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Address of the Editorial Board: *Acta Medica Academica*, Academy of Sciences and Arts of Bosnia and Herzegovina, Bistrik 7, 71000 Sarajevo, Bosnia and Herzegovina, Tel.: 00 387 33 560 718, Fax.: 00 387 33 560 703. Contact person: Nerma Tanović, E-mail: amabih@anubih.ba

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COVER PHOTO PICTURE

Vladimir Čavka, an ophthalmologist (Orašje, Bosnia and Herzegovina, 31 October 1900 – Belgrade, Serbia, 3 July 1984). He was one of the founders of the Scientific Society of Bosnia and Herzegovina, its first president (1952–1955), and a full member of the Department of Medical Sciences. After the Scientific Society of Bosnia and Herzegovina was transformed into the Academy of Sciences and Arts of Bosnia and Herzegovina in 1966, he was its full member. He founded the *Medical Archives*, the journal of the Society of Physicians of Bosnia and Herzegovina, and the *Yugoslav Ophthalmological Archives*, the journal of the Ophthalmological Section of the Society of Physicians of Bosnia and Herzegovina – the Association of Ophthalmologists of Yugoslavia. He was the recipient of the Government of Bosnia and Herzegovina Award (1948) and the AVNOJ Award (1967).

AUTHOR INFORMATION

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The Influence of Sociodemographic Characteristics, Lifestyle, and Metabolic Syndrome on Anxiety and Depression Symptoms in Adults in Banja Luka

Verica Petrović[1, 2], Maja Račić[3], Biljana Lakić[1, 2]

[1]Department of Family Medicine, Faculty of Medicine, Banja Luka, University of Banja Luka, Republic of Srpska, Bosnia and Herzegovina, [2]Health Centre Banja Luka, Banja Luka, Republic of Srpska, Bosnia and Herzegovina, [3]Department of Family Medicine, Faculty of Medicine, Foča, Republic of Srpska, Bosnia and Herzegovina

Correspondence: *verica.petrovic@med.unibl.org*; Tel.: + 387 65 638828

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Abstract

Objective. This study aimed to explore the influence of sociodemographic characteristics and lifestyle on the occurrence of anxiety and depression, and the interrelationship between metabolic syndrome (MS) and anxiety and depression. **Methods.** A total of 685 adults were divided into two groups (with and without MS) using the International Diabetes Federation's definition of MS. In both groups, we used the Beck Inventory for Anxiety and Depression. The influence of sociodemographic and other characteristics on the occurrence of MS, anxiety, and depression was observed. The multivariate logistic regression model was appropriate for determining which variables (especially anxiety and depression) affected the presence of MS in the participants. **Results.** MS was observed in 37.5% of participants. Women with mild and severe anxiety were statistically significantly more represented in the group with MS than in the group without MS (26.2% : 12.0%, P=0.001; 16.7% : 4.8%, P=<0.001), as well as women with severe depression (6.3% : 1.9%, P=0.038), while there was no significant difference in men. Sociodemographic characteristics such as female gender, older age, employment status (retirees and homemakers), lower level of education, marital status (divorced and widowed), and more children affected the occurrence of anxiety and depression in participants. Physical inactivity during leisure time, high-risk drinking, and a higher level of cardiovascular risk showed significant influence on the presence of anxiety and depression, while smoking was inversely associated with the presence of depression but not with anxiety. **Conclusion.** The association between MS and anxiety and depression was confirmed. Women with MS were at a higher risk of anxiety and depression symptoms, whereas this was not confirmed in men.

Key Words: Metabolic Syndrome ▪ Anxiety ▪ Depression.

Introduction

The metabolic syndrome (MS) is a pathological condition that includes a collection of biological factors: abdominal obesity, dyslipidaemia, hypertension, and high blood sugar (1). The most common definitions of MS in research and diagnosis are those of the Third Report of the National Cholesterol Education Program (NCEP ATP III), the International Diabetes Federation (IDF) (2), and the World Health Organization (WHO) (1). The main difference between these definitions concerns central obesity values, an obligatory component of the IDF definition, which has a lower borderline value than the National Heart, Lung and Blood Institute and the American Heart Association definitions. The IDF recommended borderline waist circumference values based on sex and ethnic characteristics using numerous studies as data sources (2).

MS incidence is usually associated with obesity and diabetes mellitus type 2 (T2DM). According to data from the Centers for Disease Control and Prevention (CDC) published in 2018, 12.2% of adults in the United States of America (USA) had T2DM, of which a quarter were unaware of their disease. The prevalence of prediabetes or MS is three times higher (3, 4). Global obesity research

conducted in 2015 in 195 countries revealed that 604 million adults and 108 million children suffer from obesity (5).

According to the results of longitudinal studies, people with MS are more likely to suffer from psychological diseases, such as depression (6). The connection between MS and anxiety and depression has specific sex-related characteristics (7). The occurrence of depression and MS was observed in a cross-sectional study conducted from 2000 to 2008 on 5125 relatively healthy women and men during preventive exams at the Cooper Center (Dallas, Texas, USA). Women and men with symptoms of depression had statistically higher MS prevalence compared to those without symptoms of depression (women, 15.4% vs. 7.2%; men, 31.6% vs. 22.8%) (8). However, the direction of causality between MS and depression remains unclear, or it could be said to be bidirectional. Akbaraly et al. evaluated MS (NCEP ATP III criteria) in middle-aged British clerks. They established that of the MS components, central obesity, high triglyceride levels, and low HDL cholesterol levels were associated with symptoms of depression (9). Depression was followed by decreased physical activity and irregular dietary habits, which are risk factors for MS. Although this association has been the subject of previous studies (10-12), little is known about the factors that contribute to the development of depression and anxiety in people with MS.

This study aimed to explore the influence of sociodemographic characteristics and lifestyle on the presence of anxiety and depression in the adult population of Banja Luka, Bosnia and Herzegovina, and the interrelationship between MS and anxiety and depression.

Methods

Study Participants

This longitudinal study was conducted from 1 October to 31 December 2012, in the region of Banja Luka, the second-largest city in Bosnia and Herzegovina. Before drawing a sample, the principal investigator defined the population. At the time of the survey, Banja Luka had 142,116 inhabitants older than 18 years of age. A list of inhabitants was obtained from the Primary Healthcare Centre Patients' Registry and used as a sampling framework. Each registered patient was assigned a unique number. Computer-generated random numbers were used to select a simple random sample. Age, gender, and geographic location were included in the sampling; however, occupation, religion, and ethnicity were not included. The Department of Informatics followed a normal distribution for the bound and confidence interval to provide correct coverage of the general population. A systematic and proportional sample of 700 individuals was selected. A list of study participants was created, containing the patient's name, demographic characteristics, family practice registration number, and family physician's name.

Invitation letters were sent to 103 family physicians whose patients were randomly selected to participate in this study. The letters described the purpose of the study in detail. After signed consents were obtained, the principal investigator provided the list of designated patients. Physicians contacted patients by telephone, informed them about the objectives of the study, and asked for enrolment permission.

The study was conducted according to the guidelines established by the Declaration of Helsinki, and the Ethical Committee of the Primary Healthcare Centre approved all procedures and measurements. All study participants provided signed informed consent.

Procedure

Definition of the Metabolic Syndrome

The metabolic syndrome was defined according to the IDF definition (2). According to this definition, the obligatory component for MS diagnosis is central obesity. The borderline value for central obesity in Europeans is ≥94 cm for men and ≥80 cm for women. To diagnose MS, in addition to this obligatory component, at least two of the following factors should be present:

- Blood pressure ≥130/80 mmHg or a previous diagnosis of hypertension (use of antihypertensive drugs),
- Triglycerides ≥1.7 mmol/l or previously treated hypertriglyceridemia,
- HDL cholesterol <1.03 mmol/l for men and <1.29 mmol/l for women, or already treated lipid disorder of this type, and
- Morning fasting glycemia ≥5.6 mmol/l or previously diagnosed type 2 diabetes.

A sociodemographic questionnaire was designed to collect personal data about the patients: age, gender, level of education (no schooling, incomplete primary or primary education, secondary school, post-secondary and university education), employment status (employed, self-employed, retirees, homemakers, students, unemployed), marital status (married, informal marriage, unmarried, divorced, widowed), and information on the number of children (one, two, and three or more children). The classification of education was made in accordance with the educational categories and levels of the International Standard Classification of Education – ISCED 97 (13). The occupational classification used for this study is the standard occupational classification established by the Republic Institute of Statistics, according to the principles and system of the International Standard Occupational Classification (14). The data were published elsewhere (15).

Clinical Measurements

Blood Pressure Measurements

Blood pressure was measured according to international standards using a calibrated mercury sphygmomanometer. Blood pressure was measured three times consecutively with a one-minute interval between measurements (to redistribute blood in the upper arm). The mean value of the second and third measurements was used as the final blood pressure value (16, 17).

Anthropometric Measurements

The anthropometric measurements performed during this study included body weight, body height, and waist circumference. To measure body weight, regularly calibrated „GIMA" scales with a balanced scale were used in the following manner. The reading values were expressed in kg. Height was measured using a measuring stick. The reading values were expressed in cm. Waist circumference was measured using a flexible non-elastic measuring tape (meter). The reading value in the mean axillary line, at breathing out, expressed in cm, was entered into the questionnaire (18).

Laboratory Analysis

For this study, laboratory analyses (blood glucose [BG] and lipid status) were performed at the biochemical laboratory of the Primary Healthcare Centre in Banja Luka. Venous blood was extracted in the morning during fasting, after 12 to 14 h of non-food consumption. Biochemical analysis of BG and lipid status was performed using the Cobas Integra 400 + ISE analyser (Roche Diagnostics). Blood glucose levels were determined using UV photometry with the hexokinase enzyme. Total cholesterol was determined using automatic photometry with cholesterol oxidase. Triglycerides were measured using photometry with glycerol oxidase, HDL was determined using a homogenous enzymatic method with polyethylene glycol (PEG), and LDL was calculated mathematically.

Depression Symptoms

Depression symptoms were evaluated using the Beck Depression Inventory (BDI–II). In its current version, the BDI-II is designed for individuals aged 13 and older, and is composed of items relating to symptoms of depression, such as hopelessness and irritability; cognitions, such as guilt or feelings of being punished; and physical symptoms, such as fatigue, weight loss, and lack of interest in sex. The BDI–II contains 21 items. Each item comprises four statements based on the intensity of

a particular depression symptom, which is scored from 0 to 3. Participants chose the answer that best described their condition or how they felt during the last two weeks, including the day they completed the questionnaire. The maximum number of points is 63. According to the score, the grade of depression in participants was determined as follows: 0–13, minimal depression; 14–19, mild depression; 20-28, moderate depression; and 29-30, severe depression (19). Cronbach's alpha coefficient of 0.893 for the BDI-II was found to be adequate.

Anxiety Symptoms

The Beck Anxiety Inventory (BAI) was used to assess anxiety symptoms. BAI contains 21 items. Each item is a simple description of anxiety symptoms and covers one of the following four aspects: subjective, neurophysiological, autonomic, and panic. Participants report the extent to which the symptoms of each of the 21 items manifested during the past month, including on the day of completing the questionnaire. Each item (symptom) has four possible answers: no (I have no feeling); mild (I feel it, but it does not bother me); moderately heavy (It was very hard, but I could handle it); and severe (It bothers me a lot, I could hardly bear it). Answers are rated: no=0; mild=1; moderately heavy=2; severe=3. The values for each item are aggregated, and the total sum ranges from 0 to 63. Scores of 0–7, 8–15, 16–25, and 26–63 are interpreted as minimum, mild, moderate, and severe anxiety, respectively (20). Cronbach's coefficient was 0.915.

Covariables

The following covariables (lifestyle of the respondents) were selected for the study: degree of leisure-time physical activity and degree of physical workload, smoking status, nutritional habits, estimated alcohol consumption, and degree of ten-year fatal cardiovascular risk. The researcher filled out this form for each participant individually based on the questionnaire data using the appropriate definitions, formulas, and scores. According to the WHO recommendations for leisure-time physical activity, participants were divided into active, moderately active, and inactive (21). The assessment of physical activity was performed based on the answer to the question: "How often, in your leisure time, do you engage in physical activities for at least 30 minutes, so that you get out of breath or sweat at least a little?" The participants answered one of the 7 answers offered. Participants were categorized into the active group if they were physically active four or more times per week. Participants were categorized into the moderately active group if they were physically active less than four times a week, but at least 2-3 times a month. Participants were categorized into the inactive group if they were physically active several times a year or not physically active at all.

In accordance with the WHO recommendations (21), the assessment of physical activity at work was performed based on the answer to the question: "How strenuous is the work you do?". Three answers were offered: 1. mostly sitting; 2. mostly standing, but not carrying a load, not walking much, not climbing stairs, and/or lifting loads; 3. hard physical work, lifting, and/or bearing of heavy loads. Based on their answers, the participants were divided into three groups: 1. they work in a sedentary job; 2. work moderately heavily; and 3. do hard physical work. In accordance with the recommendations from the "Program for the Prevention and Control of Non-Communicable Diseases in the Republic of Srpska" (18), the questionnaire included a question on smoking status with three possible answers: smoker, ex-smoker, and non-smoker. Based on their answers, the participants were classified into one of the three categories. The association between nutritional status and MS in our participants was estimated based on questions related to the regularity of eating meals. According to current recommendations, daily energy requirements should be divided into three main meals and two snacks (22). The number of meals per day the respondents ate was determined with the question: "How many times a week: 1. Do you have breakfast; 2. Have a

snack before noon; 3. Have lunch; 4. Have a snack in the afternoon, and 5. Have dinner?". The possible answers for each meal were: never, sometimes, or every day. The American guidelines (23) were used for alcohol consumption, according to which participants were divided into non-drinkers, moderate-risk drinkers (the total number of standard drinks consumed weekly for women <7, and <14 for men), and high-risk drinkers (the total number of standard drinks consumed weekly for women ≥7, and for men ≥14) (abstinence, moderate-risk drinking, high-risk drinking). The social background of the participants was determined by surveying their age, gender, occupation, educational level, marital status, employment status, and number of children. Education was classified according to the educational categories and levels of the International Standard Classification of Education – ISCED 97 (24). For each participant, fatal cardiovascular (CV) risk was determined for the next 10 years using the European electronic version of Heart Score charts and the following participant data: month and year of birth (age), sex, smoking status, systolic blood pressure, and total cholesterol. After the values were obtained in percentages, the participants were classified into one of four groups of CV risk: very high CV risk (≥10%), high CV risk (≥5%-10%), moderate CV risk (1-5%), and low CV risk (<1%) (25).

Ethics Statement

The Ethics Committee of the Banja Luka Health Centre approved this study (No. 01-1819-1).

Statistical Analysis

Participants were sorted into two groups based on the presence of MS: an MS group and a control group of participants without MS. The presence and degree of depression and anxiety were observed in both groups. The association between depression and anxiety with MS was determined based on the difference in the degree of their presence in the observed groups. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corp., Armonk, NY, USA). The chi-square test of independence was used to investigate whether there was a statistically significant association between two categorical variables. P-values smaller than 0.05 were considered significant. Cramer's V test was included as an additional test to assess the significance of the differences and their strength. Cramer's V test values were interpreted as follows: V=0, there is no relationship between the variables; V=1, there is a complete connection of variables; V<0.25, there is a weak connection between the variables; V>0.75, there is a strong relationship between the variables; and 0.25<V<0.75, there is a significant relationship between the variables. Fisher's exact test was used to check the results obtained by Pearson's chi-square test.

The analysis of MS predictors aimed to extract the participants' characteristics that significantly affected the occurrence of MS. As binary logistic regression is used for this purpose, it is first necessary to define a binary variable that will categorize the participants into two groups:

- Participants with MS (binary variable with a value of 1) and
- Participants without MS (binary variable with a value of 2).

The defined variables were dependent variables in the logistic regression models. The analysis was organized into two stages. The first stage involved the implementation of a series of univariate logistic regressions (one independent variable and one dependent variable in the model) that aimed to extract the participants' individual characteristics that were significant in the univariate models. The second stage relates to the implementation of the multivariate logistic regressions (several independent variables and one dependent variable), which includes only those characteristics of participants in the model that have been proven significant in the univariate models. The choice of variables used in the multivariate model was determined by the significance level (P<0.1) in the univariate logistic regression or the significance of the univariate model itself. All other variables that are not presented in the table were not significant

in the univariate model, the univariate model was not significant, or there was already a variable in the multivariate model that was collinear with the variable that was observed.

Results

The questionnaire was completed by 685 participants (response rate=97.85%), of whom 348 (50.8%) were men and 337 (49.2%) were women. The average age of the participants was 48.77±17.888 years. Most participants were employees (41.7%) and retirees (26.30%). The most frequent categories of occupation among the employees were service workers and traders (25.6%). The most frequent level of education was secondary school (58.1%). According to marital status, most participants were married (60.1%).

Anxiety and Sociodemographic Characteristics of Respondents

According to the BAI, out of 679 participants who completed this scale, 400 had no symptoms of anxiety or their symptoms were minimal, making up 58.9% of the sample. As shown in Figure 1, anxiety symptoms were statistically significantly more prevalent in women than in men (P<0.001). Cramer's V test confirmed (Table 1) a significant relationship between anxiety and gender (V=0.297).

Pearson's chi-square test revealed that anxiety symptoms were statistically significantly more common with increasing age, statistically significantly less common in employees than in retirees, homemakers, and the unemployed, and statistically significantly decreased with an increase in the level of education. Furthermore, anxiety symptoms were significantly more prevalent among parents with many children and among divorced persons than among other marital status categories. However, Cramer's V test showed a weak relationship between these variables.

Anxiety and Lifestyle

Table 1 shows that anxiety symptoms statistically significantly increased with decreasing leisure-time physical activity (P<0.001). Severe anxiety symptoms were statistically significantly more common in participants who drank alcohol moderately or at high risk than in those who did not drink (P<0.001). However, in both cases, Cramer's V test showed a weak relationship between the variables (V=0.132). Cardiovascular risk was associated with

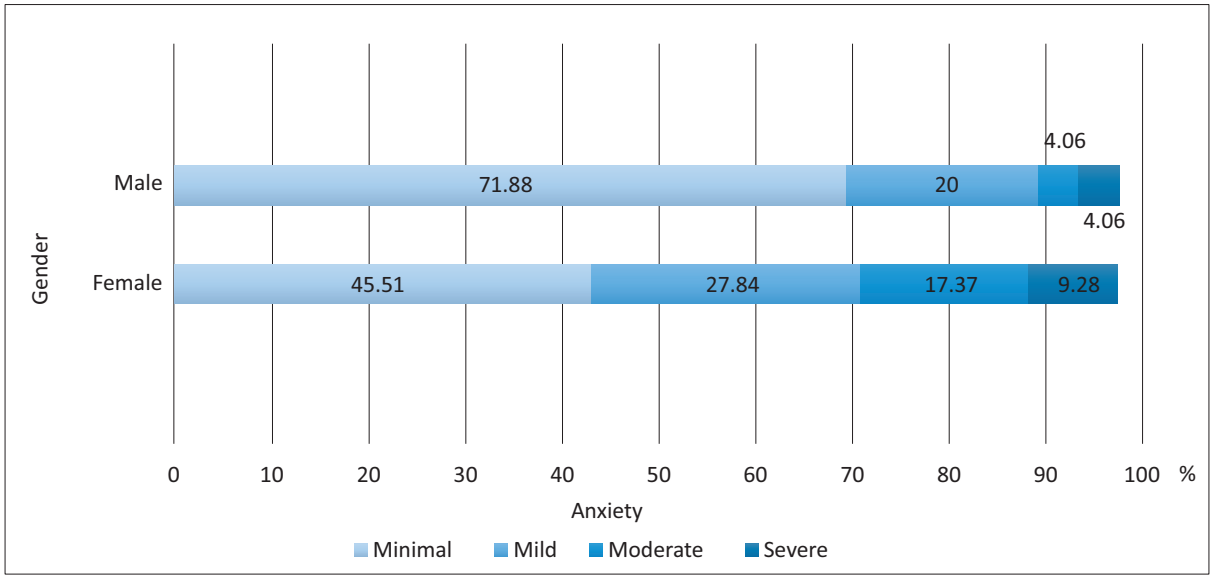

Figure 1. The presence of anxiety depending on gender.

Table 1. The Correlation Between Anxiety Levels and Sociodemographic Characteristics and Lifestyle

Sociodemographic characteristics	Anxiety N (%)				Pearson's chi-square† P	Cramer's V
	Minimal (0 – 7)*	Mild (8 – 15)*	Moderate (16 – 25)*	Severe (26 – 63)*		
Gender						
Male	248 (71.88)	69 (20)	14 (4.06)	14 (4.06)	59.744 <0.001	0.297
Female	152 (45.51)	93 (27.84)	58 (17.37)	31 (9.28)		
Age						
18-29	84 (68.85)	29 (23.77)	7 (5.74)	2 (1.64)	68.662 <0.001	0.184
30-39	98 (42.42)	26 (11.26)	7 (3.03)	2 (0.87)		
40-49	66 (68.75)	17 (17.71)	9 (9.38)	4 (4.17)		
50-59	73 (55.73)	33 (25.19)	16 (12.21)	9 (6.87)		
60-69	44 (44.44)	26 (26.26)	16 (16.16)	13(13.13)		
70+	35 (35.71)	31 (31.63)	17 (17.35)	15 (15.31)		
Employment status						
Employed	187 (66.55)	63 (22.42)	23 (8.19)	8 (2.85)	69.404 < 0.001	0.185
Self-employed	9 (50.00)	7 (38.89)	2 (11.11)	0 (0)		
Retired	80 (44.94)	47 (26.40)	28 (15.73)	23(12.92)		
Homemaker	14 (30.43)	14 (30.43)	10 (21.74)	8 (17.39)		
Student	43 (70.63)	9 (16.67)	1 (1.85)	1 (1.85)		
Unemployed	63 (64.29)	22 (22.45)	8 (8.16)	5 (5.10)		
Level of education						
No schooling	8 (29.63)	5 (18.52)	4 (14.81)	10(37.04)	69.404 <0.001	0.184
Incomplete primary or elementary education	3 (13.04)	10 (43.48)	5 (21.74)	5 (21.74)		
Secondary school	31 (46.27)	15 (22.39)	15 (22.39)	6 (9)		
Post-secondary and university education	238 (61.34)	99 (25.52)	33 (8.51)	18 (4.64)		
Marital status						
Married	243 (60.00)	96 (23.70)	41 (10.12)	25 (6.17)	55.521 <0.001	0.166
Informal marriage	6 (54.55)	1 (9.09)	4 (36.36)	0		
Unmarried	113 (11.30)	32 (20.38)	8 (5.10)	4 (2.55)		
Divorced	9 (42.86)	8 (38.10)	3 (14.29)	1 (4.76)		
Widowed	27 (33.33)	25 (30.86)	15 (18.52)	14 (17.28)		
Number of children						
No children	134 (67)	44 (22)	14 (7)	8 (4)	28.965 0.004	0.120
1 child	62 (60.19)	27 (26.21)	12 (11.65)	2 (1.94)		
2 children	157 (72.02)	73 (33.49)	39 (17.89)	22(10.09)		
3 or more children	33 (55.93)	14 (23.73)	3 (5.08)	9 (15.25)		
Covariables (lifestyle)						
Number of meals per day						
One	7 (63.63)	3 (27.27)	0	1 (9.09)	8.356 0.757	0.064
Two	42 (59.15)	16 (22.54)	7 (9.86)	6 (8.45)		
Three	159 (55.02)	78 (26.99)	34 (11.76)	18 (6.23)		
Four	149 (63.34)	50 (20.92)	22 (2.21)	18 (7.53)		
Five	43 (62.32)	15 (21.74)	9 (13.04)	2 (2.90)		

Continuation of Table 1.

Sociodemographic characteristics	Anxiety N (%)				Pearson's chi-square† P	Cramer's V
	Minimal (0 – 7)*	Mild (8 – 15)*	Moderate (16 – 25)*	Severe (26 – 63)*		
Leisure-time physical activity						
Active	136 (64.15)	43 (20.28)	24 (11.32)	9 (4.25)	36.544 <0.001	0.165
Moderately active	203 (62.65)	77 (23.77)	31 (9.57)	13 (4.01)		
Inactive	57 (42.22)	41 (30.37)	15 (11.11)	22 (16.30)		
Physical workload (employed and self-employed)						
Sedentary work	104 (61.18)	41 (24.12)	16 (7.06)	9 (5.29)	5.309 0.505	0.082
Moderately hard work	124 (64.25)	49 (25.39)	14 (7.25)	6 (3.11)		
Hard work	20 (71.43)	3 (10.71)	4 (14.29)	1 (3.57)		
Smoking status						
Smoker	107 (62.57)	38 (22.22)	19 (11.11)	7 (4.10)	4.582 0.598	0.058
Ex-smoker	57 (61.29)	21 (22.58)	7 (7.53)	8 (8.60)		
Non-smoker	236 (56.87)	103 (24.82)	46 (11.08)	30 (0.72)		
Alcohol consumption						
High risk	40 (68.97)	8 (13.79)	5 (8.62)	5 (8.62)	35.451 <0.001	0.132
Moderate risk	297 (63.60)	108 (23.13)	42 (8.99)	20 (8.43)		
Abstinence	62 (62.00)	44 (1.91)	24 (18.46)	19 (4.07)		
Cardiovascular risk						
Very high	63 (39.87)	50 (31.65)	25 (15.82)	20 (12.66)	5.4473 <0.001	0.164
High	64 (55.17)	23 (19.87)	15 (12.93)	14 (12.07)		
Moderate	186 (70.45)	54 (20.45)	17 (6.44)	7 (2.65)		
Low	87 (61.70)	35 (24.82)	15 (10.64)	4 (2.84)		

*Points; †Pearson's chi-square test results were confirmed using Fisher's exact test.

anxiety (P<0.001). The prevalence of severe anxiety symptoms increased with an increase in cardiovascular risk (2.84%, 2.65%, 12.07%, and 12.66%). Cramer's V test revealed a weak relationship between the variables (V=0.164).

Depression and Sociodemographic Characteristics of Respondents

The results of the study revealed that of the 682 participants who completed the BDI-II, 558 (81.8%) had no or minimal symptoms of depression. Figure 2 shows that the presence of depressive symptoms was statistically significantly reduced with increasing educational level (P<0.001). Cramer's V test confirmed (Table 2) the significant relationship between the mentioned variables (V=0.252).

The results showed (Pearson's chi-square) a statistically significantly higher presence of depressive symptoms in women than in men, retirees and homemakers than in other groups of work status, and widows compared to other groups of marital status. Symptoms were statistically significantly more prevalent in parents with a larger number of children and increased with age. However, Cramer's V test showed a weak relationship between these variables and depression.

Depression and Lifestyle

The results obtained by Pearson's chi-square test, presented in Table 2, show a statistically significant association between leisure-time physical activity and the prevalence of depressive symptoms

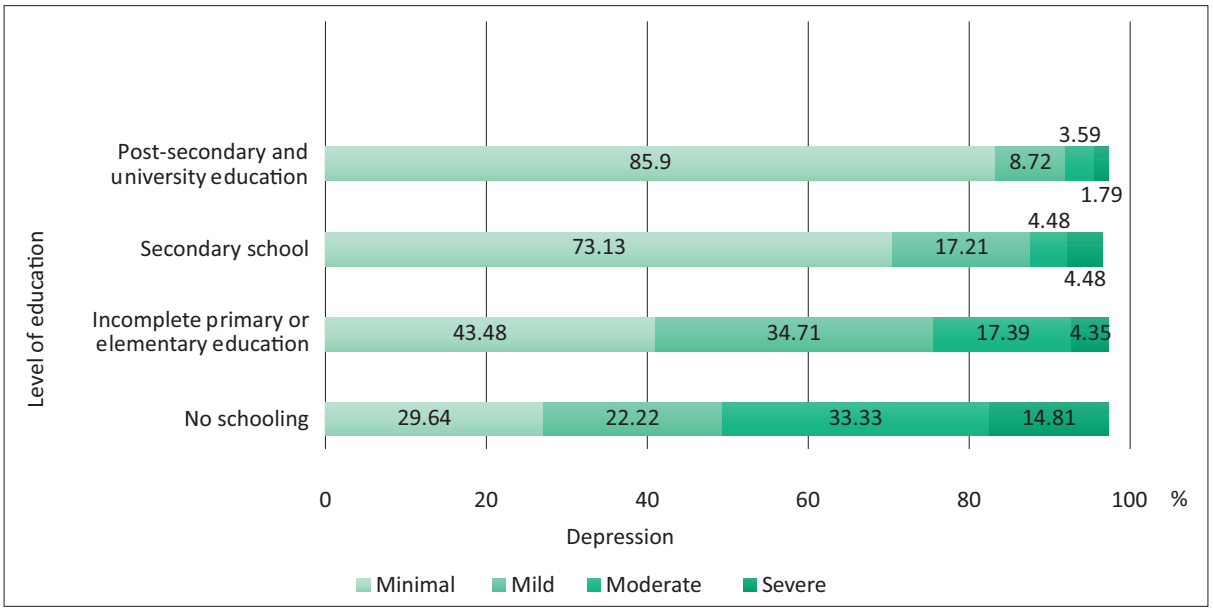

Figure 2. The presence of depression depending on the level of education.

Table 2. The Correlation Between Depression Levels and Sociodemographic Characteristics and Lifestyle

Sociodemographic characteristics	Depression N (%)				Pearson's chi-square† P	Cramer's V
	Minimal (0 – 13)*	Mild (14 –19)*	Moderate (20 – 28)*	Severe (29 –63)*		
Gender						
Male	304 (87.86)	30 (8.67)	9 (2.60)	3 (0.87)	19.925 <0.001	0.171
Female	254 (75.60)	46 (13.69)	24 (7.14)	12 (3.57)		
Age						
18-29	114 (92.68)	7 (5.69)	2 (1.63)	0	96.801 <0.001	0.218
30-39	123 (92.48)	8 (6.02)	1(0.75)	1(0.75)		
40-49	87 (90.63)	5 (5.21)	2 (2.08)	2 (2.08)		
50-59	109 (82.58)	15 (11.36)	7 (5.30)	1 (0.76)		
60-69	74 (74.00)	16 (16.00)	5 (5.00)	5 (5.00)		
70+	51 (52.04)	25 (25.51)	16 (16.33)	6 (6.25)		
Employment status						
Employed	258 (91.17)	22 (7.77)	0	3 (1.06)	109.256 <0.001	0.23
Self-employed	15 (83.33)	2 (11.11)	1 (5.56)	0		
Retired	116 (64.80)	37 (20.67)	18 (10.06)	8 (4.47)		
Homemaker	28 (60.87)	8 (17.39)	8 (17.39)	2 (4.35)		
Student	52 (89.66)	0	2 (3.45)	0		
Unemployed	86 (87.76)	7 (7.14)	4 (4.08)	1 (1.02)		
Unable to work	1 (50.00)	0	0	1 (50.00)		
Level of education						
No schooling	8 (29.64)	6 (22.22)	9 (33.33)	4 (14.81)	128.229 <0.001	0.252
Incomplete primary or elementary education	10 (43.48)	8 (34.78)	4(17.39)	1 (4.35)		
Secondary school	49 (73.13)	12 (17.21)	3 (4.48)	3 (4.48)		
Post-secondary and university education	335 (85.90)	34 (8.72)	14 (3.59)	7 (1.79)		

Continuation of Table 2.

Sociodemographic characteristics	Depression N (%)				Pearson's chi-square† P	Cramer's V
	Minimal (0 – 13)*	Mild (14 –19)*	Moderate (20 – 28)*	Severe (29 –63)*		
Marital status						
Married	343 (84.28)	41 (10.07)	16 (3.93)	7 (1.72)	55.628 <0.001	0.165
Informal marriage	10 (9.09)	0	1 (9.09)	0		
Unmarried	139 (87.97)	15 (9.49)	2 (1.27)	2 (1.27)		
Divorced	19 (90.48)	1 (4.76)	0	1 (4.76)		
Widowed	45 (55.56)	18 (22.22)	13 (16.05)	5 (6.17)		
Number of children						
No children	179 (89.50)	15 (7.50)	3 (1.50)	3 (1.50)	39.452 <0.001	0.139
1 child	89 (86.41)	8 (7.77)	5 (4.85)	1 (0.97)		
2 children	230 (78.50)	39 (13.31)	16 (5.46)	8 (2.73)		
3 or more children	46 (78.00)	8 (13.56)	3 (5.08)	2 (3.39)		
Covariables (lifestyle)						
Number of meals per day						
One	56 (76.71)	9 (12.33)	6 (8.22)	2 (2.74)	10.859 0.541	0.073
Two	236 (81.66)	37 (12.80)	12 (4.15)	4 (1.38)		
Three	201 (83.75)	20 (8.33)	12 (5)	7 (2.92)		
Four	58 (84.06)	7 (10.14)	2 (2.90)	2 (2.90)		
Five	7 (63.64)	3 (4.35)	1 (1.45)	0		
Physical activity						
Active	177 (83.10)	25 (11.74)	9 (4.23)	2 (0.94)	45.698 <0.001	0.181
Moderately active	285 (87.96)	29 (8.95)	7 (2.16)	3 (0.93)		
Inactive	91 (66.91)	19 (13.97)	17 (12.5)	9 (6.62)		
Physical workload (employed and self-employed)						
Sedentary work	147 (86.47)	14 (8.24)	4 (2.35)	5 (2.94)	4.012 0.675	0.072
Moderately hard work	172 (89.12)	15 (7.77)	4 (2.07)	2 (1.04)		
Hard work	23 (82.14)	4 (14.29)	0	1 (3.57)		
Smoking status						
Smoker	149 (87.13)	13 (7.60)	7 (4.09)	2 (1.17)	15.922 0.014	0.108
Ex-smoker	81 (86.17)	4 (4.26)	8 (8.51)	1 (1.06)		
Non-smoker	328 (78.66)	59 (14.15)	18 (4.32)	12 (2.88)		
Alcohol consumption						
High risk	53 (91.38)	2 (3.45)	3 (5.17)	0	53.867 <0.001	0.162
Moderate risk	403 (86.30)	44 (9.42)	17 (3.64)	3 (0.64)		
Abstinence	99 (65.13)	28 (18.42)	13 (8.55)	12 (7.89)		
Cardiovascular risk						
Very high	103 (65.19)	27 (17.08)	19 (12.03)	9 (5.70)	67.974 <0.001	0.182
High	85 (72.65)	21 (17.95)	7 (5.98)	4 (3.42)		
Moderate	242 (91.32)	17 (6.42)	4 (1.51)	2 (0.75)		
Low	128 (90.14)	11 (7.75)	3 (2.11)	0		

*Points; †Pearson's chi-square test results were confirmed using Fisher's exact test.

(P<0.001). Depressive symptoms were most prevalent in inactive participants compared to moderately active and active participants. Smoking was associated with depression (P=0.014). The prevalence of smokers decreased with an increasing presence of depressive symptoms. Alcohol consumption was statistically significantly associated with the prevalence of depressive symptoms. With an increase in the consumption levels of alcohol, the prevalence of depression symptoms decreased. Cramer's V test showed a weak relationship between the degree of depression and the monitored covariates (leisure-time physical activity, V=0.181; smoking, V=0.108; and alcohol consumption, V=0.162). Cardiovascular risk was statistically significantly highly associated with the presence of depression symptoms (P<0.001). With an increase in cardiovascular risk, the prevalence of depressive symptoms also increases. Cramer's V test showed a weak relationship between the variables (V=0.182).

The Association Between Metabolic Syndrome and Anxiety and Depression

MS was recorded in 37.5% of participants; 36.8% of men and 38.2% of women (Table 3). There was no confirmation of the association between MS and anxiety in men, but there was in women. Table 3 shows that women with moderate and severe anxiety were statistically significantly more represented in the MS group than in the group without MS (P<0.001). Cramer's V test confirmed a significant association between the presence of anxiety symptoms in women and MS (V=0.331). The data in Table 3 show that there was no confirmation of the association between MS and the presence of depressive symptoms in men, but there was in women. Women with severe depression were statistically significantly more represented in the group with MS than in the group without MS (P=0.007). However, Cramer's V test shows the weak strength of this relationship (V=0.191).

Table 3. The Association Between Metabolic Syndrome and Anxiety and Depression

Characteristics	Total	Metabolic syndrome		Pearson's chi-square† P	Cramer's V
		Yes (N; %)	No (N; %)		
	N=685	257 (37.5)	428 (62.5)		
The degree of anxiety according to the Beck Anxiety Inventory					
Male					
Minimal (0 – 7 points)	248 (71.9)	86 (67.7)	162 (74.3)	4.043 0.257	0.108
Mild (8 – 15 points)	69 (20.0)	26 (20.5)	43 (19.7)		
Moderate (16 – 25 points)	14 (4.1)	7 (5.5)	7 (3.2)		
Severe (26 – 63 points)	14 (4.1)	8 (6.3)	6 (2.8)		
Female					
Minimal (0 – 7 points)	152 (45.5)	34 (27.0)	118 (56.7)	36.610 <0.001	0.331
Mild (8 – 15 points)	93 (27.8)	38 (30.2)	55 (26.4)		
Moderate (16 – 25 points)	58 (17.4)	33 (26.2)	25 (12.0)		
Severe (26 – 63 points)	31 (9.3)	21 (16.7)	10 (4.8)		
Total					
Minimal (0 – 7 points)	400 (58.9)	120 (47.4)	280 (65.7)	33.903 0.000	0.223
Mild (8 – 15 points)	162 (23.9)	64 (25.3)	98 (23.0)		
Moderate (16 – 25 points)	72 (10.6)	40 (15.8)	32 (7.5)		
Severe (26 – 63 points)	45 (6.6)	29 (11.5)	16 (35.6)		

Continuation of Table 3.

Characteristics	Total	Metabolic syndrome		Pearson's chi-square† P	Cramer's V
		Yes (N; %)	No (N; %)		
	N=685	257 (37.5)	428 (62.5)		
The degree of depression according to the Beck Depression Inventory					
Male					
Minimal (0 – 13 points)	304 (87.9)	109 (85.8)	195 (89.0)	1.626 0.654	0.069
Mild (14 – 19 points)	30 (8.7)	12 (9.4)	18 (8.2)		
Moderate (20 – 28 points)	9 (2.6)	4 (3.1)	5 (2.3)		
Severe (29 – 63 points)	3 (0.9)	2 (1.6)	1 (0.5)		
Female					
Minimal (0 – 13 points)	254 (75.6)	84 (65.6)	170 (81.7)	12.266 0.007	0.191
Mild (14 – 19 points)	46 (13.7)	23 (18.0)	23 (11.1)		
Moderate (20 – 28 points)	24 (7.1)	13 (10.2)	11 (5.3)		
Severe (29 – 63 points)	12 (3.6)	8 (6.3)	4 (1.9)		
Total					
Minimal (0 – 13 points)	558 (81.8)	193 (75.7)	365 (85.5)	12.612 0.006	0.136
Mild (14 – 19 points)	76 (11.2)	35 (13.7)	41 (9.6)		
Moderate (20 – 28 points)	33 (4.8)	17 (6.7)	16 (3.7)		
Severe (29 – 63 points)	15 (2.2)	10 (3.9)	5 (1.2)		

†The results of Pearson's chi-square test were confirmed using Fisher's exact test.

As Table 4 shows, the highest value of the cross-odds ratio is for the variable related to the level of anxiety (1.525). This means that in this multivariate model, people with elevated anxiety levels have a higher chance of having metabolic syndrome. Furthermore, in this multivariate model, employed people had a higher chance of having metabolic syndrome than other work status groups (OR=0.861). Finally, in this multivariate model, individuals with low cardiovascular risk (according to variable modality) had a lower chance of having metabolic syndrome (OR=0.488).

Table 4. Risk Factors for Metabolic Syndrome: Regression Analyses of Sociodemographic, Lifestyle, Cardiovascular, Anxiety, and Depression Variables

Variable	B	S.E.	Wald	df	Sig.	95% C.I. for EXP (B)	
						Lower	Upper
Age	-0.020	0.091	0.047	1	0.828	0.821	1.171
Employment status	-0.149	0.055	7.316	1	0.007	0.773	0.960
Level of education	-0.044	0.088	0.245	1	0.621	0.805	1.138
Number of children	0.114	0.099	1.321	1	0.250	0.923	1.360
Physical activity	0.048	0.128	0.137	1	0.711	0.815	1.349
Alcohol consumption	0.098	0.175	0.311	1	0.577	0.782	1.555
Cardiovascular risk	-0.718	0.129	31.148	1	0.000	0.379	0.628
The degree of anxiety according to the Beck Anxiety Inventory	0.425	0.116	13.469	1	0.000	1.219	1.919
The degree of depression according to the Beck Depression Inventory	-0.213	0.164	1.682	1	0.195	0.585	1.115
Constant	0.928	0.940	0.975	1	0.323	-	-

Discussion

This study aimed to determine the influence of sociodemographic characteristics and lifestyle on the presence of anxiety and depression. Of all the sociodemographic characteristics, the highest association with the presence of anxiety was shown by female gender, and a low level of education with the presence of depression. Physical inactivity during leisure time and risky alcohol consumption were associated with a higher presence of anxiety and depression. Cigarette smoking showed an inverse association with the presence of depression (smokers had less depression than non-smokers), while there was no association with anxiety. The second goal of this study was to determine the relationship between metabolic syndrome and anxiety and depression, which was confirmed in this study. Anxiety and depression were statistically significantly more prevalent in the group of respondents with MS than in the group without MS.

We conducted the research on the adult population in Banja Luka, the second largest city in Bosnia and Herzegovina. The results showed that out of a total of 679 participants, according to the BAI score, 400 respondents (58.9%) had no or minimal anxiety symptoms. Dolanbay et al. (26) conducted a study on the presence of anxiety symptoms among health workers in the emergency department and the factors that influence these results. They found that 43.8% of the participants had a BAI score greater than 7, which is similar to our result (41.1%). However, Dolanbay et al.'s study included employed respondents. Our research has shown that anxiety symptoms are statistically significantly less prevalent among employees than among retirees, homemakers, and the unemployed. The aforementioned authors showed that anxiety symptoms were more prevalent in women than in men and in singles compared to those who are married. Using the χ^2 test, we also confirmed a statistically significantly higher presence of anxiety symptoms in women than in men, and Cramer's V test showed a significant strength of this relationship. In our study, anxiety symptoms were statistically significantly more common with increasing age; they decreased statistically significantly with an increase in the level of education; and they were statistically significantly more prevalent in parents with a larger number of children and in widowers than in other categories of marital status. However, for these variables, the strength of this relationship was weak. Chlapecka et al. (27) examined the relationship between the level of education and anxiety symptoms in a sample of 77,792 middle-aged and older people in Europe. Similar to our study, they showed that higher levels of education were associated with a lower likelihood of anxiety symptoms, independent of sociodemographic and health-related factors. The relationship was stronger among women, middle-aged people, and in Central and Eastern Europe, but was not evident in Northern Europe.

Many studies have shown that physical activity can have a positive impact on anxiety (28, 29), including anxiety as measured by the Beck Anxiety Inventory (BAI), while both smoking and alcohol consumption are associated with increased anxiety (30-32). Our study showed that reduced physical activity during leisure time increased the presence of anxiety symptoms. The prevalence of severe anxiety was higher among those who consumed alcohol (both moderately and at risk) than among those who did not consume alcohol. Cigarette smoking was not associated with anxiety, as measured by the BAI. Kim et al. (28) found a connection between physical activity and anxiety symptoms. Compared with the sedentary group (0–600 METs-min/week), participants who achieved 600–6,000 METs-min/week had a significantly lower risk of anxiety symptoms. However, engaging in physical activity of more than 6,000 METs-min/week was not associated with the risk of anxiety symptoms (U-curve).

The results of our research using the BDI II showed that in the examined group of 682 participants with an average age of 48.77 years, 81.8% of the respondents had minimal symptoms of depression. Using the BDI II, Economou et al. (33) investigated the presence of depressive symptoms in a Greek population of 542 participants with an average age of 64.89 years and found that

364 (67.2%) participants scored in the minimally depressed range. In our study, the average age of the subjects was lower; therefore, it is expected that the number of subjects without symptoms or with minimal symptoms of depression was higher than that in the Greek study. As we did in Bosnia and Herzegovina, the Greek authors examined the presence of symptoms of depression depending on age, level of education, and gender. In both studies, the $\chi 2$ test showed that the presence of depressive symptoms decreased with increasing education level, increased with increasing years of life, and that depressive symptoms were more frequent in women than in men. In both studies, the correlation between age and depression was weak. The association of gender and age with the onset of depressive symptoms was confirmed in a representative sample of 12,677 Brazilian students using the BDI-II with 21 items (34). Czech authors Cihrova et al. (35) examined the association between demographic characteristics and the presence of depressive symptoms among 450 respondents. Similar to our study, they showed that women and participants with lower education levels tended to have more depressive symptoms than men and participants with higher education levels. However, unlike our study, there was no significant relationship between age and the presence of depressive symptoms.

Our results showed a connection between physical activity during leisure time and the presence of depressive symptoms. The presence of depressive symptoms decreased with increasing physical activity. However, the physical workload at work among employed respondents did not show such a connection. A Brazilian study published in 2025 also investigated the association between depressive symptoms and physical activity levels in a large representative cohort of 58,445 adults (36). High physical activity, as well as any level of physical activity, was associated with a lower probability of depressive symptoms. Clinical factors (BMI, presence of hypertension, and diabetes mellitus) and behavioural factors (smoking status, perceived stress risk, and alcohol consumption level) were associated with a higher likelihood of depressive symptoms. In this study, subjects with depressive symptoms were younger, had a higher BMI, and spent more time in a sedentary lifestyle than those without depressive symptoms. However, our research showed that non-smokers had statistically significantly more depressive symptoms than smokers. Those who did not drink alcohol had a greater presence of depressive symptoms than those who drank moderately or at high risk. However, the strength of this association was weak in both cases (Cramer's V=0.108; V=0.162). In their meta-analysis of 30 articles, Maier et al. reported that alcohol consumption and smoking yielded heterogeneous results (37).

Compared to males, female study participants more frequently reported moderate to severe anxiety and depression symptoms. Considering gender, since no significant differences were found in the literature (38) regarding internal factors (neuroticism), external factors (mental disorders, substance abuse), and adverse life events (trauma, negative parenting, violence), it has been proposed that the higher prevalence of depression in women might be explained by biological contributors (39). According to previous research, contraceptive use is associated with lower rates of depression and anxiety symptoms, indicating a relationship between oestrogen balance and mental health. In addition to numerous physiological, environmental, and behavioural factors, oestrogen status may be the link between metabolic syndrome and depression symptoms in women. Oestrogen deficiency affects mood-regulating neurocircuits through the serotonergic system but simultaneously increases the deposition of adipose cells in intra-abdominal tissue (triggering visceral obesity) and has a full effect on proinflammatory cytokines. By affecting neurotransmitter systems, cytokines contribute to depression through inflammatory profiles and generate obesity-mediated insulin resistance and inflammation of the coronary arteries (40).

The lower prevalence of anxiety and depression among men may be related to hormonal and neural developmental differences, such as dimorphic brain nuclei in men or, throughout a lifetime, less variation in testosterone levels compared to

oestrogen cycles in women (38). Men experience symptoms differently (aggression, anger, and risky behaviour versus physical and emotional symptoms) (41, 42). However, they are also less inclined to report depression due to the fear of being stigmatized, as seeking medical help and treatment is often seen as a sign of weakness (43).

Consistent with other studies, participants who were physically active, non-smokers, abstained from alcohol, and had low cardiovascular risk reported moderate-to-severe anxiety and depression symptoms less frequently than individuals with high cardiovascular risk and risky habits (44, 45). Proinflammatory lifestyle choices play an essential role in the shared pathophysiology of mental disorders and metabolic syndrome, suggesting that health promotion procedures in family medicine could potentially affect the prevention and early detection of both cardiovascular disease and mental disorders (46).

Many studies have shown that metabolic syndrome is associated with both anxiety and depression (47, 48). Hiles et al. showed that the prevalence of anxiety was approximately 10% higher among people with MS than among those without MS (49). Our research has shown that anxiety symptoms are significantly more prevalent in the group with MS than in the group without MS. The greater presence of anxiety symptoms in women with MS compared to those without MS was statistically highly significant. Cramer's V test showed that the strength of the association between metabolic syndrome and the presence of anxiety symptoms in women was significant. However, there was no statistically significant difference in the presence of anxiety symptoms in the group of men with MS compared to the group of men without MS. In a meta-analysis that included 24 studies (20 studies used metabolic syndrome as a dependent variable, and four studies used anxiety as a dependent variable), Li et al. (50) concluded that the association between anxiety and metabolic syndrome remains controversial. Three studies were cohort studies: two found an association between initial anxiety and the risk of metabolic syndrome, and one showed no significant association between initial metabolic syndrome and the risk of anxiety. In our study, using a multivariate analysis in which we used metabolic syndrome as a dependent variable, we showed that individuals with a higher degree of anxiety assessed using the BAI II had a greater chance of developing metabolic syndrome.

Our research showed that depressive symptoms (score BAI II ≥14) were statistically significantly more prevalent in the group with MS than in the group without MS; however, according to the results of Cramer's V test, the relationship was weak. There was no statistically significant difference in the presence of depressive symptoms between men with MS and those without MS. Depressive symptoms were statistically significantly more prevalent in women with MS than in those without MS; however, this relationship was weak. Miettola et al. demonstrated that subjects with MS had significantly higher BDI-21 scores than those without MS (51), which is consistent with our results. Meanwhile, Moradi et al. (52) published a meta-analysis that included 49 studies, showing that the probability of metabolic syndrome was higher in depressed people than in non-depressed people. However, the multivariate regression analysis in our study did not confirm that the presence of depressive symptoms represented a risk factor for the development of MS. Contrary to the results of the studies mentioned above, but consistent with our results, Ribeiro et al. found no association between MS and depression (53). In the current study, significant associations between depression symptoms and MS detected by univariate analysis were attenuated in the multivariate regression model. It is possible that other variables, such as overall health, are stronger determinants of MS than depression. The majority of participants had minimal depression symptoms, reported by the patients, and not diagnosed by psychiatric interview, which might have influenced the findings. In the future, the effectiveness of depression screening in patients with MS at the family medicine level needs to be explored.

The results of the studies analysing the association between depression and MS are discordant (53-55). Dunbar identified depression as a

common comorbidity in patients with MS and cardiovascular diseases (54). Due to a loss of energy, interest, and negative self-perception, individuals with depression are prone to a sedentary lifestyle and the consumption of unhealthy food. Poor lifestyle choices cause glucose intolerance, obesity, hyperlipidaemia, and hypertension, which are the cardinal components of MS. Due to its chronicity, depression adversely affects short-term metabolic health (48). Womac et al. found that the association between MS and depression in women was weakened when adjusted for cardiovascular risk factors and antidepressant use, suggesting the role of neurotransmitters and the hypothalamic-pituitary-adrenal (HPA) axis in the development of this association (55). According to Rebolledo-Solleiro et al., leptin dysregulation may explain the missing link between mood disorders and metabolic syndrome (56).

Limitations of the Study

This study has several limitations. Frequencies and exposures were measured in a random sample of the population of interest, but only at one point in time. The study design does not allow for determining whether depression/anxiety symptoms or metabolic syndrome came first. The study was conducted in primary healthcare centres; therefore, the enrolment process might have been biased. Symptoms of depression and anxiety were self-reported and not diagnosed through a psychiatric interview. Various variables not analysed in this study might have affected the results. Prospective studies are needed to explore the bidirectional link between mental health and metabolic syndrome.

Conclusion

The association between MS and anxiety and depression was confirmed in adults from Banja Luka. Women with MS were at higher risk of anxiety and depression symptoms, while this was not confirmed in men. Sociodemographic characteristics such as female gender, older age, employment status (retirees, homemakers), lower level of education, marital status (being divorced or widowed), and having more children affected the presence of anxiety and depression in adults in Banja Luka. Leisure-time physical inactivity, high-risk drinking, and higher levels of cardiovascular risk showed significant influence on the presence of anxiety and depression, while smoking was inversely associated with the presence of depression but not with anxiety.

What Is Already Known on This Topic:
The simultaneous presence of several risk factors makes metabolic syndrome one of the most important causes of atherosclerosis, which results in several diseases of the heart and blood vessels, such as angina pectoris, myocardial infarction, stroke, and peripheral vascular disease. Chronic diseases also affect mental health. There is a significant connection between metabolic syndrome and mental disorders such as depression and anxiety. Individuals with mental disorders are more likely to develop metabolic syndrome.

What This Study Adds:
This study aimed to provide MS data for the adult population of Banja Luka, Bosnia and Herzegovina. The connection between depression and anxiety with MS, as well as the already known key predictors for the occurrence of MS, has been confirmed in the population of interest. We emphasize that this study identified increased glycaemia as the leading predictor, which increases the chance of MS by elevenfold. Physical inactivity during leisure time, high-risk alcohol consumption, and a higher level of cardiovascular risk have been determined to be the factors that contribute the most to depression and anxiety in the population of interest.

Authors' Contributions: Conception and design: VP; Acquisition, analysis and interpretation of data: VP; Drafting the article: VP and BL; Revising the article critically for intellectual content: VP and MR; Approved final version of the manuscript: VP.

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Cadaveric Exploration of the Anatomical Position of the Adductor Canal

Heena Singh[1, a], Noor Us Saba[1], Raghvendra Singh[2, b], Pratibha Shakya[1], Navneet Kumar[1]

[1]Department of Anatomy, King George's Medical University, Lucknow, India, [2]Department of Forensic Medicine and Toxicology, Era's Lucknow Medical College and Hospital, Lucknow, India

Correspondence: *raghavendra230518@gmail.com*; Tel.: + 91 953 2906700

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Abstract

Objective. This study aimed to precisely identify the location of the adductor canal to assist knee surgeons during procedures. **Materials and Methods.** We utilized twenty formalin-fixed cadavers to measure the length of the lower limb from the mid-inguinal point (MIP) to the base of the patella and divided the measured length into three parts: the proximal, middle, and distal. After dissecting the adductor canal, we measured the distance between the MIP and the proximal foramen and the distal foramen (adductor hiatus), the distance between the distal foramen and the base of the patella, and the length of the adductor canal. We also measured the location of the proximal and distal foramina concerning the upper and lower limits of the middle third of the thigh. **Results.** The mean lengths of the thigh and adductor canal were 39.59±3.6 cm and 15.24±2.26 cm, respectively. The average distances between the MIP and the proximal and distal foramina and between the distal foramen and the base of the patella were 14.39±1.98 cm, 29.56±2.22 cm, and 10.28±1.87 cm, respectively. In 75% of lower limbs, the proximal foramen was below the upper limit of the mid-third of the thigh, with an average distance of 1.74 cm, whereas in 85% of cases, the distal foramen was below the lower limit of the mid-third of the thigh, with an average distance of 3.3 cm. **Conclusion.** This study suggests that the ideal adductor canal block approach is within the middle third of the thigh.

Key Words: Adductor Canal Block ▪ Adductor Hiatus ▪ Mid-Inguinal Point ▪ Patella.

Introduction

For many years, postoperative analgesia after knee surgery has been achieved using peripheral nerve blocks, mostly femoral nerve blocks (FNB). However, the major problem with FNB was that it resulted in quadriceps weakness, necessitating the search for other nerve blocks. In the past few years, the adductor canal block (ACB) was first described as a purely sensory nerve block for knee surgeries and postoperative analgesia (1). In recent years, there has also been an increased acceptance of ultrasound-guided ACB during knee surgeries to enhance the delivery of anaesthetics (2). However, the procedure initially relied on surface landmarks to mark the location of the injection site (3). Although ultrasound guidance has several advantages, such technology is still lacking in many developing and underdeveloped countries due to cost and a lack of equipment and training. Hence, anaesthesiologists and clinicians in these regions still depend on the traditional surface landmark technique to perform the block. The rationale for ACB is that the saphenous nerve (sensory nerve) and a part of the obturator nerve pass through the adductor canal of the thigh, and therefore, injecting local anaesthetics in the canal blocks these nerves and provides analgesia. In some cases, a continuous ACB block of the saphenous and/or obturator nerves is essential for postoperative pain management in knee surgery (4). The advantage of ACB over FNB is that it preserves the strength of the quadriceps postoperatively, as reported in several studies (5, 6).

[a]ORCID: 0000-0003-3086-585X
[b]ORCID: 0000-0003-2389-584X

The adductor canal, a musculoaponeurotic tunnel also known as Hunter's canal, is located in the middle of the thigh. It extends to the hiatus magnus (distal foramen), an aperture within the adductor magnus muscle from the apex of the femoral triangle (proximal foramen), also referred to as Scarpa's triangle. This canal is an important route through which neurovascular structures in the lower extremities pass, as it contains vital structures such as the nerve to the vastus medialis, saphenous nerve, femoral vein, and femoral artery. In several studies, ACB for postoperative analgesia has been performed at the mid-thigh level, roughly midway between the anterior superior iliac spine (ASIS) and the superior border of the patella (4, 7).

However, there is still much contention regarding the exact location of the ACB, as found in several studies. The use of ACB is primarily confined to orthopaedic centres with high patient volumes, where skilled anaesthesiologists proficient in regional anaesthesia are available. Nevertheless, in the absence of the aforementioned facility, ACB is still a challenging procedure in many centres. While there has been detailed research on the sonographic localisation of the adductor canal, there is limited information regarding cadaveric studies on the subject in the literature.

Hence, this study aimed to fill this gap by focusing on the precise identification of the adductor canal.

Materials and Methods

The present study was conducted at the Department of Anatomy, King George's Medical University, a major tertiary care centre in Northern India. Twenty formalin-fixed cadavers of both sexes (15 male and 5 female) were included in the study. Thigh length was measured from the mid-inguinal point (MIP) to the base of the patella with the cadaver in a supine position. The thigh was then divided into three segments. The upper and lower margins of the middle segment were marked (Figure 1). The inguinal ligament was identified, and a horizontal incision was made slightly below and parallel to it. Another vertical incision was made, starting from the pubic tubercle and extending down along the medial aspect of the thigh up to the medial aspect of the knee. The skin flap was then reflected laterally. The subcutaneous tissue was removed to expose the fascia lata. It was then incised and reflected laterally. The apex of the femoral triangle (proximal foramen) was identified and marked. The boundaries of the adductor canal were identified. The neurovascular bundle,

Figure 1. Length of the thigh from the mid-inguinal point (point a); To the base of the patella (point b).

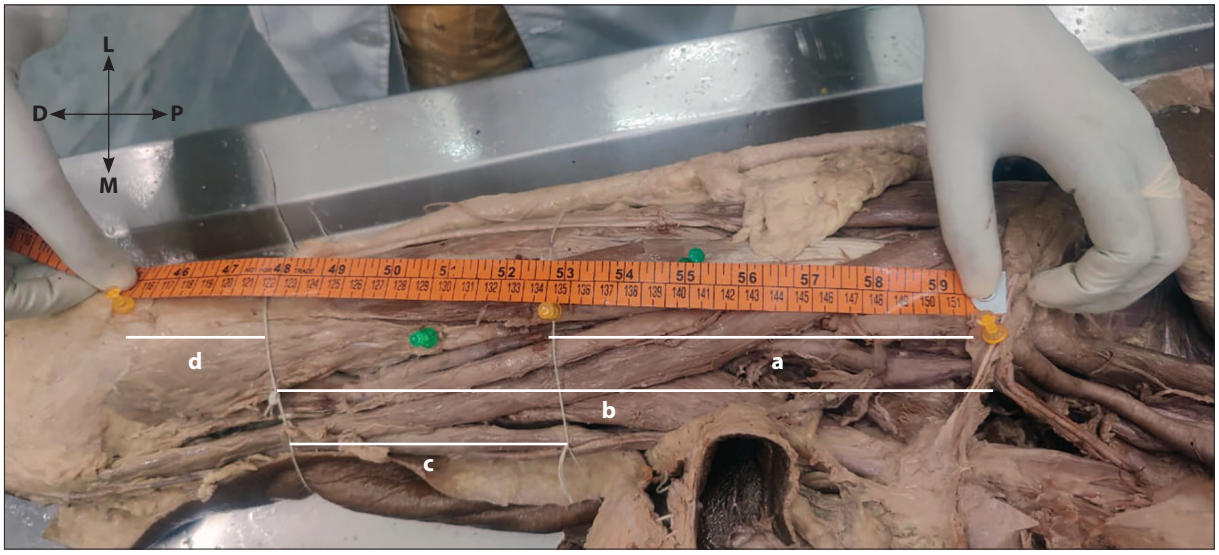

Figure 2. a - distance of the proximal foramen; b - distance of the distal foramen; c - length of the adductor canal; d - distance of the distal foramen from the base of the patella.

which typically includes the femoral artery, femoral vein, and saphenous nerve, was identified. The femoral artery was traced by a blunt dissection up to the adductor hiatus (distal foramen). The following measurements were made (Figure 2):

1) The Length of the thigh from the MIP to the base of the patella;
2) The distance of the proximal foramen from the MIP;
3) The distance of the distal foramen (from the summit of the hiatus) from the MIP, as well as from the base of the patella;
4) The length of the inguinal canal from the proximal foramen to the distal foramen.

Ethics Statement

The Institutional Ethics Committee of King George's Medical University, Lucknow, India, granted ethical approval for this study (Ref No: 131st ECMIIA/P18 dated 9 July 2024).

Statistical Analysis

The data were entered into Microsoft Excel and analysed using SPSS software version 26 (IBM Corp., Armonk, NY). Descriptive statistics, including the mean, standard deviation, and percentage distribution, were calculated for all measured parameters. An independent-sample *t*-test was used to compare the measurements between the right and left lower limbs. A P-value of <0.05 was considered statistically significant.

Results

The mean lengths of the thigh and adductor canal were 39.59±3.6 cm and 15.24±2.26 cm, respectively. The difference in the lengths of the thigh and adductor canal between the right and left sides was not statistically significant. The average distance between the MIP and the proximal and distal foramina was 14.39±1.98 cm and 29.56±2.22 cm, respectively. The mean distance between the distal foramen and the base of the patella was 10.28±1.87 cm. No statistically significant differences were observed in the above parameters between the right and left sides (Table 1).

In 75% of lower limbs, the proximal foramen was below the upper limit of the mid-third of the thigh, with an average distance of 1.74 cm, and in 20% of lower limbs, it was above the upper limit of the mid-third of the thigh, with an average distance of 0.83 cm. In 2 cases, the proximal foramen was almost at the level of the upper limit of the middle third of the thigh (Figure 3). In 97.5% of

Table 1. Paired Samples Statistics

Paired samples		Mean±3.70	Mean change	% mean change	t value	P-value
Pair 1	Length of thigh (right)	39.57±3.70	-0.04	-0.10	-0.556	0.585
	Length of thigh (left)	39.61±3.66				
Pair 2	Distance of the proximal foramen from the mid-inguinal point (right)	14.39±2.02	0	0	0	1.000
	Distance of the proximal foramen (left)	14.39±2.10				
Pair 3	Distance of the distal foramen from the mid-inguinal point (right)	29.32±2.77	-0.49	-1.67	-1.397	0.179
	Distance of the distal foramen from the mid-inguinal point (left)	29.81±2.50				
Pair 4	Length of the adductor canal (right)	15.07±2.40	-0.35	-2.32	-1.080	0.294
	Length of the adductor canal (left)	15.42±2.29				
Pair 5	Distance of the distal foramen from the base (right)	10.48±1.85	0.39	3.72	1.302	0.208
	Distance of the distal foramen from the base (left)	10.09±2.01				

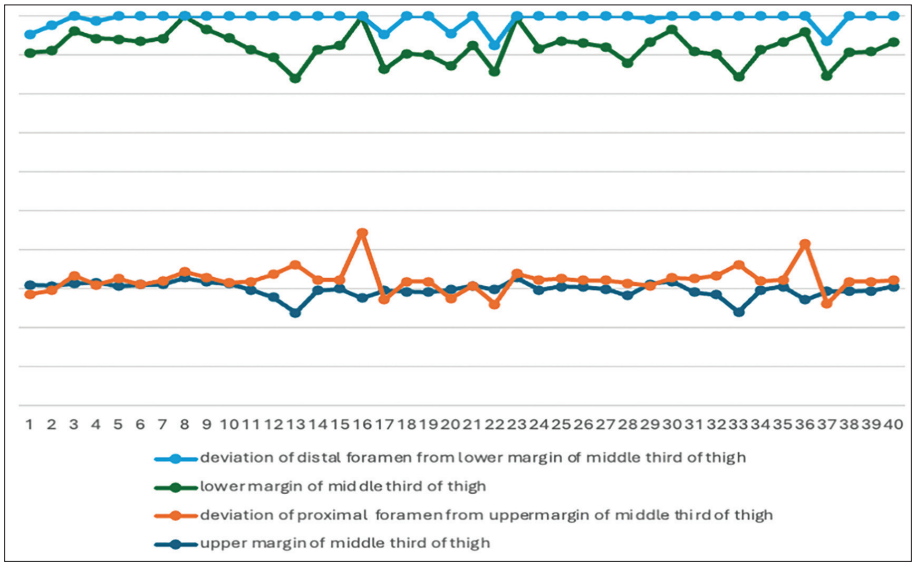

Figure 3. Plot diagram showing the deviation of the proximal and distal foramina in relation to the middle third of the thigh.

cases, the distal foramen was below the lower limit of the mid-third of the thigh, with a mean distance of 3.3 cm, whereas in 1 limb (2.5%), the distal foramen was above the lower limit of the mid-third of the thigh at 0.2 cm (Figure 3).

Discussion

This cadaveric study uniquely employed the mid-inguinal point as a reference for measurements. It revealed a mean adductor canal length of 15.24±2.26 cm and provided precise data on the anatomical position of the proximal and distal foramina relative to the middle third of the thigh. The proximal foramen was located below the upper limit of the middle third in 75% of cases, whereas the distal foramen was located below the lower limit in 97.5% of cases. No statistically significant differences were observed between the right and left sides. In a comparative analysis of the dimensions of the thigh and the adductor canal, discrepancies in the findings were observed across

different studies. In an ultrasonographic study in 2016 involving 22 volunteers, the authors reported an average thigh length of 45.7 cm, an average length of the adductor canal of 11.5 cm, and an average distance of the proximal foramen from the ASIS of 27.4 cm (8). In a cadaveric study in 2019 involving 40 limbs, the average measurements were slightly shorter, with males having a mean thigh length of 44.2 cm, a mean adductor canal length of 10.5 cm, and females having a mean of 42 cm and 8.5 cm, respectively. The mean distance of the proximal foramen from the ASIS was 25 cm and 24 cm in males and females, respectively (9). The ASIS was used as the reference point in both studies (8, 9).

However, our study had a notable deviation from the previous results, in which the mean length of the thigh measured using the MIP was 39.59±3.6 cm, which is lower than that in earlier studies. The MIP was used for thigh length in this study since the MIP and the base of the patella present in the same vertical plane.

Furthermore, the average length of the adductor canal was found to be longer, 15.24±2.4 cm. The average distance of the proximal foramen from the MIP was 14.39±2.02 cm. The author measured the mean distance of the distal foramen from the patella base as 9 cm and 9.5 cm in males and females, respectively, compared to 10.28±1.87 cm in the present study (9). A study conducted in 2016 stated that the anatomical location of the proximal foramen of the adductor canal is located caudal to the midpoint of the thigh, with an average distance of approximately 4.6 cm. Meanwhile, another study found that the proximal foramen is located caudal to the midpoint of the thigh at a mean distance of 4.5 cm in 90% of cases (8, 9). A cadaveric study with a sample size of 17 showed that in 13 specimens, the proximal foramen of the adductor canal was located distally to the midpoint of the thigh at an average distance of 6.5 cm (10).

In contrast, the present study showed that in 75% of lower limbs, the proximal foramen was located below the upper boundary of the mid-third of the thigh at an average distance of 1.74 cm. Meanwhile, the distal foramen is located below the lower boundary of the mid-third of the thigh, with an average distance of 3.3 cm. These variations highlight the importance of understanding individual anatomical variations and emphasize the need to consider multiple sources of evidence when interpreting findings related to adductor canal anatomy.

Limitations of the Study

The sample size and characteristics of the participants may not be representative of the general population. Individual anatomy, height, body habitus, and musculoskeletal differences were not considered. Further research with larger, more heterogeneous samples and possibly the use of imaging and procedural guidance may address some of these limitations and provide more information on the best way to perform ACB.

Future Scope

While the present study provides a detailed surface-based anatomical localization of the adductor canal and its foramina, future studies can build upon this dataset to explore the internal anatomy in greater detail. Specifically, cross-sectional anatomical studies at key levels of the thigh are recommended to assess the depth and spatial arrangement of the femoral artery, vein, saphenous nerve, and nerve to the vastus medialis. Such data will be valuable for refining blind adductor canal block techniques, especially in settings where ultrasound guidance is not available. Additionally, integrating depth measurements, simulated needle trajectories, and safety margins will help translate anatomical insights into safer clinical practice.

Conclusion

The precise placement of the injection is crucial when administering the drug in ACB for optimal anaesthetic effect. The observations made in this study indicate that the proximal foramen of the adductor canal is located distal to the upper border of the middle third of the thigh, and the

distal foramen lies distally to the inferior border of the same region. These findings emphasise the importance of aiming at the distal portion of the mid-third of the thigh while performing ACB. Therefore, the focus should be on this area to avoid accidental injection placement at the midpoint, which may result in an undesirable femoral block. Therefore, by directing attention to the distal end of the middle third of the thigh, anaesthesiologists can refine the precision and effectiveness of ACB procedures to improve patient comfort and results.

What Is Already Known on This Topic:

Patients experienced better quadriceps strength and earlier mobility following adductor canal blocks compared to femoral nerve blocks. No significant complications have been reported when the adductor canal is correctly located and local anaesthetic is administered. Although the technique of the adductor canal block, its anatomy, and its application in knee anaesthesia are well described, it is important to pay attention to the exact localisation of the adductor canal to perform the block and avoid complications. Some earlier studies have also described the anatomical relationships and landmarks of the adductor canal; however, variations still exist. Although the general anatomy is well understood, it is essential to investigate the exact landmarks in more detail.

What This Study Adds:

This study provides the mean distances of the proximal and distal openings of the adductor canal from the mid-inguinal point, a recognisable bony marker, which helps define the canal location more precisely. The study also assessed the reliability of the proximal and distal openings that could be identified within the boundaries of the middle third of the thigh using the MIP landmark, which helped validate the usefulness of the landmark. The study also provided information on the normal range and inter-individual variability, which will be useful in guiding injection techniques.

Authors' Contributions: Conception and design: HS and RS; Acquisition, analysis and interpretation of data: HS, NUS and PS; Drafting the article: HS and RS; Revising it critically for important intellectual content: HS and RS; Approved final version of the manuscript: HS, RS and NK.

Presentation and Awards: Presented at the 12th International Conference of the Society of Clinical Anatomists at the D.Y. Patil Medical College and Hospital, Pune, India.

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Factors Affecting the Quality of Life of Children With Transfusion-Dependent Thalassemia: A Cross-Sectional Study

Ika Purnamasari[1], Candra Dewi Rahayu[1], Tantut Susanto[2], Pratiwi Rita Peperawati[3], Amanah Supriyati[4]

[1]Department of Nursing, Faculty of Health Sciences, Universitas Sains Al Qur'an Wonosobo, Indonesia, [2]Department of Community, Family & Geriatric Nursing, Faculty of Nursing, Universitas Jember, Indonesia, [3]Pediatric Ward, Temanggung General District Hospital, Indonesia, [4]Pediatric Ward, KRT Setjonegoro Wonosobo General District Hospital, Indonesia

Correspondence: *ikapurnama@unsiq.ac.id*; Tel.: + 62 812 26953851

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Abstract

Objective. This study aimed to identify the factors affecting the quality of life (QoL) of children with transfusion-dependent thalassemia. **Materials and Methods.** A cross-sectional study was conducted on 38 hospitalized pediatric patients with thalassemia at two regional hospitals in Indonesia. We used demographic and anthropometric data, as well as the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL), to collect the data. **Results.** The median age of the participants was 11 years (range, 2–18), with a median age at diagnosis of 12.5 months (2 – 84). The average hemoglobin (Hb) level was 8.47 g/dl, and 34% of the patients had blood type O. The interval between blood transfusions was 23.74 days, with a median number of transfusions of 200.5 (range, 22 – 405). The median current weight was 25 kg (range, 9.5 – 50 kg). More than half of the fathers (52.6%) and mothers (50%) of the children with thalassemia had completed only elementary school. The mean total QoL score reported by children was 82.69±13.38, and by parents, 82.6±11.27. Among the PedsQL domains, the children reported the highest scores in social functioning (89.86±15.48) and the lowest in school functioning (74.21±18.06). Similarly, parents reported the highest score in social functioning (91.05±12.95) and the lowest in school functioning (78.42±13.9). Multivariable analysis showed that Hb level and current weight were significantly associated with QoL in children with thalassemia. **Conclusions.** The QoL of children with thalassemia is generally good and is influenced by their current body weight and Hb levels.

Key Words: Children ▪ Quality of Life ▪ PedsQL ▪ Thalassemia.

Introduction

Thalassemia is a genetic disease of blood cells that causes damage to hemoglobin (Hb), the main component of red blood cells, and an oxygen carrier. It leads to a shorter lifespan of red blood cells - 120 days - resulting in below-normal Hb levels (1)which leads to anemia. It is caused by mutation in the DNA of cells that make hemoglobin. Thalassemia should be prevented by premarital screening and prenatal diagnosis which is helpful in decreasing prevalence and future incidence of thalassemia. The most important problem in thalassemia patients are iron overload, cardiac arrhythmia, hepatitis, osteoporosis and endocrine disorder however there are typical signs and symptoms of anemia. People with thalassemia can get treatment as indicated by the degree of seriousness of their condition. Blood transfusion is the common treatment for thalassemia. This review presents the types, diagnosis, prevalence, complications and treatment of thalassemia. Thalassemias are a major public health issue in many populations which many health authorities fail to address. These requirements are notrecognized by measures such as the Global Burden of Disease project, which ranks thalassemia very low in terms of disability-adjusted life years (DALYs. This causes chronic anemia, which significantly affects children's growth, development, and quality of life (QoL). The QoL of children with thalassemia

is affected by the disease itself and its long-term therapy (2). Long-term therapy requires repeated transfusions to treat severe anemia. Repeat transfusions can also lead to hemosiderosis, which is destructive to organs such as the heart, liver, kidneys, and endocrine glands. Patients with hemosiderosis require iron chelation therapy to maintain a long-term prognosis (3). Thalassemia is classified into two main categories based on transfusion requirements: transfusion-dependent thalassemia (TDT) and non-transfusion-dependent thalassemia (NTDT) (4).

World Bank data show that 7% of the global population carries the thalassemia trait. Every year, 300.000-500.000 babies are born with severe Hb disorders, and 50,000 to 100,000 children die due to thalassemia. Indonesia has one of the highest rates of thalassemia trait carriers (3). The 2021 data from the Health Minister of the Republic of Indonesia reported 10,973 thalassemia cases. Children with thalassemia are prone to various complications and challenges that affect their QoL. These include physical and psychosocial aspects such as social, emotional, and school functioning. The factors that affect the QoL of children with thalassemia require attention (5)passed from parents to children, which can be mitigated through screening programs. Inconsistencies in blood transfusions and iron chelation therapy result in physical changes that can cause psychological problems, with anxiety being the most prominent. This study aimed to examine the factors influencing anxiety levels among adolescent thalassemia major survivors. Methods: The research utilized a quantitative approach with a correlational analytic design and cross-sectional method. It included a population of 122 adolescent survivors, all of whom were included using a total sampling technique. Data analysis involved univariate analysis by frequency distribution, bivariate analysis using the chi-square test, and multivariate analysis with logistic regression. Results: The findings of the study showed that adolescent thalassemia survivors experienced varying levels of anxiety: mild anxiety in 70.5%, moderate anxiety in 9.8%, and severe anxiety in 19.7%. Significant associations were observed between anxiety levels and factors such as body image ($P<0.001$).

Age plays an important role in determining the QoL of children with thalassemia. Each developmental stage has its own growth and developmental tasks; hence, the challenges faced also vary accordingly. Age determines children's ability to cope with these tasks and challenges, which, in turn, affects their QoL (6). When children are diagnosed at a young age, this often causes anxiety, fear, and emotional stress in both parents and children. Children also face activity restrictions, changes in physical appearance, and social interactions resulting from the treatment they must undergo, such as repeated transfusions and regular iron chelation drugs (7). Hb level is an essential parameter in thalassemia management, as it may affect the symptoms and complications experienced by the patient (8). Transfusion frequency is also an important element in thalassemia treatment, as regular blood transfusions are necessary to maintain Hb levels within a safe range (9, 10). Additionally, nutritional status plays an integral role in optimizing the health and QoL of patients with thalassemia. Nutritional deficiencies can exacerbate symptoms and increase the risk of complications. Poor nutritional status in children with thalassemia significantly impacts QoL (11). Nutritional deficiencies can lead to decreased energy, lowered resistance to infection, impaired growth and development, and a decline in overall QoL.

This study aimed to determine the QoL of children with thalassemia and to identify and analyze the factors affecting the QoL of children with thalassemia, focusing on the children's age, age at diagnosis, blood type, parents' education degree, pre-transfusion Hb level, transfusion frequency, and nutritional status, and analyzing which factors are the most dominant in influencing it.

Materials and Methods

Research Design, Setting, and Study Population

This cross-sectional study was conducted at two regional hospitals, Temanggung Regional Hospital and KRT Setjonegoro Wonosobo Regional Hospital, between May and June 2024. The sample size was calculated using G*Power 3.1. Based on an expected medium effect size of 0.5, significance level (Type I error, α) of 0.05, and power of 0.90 for a two-tailed test, the minimum required sample size was 34 children with thalassemia. However, 38 participants were studied to account for a 10% attrition rate. Of the 38 participants, 16 were from the Temanggung Regional Hospital and 22 were from KRT Setjonegoro. The inclusion criteria were children aged 2 to 18 years with beta-thalassemia major or intermedia who were receiving routine blood transfusions. A total sampling technique was applied, meaning all eligible patients available during the data collection period were included in the study. The exclusion criteria were children with thalassemia with severe cognitive impairment and parents and children with thalassemia who refused to participate in the study.

Data Collection and Instrument

Data collection was carried out using a questionnaire that covered the patient's characteristics, including initials, date of birth, birth weight, birth length, sex, blood type, parents' education, age at first diagnosis, transfusion frequency, current Hb level, and anthropometric measurements, including the child's current weight and height to determine nutritional status. The children's QoL was measured using the Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedQL) instrument, which contains 23 question items within the QoL domain. They were divided into 4 domains: physical, social, emotional, and school functioning. The domain of physical functioning consisted of 8 questions assessing the child's ability to perform daily physical activities such as walking, running, lifting objects, bathing, and participating in sports or active play. The social functioning domain assesses the child's ability to interact with peers, maintain friendships, and avoid social exclusion. Items include questions about getting along with other children, being teased, or having difficulties in group activities. The emotional functioning domain includes 5 items addressing the child's feelings of anxiety, sadness, anger, and fear, as well as difficulty sleeping due to emotional distress. The school functioning domain consists of five items related to academic engagement and school performance, such as paying attention in class, forgetting things, keeping up with schoolwork, and missing school due to health problems or doctor visits. The instrument was completed by both the children and their parents. Respondents were asked to choose from "never" (score 0 and worth 100) to "always" (score 4 and worth 0). The scale score is calculated as the sum of the item scores divided by the number of items answered. Domain scores are scaled in a positive direction, which means that higher scores indicate better QoL. The scores are divided into two categories: if the total score is less than 70, the child's QoL is considered poor, and vice versa (12).

Ethical Consideration

This study obtained a research permit and research ethics approval from the Chairperson of the Research Ethics Commission of the Institute for Research, Publishing, and Community Service (LP3M) of Universitas Sains Al-Qur'an (number 018/EC/LP3M-UNSIQ/V/2024). The researcher explained the study to the patients and their parents and requested that they sign an informed consent form as proof of the patients' approval.

Statistical Analysis

The data were statistically analyzed using the IBM SPSS Statistical Package version 26. Descriptive statistics, including frequency, percentage, mean, and standard deviation (SD), were calculated to identify the characteristics of the respondents. Bivariate analysis was performed using Spearman's correlation test to analyze the relationships between age,

birth weight, birth length, sex, blood type, parents' education, age at diagnosis, transfusion frequency, current Hb level, nutritional status, and QoL. A multiple logistic regression analysis was performed to assess the impact of various factors on the QoL of children with thalassemia.

Results

Characteristics of the Respondents

The respondents' characteristics are presented in Table 1. Regarding blood type distribution, the majority of participants had blood type O (34.2%),

Table 1. Respondents' Characteristics

Variable	Frequency	%	Mean ± SD*	Median (min – max‡)
Sex				
Male	22	57.9	-	-
Female	16	42.1		-
Nutritional status				
Underweight	10	26.3	-	-
Normal	25	65.8	-	-
Overweight	2	5.3	-	-
Obesity	1	2.6	-	-
Blood type				
A	7	18.4	-	-
B	11	28.9	-	-
AB	7	18.4	-	-
O	13	34.2	-	-
Fathers' education				
Elementary school	20	52.6	-	-
Junior high school	9	23.7	-	-
Senior/vocational high school	6	15.8	-	-
Diploma 3	2	5.3	-	-
Bachelor degree	1	2.6	-	-
Mothers' education				
Elementary school	19	50	-	-
Junior high school	9	23.7	-	-
Senior/vocational high school	6	15.8	-	-
Diploma 3	3	7.9	-	-
Bachelor degree	1	2.6	-	-
Clinical Characteristics Factors				
Age (year)	-	-	9.76±4.23	11 (2-18)
Birth weight (grams)	-	-	2865.8±465.7	2850 (1500-4000)
Birth length (cm)	-	-	47.55±1.69	47 (45-52)
Current weight (kg)	-	P20-P100‖	26.47±10.19	25 (9.5-50)
Current height (cm)	-	P20-P100‖	123.55±20.37	129.5 (68-150)
BMI†	-	-	16.74±2.95	15.59 (12.64-25.51)
Age at diagnosis (months)	-	-	23.17±20.35	12.5 (2-84)
Hb§ (g/dl)	-	-	8.37±1.39	8.35 (5.6-12.0)
Transfusion frequency (days)	-	-	23.74±9.71	21 (14-60)

*Standard deviation; †Body mass index; ‡Minimum – maximum values; §Hemoglobin; ‖Between the 20th and 100th percentiles of reference growth charts.

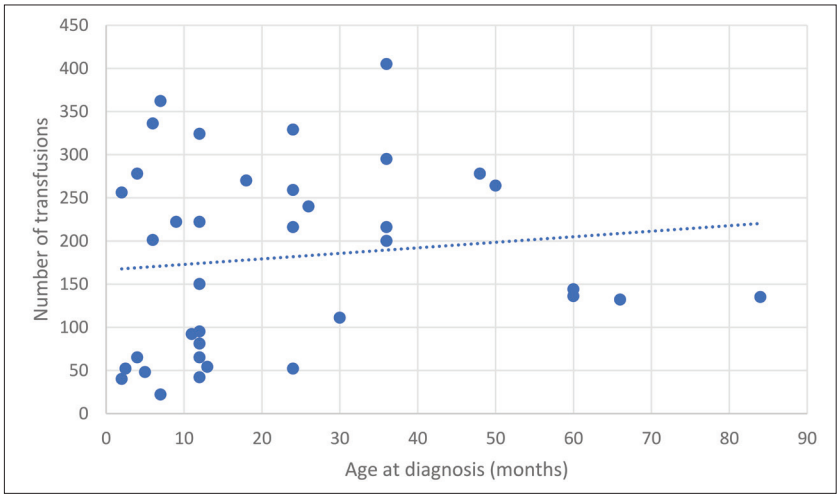

Figure 1. Distribution of age at diagnosis and number of transfusions.

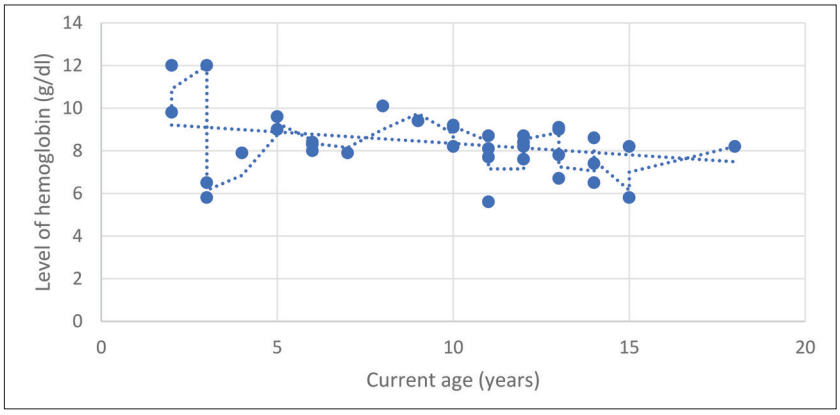

Figure 2. Distribution of hemoglobin levels and age.

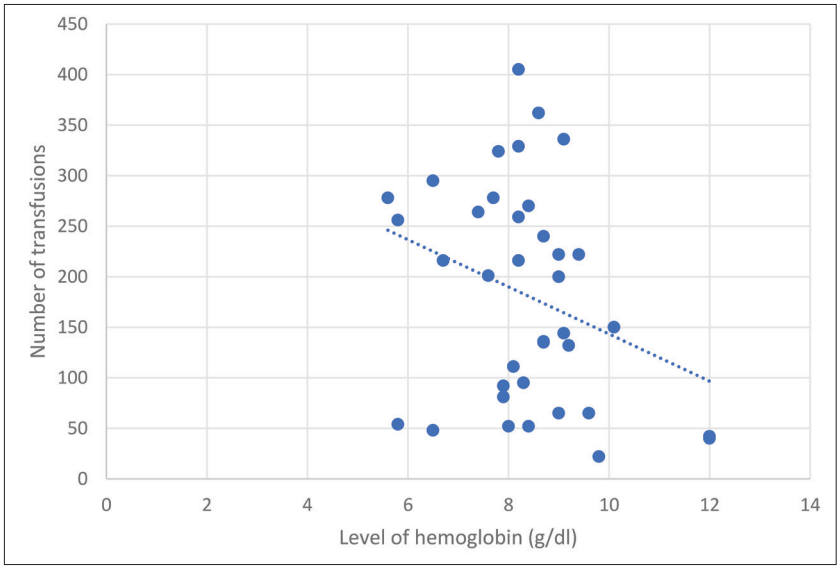

Figure 3. Distribution of hemoglobin levels and number of transfusions.

followed by blood types B (28.9%), A (18.4%), and AB (18.4%). The majority of patients were boys (22 patients, 57.9%). In terms of nutritional status, the majority of participants had a normal weight (65.8%), while 26.3% were underweight. A smaller proportion was classified as overweight (5.3%) and obese (2.6%). Most of the parents of the children with thalassemia had primary school education (20 fathers (52.6%) and 19 mothers (50%)). The respondents had an average age of 9.76 years and were in the school-age category. They also had normal birth weight (2500-4000 grams) and birth length (45-53 cm). The current weight and height averaged 26.47±10.19 kg and 123.55±20.37 cm, respectively. The age of the children at diagnosis ranged from 2 months to 7 years. The median Hb level was 8.35 (5.6–12.0) g/dl, with an interval between their transfusions of 23.74 days, and the median number of transfusions was 200.5 (range 22–405).

The distributions of Hb levels, age (current age and age at diagnosis), and number of transfusions received by patients with thalassemia are presented in the scatter plot diagrams in Figures 1-3. As shown in the figure, children aged 2–6 years demonstrated relatively higher and more stable Hb levels, particularly among those diagnosed

Table 2. Relationship Between Age, Hemoglobin Level, and Number in Children With Thalassemia

Variable 1	Variable 1	Pearson's r	Direction and Strength of Correlation
Current age	Current hemoglobin	–0.33	Weak negative
Current age	Number of transfusions	0.88	Strong positive
Current hemoglobin	Number of transfusions	–0.31	Weak negative

early and who received timely transfusion therapy. In contrast, patients aged 13 years and older showed a tendency toward lower or fluctuating Hb levels, despite having received a significantly greater number of transfusions. These findings indicate that Hb concentration may not be directly proportional to the transfusion quantity but is likely influenced by multiple factors, including transfusion frequency, individual physiological response, and the presence of complications. Additionally, patients diagnosed before the age of 12 months tended to achieve better Hb control when managed with regular transfusions, whereas those diagnosed later or with delayed initiation of transfusion therapy commonly exhibited lower Hb levels despite a higher transfusion burden.

According to the data presented in Table 2, a very strong positive correlation was found between the current age of the patients and the total number of transfusions received (r=0.88), indicating that older children had undergone significantly more transfusions. This finding was expected, given that patients with thalassemia major require lifelong regular transfusion therapy. In contrast, a weak negative correlation was observed between Hb levels and the number of transfusions (r=–0.31), suggesting that a greater number of transfusions does not necessarily result in higher Hb levels. This may be influenced by other factors, such as individual resistance to transfused red blood cells, delays in transfusion schedules, or secondary complications. Additionally, a weak negative correlation was found between patient age and Hb level (r=-0.33), indicating that older children tended to have lower Hb concentrations, which may be attributed to the cumulative effects of bone marrow damage or chronic disease-related complications.

The Quality of Life of Children with Thalassemia

Table 3 shows that the average QoL scores of children with thalassemia, as reported by both children and their parents, were in the "good" category, with scores of 82.69±13.38 and 82.6±11.27, respectively. The school function domain had the lowest score of 74.21±18.06 and 78.42±13.9, and the social function domain had the highest score of 89.86±15.48 and 91.05±12.95.

Factors Affecting Quality of Life

The factors influencing the QoL of children with thalassemia are presented in Table 4, which illustrates the relationships between QoL and various demographic and clinical parameters, including age, birth weight, birth length, current body weight, current height, body mass index (BMI), age at diagnosis, current Hb levels, and transfusion frequency. Spearman's correlation analysis was conducted to examine the association between

Table 3. The Quality of Life of Children with Thalassemia based on PedsQL

PedsQL Domain	Children report		Parents report	
	Mean+ SD	Median (min-max)	Mean + SD	Median (min-max)
Physical function	84.78+16.79	90.62 (40.63-100)	80.92+20.21	87.5 (40.63-100)
Emotional function	80.65+12.9	85 (45-100)	81.05+14.71	85 (45-100)
Social function	89.86+15.48	97.5 (35-100)	91.05+12.95	97.5 (35-100)
School function	74.21+18.06	80 (30-100)	78.42+13.9	82.5 (50-100)
Quality of life	82.69+13.38	86.95 (48.91-98.91)	82.6+11.27	85.3 (54.35-100)

Table 4. The Relationship Variables and Transfusion Frequency to Children's Quality of Life

Variable	Quality of Life		P*	r†
	Good	Poor		
Age	10.35±4.00	7.14±4.53	0.159	-0.233
Birth weight	2825.81±469.73	3042.86±435.34	0.278	0.181
Birth length	47.65±1.74	47.14±1.46	0.509	-0.11
Current weight	28.22±10.30	18.73±4.93	0.010*	-0.412
Current height	126.79±20.44	109.21±13.31	0.014*	-0.397
Body mass index	17.01±3.10	15.52±1.83	0.415	-0.136
Age at Diagnosis	2.17±1.74	1.51±1.07	0.479	-0.118
Hb‡	8.57± .35	7.51±1.32	0.013*	-0.295
Transfusion frequency	22.32±10.25	30	0.003*	0.476

*Significant (P<0.05); †Correlation coefficient between variable and children's quality of life; ‡Hemoglobin.

these variables and the children's QoL. The results indicated that BBS was significantly negatively correlated with QoL (r=-0.412, P=0.010). This relationship was classified as moderate in strength with a negative directional association. Similarly, TBS was found to have a significant negative correlation with QoL (r=-0.397, P=0.014), indicating a weak negative correlation. Furthermore, an analysis of age at diagnosis, Hb levels, and transfusion frequency using Spearman's correlation test revealed that transfusion frequency is significantly correlated with QoL (r=0.467, P=0.003). This suggests a moderate positive association between transfusion frequency and QoL (13).

A Multivariate logistic regression analysis was conducted to further investigate the factors influencing the QoL of children with thalassemia, as detailed in Table 5. The analysis revealed that current weight (OR=0.788; 95% CI=0.636–0.976; P=0.029) and Hb level (OR=0.365; 95% CI=0.146–0.914; P=0.031) were significantly associated with children's QoL. Specifically, lower weight and lower Hb levels were predictors of reduced QoL. Other variables, including age, current height, and transfusion frequency, did not show statistically significant associations (P>0.05).

Table 5. Results of Multivariate Logistic Regression Test on Children's Quality of Life

Variable	P	OR*	95% CI†
Age	0.902	0.945	0.386-2.316
Current weight	0.029‡	0.788	0.636-0.976
Current height	0.671	1.036	0.879-1.221
Hb§	0.031‡	0.365	0.146-0.914
Transfusion frequency	0.3	1.078	0.935-1.242

*Odds ratio; †Confidence interval provides a range within which the true result is likely to lie; ‡Significant (P<0.05); §Hemoglobin.

Discussion

This study explored the factors influencing QoL among children with transfusion-dependent thalassemia, highlighting that Hb level and current weight emerged as the most significant determinants. They were associated with four QoL domains, particularly school functioning. Various studies have shown that the QoL of children with thalassemia has a lower score than that of healthy children. The results of all studies also showed lower scores on all dimensions of the PedsQL, including physical, emotional, social, and school dimensions (14). This study is inconsistent with a previous study in which the assessment of QoL among children with thalassemia using the PedsQL revealed generally positive outcomes across multiple domains, as reported by both children and their parents. The highest scores were observed in the social functioning domain, with mean scores of 89.86 (children) and 91.05 (parents), indicating strong peer interactions and social integration. Emotional and physical functioning also showed favorable scores, although children rated their

physical function slightly higher than their parents did (15). It reflects a child's internal emotional well-being and potential psychological distress.

Notably, school functioning emerged as the lowest-rated domain, with mean scores of 74.21 (children) and 78.42 (parents), suggesting potential academic or cognitive challenges related to the condition. Overall life quality was rated similarly by both groups, with mean scores of 82.69 (children) and 82.6 (parents). These findings highlight the relatively good perceived QoL among children with thalassemia while underscoring the need for targeted support in the academic domain. Earlier studies have also shown that school and social functioning factors are highly influential in the QoL of children with thalassemia. Mediani et al. (16) our knowledge of the factors affecting the quality of life of thalassemic children is limited and some previous studies have shown contradictory results. The study aimed to analyze factors impacted to the QOL of school-age thalassemic children in Indonesia. A correlational analytic with a cross-sectional approach was conducted at a district hospital in Sumedang Indonesia from May to July 2017. The PedsQL generic core scale was used to assess 55 school-age thalassemic children with thalassemia major. Data were analyzed bivariate by using Pearson and Spearman Correlation Test and multivariate analysis used multiple linear regression to determine the factor that most impacting the QOL thalassemic children. The findings showed that the average of QOL of school-age thalassemic children was 66.54+12.85. There was a significant correlation between QOL with pretransfusion Hb level (P=0.018, α=0.05 stated that the most dominant factor affecting the QoL of school children is transfusion frequency. This is because frequent transfusions can compromise their school function; for example, they may be unable to attend school meetings, which may affect their QoL. A study conducted at Cut Meutia Hospital Aceh revealed that the average pediatric patient with thalassemia had a poor QoL, especially in terms of school functioning (17). Another study at Al Ihsan Bandung General Hospital in 2019 showed a similar result: thalassemic pediatric patients had poor QoL, which further interfered with their other life-affecting functions, such as physical, emotional, school, and social functioning. Children with thalassemia in Jeddah, Saudi Arabia, have a similar low QoL, especially prior to blood transfusion, despite significant improvement after the procedure.

Theoretically, the QoL of children with thalassemia is influenced by many factors, including age, sex, age at first transfusion, Hb level, underlying disease, and social support from family and community. These factors significantly affect the QoL of children with thalassemia (6). However, there are differences in the influencing factors in each study related to the QoL of children with thalassemia. This study indicates that children diagnosed at an older age tended to receive a higher number of transfusions. This may reflect delayed diagnosis or treatment initiation, which could lead to an accumulated transfusion requirement over time to correct prolonged anemia. Early diagnosis and timely initiation of transfusion therapy are essential to prevent complications and reduce transfusion burden. This study also showed that transfusion frequency, current weight, and Hb levels significantly impacted QoL. These findings are consistent with prior research, indicating that poor nutritional status and anemia significantly impair health-related quality of life (HRQoL) in this population. Malnutrition is highly prevalent among pediatric patients with thalassemia and has been shown to negatively affect growth, physical function, and overall QoL. In one study, approximately 48.2% of children were malnourished, and malnutrition was strongly associated with diminished QoL scores (18). A higher transfusion frequency is associated with a lower QoL in children with thalassemia, especially in the physical, psychological, social, and educational domains. It also increases the risk of transfusion-transmitted infections, which affect the physical and psychological aspects of children (18-20)physical activities, competencies, and family stability are all compromised in some way. Assessing HRQoL in individuals with thalassaemia and identifying variables that contribute to low quality of life is

crucial. Aim: To correlate HRQoL and factors affecting among different age groups in transfusion-dependent thalassaemia patients. Materials and Methods: A cross-sectional study was conducted at MGM College and Hospital, Navi Mumbai from October 2020 to August 2021, 70 thalassaemia patients aged 8-25 years registered for regular blood transfusions were included in the study and divided into three age groups: Group-I (8-12 years. The recommended transfusion frequency for children with thalassemia is every 3–4 weeks (approximately 12 times/year or more) to maintain Hb levels, prevent complications, and support QoL. However, it must be balanced with monitoring and iron chelation therapy to prevent long-term transfusion side effects, such as iron overload and organ damage (21, which results in anemia. Packed red blood cell (PRBC22).

In this study, the other factor that affected the QoL of children with thalassemia was their current body weight. Body weight is one of the indicators used to determine the nutritional status of children, in addition to length or height and other anthropometric measures. A previous study showed that the majority of children with thalassemia are underweight (23). This affects the nutritional needs of patients with thalassemia. Children with thalassemia often suffer from malnutrition due to the effects of long-term therapy, such as iron chelation therapy, multiple endocrinopathies, cellular hypoxia due to anemia, and frequent transfusions. In a 2021 study by Biswas et al., malnutrition had a very negative impact on the QoL of children with thalassemia, with a P-value of 0.009 (18). The findings of this study indicate that current body weight significantly affects the QoL of patients with thalassemia. This relationship is mediated by alterations in the nutritional status. Adolescents with thalassemia who exhibit poor nutritional status have a reduced QoL compared to their well-nourished peers. Undernutrition is also associated with growth impairment, such as short stature, and contributes to a diminished overall QoL (24) Scopus, Research gate, and Web of Sciences to evaluate the prevalence of nutritional disorders in patients with BTM worldwide in relation to their body composition and possible etiological factors. In addition, we reviewed the published nutritional intervention studies. Results: 22 studies on the prevalence of undernutrition (12 countries.

The next factor affecting the QoL of children with thalassemia in this study was Hb level. Higher Hb levels were associated with a better QoL in children with thalassemia. Children with higher Hb levels tended to have significantly better QoL scores (6). One of the most prominent manifestations of thalassemia is decreased Hb levels (25) i.e., homozygous β-thalassemia, β-thalassemia/Hb E, and Hb Bart's hydrops fetalis. Laboratory diagnosis of thalassemia requires a number of tests including red blood cell indices and Hb and DNA analyses. Thalassemic red blood cell analysis with an automated hematology analyzer is a primary screening for thalassemia since microcytosis and decreased Hb content of red blood cells are hallmarks of all thalassemic red blood cells. However, these two red blood cell indices cannot discriminate between thalassemia trait and iron deficiency or between α- and β-thalassemic conditions. Today, Hb analysis may be carried out by either automatic high-performance liquid chromatography (HPLC. The damage occurs due to structural disorders of Hb formation (abnormal Hb), characterized by the absent or decreased synthesis of one or more globin chains (26). Efforts to raise and maintain Hb levels are carried out by administering transfusions. Transfusion frequency influences the QoL of patients. However, the transfusion regimen administered to patients with thalassemia to maintain Hb levels above 9-10.5 g/dl improves QoL in children. Appropriate management of serum ferritin levels and the application of a collaborative approach to treatment have been shown to be effective in increasing life expectancy in patients with thalassemia (27). Consistent with the results of this study, blood Hb levels had the most significant relationship with the QoL of patients (P=0.03). QoL and blood transfusion also had a significant relationship (P=0.003) (28). Children with thalassemia in Jeddah, Saudi Arabia, also have a similar low QoL, especially before blood transfusion, despite significant improvement after

the procedure (29). Therefore, maintaining Hb ≥9 g/dl is very beneficial because it can prevent the emergence of various complications that may arise in children with thalassemia (30).

Children with thalassemia may experience impaired physical and psychological growth and development. Therefore, transfusion plays a crucial role in increasing blood Hb levels to maintain the stability of growth and development processes. Additionally, proper and adequate nutrition, nutritional counseling tailored to patients with thalassemia, provision of nutritional supplements, and periodic evaluation of nutritional status are suggested as interventions that should be addressed by parents and are necessary for patients with thalassemia (31). With proper nutrition, children's QoL, growth, and development are well maintained (32). This also serves as an intervention to prevent complications due to decreased Hb levels and malnutrition (33).

Overall, children receiving routine treatment have better QoL (29). A study by Mikael in Iraq (34) revealed that patients with major thalassemia have a lower QoL than those with intermediate thalassemia. The age of first diagnosis correlates positively with QoL. It is important to evaluate the QoL of children with thalassemia to enable targeted efforts to enhance it. A case in point is the provision of health education for parents of children with thalassemia (35).

Limitations of the Study

This study has limitations that should be acknowledged, including the variation in the number of samples and clinical parameters, such as serum ferritin levels, hepatomegaly, and splenomegaly, which lead to different factors affecting the QoL of children with thalassemia. Future research should focus on incorporating these clinical variables to provide a more comprehensive understanding of the factors influencing the QoL of children with thalassemia. Nevertheless, the results of this study can serve as a basis for determining interventions in children with thalassemia, especially in Hb level monitoring and nutritional interventions. Interventions to be considered based on the results of this study include maintaining Hb levels in children with thalassemia through regular blood transfusions, regular nutritional status observation (weight and height), and specific nutritional programs for children with thalassemia to improve their weight status and, ultimately, their QoL. Family involvement in therapy regimen compliance, educational and psychological programs, and counseling are also interventions that should be considered.

Conclusions

In this study, age, birth weight, birth length, BMI, and age at diagnosis were not correlated with the QoL of children with thalassemia. Transfusion frequency, current body weight, and pre-transfusion Hb levels were significantly associated with the QoL of children. Weight loss is closely related to malnutrition, which is strongly associated with health status. The overall QoL of the children with thalassemia was categorized as good.

What Is Already Known on This Topic:

The quality of life (QoL) of children with thalassemia is influenced by a combination of clinical signs, such as fatigue, pale, enlarged abdomen due to hepatomegaly or splenomegaly, and poor growth, as well as routine transfusions as the primary management of thalassemia and other factors, namely demographics and psychosocial factors, including family income, education level, and caregiving burden. These factors are interrelated and can impact a child's physical, emotional, social, and school functions.

What This Study Adds:

This study showed that transfusion frequency, current hemoglobin (Hb) levels, and body weight are significantly related to the QoL of children with thalassemia. The results of this study are basic data that can be used to determine more specific actions to improve the QoL of children, such as the innovation of appropriate nutritional interventions to maintain children's weight in normal nutritional status, maintain Hb levels through regular blood transfusions and chelation therapy, and family involvement in therapy regimen compliance. Educational, psychological, and counseling programs are also interventions that should be considered. In addition, these results can be further developed through research that modifies factors significantly related to the QoL of children.

Authors' Contributions: Conception and design: IP and CDR; Acquisition, analysis, and interpretation of data: IP, PRP, and AS; Drafting the article: IP and CDR; Revising it critically for important intellectual content: IP and TS; Approved final version of the manuscript: IP, TS, PR, AS, and CDR.

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Narrative Review
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Disparities in Obstetric and Anaesthetic Care Between Migrant and Native Populations in High-Income Countries: A Narrative Review

Konstantina Kalopita[1, a], Georgios Tsiotras[2, b], Rami H. Al-Rifai[3, c], Elpidoforos S. Soteriades[4, 5, d]

[1]Department of Anaesthesiology and Pain Medicine, "Helena Venizelou" General Hospital, Athens, Greece, [2]Department of Business Administration, University of Macedonia, Greece, [3]Institute of Public Health, College of Medicine and Health Sciences, United Arab Emirates University, United Arab Emirates, [4]Healthcare Management Program, School of Economics and Management, Open University of Cyprus, Nicosia, Cyprus, [5]Environmental and Occupational Medicine and Epidemiology, Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, USA

Correspondence: *ntikal@hotmail.com*; Tel.: + 30 694 4353918

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Abstract

Objective. This narrative review aimed to investigate the potential differences in antenatal care provision, perinatal outcomes, and administration of obstetric neuraxial analgesia between migrant women and their native counterparts in high-income countries. **Methods.** Between March and July 2024, we searched four electronic databases through Ovid and PubMed: Medline, Embase, Global Health, and Maternity and Infant Care. The search terms used included "migrant", "refugee", "asylum seeker", "perinatal", "antenatal", "pregnancy", "neonate", "obstetric anaesthesia", "neuraxial analgesia", and "outcome". We included peer-reviewed articles published in English that presented data on the provision of antenatal and perinatal care, as well as the administration of obstetric neuraxial analgesia to refugee mothers who migrated to high-income countries. **Results.** Among the 795 screened records, 41 studies met the inclusion criteria. Of these, ten focused on obstetric neuraxial analgesia administration, while the remaining studies highlighted the differences in antenatal care and perinatal outcomes. **Conclusion.** Access to antenatal care, utilisation of neuraxial analgesia, and perinatal and neonatal outcomes for migrant women differ from those of their native counterparts, reflecting the significant challenges encountered during the perinatal period.

Key Words: Antenatal Care ▪ Immigrants ▪ Refugees ▪ Obstetric Anaesthesia ▪ Perinatal Health.

Introduction

The significant influx of refugees resettling or seeking asylum due to poor living conditions, social conflict, and/or war has turned migration into a global health concern. Even when host countries implement supportive policies for the well-being of immigrant populations, displacement from native countries poses substantial risks to individuals and families, including their health (1). Refugee women, in particular, represent an exceptionally vulnerable group regarding adverse reproductive outcomes (1).

Antenatal care is essential for monitoring the health of both the pregnant individual and foetus, identifying potential complications, and enabling timely medical interventions (1). Although it plays a vital role in global maternity care services, antenatal care faces substantial challenges in refugee populations. Factors contributing to these challenges include language barriers, limited access to healthcare, inadequate insurance coverage, socioeconomic hardships, nutritional deficiencies, and cultural differences. Thus, insufficient provision of antenatal care is linked to adverse obstetric and neonatal health outcomes (2).

[a]ID: https://orcid.org/0000-0002-7977-9939
[b]ID: https://orcid.org/0000-0002-2618-6937
[c]ID: https://orcid.org/0000-0001-6102-0353
[d]ID: https://orcid.org/0000-0001-6224-421X

According to the World Bank (2021) (3), over 3,500,000 refugees have resettled in high-income countries (4), where healthcare provision is generally expected to be superior to that in middle- and low-income countries. The delivery of high-quality antenatal and perinatal care for migrants in these high-income settings could potentially reduce adverse obstetric and neonatal outcomes in this population. However, a recent study in the Netherlands reported a higher rate of perinatal mortality among asylum seekers compared to native Dutch women (5). Similarly, a comprehensive Swedish study reviewing migrant women's experiences of maternity care across various European countries found that migrants encountered higher risks of poor self-rated health, gestational diabetes, preterm birth, stillbirth, and low birthweight infants (6).

Conversely, numerous studies have identified a phenomenon known as the "healthy-migrant effect" or the "migrant health paradox", wherein migrants exhibit better health outcomes than the host population with similar demographic and socioeconomic characteristics (7-9). The healthy migrant effect is paradoxical because immigrants, who are associated with low socioeconomic status, disadvantaged lifestyles, and poor antenatal care, are expected to experience more adverse birth outcomes than native-born individuals. However, the majority of current evidence, as cited, indicates the contrary (7-9).

Migrants are defined as "individuals who relocate their place of residence, regardless of the reason for their migration or their legal status". In contrast, refugees or asylum seekers are described as "displaced persons in need of international protection due to fears of persecution, war, violence, or other conditions that significantly disrupt public order" (10, 11). This literature review aims to provide a thorough synthesis of the evidence regarding perinatal care for migrants, refugees, and asylum seekers—collectively referred to as "migrants"—in high-income countries. The review evaluates existing data on maternity care related to obstetric outcomes among immigrants and highlights barriers affecting the provision of antenatal care worldwide.

This study aimed to investigate whether access to antenatal care, use of labour neuraxial analgesia, and perinatal and neonatal outcomes differ between migrant women and their native counterparts in high-income countries.

Materials and Methods

Between March and July 2024, we searched four electronic databases through Ovid and PubMed: Medline, Embase, Global Health, and Maternity and Infant Care. The search terms were "migrant", "refugee", "asylum seeker", "perinatal", "antenatal", "pregnancy", "neonate", "obstetric anaesthesia", "neuraxial analgesia", and "outcome". Table 1 provides details of the search strategy and search terms used. To verify the quality of the article, both the six-point Scale for the Assessment of Narrative Review Articles (SANRA) and a seven-item checklist were utilised. The checklist facilitated the identification of key questions concerning the work, the literature search process, and its quality. It also enabled the assessment of the article as a narrative review, highlighting its implications for future research and clinical practice. The application of the SANRA scale ensured the proper structure of the article by incorporating essential components: presentation of the review's meaning and purpose, description of the literature search, references to key issues, scientific reasoning, and presentation of relevant data pertaining to the final points of the article.

We included articles published in peer-reviewed English-language journals between 1996 and 2024 that provided data on antenatal care provision, obstetric neuraxial analgesia administration, and described perinatal and neonatal outcomes of infants born to refugee mothers who migrated to high-income countries. There were no restrictions based on the time the migrants had been in the receiving country. For inclusion in this review, we identified observational studies (including cohort, case-control, and cross-sectional studies) that offered comparative analyses of outcomes between migrant and non-migrant women (Tables 2 and 3), as well as narrative reviews. Furthermore, we examined

the reference lists of pertinent papers to identify additional studies that met the inclusion criteria but were missed during the search process.

In our database search strategy, we also identified and extracted the number of publications that provided data that had not yet been published as full-text articles in scientific journals but were only available in abstracts. Publications were excluded if they were not in English, if they focused on refugee women who migrated to low- or middle-income countries, or if they analysed only obstetric outcomes of parturient refugees or solely neonatal outcomes of infants born to refugee mothers who migrated to high-income countries.

Results

The quality of narrative reviews can be assessed using the SANRA scale and six quality criteria metrics: (1) justification of the article's importance for the readership, (2) statement of concrete aims or formulation of questions, (3) description of the literature search, (4) referencing, (5) scientific reasoning, and (6) appropriate presentation of data. The first two criteria were satisfied in the Introduction and aim of the study, whereas the third and fourth criteria are further addressed in the literature search and study selection. The fourth criterion is satisfied by the statements

Table 1. Database Search Terms

Database searches through OVID: Medline, Embase, Global Health, Maternity and Infant Care – March 2024
Pregnancy AND immigrants AND outcomes
Pregnancy AND refugees AND outcomes
Pregnancy AND asylum seekers AND outcomes
Pregnancy AND immigrants AND outcomes and Pregnancy AND immigrants AND outcomes and Pregnancy AND asylum seekers AND outcomes
Antenatal care AND refugees
Antenatal care AND immigrants
Antenatal care AND asylum seekers
Antenatal care AND refugees
Perinatal care AND refugees + Antenatal care AND immigrants + Antenatal care AND asylum seekers
Perinatal care AND refugees
Perinatal care AND immigrants
Perinatal care AND asylum seekers
Perinatal care AND refugees + Perinatal care AND immigrants + Perinatal care AND immigrants
Obstetric anaesthesia AND immigrants
Obstetric anaesthesia AND refugees
Obstetric anaesthesia AND asylum seekers
Obstetric anaesthesia AND immigrants + Obstetric anaesthesia AND refugees + Obstetric anaesthesia AND asylum seekers
Neuraxial analgesia AND immigrants
Neuraxial analgesia AND refugees
Neuraxial analgesia AND asylum seekers + Neuraxial analgesia AND asylum seekers
Neuraxial analgesia AND immigrants+ Neuraxial analgesia AND refugees
PubMed searches – April 2024
Pregnancy AND outcomes AND refugees OR asylum seekers OR migrants
Antenatal care AND refugees OR asylum seekers OR migrants
Perinatal care AND refugees OR asylum seekers OR migrants
Obstetric anaesthesia AND refugees OR asylum seekers OR migrants
Neuraxial analgesia AND refugees OR asylum seekers OR migrants

Table 2. Overview of the 31 Studies Examining Perinatal Outcomes Among Migrant Women in High-Income Countries*

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Agbemenu et al. (12)	2019	To compare: (1) Pre-pregnancy health and prenatal behaviour; (2) Prenatal history and utilisation of prenatal care; and (3) Labour and birth outcomes among African refugee women, U.S.-born Black women, and U.S.-born White women.	Retrospective cohort.	Burundi, Democratic Republic of the Congo, Eritrea, Rwanda, and Somalia.	USA	789 African refugees, 17,487 Black women, and 59,615 White women.	The healthy immigrant effect extends to reproductive health in African refugee women, even with inadequate prenatal care: 1. Fewer maternal medical risk factors: 34.5% (P<0.001) vs. U.S.-born Black women (41.3%) and U.S.-born White women (44.0%). 2. Inadequate prenatal care: 27.3% of refugees vs. 11.8% of White women, 23.9% of Black women (P<0.001). 3. More vaginal births: 73.4% refugees; 65.3% U.S.-born White; 66.6% U.S.-born Black. 4. Fewer caesarean sections: 13.2% refugees; 19.1% U.S.-born White; 18.3% U.S.-born Black.
Akselsson et al. (39)	2020	To compare pregnancy outcomes between women born in Somalia and those born in Sweden.	Population-based study.	Somalia	Sweden	39,865 women with singleton pregnancies: 623 from Somalia and 26,485 from Sweden.	Women born in Somalia had a higher risk of adverse pregnancy outcomes compared to those born in Sweden. Caesarean sections were less common among Somali women (16.7% vs. 19.2%), but emergency caesareans were more frequent (10.1% vs. 8.8%).
Ammoura et al. (51)	2021	1) To document the perinatal data of refugee women at Charité Hospital in Berlin; 2) To assess potential differences in prenatal, perinatal, and postnatal outcomes compared to those of indigenous women.	Retrospective comparative study.	Syria, Serbia, Vietnam, and Afghanistan.	Germany	907 refugee women and 928 infants, including 21 twin pregnancies, were part of the 758,783 births recorded in the 2016 German Federal obstetric data.	The rates of premature birth, stillbirth, and congenital malformations were higher among pregnant refugee women, despite their younger average age.
Auger et al. (49)	2020	To investigate disparities in stillbirth rates between Arab women and the French and English majority populations of women in Quebec, Canada.	Retrospective study of all births in Quebec from 1981 through 2015.	Arab women.	The French and English majority of women in Quebec, Canada.	Of the 13,452 stillbirths in the study, 283 (2.1%) were among women with a specific mother tongue, 229 (1.7%) were among fathers with the same mother tongue, and 181 (1.3%) were among parents who used that language at home.	Women whose first language was Arabic had a higher rate of stillbirths caused by congenital anomalies, pregnancy terminations, and undetermined factors compared to those with French or English as their mother tongue. Among Arabic speakers, 18.8% of stillbirths were due to congenital anomalies, versus 12.9% among French or English speakers.

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Bakken et al. (40)	2015	To compare obstetric outcomes between women from conflict-zone countries and ethnic Norwegian women who gave birth in a low-risk setting.	Population-based observational study.	Somalia, Iraq, Afghanistan, and Kosovo.	Norway	7408 women.	Somali women faced higher risks for adverse obstetric outcomes compared to ethnic Norwegians. They had increased odds ratios (OR) for emergency caesarean section (1.81), post-term birth (1.93), meconium-stained liquor (2.39), and small-for-gestational-age infants (3.97). Conversely, they had lower ORs for epidural analgesia (0.40) and large-for-gestational-age infants (0.32).
Bakken et al. (41)	2015	To compare obstetric outcomes between immigrants and ethnic Norwegians in a low-risk birth setting.	Population-based observational study.	Immigrants of African and Asian descent originating from 141 countries.	Norway	11,540 women.	Compared to Norwegians, women from East, Southeast, and Central Asia faced higher risks of operative vaginal delivery, postpartum bleeding, and low Apgar scores. African women had increased risks for post-term birth, meconium-stained liquor, episiotomy, operative vaginal delivery, emergency caesarean delivery, postpartum bleeding, low Apgar scores, and low birthweight. Women from South and Western Asia had a higher risk of low birthweight babies.
Bastola et al. (42)	2019	To compare the mode of delivery, any complications during delivery, and the use of pain medication during delivery.	Retrospective cohort.	Somali, Kurdish, and Russian.	Finnish women.	Russian (N=318), Somali (N=583), and Kurdish (N=373) origin, along with 243 women from the general population (reference group) who had given birth in Finland.	Migrant Somali women experienced more delivery complications compared to Finnish women. Russian women had lower odds of caesarean delivery (OR 0.49; CI 0.29-0.82), while Somali and Kurdish women's odds did not differ from the reference group. Somali women faced a higher risk of any delivery complications (OR 1.62; CI 1.03-2.55) than the reference group.
Bastola et al. (46)	2020	To investigate differences in caesarean delivery and neonatal outcomes.	Retrospective cohort.	Women were classified into nine regions: Western high-income countries, Eastern Europe, Russia/USSR, South Asia, East Asia, Sub-Saharan Africa, Middle East/ North Africa, and Latin America/ Caribbean.	Finland	92% of the women were Finnish, while 8% were migrants.	Compared with Finnish women, women of Sub-Saharan African, South Asian, and East Asian origin were at greater risk of emergency caesarean delivery, preterm birth, low birthweight, and lower five-minute Apgar scores for newborns. Latin American/Caribbean-origin women were at increased risk of both elective and emergency caesarean delivery and lower five-minute Apgar scores compared with Finnish women. Women of Russian/former USSR origin overall had a lower risk of caesarean delivery and poor neonatal outcomes compared with Finnish women.

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Bastola et al. (25)	2020	To compare the prevalence of gestational diabetes and hypertensive disorders.	Retrospective cohort.	Russian-, Somali-, and Kurdish-origin women.	Finnish women.	Russian (N=318), Somali (N=583), Kurdish (N=373) General population (N=243).	Women of Kurdish origin were more likely to develop gestational diabetes. When adjusted for confounders, Kurdish women had two-fold odds for gestational diabetes (odds ratio = 1.98; 95% confidence interval = 1.20-3.32) compared with the general population, but the odds for hypertensive disorders did not differ between groups.
Bastola et al. (24)	2022	To study the prevalence of hypertensive disorders of pregnancy.	Retrospective cohort.	Women were classified into nine regional categories: Western Europe/ North America/ Oceania (later referred to as Western high-income countries), Eastern Europe, Russia and the former Union of Soviet Socialist Republics (USSR), South Asia, East Asia, Sub-Saharan Africa, Middle East/North Africa, and Latin America/ Caribbean.	Finnish	Women of Finnish origin represented nearly 92% (N=350,548), while women of migrant origin comprised 8% (N=31,454).	Hypertensive disorders of pregnancy ranged from 1.3% in East Asian women to 4.2% in Sub-Saharan African women, compared with 4.6% in Finnish women. After adjusting for confounders, migrant women had a lower risk than Finnish women, except for those from Sub-Saharan Africa.
Biro et al. (17)	2017	To investigate the correlation between maternal refugee status and severe foetal growth restriction in singleton pregnancies delivered after 40 weeks of gestation.	Retrospective cohort.	Afghanistan, Bhutan, Burma, Burundi, Democratic Republic of the Congo, Guinea, Iraq, Liberia, Rwanda, Sierra Leone, and Sudan.	Australia; non-refugee women.	1,547 refugees; 18,020 non-refugee women.	Refugee-background mothers are more likely to give birth to severely growth-restricted babies post-40 weeks (adjusted odds ratio 2.52; 95% CI: 1.44-4.42). They have higher rates of spontaneous labour (69.7% vs. 60.06%) and lower rates of induced labour (19.7% vs. 25.0%) compared to non-refugee mothers (p<0.001). They are also less likely to have instrumental (10.2% vs. 14.8%) or emergency caesarean deliveries (14.3% vs. 15.7%) (P<0.001) and severe foetal growth restriction (3.9% vs. 4.4%, P<0.01).
Bozorg-mehr et al. (20)	2018	To compare asylum seekers and residents regarding high-risk pregnancies, abortive outcomes/ stillbirths, maternal complications, neonatal complications, and caesarean sections.	Cross-sectional.	Asylum seekers.	German residents.	19,864 women; 2.9% (n=569) were asylum seekers.	Asylum-seeking women have a higher risk of abortive outcomes, stillbirths, and postnatal complications. The adjusted odds for high-risk pregnancy conditions (OR=0.76, 95% CI: 0.63-0.91, p < 0.0001), caesarean sections (OR=0.84, 95% CI: 0.66-1.07, P=0.17), and perinatal complications (OR=0.65, 95% CI: 0.55-0.78, P<0.0001) were lower. However, the odds for abortive outcomes/stillbirths (OR=1.58, 95% CI: 1.11-2.20, p=0.01) and postnatal complications (OR=1.80, 95% CI: 0.93-3.19, P=0.06) were higher compared to residents.

Continuation of Table 2.

Study	Publication year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Florian et al. (50)	2023	To investigate whether the health advantage of higher birthweight of children of immigrants relative to children of natives is transferred from parents to children.	Comparative observational cohort.	Data from nine birth cohorts in the LifeCycle Project: Etude Longitudinale Française depuis l'Enfance-France (N=12,494), Raine Study-Australia (N=2,283), Born in Bradford-UK (N=4,132), Amsterdam Born Children and their Development study-Netherlands (N=4,030), and Generation R study-Netherlands (N=4,877).	France, Australia, the UK, and the Netherlands.	Male and female babies born to immigrant and native parents (France, Australia, UK, Netherlands).	The immigrant health advantage is not universally transferred to children in the form of higher birthweight in all host countries. Higher birthweight among children of immigrants in France (+12 g, P<0.10) and Australia (+40 g, p<0.10) and lower birthweight among children of immigrants in the UK (-82 g, p<0.05) and the Netherlands (-80 g and -73 g, P<0.001) compared with natives' children.
Gibson-Helm et al. (15)	2015	To describe maternal health, pregnancy care, and pregnancy outcomes among migrant women from humanitarian and non-humanitarian source countries.	Retrospective, observational.	Migrant women born in HSCs‡.	Australia: migrants from non-HSCs‡.	HSCs‡ (N=2,713), non-HSCs‡ (N=10,606).	Women from HSCs‡ were more likely to be under 20 (2.9% vs 0.6%, P< 0.001), multiparous (76% vs 51%, P< 0.001), have a BMI†≥25 (50% vs 38%, P<0.001), anaemia (5.9% vs 3.2%, P<0.001), tuberculosis (0.4% vs 0.1%, P=0.001), and syphilis (2.5% vs 0.4%, P<0.001) compared to those from non-HSCs‡. Maternal HSC-birth correlated with poor or no pregnancy care attendance (OR 2.5 [95% CI 1.8-3.6]), late first care visit (OR 1.3 [95% CI 1.1-1.5]), and post-term birth (> 41 weeks) (OR 2.5 [95% CI 1.9-3.4]). Stillbirth (0.8 vs 1.2%, P=0.04, OR 1.5 [95% CI 1.0-2.4]) and unplanned birth before hospital arrival (0.6 vs 1.2%, P< 0.001, OR 1.3 [95% CI 0.8-2.1]) were more frequent in HSC‡-born women.
Gibson-Helm et al. (16)	2014	To describe and compare maternal health, pregnancy care attendance, and pregnancy outcomes.	Retrospective, observational.	Women from HSCs‡.	Women from "non-HSCs‡" North Africa, Middle and East Africa, and West Africa.	1,930 women from HSCs‡; 7,412 from non-HSCs‡.	Migrant women with a refugee background from various African regions are at higher risk of certain adverse pregnancy outcomes than those without a refugee background. 1) Issues such as female genital mutilation (5.1-13.8% vs. 0.3-3.3%), vitamin D insufficiency (23.3-32.0% vs. 8.7-21.5%), syphilis (1.2-7.5% vs. 0-0.3%), and hepatitis B (1.2-18% vs. 0-1.1%) are more common among refugee groups. Additionally, unplanned births before reaching the hospital were notably high in the North African refugee group (3.6%). 2) HSC‡-birth was linked to gestational diabetes mellitus (odds ratio=3.5, 95% confidence interval: 1.8-7.1) among women from Middle and East Africa, after adjusting for maternal age, parity, BMI†, and socioeconomic status. 3) The West African HSC‡ group had the highest stillbirth rate (4.4%).

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Gorman et al. (23)	2014	To explore birth outcomes in Polish migrants to Scotland.	Population-based retrospective.	Polish migrants.	Scottish natives.	119,698 Scottish and 3,105 Polish births.	The relatively lower rate of caesarean sections among Polish mothers compared to Scottish mothers in Scotland can be attributed to the slightly better overall health of Polish mothers.
Henriksson et al. (14)	2020	To assess the prevalence and odds ratios of underweight, obesity, and gestational weight gain (GWG) in the first trimester among migrant (first-generation) and Swedish-born women.	Population-based retrospective.	Migrant (first-generation) and Swedish-born women.	Swedish native.	535,609 pregnancies from the Swedish Pregnancy Register (2010-2018).	Women from North Africa, the Middle East, and Sub-Saharan Africa had higher odds of obesity—1.40 and 2.13 times, respectively—compared to women born in Sweden. Inadequate GWG was prevalent among first-generation migrant women, particularly those from Sub-Saharan Africa.
Juárez et al. (43)	2014	To examine the risk factors and prevalence of adverse pregnancy outcomes among native Portuguese and migrant populations.	Cross-sectional.	Immigrants[¶]	Spaniards	All babies born in Spain (N=1,453,571); studied live births and single deliveries (final N=1,393,095).	Immigrant mothers face higher risks of macrosomia, post-term, and preterm births. Compared to Spaniards, they generally have lower or similar risks for LBW[‖] (OR 0.65-0.87) and preterm babies (OR 0.75-0.93). Most show increased risks for macrosomic (OR 1.21-2.58) and post-term babies (OR 1.11-1.50). Sub-Saharan African mothers have higher risks in all perinatal outcomes.
Kana et al. (44)	2019	To compare risk factors and the prevalence of adverse pregnancy outcomes.	Cross-sectional analysis was conducted using information collected at delivery from the participants of the Generation XXI birth cohort study.	Migrants	Native Portuguese.	A total of 8,495 mothers (91.4% of those invited) and 8,647 children were enrolled; only births with maternal country of birth information (N=8,557) were included.	Migrant mothers had a lower risk of low birthweight and small for gestation, indicating a healthy immigrant effect. Native Portuguese had a significantly higher risk of low birthweight (OR 2.67) and small for gestational age (OR 2.01), but a similar risk for preterm birth (OR 1.38).
Kandasamy et al. (21)	2014	To determine the risk of adverse obstetric and perinatal outcomes.	Retrospective cohort.	Various, refugees.	Canada: non-refugees.	274 refugee women, 273 controls.	Multiparous refugee women had a 36.4% caesarean section rate and a 1.5-fold increase in low birthweight infants compared to non-refugee women. Women from Sub-Saharan Africa also had higher rates of low birthweight infants and caesarean sections. Refugee women had increased rates of prior caesarean sections, HIV[**] SNM[††]-positive status, homelessness, social isolation, and delays in accessing prenatal care.

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Khan et al. (18)	2017	To determine the rates of adverse clinical outcomes, healthcare utilisation, and postpartum Type 2 diabetes in refugees with GDM§, compared to other immigrants and non-immigrants.	Retrospective cohort.	Various refugees.	Canada; other immigrants and non-immigrants.	2,106 refugees, 16,232 other immigrants, 22,564 non-migrants.	Refugees exhibit a similar 'healthy immigrant effect' to other immigrants regarding adverse GDM§ outcomes. Newborns of refugees were less likely to receive well-baby care, and refugee women had a higher risk of developing diabetes postpartum. Both refugees and other immigrants had a lower rate than non-immigrants for many adverse GDM§ outcomes, including pre-eclampsia (relative risk [RR] 0.65, 95% confidence interval [CI] 0.44-0.95 and 0.61, 95% CI 0.52-0.72, respectively), preterm birth (RR‖ 0.87, 95% CI 0.75-0.995 and 0.85, 95% CI 0.80-0.91, respectively), and respiratory distress syndrome (RR‖ 0.83, 95% CI 0.70-0.97 and 0.78, 95% CI 0.72-0.84, respectively).
Kuvacic et al. (47)	1996	To examine the hypothesis that environmental stress may influence the length of gestation, data on deliveries were analysed.	Retrospective cohort.	Bosnia and Herzegovina, Serbia.	Croatia	593 refugees; 7,845 non-displaced women.	In 1990 and 1991, there was a significant difference in displaced persons (P<0.01), but this difference disappeared in 1992. 1) Perinatal mortality was significantly higher in the expatriated population (P<0.01). 2) Expatriated women more often had babies weighing under 2,500 g (P<0.01).
Leppälä et al. (26)	2022	To examine prenatal care with respect to the gestation trimester at the initial prenatal visit, the number of check-ups before birth, and prepartum hospitalisation.	Cross-sectional.	Migrants born in conflict-affected countries.	Country-born parturients in Finland.	Migrants born in conflict-affected countries (n=3155) and country-born parturients (n=93,600).	Migrant parturients had fewer check-ups and started their care later compared to country-born parturients. Among the migrants, 95.3% participated in the recommended minimum number of check-ups, while 96.4% of the Finnish-born group did (P <0.000). The likelihood of migrants having more than ten visits before term birth was lower (aOR=0.58; 95% CI 0.51, 0.66).
Liu et al. (22)	2019	To analyse indicators of perinatal health and health care usage.	Retrospective cohort.	Various, refugees, asylum seekers and undocumented migrants.	Sweden: Swedish-born women.	31,897 migrant women; 1,983 asylum seekers/ undocumented migrants, 29,914 refugees, 254,973 controls.	Migrant women from Syria, Iraq, Somalia, Eritrea, and Afghanistan had higher risks of poor health, gestational diabetes, stillbirth, and low birthweight infants compared to Swedish-born women. Asylum-seekers and undocumented migrants faced greater risks of poor maternal health (RR‖ 1.84, 95% CI 1.72-1.97), preterm birth (RR 1.47, 95% CI 1.21-1.79), inadequateantenatal care (RR ‖ 2.56, 95% CI 2.27-2.89), and missed postpartum visits (RR‖ 1.15, 95% CI 1.10-1.22) than refugee women with residency.
Margioula-Siarkou et al. (45)	2013	To examine the incidence of obstetric and neonatal outcomes between native and immigrant women.	Retrospective cohort.	Immigrants	Natives from Greece.	7,033 singleton pregnancies.	Immigrant women exhibit a reduced risk for severe obstetric and neonatal outcomes, including emergency caesarean sections, pre-eclampsia, preterm delivery, placenta praevia, and fetal distress.

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Merry et al. (38)	2016	1) To describe potential pathways, focusing on modifiable factors, by which migration—using internationally recommended indicators such as country of birth, length of time in the country, fluency in the receiving country's language, migration classification, and ethnicity—may lead to emergency caesarean sections; 2) To propose a framework to guide future research aimed at understanding "potentially preventable" emergency caesarean sections in migrant women.	Narrative review.	Various – refugee/ humanitarian migrants.	Canada; other migrant categories from low- and middle-income countries.	79 humanitarian migrants; 1,769 others.	Migrant status is associated with a higher likelihood of an unplanned caesarean (OR 4.24, CI 1.16–15.46) compared to economic immigrants or temporary residents. Emergency caesareans can occur due to health issues, insufficient support, lack of empowerment, and sub-optimal care.
Michaan et al. (13)	2014	To compare the perinatal outcome of refugees and Israeli parturients.	Retrospective cohort.	Eritrea, Sudan.	Israel; native Israeli women.	247 refugees, 247 controls.	Refugees were younger and leaner, experiencing more premature deliveries under 37 weeks (23 vs. 10, P=0.029) and under 34 weeks (9 vs. 2, P=0.036), with higher neonatal ICU¶ admissions (15 vs. 5, P=0.038). The caesarean section rate was similar, but urgent surgeries were more frequent among refugees (97% vs. 53%, P=0.0001). Refugees also had more cases of meconium and episiotomies, fewer cases of epidural analgesia, 2 intrauterine fetal deaths compared to 13 out of 11,239 deliveries (P=0.036), and 7 pregnancy terminations following sexual assault during escape.
Miller et al. (8)	2016	To examine whether immigrants and mothers from refugee countries have lower adjusted risk of preterm births than US-born mothers in Syracuse, NY.	Retrospective cohort.	Various refugees.	USA	575 presumed refugees; 966 other foreign-born women; 5,388 US-born mothers.	A healthy immigrant effect related to preterm births has been identified. Infants born to both foreign-born women and women from refugee countries demonstrated a reduced risk of being born preterm compared to infants born to US mothers. This finding remains consistent even when controlling for race, late or no prenatal care, maternal age under 18 years, and smoking.

Continuation of Table 2.

Study	Publi-cation year	Study aim	Study design	Country of origin	Recipient country	Participants	Main findings
Paquier et al. (27)	2020	To examine perinatal complications (during pregnancy, labour, delivery and neonatal period).	Monocentric observational.	Recent immigrants of less than 3 years.	Long-term residents in Brussels.	892 pregnant women.	Recent immigrants had less optimal prenatal care, but this did not result in a higher obstetrical and perinatal complication rate.
Waniga-ratne et al. (19)	2018	To examine whether: (1) Refugee mothers face higher risks of adverse maternal and perinatal health outcomes compared to non-refugee mothers from the same country; (2) Refugee and non-refugee immigrants differ from Canadian-born mothers in maternal and perinatal outcomes.	Retrospective cohort.	Sri Lanka, Somalia, Afghanistan, Iraq, and China. Canada, non-refugee immigrant mothers.	Canadian-born mothers.	34,233 refugee immigrant mothers; 243,439 non-refugee immigrant mothers, 615,394 Canadian-born mothers.	Refugees had higher rates of HIV** compared to non-refugee immigrants (0.39% vs 0.20%, AOR 1.82, 95% CI 1.19 to 2.79). Other outcomes, such as caesarean sections (AOR 1.04, 95% CI 1.00 to 1.08) and moderate preterm births (AOR 1.08, 95% CI 0.99 to 1.17), were similar between the two groups. Both refugee and non-refugee immigrants had similar outcomes when compared to Canadian-born mothers.
Waniga-ratne et al. (48)	2016	To assess whether: (1) The healthy migrant effect pertains to infants born to refugee women in relation to SNM††; (2) Refugee status is a risk factor for SNM†† among immigrants; (3) Refugee sponsorship status is a risk factor for SNM†† by comparing asylum-seekers to sponsored refugees; and (4) Refugees face a higher risk of specific SNM†† subtypes.	Retrospective cohort.	Various	Canada: other immigrants, non-immigrants.	29,765 refugees; 230,914 other; Immigrants; 860,617 Non-immigrants; 15,122 Non-sponsored refugees; 10,571 sponsored refugees.	Regarding SNM†† risk, the healthy migrant effect was evident in non-refugee immigrants but less so in refugees, and it may not apply to them. Refugee status was a weak risk factor for SNM†† among immigrants and may not hold clinical significance.

*Studies were included only if they were published in peer-reviewed journals in English, provided data on antenatal care provision and compared perinatal and neonatal outcomes of infants born to refugee mothers who had migrated to high-income countries (according to the World Bank definition) with equivalent outcomes in the native population, or non-refugee migrants resident in the host country; †Body mass index; ‡Humanitarian source countries; §Gestational diabetes; ||Relative risks; ¶Intensive care unit; **Human immunodeficiency virus; ††Severe neonatal morbidity.

Table 3. Overview of the 10 Studies Examining Anaesthetic Care in Migrant Populations Within High-Income Countries*

Study	Publi-cation year	Study aim	Study design	Study country	Population studied	Main findings
Aasheim et al. (28)	2020	To investigate associations between: 1) maternal country of birth, 2) migration-related factors (length of residence, reason for migration, paternal origin), 3) epidural analgesia for labour pain.	Population-based register study.	Norway	Nulliparous women who had given birth from gestational week 22: migrants, non-migrants.	Epidural analgesia was given to 38% of migrant women and 31% of non-migrant women. Compared to non-migrants, the odds were lowest for women from Vietnam (adjOR 0.54; CI 0.50–0.59) and Somalia (adjOR 0.63; CI 0.58–0.68), and highest for women from Iran (adjOR 1.32; CI 1.19–1.46) and India (adjOR 1.19; CI 1.06–1.33). Refugees (adjOR 0.83; CI 0.79–0.87) and newly arrived migrants (adjOR 0.92; CI 0.89–0.94) also had lower odds.
Brebion et al. (29)	2021	To investigate the relationship between maternal immigrant status—defined by both geographic continental origin and the Human Development Index (HDI) of the mother's country of birth—and the utilisation of neuraxial analgesia.	Cross-sectional.	France	6070 women; 959 (15.8%) were immigrants.	Immigrants from countries with very high HDI were more likely to give birth with neuraxial analgesia (adjusted odds ratio [aOR]=2.6; 95% confidence interval (CI), 1.2-5.8; P=0.018) and within 60 minutes after admission (aOR=1.8; 95% CI, 1.2-2.7; P=0.005) compared to native French women. There was no difference in the use of neuraxial analgesia between native French women and immigrant women from different geographic regions or from countries with low HDI.
Hamwi et al. (30)	2023	To examine whether migrant women's proficiency in the host country's language affects their use of neuraxial analgesia and satisfaction with pain management during labour compared to native women.	Secondary analysis of data collected from the Portuguese baMBINO prospective cohort study.	Portugal	1024 native and 1111 migrant women who had singleton vaginal deliveries between 2017 and 2019.	The use of differential obstetric neuraxial analgesia among migrant women in Portugal varies according to their proficiency in the host country's language. This variation does not impact their satisfaction with labour pain management.
Husarova et al. (31)	2016	To identify patterns in intrapartum analgesia use in the migrant obstetric population.	Retrospective, observational analysis.	Ireland	36 689 deliveries with neonates above 500g in weight at a university hospital in Dublin between 2009 and 2013.	African migrants were the least likely to use any pain relief. Migrants from North Africa, Sub-Saharan Africa, the Far East, India, and Eastern Europe had higher odds of not using neuraxial analgesia during delivery compared with Western Europe (all P<0.05). Similarly, those from North Africa, Sub-Saharan Africa, the Far East, North America, Eastern Europe, and India had higher odds of not receiving any analgesia during delivery compared with Western Europe (all P<0.05).
Razum et al. (32)	2017	To evaluate if care quality and responsiveness vary by migration status, using neuraxial anaesthesia (NA) during labour as an indicator.	Cross-sectional.	Germany	6391 women with migration history (first and second generations) and non-immigrant women giving birth in three obstetric hospitals in Berlin, Germany.	In vaginal deliveries, first (but not second) generation women (aOR 0.79, 95% CI 0.65 to 0.95), women with low German language skills (aOR 0.77, 95% CI 0.58 to 0.99) and women with low educational attainment (aOR 0.62, 95% CI 0.47 to 0.82) had lower chances of receiving NA; there was no evidence of overprovision among women with strong affinity to Islam, thus for religious reasons objecting to NA.
Waldum et al. (33)	2020	To assess disparities in the provision of epidural analgesia in planned vaginal birth according to maternal region of birth, compared to native-born counterparts.	Population-based cohort study.	Norway	842,496 live-born singleton deliveries in Norway between 2000 and 2015.	Primiparous women from Latin America/ Caribbean countries with instrumental vaginal delivery were most likely to receive epidural analgesia (OR 2.12, 95%CI 1.69-2.66). In contrast, multiparous women from Sub-Saharan Africa with spontaneous vaginal delivery were least likely to receive epidural analgesia (OR 0.42, 95% CI 0.39-0.44).

Continuation of Table 3.

Study	Publi-cation year	Study aim	Study design	Study country	Population studied	Main findings
Laine et al. (34)	2020	To assess intrapartum epidural use during vaginal delivery among immigrant women giving birth in Norway, compared with Norwegian-born women.	Population-based cohort study.	Norway	602,095 deliveries.	Nulliparous women born in Latin America had higher odds of using intrapartum epidurals (aOR 1.93, CI 1.79-2.09) compared to those born in Norway. Lower odds were observed for women from Sub-Saharan Africa (aOR 0.83, CI 0.78-0.88), East Asia and the Pacific (aOR 0.83, CI 0.80-0.87), and those with unknown birth countries (aOR 0.79, CI 0.71-0.89).
Glance et al. (35)	2007	To examine whether race and ethnicity were associated with the likelihood of receiving epidural analgesia.	Retrospective cohort study.	USA	81,883 women.	Black and Hispanic women in labour are less likely to receive epidural analgesia compared to non-Hispanic White women.
Wilson et al. (36)	2014	To evaluate ethnic/racial differences in labour analgesia characteristics with regard to the timing of request for neuraxial analgesia.	Prospective observational cohort study.	USA	397 parturients, non-Hispanic White, African American, Hispanic, or other.	At the time of neuraxial analgesia placement, Hispanic parturients exhibited a mean cervical dilation difference of 0.8 cm compared to non-Hispanic Whites (95% confidence interval [CI], 0.1-1.4; P=0.047). Ethnicity or race had a minimal impact on the acceptance and request for neuraxial labour analgesia.
Ekéus et al. (37)	2010	To examine the variations in the utilisation of epidural analgesia during labour between native Swedish women and immigrant women.	Population-based register study.	Sweden	455,274 women	Women from Chile (odds ratio (OR) 1.39, 95% confidence interval (CI) 1.23-1.57), Iran (OR 1.38, CI 1.26-1.53), Poland (OR 1.22, CI 1.08-1.37), and Finland (OR 1.10, CI 1.03-1.17) used epidural analgesia more frequently compared to native Swedish women. Conversely, women from Somalia (OR 0.57, CI 0.46-0.70), Iraq (OR 0.71, CI 0.64-0.78), Turkey (OR 0.77, CI 0.69-0.86), and Yugoslavia (OR 0.85, CI 0.79-0.91) used epidural analgesia less often. The use of epidural analgesia increased among immigrant women who had a native Swedish partner.

*Studies were included if they were published in peer-reviewed journals in English, provided data on anaesthetic care provision and compared perinatal and neonatal outcomes of infants born to refugee mothers who had migrated to high-income countries (according to the World Bank definition) with equivalent outcomes in the native population, or non-refugee migrants resident in the host country.

referenced throughout the review. Finally, the fifth and sixth criteria are covered in the Results, with the main findings summarised and interpreted in the Discussion. Although quality assessment for observational studies (cohort, case-control, and cross-sectional studies) is not required for narrative reviews and therefore was not conducted, all included studies were evaluated for methodological biases and limitations.

Scope of the Review

Of the 795 records screened, a total of 41 cohort, case-control, and cross-sectional studies published between 1996 and 2024 met the inclusion criteria and were included in this review (Figure 1). The studies reviewed included data from the following host regions: Europe, Australia, the United States, Canada, Israel, and Norway. The identified immigrant regions of origin included Latin America and the Caribbean, South and East Asia, Africa, and Eastern and Southern Europe.

Among the measured outcomes, ten of forty-one studies focused on the administration of obstetric neuraxial analgesia. The remaining thirty-one studies examined discrepancies in antenatal care and perinatal outcomes between refugees and their native counterparts. Table 2 provides a summary of studies detailing perinatal outcomes, while Table 3 presents a summary of studies focused on anaesthetic care. Whenever reported, we summarised the estimates of association, with

their corresponding 95% confidence intervals and p-values, between residential status (migrants vs. residents) and measured outcomes.

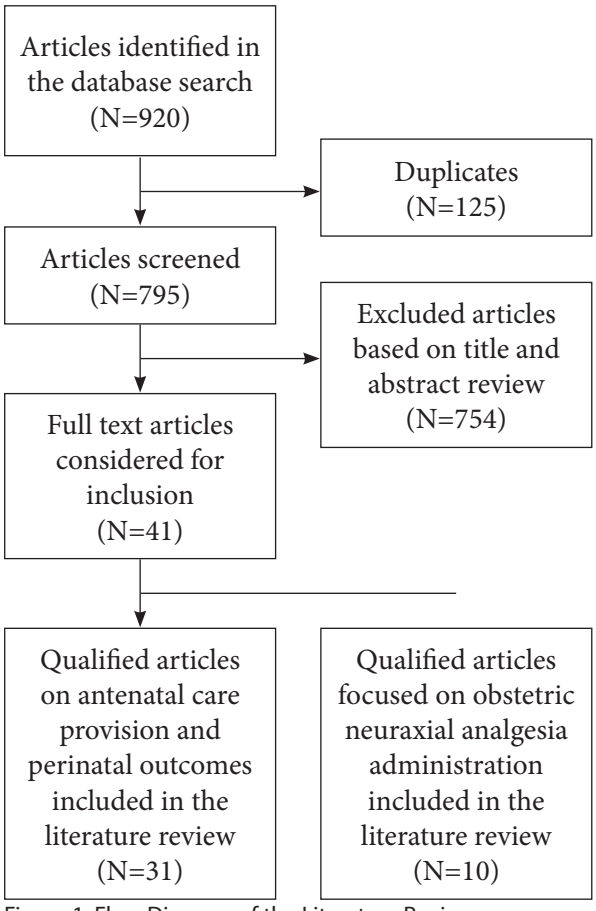

Figure 1. Flow Diagram of the Literature Review.

Synthesis of the Results

The body mass index (BMI) of refugees varied according to their country of origin. Agbemenu et al. (2019) indicated that the pre-pregnancy BMI of U.S.-born White women [mean 26.72, standard deviation (SD) 0.24] was comparable to that of U.S.-born Black women (12) (Table 2). Similarly, Michaan et al. (2014) noted no significant difference in pre-pregnancy BMI but identified a lower BMI at delivery (25.8 vs. 27.2, P=0.036) (13). Conversely, Henriksson et al. (2020) found that women born in North Africa or the Middle East, as well as Sub-Saharan Africa, had increased odds of obesity compared to those born in Sweden, with adjusted odds ratios of 1.40 (95% confidence interval [CI] 1.35-1.44) and 2.13 (95% CI 2.03-2.23), respectively (14). In contrast, inadequate gestational weight gain was frequently observed among first-generation migrant women, particularly those from Sub-Saharan Africa (14).

Most studies indicate that refugees tend to be younger (15, 16) and are more likely to have had multiple pregnancies compared to the native populations of host countries (12, 17, 18) (Table 2). Wanigaratne et al. (2018) demonstrated a 10% higher parity among non-refugee immigrant mothers with more than three previous births, compared to 3.2% for non-refugee immigrant mothers and 2.7% for Canadian-born mothers (19). Additionally, Gibson-Helm et al. (2015) observed that women from humanitarian source countries, as defined by the United Nations classification, exhibited certain characteristics more frequently than women from non-humanitarian source countries. These characteristics included: age below 20 years (0.6% vs 2.9%, P<0.001), multiparity (51% vs 76%, P<0.001), and a body mass index (BMI) of 25 or greater (38% vs 50%, P<0.001) (15).

Maternal Comorbidities

Studies have indicated that refugees are less likely to have high-risk medical conditions (20, 21), such as pre-eclampsia (13, 18) and gestational diabetes (13, 15, 16) (Table 2). However, Kandasamy et al. (2014) (21) found no significant differences in the occurrence of gestational diabetes mellitus or pregnancy-induced hypertension between refugees and the Canadian non-refugee population. Conversely, migrant women from Syria, Iraq, Somalia, Eritrea, and Afghanistan exhibited higher risks of poor self-rated health conditions, including gestational diabetes, compared to women born in Sweden (22). Khan et al. (2017) found that both refugees and other immigrants had a lower incidence of pre-eclampsia compared to non-immigrants, with relative risks (RR) of 0.65

(95% CI, 0.44-0.95) for refugees and 0.61 (95% CI, 0.52-0.72) for other immigrants (18). Gorman et al. (2014) reported that caesarean delivery rates were 19.6% among Polish migrants, compared to 24.5% among native Scottish women (23). The relatively lower rate of caesarean sections among Polish mothers compared to Scottish mothers in Scotland can be attributed to the slightly better overall health of Polish mothers (23). The study also indicated that the latter group was more likely to be overweight and smoke than migrants (23). Polish women in Scotland experienced a higher rate of instrumental deliveries (16.4%) compared to Scottish-born women, who had a rate of 10.1% (23). This difference is attributed to the comparatively better overall health observed among Polish mothers (23). In another study, after adjusting for confounders, the risk of hypertensive disorders of pregnancy was found to be lower for women of migrant origin compared to Finnish women, except for women of Sub-Saharan African origin (24). Conversely, in a separate study by the same authors, women of Kurdish origin had a higher likelihood of developing gestational diabetes (25).

Antenatal Care Utilisation, Along With the Number of Antenatal Care Visits

Five studies included antenatal care visits as an outcome measure (12, 16, 21, 26, 27) (Table 2). Migrant expectant mothers had notably fewer antenatal visits compared to their native counterparts and enrolled in the host country's prenatal care programme at a later stage (12, 13, 21, 26). Similarly, in a monocentric observational study of 892 parturients, Paquier et al. (2020) found that immigrants who had been in Brussels for less than three years received less optimal antenatal care than long-term residents. However, this did not increase obstetric or perinatal adverse outcomes (27). Gibson-Helm et al. (2015) found that African women were more likely to receive their first hospital pregnancy care after 14 weeks of gestation than resettlement country-born women (59.3% compared to 50.9%, P<0.05). Additionally, there was a higher incidence of poor or no attendance at pregnancy care appointments among this group (2.9% compared to 0.7%, P<0.05) (16).

Obstetric Neuraxial Analgesia Use

Refugees and newly arrived migrants had lower odds of receiving epidural analgesia (28-37) (Table 3). Several studies have highlighted the impact of racial disparities on the administration of intrapartum epidural analgesia. According to Glance et al. (2007), Black and Hispanic women in labour are less likely to receive epidural analgesia compared to non-Hispanic White women (35). Aasheim et al. (2020) found that the likelihood of receiving epidural analgesia was lowest among women from Vietnam (adjusted OR 0.54; CI 0.50–0.59) and Somalia (adjusted OR 0.63; CI 0.58–0.68), and highest among women from Iran (adjusted OR 1.32; CI 1.19–1.46) and India (adjusted OR 1.19; CI 1.06–1.33) (28). Husarova et al. (2016) demonstrated higher odds of not using neuraxial analgesia during delivery among migrant parturients from North Africa, Sub-Saharan Africa, the Far East, India, and Eastern Europe (31). Laine et al. (2020) examined intrapartum epidural use during vaginal delivery among immigrant women in Norway. The study found that women born in Latin America had higher odds of using intrapartum epidurals compared to Norwegian-born women (adjusted OR 1.93; CI 1.79-2.09) (34).

In a French population-based study conducted by Brebion et al. (2021), the utilisation of neuraxial analgesia did not significantly differ between native and immigrant populations when immigrant status was categorised by geographic region of origin. However, a significant difference was observed when immigrant status was defined based on the Human Development Index (HDI) of the maternal country of birth (29). Immigrants from countries with a very high HDI were significantly more likely to receive neuraxial analgesia during childbirth compared to native French women (adjusted OR 2.6; 95% CI, 1.2-5.8; P=0.018). However, no association was observed between the timeliness of administering neuraxial analgesia (within 60 minutes of admission) and the mother's country of origin (29).

Obstetric Outcomes

A total of fourteen studies reported on obstetric outcomes (12, 15, 20, 21, 23, 31, 38-45) (Table 2). In a literature review of 76 studies, Merry et al. (2013) demonstrated that parturients from Sub-Saharan Africa, Somalia, and South Asia exhibited higher caesarean rates than native populations, while women from Eastern Europe and Vietnam showed lower trends in caesarean deliveries (38). Higher emergency caesarean delivery rates were observed among populations from North Africa, West Asia, and Latin America (38). Bakken et al. (2015) identified an elevated risk of operative vaginal delivery (adjusted OR 1.28; CI 1.02-1.59) and postpartum haemorrhage (adjusted OR 1.67; CI 1.02-1.59) among women from East, Southeast, and Central Asia compared to Norwegian women (41). Notably, the data indicated that African women had a higher incidence of post-term birth (adjusted OR 1.38; CI=1.06-1.79), meconium-stained amniotic fluid (adjusted OR 1.68; CI=1.40-2.01), episiotomy (adjusted OR 1.56; CI=1.28-1.89), operative vaginal delivery (adjusted OR 1.29; CI=1.02-1.65), emergency caesarean delivery (adjusted OR 1.48; CI=1.14-1.91), postpartum haemorrhage (adjusted OR 1.30; CI=1.03-1.64), low Apgar score (adjusted OR 2.60; CI=1.31-5.18), and low birthweight (adjusted OR 2.15; CI=1.28-3.63) (41). Similarly, Bastola et al. (2020) noted that women of Sub-Saharan African, South Asian, and East Asian origin were at an elevated risk for emergency caesarean delivery (24.1%, 22,3%, 19,4%, respectively) and preterm birth (5.2%, 5.8%, 5.6%, respectively) compared to Finnish women (17%, 4,5%, respectively) (46). Women of Latin American and Caribbean origin exhibited a higher likelihood of undergoing both elective and emergency caesarean deliveries (26.8%) compared to Finnish women (17.0%). In contrast, women of Russian or former USSR origin demonstrated a lower risk of caesarean delivery (14%) (46). Gibson-Helm et al. (2015) reported that migrants were less likely to undergo induced labour (OR 0.8, 95% CI 0.7–0.9), caesarean section (adjusted OR 0.4, 95% CI 0.4–0.5), or assisted vaginal birth (adjusted OR 0.7, 95% CI 0.6–0.9) (16).

Neonatal Outcomes

The reviewed studies seldom reported neonatal outcomes (17, 26, 46-49) (Table 2). Two studies included stillbirths as an outcome measure, both of which indicated an increased risk in the refugee population (20, 48). Specifically, 18.8% (95% CI, 14.2%-23.4%) of stillbirths from mothers of Arab-speaking countries were attributed to congenital anomalies, compared to 12.9% (95% CI, 12.3%-13.5%) of stillbirths among French- or English-speaking women (48). Similarly, Bozorgmehr et al. (2018) found that asylum-seeking women had a higher risk of stillbirths and a greater association with postnatal complications (20). The majority of studies indicate that asylum-seeking parturients have a lower risk of preterm birth compared to natives (10, 13, 15). However, Kandasamy et al. (2014) and Wanigaratne et al. (2018) found no significant difference in preterm deliveries in their analyses (19, 21).

Kana et al. (2019) demonstrated that native Portuguese individuals exhibited a significantly higher adjusted risk of low birthweight (OR 2.67, 95% CI 1.30, 5.48) and small for gestational age (OR 2.01, 95% CI 1.26, 3.21) in comparison to migrants, while the risk for preterm birth remained comparable (OR 1.38, 95% CI 0.81, 2.34) (44). The data from this study indicated that migrant mothers exhibited a lower risk of adverse pregnancy outcomes, even after adjustments were made. This finding suggests the presence of a "healthy immigrant effect". Similarly, Juárez et al. (2014) concluded that the majority of immigrant groups exhibit lower risks of delivering low birthweight infants (odds ratios between 0.65 and 0.87) or preterm infants (between 0.75 and 0.93) compared to Spaniards (43). However, Florian et al. (2023) were unable to demonstrate that the immigrant health effect universally results in higher birthweight for children across all host countries (50). The study measured birthweight-related outcomes among children of immigrants. In France, there was an increase of 12 grams ($P<0.10$), and in Australia, an increase of 40 grams ($P<0.10$) was observed. Conversely, a decrease in birthweight

was noted among children of immigrants in the UK (-82 grams, P<0.05) and the Netherlands (-80 grams and -73 grams, P<0.001) compared with children of native populations (50).

Discussion

Our review of 41 studies found that refugees in high-income countries face a higher risk of adverse perinatal outcomes compared to native populations (13, 19, 21, 27, 39-42). Specifically, despite being identified as low-risk pregnancies, foetuses born to refugee women exhibited a higher likelihood of stillbirth (15, 20, 46, 48, 49), lower Apgar scores (13, 22), and increased morbidity (45, 47-48). Conversely, these pregnancies had a decreased incidence of preterm births (12, 13, 15, 16, 18, 19, 20, 22, 43, 51) and operative deliveries (12, 17, 23, 38, 42, 46, 51).

This review, based on the eligible studies, demonstrated that migrant women are more likely to receive suboptimal antenatal care. Antenatal care encompasses the medical attention provided to a pregnant individual from conception to delivery, including physical examinations, periodic measurements of blood pressure and glucose levels, blood and urine analyses, immunisations, and assessments of foetal growth and heart rate (16). The latest World Health Organization recommendation advises that pregnant women should receive at least eight prenatal check-ups before a full-term birth. These check-ups should occur at 12 weeks of gestation, followed by appointments at 20, 26, 30, 34, 36, 38, and 40 weeks (52, 53). Attending eight or more prenatal visits before a full-term birth demonstrates adherence to the majority of recommended prenatal consultations and screenings, as outlined in the guidelines (53). Despite international initiatives aimed at improving the provision of antenatal care for refugees, evidence indicates that recommended standards are more frequently not adhered to than achieved (12, 21, 26). Cultural differences, such as a preference for female obstetricians, language barriers, and a lack of awareness of host countries' healthcare systems, can pose challenges to migrants, refugees, and asylum seekers in utilising optimal antenatal care. Additionally, women who do not receive prenatal care may not disclose an undiagnosed medical condition from their history and may also miss out on other preventive interventions.

Regarding perinatal mortality, most studies defined this as the intrauterine death of a foetus at or beyond 22 weeks of gestation and/or with a weight of ≥ 500 grams if the gestational age is unknown, as well as the death of a newborn within the first week after birth (17, 26, 46-48). Perinatal morbidity outcomes included stillbirth, low birthweight, preterm birth (≤ 36+6 weeks gestation), growth restriction, congenital abnormalities, a 5-minute Apgar score <7, and neonatal intensive care unit admission (17, 26, 46-48).

Furthermore, the studies included addressed the "healthy immigrant effect" or "healthy immigrant paradox." This term refers to the observation that immigrants often exhibit better health outcomes compared to individuals in their country of origin and the population in their new host nation (7-9). The eligible studies examined the extent of this phenomenon, encompassing reproductive health outcomes (12), preterm deliveries (10), increased birthweight among migrant children (50), and reduced neonatal morbidity (48). According to Florian et al. (2023), the immigrant health effect did not consistently apply to children regarding higher birthweight across all host countries (50). The "healthy immigrant effect" results in higher birthweights among children of immigrants in France and Australia, and lower birthweights among children of immigrants in the United Kingdom and the Netherlands, compared to those of native-born children (50). Juárez et al. (2014) sought to determine whether this hypothesis applies in the Spanish context (43). Their findings indicate that most immigrant groups had either lower or not significantly different risks of delivering low birthweight or preterm infants (43). Similarly, the results of Miller et al.'s (2016) study aligned with previous studies supporting the hypothesis of the healthy immigrant paradox (8).

In relation to neuraxial analgesia usage among migrant parturients, apart from the findings of

Brebion et al. (2021), who observed no preferential treatment favouring immigrant women compared to their native-born counterparts (29), all other studies indicate evidence of differential care in terms of labour analgesia (with lower rates) among immigrant women. This discrepancy is frequently linked to limited language proficiency (28, 30-37).

Strengths and Limitations

Our review possesses several distinctive strengths that differentiate it from numerous other reviews analysing adverse perinatal care outcomes in migrant populations. The data we used, extracted from international maternity registries, were both valid and robust, as evidenced by the consistency of the results. A notable strength of this review is that it is the first to conduct a separate data analysis of obstetric neuraxial use during labour, apart from the perinatal and obstetric outcomes described in other studies.

As with all reviews, our study has certain limitations. The external validity of our findings is limited, as each country has unique healthcare system migration policies and provision patterns that are relevant to most national studies. Although comprehensive online searches were conducted, data from unverified web sources were excluded. Consequently, the findings might be influenced by studies that exclusively include data derived from nations classified as high-income by the World Bank. Additionally, only studies written in English were included, restricting access to information from other reports. Language barriers present a significant challenge to data collection, potentially leading to missing information in medical records. The majority of data in our review were derived from retrospective studies, making it impossible to fully encompass all factors related to adverse perinatal outcomes. Although the maternal country of origin is a crucial factor in evaluating birth outcomes, primary data collection is essential to thoroughly understand the underlying mechanisms of migrant-native disparities. Comprehensive data from larger populations or extended time periods are necessary to examine the healthy immigrant effect and its various aspects.

Future Implications and Research

Strategies for healthcare reform aimed at overcoming barriers to accessing antenatal care could mitigate migrant inequalities that may result in adverse perinatal outcomes. This could also inform relevant health integration policies. In this context, it is crucial to investigate the availability of antenatal programmes tailored explicitly for migrants and ensure they provide higher quality and easier access for this vulnerable group. Additionally, this review emphasises the importance of enhancing data collection on migrant perinatal health registration. This would help identify barriers that limit antenatal care provision globally and support future interventions. Understanding the factors contributing to the healthy immigrant effect may help public health interventionists improve perinatal outcomes through policy adjustments, benefiting both migrants and the native population.

Conclusion

This review analysed the existing literature on antenatal care for refugees, emphasising the adverse obstetric and neonatal outcomes experienced by migrant women in high-income countries. Access to antenatal care, utilisation of labour neuraxial analgesia, and perinatal and neonatal outcomes for migrant women differ from those of their native counterparts in high-income countries. The findings indicate that refugee women encounter various challenges during the perinatal period and suggest that social support interventions could be beneficial. Future investments in healthcare policy strategies are important for reducing inequalities and addressing barriers to antenatal care access in this population.

What Is Already Known on This Topic:

A review of studies on adverse perinatal outcomes among refugees in high-income countries indicates that migrants face a higher risk of adverse outcomes compared to native populations, although they are less likely to experience preterm births or require operative deliveries. Despite international efforts to improve antenatal care for refugees, evidence suggests that the standards recommended by the World Health Organization (WHO) are more frequently not met than achieved.

What This Study Adds:

Evidence from this narrative review indicates that refugees in high-income countries face a higher risk of adverse perinatal outcomes compared to native populations. Migrant women are more likely to receive inadequate antenatal care, which is associated with higher rates of stillbirth and perinatal mortality compared to their native counterparts.

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Review of Behavioral Risks Among Kazakhstani Adolescents and the Experience of Establishing a Health School in Kazakhstan

Zhamilya Battakova[1], Margulan Shakirov[1], Kamila Battakova[2]

[1]Republican State Enterprise "Alatau Children's Clinical Sanatorium" of the Ministry of Health of the Republic of Kazakhstan, Almaty, Kazakhstan, [2]Department of Physical and Economical Geography, L.N. Gumilyov Eurasian National University, Astana, Kazakhstan.

Correspondence: *kamila3.08@mail.ru*; Tel.: + 7 701 0394888

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Abstract

Objective. This study aimed to investigate long-term trends in the prevalence of behavioral risk factors among adolescents in Kazakhstan and highlight a successful preventive intervention, specifically the establishment of a health school. **Materials and Methods.** The authors analyzed publications from the past 10 years to monitor behavioral risk factors, existing trends among adolescents in Kazakhstan and abroad, and recommendations and guidelines from global health authorities. **Results.** Alongside a decline in tobacco and alcohol consumption, there has been an observed increase in obesity, vaping, depression, use of digital devices, and engagement with TikTok. A model is proposed based on implementing a Preventive Program by establishing a Health School, guided by international best practices and recommendations. **Conclusion.** In recent years, there has been a noticeable shift in public health behavior in Kazakhstan. While tobacco use and alcohol abuse have declined, new challenges are emerging, such as increasing rates of obesity among adolescents and excessive engagement with online games, gadgets, and social media. Simultaneously, physical activity levels have significantly decreased. To promote healthy lifestyle habits, a Health School was established at the Republican Sanatorium "Alatau" under the Ministry of Health of the Republic of Kazakhstan.

Key Words: Health School ▪ Healthy Lifestyle ▪ Prevention ▪ Adolescents ▪ Suicides.

Introduction

Kazakhstan ranks among the countries with the highest suicide rates in the world, with 80% of the cases involving adolescents. Annually, between 3,500 and 4,000 people die in the country, which corresponds to approximately 9–10 deaths per day (1). Recently, incidents have been occurring at an increasingly younger age, between 11 and 13 years (2). Notably, the leading cause of death from external factors among children and adolescents is suicide. We questioned the reasons behind such suicidal behavior in adolescents and what measures should be taken to prevent it. After reviewing the previously conducted studies, it was established that among the multifactorial influences, poor mental health combined with an unhealthy lifestyle comes to the forefront. This includes excessive consumption of alcohol and drugs, along with overuse of internet platforms, particularly TikTok, where instances of content that promotes suicide have been identified (3-6).

In the process of examining this issue, we discovered that adolescence is a critical period in a person's life, as it is a time of physical, cognitive, social, and emotional development with lifelong implications (7, 8). The main social factors influencing health include peers, schools, communities, and workplaces, complementing family life in shaping an individual's personality. Increased autonomy in decision-making, combined with psychosocial development, contributes to the formation of behaviors during adolescence that will impact health throughout adult life. These

behaviors include physical activity, dietary habits, disease management, and risky behaviors such as smoking, alcohol consumption, and illegal drug use. Risk-taking and breaking social rules are often considered inherent traits of adolescent behavior (9, 10). Modern neuroscience explains adolescence as a period of risk-taking and rebellion, supporting the theory of a developmental mismatch in the brain. This involves the prolonged maturation of brain regions responsible for judgment and self-regulation, in contrast to the rapid growth of areas involved in sensation-seeking and emotional processing (11-16).

Several public health studies (17) have been conducted on the econometrics of investing in adolescent health and the return on such simulated interventions. For interventions targeting physical, mental, and sexual health, investments of $4.6 per capita annually from 2015 to 2030 yielded an unweighted average benefit-cost ratio (BCR) of over 10.0. In contrast, interventions aimed at reducing road traffic injuries achieved a BCR of 5.9 (95% CI 5.8–6.0) with investments of $0.6 per capita annually (18, 19).

Thus, among the preventive measures for addressing suicides, behavioral risk factors, and overall health promotion of the younger generation, it is essential to consider the guiding principles for interventions based on an effective prevention strategy at three distinct levels: primary (universal), secondary (selective), and tertiary (individually indicated).

Implementing a policy of intersectoral measures that relies on legislative regulations is crucial. Of equal importance is the application of our experience in establishing and operating a Health School as an effective preventive program for promoting a healthy lifestyle among adolescents. This initiative was developed based on the Republican State Enterprise (RSE) "Alatau Children's Clinical Sanatorium" of the Ministry of Health of the Republic of Kazakhstan (hereafter referred to as the Sanatorium).

This study aimed to examine long-term trends in the prevalence of behavioral risk factors among adolescents in Kazakhstan and present a successful example of preventive intervention, namely, the establishment of a school of health.

Methods

As a result of the literature review and public health monitoring study, an analysis of publications covering the retrospective period from 1998 to 2024 was conducted. This study examined data on behavioral risk factor monitoring, existing trends among adolescents in Kazakhstan and abroad, and recommendations and guidelines from global health organizations. The study design was a non-systematic narrative literature review presented as a series of commentaries and an authorial synthesis of previously published information (20).

Results

Kazakhstan has introduced behavioral surveillance systems aimed at promoting health. Several studies have addressed issues such as overweight and obesity, dietary habits, social marketing, communication with peers, friends, and parents, leisure activities, and physical activity. In recent years, significant progress has been made in the monitoring of tobacco consumption.

Tobacco Consumption

The results of global surveys conducted in collaboration with the World Health Organization, Bloomberg Foundation, and Centers for Disease Control and Prevention, such as the Global Adult Tobacco Survey and Global Youth Tobacco Survey, have shown that smoking in Kazakhstan has been on a declining trend since 2007 (Figure 1) (21). According to household surveys, by 2023, tobacco consumption decreased from 27.0% to 19.4% among individuals aged 15 and older (22). The latest estimates, included in the World Health Organization's report on tobacco trends published on January 16, 2024, indicate that Kazakhstan has 2.9 million adult tobacco users (23).

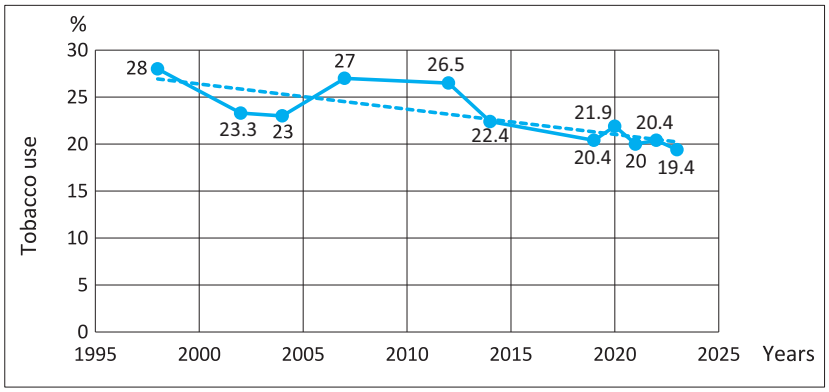

Figure 1. Tobacco consumption in Kazakhstan.

The findings revealed that 19.4% of the surveyed household members currently smoked tobacco (compared to 20.4% in 2022), with 36% of men and 8.5% of women identified as smokers. The proportion of tobacco smokers was 19.6% in rural areas and 19.3% in urban areas. Of all smokers, 92.3% consume commercially manufactured cigarettes (24).

Simultaneously, the prevalence of tobacco use among schoolchildren remains one of the most pressing socially significant issues. A comprehensive study of personal and behavioral factors and their influence on smoking status among children and adolescents represents one of the most promising directions in the system of measures aimed at reducing smoking rates among the younger generation. The study included 1,715 schoolchildren aged 13-15 years (grades 7-9 in general education schools) as part of the Global Youth Tobacco Survey (GYTS) conducted in Kazakhstan in 2014. The GYTS is a school-based survey that assesses the prevalence of tobacco use and key tobacco control indicators in a nationally representative sample. The survey is based on a standardized methodology involving a two-stage cluster sampling design of schools and classes.

The survey results indicated that 2.8% of students reported smoking tobacco. Parental smoking - whether one or both parents smoked - was significantly associated with tobacco use among children. In addition, youth who smoked had a positive perception of tobacco use. Key motivating factors for smoking included: a) the belief that smoking helps them feel more comfortable at social gatherings, b) acceptance of peer offers to smoke, and c) the appeal of hookah smoking. As a result, it can be concluded that effective psychological and educational interventions/programs are urgently needed, particularly those targeted at parents who smoke, as well as at school-aged children. These programs should be implemented at both the family and school levels to foster negative attitudes toward smoking and enhance support for those wishing to quit. Furthermore, decisive legislative action should be taken to establish smoke-free environments and reduce tobacco accessibility (22).

Consumption of Pure Alcohol in Kazakhstan

Figure 2 shows the average annual per capita consumption of pure alcohol in Kazakhstan (5, 6).

Kazakhstan has demonstrated a positive downward trend in alcohol abuse among its population.

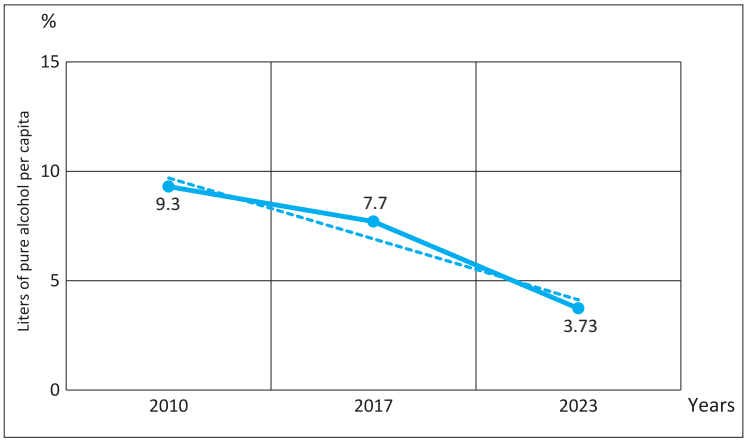

Figure 2. Alcohol consumption (liters/year) in Kazakhstan.

Tried Electronic Cigarettes

The national survey of schoolchildren in Kazakhstan, "Health Behavior in School-Aged Children", revealed that 9.8% of adolescents aged 11–15 years had tried electronic cigarettes at least once (11.3% of boys and 8.2% of girls). These rates increase significantly with age for both boys and girls (25-29).

Excess Weight

It is important to note that the first National Survey of children aged 8-9 years to assess overweight and obesity was methodologically developed and coordinated in Kazakhstan in alignment with the World Health Organization's European Childhood Obesity Surveillance Initiative (COSI). Monitoring results indicated that the prevalence of overweight among 9-year-old schoolchildren in Kazakhstan was 12.3%, while obesity was observed in 6.3% of children. The school environment contributes significantly to the development of overweight and obesity-related risk factors. One in three children with overweight or obesity do not attend sports or dance clubs. Moreover, nearly one-third of schoolchildren consume energy-dense and nutrient-poor foods daily.

A comparative analysis of Kazakhstan's data with the standardized monitoring indicators of childhood overweight and obesity across several countries in the WHO European Region revealed that Kazakhstani children fall within the middle range of prevalence rates observed in European countries (30).

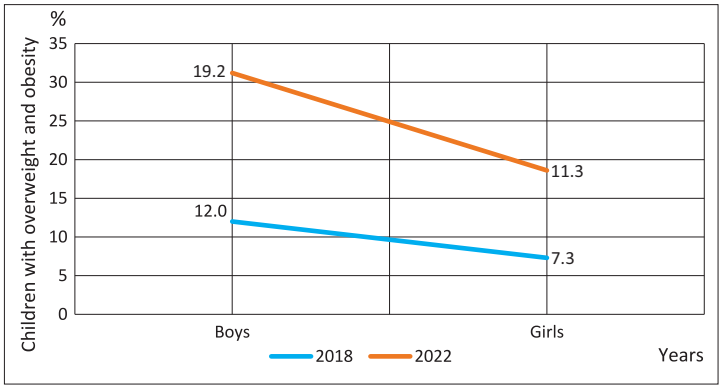

Figure 3. Children with overweight and obesity in Kazakhstan.

The indicators of behavioral risk factors were not significantly different from those observed worldwide. For instance, there has been an increase in the number of children who are overweight and obese, driven by unhealthy eating habits and a tendency towards physical inactivity. The percentage of children aged 11-15 with excess weight is shown in Figure 3 (31-35). The obtained results and their interpretation are consistent with previously published data demonstrating a temporal increase in body mass index (BMI) among children and adolescents of the same age (i.e., successive cohorts) in both rural and urban areas of each country. The authors aggregated 15 age-specific estimates, spanning ages 5 to 19, using age standardization to enable comparisons over time and between countries.

School-aged boys and girls living in urban areas had a height advantage, being taller on average than their rural counterparts. In most low- and middle-income countries, the urban BMI increased between 1990 and 2020. In contrast, high-income countries and states in Central and Eastern Europe experienced mixed trends of both increases and decreases in urban BMI, although the changes remained within a narrow range (from 0.3 to 0.6 kg/m^2) throughout the entire period of analysis (36).

Physical Activity Among Adolescents in Kazakhstan

At the same time, indicators of physical activity at moderate to high intensity for at least 60 minutes per day show a declining trend (Figure 4) (37-42).

Children's Engagement with Digital Devices

It has been found that the use of digital devices, internet engagement, TikTok, and similar activities among children has increased (Figure 5) (38, 42).

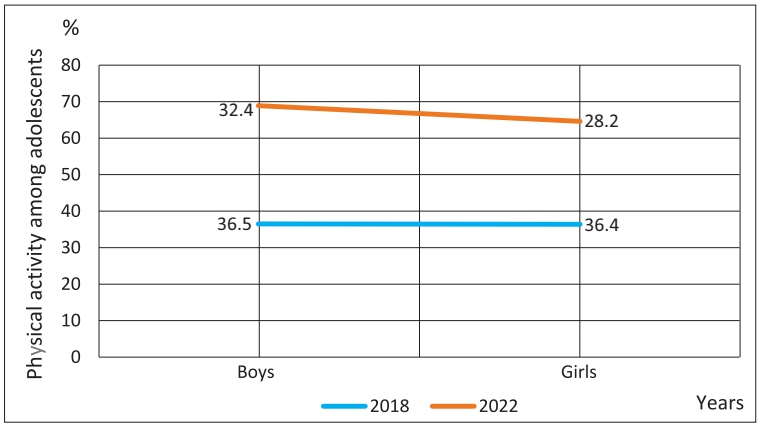

Figure 4. Trends in moderate-to-high frequency physical activity (≥60 minutes) among adolescents in Kazakhstan.

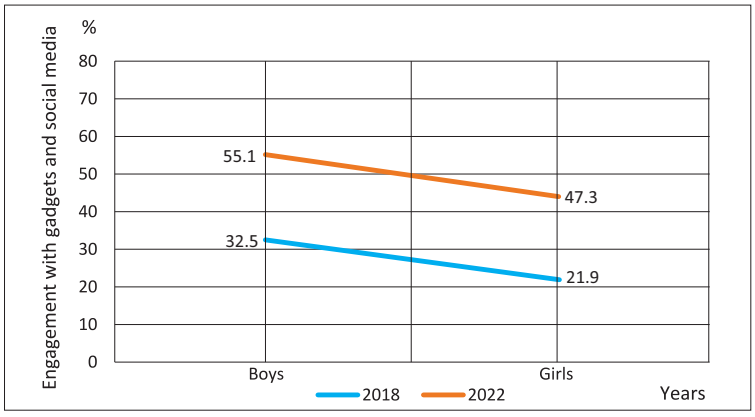

Figure 5. Trends in screen time on computers, consoles, and other gadget games (≥2 hours per day) among adolescents in Kazakhstan.

Discussion

Kazakhstan is one of the world's leaders in the number of teenage suicides. In this study, we approached this thorny issue to determine the causes of behavioral changes in relation to adolescent health by examining previously published data and the results of monitoring behavioral risk factors.

The main conclusions are, first, that a decrease in smoking prevalence (P<0.001) was reported in all age categories due to the implementation of MPOWER tobacco control measures in Kazakhstan. Second, the average annual per capita consumption of pure alcohol decreased from 9.3 liters in 2010 to 3.73 liters in 2023. Third, an increase in body mass index and obesity in children and adolescents was established (P<0.001). Fourth, there are new opportunities for risky behaviors, such as vaping, cannabis use, depression, the impact of using digital devices, and social networking through smartphones (43).

Our study findings on behavioral changes towards several factors, such as the likelihood of being influenced by a fondness for digital devices, spending time playing computer games and surfing the internet, and reduced physical activity, highlight a similarity with adolescent suicide statistics. Studies published by Doku et al. (44) and Domić et al. (45, 46) concluded that tobacco, marijuana, and other unhealthy habits were more likely to be used among those who were stable in low socioeconomic status, emphasizing the impact of cumulative socioeconomic disadvantage across generations. This situation requires comprehensive further analysis of the causes of adolescent suicides, the provision of psychological support and primary prevention in educational organizations, the application of family programs, and the training of parents and children in maintaining the values of life and health.

Globally consistent and comparable data facilitate comparative analyses across countries and territories and identify best practices. In this context, we report on the establishment of a Health School under the Ministry of Healthcare's Sanatorium, which annually serves more than 2,000 children and adolescents from 17 regions and 3 cities of republican status (Astana, Almaty, and Shymkent). This preventive initiative aims to create a comprehensive framework for the formation of healthy lifestyle habits throughout one's life.

Strengths and Limitations of the Study

A key strength of this study lies in the authors' narrative review of representative data from the national monitoring of lifestyle indicators in Kazakhstan. The study identified specific patterns of risky behaviors among youth, particularly the increasing popularity of vaping in recent years, the early initiation of such practices among children, and the rising prevalence of electronic cigarette use.

Future Directions

In Kazakhstan, as in the rest of the world, new opportunities for risky behaviors have emerged, including vaping, the prevalence of smoking among adolescents, cannabis use, increasing rates of mental health disorders and depression, childhood obesity, and the impact of digital device usage and social media through smartphones. Several factors influence these behavioral changes. This highlights the importance of investing in adolescent health and well-being, both now and in the long term. Therefore, a preventive intervention model has been proposed through the establishment of a Health School, highlighting the urgent need for primary prevention to promote healthy lifestyles among children.

Conclusion

This review of behavioral risks among adolescents demonstrated a clear association between engagement in risky behaviors and the necessity of establishing health-promoting schools as a preventive intervention to facilitate behavioral change among youth toward healthier lifestyles.

What Is Already Known on This Topic:
In Kazakhstan, five nationally representative studies on lifestyle indicators have been conducted at five-year intervals, enabling the analysis of trends in key behavioral risk factors over time.

What This Study Adds:
This study contributes to the expansion of expert knowledge through a narrative review of behavioral risks, identifying trends and contemporary characteristics of persistent health-threatening habits among the youth. Notably, it highlights the increasing use of electronic nicotine delivery systems, with adolescents favoring flavored vaping products. The rapid development of modern technologies has fostered a strong attachment to digital devices, while the internet increasingly shapes public consciousness, serving as both a medium for social interaction and a major source of information. Consequently, traditional forms of communication, particularly with parents and peers, are being displaced.

Authors' Contributions: Conception and design: ZB and MS; Acquisition, analysis and interpretation of data: ZB and MS; Drafting the article: KB, ZB and MS; Revising it critically for important intellectual content: ZB, MS and KB; Approved final version of the manuscript: ZB, MS and KB.

Conflict of Interest: The authors declare no conflict of interest.

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Supplementary Material

Establishment of a Health School

The purpose of establishing the Health School is to educate the population on healthy lifestyle practices, promote awareness of prevention, and empower patients to take proactive measures to address the behavioral risk factors for disease development. It also aims to enhance their competence in health-related matters and equip them with the skills needed to improve their lives and their surrounding environment independently.

Objectives of the Health School: 1) the establishment of a permanent information and education system focused on promoting behavioral changes in individuals regarding their health; 2) increasing patient awareness of behavioral risk factors for disease development and enhancing patient responsibility for maintaining their health; 3) developing patients' skills and abilities to reduce the adverse impact of behavioral risk factors on their health, including proper nutrition, physical activity, stress management, and the rejection of harmful habits such as smoking and alcohol abuse; 4) fostering a rational and proactive attitude toward health, motivating patients to improve their well-being, and encouraging adherence to medical professionals' recommendations; 5) developing patients' skills and abilities for self-monitoring their health status; and 6) developing patients' practical skills to analyze the causes and factors affecting their health and teaching them how to create a personalized health improvement plan.

Classes are held in a separate, well-lit room, where available, and facilities for therapeutic and wellness-related physical activities are also used. The room should be equipped with demonstration materials and educational training equipment, including both permanent wall displays (reference, informational, and educational materials) and portable resources for the mobile activities of the Health School, such as kits, discs, models, and simulators. Patient education is conducted according to standardized training programs in the Health School and consists of seven lessons (modules). Each session lasts 2 contact hours (100 minutes). Groups are limited to 8–10 patients, selected whenever possible from a homogeneous demographic.

Health School Lesson Topics

1) Physical activity - the foundation of a healthy lifestyle; 2) Healthy nutrition; 3) Prevention of tobacco smoking; 4) Prevention of excessive alcohol consumption; 5) Maintaining personal hygiene; 6) Stress prevention and development of stress-resilience skills; and 7) Communication skills.

Preventive public health interventions through the establishment of a Health School based at the Sanatorium provide an excellent example of promoting public health in Kazakhstan. This article provides a detailed account of our experience in establishing a Health School as a key area for investment. We implement interventions addressing behavioral risk factors by raising awareness and encouraging behavior change toward a healthy lifestyle through individual and group-based preventive counseling. This approach includes conducting seven health lessons.

The Sanatorium has a unique location — the protected mountainous resort area of the Ile-Alatau Medeu Park. Its exceptional therapeutic impact on patients' health is attributed to climatotherapy, as the Sanatorium's location combines a range of climatic and weather factors, including temperature, humidity, altitude (1,430 meters above sea level), atmospheric pressure, cloud cover, and precipitation levels.

Climatotherapy offers controlled exposure to the natural therapeutic and health-enhancing elements of the region, including aerotherapy, aerophytotherapy, heliotherapy, and landscape therapy. These therapies are further complemented by the terrenkur method, which involves graded physical activities, such as walking and climbing along designated routes. Together, these natural factors are designed to improve the health of pediatric patients. Experienced and highly qualified specialists provide a full range of wellness treatments,

including speleotherapy, inhalation therapy, light therapy, shungite therapy, ultraviolet irradiation, ultra-high frequency therapy, magnetotherapy, electrophoresis, Bioptron therapy, quartz therapy, hydrotherapy, Charcot showers, pearl and pine baths, as well as paraffin and mud therapy.

Rehabilitation focuses on spa and resort treatments for pulmonology patients, leveraging natural factors to strengthen the body's defenses, particularly those that positively impact respiratory function. The combination of climatotherapy and balneotherapy with a hygienic dietary regimen, as well as the use of medications, physiotherapy, bronchial tree sanitation, and therapeutic exercises, effectively supports the recovery of the body from chronic nonspecific lung diseases such as bronchial asthma, pneumonia, bronchitis, allergic rhinitis, tonsillopharyngitis, sinusitis, tracheitis, pulmonary emphysema, and others.

Spa and resort treatments are excellent methods for preventing the onset of various diseases, strengthening the immune system, and mitigating long-term complications. Each year, more than 2,000 children from all regions of the country participate in a 21-day wellness program funded by the state under the national quota. For the first time, preventive interventions have been introduced to children through the Health School program.

Thus, the Health School is an organized system of tools and methods for individual and group interventions aimed at patients and the general population. Its purpose is to enhance their knowledge, awareness, and practical skills for preventing behavioral risk factors that contribute to disease development. In essence, it is a form of primary prevention focused on eliminating the conditions that lead to the onset and progression of diseases, as well as on strengthening and preserving health. The Health School serves as a type of preventive medical service in the form of group counseling.

The Health School initiative serves as a valuable tool for promoting public health among adolescents and provides a model for scaling up efforts to prevent risky behavior and foster healthy lifestyles. The National Children's Sanatorium under the Ministry of Health of the Republic of Kazakhstan has worked to establish the Health School as a "Kazakhstani" brand aimed at influencing children's lifestyles. Preventive initiatives should place greater emphasis on mental well-being, physical activity, and healthy nutrition, as adolescents are more impressionable than adults, making this a pivotal period in life for shaping their long-term health outcomes.

Narrative Review
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The Possible Role of Immunotherapy in Locally Advanced Pancreatic Cancer Treatment*

Rouan Barakat[1, 2], Despoina Sidira[1, 2], Athanasios Stavropoulos[1], Nikias Konsolas[1], Andreas Palantzas[1], Dimitrios Filippou[1, 2]

[1]Department of Anatomy, Medical School of Athens, National and Kapodistrian University of Athens, Greece, [2]Research and Education Institute in Biomedical Sciences, Piraeus, Greece

Correspondence: *r1barakat@hotmail.com*; Tel.: +30 695 5119216

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Abstract

Objective. Locally advanced pancreatic cancer (LAPC) represents a significant subset of pancreatic cancers and is characterized by a poor prognosis and limited treatment options. Conventional therapies, including chemoradiotherapy, have demonstrated limited success, prompting interest in innovative strategies, such as immunotherapy. This review evaluates the role of immunotherapy in LAPC. **Materials and Methods.** For this review, a comprehensive search of the PubMed database was conducted in August 2024. After applying the exclusion criteria, 26 studies were included in the analysis. **Results.** Immune checkpoint inhibitors have produced inconsistent clinical outcomes, with modest improvements in progression-free survival and significant side effects. Cancer vaccines, particularly GVAX in combination regimens, have demonstrated potential, as have fibroblast activation protein (FAP) and mKRAS-specific amphiphile vaccines in preclinical and clinical settings. Chimeric antigen receptor (CAR) T-cell therapies targeting various antigens have yielded encouraging outcomes but have faced safety and efficacy challenges. Emerging approaches, including Toll-like receptor agonists, tumor-associated macrophage targeting, and radioimmunotherapy, have also shown preclinical promise but require further study. Despite numerous investigations, the overall impact of immunotherapy on LAPC remains limited. Some combination therapies involving checkpoint inhibitors, vaccines, and CAR T cells have shown positive outcomes; however, many are hindered by the immunosuppressive environment and toxicity of tumors. Recent studies emphasize the need for further research to refine these strategies and improve treatment options. **Conclusion.** LAPC remains one of the deadliest malignancies, with immunotherapy offering potential but constrained by limited survival benefits and adverse effects. Further studies focusing on novel agents, refined combinations, and overcoming tumor resistance mechanisms are critical to improve outcomes for this challenging disease.

Key Words: Locally Advanced Pancreatic Cancer ▪ Immunotherapy ▪ Oncology ▪ Immune Checkpoint Inhibitors.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a malignancy associated with a dismal prognosis and is currently the seventh most prevalent cause of cancer-related mortality globally (1). A significant proportion of pancreatic adenocarcinomas are deemed non-resectable upon diagnosis due to the presence of locally advanced or metastatic disease. The five-year survival rate for individuals diagnosed with PDAC is below 5% (2), while locally advanced pancreatic cancer (LAPC)—characterized by a tumor that has yet to disseminate to distant sites but is invasive within and surrounding the pancreas, obstructing major blood vessels—constitutes one-third of all pancreatic cancer diagnoses. In cases of locally advanced disease, the efficacy of chemoradiotherapy is increasingly scrutinized. This underscores the urgent need for the development of innovative strategies, novel

*The present work is attributed to the Department of Anatomy, Medical School of Athens, National and Kapodistrian University of Athens, Greece.

pharmacological agents, and additional research in this field. Notably, literature references from 1998 and 2002 have already advocated for the incorporation of immunotherapy in the treatment of pancreatic cancer (3, 4).

This review aimed to evaluate the potential role of immunotherapy in the management of LAPC.

Materials and Methods

This review aimed to evaluate the impact of immunotherapy on LAPC. To achieve this objective, a comprehensive search was undertaken in August 2024 on the PubMed database utilizing the search term "the role of immunotherapy in locally advanced pancreatic cancer". The search yielded a total of 55 articles published between 1991 and 2024. To focus exclusively on the most relevant and constructive details, specific exclusion criteria were applied during the evaluation of the articles. The criteria were as follows: articles must relate to LAPC; studies should discuss immunotherapy options either in experimental or current clinical contexts; and the articles must present statistically significant results. Additionally, the selected articles were required to be written in English, available in full text to maintain uniformity, and accessible in full text through the PubMed database. Following the application of these criteria, 29 articles were excluded, leaving a total of 26 articles that were included in this review.

Results

Firstly, clinical trials assessing immune checkpoint inhibitors for LAPC have shown inconsistent results. Agents targeting programmed cell death protein ligand-1 (PD-L1) and programmed cell death protein 1 (PD-1), such as pembrolizumab, nivolumab, durvalumab, and spartalizumab, were explored in early-phase studies (1, 2, 5-11). Some trials indicated a slight enhancement in progression-free survival, while most reported limited success, averaging 4-5 months for median progression-free survival (1, 6, 7, 10, 11). Additionally, some researchers have noted an increase in cluster of differentiation 8+ (CD8+) T-cell infiltration in the tumor microenvironment in several patients, although the sample sizes were too small for a statistical review (9). Treatments involving anti-cytotoxic T-lymphocyte associated protein-4 (anti-CTLA-4) agents, such as ipilimumab and tremelimumab, have produced similar results, showing no significant objective responses in the majority of studies (6, 10).

Regarding vaccines: cancer vaccine research has focused on peptide-based, whole-cell, and neoantigen-targeted strategies. Peptide vaccines (e.g., GV1001 and mesothelin) have largely failed to deliver meaningful clinical benefits (2). In contrast, the GVAX vaccine appeared promising in early-phase trials, improving disease-free survival when used in conjunction with therapies such as CRS-207 or PD-1 inhibitors such as nivolumab (8, 12). A neoantigen-targeted vaccine utilizing hyaluronic acid gel (PancVax) exhibited T-cell stimulation and decreased recurrence in preclinical settings, while an mKRAS-specific vaccine triggered a notable T-cell response in almost half of the participants in a clinical trial, albeit accompanied by mild side effects (6).

Moreover, CAR T-cell therapies targeting mesothelin, CD133, and human epidermal growth factor receptor-2 (HER-2) antigens have shown promising results but have encountered safety and efficacy issues. While preclinical evaluations of anti-mesothelin CAR T-cells indicated tumor shrinkage, clinical studies demonstrated stable disease in only a small proportion of patients (13, 14). Treatment targeting CD133 achieved partial remission in 28.57% of subjects but was linked to adverse effects, such as leukopenia and nausea (14). HER-2 CAR T-cell studies had limited efficacy, revealing isolated cases of stable disease alongside significant adverse reactions, including severe toxicity (12, 14).

We now examine the combinations of the aforementioned therapies. Combination regimens that integrate checkpoint inhibitors, cancer vaccines, and standard treatments have resulted in mixed outcomes. For example, the combination of GVAX and ipilimumab resulted in improved survival

rates compared to individual therapies, while stem cell inhibition with chemotherapy (gemcitabine/nab-paclitaxel) yielded a 35% objective response rate (2). Notably, intratumoral Toll-like receptor-7 agonists combined with PD-1 blockade have shown enhanced therapeutic benefits in preclinical studies, highlighting the potential of multifaceted treatment approaches (5).

Furthermore, adoptive T-cell therapies featuring cytokine-induced killer (CIK) cells have shown safety profiles but limited effectiveness, achieving a median period of stable disease lasting 11 weeks (8). Likewise, natural killer (NK) cell-based therapies have shown dose-responsive effects but no substantial survival advantage (5). Other experimental strategies, such as radioimmunotherapy targeting CD-147 and beta-7-homolog-3 protein (B7-H3), have yielded encouraging preclinical findings but require further examination (1).

Finally, initial trials targeting tumor-associated macrophages, myeloid suppressor cells, and innovative immune targets have shown promise in boosting immune responses and enhancing clinical outcomes. For example, vaccination using mucin-1 (MUC-1) pulsed dendritic cells allowed for long-term survival in one-third of patients observed for four years (15).

Discussion

To better understand the mechanisms underlying pancreatic cancer, several key immune-related factors influence disease progression and therapeutic response. $CD8^+$ T cells, also known as cytotoxic T lymphocytes, play a critical role as they can directly eliminate cancer cells, and their presence is generally associated with an improved prognosis. However, the tumor microenvironment often counteracts this benefit through mechanisms such as regulatory T cells (Tregs), which suppress anti-tumor immune responses, and KRAS mutations, which foster an immunosuppressive milieu that impairs effective immunity. Conversely, tumors with deficient mismatch repair or microsatellite instability (MSI) display a high tumor mutation burden (TMB) and generate abundant neoantigens, rendering them more immunogenic and more likely to respond to immunotherapy. Emerging therapeutic strategies, such as bispecific antibodies, aim to overcome these barriers. For example, CEA-TCB, which redirects $CD3^+$ T cells toward CEA-expressing pancreatic tumor cells in a manner similar to bispecific T-cell engagers (BiTEs), has shown encouraging results in preclinical pancreatic ductal adenocarcinoma (PDAC) models. It not only enhanced $CD8^+$ T-cell infiltration and reduced tumor burden but also demonstrated synergy with PD-L1 blockade, highlighting its potential to transform the typically immune-cold pancreatic tumor microenvironment into one more amenable to immune-mediated clearance (12).

In the current study, we assessed papers that employed different kinds of possible immunotherapy options for LAPC treatment. The therapies evaluated were immune checkpoint inhibitors, vaccines, CAR T-cell therapies, NK cell / other T-cell therapies, and combination therapies of the above. The results of each study are analyzed below.

Immune Checkpoint Inhibitors

The articles under review predominantly examined the utilization of immune checkpoint inhibitors as a promising therapeutic strategy for immunotherapy in LAPC. Numerous studies have emphasized the application of anti-PD-L1 and anti-PD-1 agents as potential treatment modalities for this specific type of cancer (1, 2, 5-11, 16). In particular, pembrolizumab, nivolumab, durvalumab, and, in one instance, spartalizumab, were primarily administered during phase I or II clinical trials, as detailed in the analyzed studies (11, 17). Despite the variety of these immune checkpoint inhibitors, the results have been largely unsatisfactory, characterized by brief progression-free survival rates (ranging from 4 to 5 months), attributed to factors such as limited immunogenicity and an immunosuppressive tumor microenvironment associated with pancreatic cancer (1, 7, 10, 11, 16). Moreover, although an increase in CD8(+) T-cells was noted within the tumor microenvironment, the sample size of the patient cohort was too small to attain

statistical significance, encompassing only 2 patients (9). The remaining investigations concerning PD-L1 and PD-1 inhibitors indicated more promising outcomes, exemplified by a disease control rate of 100% and a median progression-free survival of 7.9 months, particularly benefiting patients exhibiting a deficient mismatch repair phenotype or microsatellite instability (MSH-I), who demonstrated an increased overall response rate (2, 16). These findings are supported by the KEYNOTE-158 Phase II trial (NCT02628067), which demonstrated that while dMMR or MSI-H tumors are generally more immunogenic and responsive to PD-1 blockade due to their high mutational burden, pancreatic cancer shows limited responses, reflecting its highly immunosuppressive tumor microenvironment. Other studies have yielded similar results, including a response rate of 18.2%, a progression-free survival period of 2.1 months, an overall survival time of 4 months, and heightened radiosensitivity observed in PDAC tumors (5, 6). Additionally, several studies have assessed anti-CTL4 therapies, specifically ipilimumab and tremelimumab, in phase II trials (2, 9, 10, 16). Unfortunately, the majority of these studies reported a lack of objective responses (10, 16). Conversely, other studies have reported tumor reductions at the preclinical level, a decrease in carbohydrate antigen 19-9 (CA19-9) serum levels, or an enhancement in median progression-free survival by 7.9 months, along with a 100% disease control rate (2, 9). Furthermore, inhibitors targeting C-C chemokine receptor type 2 (CCR2), CC chemokine receptor (CCR), C-X-C chemokine receptor (CXCR), and colony-stimulating factor 1 receptor (CSF1R) have been similarly examined (4, 16). The use of CCR2 inhibitors alone resulted in an objective response rate of 49%, whereas their combination with CSF1R inhibitors significantly increased T-cell infiltration within the tumor microenvironment in an animal model (4, 16). In addition, the combination of CCR inhibitors with C-X-C chemokine receptor-2 (CXCR2) inhibitors produced an overall enhancement in the therapeutic response. CD 40 agonists administered alongside gemcitabine or complement C2 inhibitors were also investigated as promising treatment avenues. Unfortunately, these agents did not have a significant impact on LAPC (9, 10). Finally, indoleamine 2,3-dioxygenase (IDO) inhibitors, such as indoximod, achieved a 37% objective response rate when used in conjunction with gemcitabine and nab-paclitaxel (16).

Vaccines

This study investigated the role of cancer vaccines in the treatment of LAPC. Initially, various studies focused on peptide-based cancer vaccines featuring antigens such as mesothelin or MUC1, designed to activate autologous dendritic cells alongside telomerase phase III vaccination (GV1001) or vaccinations targeting the Wilms' tumor protein-1 (WT1) antigen in combination with gemcitabine. Unfortunately, these investigations did not yield any notable clinical benefits (2). Another significant category of vaccines examined was whole cell cancer vaccines, with GVAX being a prominent example; it is a tumor cell vaccine incorporated with the granulocyte-macrophage colony-stimulating factor (GM-CSF) gene. GVAX was utilized either as a monotherapy or in conjunction with other therapeutic agents (12). Notably, GVAX alone demonstrated enhanced disease-free survival in phase I and II clinical trials (12). When combined with cyclophosphamide administered one day prior to GVAX or with the CRS-207 vaccine, a recombinant Listeria-based cancer vaccine containing a live-attenuated strain expressing human mesothelin, a two-month improvement was observed in phase II trials. However, these results were not statistically significant in phase III trials (2, 8, 13). Furthermore, a phase II trial assessed the combination of GVAX/CRS-207 with nivolumab (anti-PD-1) or ipilimumab (a CTLA-4 inhibitor), revealing promising outcomes only when paired with nivolumab (8, 12). Subsequent investigations have uncovered additional vaccines, such as the FAP vaccine, which appears to inhibit tumor progression, enhance the efficacy of immune checkpoint inhibitors, and provoke both spontaneous and vaccine-induced immune responses (18).

Furthermore, research involving a neoantigen-targeted vaccine administered via a hyaluronic acid hydrogel (PancVax gel) demonstrated a decrease in local recurrence following incomplete tumor resection and elicited T-cell activation in response to PancVax (19). Conversely, disappointing results have been reported in studies focusing on Algenpantucel-L, which is composed of irradiated cancer cells expressing alpha-1,3-galactosyltransferase coupled with radiochemotherapy in postoperative scenarios (2). Lastly, a phase I clinical trial in 2024 evaluated an mKRAS-specific amphiphile vaccine on 25 patients harboring KRAS mutations, yielding encouraging results; 21 of the 25 patients exhibited therapeutic responses, with 52% reaching a T-cell response above the median (100% biomarker reduction and 46% tumor clearance). Nonetheless, adverse effects such as fatigue, injection site reactions, and myalgia were also noted (20).

CAR T-Cell Therapies

Among the various adoptive T-cell transfer therapies, CAR T-cell therapy is the most promising option (2). CAR T-cells are genetically engineered T-cells programmed to recognize specific tumor-associated antigens via their chimeric receptors (13). Recent studies have highlighted two antigens, anti-mesothelin and carcinoembryonic antigen, as being particularly effective for T-cell activation (2). Moreover, the efficacy of these targeted therapies is significantly augmented when they are administered in conjunction with other immune modulators, such as cyclophosphamide or anti-CTLA4 and anti-PD1 agents (2). Preclinical trials involving anti-mesothelin CARs in murine models have demonstrated prolonged survival and reduced tumor burden (14). However, in a clinical trial (NCT01897415), only one out of six patients displayed disease progression (N=1/6; 17%), while two patients achieved stable disease for durations of 3.8 to 5.4 months (N=2/6; 33.4%), and the clinical outcomes for the remaining three patients remained indeterminate (N=3/6; 50%) (13, 14). Notably, no adverse events (AEs) were observed during this clinical trial (14). In another phase I clinical trial (NCT02159716) involving lentiviral-transduced anti-mesothelin (anti-MSLN) CAR T-cells (either combined with or without cyclophosphamide), 11 out of 15 patients experienced short-term stable disease (14). Common AEs, such as nausea and mild fatigue, have also been reported (14). However, it is essential to recognize that numerous clinical trials are still in their early phases (14). Overall, CAR T-cells targeting mesothelin showed acceptable tolerance, but their efficacy remains limited (12).

Other studies have identified alternative targets for CAR T-cells. CD133, which is significantly expressed in pancreatic ductal adenocarcinoma (PDAC), is a potential target (14). In a phase I clinical trial (NCT02541370), where all participants exhibited over 50% CD133 expression, 2 out of 7 patients (28.57%) experienced partial remission, while 3 out of 7 (42.85%) achieved stable disease, with the remaining 2 (28.57%) showing disease progression (14). Post-treatment evaluations indicated that CD133-positive cells were no longer detected in the tumor biopsies (14). Additionally, serious side effects reported included leukopenia, thrombocytopenia, anemia, anorexia, nausea, and mucosal hyperemia (14). Moreover, trials utilizing epidermal growth factor receptor (EGFR) targeted CAR T-cells were specifically conducted for metastatic PDAC, which lies outside the scope of this review (14).

In addition, over 60% of patients with PDAC show HER-2 overexpression, suggesting the potential for HER-2-targeted CAR T-cells (13). In a phase I clinical trial (NCT01935843), two patients achieved stable disease lasting 5.3 and 8.3 months (14). However, previous studies have indicated that anti-HER-2 CAR T-cell treatment could lead to severe AEs (grades 2 and 3) and even fatalities within 15 min of infusion (14).

In summary, the use of CAR T-cells for LAPC presents several safety concerns (15). Finally, it should be highlighted that allogeneic CAR T-cell infusions may also incur life-threatening AEs (14).

Natural Killer Cells/Other T-Cells

In addition to CAR T-cells, another type of T-cell immunotherapy has been tested. Cytokine-induced killer cells (CIK), which are ex vivo expanded, were evaluated in a phase II study, which showed encouraging outcomes (8). Although 3 patients (15%; N=20) reported grade 3 AEs such as weakness and thrombocytopenia, this trial suggests a relatively safe therapy with uncertain efficacy, as the median period of stable disease was reported as 11 weeks, and quality-of-life measures appeared to improve (8).

Chimeric antigen receptor natural killer cells (CAR NK-cells) have also been recognized in the literature, although reliable clinical outcomes are lacking (14). However, CAR NK-cells used in other conditions have resulted in serious grade 3 and 4 AEs (14). Further studies have reported that KPC (Kras, p53, and Cre) cells genetically engineered to express the carcinoembryonic antigen (CEA) were implanted into CEA transgenic mice. When the tumors reached sizes of 100-300 mm^3, the mice received either vehicle control injections or immunotherapy treatments (CEA-transcutaneous bilirubinometers [TCB] and/or aPD-L1). Treatment with CEA-TCB, either alone or in conjunction with aPD-L1, inhibited tumor growth, whereas aPD-L1 alone had no significant impact. Additionally, therapies involving CEA-TCB appeared to be linked to an increase in CD8 T-cell numbers, which were inversely correlated with tumor size (21).

Combination Therapies

This section focuses on treatment regimens that incorporate multiple therapeutic modalities. Current studies are testing the combination of mesenchymal stem cells with various immunotherapies, although these investigations are still in their early stages (1). Moreover, ongoing phase II studies are exploring the synergy between Ulocuplumab and Nivolumab (2). The combination of GVAX with ipilimumab has shown promising outcomes, particularly concerning survival rates, compared with ipilimumab alone (2). Additionally, a large trial is examining stem cell inhibition in combination with gemcitabine/nab-paclitaxel (2). The results are summarized in Table 1.

The table presents an overview of studies evaluating combinations of immunotherapies, chemotherapies, targeted agents, radiotherapy, and cellular therapies. The reported outcomes encompass survival statistics, tumor reduction, objective response rates, and immune response indicators, and clarify whether the results stem from clinical trials or preclinical studies, alongside pertinent limitations (such as adverse effects, trial terminations, or insufficient efficacy).

Table 1. Treatment Plans That Integrate Two Types of Therapies

Type of Treatment 1	Type of Treatment 2	Efficacy	Additional Notes
GVAX	Ipilimumab	Increased survival rate (compared to ipilimumab alone) (2)	-
Napabucasin (stem cell inhibition)	Gemcitabine and nab-paclitaxel	Greater than 35% objective response (survival rate: 10.7 months) (2)	-
Stereotactic body radiotherapy	IL-12	Increase in CD8 T cell activation, leading to marked tumor reduction (5)	Preclinical mice studies
	CCX872-B	Discontinued (5)	-
	Anti-PD1	Poorer survival outcomes as a result of lymphocyte depletion (22)	-
Irreversible electroporation	Anti-PD1	Inhibited tumor progression and extended lifespan of immunocompetent mice with PDAC (5)	Preclinical mice studies
	M1-oncolytic virus	Enhanced T-cell activation in the zinc-associated protein-deficient situation (5)	Preclinical mice studies

Continuation of Table 1.

Type of Treatment 1	Type of Treatment 2	Efficacy	Additional Notes
Irreversible electroporation	Intratumoral Toll-like receptor-7 agonist and PD-1 blockade	Enhanced therapeutic outcomes (5)	-
	Natural killer cell infusion	Dose-dependent objective response. However, no impact on survival rate was observed. This therapy regimen was connected to higher levels of serum IL-2, TNF-β, and IFN-γ (compared to the IRE group after treatment) (5)	All of these comparisons were calculated as clinically significant (P<0.05).
	Anti-PDL1 (Nivolumab)	An increase in effector memory cells was noted. However, a majority of the patients experienced grade ≥3 AEs (5)	
	Anti-PD1 (Toripalimab)	The progression-free survival was calculated as 10.6 months (compared to 27.5 months for IRE alone). Furthermore, the overall survival seems to be increasing (44.3 months compared to 23.4 months for IRE alone). Notably, the number of CD4+ and CD8+ T cells also increased, while the number of CD8+ Treg cells decreased (compared with those in the IRE-only treatment group) (5)	
Anti-PDL1	CXCR4 inhibitor (Plerixafor)	Studies observed an escalation on within-tumor CD3-positive T-cells and an induced tumor regression in KPC mice (13)	Preclinical mice study
Anti-CTLA4 (Ipilimumab)	Gemcitabine and nab-paclitaxel	No response (13). Other studies showed partial response in metastatic forms of pancreatic cancers in a minority of patients (12)	
CD-40 agonist (CP-870893)	Gemcitabine	Study in early stage (13)	-
Indoleamine-2,3-dioxygenase (IDO) inhibitor (Indoximod)	Gemcitabine and nab-paclitaxel	Ongoing phase Ib clinical trial. In preclinical trials, IDO inhibitors demonstrated high anti-cancer activity by increasing T-cell activity (13)	-
5-fluorouracil, leucovorin, oxaliplatin	PEGylated human IL-10 (AM0010)	Poor results were recorded with 15% total objective response (n=20). The median progression-free survival for these patients was only 3.9 months, while the patients experienced severe grade 3 and 4 AEs such as thrombocytopenia, anemia, and neutropenia (8)	-
OK432-pulsed DCs (intratumor), lymphokine-activated killer cells stimulated with anti-CD3 monoclonal antibody (intravenous infusion)	Gemcitabine	The phase I clinical trial provided promising results as 20% showed partial response and another 40% more than six months (n=5) (23)	-
Anti-PD1	IFN-γ	(With the requirement of delayed anti-PD1 treatment) showed significant anti-tumor effects (24)	-
Anti-CD40	Gemcitabine	Studies revealed that this combination is modifying the tumor stroma, inducing T cell-mediated anti-tumor activity, and reprogramming TAMs to exhibit tumoricidal properties.	-
A-emitting radioisotopes	Monoclonal antibodies	Studies showed a strong impact on in vitro studies and a tumor growth delay in vivo studies (25)	-

IL-12=Interleukin-12; anti-PD1=Anti-programmed cell death protein 1; IL-2=Interleukin-2; TNF-β=Tumor necrosis factor beta; IFN-γ=Interferon gamma; PD-1=Programmed cell death protein 1; anti-PDL1=Anti-programmed death ligand 1; IRE=Irreversible electroporation; CXCR4=C-X-C motif chemokine receptor 4; anti-CTLA4=Anti-cytotoxic T-lymphocyte-associated protein 4; CD-40=Cluster of differentiation 40; IL-10=Interleukin-10; AEs=Adverse events; DCs=Dendritic cells; anti-CD3=Anti-cluster of differentiation 3; TAMs=Tumor-associated macrophages; KPC=KrasLSL-G12D/+;Trp53R172H/+; Pdx1-Cre cells; CD3=Cluster of differentiation 3; CD4=Cluster of differentiation 4; CD8=Cluster of differentiation 8.

Conclusion

LAPC continues to be one of the most lethal forms of cancer, as evidenced by its dismal prognosis. Regrettably, the numerous studies referenced earlier have reported only marginal improvements in survival rates regarding immunotherapy options for LAPC, either yielding disappointing outcomes or presenting significant adverse effects in many participants involved in these clinical trials. Nonetheless, certain studies have revealed promising results through the application of specific therapeutic agents. This category includes various immune checkpoint inhibitors, such as anti-PD1, anti-PD-L1, and anti-CTLA4 agents, as well as CCR, CXCR2, and IDO inhibitors. Comparable effects have been observed in several vaccine trials, notably the GVAX vaccine when employed in combination therapies, alongside the FAP vaccine and the mKRAS-specific amphiphile vaccine, which showed encouraging results in patients harboring KRAS mutations. Furthermore, some of the most promising outcomes have been reported in CAR T-cell therapies, with mesothelin and carcinoembryonic antigens serving as primary targets, along with notable mentions of radioimmunotherapy trials. Although these therapies have demonstrated highly favorable results, there remains an urgent need for further investigation into the role of immunotherapy in the treatment of LAPC.

What Is Already Known on This Topic:

Locally advanced pancreatic cancer (LAPC) is a notable category of pancreatic cancer, characterized by a dismal prognosis and restricted treatment alternatives. Traditional treatment methods, such as chemoradiotherapy, are coming under scrutiny. Consequently, there is a pressing demand for the advancement of innovative strategies, the discovery of new pharmaceuticals, and further research in this area, including immunotherapy.

What This Study Adds:

Unfortunately, many of the studies mentioned previously have indicated only slight enhancements in survival rates associated with immunotherapy for LAPC, often resulting in unsatisfactory outcomes or notable adverse effects among numerous participants in these clinical trials. However, some studies have shown encouraging results with the use of particular therapeutic agents. Despite the positive findings of these therapies, there is a pressing need for additional research to explore the potential of immunotherapy in the treatment of LAPC.

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Surgical Anatomy of Corona Mortis: A Literature Review and Its Significance in Minimally Invasive Surgery

Panagiotis Ch. Tosounidis[1], Dimosthenis Chrysikos[1], Eirini Manoli[2], Theodore Troupis[1]

[1]Department of Anatomy, Medical School, National and Kapodistrian University of Athens, Athens, Greece, [2]Department of Surgery, University of Thessaly, Larissa, Greece

Correspondence: *ttroupis@gmail.com*; *ttroupis@med.uoa.gr*; Tel: + 30 210 7462388

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Abstract

Objective. This article reviews the literature on the anatomy, incidence, and clinical significance of the corona mortis, especially in minimally invasive surgery, where inadvertent surgical complications are more likely to occur. **Methods.** A systematic search was performed using the PubMed, Google Scholar, and ScienceDirect databases. Studies with the term "corona mortis" in the title and/or abstract published between 2000 and 2025 that were relevant to the aim of this study were included in this review. Studies published in languages other than English were excluded. The studies were analyzed using narrative data synthesis. **Results.** This study reviews the relevant literature and provides a thorough overview of the anatomy of the corona mortis vessels, including different classifications, incidence, location, and size of the vessels. There was a significant discrepancy in the reported prevalence of the corona mortis between studies, especially cadaveric and intraoperative studies. Both arterial and venous 'corona mortis' vessels have been reported, with a greater frequency of venous vessels, which are present in approximately 20% and 40% of hemipelvises, respectively. A number of case reports were evaluated regarding injury to the corona mortis vessels during minimally invasive procedures. These case reports highlight that current surgical practices and techniques seem to adequately prevent damage to these structures. **Conclusion.** While there is a relative scarcity of reports showcasing adverse events due to the corona mortis, the moderately high incidence of this variable vessel in approximately half of the hemipelvises necessitates detailed anatomical knowledge and consideration when planning a minimally invasive procedure in the retropubic pelvic space.

Key Words: Corona Mortis ▪ Surgery ▪ Anatomical ▪ Variation.

Introduction

The pelvic and abdominal wall vasculature are prone to anatomical variations. The embryological basis for these variations stems from the formation of this vasculature. An initial capillary network forms, which subsequently enlarges, atrophies, and disappears, resulting in the final vascular pattern. This occurs in both arteries and veins, with the venous vasculature being more irregular, as reflected by more anatomical variations. The obturator vein is formed by the transformation of the embryonic posterior cardinal vein into the iliac vein during weeks 6 and 7 of embryonic development (1).

As for the umbilical artery, its dorsal root forms two connecting arterial plexuses, the abdominal and the pelvic. The external and internal iliac arteries are formed from the pelvic plexus, whereas the obturator artery is formed from the varied anastomosis between these vessels (2). These variations are, in turn, reflected in the diverse definitions of the term corona mortis among authors. This review defines the corona mortis (CM) as a vascular connection between the obturator and external iliac or inferior epigastric arteries or veins occurring near the superior pubic ramus in the retropubic space (3). This connection can be arterial, venous, or, more rarely, both simultaneously (4). The corona mortis, Latin for 'crown of death', is aptly named as it constitutes a major source of bleeding if damaged (5) and is at risk during pelvic surgery and

minimally invasive procedures such as laparoscopic hernia repair (5-9), minimally invasive groin exploration for chronic post-herniorrhaphy inguinal pain (10), laparoscopic procedures for gynecological malignancies (11), laparoscopic removal of deep infiltrating endometriosis of the obturator internus muscle (12), mid-urethral sling procedure (13), and robotic radical prostatectomy (14, 15).

A laceration of the corona mortis can lead to severe bleeding, as these vessels link high-volume systems and may retract into the obturator canal (16). Furthermore, injury to the corona mortis vessels may require conversion to open surgery (17), although it can still be managed without it (5). As more surgeries are performed laparoscopically or robotically, accurate anatomical knowledge is required to improve patient outcomes. The anatomy of the corona mortis is particularly relevant in the context of minimally invasive surgery, where a limited visual field and restricted tactile feedback increase the risk of inadvertent vascular injury. Unlike open procedures, where bleeding can be more easily identified and controlled, laparoscopic and robotic approaches offer less immediate access to bleeding sites, making preoperative knowledge of anatomical variations critical. Furthermore, common dissection planes in minimally invasive procedures—such as during hernia repair—bring the surgeon in closer proximity to the corona mortis compared to open approaches. CM has been widely studied due to its relevance in pelvic surgery, with a reported prevalence mainly ranging from 20% to over 60%, depending on the definitions and methodologies. The existing literature includes cadaveric, imaging, and intraoperative studies, systematic reviews and meta-analyses, and case reports of injury to the vessel. However, variability in terminology, particularly regarding anastomosing versus aberrant vessels, has led to inconsistent incidence rates. While anatomical details are well documented, few studies have linked these findings to surgical outcomes. This literature review presents the most relevant data where corona mortis was the main subject of study.

This review aimed to clarify the anatomical characteristics and incidence of this unique connecting vessel and highlight its importance during minimally invasive surgical approaches to the pelvis.

Materials and Methods

Search Strategy

A literature review was conducted using an online article search. The databases used were PubMed, Google Scholar, and ScienceDirect. The search term "corona mortis" was used, and studies were required to include this term in their title. For the PubMed and ScienceDirect databases, the search was expanded to include abstracts. The dates ranged from 2000 to 2025. Additionally, the references cited in the included studies were searched, and all relevant articles were incorporated into the review. A secondary search was then performed, combining the search terms 'corona mortis' and looking specifically at case reports, as well as a search combining the search terms 'corona mortis' and 'laparoscopic' or 'minimally invasive' or 'robotic' to gauge the impact of corona mortis on minimally invasive procedures specifically. From this secondary search, as well as the initial search, 15 case reports were included in this review.

Study Analysis

The number of articles found after the initial search was 271. Duplicates were then removed. The studies were then analyzed, and data were extracted. The inclusion criteria for this literature review were based on whether the study: (1) defined the corona mortis in line with this review's definition, (2) reported on the anatomical characteristics of the corona mortis, or (3) had a different definition of the corona mortis but presented a detailed analysis of the vessels discussed, from which data regarding the corona mortis with a definition in line with this review's could be extracted and used. Articles relevant to the aim of this study that fit the above criteria were included, while studies in languages other than English were excluded. Articles without online versions were also excluded. Additionally, the references of the studies

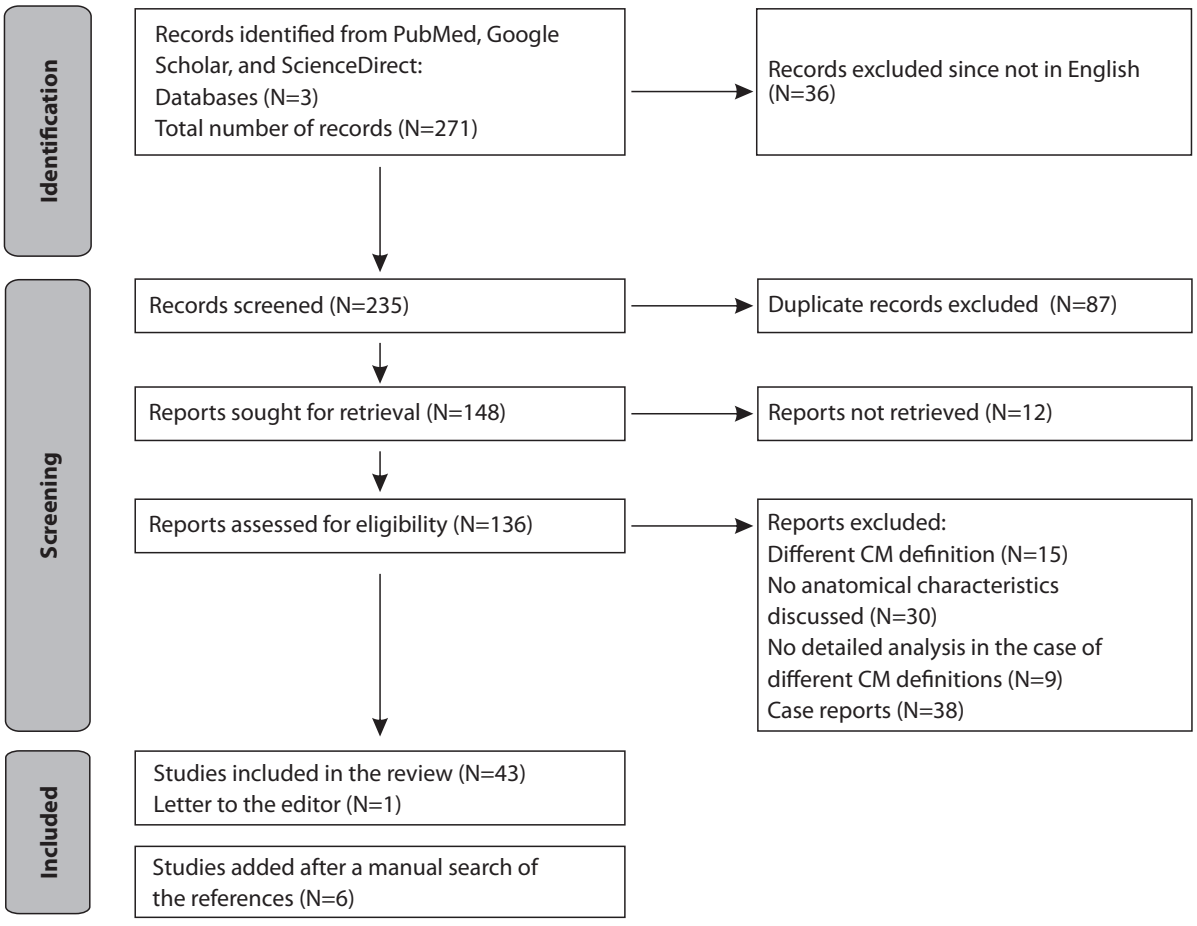

Figure 1. Flowchart of the included studies.

fitting the above-mentioned criteria were manually scoured, and any relevant articles were added to the review. Finally, 71 articles were included in this literature review. Of the articles that remained in this literature review, there was one meta-analysis, three systematic reviews, and the remainder were original studies and case reports. The original studies were cadaveric, intraoperative, or imaging studies, or, in some cases, a combination of the aforementioned studies. Finally, the studies were analyzed using narrative data synthesis.

Results

Anatomy Overview

CM has been described in most classical anatomy textbooks as an arterial anastomosis; however, since the name most accurately represents a structure with potential risk for the patient (18), the current literature accepts any vascular structure connecting the obturator and external iliac or inferior epigastric at the superior pubic ramus as corona mortis. For some authors, an aberrant obturator artery or vein is no different in this regard and could be considered as CM (18, 19). Specifically, in an intraoperative study, Ates et al. (18) proposed a classification system based on the thickness of the anastomotic vessels, where CM was classified as thin or thick with a cutoff of 2 mm, the same as the diameter of the dissector tip. In another in vivo study by Pellegrino et al. (11), vessels smaller than 2 mm in diameter were excluded altogether and could not be classified. This multitude of definitions, which varies between authors,

is primarily caused by the obturator artery, which is known to have a highly diverse origin, especially for a vessel of its size (20). Different types of anastomoses have been documented in several articles, such as Rusu et al. (19), who distinguished four arterial and three venous subtypes of anastomotic vessels.

The different types are as follows:

- Type 1: The obturator artery originates from the external iliac artery.
- Type 2: The obturator artery originates from the inferior epigastric artery.
- Type 3: Anastomosis of the obturator and inferior epigastric arteries.
- Type 4: Pubic branch(es) from the obturator artery are unanastomosed to the external iliac system but cross over the superior pubic branch.

The venous corona mortis was categorized into three subtypes as follows:

- Type 1: The obturator vein drains into the external iliac vein.
- Type 2: The obturator vein drains into the inferior epigastric vein.
- Type 3: Venous anastomosis of the obturator and inferior epigastric veins.

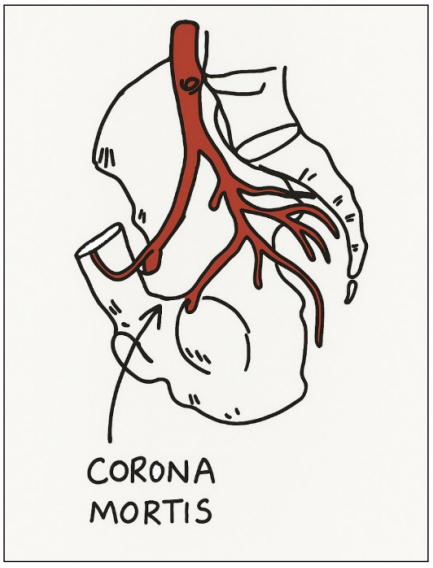

Figure 2. The classic definition of the arterial corona mortis is the connection between the obturator and inferior epigastric vessels.

In surgical practice, many patients have a combined pattern of CM, making such classifications less meaningful (21). The anastomosing vessels typically have a diameter between 0.8 and 4.9 mm, with a mean diameter of 2.8 mm (21); however, in most cases, the diameter ranges between 2 and 4.2 mm (22). In a systematic review by Cardoso et al., no relationship was found between the incidence of corona mortis and anthropometric characteristics (21).

Incidence

The highest reported incidence of both arterial and venous corona mortis was reported by Berberoglu et al., with 86% and 100%, respectively. This study included a total of 50 hemipelvises, of which 14 were cadaveric and 36 were intraoperatively examined while treated laparoscopically for hernia repair. The study reported on the Turkish population, but further anthropomorphic or sex-related differences were not described. In contrast, the lowest percentages were reported by Selçuk et al. (4% venous CM) and Pillay et al. (1% arterial CM). Selçuk et al. reported on a sample of 96 hemipelvises from a Turkish population examined intraoperatively for pelvic lymphadenectomies. No further anthropomorphic or sex-related differences were noted. Pillay et al. examined 67 cadaveric hemipelvises from an Indian population. The sample mainly consisted of male cadavers, with 63 of the 67 hemipelvises being from males. However, these studies are outliers, with most studies reporting an arterial prevalence of approximately 20-40% and a venous prevalence of approximately 40-60%. These results are represented in systematic reviews on the subject (4, 21, 23), with subsequent studies reporting comparable results.

The differences in the reported incidence could be attributed to the non-homogeneous definition of CM or the varying ethnic groups on which the different studies were performed. Another reason could be the secondary circulatory routes, which correlate with older age and cardiovascular disease, and most cadaveric studies have a relatively old mean age (24). These secondary arterial

routes are created by arteriogenesis or angiogenesis. Angiogenesis is insignificant in the context of this review, as capillaries cannot be classified as corona mortis vessels. On the other hand, arteriogenesis, in the presence of peripheral arterial disease, the transformation of preexisting collateral arterioles into larger connecting vessels, could create a corona mortis (25). Finally, depending on the study type, several limitations may be inevitable; for example, imaging and intraoperative studies primarily report on arterial CM, whereas some cadaveric studies focus only on venous CM.

Location and Size

Of all the studies included in this review, 14 reported the size of the anastomosing vessel of the corona mortis, and 21 reported the distance from the pubic symphysis. Some studies differentiated between gender, others between left and right or arterial and venous, while a single study focused on different dissection protocols. The same was true for the reported distances. For completeness, these results were included, although they were not always directly comparable. The reported mean size ranged from 1.2 mm to 5 mm, with most studies reporting a mean size of approximately 3 mm. The distance from the pubic symphysis was between 33.4 mm and 71 mm, while most studies ranged from 50 mm to 60 mm.

Table 1 summarizes the results of the different studies (3, 4, 11, 16, 18, 19, 21, 23, 26-66), presenting the sample size (hemipelvises), arterial and venous prevalence, mean size of the anastomosis in mm, and average distance of 'corona mortis' vessels from the symphysis pubis (mm) in chronological order, including the country of origin and type of study. Among the included studies, there is a meta-analysis and two systematic reviews, which are presented first.

Table 1. Characteristics of the Studies and Summary of Their Results

Study	Year*	Country	Study type	Hemipelvises	Article type	Prevalence (%)		Size (mm)	Distance (mm)
						Arterial	Venous		
B. Sanna et al. (4)	2018	-	-	A) 1284 B) 850	Meta-analysis	A) 17	B) 42	-	Arterial: 59.9 Venous: 50.7
Cardoso et al. (21)	2021	-	-	3107	Systematic review	22	47	2.8	-
Noussios et al. (23)	2020	-	-	1455	Systematic review	25	42	-	-
Naicker et al. (26)	2024	South Africa	Imaging	145	Original article	13	29	2.83	SPS†: 61.7; PPS‡: 54.6
Khirul-Ashar N et al. (27)	2024	Malaysia	Cadaveric	164	Original article	49	51	2.86	54.7
Konarska-Włosińska et al. (28)	2024	Poland	Imaging	138	Original article	22	-	-	62.7
Naicker et al. (29)	2024	South Africa	Cadaveric	123	Original article	6	62	-	-
Schaible et al. (30)	2024	Switzerland	Intraoperative	210	Original article	22	76	Arterial: 3 Venous: 5	-
Atlihan et al. (31)	2023	Turkey	Cadaveric	20	Original article	25	60	-	-
Beya et al. (32)	2023	France	Cadaveric	24	Original article	21	46	Dissection protocol A) 2.75 Dissection protocol B) 3.08	Dissection protocol A) 58 Dissection protocol B) 60.9
Sambhav et al. (33)	2022	India	Cadaveric	62	Original article	40	65	-	-

Continuation of Table 1.

Study	Year*	Country	Study type	Hemipelvises	Article type	Prevalence (%)		Size (mm)	Distance (mm)
						Arterial	Venous		
Sripadungkul et al. (34)	2022	Thailand	Cadaveric	68	Original article	10	19	2.98	45
Sengodan et al. (35)	2022	India	Cadaveric	40	Original article	18	78	-	55.6
Wada et al. (36)	2022	Japan	Cadaveric	113	Original article	28	76	>2 mm	47.7
Bharathi et al. (37)	2022	India	Cadaveric	55	Original article	-	64	Male: 1.62 Female: 1.2	Male: 52.6 Female: 56.3
Zorina et al. (38)	2021	Moldova	Imaging	197	Original article	27	-	-	-
Abbas et al. (39)	2021	Sudan	Intraoperative	30	Original article	40	30	4.33	-
Bhoil et al. (40)	2020	India	Imaging	200	Original article	14	-	Right: 2.6 Left: 2.3	Right: 54.55 Left: 54.26
Du et al. (41)	2020	China	Cadaveric	16	Original article	31	56	2.5	-
Güzel et al. (42)	2020	Turkey	Intraoperative	34	Original article	44	65	-	35.9
Kashyap et al. (43)	2019	India	Cadaveric	24	Original article	4	58	-	Arterial: 57 Venous: 41
D'Souza Dias and Patil (44)	2019	India	Cadaveric	50	Original article	4	40	-	Arterial: 42.7 Venous: 41.5
Selçuk et al. (45)	2018	Turkey	Intraoperative	96	Letter to the Editor	2	4	-	-
Pillay et al. (46)	2017	India	Cadaveric	67	Original article	1	46	-	54.5
Zhou et al. (47)	2017	China	Cadaveric	20	Original article	15	55	-	65.3
Han et al. (48)	2017	China	Imaging	660	Original article	14	51	Arterial: 2.56 Venous: 3.63	Arterial: 59.6 Venous: 66.8
Leite et al. (49)	2017	Brazil	Cadaveric	60	Original article	45	-	2.56	49.6
Steinberg et al. (50)	2017	Israel	Imaging	200	Original article	33	-	Right: 2.4 Left: 2.24	Right: 55.2 Left: 57.2
Nayak et al. (51)	2016	India	Cadaveric	73	Original article	-	45	-	-
Castellani et al. (52)	2016	Italy	Imaging	94	Original article	23	-	-	-
Pellegrino et al. (11)	2015	Italy	Intraoperative	50	Original article	16	36	-	-
Jensen et al. (53)	2015	Switzerland	Intraoperative	130	Original article	42	-	-	-
Ates et al. (18)	2015	Turkey	Intraoperative	398	Original article	28	-	-	-
Bible et al. (54)	2014	USA	Cadaveric	10	Original article	60	80	-	-
Stavropoulou-Deli and Anagnostopoulou (55)	2013	Greece	Cadaveric	70	Original article	11	17	Arterial: 3 Venous: 3.13	Arterial: 54.4 Venous: 46.7
Kacra et al. (56)	2011	Turkey	Cadaveric	10	Original article	20	40	-	-
Rusu et al. (19)	2010	Romania	Cadaveric	40	Original article	38	53	-	-

Continuation of Table 1.

Study	Year*	Country	Study type	Hemipelvises	Article type	Prevalence (%)		Size (mm)	Distance (mm)
						Arterial	Venous		
Smith et al. (57)	2009	USA	Imaging	100	Original article	29	-	-	-
Pai et al. (58)	2009	India	Cadaveric	98	Original article	2%	-	-	-
Pathi et al. (59)	2009	USA	Cadaveric	24	Original article	-	67	-	-
Kawai et al. (60)	2008	Japan	Cadaveric	560	Original article	22	-	-	-
Darmanis et al. (3)	2007	England	Cadaveric	80	Original article	36	60	-	Arterial: 71 Venous: 65
Namking et al. (61)	2007	Thailand	Cadaveric	204	Original article	23	71	-	-
Drewes et al. (16)	2005	USA	Cadaveric	30	Original article	17	30	-	54
Okcu et al. (62)	2004	Turkey	Cadaveric	150	Original article	19	52	-	Arterial: 64 Venous: 56
Ersoy et al. (63)	2004	Turkey	Cadaveric	10	Original article	-	100	-	-
Sarikcioglu et al. (64)	2003	Turkey	Cadaveric	54	Original article	-	20	-	39.79
Karakurt et al. (65)	2002	Turkey	Angiography	98	Original article	28	-	-	Arterial: 33.4
Berberoglu et al. (66)	2001	Turkey	1) Cadaveric 2) Intraoperative	1) 14 2) 36	Original article	1) 86 2) 86	1) 100 2) 94	1) 3.3-Venous 0.98; Arterial 2) <1 mm	40.4 (Cadaveric)

*Publication; †Superior pubic symphysis; ‡Posterior pubic symphysis; Dissection protocol A (classic dissection); Dissection protocol B (pulsatile vascularization).

Discussion

Corona mortis vessels cross the pubic rami and, as such, are at risk in several different surgeries, mainly in urological, gynecological, orthopedic, and general surgery procedures. For some authors, such as Rusu et al. and others, any vessel coursing over the superior pubic ramus could be called corona mortis regardless of whether it is an anastomosing vessel or an aberrant or accessory obturator artery (19, 67-70). In turn, this creates further discrepancies in the reported incidence beyond the different ethnic groups and study methodologies, as discussed earlier.

In a systematic review by Marvanova and Kachlik (67), which defined corona mortis as any vessel coursing over the superior pubic ramus, the overall incidence of arterial corona mortis was 26%, while only approximately half were anastomosing vessels, with 54% of the total vessels found. Further studies could provide a better understanding of its true incidence, provided that a universal definition is adopted. Furthermore, another area of possible future research could be studies combining pre-surgical with intraoperative imaging, a type of combined study that is not widely explored but could provide valuable knowledge.

While the arterial corona mortis has been more widely researched, with more studies reporting on its prevalence either due to greater interest in cadaveric anatomical studies of the obturator artery or the inherent limitations of some intraoperative studies, the venous corona mortis is more prevalent. In a study by Kinaci et al., the pressure of the pneumoperitoneum played a significant role in the vessels, which could be identified intraoperatively and were, in turn, protected by lowering the pressure from 14 mmHg to 8 mmHg for at least their identification (17). Nevertheless, the incidence of the corona mortis vessels, either arterial or the more prevalent venous, suggests that such a connection should be expected in most hemipelvises.

These CM anastomosing vessels are prone to injury due to their positioning proximal to the hernial sac, either during dissection or tack fixation in laparoscopic hernia repair, specifically (24). A laceration of the corona mortis can result in massive hemorrhage, requiring transfusion protocols (3). It could also be unassuming, and if undetected and left unchecked, it could result in hematoma formation (65). Despite this almost inevitable encounter with the corona mortis when operating on the pelvis, there is a lack of case reports documenting life-threatening injuries to these vessels. Even when its presence was confirmed, the course of these patients was uneventful (52). Darmanis et al. (3) also reached a similar conclusion, with little correlation between hemorrhage and CM during pelvic operations. In an in vivo study by Ates et al. (18), injury to the corona mortis was a rare event occurring in 1.5% of TEP hernia repairs, mostly during tack stapling on the Cooper ligament during mesh fixation. The injured vessels were <2 mm in size. The authors of this study also concluded that the tacks should be stapled near the symphysis pubis to minimize this risk. In a study by Schaible et al. (30), in which patients underwent surgeries for pelvic ring injuries, acetabular fractures, or combined injuries, the corona mortis was injured in ten of the 185 cases due to prior trauma and in one case due to surgical manipulation. In all these cases, bleeding was controlled, and there were no unfavorable patient outcomes. Similarly, Jensen et al. (53) examined the relevance and outcomes of pelvic trauma and showed no correlation between the existence of the corona mortis and mortality or bleeding, and posed little threat to surgeons operating on the pelvis, as it could be managed even if damage occurred (53).

However, most life-threatening hemorrhages from the corona mortis vessels reported in the accessed case reports were associated with pelvic trauma (59, 62-64). Nevertheless, a detailed knowledge of the pelvic anatomy and possible vascular variations is a must for the surgeon operating in the area, as it is difficult to assess whether the absence of reported adverse events regarding minimally invasive pelvic procedures is because of the lack of correlation between corona mortis and these events or the extra attention and the accumulated technical prowess of the surgeons operating in the area. In clinical practice, recognizing the high likelihood of encountering corona mortis vessels during pelvic procedures should encourage routine anticipation rather than alarm. Although the presence of the vessel is not typically associated with adverse outcomes, its identification can guide safer dissection strategies. For example, placing mesh tacks closer to the symphysis pubis during TEP repairs, as recommended by Ates et al. (18), minimizes the risk of vascular injuries.

Similarly, intraoperative adjustments, such as reducing pneumoperitoneum pressure, as demonstrated by Kinaci et al. (17), can facilitate vessel visualization and protection. Understanding the course and variability of CM allows for early identification and control if bleeding occurs, contributing to greater surgical confidence and better patient outcomes. Ultimately, integrating this anatomical awareness into surgical planning and training supports better intraoperative decision-making and enhances patient safety. The main limitation of the assessed studies was the heterogeneity among them in terms of study type, ethnic group, and sample size, which was reflected in their results. A statistical comparison between them may introduce errors due to inherent differences when comparing cadaveric and intraoperative or imaging studies. Intraoperative studies are prone to bias arising from differences in surgical techniques, surgeon expertise, and institutional capabilities, variables that are rarely controlled for and are challenging to quantify.

Limitations of the Study

This review is limited by the number of assessed case reports, which stemmed from the number of databases utilized. Although a broader database search might have identified additional case reports, the studies included in this review are deemed representative of the current evidence.

Conclusion

The corona mortis is a widely researched anatomical variant, and many studies have documented its presence and characteristics. The high incidence of the corona mortis vessels, regardless of their definition, being present in approximately half of the population, underscores the vital role of excellent anatomical knowledge for surgeons operating in the retropubic space. Accordingly, the traditional designation "Crown of Death" appears to be a misnomer that does not reflect current surgical outcomes. Despite its prevalence, the low rate of documented intraoperative complications, as reflected in published case reports related to this vessel across various pelvic surgeries, suggests that its clinical significance may be overstated.

Surgeons should remain vigilant and could incorporate the following practical strategies into their operative planning and techniques:

- Preoperative imaging, such as contrast-enhanced CT or MRI angiography, when indicated, can help identify vascular variations in complex or high-risk cases.
- Meticulous dissection of the retropubic and superior pubic ramus regions is essential to avoid inadvertent injury, particularly during minimally invasive procedures.
- Prompt recognition and control of bleeding from a corona mortis vessel—should it occur
- Anatomical education and simulation training should include recognition of vascular variants, such as the *corona mortis,* to prepare surgeons for intraoperative identification and management.

In summary, emphasis should remain on meticulous dissection, thorough preoperative evaluation, and intraoperative vigilance to minimize the risk of injury, and its presence should not, in itself, necessitate changes to standard surgical approaches.

What Is Already Known on This Topic:

Corona mortis has been extensively reviewed, with many studies reporting on its incidence and other anatomical characteristics, primarily through cadaveric studies. Due to the anatomical nature of these studies, the impact of this anatomical variation on actual surgical complications is reflected more accurately in case reports of complications.

What This Study Adds:

This study begins with a comprehensive review of the available literature and then examines the available case reports. Some studies offer a different perspective on this topic, highlighting the scarcity of complications reported associated with the corona mortis, especially considering how commonplace these surgeries are.

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Virtual and Augmented Reality in Anatomy Education: Exploring New Horizons

Dimitrios Nikas[1, 2], Margarita Toumanidou[3], Dimitrios Vergados[4], Theodoros Mariolis-Sapsakos[1, 5, 6], Nikolaos Tsolis[4], Dimitrios Filippou[7], Theodoros Troupis[7], Andreas Koumenis[1, 2], Ioannis Kalemikerakis[8], Stamatis Karakatsanis[9], Evangelos Dimakakos[3, 10]

[1]Laboratory of Anatomy, Advanced Anatomical Applications, Artificial Intelligence, and Experimental Surgical Research (AAAAAIES Lab), Athens, Greece, [2]Nursing School, University of Athens, Greece, [3]Center of Diagnosis, Prevention, and Treatment of Lymphedema-Lymphatic Diseases of Metropolitan Hospital, Athens, Greece, [4]University of Piraeus, Greece, [5]National and Kapodistrian University of Athens, Greece, [6]Faculty of Nursing, University of Athens, Greece, [7]Department of Anatomy, Faculty of Medicine, School of Health Sciences, National and Kapodistrian University of Athens, Greece, [8]Laboratory of Nursing Rehabilitation of the Chronically Ill (NRCILab), Community Nursing Department, Nursing School, University of West Attica, Greece, [9]Third Department of Internal Medicine, Sotiria General Hospital for Chest Diseases, National and Kapodistrian University of Athens, Greece, [10]Anatomy-Physiology, Nursing School, University of West Attica, Greece

Correspondence: *edimakakos@yahoo.gr*, *ritatoum89@gmail.com*; Tel.: +30 697 2000842, + 30 698 5978653

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Abstract
This review explores how virtual and augmented reality technologies are transforming medical education and clinical practice, particularly in anatomy instruction. Virtual and augmented reality technologies are reshaping our perception and interaction with anatomical structures. Their integration into medical practice has introduced opportunities in diagnostics, surgical training, rehabilitation, and patient education. With the increasing number of U.S. Food and Drug Administration approvals, these technologies offer a transformative shift in the teaching and practice of medicine. Virtual environments facilitate detailed anatomical visualization, offering students and trainees immersive and interactive experiences. This paper highlights the role of these technologies in enhancing educational methods, improving knowledge retention, and overcoming traditional limitations, such as the scarcity of cadavers. **Conclusion.** Virtual and augmented reality offer novel educational tools in the health sciences, providing cost-effective, accessible, and innovative approaches to anatomy education and clinical application. Further research is required to elucidate the benefits of these technologies in the education and training of medical students.

Key Words: Anatomy Education ▪ Virtual Reality ▪ Augmented Reality ▪ Medical Technology ▪ Health Sciences.

Introduction

Reminiscent of the 1966 science fiction film "Fantastic Voyage", we were amazed to see how medical professionals 'traveled' inside a patient's body to treat a brain injury. Virtual Reality (VR) and Augmented Reality (AR) now offer a similar, albeit safer, immersive, and interactive visualization of a patient's anatomy as never before. These technologies provide operators with the opportunity to "travel" through the body, merging the real world with digital imaging of anatomical structures and their associated pathologies.

The impact of these technologies on every aspect of patient care is expanding as the U.S. Food and Drug Administration (FDA) begins approving them for applications in all areas of the health sciences, including medicine, nursing, surgery, and psychology. These applications in clinical practice are considered to be technologies poised to transform the way healthcare is delivered across nearly all specialties. These technologies play an increasingly important role in education, preoperative planning, intraoperative guidance, and even perioperative pain management and rehabilitation (1).

Augmented and Virtual Reality

By definition, augmented reality adds digital information to the real world, whereas virtual reality completely replaces the real world with a digital one, offering an immersive experience that excludes the physical world entirely. Augmented digital information is embedded in the real world and perceived by one or more senses. In this way, videos or computer-generated images are overlaid onto the physical world.

According to Azuma et al. (2), an augmented reality system must: 1) combine real and virtual objects in the physical environment, 2) operate interactively and in real time, and 3) align real and virtual objects with each other. Such a system usually includes a camera to detect the user's movements, which are then merged with the virtual objects. An optical display enables the user to see digital objects overlaid on the real physical world.

In the early 1990s, Boeing introduced the first augmented reality system to assist workers with assembling wiring systems (3). Loomis introduced the first medical application in 1993 (4). It involved a GPS-based system that helped blind individuals navigate by adding cues to convey spatial information. Fuchs et al. (5) demonstrated the clinical benefits of augmented reality with a system that superimposed anatomical images onto a patient during biopsy procedures.

In the past decade, software tools for developers, such as "HoloLens SDK" and "ARToolkit", have accelerated the development of augmented reality applications. The "Total Immersion" of D'Fusion enabled developers to design simpler applications, making them more accessible to users. Google developed "Google Glass", and in 2016, Microsoft developed "HoloLens", both of which have been used in clinical research and FDA-approved commercial applications. Their usability is currently being tested in many areas of daily clinical practice (6). These technologies have enormous potential to transform the education of students and trainees in human anatomy and invasive clinical interventions. For example, through interactive simulations, students can explore the human body and study its physiological processes. The simulations can also integrate other digital biomedical data, such as CT and MRI images. Additionally, simulation can be particularly useful for learning anatomy and its processes, as it allows learners to prepare, practice, and review their performance repeatedly in a risk-free environment (7).

Virtual reality educational applications can provide satisfactory quality and fidelity virtual environments capable of providing incentives for active learning (8). A plethora of such educational applications have been developed over time, featuring a variety of tools to support subjects such as physics, chemistry, mathematics, biology, history, engineering, and many other cross-curricular approaches. The basic principle of utilizing virtual reality in education lies in experiential learning (the experience of direct contact) with the object of study, along with a participative approach to the course material.

Methods

Purpose and Objectives of the Study

This section presents the methodology for the systematic review of empirical studies and reviews on the application of virtual and augmented reality in education in health sciences schools. Specifically, we searched for and analyzed the studies that met the research criteria based on the research questions of this paper.

The first research question distinguishes between two emerging digital technologies—virtual and augmented reality—exploring their educational role in the training of health professionals, as well as the contributions and usefulness of each technology. The second question examines the potential for integrating these technologies into both educational processes and clinical applications within the healthcare industry.

Bibliographic Search Strategy

The purpose of this systematic review is to document the findings of studies conducted between

2010 and 2025 on the use of virtual and augmented reality in medical education and surgery. The search was conducted online, specifically on the NCBI website (National Center for Biotechnology Information, USA), using the PubMed, Google Scholar, and ResearchGate databases, which include authoritative articles and reports published in scientific journals and conferences of health organizations. The keywords used in the search were: "Virtual Reality", "Augmented Reality", "Health Sciences", "Medical Education", and "Medical Applications".

The terms used in the field of new digital technologies are often employed interchangeably. In this study, we define the terms as follows:

- Virtual reality refers to a fully digitized environment.
- Augmented reality refers to the real world, enhanced by superimposed digital information.
- Medical education is defined as the teaching, training, and testing of knowledge and skills used by students in health sciences schools.
- Medical surgery is defined as a medical specialty that uses surgical protocols and instruments to investigate or treat a medical condition in a person.

We performed two searches using the following key terms. To search the literature in the field of "medical education", we used a title search ("virtual and augmented reality") AND a subject search ("medical education"). To search the literature in the field of "medical surgery", we used a title search ("virtual and augmented reality") AND a subject search ("medical surgery").

Data were collected from the NCBI online database to answer our research questions regarding the integration of these technologies into the fields of medical education and surgery. Fields that overlap with other professions, such as nursing, were included. However, veterinary and dental studies were excluded to maintain our focus solely on medical investigations. This decision was based on the fact that different universities have distinct anatomy fields, use technologies differently, and apply diverse methodologies in training and teaching.

Methodological Framework

More specifically, we reviewed titles and abstracts to exclude studies not relevant to the topic of discussion. For this reason, we established inclusion and exclusion criteria for the studies under evaluation. We considered abstracts eligible if the study met the following inclusion criteria:

- The articles reported a correlation between virtual and augmented reality in medical education and clinical application.
- The articles were written in English and/or Greek.
- The articles were published after 2010. The literature search was completed in 2025.

On the other hand, we excluded from this review studies that did not show a clear correlation between new technologies and the health sciences. Specifically, we did not include the following in the search:

- Reports and studies related to fields outside the health sciences (e.g., the commercial sector).
- Articles written in languages other than English or Greek.
- Articles published before 2010.

The search identified 366 articles. However, not all were included in the literature review, as some were not relevant to the search purpose and did not meet the keyword criteria. Of the 230 highlighted articles, only 107 were systematic or original studies that met the inclusion criteria. The authors identified a total of 81 freely accessible scientific studies, which they included in this study.

Figure 1 schematically illustrates the process followed to search and evaluate the studies included in this systematic review.

Advances in computing, communications, and technology since 1990 may have contributed to the increase in research on virtual reality, while the advent of the smartphone in 2008 may explain the rise in research on augmented reality. Both virtual and augmented reality technologies are used in surgical training and anatomy teaching. However, we identified potential applications of virtual reality in counseling and of augmented reality in practical skills training. Although research has

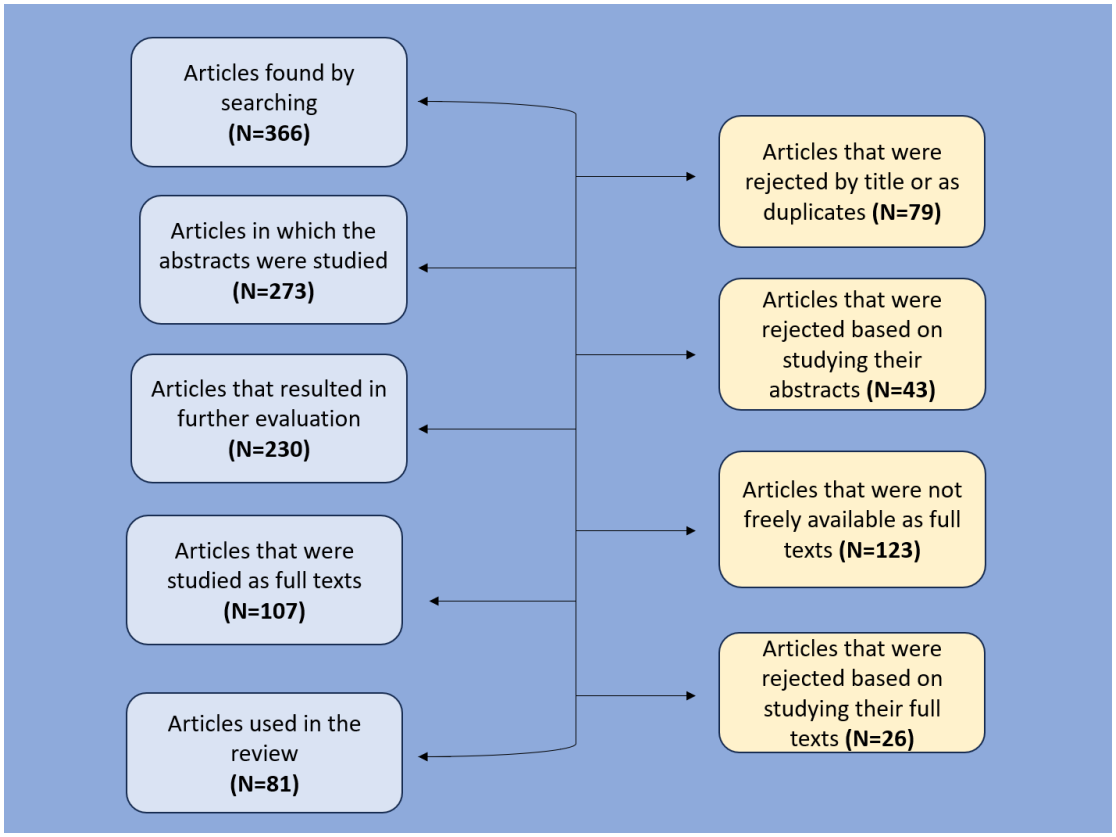

Figure 1. Flow diagram of the article selection process for this critical review.

validated the use of virtual and augmented reality in medical education, few studies have examined the integration of these new technologies into the education of health scientists.

Results

Anatomy is one of the most complex subjects in the health sciences due to the vast amount of knowledge that students must acquire (9). The use of cadaveric material is inextricably linked to the teaching of anatomy and is superior to anatomical atlases, which only provide two-dimensional images. Throughout history, the use of cadaveric material in medical and allied health curricula has been a source of serious social controversy. One such controversy revolves around whether the use of cadaveric material is an appropriate modern method for teaching human anatomy. On the other hand, some advocates argue that the use of cadaveric material is one of the most fundamental components for comprehensive knowledge and that students may not acquire sufficient anatomical knowledge if it is absent. Medical professionals often refer to anatomy as the language of medicine. However, the 21st-century medical curriculum has shown a significant reduction in the hours devoted to anatomy education (10). This decline is partly due to economic factors related to the preservation of cadaveric material and the limited access to human cadavers. Additionally, the maintenance of modern laboratories and storage facilities that meet health and safety standards for students and staff adds an additional financial burden.

Cultural and ethical considerations also play a crucial role, as they create limitations that make it difficult for educational institutions to obtain or access human cadavers for health science education. Consequently, many medical schools and departments that teach anatomy are seeking

alternative or complementary methods for teaching the human body, such as laminated anatomy charts and two-dimensional (2D) and three-dimensional (3D) imaging (11).

With the advancement of technology, particularly 3D imaging and virtual reality, teaching anatomy has become easier. The use of this technology by educators has led to the development of models that represent anatomical structures more effectively than cadavers, while also eliminating the need for the time-consuming and complex process of cadaver dissection (12). Additionally, this technology has greatly assisted instructors in explaining the features or functions of anatomical structures that may not be immediately visible.

Virtual and Augmented Reality in Anatomy Education

The use of 3D models is widespread in anatomy education. Virtual and Augmented reality enable users to bypass the hassle and complexity of cadaver preparation and can provide a better understanding of the features or functions of anatomical structures that may not be immediately apparent (13). Moreover, these models are particularly useful in explaining anatomical relationships and functions that may not be clearly discernible in a cadaver or may be obstructed by other structures. Consequently, anatomy education is enhanced and facilitated through the use of digitized anatomical models (14). These models can focus on specific features of anatomical structures that are relevant to the curriculum's educational goals.

The goal of incorporating digital anatomical models into the curriculum is to enhance student learning. These models can be used as stand-alone learning tools or in combination with other learning resources to help students develop knowledge and achieve their educational objectives (15).

Discussion

This paper highlights the various advantages of virtual and augmented reality in medicine, particularly in the field of surgery:

1. Using VR and AR atlases of the human body, with detailed analyses of physiology and pathology, provides better knowledge transfer and job training for trainees.
2. Virtual and augmented reality can closely mimic the clinical environment of the operating room while simultaneously depicting the patient's anatomy and physiology.
3. Radiological data can be integrated into VR or AR applications to visualize anatomical structures—such as organs and various pathologies—providing a realistic representation of human anatomy or even a patient's clinical condition. In addition, VR/AR-based preoperative planning can help users become familiar with complex surgical procedures.
4. Intraoperative guidance reduces the likelihood of serious complications and enhances trainees' surgical skills.
5. The use of 3D models in specialized training programs contributes to anatomy education, providing students with a more practical approach. Virtual and augmented reality create a friendly learning environment, enabling learners to engage in independent learning and research activities.

Beyond these educational and surgical advantages, virtual and augmented reality technologies can also play an active role in telemedicine, ranging from remote diagnosis to complex tele-interventions. In such contexts, good knowledge of anatomy, physiology, and pathophysiology, supported by VR and AR technologies, could help physicians in diagnosing, providing initial management, and providing treatment instructions for a patient's disease (16, 17). As an example of this application, McCoy et al. showed that live streaming and real-time connection made it possible to assess the viability and efficiency of using telesimulation and wearable/mobile technology to teach medical professionals abroad about mass casualty incidents in emergency medical services (18). The FDA approves these technologies based on their continuous evolution. While there is still room for improvement, it is evident that these technologies have the potential to impact every aspect of medical care.

Understanding human anatomy is essential to the practice of medicine, as anatomical knowledge supports the formulation of diagnoses and their communication to patients and colleagues. Traditionally, anatomy training has been performed using cadaveric dissection. According to Winkelmann (19), anatomical dissection is the "systematic exploration of a preserved human cadaver through the sequential division of tissue layers and the liberation of certain structures by removing regional fat and connective tissue, with the aim of supporting the learning of gross anatomy through visual and tactile experience".

Recent literature further supports the role of immersive technologies in healthcare education. For instance, the systematic review by Faizan S. et al. underscores the transformative potential of immersive technologies such as extended reality, VR, and AR in healthcare, ranging from enhancing surgical accuracy to democratizing medical education (20). Similarly, Kyaw et al. found evidence indicating that VR, when compared to traditional education or other forms of digital education (online or offline), improves post-intervention knowledge and skill outcomes among health professionals (21). In line with this, Baashar et al. reported that AR significantly increases performance speed, satisfaction, and confidence, although it is less effective in improving knowledge and skill (22).

However, it is also essential to acknowledge that not all findings are uniformly positive. Several important studies have presented opposing results regarding AR and VR technologies. For example, a meta-analysis by Yeung et al. assessed the effectiveness of AR in medical training (23). This analysis included 13 studies with 654 participants, comparing AR to other educational methods, such as conventional teaching and non-AR techniques, in terms of skills, knowledge, confidence, performance time, and satisfaction. Results showed that AR improved performance time ($I^2 = 99.9\%$; $P < 0.001$), confidence ($I^2 = 97.7\%$; $P=0.02$), and satisfaction ($I^2 = 99.8\%$; $P=0.006$), but had no significant effect on knowledge or skill levels compared to control conditions (I^2 — knowledge: 99.4%; skill: 97.5%). This meta-analysis suggests that although AR and VR are promising technologies for the future, they are not yet fully effective as training tools.

Moreover, Barteit et al. included 27 studies comprising 956 participants (24). The participants represented all types of healthcare professionals, particularly medical students (N=573, 59.9%) and residents (N=289, 30.2%). Most of these studies showed that AR and VR achieved results that were at least non-inferior to conventional teaching and training. Furthermore, in the study by Tene et al., which analyzed 28 studies, the majority reported positive or increased effects from the use of immersive technologies (25). However, statistical analysis did not reveal a significant association with improvements in medical education and training compared to traditional educational methods, highlighting the need for further research with larger sample sizes.

The value of anatomy courses lies in the fact that they provide a three-dimensional view of human anatomy, including tactile learning experiences. These courses enable students to expand on the knowledge gained from lectures and textbooks, providing a comprehensive perspective on anatomical structures and their interrelationships throughout the body. Nevertheless, this form of training is costly, and to date, there is no objective empirical evidence on the effectiveness of traditional laboratory courses for training anatomy.

In this regard, augmented reality technology could serve as an additional training method for anatomy education, depending on its implementation. Its strengths lie in its visualization capabilities, including 3D depiction of anatomical images. Other sensory experiences, such as tactile feedback, could also be incorporated. Augmented reality enables the real-time manipulation of these visualizations, providing immediate feedback to students and offering some of the benefits of traditional anatomy courses at a potentially lower cost (19).

Similarly, virtual reality combines a fictitious environment that is similar or identical to the real world and enhances information through visual or other sensory stimuli. Training supported by

virtual and augmented reality technology enables collaborative learning, providing a sense of immediacy and resulting in multiple benefits for the training process (26). These learning environments offer many possibilities, with the goal of fostering meaningful learning—a necessary condition for transferring knowledge to learners. Toward the end of this paper, we focus on health professionals in clinical practice.

In conclusion, the growing interest in virtual reality systems will contribute to the advancement of education in the health sciences, particularly in clinical practice. As technology advances, 3D modeling can be applied to a wide range of technological systems.

Conclusion

The growing interest in augmented reality and virtual reality technologies will contribute to the advancement of education in the health sciences, particularly in clinical practice. As technology progresses, 3D modeling can be integrated into a wide range of technological systems. These training environments offer numerous possibilities, aiming to foster meaningful learning—a necessary condition for the effective transfer of knowledge to trainees. However, further studies are needed to clarify the benefits of these technologies in the training of medical students.

What Is Already Known on This Topic:
Traditional anatomy education relies heavily on cadavers, which are expensive and raise ethical and logistical issues.

What This Study Adds:
This review demonstrates how virtual reality and augmented reality can serve as effective supplements or alternatives to cadaver-based teaching.

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Case Report and Review of Literature
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Primary Retroperitoneal Cavernous Hemangioma With Extrahepatic Tissue: A Case Report and Literature Review

Christos Vrysis[1, 2], Marios Ponirakos[1], Konstantinos Koufatzidis[1], Athanasios Gkirgkinoudis[2], Aristotelis-Marios Koulakmanidis[2], Dimitrios Giovanitis[3], Konstantinos Papadimitropoulos[1]

[1]Second Department of Surgery, 251 Hellenic Air Force General Hospital, Athens, Greece, [2]First Department of Obstetrics and Gynecology, Alexandra Hospital, National and Kapodistrian University of Athens, Greece, [3]Department of Pathological Anatomy, 251 Hellenic Air Force General Hospital, Athens, Greece

Correspondence: *vryschri@hotmail.com***;** Tel.: + 30 697 8458371

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Abstract

Objective. We present a rare case of primary retroperitoneal cavernous hemangioma, highlighting its clinical, imaging, and histological parameters. **Case Report.** A 54-year-old patient presented with chronic abdominal pain that had been experienced for the past six months. No notable findings were identified in the patient's medical history, clinical examination, or laboratory tests. Full imaging was performed using magnetic resonance imaging and abdominal computed tomography (CT). A mass was found in the retroperitoneal area, located posterior to the stomach and close to the splenic portal, the left lobe of the liver, and the left hemidiaphragm. CT-guided fine-needle aspiration confirmed the presence of a benign tumor, which was surgically excised. Histological and immunohistochemical investigations confirmed the presence of a retroperitoneal cavernous hemangioma with extrahepatic tissue. **Conclusion.** Primary retroperitoneal cavernous hemangiomas are rare retroperitoneal tumors with nonspecific clinical and radiological characteristics, making diagnosis difficult. This case demonstrates the occurrence of extrahepatic tissue involvement, a feature that has been reported only exceptionally in the literature. Surgical resection is the primary treatment for symptomatic patients with a favorable prognosis, and histological examination of the surgical specimen confirms the diagnosis.

Key Words: Cavernous Hemangioma ▪ Retroperitoneum ▪ Primary Retroperitoneal Tumors ▪ Extrahepatic ▪ Case Report.

Introduction

Cavernous hemangiomas are tumors characterized by rapidly multiplying vascular endothelial cells and the ability to induce blood vessel formation (1). This benign tumor is commonly found in the orbital, mucosal, and hepatic regions (2). Rarely, cavernous hemangiomas are located in the retroperitoneal cavity (3).

The most prevalent sites of retroperitoneal hemangiomas include the pancreas, adrenal glands, and kidneys (4). An uncommon manifestation of this condition is a primary retroperitoneal cavernous hemangioma (PRCH), which is distinguished by its clear separation from the surrounding organs. Only five case reports have been published in the literature (3-7). The present study is the sixth report on the occurrence of this condition. Given the extremely limited number of reported cases, this study provides additional clinical and histological evidence, further clarifying the presentation and management of PCRH.

The diagnostic techniques of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are crucial for the detection and accurate localization of retroperitoneal cavernous hemangiomas (6, 7). Undoubtedly, the preoperative identification of this clinical entity remains challenging. In our case, the primary diagnosis was angiomyolipoma, and the presence of PRCH was revealed by histological examination after surgical excision.

This study aimed to present an unusual case of primary retroperitoneal cavernous hemangioma, emphasizing its clinical, imaging, and histological features. This case also highlights extrahepatic tissue involvement, which is rarely reported in the literature.

Case Presentation

A 54-year-old patient visited the outpatient clinic of the 251 Hellenic Air Force General Hospital (Athens, Greece) due to chronic abdominal pain experienced over the past six months. The patient's medical history, clinical examination, and laboratory evaluations were unremarkable. There were no signs of other disorders, such as fever, chills, jaundice, nausea, vomiting, melena, or hematuria. Analysis of laboratory parameters, such as serum amylase, creatinine, alanine and aspartate aminotransferases, bilirubin, and urea nitrogen levels, yielded normal findings. The tumor markers were within the normal range. Imaging studies were performed. An abdominal CT scan revealed a well-circumscribed mass with no significant contrast enhancement during the arterial and portal venous phases (Figure 1). Based on these imaging results, there was no indication of the mass invading adjacent organs, the presence of feeding arteries, or retroperitoneal lymphadenopathy.

Considering the limited spread of the tumor and the absence of invasion or metastasis to other organs, the suspected diagnosis was a benign tumor, such as a lymphangioma cyst, gastrointestinal stromal tumor, or primary retroperitoneal benign tumor. CT-guided fine-needle aspiration was performed, and angiomyolipoma was suspected. However, the definite nature of the lesion could not be established preoperatively. Laparotomy was performed because of the size of the lesion and to alleviate the patient's discomfort.

Beyond the surgical issue, no concurrent diseases were discovered during routine preoperative examination. The patient received both general and epidural anesthesia throughout the surgical procedure. A left Kocher incision was performed. A thorough examination of the peritoneum and abdominal organs revealed no metastatic lesions. The gastrocolic ligament was then opened, the short gastric vessels were tied off, and access to the smaller sac was gained. The mass was identified

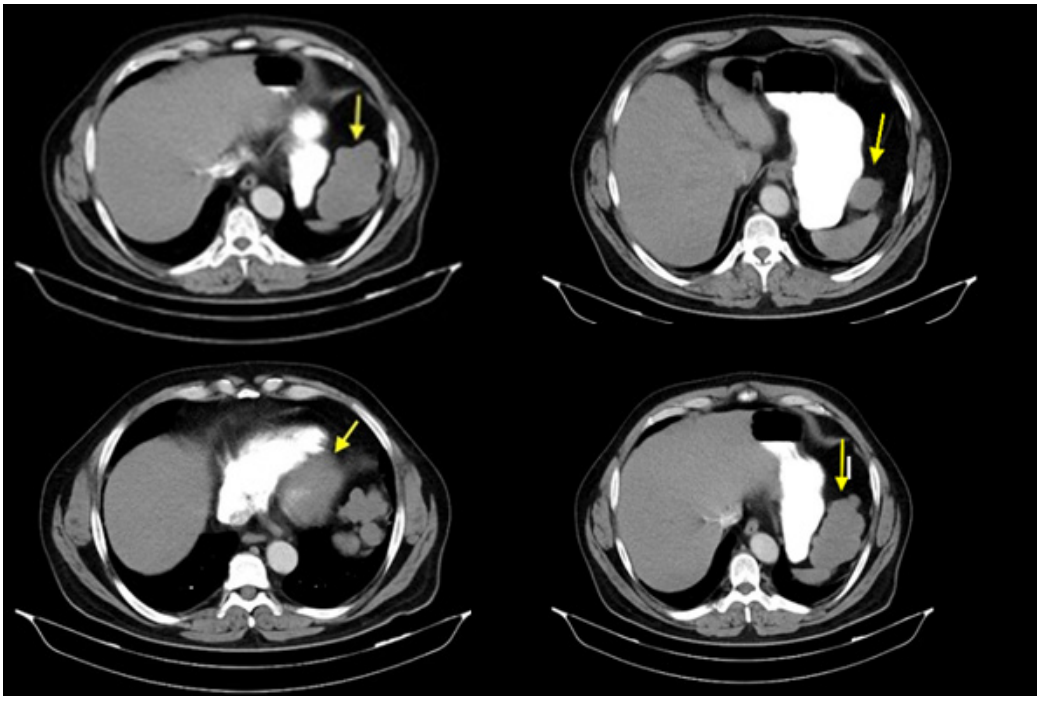

Figure 1. Computed tomography of the abdomen with oral and intravenous contrast.

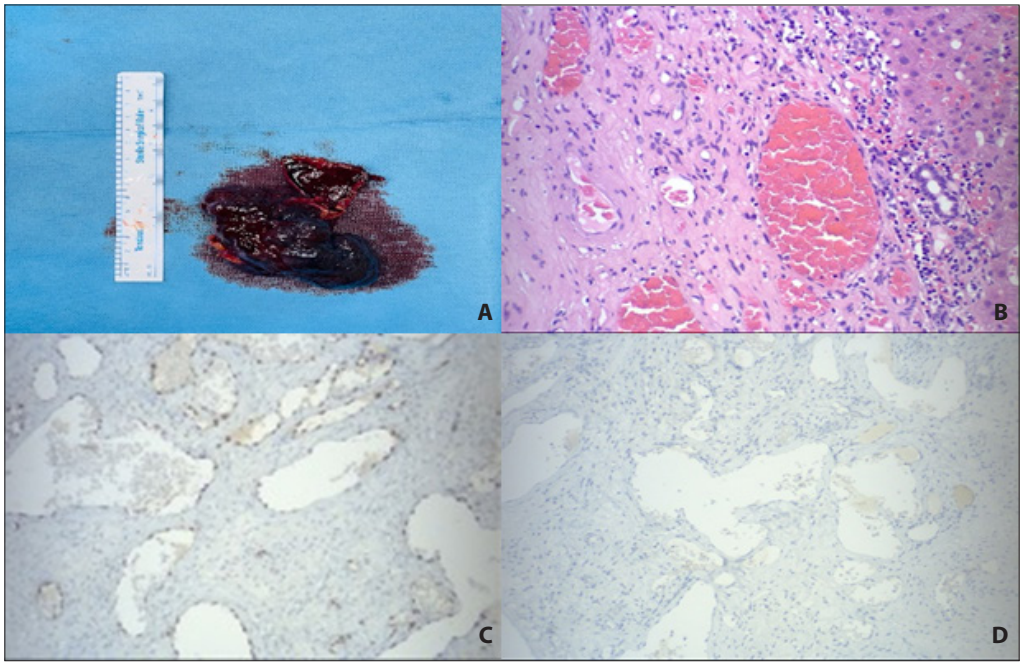

Figure 2. Macroscopic and microscopic examinations. (A) Surgical specimen; (B) Dilated and congested blood vessels with adjacent liver parenchyma (H&E, 10 ×); (C) ERG nuclear positivity (10 ×); (D) Absence of HMB-45 expression (10 ×).

in the posterior region of the stomach, adjacent to the splenic portal, and in direct contact with the left hemidiaphragm and left lobe of the liver. The tumor's blood supply was determined to arise from the retroperitoneal tissue rather than from the abdominal artery or other organs. The operation did not reveal any signs of invasion into the inferior vena cava, stomach, liver, renal capsule, pancreas, spleen, or any other nearby organs. The process involved surgically removing the lesion and establishing thorough control of bleeding. The tumor measured approximately 10 cm × 5 cm × 3 cm and had a propensity to bleed upon contact. At the macroscopic level, the tumor was characterized by large cavities filled with blood clots, surrounded by numerous small fluid-filled spaces (Figure 2A).

Histopathological examination of the resected specimen confirmed the diagnosis of a retroperitoneal cavernous hemangioma with extrahepatic tissue. Histological examination revealed numerous vascular spaces of different sizes, lined by a single layer of flattened cells in close proximity to the liver parenchyma. The tissues also showed blood vessels with varying lumen sizes and uneven wall thicknesses. Furthermore, there was evidence of coagulation in certain blood arteries, which is consistent with the features of a cavernous hemangioma. Immunohistochemical analysis revealed positive expression of CD34, CD31, SMA, and ERG, indicating that the cells were derived from endothelial tissue. As the HMB-45 and MelanA tests yielded negative results, the preoperative diagnosis of angiomyolipoma was excluded. No evidence of malignancy was detected (Figure 2B-D). The patient was discharged on postoperative day 7. The patient did not receive any adjuvant therapy. At the 10-month follow-up, the patient had not developed recurrence, their condition remained satisfactory, and they reported excellent quality of life.

Discussion

Retroperitoneal tumors are highly uncommon, comprising less than 0.2% of all tumor types (8). Liposarcoma and leiomyosarcoma are the most common malignant tumors in the

retroperitoneum, whereas teratomas, cysts, and neuromas are the most common benign tumors (9, 10). A cavernous hemangioma is a benign proliferation composed of blood vessels, commonly located on the skin or mucosal surfaces. The liver, spleen, kidneys, adrenal glands, and pancreas give rise to more visceral cavernous hemangiomas (CH). Occasionally, hemangiomas have been associated with the Kasabach-Merritt phenomenon, a congenital genetic abnormality that occurs during childhood (11).

While case reports of adult CHs in retroperitoneal organs are scarce, adult PRCH is even rarer, with only five recorded occurrences in the published literature (3-7). In line with these observations, our case adds further evidence by documenting an additional occurrence of PRCH and describing its distinct clinical and histological characteristics. The clinical data from these studies are presented in Table 1.

Early-stage cavernous hemangiomas often lack distinct clinical manifestations owing to their limited spatial distribution. Nonspecific symptoms and indications, such as stomach pain and anemia, manifest only when there is compression or invasion of the adjacent tissues involved (12). In terms of complications, there is evidence of hemorrhagic shock occurring from CH, highlighting the substantial risk associated with this tumor in the case of rupture or hemorrhage (13).

Table 1. Literature Review of Primary Retroperitoneal Cavernous Hemangiomas

*Publication	Age†/Sex	Symptoms	Preoperative imaging	Preoperative diagnosis	Surgery method	Outcome
Matsui et al., 2024 (6)	73 / M‡	Chronic abdominal pain and distension	CT¶ scan: a 35 cm mass adjacent to the left kidney, no contrast enhancement, no indication of lymphadenopathy or vascular supply from nearby organs MRI**: a heterogeneous signal intensity mass	Retroperitoneal chronic expanding hematoma	Open surgery	No recurrence of symptoms during the 6-month follow-up
AlBishi et al., 2023 (4)	43 / M‡	No	CT¶ scan: a 7.9 × 7.3 × 7.2 cm mass abutting the kidney, heterogeneous contrast enhancement implying cystic and solid components	Sarcoma	Laparoscopic surgery	NA††
Debaibi et al., 2022 (7)	35 / M‡	Chronic abdominal pain	CT¶ scan: a 4.5 × 2.7 × 2.2 cm cyst-like mass near the inferior vena cava and the third part of the duodenum, no contrast enhancement, no evidence of vascular supply from surrounding organs or lymphadenopathy	Benign tumor	Open surgery	No recurrence of symptoms during the 12-month follow-up
Fathi et al., 2018 (5)	58 / F§	Right hypochondriac discomfort for one month	US‖: a 12.5 × 14.5 × 16.5 cm mass with central cystic areas. CT¶ scan: a 16 × 14.4 × 18.2 cm well-defined heterogeneous mass at the right suprarenal area with irregular nodular enhancement	Hemangioma of the right lobe of the liver	Open surgery	NA††
He et al., 2012 (3)	38 / M‡	Epigastralgia	US‖: a cystic mass in the right upper quadrant, accompanied by right hydronephrosis and right upper ureter ectasia CT scan: an 8.7 cm cyst-like mass, hypodense, mild enhancement of the thick wall, no evidence of vascular supply from the nearby organs or of lymphadenopathy	Benign isolated retroperitoneal lesion	Open surgery	No recurrence of symptoms during the 3-month follow-up

*Authors and year of publication; †Year; ‡Male; §Female; ‖US=Ultrasound; ¶CT=Computed tomography; **MRI=Magnetic resonance imaging; ††NA=Non-available.

In addition to clinical presentation, radiological findings were also critical for diagnosis. The imaging modalities for CH are diverse, partly due to the limited presence of distinctive radiographic features, which makes it particularly susceptible to misdiagnosis. Potential causes of atypical findings include the presence of new blood vessels (neovascularity), blood clot formation (thrombosis), and bleeding (hemorrhage) (14). A CT scan precisely determined the placement of the tumor and distinguished variations in density. Typically, cavernous hemangiomas appear as low-density lesions with no significant contrast enhancement throughout the arterial or portal phase (6, 7, 15, 16). Magnetic resonance imaging may have been valuable in elucidating the internal architecture of the tumor (17, 18). On T1-weighted imaging, hemorrhage often appears as a dark signal, whereas on T2-weighted imaging, it may appear as a bright signal (13, 15).

The definitive diagnosis of cavernous hemangiomas primarily relied on histological examination. Microscopic examination revealed that the CH was composed of enlarged, aberrant blood vessels lined with a single layer of cells. These blood vessels are surrounded by fibrous tissues that are unevenly distributed, resulting in a sponge-like structure (19). Additionally, immunohistochemical staining commonly reveals a substantial positive response for CD31, CD34, and EGR, while the Ki-67 index displays a low value (20-22). A significant finding of our study is that examination of the surgical sample confirmed the presence of hepatic parenchyma despite not being attached to the liver during its surgical removal. To the best of our knowledge, this is the first documented case of its kind.

No significant complications were observed following surgery in our case or in previously reported cases of large retroperitoneal CHs (3, 6, 7, 18). Based on the consensus in the published literature, surgical intervention appears to be the optimal choice for two distinct reasons. The primary objective is to obtain histological confirmation of the mass, thereby ruling out any potential malignancy. The second purpose is to attain therapeutic goals while reducing the potential risk of complications, such as bleeding, infiltration, and compression (13). The predominant method of operation in the listed cases was open surgery (3, 5-7). Laparoscopic surgery was performed in only one case of PRCH, indicating that minimally invasive techniques may be considered depending on the characteristics and location of the tumor (4).

Conclusion

Retroperitoneal cavernous hemangioma is a rare type of tumor. Its vague clinical and imaging characteristics make diagnosis challenging. In our case, it was identified as primary, as it was not connected to any specific feeding artery and was detached from the surrounding organs. Both a multidisciplinary approach and an early acquisition of tissue biopsy are required. The primary approach for treating symptomatic patients is surgical resection, which often results in a favorable prognosis. Surgical resection remains the primary treatment for symptomatic patients and often results in a favorable prognosis. This case highlights the clinical relevance and uniqueness of identifying extrahepatic liver tissue within the tumor, a finding that has not been previously reported.

What Is Already Known on This Topic:

Retroperitoneal tumors are quite rare. The most commonly observed malignant tumors in the retroperitoneum are liposarcoma and leiomyosarcoma. On the other hand, cavernous hemangiomas are benign tumors composed of a proliferation of blood vessels. Adult primary retroperitoneal cavernous hemangiomas are even rarer, with only five reported cases in the literature. Early-stage cavernous hemangiomas often do not exhibit distinct clinical symptoms. Various imaging modalities can be used to identify them. On a CT scan, a cavernous hemangioma typically appears as a low-density lesion with no significant contrast enhancement during either the arterial or portal phase. The definitive diagnosis of cavernous hemangiomas primarily depends on histological examination. Surgical intervention is generally considered the optimal treatment option for these tumors, with open surgery being the predominant method used in reported cases.

What This Study Adds:

This study provides detailed insights into the imaging, histological diagnosis, and management of these rare tumors. Preoperative imaging, which included both CT and MRI scans, offered a precise representation of the anatomical structures surrounding the tumor. Histological and immunohistochemical markers were used to identify and analyze this condition, providing valuable information for future research in this area. A significant finding of our study is that examination of the surgical sample revealed the presence of hepatic parenchyma, despite

it not being attached to the liver during surgical removal. To the best of our knowledge, this is the first documented case of such a finding. Our primary objective was to expand the limited body of research on retroperitoneal cavernous hemangiomas by highlighting the importance of being aware of and conducting thorough assessments of similar cases.

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Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical Approval and Consent: Informed consent was obtained from the patient for the publication of this case report and accompanying images.

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Case Report
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Lodder–Merla Syndrome, a Multisystemic Disorder: Perioperative Anesthetic Management of an Infant

Elsa Astyrakaki, Eleanna Garini, Savva Georgousi, Dimitra Tsitoura, Eirini Gazelopoulou

'Children's Hospital Aghia Sophia', Department of Anesthesiology, Athens, Greece

Correspondence: *astyrakaki@hotmail.com*; Tel.: + 30 693 6818140

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Abstract

Objective. This paper aims to present the perioperative anesthetic challenges in an infant with Lodder–Merla syndrome. **Case Report.** We present a case report of a 7-month-old infant with Lodder–Merla syndrome, a pacemaker, epileptic spasms, and severe reflux, who was scheduled for open gastrostomy and gastrojejunal tube insertion. Such an intervention would constitute a second consecutive procedure under general anesthesia, shortly after pacemaker implantation. Perioperatively, emphasis was given to maintaining respiratory and cardiac stability, avoiding drugs with parasympathomimetic effects, preventing aspiration, optimizing ventilation, and controlling seizures. **Conclusion.** Since Lodder–Merla syndrome affects many organs, perioperative multidisciplinary collaboration and optimization of the affected systems are fundamental.

Key Words: Lodder-Merla ▪ Sick Sinus Disease ▪ Child.

Introduction

Lodder-Merla syndrome type 1 (OMIM® genetic database 617173) is a very rare autosomal recessive multisystem disorder caused by mutations in the GNB5 gene (15q21.2). The first cases were described in 2016 (1), and only 41 cases have been reported until 2021 (2). The GNB5-related neurodevelopmental disorder (GNB5-NDD) is characterized by a spectrum of neurodevelopmental phenotypes. A specific feature is bradycardia caused by sinoatrial node dysfunction (sick sinus disease). Most individuals also present with profound cognitive disorders, epileptic encephalopathy, visual impairment, feeding difficulties, hypotonia, hyporeflexia, and gastroesophageal reflux disease. The risk of early mortality is higher. Management should be tailored to individual needs and requires a multidisciplinary team approach, including pediatricians, pediatric cardiologists, neurologists, speech therapists, orthopedists, and physical medicine and rehabilitation specialists (2).

We present the anesthetic management of an infant with Lodder-Merla syndrome type 1 undergoing open gastrostomy for impaired feeding (severe gastroesophageal reflux disease).

Case Description

The 7-month-old male infant (5 months corrected age), weighing 6 kg, was scheduled for gastrostomy because of poor thriving due to severe gastroesophageal reflux. The infant was born prematurely at 32 + 6 weeks of gestation (1670 g) from a primigravida mother after an emergency Caesarean section prompted by a pathological non-stress test. The Apgar score was 5 at 1 minute and 9 at 5 minutes. Immediately after birth, the neonate required respiratory support, initially with nasal continuous positive airway pressure, followed by high-flow nasal cannula oxygen therapy due to episodes

of apnea and desaturation. From day one of life, the infant presented with episodes of severe sinus bradycardia that were confirmed by Holter monitoring and cardiological consultation. From the first month of life, the child also developed epileptic seizures that initially required antiepileptic treatment with oral levetiracetam. However, due to poor control, oral valproic acid and vigabatrin had to be added. Oral prednisolone was also administered to treat possible neuroinflammation of the brain. Genetic testing revealed a mutation in the GNB5 gene, and a diagnosis of Lodder–Merla syndrome was confirmed at 2 months of age. Due to the progression of bradycardia (Figure 1), a permanent epicardial pacemaker was placed on the right ventricle at three months of age (41 days corrected age).

The procedure involved a partial median sternotomy and was performed by a specialized team of cardiac surgeons and anesthesiologists. The body weight at that time was 3.7 kg. On arrival to the theatre, the infant was stable with good vitals and breathing spontaneously with a face mask (oxygen, 4 L/min). Prior to induction, intravenous (IV) atropine (0.02 mg/kg) was administered, followed by IV propofol (3 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (1.5 microg/kg). After ventilation with a mask, orotracheal intubation (with an endotracheal tube (ETT) of 4 internal diameter (ID), uncuffed, Portex®) was successful. Two 24G iv peripheral veins and a right radial arterial catheter were secured. Sevoflurane was used for maintenance, while higher doses of fentanyl (10 microg/kg) were required for analgesia. For ventilation, volume control mode was preferred with tidal volumes of 7 ml/kg, with positive end–expiratory pressure (PEEP) of 4 cmH2O and FiO_2 titrated accordingly, aiming for SpO_2 values above 98%. A total of 20 ml/kg of balanced crystalloids with 1.5% dextrose was administered. No inotropic agents were required. The procedure was uneventful and lasted for one hour and twenty-five minutes. The infant was hemodynamically stable and transferred to the cardiac intensive care unit (ICU). The following day, the infant was extubated, and the chest drain was removed. After a brief stay, the patient was transferred back to the neonatal high-dependency unit and received oxygen via a high-flow nasal cannula (25%, 5 L/min).

At 7 months of age (5 months corrected age), an open gastrostomy procedure (Open Stamm gastrostomy modification) was scheduled for nutritional support because of poor weight gain and impaired feeding despite nasogastric tube (NGT) feeding with a special formula at a rate of 80 ml per 24 hours. Preoperatively, a meeting that involved all relevant specialists was organized, with emphasis placed on the potential risks arising from airway management, aspiration, pacemaker dysfunction, difficult ventilation, cardiac instability, uncontrolled seizures, and prolonged postoperative mechanical ventilation. It was decided to insert a gastrojejunal feeding tube through the gastrostomy site to temporarily bypass the stomach and manage reflux without performing a more invasive antireflux procedure.

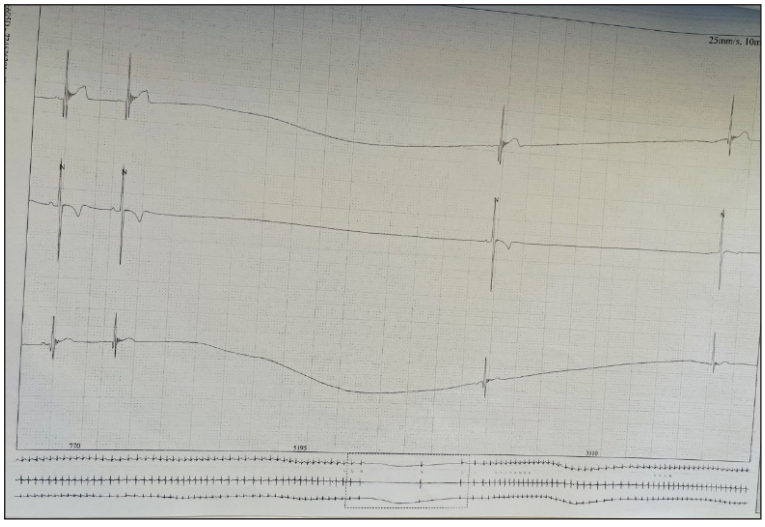

Figure 1. The last 24-hour Holter before pacemaker implantation: Detection of three sinus pauses lasting more than 3 seconds.

Medical treatment included vitamin D, omeprazole, levetiracetam, valproic acid, vigabatrin, and carnitine. Examination of the pacemaker showed good function, in VVI mode with an HR of 100 bpm. IV

hydrocortisone was also administered as a tapering scheme for previous prednisolone therapy.

Prior to surgery, the infant was in the neonatal high-dependency unit, spontaneously breathing on a simple O2 face mask (4 L/min), with a SpO2 of 96 – 97% and an HR of 100 – 120 bpm. Laboratory test results were within the normal range for age. NGT feeding was stopped 6 hours prior to surgery, and IV maintenance fluid administration was initiated. Antiepileptics were continued via the intravenous route (except Sabril, which is only available in oral form; therefore, it was stopped perioperatively).

After preoxygenation, rapid sequence induction with IV propofol (3 mg/kg), fentanyl (1.5 microg/kg), and rocuronium (1 mg/kg) was followed by orotracheal intubation (with an ETT of 4 ID, uncuffed, Portex®). Two IV peripheral lines were secured. In addition to standard monitoring, we added Pulse CO-Oximetry to noninvasively monitor Hb continuously (Masimo®) and a Train of Four (TOF) monitor (NMT Pediatric Mechanosensor, General Electric®). Sevoflurane and remifentanil infusion (0.1μg/kg/min) were used for maintenance. For ventilation, pressure control mode was preferred, aiming at tidal volumes of 6 – 8 ml/kg, with PEEP of 4 cmH2O and FiO2 titrated accordingly, aiming for SpO2 values above 98%. The surgical wound was infiltrated with ropivacaine 0.1% (1 mg/kg), and IV dexamethasone (0.15 mg/kg) and IV paracetamol (10 mg/kg) were also administered. Bipolar cauterization was preferred for surgical electrocautery. The procedure was uneventful and lasted for 40 minutes. After the completion of surgery, the TOF ratio was 0.7, and sugammadex (2mg/kg) was administered. Extubation was successful when TOF was >0.9. After completing the required time in a post-anesthesia care unit, the infant was transferred to a neonatal ICU with O2 by face mask (4L/min). Enteral feeding was initiated on the fourth postoperative day. Overall, the postoperative period was stable, with gradual weaning from oxygen. After forty days, the child was discharged home. Six months after pacemaker implantation, a routine follow-up confirmed proper function. However, readmissions due to poorly controlled seizures were noted.

Discussion

GNB5-NDD is a very rare multisystem disorder characterized by a spectrum of neurodevelopmental phenotypes (intellectual disability, language disorder, attention–deficit/hyperactivity disorder, and autism spectrum disorder) and bradycardia. Other features include epileptic encephalopathy with focal seizures or epileptic spasms, visual impairment (central or retinal) with nystagmus, difficulty in feeding, hypotonia, hyporeflexia, and gastroesophageal reflux disease (1, 2). In our case, the infant had symptomatic sinus bradycardia, poorly controlled epileptic seizures, and severe gastroesophageal reflux. Bradycardia due to sick sinus syndrome is the most common arrhythmia in Lodder-Merla syndrome, and it may be present with apnea and cyanosis or may be asymptomatic. In animal models, the GNB5 protein is crucial for the parasympathetic control of heart rate (3).

Parasympathomimetics should therefore be used with extreme caution because of the potential to cause asystole, at least until a pacemaker has been inserted, and access to emergent pacing is desirable. Drugs that can potentiate bradycardia, particularly beta-blockers, high-dose synthetic opioids, and alpha2 agonists, should be avoided (2). In our case, we preferred to use rocuronium to be able to administer sugammadex for the reversal of neuromuscular blockade instead of neostigmine (even if the latter is always administered in combination with atropine); therefore, TOF monitoring was mandatory.

Until 2021, only six children had been reported to have undergone pacemaker implantation, and only two cases required long-term gastrostomy (2, 4). An anesthetic plan was not documented in any of the reported cases. This is the first documented perioperative management of an infant who underwent two consequent operations (pacemaker insertion and gastrostomy). Regarding surgical electrocautery, due to the proximity of the surgical area and the heart, bipolar cauterization

was favored over monopolar to reduce the risk of interference with the pacemaker's function. Cardiologists had suggested that an isoprenaline infusion should be readily available at a dose of 0.1 – 0.5 microgram/kg/min, in case of pacemaker failure. In the case of uncontrolled seizures, IV midazolam was recommended.

Conclusion

Lodder–Merla syndrome presents significant perioperative challenges due to various associated risks. The involvement of multiple systems, along with the limited available literature, requires a comprehensive plan that includes the participation of all relevant specialties. Therefore, it is crucial to optimize all affected systems. Ensuring cardiorespiratory stability is essential, as is preventing aspiration, securing adequate ventilation, implementing multimodal analgesia, avoiding pharmacologic agents presenting parasympathomimetic effects, and controlling seizures.

What Is Already Known on This Topic:
Lodder-Merla syndrome is a very rare autosomal recessive multisystem disorder that was first described in 2016. Until 2021, only 41 cases have been reported. To the best of our knowledge, there is no documentation regarding the perioperative anesthetic management of such patients.

What This Study Adds:
This is the first case of an infant who underwent two surgeries under general anesthesia within a short time interval, with documented perioperative anesthetic management. The scarcity of data and multisystem presentation necessitate an organized perioperative anesthetic plan in which the collaboration of relevant specialties and optimization of the affected systems are essential.

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Consent to Participate: Written consent was obtained from the parents for the publication of their child's case.

Authors' Contributions: Conception and design: EA, EG, SG, DT and EG; Acquisition, analysis and interpretation of data: EA and EG; Drafting the article: EA and EG; Revising it critically for important intellectual content: EA, EG, SG, DT and EG; Approved final version of the manuscript: EA, EG, SG, DT and EG.

Conflict of Interest: The authors declare no conflict of interest.

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