure hospitalisations and preservation of clinical advantage compared with medical therapy alone, as demonstrated by M.J. Mack *et al.* [12], while five-year data additionally support persistent benefit in selected populations, as reported by G.W. Stone *et al.* [13], highlighting the importance of long-term regurgitation control and favourable remodelling response over time. Collectively, these findings reinforce a central principle that is equally relevant to surgical correction: durable elimination or substantial reduction of regurgitation should promote reverse remodelling, although the extent and tempo of functional recovery remain variable and are largely determined by pre-intervention myocardial condition.

In primary degenerative mitral regurgitation, contemporary imaging studies indicate that reverse remodelling after valve repair extends beyond reduction in chamber dimensions and also encompasses changes in myocardial tissue characteristics. Previous studies indicate that apparently preserved preoperative left ventricular systolic function does not always reflect normal myocardial reserve, and that postoperative dysfunction may still occur despite seemingly acceptable baseline parameters [14]. This strengthens the rationale for early postoperative assessment using sensitive markers of myocardial recovery, since pre-existing fibrosis or advanced remodelling may limit reversibility and contribute to incomplete normalisation of function.

Surgical strategies also continue to evolve with respect to choosing between repair and replacement across different aetiologies and high-risk scenarios. Evidence indicates that outcomes differ between repair and replacement strategies, as demonstrated by A. Tomšič *et al.* [15], underscoring that procedure selection, underlying substrate, and the durability of effective regurgitation elimination influence long-term results. Recurrent regurgitation after repair remains a clinically relevant issue – particularly in ischemic/functional settings – since recurrent mitral regurgitation is associated with less favourable reverse remodelling, as reported by A. Salsano *et al.* [16], supporting the value of durable regurgitation control and meticulous selection of reconstructive techniques to maximise long-term valve competence. In parallel, contemporary reports in high surgical-risk populations with mitral regurgitation, such as those by M. Sudo *et al.* [17], emphasise outcome heterogeneity and the importance of baseline status and treatment strategy for functional recovery and survival.

Reviews and expert syntheses increasingly focus on the early postoperative period as a critical "window" for understanding myocardial adaptation after intervention. Current approaches to surgical management of mitral regurgitation, as summarised by S.R. Eapen *et al.* [18], highlight that early changes in systolic performance and remodelling parameters may provide clinically meaningful insight into procedural effectiveness and the direction of subsequent recovery, while acknowledging that interpretation is complicated by immediate post-repair changes in loading conditions after regurgitant volume is reduced. Accordingly, systematic evaluation of early postoperative dynamics is important for risk stratification, follow-up planning, and optimisation of postoperative management.

Materials and Methods

The study was conducted between 1 August 2025 and 30 November 2025 in I. Horbachevsky Ternopil National Medical University in Ukraine. This study enrolled 40 patients with hemodynamically significant grade III-IV mitral regurgitation who met established indications for surgical treatment. All patients were consecutively included during the study period among individuals fulfilling predefined eligibility criteria and referred for surgical correction of mitral regurgitation. This consecutive recruitment strategy minimised selection bias and yielded a clinically relatively homogeneous cohort. The primary endpoint was the early postoperative change in left ventricular ejection fraction (LVEF). Adult patients with confirmed severe mitral regurgitation were eligible provided that indications for surgical intervention were established by a multidisciplinary Heart Team and patients were able to undergo standardised echocardiographic follow-up at prespecified time points. Exclusion criteria comprised acute conditions requiring emergency surgery, previous mitral valve interventions, significant concomitant valvular disease necessitating multivalve correction, and inability to complete the follow-up protocol.

The study was conducted in accordance with generally accepted ethical standards for medical research. Written informed consent for study participation and publication of anonymised results was obtained from all participants. The protocol adhered to the ethical principles of the World Medical Association's Declaration of Helsinki [19] for research involving human subjects and complied with European Commission requirements regarding ethics and data protection. Confidentiality was ensured through data anonymisation and restricted access to personal information. Postoperative management followed contemporary clinical

guidelines. All patients received standardised pharmacotherapy, including guideline-directed heart failure treatment and anticoagulation when indicated. Rehabilitation was performed according to a unified clinical protocol incorporating early mobilisation and gradual escalation of physical activity. Any individualised treatment modifications were documented and considered in the analysis as potential confounders.

Degenerative (myxomatous) mitral valve disease was the most frequent aetiology, identified in 18 patients (45%). Functional ischemic mitral regurgitation associated with left ventricular remodelling and altered mitral annular geometry was diagnosed in 14 patients (35%). Rheumatic mitral valve disease accounted for 6 cases (15%), whereas other causes – including infective endocarditis and post-traumatic changes – were documented in 2 patients (5%). The mean age of the cohort was 61.8 ± 9.4 years; 60% were men and 40% women. All patients exhibited symptoms of heart failure classified as NYHA functional class II-III according to the New York Heart Association functional classification [20], reflecting clinical decompensation with symptom duration ranging from 6 months to 4 years.

Patients were allocated into two groups based on the surgical strategy: the repair group included 18 individuals (45%) who underwent mitral valve repair using contemporary annuloplasty and leaflet reconstruction techniques; the replacement group comprised 22 individuals (55%) who underwent mitral valve replacement with either bioprosthetic or mechanical prostheses. A substantial proportion of patients had clinically significant comorbidities that could potentially influence postoperative myocardial recovery. Arterial hypertension was the most prevalent condition, present in 30 patients (75%), followed by chronic ischemic heart disease in 13 patients (32.5%) and atrial fibrillation in 12 patients (30%). Type 2 diabetes mellitus was diagnosed in 8% of patients, while chronic kidney disease stage I-II was observed in 6% of the cohort. Follow-up assessments were performed at three time points: preoperatively, at 1 month, and at 3 months after surgery. The principal parameter of interest was LVEF, which was regarded as a key marker of systolic functional recovery and early reverse myocardial remodelling. Echocardiographic examinations were performed using high-resolution expert-grade ultrasound systems available in the cardiovascular imaging unit, employing standard apical two- and four-chamber views. All studies were conducted by experienced cardiologists with formal echocardiography training in accordance with current professional standards. LVEF was calculated using the biplane Simpson method in line with recommendations from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [21].

The free version of ChatGPT was used solely for grammar and spelling checks. All data, research results, and their interpretation are the authors' own. Data analysis was performed in Microsoft Excel (Microsoft Corp., USA). Descriptive statistics were computed using standard spreadsheet functions, including means, standard deviations, and percentage changes. All LVEF values were entered into a structured database encompassing three measurement points: baseline (preoperative), 1 month, and 3 months. For each interval, the mean LVEF, standard deviation (SD), range, and percentage change relative to the preceding time point were calculated. Normality of distribution was assessed using the Shapiro-Wilk test. Temporal changes in LVEF were analysed using a two-way repeated-measures analysis of variance (ANOVA), with time (preoperative, 1 month, 3 months) as the within-subject factor and intervention type (mitral valve repair vs replacement) as the between-subject factor. This approach enabled assessment of the main effects of time and group, as well as their interaction. When the assumption of sphericity was violated, the Greenhouse-Geisser correction was applied. In the absence of normality, nonparametric alternatives were used. Post hoc pairwise comparisons were performed with Bonferroni adjustment for multiple testing. A two-sided p value <0.05 was considered statistically significant.

Results and Discussion

Based on echocardiographic assessment, LVEF was evaluated at three time points: prior to surgical correction, 1 month postoperatively, and 3 months after the intervention. Analysis of a cohort of 40 patients demonstrated early patterns of recovery of systolic function and the dynamics of reverse myocardial remodelling following the correction of mitral regurgitation. Preoperative evaluation showed that in 6 patients (15%), LVEF was ≥60%; in 14 patients (35%), it ranged from 50-59%; and in 20 patients (50%), it was <50%. In the mitral valve repair group (n = 18), LVEF ≥60% was observed in 4 patients (22%), LVEF 50-59% in 7 patients (39%), and LVEF <50% in 7 patients (39%). In the mitral valve replacement group (n = 22), LVEF ≥60% was found in 2 patients (9%), LVEF 50-59% in 7 patients (32%), and LVEF <50% in 13 patients (59%). The results of this study demonstrate a clear, consistent, and clinically significant improvement in left ventricular systolic function following surgical correction of mitral regurgitation. A detailed analysis of changes in ejection fraction during the early postoperative period not only enables quantitative assessment of surgical efficacy but also provides deeper insight into the pathophysiological mechanisms of reverse myocardial remodelling that determine long-term patient outcomes.

Preoperative cohort characteristics indicate substantial heterogeneity in left ventricular functional status. Half of the patients (50%) had an ejection fraction <50%, indicating established systolic dysfunction. Another 35% had an ejection fraction in the range of 50-59%, which may be considered a borderline state, where early signs of impaired contractility are already present but partial compensation is still maintained. Only 15% of patients had an ejection fraction ≥60%, corresponding to normal systolic function. This distribution highlights that most patients undergo surgical treatment at a stage of significant cardiac remodelling. Following surgical correction of mitral regurgitation, a marked shift in hemodynamic conditions occurs.

Elimination of regurgitation reduces volume overload, but simultaneously increases effective afterload on the left ventricle. This restructuring is key to interpreting early postoperative changes in ejection fraction. In some cases, a transient decrease in ejection fraction may be observed in the early period; however, in this study, overall improvement was already evident at 1 month.

Overall, 75% of patients demonstrated positive dynamics as early as 1 month after surgery. This indicates rapid activation of adaptive mechanisms and the initiation of reverse remodelling processes. Thus, the first postoperative month can be considered a critical period for evaluating the effectiveness of the intervention. In the group of patients who underwent mitral valve repair, the most pronounced improvement in functional parameters was observed. The mean ejection fraction increased from 49.5% to 53.4% at 1 month and to 57.2% at 3 months, corresponding to an overall increase of +7.7% (Table 1).

Table 1. Dynamics of LVEF after mitral valve repair

Time period	LVEF(M ± SD), %	Increase, %	p-value
Before surgery	49.5 ± 7.2	-	-
At 1 month	53.4 ± 6.9	+3.9	$p < 0.05$
At 3 months	57.2 ± 6.5	+7.7	$p < 0.01$

Source: compiled by authors

Analysis of Table 1 allows several important conclusions to be drawn. First, the improvement in ejection fraction is gradual in nature and is not limited to the early postoperative period but continues throughout the entire three-month follow-up. Second, the reduction in standard deviation indicates a more homogeneous patient response, which may be associated with the more physiological nature of the intervention. Third, the achievement of ejection fraction values above 55% in the majority of patients suggests effective recovery of systolic function.

The obtained results are consistent with current clinical guidelines. According to A. Vahanian *et al.* [1], mitral valve repair is associated with better preservation of left ventricular function compared with valve replacement. This is explained by the fact that repair preserves the subvalvular apparatus, which plays a crucial role in maintaining left ventricular geometry and function. In the mitral valve replacement group, improvement was also observed; however, it was less pronounced. The mean ejection fraction increased from 47.1% to 50.3% at 1 month and to 52.6% at 3 months, corresponding to an overall increase of +5.5% (Table 2).

The smaller magnitude of improvement after mitral valve replacement may be attributable to the absence of native valvular structures, partial excision of the subvalvular apparatus, alterations in left ventricular geometry, and increased afterload associated with the presence of a prosthesis. The presence of a prosthesis may influence ventricular geometry and loading conditions, thereby contributing to a slower regression of dilatation and a less rapid increase in ejection fraction. According to M. Sudo *et al.* [17], the extent of reverse remodelling after mitral valve replacement may be constrained by the mechanical characteristics of prosthetic valves. A similar trend was observed in this study, in which recovery of LVEF in the replacement group occurred more slowly.

Table 2. Dynamics of LVEF after mitral valve replacement

Time period	LVEF (M ± SD), %	Increase (%)	p-value
Before surgery	47.1 ± 7.6	-	-
At 1 month	50.3 ± 7.3	+3.2	$p < 0.05$
At 3 months	52.6 ± 7.0	+5.5	$p < 0.05$

Source: compiled by authors

Conversely, V. Osaulenko *et al.* [22] emphasised that preservation of the subvalvular apparatus plays an important role in maintaining the physiological interaction between the valve and the myocardium. Present findings are consistent with these data and suggest that early recovery of systolic function largely depends on preservation of mitral-ventricular continuity. Comparative analysis demonstrated that mitral valve repair provides a statistically significantly faster and more pronounced restoration of left ventricular systolic function compared with valve replacement (Table 3).

Table 3. Comparison of LVEF between mitral valve repair and replacement

Indicator	Repair (M ± SD)	Replacement (M ± SD)	Difference Δ, %	p-value
LVEF before surgery	49.5 ± 7.2	47.1 ± 7.6	+2.4	$p = 0.21$
LVEF at 1 month	53.4 ± 6.9	50.3 ± 7.3	+3.1	$p < 0.05$
LVEF at 3 months	57.2 ± 6.5	52.6 ± 7.0	+4.6	$p < 0.01$
ΔLVEF (0-1 month)	+3.9%	+3.2%	+0.7	$p = 0.34$
ΔLVEF (0-3 months)	+7.7%	+5.5%	+2.2	$p < 0.05$

Source: compiled by authors

As shown in Table 3, the preoperative difference between the groups was not statistically significant ($p = 0.21$), confirming their baseline comparability. However, as early as 1 month after surgery, the difference becomes significant ($p < 0.05$), and by 3 months it is even more pronounced ($p < 0.01$). This indicates that mitral valve repair provides faster and more effective functional recovery. According to V. Osaulenko *et al.* [22], preservation of the subvalvular apparatus plays a crucial role in maintaining physiological ventricular mechanics and improving postoperative outcomes. The findings of this study are fully consistent with this statement.

An important factor influencing outcomes is the baseline level of ejection fraction. In this study, patients with an ejection fraction <50% demonstrated the greatest improvement (up to 8-10%). This can be explained by their greater potential for reverse remodelling. Patients with reduced baseline myocardial function may demonstrate greater relative improvement after intervention because of a higher potential for reverse remodelling [3]. At the same time, in patients with preserved ejection fraction, the improvement was less pronounced, which may indicate a limited functional reserve. As noted by G. Benfari *et al.* [7], the severity and clinical impact of functional mitral regurgitation strongly depend on the degree of left ventricular remodelling. This may explain why some patients demonstrate slower recovery even after successful intervention.

In addition, recent studies emphasise the importance of patient stratification. Recent studies suggest that more detailed patient stratification according to baseline ventricular function and remodelling severity may improve prediction of response to treatment [8]. Although such classification was not applied in this study, the obtained results support its potential relevance. Comorbidities also have a significant impact on the recovery process. Arterial hypertension, present in the majority of patients, contributes to the persistence of increased afterload even after surgery. Ischemic heart disease limits recovery of contractility, while atrial fibrillation negatively affects diastolic function. Previous studies of surgical correction of mitral regurgitation suggest that adverse baseline ventricular remodelling may limit the extent of postoperative functional recovery [11].

Another important aspect is the time factor. Early changes in ejection fraction have significant prognostic value. As stated by to S.R. Eapen *et al.* [18], early postoperative changes in ventricular function represent a critical window for assessing procedural success and predicting long-term outcomes. This highlights the need for regular patient monitoring during the first months after surgery. The physiological mechanisms underlying improvement in ejection fraction include a complex interplay of processes: elimination of volume overload, normalisation of left ventricular geometry, reduction of wall stress, improvement of myocardial contractility

However, it is important to note that part of the improvement may be related not only to myocardial recovery but also to changes in loading conditions. Previous reports suggest that postoperative changes in left ventricular function reflect not only recovery of contractility but also the unmasking of pre-existing myocardial dysfunction after elimination of regurgitant unloading [14]. This indicates that the recovery process is complex and includes both functional and morphological adaptations. Additionally, the rate and extent of remodelling may depend on patient age, disease duration, and timing of surgical intervention. Early surgery is associated with better outcomes, as it helps prevent the development of irreversible myocardial changes.

In summary, the findings suggest that the dynamics of ejection fraction in the early postoperative period represent a reliable and sensitive marker of the effectiveness of surgical treatment for mitral regurgitation. Mitral valve repair demonstrates clear advantages over valve replacement, as evidenced by faster and more pronounced recovery of left ventricular systolic function. Overall, the results of the study allow the following key conclusions to be formulated: early improvement in ejection fraction is an important indicator of procedural success; the type of surgical intervention determines the rate and pattern of recovery; baseline myocardial status influences the potential for reverse remodelling; and comorbidities may significantly modify treatment outcomes.

Conclusions

The present study demonstrated that surgical correction of mitral regurgitation is associated with a significant improvement in left ventricular systolic function in the early postoperative period. The analysis revealed a statistically significant increase in ejection fraction as early as 1 month after intervention, with further improvement by 3 months of follow-up. This favourable trajectory was accompanied by signs of early reverse myocardial remodelling, reflecting left ventricular adaptation to the reduction of chronic volume overload. In the overall cohort, mean LVEF increased from 48.2% preoperatively to 51.7% at 1 month and to 54.9% at 3 months. In subgroup analysis, LVEF after mitral valve repair increased from $49.5 \pm 7.2\%$ to $57.2 \pm 6.5\%$ (+7.7%), whereas after mitral valve replacement it increased from $47.1 \pm 7.6\%$ to $52.6 \pm 7.0\%$ (+5.5%).

Comparative analysis showed that recovery of pump function was faster and of greater magnitude in patients undergoing mitral valve repair than in those undergoing valve replacement. A larger increase in ejection fraction was observed in the repair group both at 1 month and at 3 months. These findings suggest that preservation of mitral-ventricular continuity may play an important role in maintaining physiological ventricular mechanics and facilitating more effective restoration of contractile function.

It was also found that comorbid conditions – particularly arterial hypertension, atrial fibrillation, and ischemic heart disease – frequently accompany severe mitral regurgitation and may influence the rate of postoperative functional recovery. At the same time, standardised perioperative management, including guideline-directed heart

failure therapy and anticoagulation when indicated, contributed to early postoperative clinical stability and enabled an objective assessment of changes in systolic function. Further studies should focus on long-term patterns of left ventricular remodelling over extended follow-up intervals. Longer surveillance may provide deeper insight into myocardial adaptation processes after surgical correction of mitral regurgitation.

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Conflict of Interest
None.

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Динаміка змін фракції викиду лівого шлуночка після хірургічної корекції мітральної недостатності

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Анотація. Мітральна недостатність є однією із найпоширеніших уражень клапанного апарату серця та призводить до хронічного перевантаження об'ємом, дилатації та ремоделювання лівого шлуночка. Попри ефективність сучасних хірургічних методик корекції мітральної регургітації, питання раннього відновлення систолічної функції та темпів зворотного ремоделювання залишаються клінічно значущими. Метою цього дослідження було оцінити ранні післяопераційні зміни систолічної функції лівого шлуночка та проаналізувати динаміку фракції викиду як маркера ефективності хірургічної корекції мітральної регургітації. У дослідженні взяли участь 40 пацієнтів із мітральною недостатністю III-IV ступеня, яким було виконано пластичну реконструкцію мітрального клапана (45 %) або протезування (55 %). Ехокардіографію проводили тричі – до операції, через 1 місяць та через 3 місяці після хірургічного втручання. Фракцію викиду визначали методом двоплощинного Сімпсона відповідно до рекомендацій ASE/EACVI. Статистичну обробку було виконано із використанням вбудованих інструментів Microsoft Excel із розрахунком середніх значень, стандартного відхилення та відсоткової зміни показників. До операції середня фракція викиду становила 48,2 %. Через 1 місяць вона зросла до 51,7 %, а через 3 місяці – до 54,9 %, що свідчило про ранні процеси зворотного ремоделювання. Найбільш виражене покращення відзначено у пацієнтів із вихідною фракцією викиду менше 50 % (приріст 8-10 %). Після пластики мітрального клапана динаміка була кращою порівняно з протезуванням (7-9 % проти 5-6 %). 75 % пацієнтів продемонстрували позитивну динаміку вже через місяць після операції. Хірургічна корекція мітральної недостатності забезпечує суттєве раннє покращення систолічної функції лівого шлуночка. Динаміка фракції викиду у перші 1-3 місяці є важливим прогностичним інструментом, що дозволяє оцінити ефективність втручання, темпи зворотного ремоделювання та оптимізувати подальше лікування пацієнтів

Ключові слова: зворотне ремоделювання; ехокардіографія; систолічна функція; анулопластика; протезування клапанів; післяопераційне відновлення; скоротливість міокарда

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Efficacy and safety of intrathecal clonidine vs fentanyl added to bupivacaine for lower abdominal procedures

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Abstract. Intrathecal adjuvants such as fentanyl and clonidine may enhance the quality and duration of spinal anaesthesia and postoperative analgesia with bupivacaine, but their comparative efficacy and side-effect profiles remain important. The present study aimed to compare the effects of intrathecal fentanyl and clonidine as adjuvants to 0.5% bupivacaine on block characteristics, postoperative analgesia, haemodynamic, sedation, and adverse effects in patients undergoing lower abdominal surgery. This randomised double-blind comparative study was conducted in the Department of Anaesthesiology, Balrampur Hospital, Lucknow, among 96 patients aged 18-60 years, ASA physical status I-II, scheduled for lower abdominal surgeries. Patients were randomly allocated into three groups (n = 32 each): Group B received 2.5 mL of 0.5% bupivacaine with 0.5 mL normal saline, Group F received 2.5 mL of 0.5% bupivacaine with fentanyl 25 ug, and Group C received 2.5 mL of 0.5% bupivacaine with clonidine 30 ug. Outcomes included block onset and duration, rescue analgesia time, VAS score, haemodynamic, sedation, and adverse events. Baseline characteristics were comparable among groups. Group C showed the fastest onset of sensory block (1.45 ± 0.30 min) and the longest duration of sensory block (150.23 ± 28.47 min), followed by Group F and Group B ($p < 0.0001$). A similar pattern was observed for motor block onset and duration ($p < 0.0001$). Time to first rescue analgesia was significantly prolonged in Group C (6.00 ± 1.50 h) compared with Group F (4.50 ± 1.22 h) and Group B (2.80 ± 0.76 h) ($p < 0.0001$). Postoperative VAS scores were significantly lower in Group C. Haemodynamic variables remained largely comparable. Sedation was higher with clonidine, with marked sedation observed only in Group C. Intrathecal clonidine 30 ug with bupivacaine provided better block characteristics and longer postoperative analgesia than fentanyl 25 ug or bupivacaine alone, but with higher sedation

Keywords: spinal anaesthesia; postoperative analgesia; lower abdominal surgery; haemodynamic; sedation

Introduction

Spinal anaesthesia is widely used for lower abdominal surgery because it is simple, effective, economical, and provides reliable sensory and motor blockade with early postoperative recovery. However, intrathecal bupivacaine alone has a limited duration of action, which may not provide adequate postoperative analgesia in all patients. To overcome this limitation, several intrathecal adjuvants have been studied to prolong block duration, improve analgesia, and reduce postoperative analgesic requirements. Among these, fentanyl and clonidine are commonly used because they act through different mechanisms and have distinct efficacy and adverse-effect profiles [1].

N.M. Fonseca *et al.* [1] evaluated the addition of fentanyl and sufentanil to spinal local anaesthetics in a systematic review and meta-analysis and found that these opioids reduced postoperative pain and opioid consumption and prolonged analgesia, although pruritus increased significantly. Their work confirmed the analgesic efficacy of intrathecal fentanyl but also highlighted opioid-related adverse effects as a relevant limitation. R. Jouybar *et al.* [2] studied the effect of intrathecal fentanyl in patients undergoing caesarean section and reported improved quality of spinal anaesthesia and better postoperative pain relief when fentanyl was added to bupivacaine. Although their findings

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support fentanyl as an effective intrathecal adjuvant, the study was limited to obstetric patients and therefore cannot be directly generalised to lower abdominal surgeries in the general adult population.

J. Bhatia & C. Suryawanshi [3] compared intrathecal bupivacaine-fentanyl with bupivacaine-midazolam in lower abdominal and lower limb surgeries and showed that fentanyl improved intraoperative conditions and prolonged analgesia. However, their study compared fentanyl with another adjuvant rather than with clonidine, which remains an important alternative non-opioid intrathecal additive. M.M. Manoharan *et al.* [4] compared intrathecal dexmedetomidine and clonidine as adjuvants to spinal anaesthesia and observed that α2-adrenergic agonists significantly prolonged sensory and motor block as well as postoperative analgesia. Their findings emphasised the usefulness of clonidine-like drugs in neuraxial anaesthesia, but the study did not address whether clonidine is superior or inferior to fentanyl in routine lower abdominal surgery.

S. Dattatri *et al.* [5] assessed different doses of intrathecal clonidine with bupivacaine and found that low-dose clonidine effectively prolonged sensory and motor block while maintaining acceptable haemodynamic stability. This study supported the role of clonidine as an effective spinal adjuvant, but it did not compare clonidine directly with fentanyl, which is commonly used in clinical practice. E.E. Shchegolkov & O.A. Loskutov [6] analysed the principles of pain management and the role of neuraxial and regional anaesthesia in surgical patients and emphasised that regional techniques are valuable for improving perioperative outcomes and reducing complications. Although this review was not limited to intrathecal fentanyl or clonidine, it supports the continuing relevance of optimising neuraxial analgesic strategies. In another Ukrainian study, T. Ovsiienko *et al.* [7] evaluated low-opioid multimodal anaesthesia and demonstrated that opioid-sparing approaches can provide adequate antinociceptive protection with improved perioperative pain control. Their work is important because it underlines the need for alternatives that reduce opioid exposure while preserving effective analgesia.

Thus, existing evidence suggests that intrathecal fentanyl improves spinal block quality and postoperative analgesia, whereas clonidine and other α2-agonists may prolong block duration and analgesia, though often with more sedation. L.H. Sun *et al.* [8] demonstrated the efficacy of intrathecal fentanyl with bupivacaine in caesarean delivery, but their results were limited to obstetric patients. A. Nayak *et al.* [9] also supported the analgesic value of fentanyl in abdominal hysterectomy, although clonidine was not included in the comparison. A. Sabertanha *et al.* [10] and Y. Gu *et al.* [11] reported beneficial effects of intrathecal fentanyl in orthopaedic populations, but these findings cannot be directly extrapolated to lower abdominal surgery. R.B. Joseph *et al.* [12] compared clonidine, fentanyl, and buprenorphine in lower abdominal and lower limb procedures, yet the mixed surgical sample limited procedure-specific conclusions. Therefore, a direct comparison of fentanyl and clonidine with 0.5% bupivacaine in adult patients undergoing lower abdominal surgery remains necessary. Therefore, the present study was undertaken to compare intrathecal fentanyl and clonidine as adjuvants to 0.5% bupivacaine in lower abdominal surgery and to determine which drug provides a better balance between effective block characteristics, prolonged postoperative analgesia, haemodynamic stability, and tolerable side effects.

Materials and Methods

This prospective randomised double-blind comparative study was conducted in the Department of Anaesthesiology, Balrampur Hospital, Golaganj, Lucknow, Uttar Pradesh, India. The study was carried out over a period of 18 months (January 2023 – June 2024). The study protocol was approved by the Institutional Ethics Committee of Balrampur Hospital (Approval No.: 10/IEC-DHR/2023) prior to patient enrolment. Written informed consent was obtained from all participants. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki [13] and complied with international guidelines on ethics and data protection issued by the European Commission [14].

A total of 96 adult patients scheduled for elective lower abdominal surgeries under spinal anaesthesia were included in the study. Patients were aged between 18 and 60 years and belonged to American Society of Anesthesiologists (ASA) [15] physical status I or II. The sample size consisted of 32 patients in each group, which was considered adequate to allow meaningful comparison of block characteristics and analgesic duration between the three treatment groups based on previous similar studies evaluating intrathecal adjuvants. Patients were randomly allocated into three groups using computer-generated randomisation. Allocation concealment was achieved using sealed opaque envelopes. Both the patient and the anaesthesiologist assessing outcomes were blinded to the study drug, while drug preparation was performed by an independent anaesthesiologist not involved in data collection. Patients of either sex, aged 18-60 years, weighing 50-80 kg, and classified as ASA grade I-II undergoing elective lower abdominal surgeries were included in the study. Patients were excluded if they refused consent, had ASA grade III-IV, pregnancy or lactation, hypersensitivity to local anaesthetic drugs or study medications, chronic opioid use, neurological disorders, infection at the puncture site, coagulation abnormalities, or were receiving long-term analgesic therapy.

Standard monitoring including electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse rate, and oxygen saturation (SpO_2) was applied before the procedure. Patients were preloaded with 10-15 mL/kg of Ringer's lactate solution. Spinal anaesthesia was administered in the sitting position at the L3-L4 or L4-L5 intervertebral space using a 25-gauge Quincke spinal needle under strict aseptic precautions. After confirmation of free flow of cerebrospinal fluid, the study drug was injected intrathecally. Patients were divided into three groups:

- Group B (Control group): 2.5 mL of 0.5% hyperbaric bupivacaine + 0.5 mL normal saline;
- Group F: 2.5 mL of 0.5% hyperbaric bupivacaine + fentanyl 25 µg;
- Group C: 2.5 mL of 0.5% hyperbaric bupivacaine + clonidine 30 µg.

The doses of fentanyl (25 µg) and clonidine (30 µg) were selected based on previous clinical studies [16,17] demonstrating effective prolongation of spinal anaesthesia with minimal haemodynamic instability and acceptable side-effect profiles. Sensory block onset was defined as the time from intrathecal drug injection to loss of pinprick sensation at the T10 dermatome level, assessed using a sterile needle. Duration of sensory block was defined as the time from drug administration to regression of sensory level to S1 dermatome. Motor block was evaluated using the Modified Bromage Scale: 0 = full movement of hip, knee and ankle; 1 = inability to raise extended leg; 2 = inability to flex knee; 3 = inability to flex ankle. Motor block onset was defined as the time to achieve Bromage grade 3, while duration was defined as the time until regression to Bromage grade 0.

Pain intensity was assessed using the Visual Analogue Scale (VAS). The time to first rescue analgesia was recorded when VAS ≥ 4. Sedation was evaluated using the Ramsay Sedation Scale. Haemodynamic parameters and adverse effects such as hypotension, bradycardia, nausea, vomiting, and respiratory depression were monitored. Data were analysed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) and compared using one-way ANOVA, while categorical variables were analysed using the Chi-square test. A p-value < 0.05 was considered statistically significant.

Results

A total of 96 patients were enrolled and completed the study, with 32 patients in each of the three groups. No patient was excluded after randomisation, and all participants were included in the final analysis. The results are presented in tabular and graphical form to improve clarity and to facilitate comparison among the groups. The three groups were comparable with respect to age, sex distribution, body mass index (BMI), ASA physical status, and type of surgical procedure. The mean age was 46.12 ± 10.98 years in Group B, 45.23 ± 11.56 years in Group F, and 44.78 ± 12.34 years in Group C, with no statistically significant difference (F = 0.1098, p = 0.8961). Similarly, age-group distribution was comparable across the groups ($\chi^2 = 2.229$, p = 0.9732). The baseline demographic and clinical characteristics of the patients are summarised in Table 1.

Table 1. Clinico-demographics parameters

Parameter	Group-B (n = 32)	Group-F (n = 32)	Group-C (n = 32)	p-value
Age (years) (Mean ± SD)	46.12 ± 10.98	45.23 ± 11.56	44.78 ± 12.34	F = 0.1098, p = 0.8961
Age group (years)				
18-30	5	7	6	
31-40	11	6	8	X = 2.229,
41-50	9	10	8	p = 0.9732
51-60	5	8	6	
61-70	2	1	3	
Gender				
Male	18	16	15	X = 0.2510,
Female	14	16	17	p = 0.8821
BMI (kg/m²) (Mean ± SD)	26.89 ± 3.91	27.34 ± 4.27	28.15 ± 4.05	F = 0.7840, p = 0.4596
ASA Grade				X = 0.6563, p = 0.7203
I	21	23	20	
II	11	9	12	

Note: values are presented as mean ± standard deviation (SD) or number of patients (n), as appropriate. Group comparisons for continuous variables were performed using one-way ANOVA, and categorical variables were analysed using the Chi-square test. A p-value < 0.05 was considered statistically significant

Source: developed by author

Sex distribution was also balanced: Group B had 18 males and 14 females, Group F had 16 males and 16 females, and Group C had 17 males and 15 females ($\chi^2 = 0.2510$, p = 0.8821). Mean BMI values showed no significant difference among the groups (Group B: 26.89 ± 3.91 kg/m²; Group F: 27.34 ± 4.27 kg/m²; Group C: 28.15 ± 4.05 kg/m²; F = 0.7840, p = 0.4596). ASA grade distribution was likewise similar, with no statistically significant variation ($\chi^2 = 0.6563$, p = 0.7203). The distribution of surgical procedures was also comparable. Appendectomy, inguinal hernia repair, and hydrocele surgery were similarly represented in all three groups ($\chi^2 = 1.214$, p = 0.8757). This baseline comparability is important because it indicates that the observed differences in analgesia, block characteristics, and sedation are likely related to the intrathecal adjuvants rather than to differences in patient profile or

surgical type. The haemodynamic variables recorded during the intraoperative period included pulse rate, systolic blood pressure, diastolic blood pressure, and oxygen saturation. These findings are shown in Figures 1-4.

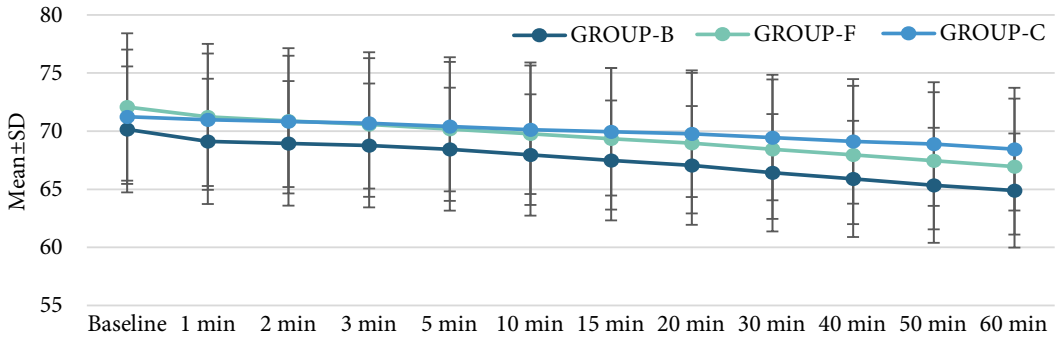

Figure 1. Graphical representations of Mean Pulse (min)

Source: developed by author

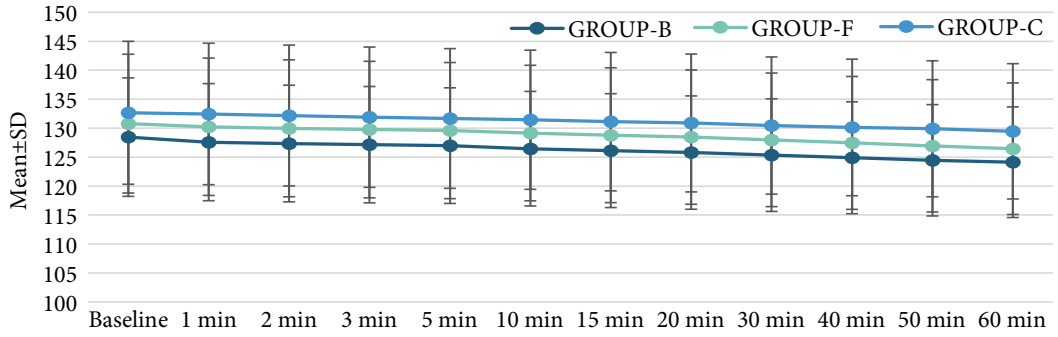

Figure 2. Graphical representations of Mean Systolic Blood Pressure (SBP)

Source: developed by author

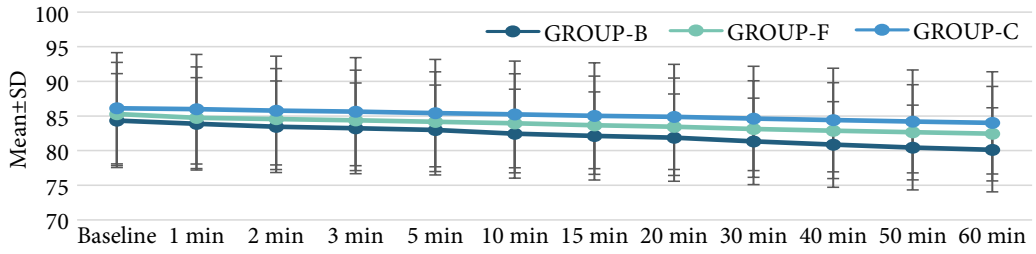

Figure 3. Graphical representation of Mean Diastolic Blood Pressure (DBP)

Source: developed by author

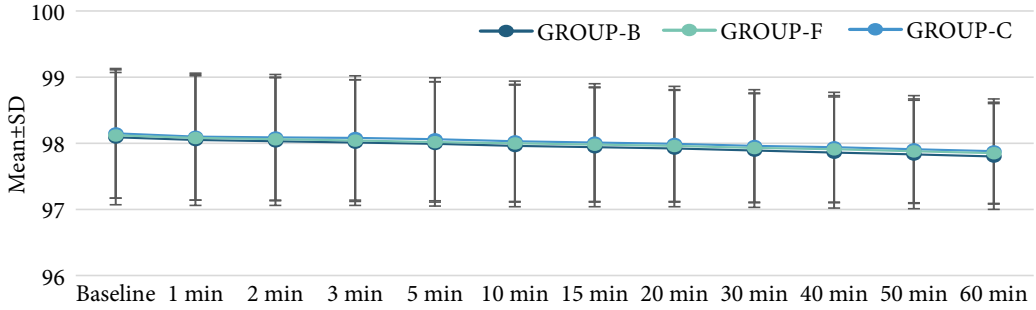

Figure 4. Graphical representation of Mean SpO_2

Source: developed by author

Baseline pulse rates were similar in all groups: 70.15 ± 5.42 beats/min in Group B, 72.08 ± 6.34 beats/min in Group F, and 71.24 ± 5.78 beats/min in Group C (F = 0.8730, p = 0.4211). No significant intergroup differences were observed from 1 minute to 40 minutes after spinal anaesthesia. However, at 50 minutes and 60 minutes, Group B showed a slightly lower pulse rate compared with Groups F and C. At 50 minutes, pulse rates were 65.34 ± 4.95, 67.45 ± 5.90, and 68.89 ± 5.32 beats/min, respectively (F = 3.493, p = 0.0345). At 60 minutes, the corresponding values were 64.89 ± 4.91, 66.95 ± 5.85, and 68.45 ± 5.28 beats/min (F = 3.557, p = 0.0325). Although these differences were statistically significant, their actual magnitude was small and did not indicate clinically important haemodynamic instability. Thus, while pulse rate varied slightly at later time points, none of the study regimens caused a major adverse cardiovascular effect.

Systolic blood pressure remained stable throughout the observation period. Baseline values were 128.45 ± 10.23 mmHg in Group B, 130.78 ± 11.98 mmHg in Group F, and 132.65 ± 12.34 mmHg in Group C, with no significant difference among groups. Similar findings were noted at all subsequent time intervals. Diastolic blood pressure also showed no significant variation. Baseline values were 84.34 ± 6.78 mmHg in Group B, 85.29 ± 7.45 mmHg in Group F, and 86.12 ± 8.03 mmHg in Group C (F = 0.4589, p = 0.6334), and no statistically significant differences were seen during follow-up. Oxygen saturation remained highly stable and comparable across all groups at all measured intervals. Baseline SpO_2 values were 98.15 ± 0.98% in Group B, 98.09 ± 1.02% in Group F, and 98.12 ± 0.95% in Group C (F = 0.02976, p = 0.9707). No episodes of clinically significant desaturation were observed. These results suggest that the addition of fentanyl or clonidine to intrathecal bupivacaine did not adversely affect haemodynamic or respiratory stability.

Clear and consistent differences were observed among the groups at all postoperative time points. At 0.5 hours, mean VAS scores were 2.05 ± 0.22 in Group B, 2.00 ± 0.20 in Group F, and 1.03 ± 0.18 in Group C (F = 262.8, p < 0.0001). At 1 hour, the pattern remained similar, with values of 2.04 ± 0.21, 2.00 ± 0.20, and 1.02 ± 0.17, respectively (F = 283.5, p < 0.0001). By 3 hours, the difference became more pronounced: Group B had a mean VAS score of 3.02 ± 0.25, Group F 2.01 ± 0.21, and Group C 1.04 ± 0.16 (F = 711.8, p < 0.0001).

At 6 hours, Group B continued to show the highest pain score (3.14 ± 0.24), followed by Group F (2.04 ± 0.20), while Group C maintained the lowest value (1.01 ± 0.16) (F = 884.1, p < 0.0001). At 12 hours, Group C still had a lower mean pain score (2.02 ± 0.18) than Groups B and F, both of which were around 3.0 (F = 232.2, p < 0.0001). At 24 hours, the same trend persisted, with values of 2.07 ± 0.20 in Group B, 2.01 ± 0.21 in Group F, and 1.00 ± 0.16 in Group C (F = 316.3, p < 0.0001).

These findings demonstrate that clonidine provided the most effective postoperative analgesia among the three regimens. Fentanyl also improved pain control compared with bupivacaine alone, but its effect was less pronounced than that of clonidine. Clinically, the lower VAS scores in Group C indicate better patient comfort and a more sustained analgesic benefit during the postoperative period. Postoperative pain intensity was assessed by the VAS and is presented in Table 2.

Table 2. Mean VAS Score

VAS score (time interval)	Group-B (n = 32)	Group-F (n = 32)	Group-C (n = 32)	p-value
Baseline	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	—
0.5 hrs	2.05 ± 0.22	2.00 ± 0.20	1.03 ± 0.18	F = 316.3, p < 0.0001*
1 hr	2.04 ± 0.21	2.00 ± 0.20	1.02 ± 0.17	F = 262.8, p < 0.0001*
3 hrs	3.02 ± 0.25	2.01 ± 0.21	1.04 ± 0.16	F = 283.5, p < 0.0001*
6 hrs	3.14 ± 0.24	2.04 ± 0.20	1.01 ± 0.16	F = 711.8, p < 0.0001*
12 hrs	3.01 ± 0.23	3.00 ± 0.22	2.02 ± 0.18	F = 884.1, p < 0.0001*
24 hrs	2.07 ± 0.20	2.01 ± 0.21	1.00 ± 0.16	F = 232.2, p < 0.0001*

Note: values are expressed as mean ± SD. Group comparisons were performed using one-way ANOVA. $p < 0.05$ was considered statistically significant

Source: developed by author

Baseline sedation scores were identical in all groups (1.00 ± 0.00), indicating that all patients were fully awake and comparable before anaesthesia. In the early postoperative period, Group C consistently exhibited higher sedation scores than Groups B and F. At 0.5 hours, the mean sedation score was approximately 2.02 in Group B, 2.06 in Group F, and 3.08 in Group C. At 1 hour, the values were 2.00, 2.06, and 3.04, respectively. A similar pattern was seen at 3 hours and 6 hours, with Group C remaining around a score of 3 while the other two groups remained close to 2.

By 12 and 24 hours, Groups B and F had returned to baseline sedation levels, while Group C remained slightly above baseline. This indicates that clonidine was associated with greater postoperative sedation than fentanyl or bupivacaine alone. However, the sedation observed in Group C was not accompanied by respiratory depression or oxygen desaturation, suggesting that although clonidine caused more sedation, it remained clinically manageable under routine monitoring. Sedation was evaluated using the Ramsay Sedation Scale, and the findings are depicted in Figure 5.

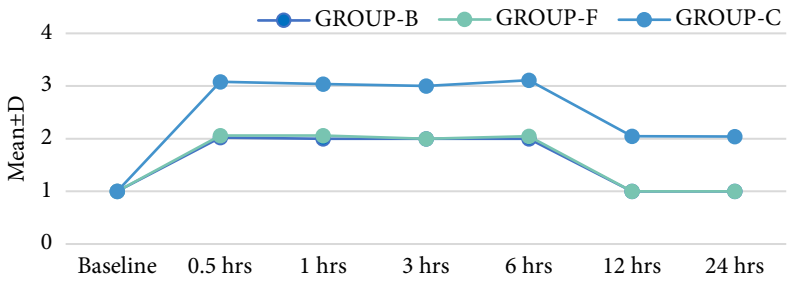

Figure 5. Graphical representation of mean Ramsay sedation scores
Source: developed by author

Sensory and motor block characteristics

Significant differences were observed among the groups in terms of onset and duration of both sensory and motor block. The onset of sensory block was fastest in Group C (1.45 ± 0.30 min), followed by Group F (1.52 ± 0.28 min), and slowest in Group B (2.01 ± 0.35 min), with a highly significant difference (F = 30.72, p < 0.0001). This suggests that both adjuvants accelerated the onset of sensory block compared with bupivacaine alone, with clonidine showing the greatest effect. The duration of sensory block was longest in Group C (150.23 ± 28.47 min), intermediate in Group F (119.78 ± 19.65 min), and shortest in Group B (90.15 ± 14.72 min) (F = 61.30, p < 0.0001). Thus, clonidine prolonged sensory blockade by about one hour compared with bupivacaine alone and by about 30 minutes compared with fentanyl. This is clinically meaningful because longer sensory block generally translates into improved early postoperative pain relief.

A similar trend was observed for motor block. The onset of motor block was fastest in Group C (2.84 ± 0.81 min), followed by Group F (3.08 ± 0.78 min), and slowest in Group B (4.12 ± 0.95 min) (F = 20.51, p < 0.0001). The duration of motor block was also significantly prolonged in Group C (110.47 ± 18.76 min), followed by Group F (100.32 ± 15.45 min), while Group B had the shortest duration (74.95 ± 10.23 min) (F = 46.22, p < 0.0001). From a practical point of view, faster onset of block may improve operating room efficiency, while prolonged sensory blockade can reduce the need for immediate postoperative analgesics. Although longer motor block may potentially delay ambulation, the extension seen with clonidine was moderate and accompanied by a clear analgesic benefit. The main efficacy outcomes related to spinal block are presented in Table 3.

There was a highly significant difference among the groups (F = 57.02, p < 0.0001). Group B required rescue analgesia after 2.80 ± 0.76 hours, Group F after 4.50 ± 1.22 hours, and Group C after 6.00 ± 1.50 hours. The time to first rescue analgesia is one of the most clinically relevant outcomes. This finding clearly demonstrates that both fentanyl and clonidine prolonged the duration of postoperative analgesia compared with bupivacaine alone, but clonidine produced the longest analgesic effect. Compared with the control group, fentanyl extended analgesia by approximately 1.7 hours, whereas clonidine extended it by approximately 3.2 hours. Compared with fentanyl, clonidine provided an additional 1.5 hours of postoperative pain relief. Clinically, this reduction in early rescue analgesic requirement may improve patient comfort and reduce the need for additional systemic analgesics.

Table 3. Mean block parameters, min

Block parameters	Group-B (n = 32)	Group-F (n = 32)	Group-C (n = 32)	p-value
Onset of sensory block	2.01 ± 0.35	1.52 ± 0.28	1.45 ± 0.30	F = 46.22, p < 0.0001*
Duration of sensory block	90.15 ± 14.72	119.78 ± 19.65	150.23 ± 28.47	F = 30.72, p < 0.0001*
Onset of motor block	4.12 ± 0.95	3.08 ± 0.78	2.84 ± 0.81	F = 61.30, p < 0.0001*
Duration of motor block	74.95 ± 10.23	100.32 ± 15.45	110.47 ± 18.76	F = 20.51, p < 0.0001*

Note: values are expressed as mean ± SD. Group comparisons were performed using one-way ANOVA. *p < 0.05 was considered statistically significant
Source: developed by author

Overall, the frequency of complications was low and comparable among groups. Excessive sedation was observed only in Group C, where it occurred in 25% of patients. Hypotension was recorded in 6.25% of Group B, 15.6% of Group F, and 3.12% of Group C, but this difference was not statistically significant. Other complications, including bradycardia, nausea, vomiting, pruritus, urinary retention, post-dural puncture headache, and respiratory depression, did not differ significantly among groups. Notably, no patient developed clinically significant respiratory depression, which supports the safety of both adjuvants at the doses used.

Taken together, the results show a clear pattern. Bupivacaine alone provided the least favourable profile, with slower block onset, shorter block duration, earlier need for rescue analgesia, and higher postoperative pain scores. The addition of fentanyl improved these outcomes, but the combination of clonidine with bupivacaine produced the best overall results.

Intrathecal clonidine was associated with the fastest onset of sensory and motor block, the longest sensory and motor block duration, the longest time to first rescue analgesia, and the lowest postoperative VAS scores at all measured intervals. These results indicate superior analgesic efficacy and better prolongation of spinal anaesthesia. The main drawback of clonidine was increased sedation, but this did not result in respiratory compromise or major haemodynamic instability. The adverse effects observed in the three groups are presented in Figure 6.

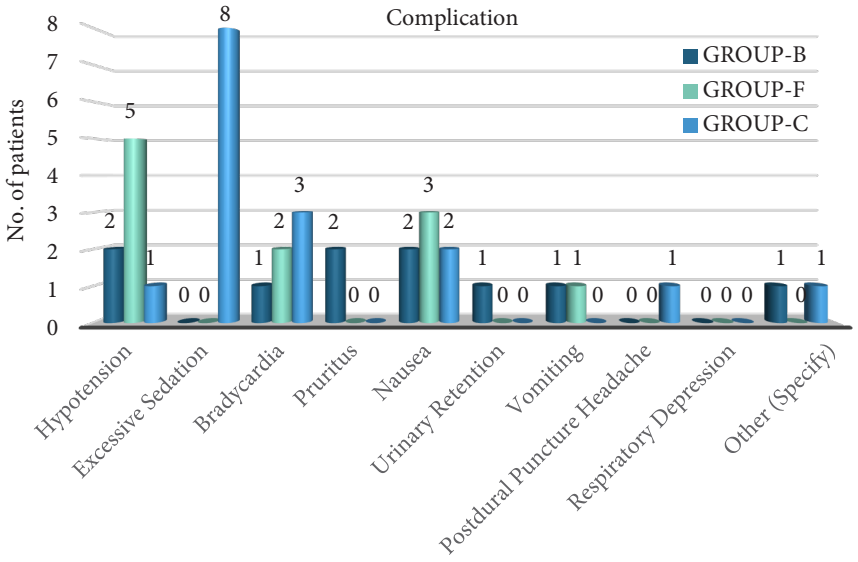

Figure 6. Graphical representation of complications

Source: developed by author

From a clinical perspective, these findings suggest that clonidine at a dose of 30 µg is a useful intrathecal adjuvant to 0.5% bupivacaine in lower abdominal surgery when prolonged analgesia is desired. Fentanyl also provides benefit over bupivacaine alone, but its effect appears less pronounced than that of clonidine. Overall, the present results support the use of low-dose clonidine as an effective and relatively safe option for improving spinal anaesthesia and postoperative pain control.

Discussion

Clonidine, as an α2-agonist, suppresses the transmission of Aδ and C fibres, hence prolonging the effects of local anaesthetics. When administered intrathecally, it induces analgesia by activating postsynaptic α2-receptors in the substantia gelatinosa of the spinal cord [18]. To mitigate the adverse effects of fentanyl, the combination of intrathecal clonidine and bupivacaine has been investigated for its potential to provide prolonged analgesia. Unlike intrathecal fentanyl, intrathecal clonidine used as an adjunct to bupivacaine in present study yielded prolonged analgesia. M.B. Khezri *et al.* [19] demonstrated as early as 2014 that intrathecal clonidine added to bupivacaine provided longer postoperative analgesia than fentanyl. Likewise, B.S. Bajwa *et al.* [16] reported superior analgesic prolongation with clonidine, though at the cost of higher sedation. The present findings corroborate these previously published results, confirming that clonidine offers greater prolongation of postoperative analgesia than fentanyl when used as an intrathecal adjuvant to bupivacaine.

Present study data indicate that the mean ages were similar among groups: Group-B (46.12 ± 10.98 years), Group-F (45.23 ± 11.56 years), and Group-C (44.78 ± 12.34 years) ($F = 0.1098$, $p = 0.8961$). The age distribution exhibited no significant difference ($X = 2.229$, $p = 0.9732$). The gender distribution exhibited parallels, with male-to-female ratios of 18:14 in Group-B, 16:16 in Group-F, and 17:15 in Group-C ($X = 0.2510$, $p = 0.8821$). The BMI values exhibited no significant differences across the groups (Group-B: 26.89 ± 3.91, Group-F: 27.34 ± 4.27, Group-C: 28.15 ± 4.05; $F = 0.7840$, $p = 0.4596$). The consistent demographic and health indicators underscore the robustness and reliability

of present study's participant profiles. The ASA grade distribution was consistent among all groups, primarily comprising ASA grade I (X = 0.6563, p = 0.7203). Appendectomies were conducted on 15 patients in Group B, 13 in Group F, and 14 in Group C. Inguinal hernia repair surgery was performed on 12 patients in Group B, 16 in Group F, and 14 in Group C. Hydrocele surgery was conducted on 5 patients in Group B, 3 in Group F, and 4 in Group C. The variations in the distribution of surgical types among the groups were not statistically significant (X = 1.214, p = 0.8757). The data demonstrate uniformity in ASA grades and surgical procedures among the study groups, hence ensuring comparability in clinical characteristics. At baseline, pulse rates were similar among Group-B (70.15 ± 5.42), Group-F (72.08 ± 6.34), and Group-C (71.24 ± 5.78), indicating no significant difference (F = 0.8730, p = 0.4211). The SBP exhibited a progressive decline over time across all groups; however, these variations did not attain statistical significance among the groups. The DBP exhibited a small decline across all groups with time; however, the variations among the groups remained statistically insignificant at each interval. At baseline, mean SpO2 values were comparable among Group-B (98.15 ± 0.98), Group-F (98.09 ± 1.02), and Group-C (98.12 ± 0.95), indicating no significant difference (F = 0.02976, p = 0.9707). The consistent SpO2 readings throughout groups suggest no significant differences in oxygen saturation levels among the three groups over the follow-up period. At baseline, all groups exhibited a VAS score of 0.00 ± 0.00, signifying the absence of first pain. Notable disparities in pain assessments were seen at later time intervals following treatment. The data demonstrate that during the post-operative period, patients in Group-C consistently reported much lower pain levels than those in Group-B and Group-F. The combination of Bupivacaine and Clonidine in Group-C seems to offer enhanced analgesic efficacy, as indicated by the VAS values recorded at all assessed time intervals. S. Kaushik [20] also observed no significant changes in demographic factors, including age, height, weight, sex ratio, and duration of operation, between the two groups examined. No statistically significant differences were observed in intra-operative haemodynamic measures, including mean arterial pressure (MAP) and heart rate (HR), during the procedure. Present study investigation and that of B.S. Bajwa *et al.* [16] revealed similar demographic profiles and haemodynamic parameters across study groups, demonstrating consistency and baseline comparability. B.S. Bajwa *et al.* [16] found that intrathecal clonidine, when combined with hyperbaric bupivacaine, produced longer postoperative analgesia and delayed the first request for rescue analgesia compared with fentanyl. The present study confirms these findings, as the clonidine group showed significantly lower postoperative VAS scores and a longer time to first rescue analgesia than the fentanyl group. This agreement may be attributed to the α2-adrenergic action of clonidine, which prolongs spinal analgesia by suppressing nociceptive transmission at the spinal cord level. The higher sedation seen in the clonidine group in both studies is also consistent with the known pharmacological profile of the drug.

Present study examined the anaesthetic effectiveness of three distinct combinations: Bupivacaine alone (Group-B), Bupivacaine combined with Fentanyl (Group-F), and Bupivacaine combined with Clonidine (Group-C). The results indicated substantial disparities in the onset and duration of sensory and motor blockages across the groups. Group-C demonstrated the longest duration until the initial analgesic demand (6.00 ± 1.50 hours), which was considerably greater than that of Group-F (4.50 ± 1.22 hours) and Group-B (2.80 ± 0.76 hours), F = 57.02, p < 0.0001. The results demonstrate that Bupivacaine combined with Clonidine (Group-C) generated a more rapid onset and extended duration of both sensory and motor blocks, leading to a postponed requirement for rescue analgesia in comparison to Group-B and Group-F. Consistent with present research, A.R. Chhabra *et al.* [21] shown that 60 μg of clonidine outperformed fentanyl, prolonging both the duration of the subarachnoid block and postoperative analgesia. V. Mahendru *et al.* [17] found that 30 μg intrathecal clonidine and 25 μg fentanyl produced comparable sensory and motor block characteristics, whereas the present study demonstrated superior block prolongation with clonidine. This difference may be related to variations in surgical population, methodology, and criteria used for block assessment, since V. Mahendru *et al.* [17] studied lower limb surgery and included a different comparative framework. Such variability suggests that the effect of intrathecal adjuvants may be context-dependent rather than unpredictable. Therefore, the present study remains relevant because it provides procedure-specific evidence for lower abdominal surgery and shows that clonidine may offer greater analgesic benefit than fentanyl, albeit with more sedation. The clonidine cohort exhibited analgesia for a significantly extended period (497.20 ± 139.78 min) in contrast to the fentanyl cohort (416.87 ± 105.67 min) (P < 0.05).

The start, peak, and duration of sensory and motor block are same in both groups; however, the analgesic duration in the clonidine group significantly exceeds that of the fentanyl group (P < 0.05). In present study, the clonidine cohort exhibited elevated sedation scores compared to the fentanyl cohort (P < 0.05). N. Kothari *et al.* [22] found that the addition of 50 μg of clonidine to bupivacaine induced drowsiness in 35-45% of subjects. The preceding finding clearly indicates that clonidine sedation is dose-dependent. In the research conducted by B.S. Bajwa *et al.* [16], the dosage of clonidine was limited to 50 μg to mitigate adverse effects.

In present study investigation, all groups commenced with a Ramsay Sedation Score of 1.00 ± 0.00 at baseline, signifying the absence of sedation. At 12 and 24 hours, sedation scores reverted to baseline for Group-B and Group-F (1.00 ± 0.00), however Group-C exhibited somewhat higher values (2.05 ± 0.00 and 2.04 ± 0.00, respectively). The results demonstrate that patients administered Bupivacaine with Clonidine (Group-C) exhibited markedly

elevated sedation levels relative to those in Group-B and Group-F, especially during the immediate postoperative phase, with lingering effects noted for up to 24 hours following administration. Likewise, B.S. Bajwa *et al*. [16] study indicates that the haemodynamic stability seen in both groups of present study experiment corroborates the principle that minimal dosages of intrathecal clonidine or fentanyl are not associated with systemic side effects such as bradycardia, hypotension, or sedation. Only one patient required intravenous atropine administration due to significant bradycardia. A. Bhattacharjee *et al*. [23] concluded that the addition of 75 μg of clonidine and 25 μg of fentanyl to bupivacaine prolonged perioperative analgesia during caesarean operations. The principal finding of present study investigation was the elevated incidence of excessive sedation in Group-C (25%), in contrast to the absence of reported cases in Group-B and Group-F. Group-C also showed a lower but non-significant incidence of hypotension (3.12%) compared to Group-B (6.25%) and Group-F (15.6%). No statistically significant differences were observed among the groups for complications such as bradycardia, pruritus, nausea, urinary retention, vomiting, post-dural puncture headache, respiratory depression, and specified minor issues. On the other hand, fentanyl prolonged postoperative analgesia more than clonidine did, and clonidine caused more side symptoms, such as nausea, vomiting, and hypotension studied by A. Bhattacharjee *et al*. [23]. Similar to present findings, G. Singh *et al*. [24] study in patients scheduled for transurethral resection of the prostate found that intrathecal clonidine combined with bupivacaine produces more satisfying anaesthesia and analgesia and has less side effects than fentanyl.

Present study contributes to the growing body of research on intrathecal anaesthesia by highlighting the varied sedative effects and impact on hypotension associated with different combinations of intrathecal analgesics. While the present study observed a higher incidence of sedation in Group-C and a potential benefit in mitigating hypotension compared to other groups, present study findings are consistent with previous studies regarding the efficacy of clonidine in extending postoperative analgesia. The present study used fixed low doses of fentanyl (25 μg) and clonidine (30 μg) as intrathecal adjuvants to 0.5% bupivacaine and therefore does not support conclusions regarding individualised dosing. No widely accepted national or international protocol was identified that specifically recommends this exact combination and dose for lower abdominal surgery. Current formal guidance more commonly addresses intrathecal opioids in obstetric neuraxial anaesthesia rather than clonidine-based non-obstetric spinal regimens. Therefore, the significance of the present study lies in providing procedure-specific comparative evidence rather than in refining an established protocol. Its novelty is the direct comparison of bupivacaine alone, bupivacaine with fentanyl, and bupivacaine with clonidine in lower abdominal surgery, with simultaneous assessment of block characteristics, postoperative analgesia, haemodynamic effects, sedation, and adverse events. The findings indicate that clonidine produced longer analgesia and lower postoperative pain scores than fentanyl, although with greater sedation.

Conclusions

This study showed that both fentanyl and clonidine improved the quality of spinal anaesthesia and postoperative analgesia when added intrathecally to 0.5% bupivacaine for lower abdominal surgery. However, clonidine 30 μg produced the most favourable analgesic profile. It was associated with a faster onset of sensory and motor block, longer duration of both blocks, lower postoperative VAS scores, and a significantly prolonged time to first rescue analgesia compared with fentanyl 25 μg and bupivacaine alone. These findings indicate that clonidine provides more sustained postoperative pain relief and better overall block characteristics in this surgical setting. From a practical perspective, the results suggest that low-dose intrathecal clonidine may be a useful adjuvant when prolonged analgesia is desired after lower abdominal procedures. At the same time, the greater sedation observed in the clonidine group should be taken into account, particularly in patients in whom early alertness is important. Thus, the choice of intrathecal adjuvant should balance analgesic benefit against the potential for increased sedation.

The study has some limitations. It was conducted at a single centre with a relatively small sample size, and only fixed doses of fentanyl and clonidine were evaluated. In addition, longer postoperative follow-up and broader assessment of patient-centred outcomes were not included. These factors may limit the generalisability of the findings. Overall, clonidine appears to be a more effective intrathecal adjuvant than fentanyl for prolonging postoperative analgesia in lower abdominal surgery, although with higher sedation. Further multicentric studies with larger samples are needed to confirm these findings, evaluate different dose regimens, and better define the balance between analgesic efficacy and adverse effects.

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Conflict of Interest

Author declares no conflict of interest.

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Ефективність та безпека інтратекального введення клонідину порівняно з фентанілом у поєднанні з бупівакаїном при операціях у нижній частині живота

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Анотація. Інтратекальні ад'юванти, такі як фентаніл і клонідин, можуть покращувати якість та тривалість спінальної анестезії та післяопераційної аналгезії з використанням бупівакаїну, проте їх порівняльна ефективність та профіль побічних ефектів залишаються важливими питаннями. Метою даного дослідження було порівняння впливу інтратекального фентанілу та клонідину як ад'ювантів до 0,5 % бупівакаїну на характеристики блокади, післяопераційну аналгезію, гемодинаміку, седацію та побічні ефекти у пацієнтів, яким проводили операції на нижній частині живота. Це рандомізоване подвійне сліпе порівняльне дослідження було проведено у відділенні анестезіології лікарні Балрампур, Лакхнау, серед 96 пацієнтів віком 18-60 років, фізичний статус ASA I-II, яким було призначено операції на нижній частині живота. Пацієнтів було випадково розподілено на три групи (n = 32 у кожній): Група B отримала 2,5 мл 0,5 % розчину бупівакаїну з 0,5 мл фізіологічного розчину, група F отримала 2,5 мл 0,5 % розчину бупівакаїну з 25 мкг фентанілу, а група C – 2,5 мл 0,5 % розчину бупівакаїну з 30 мкг клонідину. Результати включали час настання та тривалість блокади, час застосування додаткової аналгезії, оцінку за шкалою VAS, гемодинаміку, седацію та побічні ефекти. Базові характеристики були порівнянними між групами. Група C показала найшвидший початок сенсорної блокади (1,45 ± 0,30 хв) та її найдовшу тривалість (150,23 ± 28,47 хв), за нею йшли група F та група B ($p < 0,0001$). Подібна закономірність спостерігалася щодо початку та тривалості моторної блокади ($p < 0,0001$). Час до першого застосування додаткової аналгезії був значно довшим у групі C (6,00 ± 1,50 год) порівняно з групою F (4,50 ± 1,22 год) та групою B (2,80 ± 0,76 год) ($p < 0,0001$). Післяопераційні показники за шкалою VAS були значно нижчими у групі C. Гемодинамічні показники залишалися в основному порівнянними. Седативний ефект був сильнішим при застосуванні клонідину, причому виражена седація спостерігалася лише у групі C. Інтратекальне введення 30 мкг клонідину разом з бупівакаїном забезпечило кращі характеристики блокади та тривалішу післяопераційну аналгезію, ніж 25 мкг фентанілу або бупівакаїн окремо, але з вищим рівнем седації

Ключові слова: спінальна анестезія; післяопераційна аналгезія; хірургія нижньої частини живота; гемодинаміка; седація

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Comparative clinical efficacy and procedural efficiency of nebuliser vs valved holding chamber in paediatric obstructive bronchitis

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Abstract. Obstructive bronchitis remains a frequent cause of acute respiratory distress in paediatric care. While bronchodilators remain the standard therapeutic approach, the choice between a nebuliser and a pressurised metered-dose inhaler (pMDI) with a valved holding chamber continues to be a subject of clinical debate, particularly regarding younger children. In this prospective observational study, a cohort of 30 children aged 2-8 years was examined to compare the clinical efficacy and usability of these delivery methods. Group A (n = 16) received salbutamol via a jet nebuliser, while Group B (n = 14) utilised a pMDI with a Vortex-type spacer. Despite comparable baseline characteristics ($p > 0.05$), Group B demonstrated accelerated clinical stabilisation, higher levels of child cooperation, and a reduction in the total number of required inhalations. Notably, the incidence of repeat medical consultations and hospitalisations was lower in the spacer group (7.1% for each outcome) compared to the nebuliser group (25.0% and 12.5%, respectively). These findings suggested that a pMDI with a spacer is a highly effective primary tool for managing mild-to-moderate episodes in outpatient and home settings. Nebuliser therapy should be reserved for severe clinical presentations or patients with significant hypoxia and coordination difficulties, typically requiring supervised clinical observation. Integrating spacers into primary care protocols can optimise treatment efficiency and alleviate the burden on hospital facilities by providing reliable management of less severe obstructions

Keywords: bronchial obstructive syndrome; respiratory conditions; bronchodilators; spacer

Introduction

Obstructive bronchitis is one of the most common acute respiratory conditions in early childhood, accounting for a significant proportion of visits to paediatric emergency departments. A.A.B. Wolters *et al.* [1] found that in some countries the prevalence of wheezing in preschool children reaches 30-50%, with a substantial proportion of these children subsequently exhibiting recurrent episodes of obstruction. The pathogenetic basis of bronchial obstructive syndrome includes bronchospasm, mucus hypersecretion, and oedema of the bronchial mucosa, which leads to impaired pulmonary ventilation and an increased risk of respiratory failure.

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C. Schorlemer & E. Eber [2] demonstrated that short-acting β_2-agonists, particularly salbutamol, remain the first-line treatment for obstructive bronchitis in children. Inhalation therapy is the main method of delivering bronchodilators in bronchial obstructive syndrome in paediatric practice. The two principal delivery methods are nebuliser therapy and the use of a pressurised metered-dose inhaler (pMDI) with a spacer. A. Emeryk *et al.* [3] demonstrated that the clinical effectiveness of nebuliser therapy in children is significantly influenced by the technical characteristics of the device and the patient's breathing pattern, as both factors directly determine pulmonary drug deposition and, consequently, the bronchodilator response. E. Bhatt & R.A. Malkin [4] demonstrated that errors in MDI technique remain highly prevalent among children despite prior in-person instruction: 81% of paediatric patients used their inhalers incorrectly, with the most frequent errors being rapid shallow breathing, inadequate breath-holding, and excessive actuations, all of which significantly reduce the amount of medication reaching the airways.

The comparative effectiveness of these two delivery methods has been investigated in a number of randomised controlled trials. C. Lemaçon & A.A. Lopes [5], in a two-centre study conducted in paediatric emergency departments, demonstrated that salbutamol delivered via pMDI with a holding chamber was as effective as nebulisation for mild to moderate asthma exacerbations, with significantly lower hospitalisation rates, fewer side effects, and shorter emergency department visits in the pMDI group – particularly pronounced in children under 6 years of age. C. Graybill *et al.* [6], in a retrospective study of paediatric patients with asthma exacerbations at a primary care centre, found that albuterol delivered via MDI with a spacer was more effective than nebulisation in reducing follow-up visits: none of the MDI-treated patients returned to care within 30 days, compared with 61% of those who received nebulised treatment ($p < 0.00001$). P.K. Gleeson *et al.* [7] emphasised that improper inhaler technique in persistent asthma is a widespread problem, and standardised checklists for assessing inhalation technique are still lacking. In this context, the choice of a specific spacer model is important. In this context, the choice of a specific spacer model carries direct clinical relevance.

L. Ojanperä *et al.* [8], in an *in vitro* study simulating paediatric breathing patterns in children aged 4 and 6 years, demonstrated that salbutamol fine particle dose (FPD, 1-5 μm) differed substantially between devices: EasyChamber delivered a median FPD of 30.7 μg in the 6-year-old profile and 25.0 μg in the 4-year-old profile, compared with 8.2-13.5 μg and 6.8-11.6 μg, respectively, for the remaining spacers ($p < 0.001$). Under simulated obstructive breathing, FPD declined markedly across all devices, with EasyChamber still outperforming others (6.4 μg vs 1.4-1.7 μg; $p < 0.001$), reinforcing that findings from one spacer model cannot be extrapolated to another. M.M. Alotaibi *et al.* [9] demonstrated that the majority of asthma patients do not use their inhalers appropriately, with poor technique observed in 67% of participants, and emphasised that prescribing an inhaler device matched to the patient's ability to generate adequate inspiratory flow is essential for optimal drug delivery to the airways and effective disease management. M. Ruszczyński *et al.* [10], in a systematic review, assessing the quality of guidelines on preschool wheezing and asthma using the AGREE II instrument, demonstrated considerable variability in methodological rigour across available recommendations, with particularly low scores in the domains of applicability and stakeholder involvement, highlighting the need for higher-quality evidence to inform clinical decision-making in this patient population.

Despite the available data on the comparable effectiveness of pMDIs with spacers and nebulisers, the question of the optimal delivery method for specific age groups and degrees of obstruction remains insufficiently studied, particularly regarding Vortex-type spacers in children with obstructive bronchitis in real-world clinical practice. Therefore, the purpose of this study was to conduct a comparative evaluation of the clinical effectiveness, ease of use, and safety of nebuliser therapy and pMDIs with a Vortex-type spacer in children with obstructive bronchitis by analysing the dynamics of clinical parameters (degree of obstruction, oxygen saturation), the frequency of adverse effects, and the convenience of device use depending on the child's age.

Materials and Methods

This prospective observational cohort study was conducted in the outpatient paediatric department of Municipal Non-Profit Enterprise "City Children's Clinical Hospital No. 16" of Kharkiv City Council between February 2024 and May 2025. The study protocol was approved by the Institutional Ethics Committee (reference No. 2023/06) and was carried out in full accordance with the principles of the Declaration of Helsinki [11]. Written informed consent was obtained from the parent or legal guardian of each participant following a comprehensive explanation of all study procedures. Out of 32 children aged 2-8 years consecutively screened with a clinical diagnosis of obstructive bronchitis, 30 patients fulfilled all per-protocol criteria and were retained in the final analysis; two children were excluded due to post-enrolment protocol deviations. The enrolled cohort comprised three age strata: 9 children (30.0%) aged 2-3 years, 12 children (40.0%) aged 4-5 years, and 9 children (30.0%) aged 6-8 years, with a mean age of 5.0 ± 1.8 years for the total sample. The overall sex distribution was 18 males and 12 females (60.0% and 40.0%; $p > 0.05$). Inclusion criteria were: clinical diagnosis of obstructive bronchitis, age 2-8 years, and written parental/guardian consent. Diagnosis was established based on productive cough, diffuse expiratory wheeze, tachypnoea, expiratory dyspnoea, and accessory muscle recruitment; chest radiography was performed when clinically indicated in accordance with R. Axinte *et al.* [12], Ministry of Health of Ukraine [13-14], Global Initiative for Asthma Management and Prevention [15]. Baseline SpO_2 ranged from 90-94%. Exclusion criteria included bronchial asthma, congenital

cardiopulmonary disease, cystic fibrosis, severe central nervous system pathology, immunodeficiency, gastroesophageal reflux disease, systemic corticosteroids within the preceding four weeks, and salbutamol hypersensitivity.

All patients were treated per current clinical guidelines and were initially seen on an outpatient basis; hospitalisation during the follow-up period was recorded as a primary outcome measure rather than a baseline condition. Allocation was based on clinical severity and the physician's assessment of the child's ability to cooperate with the device. Disease severity at presentation was classified as mild (SpO_2 92-94%, dyspnoea absent or minimal) or moderate (SpO_2 90-91%, expiratory dyspnoea present); no severe cases (SpO_2 <90%) were enrolled. In Group A, 10 patients (62.5%) presented with mild and 6 (37.5%) with moderate disease; in Group B, 9 patients (64.3%) presented with mild and 5 (35.7%) with moderate disease. Severity distribution was comparable between groups ($p > 0.05$). Group A (n = 16; 53.3%) received salbutamol (2.5 mg/mL) via jet nebuliser; Group B (n = 14; 46.7%) received salbutamol via pMDI with a Vortex valve-controlled spacer. Primary outcomes included: session duration, number of sessions to full resolution, repeat visit rate, hospitalisation rate, and overall clinical improvement (resolution of dyspnoea, SpO_2 ≥96%, absence of wheeze, and meaningful cough reduction). Secondary outcomes comprised post-treatment changes in respiratory rate, dyspnoea, SpO_2, cough grade, and auscultatory findings.

A structured questionnaire was administered to 34 paediatricians with experience of both devices, evaluating five domains – ease of use, procedure duration, child cooperation, technique error rate, and tolerability – each on a five-point Likert scale. Continuous data were expressed as mean ± SD or median interquartile range. Between-group comparisons used the Mann-Whitney U test and Fisher's exact test for continuous and categorical variables, respectively. The Holm-Bonferroni correction was applied for multiple comparisons; 95% CIs were estimated by bootstrap resampling (1,000 iterations). Statistical significance was set at $p < 0.05$. Analyses were performed in SPSS v26.0 and Python 3.x (SciPy). Baseline characteristics were comparable between groups ($p > 0.05$ for all parameters).

Results

Baseline characteristics. Detailed demographic, clinical, and laboratory parameters for both cohorts are presented in Table 1. Two baseline asymmetries of potential clinical relevance warrant explicit commentary. First, Group B exhibited a more pronounced male predominance (64.3%) compared with Group A (56.3%), which, although not statistically significant, merits acknowledgment given that male sex is a recognised modifier of airway reactivity in early childhood and may have introduced a subtle directional influence on Group B outcomes. This observation is consistent with the findings of M. Attanasi *et al.* [16], who reported that boys demonstrated consistently higher odds of wheezing than girls from birth through age 13 years (OR 0.86, 95% CI 0.74-0.98) in a multi-ethnic population-based cohort of 3,418 children. Second, the distribution of prior episode history differed noticeably between groups: only 6.3% of Group A patients were experiencing their first obstructive episode versus 21.4% in Group B – a 15.1-percentage-point differential carrying potential clinical implications, as first-episode patients may exhibit a more pronounced initial bronchodilator response. Conversely, Group B contained a nominally higher proportion of patients with three or more prior episodes (35.7% vs 25.0% in Group A), suggesting a greater burden of recurrent airway disease in the spacer cohort. These distributional nuances are reported transparently to support unbiased interpretation of the efficacy data. Beyond these specified asymmetries, formal statistical testing confirmed cohort parity across all remaining parameters at baseline (all $p > 0.05$).

Table 1. Baseline demographic, clinical, and laboratory characteristics of study participants

Characteristic	Total (n = 30)	Group A – Nebuliser (n = 16)	Group B – Spacer (n = 14)	p-value
Sex distribution, M/F	18/12	9/7	9/5	> 0.05
Age, years (mean ± SD)	5.0 ± 1.8	5.2 ± 1.6	4.8 ± 2.0	> 0.05
First episode of obstruction, n (%)	4 (13.3)	1 (6.3)	3 (21.4)	> 0.05
≥3 prior episodes of obstruction, n (%)	9 (30.0)	4 (25.0)	5 (35.7)	> 0.05
Atopic dermatitis, n (%)	3 (10.0)	1 (6.3)	2 (14.3)	> 0.05
Food allergy, n (%)	4 (13.3)	2 (12.5)	2 (14.3)	> 0.05
Allergic rhinitis, n (%)	3 (10.0)	1 (6.3)	2 (14.3)	> 0.05
Family history of allergic diseases, n (%)	8 (26.7)	4 (25.0)	4 (28.6)	> 0.05
Eosinophils > 0.3×10^9/L, n (%)	4 (13.3)	2 (12.5)	2 (14.3)	> 0.05
Lymphocytes > 4.0×10^9/L, n (%)	16 (53.3)	9 (56.3)	7 (50.0)	> 0.05
Elevated CRP (>5 mg/L), n (%)	10 (33.3)	5 (31.3)	5 (35.7)	> 0.05
Leukocytosis (>10×10^9/L), n (%)	14 (46.7)	7 (43.8)	7 (50.0)	> 0.05
Recurrent URTIs, n (%)	26 (86.7)	14 (87.5)	12 (85.7)	> 0.05
Passive smoking exposure, n (%)	11 (36.7)	6 (37.5)	5 (35.7)	> 0.05
Dyspnoea before treatment, n (%)	24 (80.0)	13 (81.3)	11 (78.6)	> 0.05
SpO_2 before treatment (mean, %)	91.7	91.8	91.5	> 0.05

Continued Table 1

Characteristic	Total (n = 30)	Group A – Nebuliser (n = 16)	Group B – Spacer (n = 14)	p-value
Moderate/severe cough, n (%)	27 (90.0)	14 (87.5)	13 (92.9)	> 0.05
Auscultatory wheezing, n (%)	27 (90.0)	14 (87.5)	13 (92.9)	> 0.05

Note: PM/F – male/female; SpO_2 – oxygen saturation; CRP – C-reactive protein; URTI – upper respiratory tract infection; SD – standard deviation. All $p > 0.05$ (Mann-Whitney U/Fisher's exact tests with Holm-Bonferroni correction)
Source: compiled by the authors

Collectively, the data in Table 1 confirm that Groups A and B entered the study with broadly equivalent disease burden and clinical presentation profiles. The absence of statistically significant differences across all 18 assessed baseline parameters provides a valid analytical foundation for attributing observed inter-group differences in clinical outcomes to the inhalation modality rather than to pre-existing cohort heterogeneity. The two qualitative asymmetries identified above – the higher proportion of first-episode patients in Group B and the mild male predominance in that cohort – constitute acknowledged observational features of the pragmatic allocation design and should be considered in the contextual interpretation of subsequent efficacy findings.

Atopic and allergic profiles. Allergic predisposition profiling was undertaken systematically in all 30 participants; group-level prevalence figures for each condition are provided in Table 1. Notably, the recorded allergic conditions were not mutually exclusive. Two children with concurrent atopic dermatitis and allergic rhinitis were both from Group B (6.7% of the total cohort; 14.3% of Group B), and one child with co-existing atopic dermatitis and food allergy was from Group A (3.3% of the total cohort; 6.3% of Group A). No child presented simultaneously with allergic rhinitis and food allergy, and no case of all three conditions co-occurring was documented. In total, three children (10.0%) carried two simultaneous allergic diagnoses – a pattern consistent with early-stage atopic march progression, as highlighted by Y.D. Bondarenko *et al.* [17], who reported frequent allergic comorbidities in children with allergic rhinitis, including bronchial asthma (28%), allergic conjunctivitis (32%), and atopic dermatitis (4.7%), underscoring the concept of allergic multimorbidity as a hallmark of the atopic march. Accounting for overlap, children with any form of allergic predisposition constituted approximately 23-27% of the cohort. Although none of the inter-group differences in allergic conditions reached statistical significance (all $p > 0.05$; Table 1), the marginally higher aggregate atopic burden in Group B warrants acknowledgment as a potential modulatory factor when interpreting treatment response data, given that allergic airway inflammation may independently influence bronchodilator responsiveness. Concomitant non-allergic comorbidities – primarily acute rhinitis – were identified in 6 children across the cohort (20.0%). Symptom duration prior to initiation of bronchodilator therapy ranged from 1 to 4 days, with 2-3 days being the most frequently reported interval, reflecting an acute clinical presentation at enrolment. All patients were managed in accordance with the current clinical guideline for children with acute expiratory airway obstruction and bronchial asthma exacerbation.

Clinical outcome. Both inhalation modalities produced clinically meaningful improvements across all assessed respiratory parameters (Fig. 1). The magnitudes of symptomatic improvement were broadly similar between groups across all five parameters (Table 2), confirming that both delivery systems achieve effective acute bronchodilation. The clinically decisive differentiation lies not in the quality of therapeutic response but in the efficiency with which it is achieved. As shown in Table 2, spacer use resulted in a two-fold reduction in mean session duration ($p < 0.001$), accompanied by a significantly lower total number of sessions required to reach complete symptom resolution ($p = 0.038$). Together, these parameters indicate a dual efficiency advantage with direct implications for outpatient clinical throughput and caregiver treatment burden.

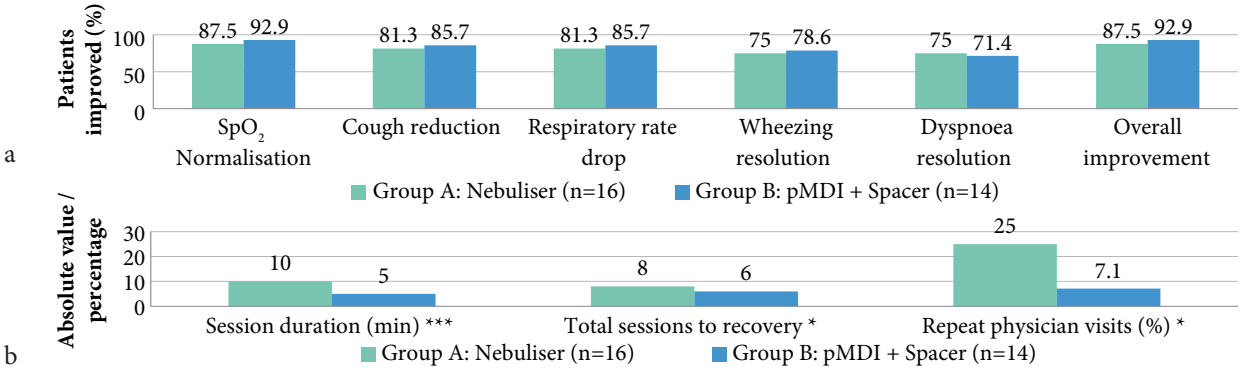

Figure 1. Comparison of paediatric treatment effectiveness
Note: a – clinical effectiveness (equivalence between groups); b – treatment efficiency and burden (advantage of spacer); clinical outcomes: Group A (nebuliser, n = 16) vs Group B (pMDI+Vortex, n = 14): respiratory rate, SpO_2, dyspnoea, cough, and wheezing. Values = % of patients improved; * $p < 0.05$, *** $p < 0.001$ (statistical significance for procedural advantage)
Source: compiled by the authors

Table 2. Clinical outcomes and procedural efficiency by inhalation modality

Parameter	Nebuliser		Spacer		Δ (%) A vs B	p-value
	Before	After	Before	After		
Respiratory rate (RR), elevated, n (%) / MD ± SD	16 (100) / 32 ± 4	3 (18.7) / 20 ± 3	14 (100) / 31 ± 5	2 (14.3) / 19 ± 2	-81.3 vs -85.7	> 0.05
Dyspnoea, n (%)	13 (81.3)	1 (6.3)	11 (78.6)	1 (7.1)	-75.0 vs -71.4	> 0.05
SpO_2 <96%, n (%) / MD ± SD	16 (100) / 91.8 ± 2.1	2 (12.5) / 97.0 ± 1.2	14 (100) / 91.5 ± 2.3	1 (7.1) / 97.5 ± 0.8	+87.5 vs +92.9	> 0.05
Moderate/severe cough, n (%)	14 (87.5)	3 (18.7)	13 (92.9)	2 (14.3)	-81.3 vs -85.7	> 0.05
Auscultatory wheezing, n (%)	14 (87.5)	2 (12.5)	13 (92.9)	2 (14.3)	-75.0 vs -78.6	> 0.05
Duration of inhalation (min, MD ± SD)	10.0 ± 1.2		5.0 ± 0.8		–	< 0.001
Total sessions to recovery (MD ± SD)	8.0 ± 1.6		6.0 ± 1.2		–	0.038
Repeat physician visits, n (%)	4 (25.0)		1 (7.1)		-17.9 pp	< 0.05
Hospitalisations, n (%)	2 (12.5)		1 (7.1)		-5.4 pp	> 0.05
Overall clinical improvement, n (%)	14 (87.5)		13 (92.9)		+5.4 pp	> 0.05

Note: SD – standard deviation; n – absolute number of patients. Mann-Whitney U test for continuous variables. Fisher's exact test for categorical variables with Holm-Bonferroni correction. Overall clinical improvement defined as composite endpoint: SpO_2 ≥96%, resolution of dyspnoea and auscultatory wheezing, and clinically meaningful reduction in cough severity

Source: compiled by the authors

Secondary healthcare utilisation outcomes reinforced this pattern. Repeat physician visits were significantly less frequent in Group B ($p < 0.05$), while hospitalisation rates, though numerically lower in the spacer group, did not reach statistical significance – a finding attributable to limited statistical power for this infrequent outcome. Overall clinical improvement rates were comparable between groups, with a numerically – though not significantly – superior composite response in the spacer group (Table 2). The data in Table 2 delineate a consistent clinical pattern in which the pMDI + Vortex spacer confers statistically significant and clinically meaningful advantages in treatment efficiency – specifically in session duration ($p < 0.001$), total session count ($p = 0.038$), and unscheduled return visit rate ($p < 0.05$) – without compromising the quality of therapeutic response relative to jet nebuliser therapy. The non-significant difference in hospitalisation rates may reflect adequate clinical safety provision in both arms rather than genuine equivalence in the most severely affected patients; this question warrants evaluation in adequately powered future studies.

Usability and paediatricians' satisfaction. The structured usability questionnaire administered to 34 paediatric physicians yielded a domain-specific performance profile providing critical context for interpreting the aggregate scoring differential between modalities (Table 3). Notably, both devices received identical physician ratings for ease of use and frequency of inhalation technique errors – confirming that physicians perceive the two modalities as equally straightforward to prepare and operate, with an equivalent margin of procedural error. The aggregate advantage of the spacer ($p < 0.001$) therefore cannot be attributed to differences in device complexity or physician familiarity with the equipment. Statistically significant between-device differences were identified exclusively in three domains: procedure duration, child cooperation, and child tolerability (all $p \leq 0.05$). The procedure duration differential is the most objectively grounded of the three, directly corroborating the two-fold session time reduction. The cooperation and tolerability domains, in contrast, reflect physician-perceived behavioural and experiential assessments. In children aged 2-8 years, responses to inhalation procedures are substantially modulated by developmental stage, anticipatory anxiety, sensitivity to the nebuliser's motor noise, and physical encumbrance of the mask – factors that cannot be fully disentangled from device-specific performance characteristics in an observational design. These ratings therefore represent important observational signals regarding the paediatric patient experience, and should be interpreted as such rather than as strictly objective device performance metrics.

Table 3. Paediatric physician ratings of inhalation device usability

Criterion	Group A Nebuliser	Group B Spacer	Difference (Δ)	Statistical significance
Ease of device use	5	5	0	n.s.
Procedure duration	1	5	4	$p < 0.01$
Child cooperation during procedure*	2	5	3	$p < 0.05$
Child tolerability*	1	5	4	$p < 0.01$
Frequency of inhalation technique errors	3	3	0	n.s.
Total mean score	2.4	4.6	2.2	$p < 0.001$

Note: *domains of child cooperation and tolerability reflect physician observational assessments in children aged 2-8 years and contain an inherent subjective component attributable to age-dependent behavioural variability and developmental stage

Source: compiled by the authors

The domain-level analysis of Table 3 reveals that the aggregate physician preference for the pMDI + Vortex spacer is driven by a combination of objectively faster procedure delivery and the perceived superiority of the spacer in terms of child tolerability and cooperation – with no contribution from device-complexity differences, as evidenced by the identical ease-of-use and technique-error scores. These findings support the preferential use of pMDI + Vortex spacer therapy as the first-line bronchodilator delivery modality in cooperative paediatric outpatients with obstructive bronchitis, while affirming the continued clinical utility of jet nebuliser therapy in patients with more severe respiratory distress or inadequate inhalation coordination – a stratified deployment model aligned with current evidence-based recommendations – Order of the Ministry of Health of Ukraine No. 00129 and No. 00613 [13-14] and Global Initiative for Asthma Management and Prevention [15].

Discussion

The present study evaluated jet nebuliser therapy versus pMDI with a Vortex-type valved holding chamber for bronchodilator delivery in children aged 2-8 years with mild-to-moderate obstructive bronchitis. Both modalities produced clinically equivalent therapeutic responses across all assessed respiratory parameters. On the other hand, the spacer-based approach conferred statistically significant advantages in procedural efficiency and secondary healthcare utilisation.

*Equivalence of therapeutic response***.** Overall clinical improvement was achieved in 87.5% and 92.9% of patients in Groups A and B respectively ($p > 0.05$), with all individual parameter response rates likewise statistically equivalent (all $p > 0.05$). This aligns with the growing evidence base confirming pharmacological equivalence of the two delivery platforms. K. Sugiura *et al.* [18] demonstrated that pMDI with a spacer was comparable to nebuliser in clinical effectiveness among children aged 4-16 years with moderate-to-severe acute asthma exacerbations (MPIS reduction: 4.3 vs 3.7; $p = 0.13$), while being associated with a significantly shorter length of stay (61 vs 94 min; $p < 0.001$) and a lower incidence of adverse events. C. Graybill *et al.* [6] similarly confirmed the superiority of pMDI with spacer in reducing unscheduled follow-up visits, with zero MDI-treated patients returning within 30 days compared to 61% in the nebuliser group ($p < 0.00001$). The present data confirm that this equivalence in therapeutic response – alongside the efficiency advantage of the spacer – holds in a real-world outpatient cohort using the Vortex device specifically.

Procedural efficiency: the decisive differentiator. Mean session duration was reduced by 50% in Group B (5.0 ± 0.8 vs 10.0 ± 1.2 min; $p < 0.001$), and total sessions to full recovery were significantly fewer (6.0 ± 1.2 vs 8.0 ± 1.6; $p = 0.038$), yielding cumulative time savings of 24-40 minutes per treatment course. The reduced session count suggests more efficient bronchial deposition per dose – consistent with cost-effectiveness data from J. Witnalakorn *et al.* [19], who demonstrated that MDI with spacer incurred lower direct medical costs than nebulisation in children with asthma exacerbation (ICER: −4.60 USD per one-point asthma score improvement; −20.07 USD per hospitalisation averted), and with resource utilisation data from S.A. Alhaider *et al.* [20], who reported a 48% reduction in treatment delivery time and up to 87% medication cost savings following conversion from nebuliser to MDI-spacer in hospitalised children. These efficiency advantages persisted under outpatient conditions in children as young as 2 years, including those with no prior device familiarity.

Secondary healthcare utilisation and implications for outpatient management. One of the most clinically significant findings of this study was the substantially lower rate of unscheduled repeat physician visits in Group B. Four of 16 Group A patients (25.0%) required a repeat visit due to clinical deterioration, compared with only 1 of 14 Group B patients (7.1%) – a statistically significant 17.9-percentage-point reduction ($p < 0.05$). Hospitalisation rates, while numerically lower in Group B (7.1% vs 12.5%), did not reach statistical significance ($p > 0.05$), a finding attributable in part to the limited statistical power for this low-frequency outcome in a 30-patient cohort. Taken together, these utilisation data suggest that superior procedural efficiency and better child tolerance in the spacer group contribute to more sustained therapeutic adherence at home, reducing clinical rebound. The directional finding on hospitalisations, though non-significant, is consistent with findings in the literature: O. Nomura *et al.* [21], in a prospective observational study of 158 paediatric ED patients, similarly found no statistically significant difference in admission rates between MDI-delivered ipratropium and non-MDI groups (25.9% vs 31.5%; $p = 0.67$), suggesting that detection of hospitalisation differences in real-world outpatient cohorts is inherently limited by event frequency and sample size. But it is worth mentioning that parental perception of device efficacy is a key mediator of home adherence: A.A. Alzayed *et al.* [22], in a cross-sectional survey of 1,021 Saudi caregivers, found that 70.2% suggested there is a therapeutic difference between MDI and nebuliser, with 45.2% considering the nebuliser more effective, despite evidence to the contrary; moreover, parents who received adequate device education reported significantly higher satisfaction scores (6.38 vs 5.28; $p < 0.001$). Proper inhaler technique further conditions home-based outcomes – B.A. Almomani *et al.* [23] reported that correct MDI use was observed in only 13.4% of paediatric patients, and that higher parental knowledge was independently associated with a greater number of correct inhaler steps (OR = 1.066; 95% CI = 1.010-1.125; $p = 0.020$). Institutional barriers to MDI adoption also affect utilisation patterns at the system level: N.F. Sakrani *et al.* [24] demonstrated that targeted physician education at a tertiary paediatric ED increased MDI + spacer prescribing from 28% to 41% ($p = 0.046$), and raised the proportion of physicians confident in convincing parents to accept spacer-based therapy from 35% to 66% ($p < 0.0001$). The Vortex spacer's advantages –

portability, absence of power-source requirements, and shorter procedure duration – make it particularly suited to home-based maintenance therapy in resource-limited outpatient contexts, aligning with the practical recommendations of Ukrainian Ministry of Health clinical guidelines [13-14].

Child cooperation, tolerability, and the paediatric patient experience. The paediatrician usability survey (n = 34) revealed that aggregate preference strongly favoured the spacer (mean score 4.6 vs 2.4; $p < 0.001$), with significant between-device differences in procedure duration ($p < 0.01$), child cooperation ($p < 0.05$), and tolerability ($p < 0.01$) – while ease of use and technique error rates were identical. The nebuliser's lower ratings reflect its well-documented behavioural stressors: continuous motor noise, prolonged mask contact, and substantial drug losses during crying – factors disproportionately affecting toddlers and pre-schoolers, who comprised 70% of this cohort. As A. Ari [25] noted in a narrative review of aerosol delivery in children, lung deposition in crying infants receiving nebulised therapy was approximately fourfold lower than in cooperative patients, and up to 49% of children do not tolerate facemasks during treatment, with fussing and crying substantially reducing the inhaled dose. The Vortex spacer eliminates the noise source, halves session time, and requires only a few cooperative breaths, substantially lowering the behavioural threshold for effective inhalation. An additional practical advantage relates to the device interface: S.H. Chen *et al.* [26] demonstrated in an in vitro infant and paediatric model that aerosol drug delivery efficiency is significantly influenced by the degree of enclosure sealing and the delivery interface used, confirming that device configuration directly determines the inhaled dose available to the child.

Interpretation of baseline asymmetries and allocation design. Allocation was based on clinical severity and assessed cooperation capacity, reflecting real-world outpatient practice. Two baseline asymmetries warrant consideration: a higher proportion of first-episode patients in Group B (21.4% vs 6.3%), and greater recurrent obstruction burden in the same group (≥3 episodes: 35.7% vs 25.0%). These forces are directionally opposing and difficult to quantify in a cohort of this size. The allocation design – directing more severely affected or uncooperative children toward nebuliser therapy – may itself account for Group A's higher session count and repeat visit rate, independent of any pharmacological inferiority. This allocation-severity confound is the primary study limitation and should be addressed through prospective randomisation in future research.

Device selection context: the role of clinical severity. The Vortex spacer is a valved holding chamber that temporarily retains the pMDI aerosol cloud, eliminating the coordination requirement and selectively delivering the 2-5 μm therapeutic fraction to the distal bronchi. O.A. Sayed *et al.* [27] demonstrated in an in-vitro model that conventional spacers significantly enhance the delivery of fine particles (<5 μm) and improve aerodynamic distribution compared to using a pMDI alone. This mechanism presupposes a minimum level of respiratory effort and cooperation, which is reliably available in children with mild-to-moderate obstruction but becomes compromised under conditions of marked respiratory distress, hypoxia-driven reduction in β_2-receptor sensitivity, or impaired consciousness. E. Poplicean *et al.* [28] reported that up to 70-80% of asthma patients do not use their inhalers correctly, with technique errors such as incorrect inhalation speed directly contributing to poor asthma control and increased emergency department visits. The nebuliser, by contrast, enables passive aerosol delivery independent of patient effort, making it the appropriate default in severe obstruction with desaturation (SpO_2 <90%), pronounced intercostal retractions, or inability to sustain mask contact. J.M. Lizzo *et al.* [29] emphasised that because paediatric asthma severity can range from intermittent symptoms to life-threatening airway compromise, treatment decisions must be strictly guided by symptom intensity and exacerbation risk. R. Chu & P. Bajaj [30] noted that a stepwise approach to management is essential, ensuring that the escalation of medication and device selection matches the severity of the patient's presentation and their physical capacity to use the delivery device.

In the present cohort, baseline SpO_2 was comparable across groups (91.8% vs 91.5%), and all enrolled children fell within the mild-to-moderate severity range – a design condition that appropriately isolated the efficiency and tolerability dimensions of the comparison rather than the pharmacological ceiling of either device. The current Global Initiative for Asthma Management and Prevention [15] states that "the preferred device is a pressurised metered-dose inhaler (pMDI) and spacer, with face mask for <3 years and mouthpiece for most children aged 3-5 years, highlighting that in children, pMDI should always be used with a spacer as delivery of short-acting beta-agonist via a pMDI and spacer or a DPI leads to a similar improvement in lung function as delivery via nebuliser (Evidence A).

Conclusions

Both nebuliser therapy and pMDI with a Vortex-type spacer demonstrated comparable clinical efficacy in the treatment of mild-to-moderate obstructive bronchitis in children aged 2-8 years, with statistically equivalent improvements across all assessed respiratory parameters (overall clinical improvement: 87.5% in Group A vs 92.9% in Group B; $p > 0.05$), confirming pharmacological equivalence of both delivery platforms. The Vortex spacer demonstrated a significant advantage in procedural efficiency: mean session duration was two-fold shorter (5.0 ± 0.8 vs 10.0 ± 1.2 min; $p<0.001$), total number of sessions required for full recovery was lower (6.0 ± 1.2 vs 8.0 ± 1.6; $p = 0.038$), and the rate of unscheduled repeat visits markedly reduced (7.1% vs 25.0%; $p < 0.05$). Hospitalisation rates were lower in Group B (7.1% vs 12.5%), though non-significant due to limited sample power. Physician usability ratings strongly favoured the spacer (4.6 vs 2.4; $p < 0.001$), with superiority in procedure duration, child cooperation, and

tolerability – most pronounced in children aged 2-5 years. No severe adverse effects were recorded in either group. Baseline asymmetries – higher male proportion in Group B (64.3% vs 56.3%) and more first-episode cases (21.4% vs 6.3%) – and the absence of formal severity stratification within groups represent methodological limitations. Future prospective multicentre RCTs stratified by age, sex, and severity grade with standardised caregiver technique assessment are needed to confirm these findings and to determine whether the spacer's efficiency advantage translates into a significant reduction in hospitalisation rates.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Порівняльна клінічна ефективність та процедурна результативність небулайзера та клапанної утримувальної камери при дитячому обструктивному бронхіті

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Анотація. Обструктивний бронхіт залишається частою причиною гострого респіраторного дистресу в педіатричній практиці. Хоча бронхолітики є «золотим стандартом» лікування, вибір між небулайзером і дозованим аерозольним інгалятором під тиском (pMDI) із клапанною утримувальною камерою й надалі є предметом клінічних дискусій, особливо щодо дітей молодшого віку. У цьому проспективному обсерваційному дослідженні було обстежено когорту з 30 дітей віком 2-8 років з метою порівняння клінічної ефективності та зручності використання цих методів доставки. Група А (n = 16) отримувала сальбутамол через струминний небулайзер, тоді як група В (n = 14) використовувала pMDI зі спейсером типу Vortex. Попри зіставні вихідні характеристики (p > 0,05), у групі В спостерігалися швидша клінічна стабілізація, вищий рівень співпраці дітей та зменшення загальної кількості необхідних інгаляцій. Примітно, що частота повторних медичних звернень і госпіталізацій була нижчою у групі спейсера (по 7,1 % для кожного показника) порівняно з групою небулайзера (25,0 % і 12,5 % відповідно). Отримані результати свідчили, що pMDI зі спейсером є високоефективним основним засобом для лікування епізодів легкої та середньої тяжкості в амбулаторних і домашніх умовах. Небулайзерну терапію доцільно резервувати для тяжких клінічних випадків або пацієнтів зі значною гіпоксією та труднощами координації, які зазвичай потребують клінічного нагляду. Інтеграція спейсерів у протоколи первинної медичної допомоги може оптимізувати ефективність лікування та зменшити навантаження на стаціонари, забезпечуючи надійне ведення менш тяжких обструктивних станів

Ключові слова: бронхообструктивний синдром; респіраторні захворювання; бронхолітики; спейсер

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Anti-smoking programmes in dentistry: A comparative analysis of approaches in Ukraine and the EU countries

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Abstract. The aim of the study was to compare approaches to tobacco smoking prevention in dental practice in Ukraine and the European Union countries. The study was carried out as an analytical review of the literature with elements of comparative analysis, within which 38 sources were processed for the period 2005-2026; the analysis studied the dental consequences of tobacco smoking and approaches to preventive counselling, the practices of Ukraine and the European Union countries were compared, and the generalisation formulated common features, differences, and directions for adapting European experience. The analysis of the sources showed that tobacco smoking and the use of alternative nicotine products are associated with a complex of dental changes that include periodontal tissues, oral mucosa, oral hygiene status, dental hard tissues and restorative materials. It was found that dental practice has a preventive potential for early detection of tobacco use, brief counselling and support for smoking cessation, however, the level of formalisation of such interventions is uneven. In Ukraine, the general regulatory framework for tobacco control is more clearly presented, while in the European Union countries, professional guidelines, educational support and structured counselling models are more clearly traced. It was determined that the most realistic directions for adapting European experience to Ukrainian dental practice are standardisation of preventive counselling, routine assessment of tobacco status, professional training of dentists and implementation of brief clinical algorithms. The results confirmed the feasibility of integrating anti-smoking interventions into routine dental practice and adapting structured European approaches to the Ukrainian context. The obtained data can be used by dentists, teachers of higher medical education institutions, health care organisers, developers of clinical recommendations and postgraduate training programmes to improve preventive counselling, professional algorithms of actions and organisation of anti-smoking interventions in dental care

Keywords: tobacco; nicotine; periodontium; oral cavity; preventive counselling; tobacco smoking; alternative nicotine products

Introduction

Tobacco smoking remains a common behavioural factor that is directly associated with damage to oral tissues, worsening of dental diseases and reduced treatment effectiveness. According to the World Health Organisation (WHO), in 2024, 24.1% of adults in the European Region used tobacco, which corresponded to 173 million people [1]. In Ukraine, in 2024, the prevalence of cigarette smoking among the adult population was 17.8%, and the total current use of tobacco and nicotine products reached 26.0%, including 5.3% of e-cigarette users and 2.6% of consumers of heated tobacco products [2]. Under such conditions, insufficient integration of anti-smoking approaches into dental care can lead to late detection of tobacco-associated changes, progression of periodontal pathology, deterioration of dental hard tissues and oral mucosa, reduced effectiveness of therapeutic and preventive measures, and an increase in the frequency of repeated clinical interventions.

The impact of smoking on the oral cavity is manifested both in the formation of periodontal lesions and in broad-

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er changes in dental status. As shown by I.S. Lisetska & M.M. Rozhko [3], smoking is associated with an increased risk of periodontal tissue diseases. The authors found that tobacco exposure is accompanied by impaired microcirculation, changes in vascular response, weakening of local tissue resistance and an increase in the frequency of periodontal lesions, which contributes to the chronicity of the pathological process. In the work of N.B. Kuzniak *et al.* [4], the authors investigated the structure and prevalence of periodontal tissue diseases in smokers who used tobacco heating devices. The results showed that the use of such devices does not eliminate periodontal risk, but is associated with an increased frequency of periodontal tissue lesions and variability of the clinical forms. The impact of alternative nicotine products on objective and subjective indicators of oral health was studied by L.S. Kryvenko *et al.* [5]. Scientists proved that alternative nicotine products are also accompanied by negative changes in dental status, which confirms the harmful effects not only of traditional nicotine consumption, but also of modified nicotine.

Clinical and hygienic changes in tobacco use vary in severity depending on the type of product consumed, the age of patients, and behavioural characteristics of oral care. In the article by B. Kravchenko [6], the incidence of dental caries, the number of extracted and filled teeth, and hygiene indices in different groups of smokers were compared. The results of the study showed that the nature of dental disorders depends on the type of product consumed: cigarette smokers had the highest values of the index of carious, filled, and extracted teeth, users of tobacco heating systems had the most pronounced accumulation of soft plaque and tartar, and smokeless tobacco users had the highest rates of gingivitis. The state of oral hygiene and the level of sanitary and hygienic knowledge in adolescents and young adults who smoke were analysed by I.S. Lisetska & M.M. Rozhko [7]. Scientists found that the combination of poor oral hygiene with insufficient preventive awareness contributes to the accumulation of dental plaque, increased inflammatory changes in periodontal tissues and an increased likelihood of progression of dental pathology at a young age. In the study of O.M. Boychenko *et al.* [8], the prevalence of dental diseases in young people was characterised. The authors identified the frequency of pathology of dental hard tissues and inflammatory periodontal lesions, which gives grounds to consider young age as a period of increased sensitivity to the action of adverse behavioural factors.

The use of electronic cigarettes and heated tobacco products expands the range of dental problems, since the impact covers not only periodontal status, but also the conditions of clinical management of patients and the condition of dental hard tissues. Ya.T. Vasylyshyn [9] investigated the condition of periodontal tissues in young people who used electronic devices for smoking. As a result, it was found that the use of such devices is accompanied by a deterioration in periodontal indicators, and with an increase in the duration of the use, the severity of pathological changes increases. Dental and anaesthetic problems in nicotine-dependent individuals were summarised by O.V. Kravets *et al.* [10]. The authors showed that nicotine addiction is combined not only with damage to the organs and tissues of the oral cavity, but also with complications in the clinical management of patients, in particular during anaesthetic support of dental interventions. The effect of cigarette smoke and aerosol from heating tobacco on the colour stability of hard tooth tissues and restorative materials was studied by F. Zanetti *et al.* [11]. The researchers proved that both types of aerosol loading worsen the colour stability of enamel, dentin and composite materials, which expands the understanding of the dental consequences of tobacco exposure from the periodontal level to aesthetic and restorative aspects.

Despite the existence of works devoted to the dental consequences of smoking and the use of alternative nicotine products, information on preventive and advisory practices in dentistry, taking into account the differences between Ukraine and the countries of the European Union (EU), remains insufficiently systematised. The aim of the study was to identify and study the features of anti-smoking approaches in dentistry in Ukraine and the EU countries. The objectives of the study were as follows: to analyse the dental consequences of smoking and the use of alternative nicotine products as a basis for anti-smoking interventions; to generalise approaches to prevention, counselling and reducing tobacco exposure in dental practice in Ukraine and the EU countries; to identify common features, differences, and directions for adapting European experience to Ukrainian dental practice.

Materials and Methods

The study was conducted as an analytical review of the literature with elements of comparative analysis. The subject of the study was approaches to the prevention of smoking in dental practice, forms of the implementation at the clinical, organisational and preventive levels, as well as the features of the integration of anti-smoking interventions into dental care in Ukraine and the EU. The element of comparison was not individual countries of the European Union, but regulatory and professional approaches common in EU countries. The choice of such a comparison format was due to the need to compare the Ukrainian experience with models characterised by a higher degree of legal regulation, professional standardisation of preventive counselling and institutionalisation of the participation of the dentist in smoking cessation.

The search for sources was carried out in scientometric and bibliographic databases (PubMed, Scopus, Web of Science, Google Scholar) in Ukrainian and English using the following keywords and search queries: "tobacco smoking and dentistry", "tobacco prevention in dentistry", "anti-smoking approaches in dental practice", "smoking and periodontitis", "electronic cigarettes and oral health", "smoking cessation in dentistry", "tobacco prevention in dental practice", "dentist-delivered smoking cessation", "smoking and periodontal disease", "heated tobacco products and oral

health", "e-cigarettes and oral health", "anti-smoking interventions in dental care". The review included publications that were relevant to the research topic, contained data on the dental consequences of tobacco smoking or alternative nicotine use, covered preventive, advisory or organisational approaches in dentistry, were published in Ukrainian or English, and had full text in open or institutional access. Exclusion criteria were duplicate entries, publications without a clear connection to dental practice, sources without available full text, short abstracts without sufficient description of the results, and materials that considered tobacco smoking without analysing the dental context.

In addition to scientific publications, the analysis included the official WHO analytical report for 2020, dedicated to assessing the state of tobacco control in Ukraine and the possibilities for its further development [12], the current Law of Ukraine No. 2899-IV [13], which regulated measures to prevent and reduce the use of tobacco products and the harmful effects on the health of the population, the Council of the European Union recommendation document [14] on an environment free of tobacco smoke and aerosols, as well as professional documents of the FDI World Dental Federation [15; 16], which defined approaches to smoking cessation in dental practice and the role of the dentist in such an intervention. The selection of sources was carried out in three stages: at the first stage, a search, and initial extraction of records by keywords were carried out; at the second stage, the title, annotation, and relevance to the topic were assessed; in the third – analysis of full texts and final formation of the corpus of sources for the review. The selection was carried out by two reviewers with higher medical education and experience in preparing scientific review publications in the field of dentistry and public health; agreement on controversial positions was achieved through repeated independent review and discussion until consensus was reached. The final review included 38 sources published during 2005 – January 2026.

The work used a complex of general theoretical methods of cognition, which ensured consistent processing and interpretation of the selected sources. The analysis studied the dental consequences of smoking [17-19] and the use of alternative nicotine products [20-22], the content and forms of preventive counselling in dentistry [23; 24], features of dentist participation in smoking cessation [25-27], as well as ways of implementing anti-smoking interventions in routine dental care [28; 29]. The synthesis method was used to combine disparate information into a holistic view of the structure of anti-smoking approaches in dental practice, including clinical, preventive and organisational components. The comparison was used to compare approaches to tobacco prevention in dentistry, represented in Ukraine by regulatory, preventive and informational and clinically oriented, but less formalised approaches to dentist participation in anti-smoking counselling [12; 30], and in the European professional space – by regulatory and recommendation, professionally standardised, structured clinical counselling and integrated approaches [14-16]. The comparison was carried out according to the criteria of regulatory support for anti-smoking measures, professional regulation of the participation of the dentist in smoking cessation, forms, and level of standardisation of preventive counselling, as well as the degree of integration of anti-smoking interventions into routine dental care. The abstraction method made it possible to identify the most representative features of anti-smoking practices, which were important for comparative assessment. The generalisation method was used to formulate final provisions on common features, differences, limitations and promising directions of adapting European experience to dental practice in Ukraine.

Results and Discussion

Dental consequences of tobacco smoking and the use of alternative nicotine products. The dental dimension of tobacco smoking is determined by the fact that tobacco use affects not only the general state of health, but also the structures of the oral cavity, the course of inflammatory processes, oral hygiene status, aesthetic characteristics of teeth and long-term results of restorative treatment. The analysis showed that conventional cigarette smoking, e-cigarette use and heated tobacco products were considered factors that could change the clinical course of dental pathology, rather than merely accompany it [20; 22]. That is why the study of the dental consequences of tobacco and nicotine consumption is a necessary prerequisite for substantiating anti-smoking interventions in dental practice.

Periodontal disorders are one of the main dental consequences of tobacco smoking. The analysis revealed that smoking is associated with a deterioration in periodontal status, an increase in the frequency of periodontal tissue lesions and a less favourable course of the inflammatory process [31; 32]. Such changes indicate that tobacco exposure affects not only the occurrence of periodontal pathology, but also its clinical dynamics, deepening structural and functional disorders in periodontal tissues. It was also found that the relationship between smoking, periodontal pathology and other systemic disorders is multicomponent, since periodontal damage is combined with broader negative effects of tobacco exposure on the body [19]. This makes it possible to interpret periodontal changes not as a local isolated process, but as a component of the complex pathological impact of tobacco smoking. Separately, it was observed that the use of tobacco heating systems does not eliminate the risk of periodontal changes, but only changes the format of tobacco exposure [31; 32]. Such results are consistent with the work of P.J. Ford & A.M. Rich [17], in which tobacco smoking was presented as a factor in a wide range of oral lesions, including periodontal diseases. Similarly, D.A. Apatzidou [18] emphasised that the role of smoking is not only related to the development of periodontal disease, but also to the outcomes of dental treatment, in particular implant therapy, which expands the clinical understanding of tobacco exposure from an etiological factor to a predictor of the course and prognosis of treatment.

Deterioration of oral hygiene is one of the most reproducible dental consequences of tobacco exposure. Smoking was associated with poorer oral hygiene, a higher likelihood of gingival inflammation, and a general deterioration in dental status, suggesting a combination of clinical and behavioural risk factors [33]. The analysis demonstrated that adverse dental manifestations associated with tobacco smoking are recorded not only in adults, but also in adolescents and young adults (up to 18 years of age), i.e., at the stage of early formation of stable behavioural patterns [34]. This gives grounds to consider young age as a period in which tobacco exposure is already reflected in the clinical condition of the oral cavity. In addition, it was shown that the level of patients' awareness of the consequences of smoking for the oral cavity and attitudes towards quitting smoking are directly related to the preventive capabilities of the dental appointment [35]. In this context, S. Gajendra *et al.* [26] emphasised that the detection of such changes during a dental appointment creates grounds for early counselling and involvement of the dentist in supporting smoking cessation. Thus, hygiene violations, early appearance of adverse dental changes and insufficient preventive awareness form an interconnected clinical and preventive complex that enhances the need for early dental intervention.

A separate area of analysis covered the dental consequences of using alternative nicotine products. The analysis of sources showed that electronic cigarettes and vaping are associated with changes in oral status, in particular with changes in the oral mucosa, xerostomia, and potential deterioration of periodontal status [21; 36]. This indicates that the effect of new nicotine products extends simultaneously to several aspects of oral health and is not reduced to an isolated local effect. It was also found that the systematic data do not provide grounds to interpret electronic cigarettes and heated tobacco products as safe for dental health [22]. Therefore, it is advisable to consider electronic cigarettes and heated tobacco products not as a neutral replacement for traditional smoking, but as another format of nicotine exposure with its own spectrum of clinical consequences. Along with this, it was emphasised that the clinical assessment of new nicotine products should take into account not only short-term effects, but also potential long-term changes in oral tissues [20; 22]. Similarly, O. Bilynskyi *et al.* [37] concluded that electronic nicotine delivery systems have an adverse effect on the oral cavity, which confirms the need to consider these systems as a separate dental risk factor, and not as a safe alternative to traditional smoking. Therefore, during a dental examination, the use of electronic cigarettes and heated tobacco products requires separate clinical consideration when assessing the state of oral tissues and planning preventive counselling.

Changes in dental hard tissues and restorative materials are also among the dental consequences of tobacco exposure. Electronic cigarettes and heated tobacco products affect the colour parameters of teeth, changing the aesthetic characteristics and potentially worsening the appearance of the dentition [38]. This indicates that the effect of new nicotine products extends not only to soft tissues and inflammatory processes, but also to indicators that are important for the aesthetic assessment of dental status. The impact of traditional smoking and new tobacco products on materials manufactured using computer-aided design and computer-aided milling technologies was also found, indicating the possibility of changing the properties during use [39]. Similarly, K.F. Irusa *et al.* [21] pointed out that the assessment of the consequences of using electronic cigarettes should include not only pathological changes in the tissues of the oral cavity, but also clinical aspects that may affect the results of dental interventions. Therefore, tobacco and nicotine exposure should be considered as a factor that can affect not only the development of dental pathology, but also the long-term aesthetic and functional prognosis of restorative treatment. To summarise the dental consequences of smoking and the use of alternative nicotine products, these consequences are presented in Table 1.

Table 1. Tobacco exposure factors and dental manifestations

Factors	Manifestations (consequences)
Traditional tobacco smoking	deterioration of periodontal status, higher frequency of periodontal tissue lesions, less favourable course of periodontal pathology
Use of electronic cigarettes, vaping, and heated tobacco products	changes in the oral mucosa, xerostomia, potential deterioration of periodontal health
Tobacco and nicotine exposure as a factor in oral hygiene disorders	worse oral hygiene indicators, signs of gingivitis, general deterioration of dental status
Tobacco and nicotine exposure as a factor in aesthetic and material-related changes	changes in tooth colour parameters, deterioration of aesthetic characteristics of restorations, impact on the properties of dental materials

Source: compiled by the author based on C. Schwarz *et al.* [19], D. Cichońska *et al.* [20], N. Camoni *et al.* [22], I.D. Kiiun [31], I. Mišković *et al.* [32], A. Beklen *et al.* [33], D. Olczak-Kowalczyk *et al.* [34], A.B. More *et al.* [35], S. Niemczyk *et al.* [36], S. Gupta *et al.* [38], F. Makkeyah *et al.* [39], P.M. Duarte *et al.* [40]

The data in Table 1 showed that the dental manifestations of tobacco and alternative nicotine exposure are multilevel in nature and are not limited to periodontal pathology. The most consistent sources trace changes in periodontal tissues, but alongside these changes, there are disturbances in oral hygiene status, changes in the mucous membrane, as well as aesthetic and material effects. This means that the patient's tobacco status should be taken into

account during a dental examination as a clinically significant factor that affects the course of the disease, the choice of treatment tactics and the prognosis of its results. Thus, the results showed that smoking and the use of alternative nicotine products form a complex of dental changes that has not only diagnostic but also preventive significance. This justifies the feasibility of integrating preventive counselling and anti-smoking interventions into dental practice.

Preventive counselling and dentist participation in smoking cessation. Preventive counselling in dentistry is considered one of the areas of reducing tobacco exposure, since the dental appointment combines the possibilities of detecting tobacco consumption and assessing its consequences for the oral cavity. Direct contact with the patient makes it possible to link the detected dental changes with tobacco exposure and use this as a basis for motivation to quit smoking. In this regard, the participation of the dentist includes informing about the risks, brief preventive interventions, supporting behavioural changes and integrating anti-smoking practices into routine dental care. In preventive counselling in dentistry, it is advisable to distinguish several interrelated approaches: screening and identification, informational and motivational, brief structured intervention, guidance, and support and integrated routine. This classification reflects the sequence of actions of the dentist – from identifying the patient's tobacco status to primary behavioural support and organising further care.

Dental practice provides the conditions for early detection of tobacco use and preventive counselling, as it is during the examination that the effects of smoking on the tissues of the oral cavity can be visualised. The analysis of sources showed that the dental office is considered a suitable environment for brief anti-smoking interventions, motivational talk and referral of the patient to further care [25; 27]. The participation of the dentist in smoking cessation is associated not only with a preventive but also with a clinical function, since the discussion of tobacco status is integrated into the assessment of dental health [23]. This means that counselling in dentistry is considered as part of the professional interaction with the patient, and not as an activity external to the treatment. In this context, R. Holliday *et al.* [41] showed that the effectiveness of the dentist's advice depends on how it is perceived by the patient within the clinical interaction. Therefore, the participation of the dentist in smoking cessation has an informational and communicative-motivational dimension. Within the proposed classification, this stage corresponds to the screening-identification approach, in which the dentist detects the fact of tobacco consumption, records its connection with the clinical condition of the oral cavity and transfers the topic of smoking from an optional discussion to the level of a clinically significant parameter.

The content of preventive counselling in dentistry includes several sequential actions: detecting the fact of tobacco consumption, briefly informing about the risks to the oral cavity, assessing the patient's readiness for change and providing initial motivational support [23; 27]. It was found that the effectiveness of such counselling increases when the dentist's recommendation is specific, tied to the identified clinical changes and understandable to the patient [25]. In addition, it was found that the preventive potential of the counselling increases if the topic of smoking is systematically raised, rather than its episodic mention [27]. A comparison of these data is consistent with the conclusions of B.W. Chaffee *et al.* [24] that dental counselling should cover a wider range of nicotine and behavioural risks, and therefore requires a clear communicative structure. Preventive counselling in dentistry is a structured process, the effectiveness of which depends on the content of the message, the way it is presented and the connection to the clinical situation. This segment corresponds to the information-motivational approach, the essence of which is to provide the patient with a brief, clinically relevant and personalised message about the consequences of smoking for the oral cavity and the benefits of quitting smoking.

A separate area of research concerns briefs anti-smoking interventions that can be implemented directly into routine dental care. It was established that brief intervention models involve the detection of smoking, brief advice on quitting, recording readiness for change and offering additional support or referral [28]. The use of such a tool in public dental services is practically feasible and does not require a radical restructuring of the usual appointment [28]. In dental research protocols, there is a tendency to compare very brief counselling with extended intervention models, indicating the development of this direction from the general idea of counselling to the testing of specific formats of care [29]. In this regard, J.A. Alblowi & H. Mohamed [23] actually confirmed that brief advice is clinically appropriate if it is embedded in standard patient interactions. In contrast, J. Byakodi [27] considered brief intervention as a basic professional tool capable of initiating further smoking cessation even in the limited time of the dental appointment. Therefore, brief anti-smoking interventions have not only conceptual but also practical applicability in dentistry. The above provisions correspond to a brief structured intervention approach, which includes four basic components: identification of tobacco use, brief clear advice to stop smoking, assessment of the patient's readiness for change, and provision of initial support or referral. This approach is the most suitable for routine dental practice, as it does not require a long time, a separate consultation visit, or a specially created infrastructure.

The analysis of sources showed that the effectiveness of the dentist's participation in smoking cessation depends on the motivational component of the counselling. Linking the advice to the patient's real dental status, visual changes in the oral cavity and the prognosis of treatment increases the persuasiveness of the intervention [25]. It was observed that the dental appointment has the potential to influence the patient's attitude towards smoking, precisely by demonstrating the direct consequences of tobacco exposure for oral health [27]. The participation of the dentist is interpreted as a form of primary behavioural support, and not

only informing about the harms [25]. Similarly, S. Rajput *et al.* [42] established that counselling on smoking cessation is part of the professional tasks of the dentist and requires practical readiness to implement it in everyday clinical work. At this stage, preventive counselling takes on the characteristics of a guidance-supportive approach, as the dentist not only informs the patient, but also initiates further movement towards behaviour change by supporting the intention to quit smoking, re-raising the topic during subsequent visits, or referring to other available forms of care.

Along with the possibilities of implementation, the literature also highlighted barriers to the implementation of such practices. It was found that these include insufficient training of dentists, uncertainty about the dentist's own role, limited appointment times, lack of established algorithms, and insufficient inclusion of this topic in professional education. Gaps in knowledge and skills are already evident at the undergraduate level, which may further reduce the dentist's readiness for behavioural counselling [43]. With the availability of a short-standardised tool and organisational support, these barriers can be partially overcome [28]. In this context, A. Beklen *et al.* [33] linked the assessment of oral health with the issue of supporting smoking cessation, which indicates the possibility of integrating this practice into clinical interaction. Thus, the barriers are educational and organisational in nature, but do not exclude the real implementation of anti-smoking counselling in dentistry. From a practical point of view, the most realistic approach for Ukrainian dental care is an integrated routine approach, in which preventive counselling is not separated into an independent resource-intensive service, but is built into a standard dental appointment. Given the organisational limitations of the health care system, it is advisable to use very brief standardised interventions that can be implemented without significantly increasing the duration of the visit. Given the staffing constraints and the unequal level of training of dentists, the implementation of short action algorithms, templates for recording the patient's smoking status, and targeted training modules in undergraduate and postgraduate education is of paramount importance. Given resource constraints, a more realistic implementation model is a phased approach that does not require the creation of separate offices or dedicated services in dental facilities, but involves routine inquiry about smoking status, brief personalised advice, and, if necessary, referral to a family doctor or other available smoking cessation support services. This is the adaptation model that combines clinical feasibility, organisational feasibility, and relatively low resource cost.

Thus, a review of the literature suggests that preventive counselling in dental practice includes tobacco use screening, brief structured interventions, motivational support, and the possibility of further referral. Dentist participation in smoking cessation is based on clinical feasibility, communicative readiness, and the availability of organisational conditions for such activities. The generalised classification of approaches to preventive counselling in dentistry includes screening and identification, informational and motivational, brief structured intervention, guidance and support, and integrated routine approaches. This makes it possible to consider dental practice as a real tool for reducing tobacco exposure, provided that it is professionally regulated and standardised intervention models are implemented. For Ukrainian practice, the most appropriate is the phased implementation of integrated brief counselling models, adapted to the limitations of the appointment time, the level of personnel training, and the available resources of the health care system.

Comparative characteristics of approaches in Ukraine and EU countries. Approaches to tobacco prevention in dental practice in Ukraine and the EU differ in the level of regulatory support, professional regulation and the degree of inclusion of the dentist in the process of smoking cessation. These differences are traced in the forms of preventive counselling, the nature of professional recommendations, approaches to limiting tobacco and nicotine products, as well as in the level of integration of anti-smoking interventions into routine dental care. The comparative analysis showed that between Ukrainian practice and the approaches presented in the European professional space, there are differences in regulatory support, professional regulation of the role of the dentist, forms of preventive counselling and the level of integration of anti-smoking interventions into routine dental care. That is why a comparison of Ukrainian and European experience is necessary to identify common features, differences, and practices that may be relevant for dental prevention.

The results of the analysis showed that in Ukraine, the regulatory framework for tobacco control is available and sufficiently clearly formulated at the national level. This was observed both in the World Health Organisation report on the assessment of the state of tobacco control in Ukraine and in the current legislation regulating measures to prevent and reduce the use of tobacco products and the harmful effects on the health of the population [12; 13]. This regulatory framework is primarily focused on the regulation of tobacco products, limiting the use and protecting the population from smoke exposure, and not on the detailed implementation of dental-oriented anti-smoking practices. This coincides with the conclusions of I. Demchenko & P. Vasylkivskyi [30] that in Ukraine there are already mechanisms to assist individuals who want to quit smoking, but these mechanisms need a clearer connection with clinical environments, in particular dental ones. A. Skipalskyi *et al.* [44] considered the Ukrainian context as one in which tobacco control is developing under the influence of complex external circumstances, which further complicates the stable implementation of preventive practices. Thus, in Ukraine, the normative field is more pronounced than the level of dental operationalisation of anti-smoking interventions. Thus, the Ukrainian context is more characterised by regulatory and general preventive approaches, while the clinical integration of the dentist into the system of assistance for smoking cessation remains less formalised.

In contrast, sources related to the European professional space show a higher level of combination of regulatory and professional regulation. It was found that the EU Council recommendation document on smoke-free environments and aerosols reflects the desire to extend control not only to traditional smoking, but also to new formats of tobacco and nicotine consumption [14]. The professional documents of the World Dental Federation explicitly define the role of dental professionals in smoking cessation and offer guidelines for integrating relevant interventions into practice [15; 16]. This means that in the European space, the dentist is considered not only as a specialist who records the dental consequences of smoking, but as a formalised participant in preventive intervention. In this context, D. Gurung *et al.* [45] consistently emphasised that the dental professional has professional grounds for systematic participation in the anti-smoking system. Similarly, H. Bendotti *et al.* [28] showed that brief interventions can already be built into public dental services as a routine tool. Therefore, the formalisation of the dentist's role at the interface of professional recommendation and organisational implementation is more characteristic of the European professional space. Thus, the normative-recommended, professionally standardised and integrated clinical approaches to anti-smoking interventions in dentistry are more clearly presented in the European space.

A comparison of forms of preventive counselling showed that in the Ukrainian context these forms are mostly described as a promising or necessary direction, while in European sources – as an already structured tool of clinical practice. In the analysed Ukrainian materials, the emphasis is on general promotion of smoking cessation, informing the population and strengthening the preventive component of health care [30; 46]. In contrast, in sources reflecting European professional experience, very brief counselling, short clinical algorithms, assessment of the patient's readiness for change and the connection of counselling with routine dental appointments were more clearly traced [28; 29]. This difference is fundamental, as it indicates not only a different level of description of practices, but also a different degree of the institutional maturity. J.A. Alblowi & H. Mohamed [23] showed that the perception of tobacco counselling by dentists is already part of the plane of professional self-identification. In contrast, S. Rajput *et al.* [42] demonstrated that even with awareness of the dentist's role, the practical implementation of counselling depends on the readiness of the specialist, that is, on the transition from declarative recognition to real practice. Thus, the main difference is that in the European space, counselling is more often presented as an algorithmised practice, and in the Ukrainian space – as a less formalised direction of prevention. In agreement with this conclusion with the previously presented classification of approaches to preventive counselling, it can be stated that in Ukrainian practice, screening-identification and general information-motivational components prevail, while in the European professional space, brief structured intervention, guidance-support and integrated routine approaches are more clearly represented.

The comparative analysis also revealed a difference in the degree of professional training and educational support of anti-smoking interventions. In the European academic environment, dental students' knowledge about smoking, the attitude towards smoking cessation programmes and the effectiveness of special training modules are separately considered [47; 48]. This indicates the inclusion of the topic of smoking cessation in the educational and professional discourse. In works related to Ukraine, the emphasis is more often on general mechanisms of assistance and preventive awareness of patients than on the formal training of dentists in anti-smoking counselling [30; 46]. This coincides with the results of S.E. Vollath *et al.* [47], who showed that a specially designed training module can improve the readiness of future dentists to help with smoking cessation. Similarly, C. Bauer-Kemeny *et al.* [49] found that the level of knowledge about the risks of smoking and its prevention among dental students is insufficient and requires targeted educational reinforcement. So, another difference between Ukraine and the European professional space is that in the European environment the problem is more often institutionalised already at the stage of professional training, while in Ukraine it is more represented in the plane of general prevention and information. The differences between anti-smoking approaches in Ukraine and the EU are summarised in Table 2.

Table 2. Comparative characteristics of anti-smoking approaches in dentistry

Criterion of comparison	Ukraine	European professional space
Regulatory support	there is a national legal framework for tobacco control; emphasis on regulating tobacco use and protecting the population	supranational guidance documents on smoke-free and aerosol-free environments are available
Dentistry-specific professional guidelines	limitedly represented, the general preventive context prevails	specialised professional guidelines for dentists are available
Forms of preventive counselling	less formalised, more often described as a necessary direction of development	more structured; brief interventions, very brief counselling algorithms, clinical referral models are used
Role of the dentist in smoking cessation	justified by clinical feasibility and preventive potential	formalised as a professional function of the dental professional

Continued Table 2

Criterion of comparison	Ukraine	European professional space
Educational integration	less pronounced	separately researched and supported through training modules and assessment of student training

Source: compiled by the author based on World Health Organisation [12], Law of Ukraine No. 2899-IV [13], Council of the European Union [14], FDI World Dental Federation [15; 16], J.A. Alblowi & H. Mohamed [23], H. Bendotti *et al.* [28], R. Holliday *et al.* [29], I. Demchenko & P. Vasylkivskyi [30], D. Gurung *et al.* [45], S.E. Vollath *et al.* [47], E. Rodakowska *et al.* [48], C. Bauer-Kemeny *et al.* [49]

The data in Table 2 showed that the differences between Ukraine and the European professional space are most clearly visible in the level of dental operationalisation of anti-smoking approaches. In Ukraine, the regulatory framework of the general anti-tobacco policy is well presented, but dental intervention models are described less formally. In the European professional space, along with regulatory recommendations, professional and educational reinforcement of the dentist's role is observed, and brief anti-smoking interventions are more often presented as routinely suitable. This indicates a higher degree of integration of the dentist into the process of smoking cessation in the European professional space. Thus, the comparative analysis showed that the common orientation towards reducing the tobacco exposure is implemented in Ukraine and the European professional space in different ways. For Ukrainian dental practice, the most realistic is the gradual adaptation of individual elements of European experience, primarily brief clinical interventions, professional algorithms of dentist actions and educational support for the implementation.

The limitations of Ukrainian practice and directions for adapting European experience. The analysis showed that the main limitations of Ukrainian practice in the field of anti-smoking interventions in dentistry are associated with insufficient standardisation of preventive counselling, limited formalisation of the dentist's role, and weak integration of such interventions into routine clinical care. There are no clear algorithms for brief counselling, standardised recording of the patient's tobacco status, and defined routing of individuals who need help in quitting smoking. This indicates that the dental office in Ukraine is viewed as a potential, rather than an institutionally established, environment for preventive intervention. This situation reduces the reproducibility of anti-smoking practices in the dentist's daily work and increases the dependence of the implementation on the individual initiative of the specialist. Additionally, the implementation of such approaches is complicated by organisational, personnel, and resource limitations of the health care system, which reduces the possibility of direct transfer of developed European models to domestic dental practice. Organisational constraints include the lack of standardised action algorithms, insufficient formalisation of patient routing, and weak integration of anti-smoking counselling into the standard clinical route. Staffing constraints are manifested in the uneven level of training of dentists in brief behavioural intervention, the deficit of communication skills in motivational counselling, and uncertainty in the own professional role. Resource constraints are associated with the lack of time within the framework of a regular appointment, the absence of a separate infrastructure for specialised care, and the need to implement new elements of prevention without significantly increasing the burden on the existing dental service.

One of the most notable constraints is the lack of standardisation of preventive counselling in everyday dental work. In the Ukrainian context, a general understanding of the feasibility of helping people who want to quit smoking prevails, but clear clinical steps that the dentist should perform during each appointment are less often described [30]. This situation reduces the reproducibility of preventive practice, since the effectiveness of the intervention begins to depend on the individual initiative of a particular doctor, and not on an established professional algorithm. In the European professional space, on the contrary, there is a tendency to use more structured models – very brief counselling, short clinical algorithms, assessment of the patient's readiness for change and further guidance [15; 28]. It is such algorithmisation that creates the conditions for preventive counselling to become not a random element of the appointment, but its expected component. Given the organisational limitations of Ukrainian practice, the most realistic is the implementation of short standardised algorithms suitable for use during each dental appointment without complex restructuring of the clinical process.

Another limitation of Ukrainian practice is the insufficient formalisation of the role of the dentist as a participant in helping to quit smoking. The emphasis is on general mechanisms for supporting people who want to quit smoking, or on the level of preventive awareness of patients [30; 46]. However, the professional role of the dentist as a specialist who should not only record the consequences of tobacco use, but also initiate behavioural intervention, is not clearly described. In the documents of the World Dental Federation, this role is better defined: the dental worker is considered as a subject of early detection of tobacco use, brief counselling, motivation to quit and inclusion of the patient in the further path of care [15; 16]. This creates an important guideline for Ukraine: the adaptation of European experience should begin not only with individual counselling techniques, but with a clear professional recognition that anti-smoking intervention is part of the dentist's tasks. In practical terms, this means the need for regulatory and organisational consolidation of the minimum scope of

actions of the dentist: routine inquiry about tobacco status, brief advice on smoking cessation and, if necessary, basic referral of the patient to further care.

The educational component also remains a deterrent. The comparison showed that in the European academic environment, the topic of smoking cessation is integrated at the undergraduate and postgraduate levels, where the knowledge of dental students, the attitude to anti-smoking programmes and the results of special training modules are studied separately [47; 49]. This indicates the institutionalisation of the topic even before the young specialist enters independent practice. In Ukrainian publications, the educational aspect is less evident, which indicates the limited preparedness of the dentist to confidently conduct anti-smoking counselling. In this regard, the most realistic areas of adaptation are the inclusion of the topic of tobacco counselling in dentist training programmes, cycles of continuous professional development and internal clinical training. Such a solution is practically achievable, since it does not require a radical restructuring of the dental care system, but it can change the level of readiness of specialists for intervention. Given staffing constraints, priority is given to short training modules, typical counselling scenarios, internal protocols and postgraduate educational formats aimed at developing basic competencies: identifying tobacco status, briefly explaining dental risks, assessing patient readiness for change and providing basic referrals. This approach is important in conditions where dentists work in different organisational circumstances, have different previous experience and cannot always undergo long-term specialised training.

The issue of routine integration of anti-smoking interventions into dental practice also requires attention. Based on a comparison of Ukrainian and European experience, it can be argued that one of the most realistic steps for Ukraine is to include an assessment of tobacco status in a standard patient survey. Such an action is technically not difficult, but has high practical value, since it moves the problem from the level of an optional conversation to the level of a mandatory clinical parameter. The next step could be a short-standardised counselling tied to specific dental changes identified during the examination. The advantage of this approach is that it uses the existing clinical situation as an argument for motivating the patient and does not require a separate long visit. Further implementation may include the development of local algorithms for referring the patient to a family doctor, addiction treatment specialist, or appropriate smoking cessation support programmes. It is this kind of phased integration that seems more realistic for Ukrainian practice than an attempt to introduce comprehensive multi-component models all at once. Given resource constraints, it is important that such a model does not require the creation of separate offices, additional staff, or specialised infrastructure, but can be implemented within the existing clinical practice. That is why the most appropriate model for Ukrainian dental practice is a resource-saving implementation model that combines standardised inquiry about tobacco status, brief personalised advice, recording the answer in clinical documentation, and a simple mechanism for further referral. A flowchart is presented to summarise the logic of adapting European experience to Ukrainian dental practice (Fig. 1).

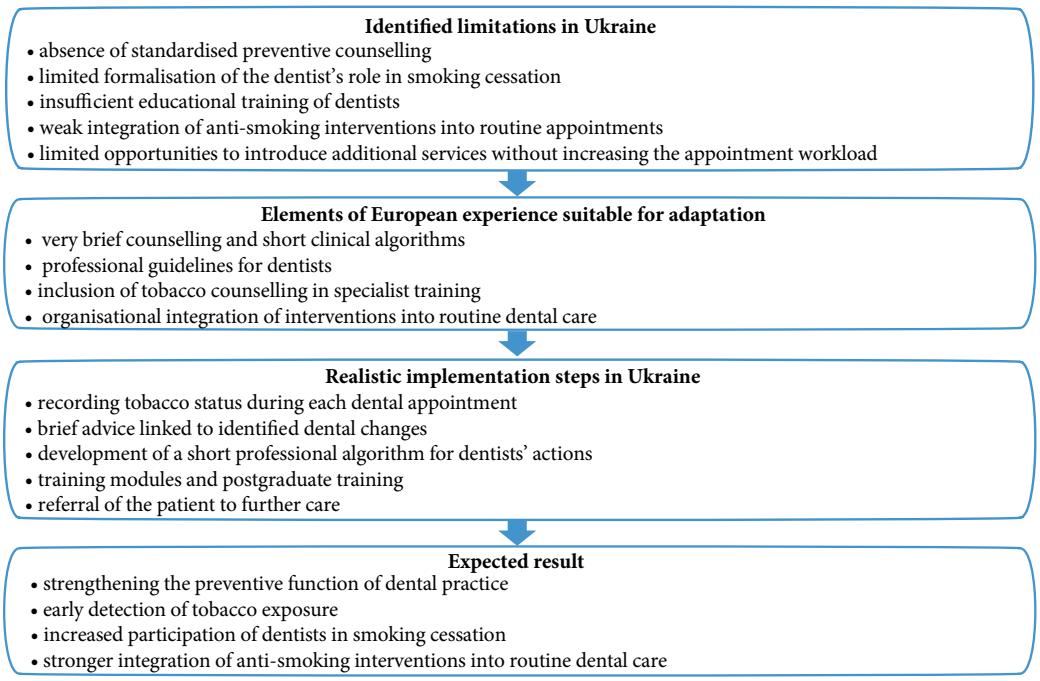

Figure 1. Step-by-step adaptation of the European standard in Ukrainian dentistry
Source: compiled by the author based on World Health Organisation [12], Law of Ukraine No. 2899-IV [13], Council of the European Union [14], FDI World Dental Federation [15; 16]

The above flowchart shows that the adaptation of European experience does not require mechanical transfer of all models in an unchanged form. A more appropriate step-by-step approach is one that first eliminates the most obvious gaps: the lack of a standardised question on tobacco status, the lack of short action algorithms and insufficient training of dentists. After that, elements of routing, postgraduate training and professional regulation can be expanded. Such a sequence is realistic for the Ukrainian context, as it combines clinical feasibility with organisational feasibility. The practical value of this model is that each subsequent stage can be implemented without a critical increase in the load on dental appointment and without the need for significant additional resources. Thus, the adaptation of individual European approaches can become practically achievable by strengthening the preventive function of dentistry in Ukraine and increasing the role of the dentist in the system of assistance for smoking cessation.

In general, the results of the analysis showed that smoking and the use of alternative nicotine products have a multi-vector negative impact on the condition of the oral cavity, covering periodontal tissues, mucous membrane, oral hygiene status, dental hard tissues and the results of restorative treatment. It was established that dental practice has real potential for early detection of tobacco consumption, preventive counselling and support for smoking cessation, however, the level of formalisation of such interventions in Ukraine remains lower than in the European professional space. This gave grounds to consider the standardisation of short clinical interventions, routine assessment of tobacco status, professional training of dentists and adaptation of relevant European models as the most realistic directions for strengthening the preventive function of dentistry. Taking into account the organisational, personnel and resource limitations of the health care system, such changes should be implemented in stages, starting with those solutions that can be integrated into everyday dental practice without structural complications.

Conclusions

The results of the analysis showed that smoking and the use of alternative nicotine products are associated with a complex of dental changes that include periodontal tissues, oral mucosa, oral hygiene status, dental hard tissues and restorative materials. The most consistent link between smoking and worsening periodontal status, a higher incidence of periodontal tissue lesions and an unfavourable course of the inflammatory process, was observed in the sources. It was shown that electronic cigarettes, vaping, and heated tobacco products do not eliminate dental risk, but form a different format of nicotine exposure, which is also accompanied by changes in oral health. Preventive counselling in dental practice includes identifying tobacco status, brief advice on smoking cessation, assessing the patient's readiness for change and further support or referral. It was established that the dental office is a suitable environment for anti-smoking interventions, since clinical changes in the oral cavity enhance the persuasiveness of the preventive message. At the same time, the implementation of such approaches depends on the training of the dentist, the availability of clear algorithms of actions and communicative readiness for behavioural support of the patient.

The comparative analysis showed that Ukraine and the EU countries have a common orientation towards reducing the tobacco exposure, but differ in the level of inclusion of dentistry in this policy. In Ukraine, the general regulatory framework of tobacco control is well presented, however, dental intervention models are less formalised. In the European professional space, along with regulatory recommendations, professional guidelines, educational support and more structured models of brief counselling are observed. This gives grounds to consider the standardisation of preventive counselling, routine assessment of tobacco status, professional training of dentists, development of clinical algorithms and phased integration of anti-smoking interventions taking into account organisational, personnel and resource constraints as realistic directions for adapting European experience to Ukrainian dental practice.

The limitations of the study were that its conclusions were formed on the basis of theoretical generalisation of scientific, normative and analytical sources without involving its own empirical data, which limited the possibility of directly assessing the effectiveness of anti-smoking interventions in real dental practice. Further research should be associated with conducting empirical work aimed at assessing the effectiveness of standardised preventive counselling, brief anti-smoking interventions and patient routing models in routine dental practice in Ukraine.

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Conflict of Interest

None.

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Антисмокінгові програми в стоматології: порівняльний аналіз підходів України та країн ЄС

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Анотація. Мета дослідження полягала у порівнянні підходів до профілактики тютюнопаління в стоматологічній практиці України та держав Європейського Союзу. Дослідження було виконано як аналітичний огляд літератури з елементами порівняльного аналізу, у межах якого було опрацьовано 38 джерел за період 2005-2026 років; за допомогою аналізу вивчали стоматологічні наслідки тютюнопаління та підходи до профілактичного консультування, за допомогою порівняння зіставляли практики України і держав Європейського Союзу, а за допомогою узагальнення формулювали спільні риси, відмінності та напрями адаптації європейського досвіду. Аналіз джерел засвідчив, що тютюнопаління та використання альтернативних нікотинових продуктів пов'язані з комплексом стоматологічних змін, які охоплюють тканини пародонту, слизову оболонку порожнини рота, гігієнічний статус, тверді тканини зубів і реставраційні матеріали. Встановлено, що стоматологічна практика має профілактичний потенціал для раннього виявлення тютюнового споживання, короткого консультування та підтримки відмови від куріння, однак рівень формалізації таких втручань є нерівномірним. В Україні чіткіше представлений загальний нормативно-правовий каркас тютюнового контролю, тоді як у державах Європейського Союзу більш виразно простежуються професійні настанови, освітня підтримка та структуровані моделі консультування. Визначено, що найреалістичнішими напрямами адаптації європейського досвіду до української стоматологічної практики є стандартизація профілактичного консультування, рутинна оцінка тютюнового статусу, професійна підготовка стоматологів і впровадження коротких клінічних алгоритмів. Одержані результати підтвердили доцільність інтеграції антисмокінгових втручань у рутинну стоматологічну практику та адаптації структурованих європейських підходів до українського контексту. Отримані дані можуть бути використані стоматологами, викладачами закладів вищої медичної освіти, організаторами охорони здоров'я, розробниками клінічних рекомендацій і програм післядипломної підготовки для вдосконалення профілактичного консультування, професійних алгоритмів дій та організації антисмокінгових втручань у стоматологічній допомозі

Ключові слова: тютюн; нікотин; пародонт; порожнина рота; профілактичне консультування; тютюнопаління; альтернативні форми паління

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