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Lipedema and Postoperative Care

A Cross-Sectional Comparative Study

Highlights

Endoscopic Treatment of Children

Ischemic Heart Disease after Coronary

Discovering Thoughts, Inventing Future

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The Role of Hemolysis in the Development of Arrhythmias in Patients with Ischemic Heart Disease after Coronary Artery Bypass Grafting under Artificial Circulation

By Maksimovich Yelizaveta N. & Maksimovich Nataliya Ye

Grodno State Medical University

Abstract- *Introduction:* The operation of coronary shunting in patients with coronary heart disease leads to the development of various complications in the postoperative period, the most frequent are heart rhythm disturbances.

Purpose: To establish the connection of intraoperative hemolysis (IOH) with the development of cardiac rhythm disturbances in patients with coronary artery disease after coronary shunting in conditions of cardiopulmonary bypass (CB).

Keywords: *coronary artery bypass grafting, hemolysis, arrhythmias.*

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The Role of Hemolysis in the Development of Arrhythmias in Patients with Ischemic Heart Disease after Coronary Artery Bypass Grafting under Artificial Circulation

Maksimovich Yelizaveta N. [α] & Maksimovich Nataliya Ye [σ]

Abstract- Introduction: The operation of coronary shunting in patients with coronary heart disease leads to the development of various complications in the postoperative period, the most frequent are heart rhythm disturbances.

Purpose: To establish the connection of intraoperative hemolysis (IOH) with the development of cardiac rhythm disturbances in patients with coronary artery disease after coronary shunting in conditions of cardiopulmonary bypass (CB).

Material and Research Methods: The assessment of the degree of IOH was made by the level of free hemoglobin [Hb] in the blood plasma at the beginning of the operation, immediately after the patient was connected to the CB device and 15 minutes before removal from the CB, using the Hemo Cue Plasma / Low Hb analyzer. According to the degree of IOH, patients (n = 123) are divided into 3 groups (gr.) in accordance with free [Hb]: gr.1 – ≤0,1 g/l; gr.2 > 0.1 g/l and <0,5 g/ l; gr.3 – ≥0,5g/l. Were used the following instrumental methods of investigation: electrocardiography, 24-hour ECG monitoring. Was analyzed the frequency of heart rhythm disturbances in patients after coronary shunting with various levels of IOH in the early (up to 1 month) periods.

Results: Arrhythmias were observed in 2.3% of patients of the 1st group, in 11.9% - the 2nd group, in 52.6% - the 3rd group. Associations were noted between [Hb]. In plasma at the end of cardiopulmonary bypass and the frequency of arrhythmias (rs=0,70, p<0.001). The share of life-threatening and hemodynamically significant arrhythmias in the study period in the group with a high degree of IOH accounted for about half of all arrhythmias that occur, which is significantly more than in the group without IOH and with low IOH, p <0.001.

Conclusion: The operation of coronary artery bypass surgery in conditions of artificial blood circulation leads to the development of arrhythmias in the postoperative period in 22% of patients with ischemic heart disease. A significant proportion of these are arrhythmias that pose a threat to the patient's life and arrhythmias, causing hemodynamic disturbances and hypoperfusion of vital organs.

The largest number of patients with cardiac rhythm disturbances after coronary artery bypass grafting was observed in the group with the level of free hemoglobin in the blood plasma of 0.5 g / l or more (p <0.001), which indicates the relationship between the occurrence of arrhythmias and the degree of intraoperative hemolysis. The high risk of arrhythmias in patients with coronary heart disease after coronary artery bypass surgery is determined when the content of free hemoglobin is more than 0.85 g / l.

One of the ways to assess the risk of heart rhythm disturbances should be to determine the level of free hemoglobin in the blood plasma of patients in the intraoperative period of coronary artery bypass grafting, which is necessary for the timely prevention and correction of possible hemodynamic disorders.

Keywords: coronary artery bypass grafting, hemolysis, arrhythmias.

I. Introduction

Coronary artery bypass surgery in patients with coronary heart disease (CHD) is frequently associated with postoperative complications, with arrhythmias being a significant concern [1, 2]. Potentially life-threatening arrhythmias, such as ventricular fibrillation and tachycardia, and third-degree atrioventricular block, as well as hemodynamically significant arrhythmias like atrial fibrillation (AF), severe bradycardia, and severe sinus tachycardia, are common. AF, a highly prevalent and dangerous postoperative arrhythmia, is frequently observed (25-65% of cases) [3] and is associated with adverse outcomes, including increased risk of heart failure progression, thromboembolism, prolonged hospitalization, and mortality [4]. Patients experiencing AF after CABG have a higher risk of mortality related to cerebrovascular accidents and myocardial infarction [4]. The pathogenesis of CABG-related arrhythmias is complex and not fully understood. Perioperative and early postoperative arrhythmias likely represent a reaction of the conduction system to the altered blood flow during the surgery, including the transition from cold cardioplegia to reperfusion [5-11]. Reoxygenation following the restoration of coronary blood flow can induce oxidative stress, metabolic disturbances, and electrical heterogeneity in the myocardium [5]. Further, the use of cardiopulmonary bypass (CPB) during CABG, necessary for maintaining blood circulation during the operation, is associated with potential red blood cell

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damage. This hemolysis may contribute to the development of cardiovascular complications in the postoperative period [12]. However, the specific relationship between intraoperative hemolysis (IOH) and the development of arrhythmias following CABG remains unclear in the existing literature.

II. Purpose of the Study

To establish the connection of intraoperative hemolysis (IOH) with the development of cardiac rhythm disturbances in patients with coronary artery disease after coronary shunting in conditions of cardiopulmonary bypass (CB).

III. Materials and Methods

It was performed a prospective study of 123 patients with coronary heart disease undergoing CABG. The study was consistent with the Helsinki Declaration of the World Medical Association «Ethical Principles for Conducting Scientific Medical Research with Human Participation» and was approved by the ethics committees of the Grodno State Medical University and the Grodno Regional Clinical Cardiology Center healthcare institution.

All patients underwent CB surgery in a planned manner under IR conditions. According to the level of free hemoglobin [Hb] in blood plasma, which is a marker of the degree of IOH, patients are divided into three groups: group 1 – without IOH (Hb ≤ 0.1 g/l), n=43, group 2 - with low IOH(lIOH) - with [Hb]>0.1g/l and <0.5 g/l, n=42, group 3 – with a high IOH (hIOH) corresponded to [Hb]≥0.5 g/l, n=38. The degree of IOH was assessed by the level of free hemoglobin [Hb] in the blood plasma at the beginning of the operation, immediately after connecting the patient to the artificial device and 15 minutes before removal from the artificial device (Fig. 1), using a Hemo Cue Plasma/Low Hb analyzer, Sweden [12].

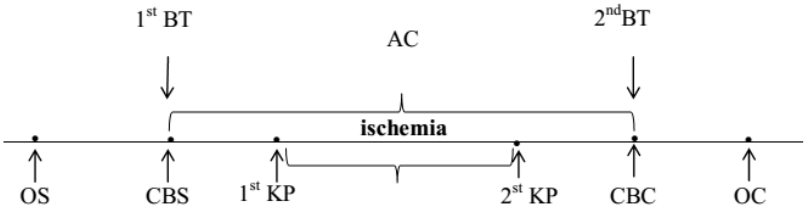

Figure 1: Diagram of the Coronary Bypass Surgery Operation

CB – Cardiopulmonary Bypass
CB – Cardiopulmonary Bypass Start
CB – Cardiopulmonary Bypass Completion
KP – Cardioplegia
OS – Operation Start
OC – Operation Completion
1st BT – First Blood Test
2nd BT – Second Blood Test

Patients of all groups are comparable by age and gender (Table 1).

Table 1: Clinical Characteristics of the Subjects

Indicator	Group 1 n=43	Group 2 n=42	Group 3 n=38
Age, years	60 (56; 63)	64 (58; 66)	66 (60; 68)
Gender (male), %	36 (87,8%)	32 (78,0%)	31 (78,0%)
BWI (kg / m^2)	27,8(24,7; 29,2)	27,7 (24,8; 29,2)	29,1(25,9; 32,2)
Total protein (g / l)	69 (62; 71)	69(58; 68)	66(57; 67)
Glucose, mmol /L	5,0(4,5; 5,6)	5,2(4,4; 6,1)	5,3(4,5; 6,2)
Cholesterol, mmol /L	4,1(3,3; 5,0)	4,6(3,2; 5,7)	5,0(4,6; 5,6)
Urea, mmol /L	5,3(4,8; 5,6)	6,0(5,5; 7,6)	6,4(5,5; 7,2)
Creatinine, mmol /l	99(89; 104)	105(98; 110)	106(99; 112)
CRP (mg / ml)	1,2(0,8; 1,4)	1,1(0,8; 1,3)	1,0(0,6; 1,2)

Notes: Data are presented as Me [Q_{25}; Q_{75}], where Me is the median, Q_{25} is the value of the lower quartile; Q_{75} is the value of the upper quartile.

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All patients underwent surgical intervention using a standard anesthetic protocol under normothermic artificial sirculation conditions with a hemodilution level of hematocrit of 25-30%.

The groups did not differ in the duration of artificial sirculation and the time of myocardial ischemia (p> 0.05), Table 2.

Table 2: Duration of Cardiopulmonary Bypass (CB) and Myocardial Ischemia in Patients with Varying Degrees of IOH during Coronary Artery Bypass Grafting

Indicator	Group 1 n=43	Group 2 n=42	Group 3 n=38
Ischemia-reperfusiontime (min)	69(65; 89)	74 (68; 78)	80 (75; 94)
Ischemiatime (min)	46(39; 64)	58(56; 62)	59(51; 68)

Note: The data are presented in the form Me (Q_{25}; Q_{75}), where Me is the median of the indicator; Q_{25} - value of the lower quartile; Q_{75} is the value of the upper quartile.

Most patients (85%) underwent mammary-coronary bypass surgery in combination with aortic-coronary bypass surgery. Mammary-coronary bypass surgery was performed in 4% of patients (p <0.05), aortic-coronary bypass surgery - in 11% of patients (p <0.05). Groups were comparable in frequency (p> 0.05).

More often, lesions of three or more coronary arteries, CA (63.1%) and significantly less often than one CA (7.1%) were revealed, Table 3.

Table 3: Characterization of Shunts in Patients with Coronary Heart Disease in Groups with Different Levels of IOH

Number of Shunts	Group1 n=43	Group 2 n=42	Group 3 n=38	p_{1-2}	p_{1-3}	p_{2-3}
1	9,9	7,5	10,8	0,412	0,510	0,314
2	31,0	26,8	39,2	0,510	0,610	0,094
3 andmore	59,1	65,7	50,0	0,462	0,130	0,318
Left anterior interventricular coronary artery	87,8	100	100	0,21	0,31	0,31
Left circumflex artery	4,9	7,3	19,5	0,644	0,420	0,105
Posterior interventricular branch of left circumflex artery	14,6	39,0	61,0	0,210	0,310	0,406
Left marginal artery	56,1	65,9	80,5	0,172	0,22	0,324
Right coronary artery	24,4	58,5	61,0	0,231	0,341	0,821
Right interventricular branch artery	17,07	34,15	26,8	0,706	0,285	0,471

Note: Accordingly, with myocardial revascularization, three or more coronary arteries (CA) were shunted more often - 56.9% of patients. The most common lesions were observed in the anterior interventricular branch of left coronary artery(p<0.05), posterior interventricular branch of the of left circumflex artery (p<0.05) and the left marginal artery (p <0.05). Table 4 presents the nosological characteristics of patients.

Table 4: Nosological Characteristics of Patients with Coronary Artery Disease before Coronary Bypass Surgery with Varying Degrees of Intraoperative Hemolysis (IOH)

Indicator	Gr 1 n=43	Gr 2 n=42	Gr 3 n=38
Ischemic heart disease duration	8,5 (4,2; 11,4)	8,9 (4,6; 10,8)	9,5 (6,2; 12,1)
Durationofhypertension	10 (6; 11)	8 (5; 10)	11,5 (9; 15)
Functional class II	9 (20,1%)	11 (26,2%)	6 (15,8%)
Functional class III	34 (79,9%)	31(73,8%)	32 (84,2%)
Postinfarctioncardiosclerosis	37 (86,1%)	36 (85,7%)	33 (86,8%)
The number of myocardial infarction (2 MI) in the history	16(37,2%)	18(42,8%)	13(34,2%)
$NYHA_{II}$	36(83,7%)	31(73,8%)	33(86,8%)
$NYHA_{III}$	7(16,3%)	11(26,2%)	5(13,2%)
Ischemic cardiomyopathy	2 (0,86%)	3 (1,26%)	2 (0,76%)
Historyofarrhythmias	7(16,3%)	7(16,6%)	6(15,4%)
Paroxysmofatrial fibrillation	0 (9%)	1(0,42)	1 (0,38%)
supraventricular extrasystole	4(1,72%)	2 (0,84)	2(0,76%)
ventricular extrasystole	1(0,43%)	1 (0,42%)	1(0,38%)
right His bundle branch block	1(0,43%)	1 (0,42%)	1(0,38%)
left His bundle branch block	1(0,43%)	2 (0,42%)	2(0,76%)
bloodhypertension	36 (87,8%)	38(90,2%)	38(92,7%)
chronicbronchitiswithoutexacerbation	7(16,3%)	9(21,4%)	12(31,6%)

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gastropathy	18(41,9%)	17(40,5%)	20(52,6%)
urolithiasis	6(13,9%)	9(21,4%)	7(18,4%)
osteoarthritis	0(0%)	3(7,1%)	1(2,6%)
excessBWIandobesity	36(83,7%)	31(73,8%)	33(86,8%)
excessBWI	22(51,2%)	18(42,9%)	18(47,4%)
obesity	14(32,6%)	13(31%)	15(39,5%)

Note: Quantitative data are presented in the form Me [LQ; UQ], where Me is the median, LQ is the value of the lower quartile; UQ is the value of the upper quartile, and categorical – in the form of absolute and relative frequencies of signs; for all presented indicators, differences between the studied groups were absent (p> 0.05).

Most patients had one previously suffered myocardial infarction, MI. Patient groups were comparable in the number of MI (p> 0.05), the presence of ischemic cardiomyopathy (p> 0.05) and a history of cardiac arrhythmias (A), p> 0.05. Table 4 presents the frequency and structure of cardiac arrhythmias in patients with varying degrees of intraoperative hemolysis before coronary artery bypass surgery. As you can see, before surgery, cardiac arrhythmias were found in 22 people (17.89%). Among cardiac arrhythmias, AF paroxysms, supraventricular and ventricular extrasystoles, as well as blockade of the right and left legs of the bundle of His were found. At the same time, AF paroxysms were observed in 2 (1.63%) patients, extrasystoles were found in 11 (8.94%), including supraventricular extrasystoles, and in 3 (2,44%) – ventricular extrasystoles were noted. Dysfunction of the conduction function was noted in 8 people (6.5%), including blockade of the left leg of the bundle of His was noted in 5 people (4.07%), blockade of the right leg of the bundle of His - in 3 people (2.44%). The groups were comparable in the frequency and nature of cardiac arrhythmias in the anamnesis (p>0.05).

Patients before CB (1-5 days) and after surgery (within 1-5 days) underwent daily ECG monitoring, as well as standard electrocardiography (ECG). In order to clarify the role of hemolysis in the development of postoperative arrhythmias in the studied groups of patients with different levels of IOH, we analyzed the incidence of cardiac arrhythmias in the perioperative (during the operation and during the first day after it) and in the early period (up to 1 month) and their structure.

The examined patients received standard therapy consisting of antiplatelet agents (79.7%), statins (76.4%), beta-blockers (84.6%), angiotensin-converting enzyme inhibitors (76.4%), antianginal drugs (79.7%), table 5.

The drug treatment among patients of the studied groups did not differ in the administration of clopidogrel (χ^2 = 5.35; p = 0.069), β-blockers (χ^2 = 3.18; p = 0.204), but it differed in the reception of statins (χ^2 = 12.2; p = 0.006), inhibitors of the angiotensin-converting enzyme, ACE inhibitors (χ^2 = 7.13; p = 0.028) and antianginal drugs (χ^2 = 13.7; p<0.001). In particular, fewer patients in the third group took statins (57.9%, p <0.05), inhibitors (63.2%, p<0.001) and antianginal drugs (60.5%, p<0.001). Patients with a history of cardiac arrhythmias (paroxysmal AF) were treated with antiarrhythmic drugs 5-7 days before surgery.

Table 5: Characterization of Drug Therapy for Examined Patients with Coronary Artery Disease before Coronary Artery Bypass Surgery with Varying Degrees of IOH

Index (%)	Gr 1 n=43	Gr 2 n=42	Gr 3 n=38	Gr 1-3 n=123	χ^2	p
betablockers	86,0	90,5	76,3	84,6	3,18	0,204
ACE inhibitors	88,4	76,2	63,2°	76,4	7,13	0,028
statins	90,7	78,6	57,9°•	76,4	12,2	0,006
antianginal	93,0	83,3	60,5°•	79,7	13,7	0,0001
antiplateletagents	88,4	81,0	68,4	79,7	5,35	0,069

Note: ° - p <0.05, °° - p <0.001– statistical differences with the group without IOH;
• - p <0.05, •• - p <0.001 - statistical differences with group 2 (with IIOH)

To prevent arrhythmias during the operation, lidocaine was infused in a cardioplegic solution (1-1.5 mg/kg/min). After the operation, antiarrhythmic drugs were administered to arrest AF paroxysm (AF - 5 mg /kg intravenously dropwise for 60 min). Patients after CB took β-blockers (atenolol 25-50 mg/day, metoprolol at a dose of 25-50 mg/day, bisoprolol at a dose of 2.5-5 mg /day) depending on the level of blood pressure. In patients with atrial flutter and ventricular tachycardia in the perioperative period, temporary atrial pacemaker was performed, which was maintained for 72 hours with a frequency of 10 beats/min more than their own heart rate.

Statistical data processing was carried out using the program Statistica 10.0 for Windows (StatSoft, Inc., USA). Given the abnormality of the distribution of attributes, nonparametric methods of descriptive statistics were used for processing: quantitative data are

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presented in the form Me [LQ; UQ], where Me is the median, LQ is the value of the lower quartile; UQ is the value of the upper quartile; categorical data are presented in the form of absolute and relative frequencies. When comparing the medians of quantitative variables of several independent groups, the Kruskell-Wallis test was used, to compare categorical data, the exact Fisher test, the $\chi 2$ criterion, with the Yeats correction at low frequencies were used. The strength of the relationship between the indicators was estimated using a correlation analysis based on the association coefficient (Kendall criterion) by its value ($rs \leq 0.25$ - weak; $0.25 < rs < 0.75$ - moderate and ≥ 0.75 - strong). In order to check the dependence of the incidence of arrhythmias on the degree of IOG, determined by the level of free hemoglobin, a logistic regression analysis and ROC analysis were performed in the statistical program SPSS Statistics 21.0 (SPSS, USA). Differences were considered significant at $p < 0.05$.

IV. Results

Of the 123 examined with CB, 29 (23.6%; $p<0.001$) patients had cardiovascular complications. Moreover, complications in the perioperative period were noted in 17 people (13.8%, $p> 0.05$), in the early period - in 13 people (10.6%, $p> 0.05$). More often, in the operated patients, arrhythmias were revealed in 27 patients (21.95%, $p <0.001$), less often – heart failure progression - in 12 patients (9.8%, $p<0.001$), 5-person CB-associated myocardial infarction developed (4.1%; $p = 0.003$), and stroke in 2 patients (1.6%, $p = 0.323$).

The most common complications of CB during myocardial revascularization in patients with coronary artery disease were various types of arrhythmias, which were observed both in the perioperative period and during the month of observation - an early period (Table 6).

Table 6: The Frequency of Arrhythmias in Patients with Coronary Heart Disease after CB Surgery with Varying Degrees of Intraoperative Hemolysis (IOH)

Types of Complications	Group 1 n=43		Group 2 n=42		Group 3 n=38		All n=123		χ^2	p
	n	%	n	%	n	%	n	%		
Arrhythmias	2	4,7	5	11,9	20	52,6	27	22,0	21,95	0,000

d

After surgery, arrhythmias developed in 27 (21.95%) patients. At the same time, 5 (4.9%) patients had life-threatening arrhythmias (ventricular fibrillation, ventricular tachycardia), 7 (5.7%) patients had hemodynamically significant arrhythmias – atrial fibrillation and flutter, supraventricular tachycardia. Atrial fibrillation was the most common type of postoperative arrhythmias (5.7%, $p<0.001$), which is consistent with the literature. In 11 (8.9%) patients after CB, other types of arrhythmias (supraventricular extra systoles and ventricular extra systoles of I-II classes (according to the classification of Myerburg RJ, 1984), as well as AV blockade of the 1st or 2nd degree) were observed, accounting for about half of the occurring during and after surgery arrhythmias.

Most often, arrhythmias were observed in patients with a high degree of IOH (Table 7).

In the group with high IOH, the frequency of arrhythmias was 52.6%, which is higher than in the group with low IOH - 11.9%, $p <0.001$ and in the group without IOH - 2.32%, $p<0.001$ (table 8).

Table 7: Frequency and Structure of Arrhythmias in Patients with Coronary Artery Disease after CB with Different Degree in Intraoperative Hemolysis (IOH)

Types of Arrhythmias	n	Group 1 n=43 without IOH	n	Group 2 n=42	n	Group 3 n=38	χ^2	p
Total Arrhythmias	2	4,65	5	11,9°°°•••	20	52,6°°°•••	28,75	0,0000
Ventricular fibrillation	-	-	1	2,38	2	5,26	4,547	0,1020
Ventricular tachycardia	-	-	-	-	3	7,89	6,878	0,032
Atrial fibrillation	2	2,32	3	7,18	13	34,20°°°•••	14,132	0,132660
Atrial flutter	-	-	1	2,38	1	2,63	1,100	0,5760
Supraventriculartachy cardia	-	-	-	-	1	2,63	2,255	0,3238

Note: Data are presented in the form of absolute and relative frequencies of signs;

I IOH – low IOH; hIOH – high IOH;

 # – p<0,05, ## – p<0,01, ###– p<0,001 – statistical differences with control group;

° – p<0,05, °°° – p<0,001– statistical differences with group without IOH;

• – p<0,05, ••• – p<0,001 – statistical differences with control group 2 (with low IOH);

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As can be seen from the table, in patients of the second (IIOH) and third (hIOH) groups, arrhythmias were more common than in the first group (without IOH), p<0.001, and in patients of the 3rd group more often than in the second group, p <0.001. Moreover, a significant part of arrhythmias (10.5%) in patients of the third group belonged to life-threatening arrhythmias and hemodynamically significant arrhythmias (13.2%). In 21.1% of patients with hIOH, other types of arrhythmias were noted (p <0.05).

On the 1st day after CB (perioperative period), arrhythmias were noted in 14 patients, 11.4%, p <0.00. Most often (26.31%) of perioperative period arrhythmias were noted in the third group with hIOH, p <0.001). Life-threatening and hemodynamically significant arrhythmias in this period in the group with a high degree of IOH accounted for about half of all arrhythmias, which is significantly more than in the 1st and 2nd groups, p <0.001.

In the early period, arrhythmias developed in 10.6% of examined patients with CB. In the group with hIOH, arrhythmias were observed in 10 (26.3%) patients, in the group with IIOH – in 3 people (7.14%, p<0.001), in the group without IOH – arrhythmias were not observed (p<0.001).

Correlation analysis using the non-parametric Kendall criterion (Rs) revealed the presence of associations between the indicator characterizing the degree of IOH – [Hb] in blood plasma and the frequency of arrhythmias in the postoperative period (Rs = 0.70, p <0.001), including in perioperative period (Rs = 0.46; p <0.001) and in the early period (Rs = 0.33; p <0.001) afterCB.

A correlation analysis revealed a moderate associative relationship between postoperative arrhythmias and a history of arrhythmias (Rs=0.4167, p=0.000003). There were also weak associations of the frequency of arrhythmias with the duration of the operation (Rs = 0.21, p = 0.018) and the time of clamping of the aorta (cardioplegia, Rs = 0.19, p = 0.026).

Based on logistic regression and ROC analysis, data were obtained that testify to the significance of the [Hb] indicator in assessing the likelihood of arrhythmias (Fig. 2).

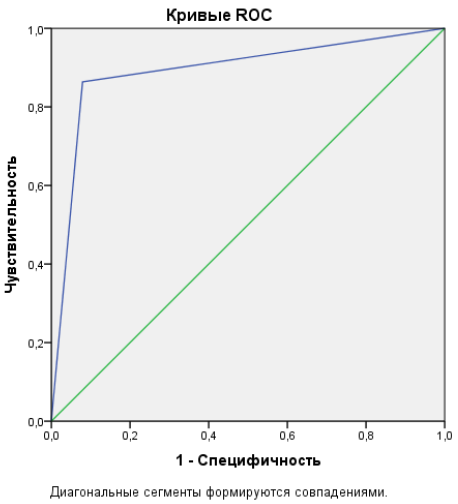

Fig. 2: ROC Curve Characterizing the Sensitivity and Specificity of the Method for Assessing the Likelihood of Developing Postoperative Arrhythmias by the Concentration of Free Hemoglobin in Blood Plasma

A high risk of developing arrhythmias in patients with coronary heart disease after CB was determined with a value of [Hb]>0.85 g/l (sensitivity - 86.4%, specificity - 92.7%, PPV (predictive value of a positive result) = 96.9 %, NPV (predictive value of a negative result) = 70.4%, area under the ROC-curve (AUC) = 0.892 (0.803-0.981), 95% confidence interval.

Discussion. As noted earlier, before the operation, cardiac arrhythmias occurred in 22 people (17.89%). Among arrhythmias, AF paroxysms, supraventricular and ventricular extra systoles, as well as blockade of the right and left legs of the bundle of His were found. AF paroxysms were observed in 2 people (in 1 – in groups with IIOH and in 1 – in group with hIOH. The groups were comparable in history and frequency of arrhythmias in history (p>0.05). However, the incidence of arrhythmias in postoperative the period was highest in the third group with hIOH, and in the second group with IIOH it was greater than in the group without IOH According to the literature, the occurrence of arrhythmias associated with CB is caused by the restoration of blood flow in the ischemic zone, as a result of which the resumption of oxygenation initiates the development of oxidative stress. Action a reactive forms of oxygen and nitrogen leads to structural and metabolic disturbances, manifested by damage to cell membranes, electrolyte imbalance, forming a state of electrical myocardial heterogeneity, impaired excitability,

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pulse generation and conduction in the heart. Post-traumatic remodeling of heart chambers can contribute to the development of arrhythmias [6,7,9].

It was shown that not only the frequency of arrhythmias in groups after CB has changed, but also the structure. Transformation of less life-threatening arrhythmias (extrasystole, blockade of the bundle of His) into arrhythmias was noted, which had more serious consequences for hemodynamics and posed a greater threat to the lives of patients (atrioventricular block of the 1st degree, atrial fibrillation and flutter, paroxysmal ventricular and supraventricular ventricles).

Some authors have identified the relationship between arrhythmias and the features of surgical treatment (inadequate myocardial protection during surgery, due to the composition of the cardioplegic solution used, the direction of its administration, temperature, and the duration of cardioplegia). A positive correlation was revealed between the occurrence of arrhythmias and the duration of IR, the intensity of inotropic support, blood transfusion, and the level of leukocytosis after surgery. Other authors have not found such a dependence on the duration of artificial circulation.

CB has been shown to be most conducive to the development of arrhythmias in patients who had morphological changes in the heart (post-infarction cardiosclerosis) and a history of arrhythmias.

Studies on the study of arrhythmias after CB using correlation, as well as logistic and ROC analysis revealed the dependence of the frequency of arrhythmias on the level of free hemoglobin as an indicator of the degree of intraoperative hemolysis. The destruction of red blood cells due to their mechanical damage in the artificial circuits of the exerts a pathogenic effect on the state of the rhythmogenic function of the cardiac conduction system and myocardial excitability, predisposing to the development of arrhythmias. The largest number of arrhythmias in the group with a high level of free hemoglobin, as well as the presence of correlation between the frequency of arrhythmias and [Hb] In the blood plasma at the end of the operation, as well as the results of the logistic and ROC analysis, indicate the important role of intraoperative hemolysis in their occurrence in perioperative and early periods. The pathogenetic role of free hemoglobin in the development of rhythm disturbances in CB, it is advisable to develop a set of perioperative preventive measures aimed at chelation of free iron, which reduce the activity of oxidative processes. Elimination of patient-dependent risk factors for increased hemolysis (smoking, alcohol consumption, normalization of blood pressure, body weight and cholesterol) is also important for the prevention of cardiac arrhythmias, as one of the most common complications of coronary artery bypass surgery.

V. Conclusions

1. Postoperative arrhythmias occur in approximately 22% of patients undergoing CABG with cardiopulmonary bypass. A substantial portion of these arrhythmias are life-threatening or cause significant hemodynamic compromise and organ hypoperfusion.
2. Analysis demonstrated a strong correlation ($p<0.001$) between the incidence of postoperative arrhythmias and the degree of intraoperative hemolysis. Specifically, a higher plasma hemoglobin level of 0.5 g/l or greater was associated with a significantly increased risk of arrhythmias. A critical threshold for heightened arrhythmia risk was identified at free hemoglobin levels exceeding 0.85 g/l.
3. These findings suggest that monitoring free plasma hemoglobin levels during CABG procedures may serve as a crucial indicator for predicting and preventing postoperative arrhythmias, and potentially guiding interventions to correct any hemodynamic complications.

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Endoscopic Treatment of Children with Impacted Ureteral Stones

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Abstract- Ureteroscopy is the method of choice for treating children with impacted ureteral stones. In this study, ureterolithotripsy were used to assess the treatment outcomes for pediatric patients with impacted ureteral stones. The treatment results of 73 children aged 5 to 18 years were retrospectively evaluated. The average stone size was 10.0 ± 0.6 mm in length and 5.5 ± 0.7 mm in width. Complete stone removal was achieved in 71 patients (97.2%). The total number of intraoperative complications was 24 (33.8%). Conversion from endoscopic intervention to open surgery was required in two cases (2.8%) (Grade III). Ureteral mucosal injury was observed in 6.8% of children (Grade I), and ureteral perforation in 1.4% of cases (Grade II-a). Ureteral mucosal burns occurred in 4.1% of patients (Grade II-a) during laser lithotripsy.

Keywords: *children, ureteral stones, contact ureterolitho- tripsy.*

GJMR-I Classification: *NLMC Code: WJ 302*



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Endoscopic Treatment of Children with Impacted Ureteral Stones

Nadjimitdinov Y. S. [α] & Zakirov H. K. [σ]

Abstract- Ureteroscopy is the method of choice for treating children with impacted ureteral stones. In this study, ureterolithotripsy were used to assess the treatment outcomes for pediatric patients with impacted ureteral stones. The treatment results of 73 children aged 5 to 18 years were retrospectively evaluated. The average stone size was 10.0 ± 0.6 mm in length and 5.5 ± 0.7 mm in width. Complete stone removal was achieved in 71 patients (97.2%). The total number of intraoperative complications was 24 (33.8%). Conversion from endoscopic intervention to open surgery was required in two cases (2.8%) (Grade III). Ureteral mucosal injury was observed in 6.8% of children (Grade I), and ureteral perforation in 1.4% of cases (Grade II-a). Ureteral mucosal burns occurred in 4.1% of patients (Grade II-a) during laser lithotripsy. Deformation of the tip of the metal guidewire during an attempt to pass it retrogradely into the kidney occurred in 16.4% of cases (Grade I). Postoperative complications were observed in 23 patients (31.5%). Elevated body temperature was noted in 8.2% of cases (Grade I), and hematuria in 9.6% (Grade I). Urinoma (Grade III-b) and steinstrasse (Grade II-a) were each observed in one child (1.4%). Systemic inflammatory response syndrome was also reported in one case. Ureteroscopic contact lithotripsy for impacted ureteral stones in children is an effective and safe treatment method.

Keywords: children, ureteral stones, contact ureterolithotripsy.

I. Introduction

Urolithiasis is very common in some parts of the world, like Central Asia, the Middle East, South Asia, and North Africa. Treating it is very important for pediatric patients who have it. However, epidemiological studies have shown that the incidence of pediatric urolithiasis is increasing even in developed countries [2]. It should be noted that stone formation in children tends to recur, so minimally invasive surgical methods that can be reused if necessary should be preferred. These methods also allow for stone removal without disrupting the anatomical structure of the urinary tract and reducing the potential adverse effects of surgery on the growing body.

In cases where stones are located in the ureter, spontaneous passage is unlikely, and the risk of complications is high. Therefore, active surgical intervention is recommended in children [11]. Although guidelines from the European Association of Urology and the European Society for Paediatric Urology suggest that both minimally invasive and traditional approaches can be used to remove ureteral stones, only a small subset of pediatric patients require open surgery. Nevertheless, every effort should be made to completely remove the stones, as postoperative residual fragments pass spontaneously in only 20–25% of cases [5].

Ureteroscopy is considered the method of choice in treating children with ureteral stones, particularly when the disease duration exceeds 2-3 months and the calculus is tightly adherent to the ureteral mucosa (i.e., impacted). In adults, impacted stones are defined as those that have remained in the exact ureteral location for at least two months. In such cases, intravenous urography typically fails to demonstrate contrast distal to the stone, and it is generally impossible to pass a metal guidewire into the renal pelvis [7]. It is important to emphasise that ureterolithotripsy for impacted stones requires a high level of surgical skill, as there is a significant risk of ureteral wall injury and subsequent stricture formation.

This study sought to evaluate the efficacy of antegrade and transurethral ureterolithotripsy (TUULT) in resolving the challenging clinical scenario of impacted ureteral stones in pediatric patients, with a specific focus on treatment outcomes.

II. Materials and Methods

Between January 2019 and December 2024, we embarked on a retrospective journey through the medical records of 73 children, their ages ranging from 5 to 18, each grappling with the challenge of ureteral obstruction. Our aim was to illuminate the landscape of their treatment outcomes, casting light on the paths to recovery and the shadows of adversity they faced. The study included patients who experienced their first episode of renal colic 30-40 days before presentation, but for various reasons had not undergone surgical intervention. Multislice computed tomography (CT) with contrast of the urinary tract confirmed the presence of ureteral stones in all cases, with preserved renal function.

All patients exhibited ureterohydronephrosis, and tortuosity of the ureter was observed proximal to the stone. Patients with congenital anomalies of the urinary tract or strictures of the ureteropelvic junction,

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ureterovesical junction, or ureter were excluded from the study.

Before the surgical intervention, each patient was subjected to a comprehensive clinical and laboratory workup. This included meticulous urine and blood analyses, with bacteriological studies conducted as indicated. The diagnostic process was further augmented by ultrasonography and detailed radiographic imaging of the urinary tract, painting a complete picture of the patient's condition. If pyuria or bacteriuria were detected in a urinalysis, and further confirmed by a positive urine culture, a specific antibiotic treatment was initiated to effectively cleanse and restore the urinary tract to its normal, healthy state. Parents or guardians were thoroughly informed about the planned surgical procedures, possible complications, and additional interventions. Following this detailed discussion, their informed consent was obtained, signifying their agreement with the proposed course of action. The study protocol was approved by the Ethics Committee of the Republican Scientific and Practical Medical Centre of Urology, where the study was conducted (Protocol No. 1, January 23, 2023).

All procedures were performed under general anaesthesia. Transurethral ureterolithotripsy (TUULT) was performed with the patient in the supine position, whereas antegrade ureterolithotripsy was performed in the prone position. During the procedures, TUULT employed a 7 Fr rigid ureteroscope manufactured by Karl Storz® (Germany). Antegrade interventions were performed percutaneously, accessing the posterior calyx of the lower renal pole through a 14 Fr rigid endoscope also produced by Karl Storz® (Germany). Ureteral orifice dilation was not performed in any case. Before lithotripsy, a flexible guidewire was inserted into the ureter, ideally advanced into the renal pelvis and calyceal system; if not feasible, it was positioned at the level of the stone. Stone fragmentation was achieved using either a pneumatic lithotripter (LithoClast® Master, EMS, Switzerland) or a thulium laser (Cyber Ho®, Quanta System, Italy). To reduce the risk of damage to the ureteral mucosa due to heat, fragmentation of the stone began from its central part. This approach allowed for a gradual reduction in stone volume, minimizing the contact time between the laser fiber and the ureteral wall. Furthermore, the resulting smaller fragments were more easily extracted, further decreasing the potential for trauma to the delicate lining of the ureter. The power settings were carefully adjusted to achieve effective fragmentation while minimizing thermal energy dissipation. After the calculus had shattered into smaller fragments, the lithotripsy continued, relentlessly grinding the remnants until only granules resembling fine sand remained. Fragments larger than 4-5 mm were extracted using forceps; in cases with only smaller fragments, the procedure was concluded, assuming spontaneous passage with urine flow. At the end of the procedure, a Double J stent was inserted into the ureter and removed on postoperative days 7–10 under general anaesthesia. The stent placement aimed to ensure adequate drainage and prevent ureteral stricture formation during the healing process. Its removal, performed under general anaesthesia for patient comfort and to minimize potential discomfort or trauma, was uneventful in all cases. Post-removal, patients were monitored for any signs of urinary obstruction or flank pain, and discharged home with instructions on increased fluid intake and reporting any concerning symptoms. Nephrostomy drainage was additionally established in patients who underwent antegrade ureterolithotripsy. Intraoperative complications were classified using the modified Satava system, and postoperative complications were assessed according to the Clavien–Dindo classification [4].

The outcomes were compared using Fisher's exact test and Student's t-test. The descriptive statistics were calculated, and data processing was performed using Microsoft Office Excel 2007, Stat Soft Statistica 8.0, and statistical formulas.

III. Results

The mean age of the patients was 13.3 ± 2.7 years (range: 5–18 years). Demographic characteristics are summarised in Table 1. Among the 73 children, 48 (65.8%) were boys and 25 (34.2%) were girls. The mean stone size was 10.0 ± 0.6 mm in length and 5.5 ± 0.7 mm in width. Stone location was distributed as follows: distal ureter in 35 children (47.9%), mid-ureter in 24 (32.9%), and proximal ureter in 14 (19.2%). Stones were located in the right ureter in 45 patients (64.6%) and in the left ureter 28 (35.4%). One patient had previously undergone an unsuccessful attempt at extracorporeal shock wave lithotripsy (ESWL), and in another, stone extraction via ureteroscopy had failed.

TUULT was used for stones located in the distal and mid-ureter, while antegrade ureterolithotripsy was performed for proximally located stones. Complete stone clearance, including large fragments, was achieved in 71 patients (97.2%). Due to severe edema and hypertrophy of the mucous membrane, which made endoscopic visualization of the stone difficult, in two cases (2.8%) it was necessary to switch to open surgery (Table 2).

Resection of the ureter at the site of the stone was performed in one case, and a uretero-ureteroanastomosis was created; in another child, a ureterocystoanastomosis was performed (Grade III). Ureteral mucosa injury was observed in 6.8% of children (Grade I), and ureteral perforation in 1.4% of cases (Grade II-a), with the stone migrating extraureterally. These complications occurred in the group of children under 7 years of age. Ureteral mucosal burns were observed in 4.1% of patients (Grade II-a) when using a laser for lithotripsy. In 16.4% of cases (Grade I),

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deformation of the tip of the metal guidewire occurred during an attempt to retrogradely pass it beyond the stone, and it was replaced with another one. This complication was primarily attributed to excessive force applied during manipulation, leading to a loss of tactile feedback and potential damage to the guidewire's integrity. The replacement procedure, while successful in most instances, contributed to a slight increase in procedural time and resource utilization. Thus, the total number of intraoperative complications was 24 (33.8%) cases.

After surgery, the children stayed in the intensive care unit for 6–8 hours; once their condition stabilised, they were transferred to the general ward.

Table 1: Some Demographic Data and Clinical Characteristics of Patients (N=73)

Characteristic	Age (years)			
	5-7	8-10	11-14	15-18
Numberofpatients	11 (15%)	26 (36%)	24 (33%)	12 (16%)
Boys/Girls	6/5	19/7	16/8	7/5
Duration of disease (days, mean±SD)	41,9±6,8	42,7±7,2	41,9±6,9	41,3±7,4
Unsuccessful ESWL	1 (1,4%)	-	2 (2,7%)	-
Unsuccessful TUULT		1 (1,4%)		
Stone length (mm, mean±SD)	9.3±1,0	9,9±1,3	10,4±0,8	10,5±0,7
Stone width (mm, mean±SD)	5,3±0,9	5,4±0,8	5,5±0,7	5,6±0,7
Lengthofhospitalstay	4,1±0,8	4,2±0,9	4,3±0,8	4,0±0,7

Complications in the postoperative period were observed in 23 cases (31.5%). Increased body temperature without signs of sepsis after surgery occurred in 8.2% of cases (Grade I); in these patients, growth of microorganisms was detected during bacteriological examination of urine before the intervention. After intensification of antibacterial therapy, body temperature returned to normal. Hematuria without blood clots was observed in 9.6% of patients (Grade I) who underwent antegrade ureterolithotripsy. The use of hemostatic drugs and increased diuresis made it possible to eliminate the bleeding.

Table 2: Intraoperative Complications from the Perspective of the Modified Satava Classification (N=73)

Grade	Injury	Number of patients
Grade I	– Minimal mucosal injury of the ureter (mucosal tears);	5 (6,8%)
	– Malfunctioning or breakage of instruments;	12 (16,4%)
Grade II-a	– Mucosal injury (thermal injury);	3 (4,1%)
	– Extraureteral stone migration requiring stent insertion;	1 (1,4%)
	– Ureteral perforation requiring stent or nephrostomy insertion and secondary ureteroscopy;	1 (1,4%)
Grade III	– Inability to access the ureter or reach the stone requiring conversion to open surgery;	2(2,8%)

All children after endoscopic intervention were prescribed non-steroidal anti-inflammatory drugs during the first two days. However, in 9.6% of cases (Grade IIa), the use of these drugs was required for more than three days due to discomfort caused by nephrostomy drainage. A small urinoma (Grade IIIb) in the region of the lower pole of the kidney was detected by ultrasonography in one child (1.4%) after percutaneous access to the ureter. Without any additional interventions, the urinoma resolved by the fifth day after the operation. Steinstrasse (Grade IIa) located in the lower section of the ureter was observed in one child (1.4%). The reason for this was that, during pneumatic lithotripsy, fragments of the calculus located in the middle section migrated into the renal cavity and, after the operation, moved to the ureter. The use of an alpha-blocker made it possible to eliminate the fragments. Systemic inflammatory response syndrome (hyperthermia up to 38°C, chills, pulse 120 per minute, respiratory rate 28 per minute, leukocyte count in peripheral blood 16,000 per ml) was observed in one child, who was transferred to the intensive care unit. Appropriate treatment (infusion therapy, additional antibiotics) allowed sepsis to be controlled.

Of the 73 patients, 70 were re-examined within 12 months. No patient experienced recurrent stone formation. However, in one case, a clinically insignificant narrowing of the mid-ureter (where the calculus had been located) was detected via intravenous urography. The thickness of the renal parenchyma was consistent with age norms, and its function remained preserved.

IV. Discussion

Ritchey M. et al. first described a case of stone removal in a child using ureteroscopy with a laser lithotripter in 1988 [10]. Due to the lack of small-caliber endoscopes at the time, pediatric urologists remained skeptical about the use of lithotripsy for ureteral stones

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for many years. The inherent anatomical differences in the pediatric urinary tract, particularly the smaller diameter of the ureters, presented significant technical challenges. Concerns were raised regarding the potential for trauma, perforation, and incomplete stone fragmentation when using instruments designed for adult anatomy, leading to a preference for more established, albeit often more invasive, surgical techniques. Over the past decade, however, concerns about urinary tract injury when using endoscopes to treat ureteral and renal pathology have been largely overcome. Small-calibre devices have been developed and introduced into practice, making laser stone fragmentation feasible and establishing ureterolithotripsy as a first-line treatment for children with ureteral stones.

Table 3: Distribution of Patients Depending on the Degree of Postoperative Complications According to the Modified Clavien-Dindo Classification (N=73)

Grade	Complication	Number of Patients
Grade I	Hyperthermia Blood in the urine requires the use of hemostatic agents, additional infusion therapy and diuretics	6 (8,2%) 7 (9,6%)
Grade IIa	The need for non-steroidal anti-inflammatory drugs is more than 48 hours after surgery. Steinstrasse	7 (9,6%) 1 (1,4%)
Grade IIIb	Urinoma	1 (1,4%)
Grade IVb	Urosepsis (including SIRS)	1 (1,4%)

Despite these advances, the optimal treatment approach for impacted stones remains a challenge. Ghoneim I. A. et al. [6] consider extracorporeal shock wave lithotripsy (ESWL) to be effective for impacted proximal ureteral stones less than 2 cm. However, ESWL is often ineffective when there is limited space for stone expansion after fragmentation within the ureteral lumen [9]. Bres-Niewada E. points out that ESWL rarely eliminates stones in a single session, often requiring repeated interventions or additional procedures, which can negatively impact the patient's quality of life [3]. In our study, ESWL was attempted in one patient but failed to clear the stone. During ureteroscopy, the stone was found to be fragmented, but oedema of the ureteral mucosa prevented its migration through the lumen.

While numerous studies address the treatment of impacted stones in adults, we found only one report describing ureterolithotripsy in similar cases in children. Adanur S. et al. [1] achieved complete stone clearance in 93.75% of pediatric cases using a semirigid endoscope and laser lithotripsy, with a complication rate of 15.6%. ESWL was additionally used for stones that migrated into the renal pelvis. In our practice, we did not employ ESWL. However, in two cases, traditional surgery was required to remove the stones. The Clavien-Dindo classification was used by Adanur et al. to assess intraoperative complications; we utilised the Satava classification instead. According to our data, a stone-free status was achieved in 71 (97.2%) children, though complication rates were higher: intraoperative complications occurred in 33.8%, while postoperative complications were observed in 31.5%. These higher rates may be attributed to longer durations of obstruction, the use of larger-calibre rigid endoscopes, and the application of a pneumatic lithotripter.

The endoscope's calibre is paramount in surgical interventions, proving crucial not only for delicate pediatric procedures but also in navigating the challenging terrain of impacted stones in adults. Nagata M. et al. reported successful treatment using rigid and flexible 6.9 Fr ureteroscopes in patients with obstruction due to ureteral stones lasting from 14 months to 10 years [8]. Complete stone removal via ureteroscopy was achieved in 96.2% of cases; with adjunctive ESWL, the stone-free rate reached 100%. Small-calibre endoscopes enabled surgery without significant complications. The authors noted that chronic obstruction leads to inflammatory oedema of the ureteral mucosa and formation of fibroepithelial polyps, which require laser removal. We also observed hypertrophy of the ureteral mucosa in the area surrounding the stone, which hindered visualisation and lithotripsy. An attempt to use a laser to remove the hypertrophied mucosa resulted in thermal injury, leading us to discontinue that technique.

In conclusion, ureteroscopic contact lithotripsy is an effective and safe treatment for impacted ureteral stones in children. For stones in the middle and lower ureter, transurethral ureterolithotripsy (TUULT) is recommended. For stones in the upper ureter, antegrade ureterolithotripsy is preferable.

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A Clinical Study on the Diagnostic Significance of Sepsis Markers in Neonatal Sepsis in a Tertiary Care Center

By Vamsee Krishna Polepalli, Rohini Reddy Vanukuri & Nayan Baba Pelala

Abstract- *Background:* In neonatal period after prematurity, sepsis is considered as the second leading cause of mortality.

Aims & Objective: To know the sensitivity, specificity, positive predictive value and negative predictive value of sepsis markers in a neonate.

Materials & Methods: All babies< 28 days of life with sepsis risk factors, and clinical features suggesting sepsis were included in this study.

Results: A total of 100 neonates admitted to NICU were enrolled in the study. 32% of the cases had abnormal WBC levels, 44% of cases had thrombocytopenia and CRP was positive in 89% of the cases.18% of the cases had culture-proven sepsis, 29% cases had probable sepsis and 53% cases had suspected sepsis.

Keywords: *neonatal sepsis, sepsis markers, platelet count, CRP.*

GJMR-I Classification: *NLMC Code: WS 421*



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A Clinical Study on the Diagnostic Significance of Sepsis Markers in Neonatal Sepsis in a Tertiary Care Center

Vamsee Krishna Polepalli [α], Rohini Reddy Vanukuri [σ] & Nayan Baba Pelala [ρ]

Abstract- ***Background:*** In neonatal period after prematurity, sepsis is considered as the second leading cause of mortality.

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Results: A total of 100 neonates admitted to NICU were enrolled in the study. 32% of the cases had abnormal WBC levels, 44% of cases had thrombocytopenia and CRP was positive in 89% of the cases.18% of the cases had culture-proven sepsis, 29% cases had probable sepsis and 53% cases had suspected sepsis. Total leucocyte count had a moderate Negative predictive value (62.5%), low Sensitivity (33.3%), low Specificity (24.4%), and low Positive predictive value (8.8%) in detecting sepsis. Platelets had a high negative predictive value (91.1%), moderate sensitivity (72.2%), moderate specificity (62.2%), and low positive predictive value (29.5%). In detecting sepsis CRP levels had high Sensitivity (83.3%), and moderate Negative predictive value (72.7%) with low Specificity (9.8%), and low positive predictive value (16.9%). In diagnosing culture-proven sepsis high sensitivity was observed by increased CRP levels(83.3%), moderate Sensitivity by thrombocytopenia (72.2%), moderate Specificity by thrombocytopenia (62.2%), high Negative predictive value by thrombocytopenia (91.1%), moderate Negative predictive value by CRP levels (72.7%), and leucopenia (62.5%).

Conclusions: No single individual test is better than others in detecting neonatal sepsis. The conjunction of tests like Total WBC, Platelets, and CRP are to be utilized for better sepsis screening.

Keywords: neonatal sepsis, sepsis markers, platelet count, CRP.

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I. Introduction

The neonatal period is vulnerable to infections and its impact can have long term effects. In this period more than 50% of deaths are reported among under five children. [1]NNPD 2002 -2003 report had showed incidence of neonatal sepsis as 30/1000 live births. [2]Sustainable Developmental Goals (SDG) 3 aims to reduce neonatal mortality to less than 12 deaths for 1000 live births by 2030. W. H. Ohas given guidelines that can be utilized to achieve SDG 3.[3]

After prematurity, sepsis is considered as the second leading cause of mortality. Incidence of clinical sepsisis very high in India. [4]Presence of signs and symptoms of infection within one month of birth are considered as neonatal sepsis.[5]

Neonatal sepsis can be divided into Early-onset sepsis (EONS), and Late-onset sepsis (LONS). Early-onset sepsis occurs within the first 72 hours of life. Late-onset sepsis generally occurs after 3 days of birth. Mortality is more with EONS than LONS.[6]

On time diagnosis and management of neonatal sepsis is very essential to prevent mortality. Blood culture is the confirmatory method of neonatal sepsis. But among all the neonatal sepsis, only 25 to 40% have culture positivity.[7] In developing countries like India, with the resource-limited setting and the delay in obtaining culture positivity report (up to 48 hrs), confirmation of neonatal sepsis can be done based on the clinical presentation, and use of sepsis markers. Hence, this study was taken up to prove the diagnostic significance of sepsis markers in neonatal sepsis.

II. Materials & Methods

This is an observational study done from May 2020 to November 2021 at GEMS NICU, Ragolu, Srikakulam.

a) Inclusion Criteria

All babies< 28 days of life with sepsis risk factors and clinical features suggesting sepsis were included in this study.

b) Exclusion Criteria

Babies with birth asphyxia, with birth weight <1500 grams, with gestational age <32 weeks and

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neonates who had taken antibiotics were excluded from the study.

In this observational study, neonates clinically suspected to have sepsis were enrolled. On meeting the inclusion criteria, prior informed, written parental consent was obtained before enrollment in the study. The study has been cleared by Hospital Ethics Committee and Hospital Research Committee. During the study, a pre-designed and pre-tested proforma was implemented.

On admission, as per the hospital protocol, detailed information was noted in the medical case sheet. When sepsis was suspected, clinical features were noted. Investigations like complete blood picture, CRP, and blood culture were done. Various biomarkers are used as diagnostic tools for neonatal sepsis. But the gold standard for the detection of sepsis is blood culture, but blood culture takes 2-3 days for a diagnosis. This study evaluates the Sensitivity, specificity, positive predictive value, and negative predictive value of the sepsis markers i.e., Total Leukocyte Count, CRP, Platelet count. Data was analyzed with Microsoft Excel and SPSS (Statistical package for social sciences) version 25. Statistical analysis was done by using the Chi-square test and ANOVA. Results were expressed in terms of mean, percentages, and depicted as tables, graphs. P-value <0.05 was considered statistically significant.

III. Results

All the 100 neonates enrolled were survived without any mortality.

Of the 100 neonates, males were 63%, and females were 37%.

Table 1: Birth Weight Wise Distribution of Study Population

Birth weight	No. of Cases	Percentage
≤2.5kg	71	71
>2.5kg	29	29
Total	100	100

The average birth weight of preterm neonates was 2336.76 ± 148.23 grams, and term neonates were 2661.03 ± 129.16 grams. The average birth weight of all (100) neonates was 2430.80 ± 205.238 grams.

Table 2: Gestational Age-Wise Distribution of Study Population

Gestational age	No. of Cases	Percentage
≤ 37 weeks	62	62
>37 weeks	38	38
Total	100	100

The average gestational age of the preterm neonates was 34.29±0.67 weeks, term neonates were 37.88±0.73 weeks, and the average gestational age of total neonates was 35.65±1.88 weeks.

Of the total neonates, 57% were delivered by caesarean section and 43% were delivered by normal vaginal delivery (NVD).

In this study, regarding indication for caesarean section, foetal distress was the most often reason (16%), followed by meconium stained liquor (12%), CPD (10%), Non-reactive NST (9%), non-progression of labour (8%), and compound presentation (2%) were the other causes for indication of caesarean section.

In this study regarding the distribution of risk factors for sepsis, 20% of the cases had single unclean or more than 3 Vaginal Examinations, 34% of cases had PROM more than 18 hrs, 21% of cases had meconium-stained liquor, 17% of cases had a febrile illness in mother, and 8% of the cases had foul Smelling Liquor.

Table 3: Manifestation of Sepsis

Manifestations of Sepsis	No. of Cases	Percentage
Shock	82	82
Congenital Pneumonia	9	9
Necrotizing enterocolitis (NEC)	5	5
Meningitis	4	4
Total	100	100

In this study, the majority (82%) of the neonates had a shock, followed by congenital pneumonia (9%).

In this study, early onset of neonatal sepsis (EONS) was observed among 56% of the neonates, and late-onset of neonatal sepsis (LONS) was observed among 44% of neonates.

The average duration of EONS was 18 ± 9.12 hrs, and LONS was 168.1 ± 74.35 hrs.

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Table 4: Distribution of Cases based on Blood Culture

Blood Culture Positive	No. of Cases	Percentage
Yes	18	18
No	82	82
Total	100	100

Table 5: Distribution of Cases based on Organisms in Culture

Organisms	No. of Cases	Percentage
Actinobacter species	1	1
E.coli	4	4
Haemophilus	1	1
Klebsiella	3	3
Methicillin-resistant staphylococcal aureus	1	1
Pseudomonas aerugonsia	1	1
Staphylococcal species	7	7
Total	18	18

In this study, of all the neonates, 68% of the neonates had normal WBC levels and 32% of cases had abnormal WBC levels.

In this study, of the total neonates, 56% of the neonates had >1.5 Lakhs platelets and 44% of neonates had ≤1.5 Lakhs platelets.

Table 6: Distribution of Cases based on CRP

CRP Positive	No. of Cases	Percentage
Yes	89	89
No	11	11
Total	100	100

Among the total neonates, CRP was positive in 89% of the cases and was negative in 11% of cases.

Table 7: Distribution of Sepsis

Category	No. of Cases	Percentage
Suspected sepsis	53	53%
Probable sepsis	29	29%
Culture proven sepsis	18	18%
Total	100	100

Of the total cases, only 18% of the cases had culture-proven sepsis, 29% of cases had Probable sepsis, and 53% of the cases had suspected sepsis.

Table 8: Gender wise Distribution of Neonatal Sepsis

Gender	Suspected Sepsis	Probable Sepsis	Culture Proven Sepsis	Total
Male	35(55.6%)	15(23.8%)	13(20.6%)	63(63%)
Female	18(48.6%)	14(37.8%)	5(13.5%)	37(37%)
Total	53(53%)	29(29%)	18(18%)	100(100%)

Pearson chi square 2.448; P value 0.294(No significance)

The association between gender and sepsis was statistically not significant (P-value 0.294).

Table 9: Gestational Age-Wise Distribution of Neonatal Sepsis

Gestational Age	Suspected Sepsis	Probable Sepsis	Culture Proven Sepsis	Total
≤ 37 weeks	26(41.9%)	20(32.3%)	16(25.8%)	71(71%)
>37 weeks	27(71.1%)	9(23.7%)	2(5.3%)	29(29%)
Total	53(53%)	29(29%)	18(18%)	100(100%)

Pearson chi-square 9.89; P value 0.007(Significant)

The association between Gestational Age and sepsis was statistically significant (P-value 0.007).

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Table 10: Birth Weight Wise Distribution of Neonatal Sepsis

Birth weight	Suspected Sepsis	Probable Sepsis	Culture Proven Sepsis	Total
≤2.5kg	32(45.1%)	23(32.4%)	16(22.5%)	71(71%)
>2.5kg	21(72.4%)	6(20.7%)	2(6.9%)	29(29%)
Total	53(53%)	29(29%)	18(18%)	100(100%)

Pearson chi square 6.675; P-value 0.036 (Significant)

The association of birth weight with sepsis was statistically significant (P-value 0.036).

Table 11: Mean Total Leucocyte Count (TLC) vs Neonatal Sepsis

		N	Mean ± SD	95% Confidence Interval for Mean		P-value
				Lower Bound	Upper Bound	
Mean TLC	Suspected Sepsis	53	12515.09±2554.73	11810.92	13219.27	0.0001 (Highly sig.)
	Probable Sepsis	29	7855.17± 4868.6	6003.26	9707.09	
	Culture Proven Sepsis	18	7805.56 ± 5534.11	4953.50	10557.6	
	Total	100	10316.00±4571.64	9408.89	11223.1	

In the above table, lower bound values were lowest in the Culture Proven Sepsis and higher bound values were observed in Suspected Sepsis. Thus Leucopenia, an adverse marker of sepsis, was observed in the study had differentiated the Culture Proven Sepsis and Suspected Sepsis. This difference reached levels of the highest statistical significance (p=0.0001).

Table 12: Mean Platelet Count (PLT) VS Neonatal Sepsis

		N	Mean ± SD	95% Confidence Interval for Mean		P-value
				Lower	Upper	
Mean PLT	Suspected Sepsis	53	202113.21 ± 39406.003	191251.57	140359.60	0.0001 (Highly significant)
	Probable Sepsis	29	99172.41 ± 31399.578	87228.65	111116.17	
	Culture Proven Sepsis	18	95833.33 ± 42726.559	74585.92	117080.75	
	Total	100	153130.00 ± 64359.887	140359.60	165900.40	

In the above table, lower bound values were lowest in the Culture Proven Sepsis and higher bound values were observed in Suspected Sepsis. Thus thrombocytopenia was a significant marker in diagnosing proven and probable sepsis. This trend reached levels of the highest statistical significance (p <0.0001).

Table 13: Mean CRP levels VS Neonatal Sepsis

		N	Mean ± SD	95% Confidence Interval for Mean		P-value
				Lower Bound	Upper Bound	
Mean CRP	Suspected Sepsis	53	14.47±6.863	12.58	16.36	0.0001 (Highly significant)
	Probable Sepsis	29	48.00±28.864	37.02	58.98	
	Culture Proven Sepsis	18	78.17±35.499	60.51	95.82	
	Total	100	35.66± 33.019	29.11	42.21	

In the above table, lower bound values were lowest in the Suspected Sepsis and higher bound values were found in Culture Proven Sepsis. Thus raised CRP levels was a significant marker in diagnosing proven and probable Sepsis. This trend reached levels of the highest statistical significance (p <0.0001).

Table 14: Total leucocyte Count VS Blood Culture Positivity

		Blood Culture				Total	
		Positive		Negative			
		No.	%	No.	%	No.	%
Total leucocyte Count	5000-20000	6	3.3	62	75.6	68	68
	<5000/>20000	12	66.7	20	24.4	32	32
Total		18	18	82	82	100	100

Pearson chi-square 12.123, P-value 0.0001 (Highly significant)

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In the above table, abnormal total leucocyte count was observed in 66.7% of the culture-positive sepsis and 24.4% of culture-negative cases. This abnormal trend of total leucocyte count in Proven Sepsis showed highly statistical significance (P-value 0.0001).

Table 15: Prediction of Sepsis with Total Leucocyte Count

Sensitivity	33.3%
Specificity	24.4%
PPV	8.8%
NPV	62.5%

The total leucocyte count of this study had a moderate Negative predictive value (62.5%) with low Sensitivity (33.3%), low Specificity (24.4%), and low Positive predictive value (8.8%).

Table 16: Platelet Count (PLT) VS Blood Culture Positivity

		Blood Culture				Total	
		Positive		Negative			
		No.	%	No.	%	No.	%
PLT	≤1.5L	13	72.2	31	37.8	44	44
	>1.5L	5	27.8	51	62.2	56	56
Total		18	18	82	82	100	100

Pearson chi square 7.096; P value 0.008 (significant)

In this study, thrombocytopenia occurred in 72.2% of the culture-positive sepsis, and 37.8% of culture-negative cases. This increased trend of thrombocytopenia in Proven Sepsis showed statistical significance (P-value 0.008).

Table 17: Prediction of Sepsis with Platelets

Sensitivity	72.2%
Specificity	62.2%
PPV	29.5%
NPV	91.1%

In this study, Platelets had a high negative predictive value (91.1%), and moderate Sensitivity (72.2%) with moderate Specificity (62.2%), and a low positive predictive value (29.5%).

Table 18: CRP levels VS Blood Culture Positivity

		Blood Culture				Total	
		Positive		Negative			
		No.	%	No.	%	No.	%
CRP	Positive	15	83.3	74	90.2	89	89
	Negative	3	16.7	8	9.8	11	11
Total		18	18	82	82	100	100

Pearson chi-square 0.72, P-value 0.396 (No significance)

In the above table, increased CRP levels was observed in 83.3% of the culture-positive sepsis and 90.2% of culture-negative cases. This association between CRP levels and culture did not show statistical significance (P-value 0.396).

Table 19: Prediction of Sepsis by CRP

Sensitivity	83.3%
Specificity	9.8%
PPV	16.9%
NPV	72.7%

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In this study, CRP levels had high Sensitivity (83.3%), moderate Negative predictive value (72.7%) with low Specificity (9.8%), and low positive predictive value (16.9%).

IV. Discussion

In this study, males were more (63%) compared to females (37%) which showed a male preponderance with a male to female ratio of 1.7:1. Similar male preponderance was reported by studies done by Bhalodia MJet al. [8] (66.7%), Vinay BS et al. [9](66.6%), Emad A. Morad et al.[10] (66%), Abebe Sorsa[11] (65.3%), Mittal A et al.[12] (58.8%), Arnab Sengupta et al.[13] (58.2%), Flora Chacha et al.[14] (51.2%).

In the present study, low birth weight was reported in the majority (71%) of the study population. Similar reports were obtained in the study by Vinay BS et al.[9] (70%), Mittal Aet al.[12] (56.1%), Arnab Sengupta et al.[13] (56.6%), Emad A. Morad et al.[10] (54%). Contrast findings were seen in Flora Chacha et al.[14] (29.8%), Abebe Sorsa study[11] (24.1%).

In this study, more (62%) preterm babies were seen than term babies (38%). Similar to this finding preterm babies were more in Vinay BS et al.[9] (68.4%), Choudhary D.K et al.[15](76%) studies, whereas preterm babies were less in the study by Flora Chacha et al.[14] (22.6%), Abebe Sorsa study[11] (22.9%), Bhalodia MJet al.[8] (26.7%), Emad A. Morad et al.[10] (38%).

Of the total babies, 57% of the neonates were delivered by caesarean section (57%) and 43% were delivered by normal vaginal delivery (NVD). Whereas study by Flora Chacha et al.[14] (22%), Abebe Sorsa study[11] (24.1%), and Emad A. Morad et al.[10] (46%) caesarean sections was less compared to normal deliveries.

Early-onset of neonatal sepsis was observed among 56% of the neonates, and late-onset of neonatal sepsis was observed among 44% of neonates. Similar to this finding in Abebe Sorsa study[11], early onset of neonatal sepsis was seen in 61.2% of cases, and in 38.8% of cases late-onset of neonatal sepsis was reported, and Vinay BS et al.[38] also reported early-onset sepsis in 90% of cases.

In contrast to this study finding in the study by Choudhary D.K et al.[15] early-onset sepsis was present in 27% of cases, while late-onset neonatal sepsis was present in 73% of cases.

In this study, Blood culture was positive in only 18% of the cases and was negative in 82% of cases. Similar findings were reported by Choudhary D.K et al.[15] (17%), Harshitha M. Swamy et al.[16] (20%), Flora Chacha et al.[14] (20.3%), Bhalodia MJ et al.[8] (38%), whereas the higher incidence of positive blood culture was reported in the studies by Sriram R. [17] (50.4%), Vinay BS et al.[9](80%).

In this study regarding culture, Staphylococcal species were present in 7% of the cases, followed by E.coli (4%), Klebsiella (3%), whereas Actinobacter species, Haemophilus, Methicillin-resistant staphylococcal aureus, and Pseudomonas aerugonsia was observed in each one percent of the cases. Staphylococcal species were the predominant organism. Similar to this study, S. aureus was the commonest organism in the studies by Karthikeyan G et al.[18], Misquith R et al.[19], Jaswal RS et al.[20], Tushar Priyanka et al.[21]

CRP was positive in 89% and was negative in 11% of cases. Similar to this finding in Sriram. R study[17], CRP was positive in 88.7% cases and negative in 11.3% cases. In contrast to this finding Gurpreet Singh Chhabra et al.[22] studies had 3% CRP positivity.

a) Total WBC Count vs Blood Culture Positivity

In this study, abnormal total leucocyte count was observed in 66.7% of the culture-positive sepsis and 24.4% of the culture-negative cases. The total leucocyte count of this study had reported 33.3% Sensitivity, which was in accordance with studies by Tushar Priyanka et al.[21] (23.63%), Harshitha M. Swamy et al.[16](20%), and Makkar M et al. [23] (43.18%).

In this study total leucocyte count had shown specificity of 24.4%, which was lower than other studies by Tushar Priyanka et al.[21] (71.27%), Bhalodia et al.[8] (74.5%), and Majumdar A et al.[24] (85%).

This variation might be due to different selection criteria adapted while selecting the participants, and different levels of infections in neonates.

In this study total leucocyte count had a low positive predictive value (8.8%), which was similar to the study by Hiral PS [25](15.38%). Contrast results were obtained in the studies by Punyashetty KB et al.[26] (87.5%), Makkar M et al. [23] (86.36%), and Narasimha A et al. [27](80%).

The total leucocyte countof this study had a moderate Negative predictive value (62.5%), which was in accordance with Makkar M et al. [23] (56.89%), Majumdar A et al.[24] (87%), and Bhalodia et al.[8] (87%) studies.

b) Platelet Count vs Blood Culture Positivity

This study had high Sensitivity (72.2%) for platelets which was in accordance with Makkar M et al.[23] (70.45%), Majumdar A et al.[24] (70%), Hiral PS [25] (73.68%), Mittal Aet al.[12] (83.08%).

For platelets, moderate Specificity (62.2%) was observed in this study which was in line with studies by Bhalodia et al.[8] (55.9%), Hiral PS [25] (53.09), and Narasimha A et al. [27] (75%). Low Positive predictive value (29.5%) was reported which was in concordance with Khair BK et al. [28] (31%), Hiral PS [25](26.92%), Mittal Aet al.[12](35.53%), and Harshitha M. Swamy et al.[16] (21.4%).

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In this study, Platelets had a high negative predictive value (91.1%), which was similar to studies of Hiral PS [25](89.58%), Punyashetty KB et al.[26] (93.5%), Khair BK et al. [28] (94%), Majumdar A et al.[24] (95%), and Narasimha A et al. [27] (85.71%)

c) CRP vs Blood Culture Positivity

In this study in 83.3% of the culture-positive sepsis and 90.2% of culture-negative cases increased CRP levels were reported. This increased CRP levels in culture-proven sepsis did not show statistical significance (P-value 0.396).

In this study, CRP levels had high sensitivity (83.3%), which was similar to Chandna A et al.[29](83%), Patel U et al.[30] (81.7%), Vinay BS et al. study[9] (81.2%), Sharma CM et al.[31] (80%), Harshitha M. Swamy et al.[16] (90%).

CRP levels in this study had low specificity (9.8%), which was less than studies of Chandna A et al.[29] (42%), Harshitha M. Swamy et al.[16] (47.5%). This variation could be because of the different methodologies used to measure CRP and the cut off used.

CRP levels in this study had low PPV (16.9%), which was similar to studies of Flora Chacha et al.[14] (37.5%), Harshitha M. Swamy et al.[16] (30%).

In this study, CRP levels had moderate NPV (72.7%), which was similar to studies of Sucilathangam G et al.[32] (78.1), Flora Chacha et al.[14](84.5%), Harshitha M. Swamy et al.[16] (95%).

Table 21: Comparison of Sensitivity, Specificity, PPV, NPV with other Studies

Test	Authors	Sensitivity	Specificity	PPV	NPV
Total WBC count	Khair KB et al. [28] (2010)	50%	91%	43%	93%
	Narasimha A et al. [27] (2011)	10.5%	91.66%	80%	24.4%
	Makkar M et al. [23] (2013)	43.18%	86.36%	86.36%	56.89%
	Majumdar A et al.[24] (2013)	45%	85%	40%	87%
	Bhalodia et al.[8] (2017)	66.7%	74.5%	48%	87%
	Punyashetty KB et al.[26] (2016)	100%	90.62%	87.5%	100%
	Hiral PS [25] (2019)	10.53%	86.42%	15.38%	80.46%
Total WBC count <5000/ >20000	Harshitha M. Swamy et al.[16] (2020)	20%	90%	33.3%	81.8%
	Tushar Priyanka et al.[21] (2018)	23.63%	71.27%	35.83%	-
	Present Study	33.3%	24.4%	8.8%	62.5%
Platelets ≤1.5L	Narasimha A et al. [27] (2011)	47.36%	75%	85.71%	31%
	Khair BK et al. [28] (2010)	60%	82%	31%	94%
	Makkar M et al.[23] (2013)	70.45%	93.9%	93.9%	72.3%
	Majumdar A et al.[24] (2013)	70%	80%	40%	95%
	Bhalodia et al.[8](2017)	56.3%	55.9%	56%	58%
	Punyashetty KB et al.[26] (2016)	91.3%	100%	100%	93.5%
	Mittal Aet al.[12]	83.08%	20.33%	35.53%	69.4%
	Hiral PS [25](2019)	73.68 %	53.09%	26.92%	89.5%
	Harshitha M. Swamy et al.[16](2020)	60%	45%	21.4%	81.8%
	Tushar Priyanka et al. [21](2018)	34.6%	78.7%	52.5%	63.9%
	Present study	72.2%	62.2%	29.5%	91.1%
CRP levels (>6mg/dl)	Patel U et al.[30] (2014)	81.7%	88%	95.7%	59.5%
	Vinay BS et al. study[9] (2015)	81.2%	50%	86.6%	40%
	Flora Chacha et al.[14] (2014)	40.4%	82.7%	37.5%	84.5%
	Chandna A et al.[29] (1988)	83%	42%	57%	-
	Sharma CM et al.[31] (2103)	80%	93%	-	-
	Harshitha M. Swamy et al.[16]	90%	47.5%	30%	95%
	Sucilathangam G et al.[32] (2012)	50%	69.4%	38.8%	78.1%
	Sriram R study[17]	52.0%	61.5%	91.4%	14%
	Present study	83.3%	9.8%	16.9%	72.7%

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Table 22: Comparison of Sensitivity, Specificity, PPV, NPV of Total WBC with Other Studies

Test	Authors	Sensitivity	Specificity	PPV	NPV
Total WBC count <5000/ >20000	Khair KB et al. [28] (2010)	50%	91%	43%	93%
	Narasimha A et al. [27](2011)	10.5%	91.66%	80%	24.4%
	Makkar M et al. [23] (2013)	43.18%	86.36%	86.36%	56.89%
	Majumdar A et al.[24] (2013)	45%	85%	40%	87%
	Bhalodia et al.[8] (2017)	66.7%	74.5%	48%	87%
	Punyashetty KB et al.[26](2016)	100%	90.62%	87.5%	100%
	Hiral PS [25] (2019)	10.53%	86.42%	15.38%	80.46%
	Harshitha M. Swamy et al.[16] (2020)	20%	90%	33.3%	81.8%
	Tushar Priyanka et al.[21] (2018)	23.63%	71.27%	35.83%	-
	Present study	33.3%	24.4%	8.8%	62.5%

Table 23: Comparison of Sensitivity, Specificity, PPV, NPV of Platelets with Other Studies

Test	Authors	Sensitivity	Specificity	PPV	NPV
Platelets ≤1.5 Lakhs	Narasimha A et al. [27] (2011)	47.36%	75%	85.71%	31%
	Khair BK et al. [28] (2010)	60%	82%	31%	94%
	Makkar M et al.[23] (2013)	70.45%	93.9%	93.9%	72.3%
	Majumdar A et al.[24] (2013)	70%	80%	40%	95%
	Bhalodia et al.[8] (2017)	56.3%	55.9%	56%	58%
	Punyashetty KB et al.[26](2016)	91.3%	100%	100%	93.5%
	Mittal Aet al.[12] (2018)	83.08%	20.33%	35.53%	69.44%
	Hiral PS [25] (2019)	73.68 %	53.09%	26.92%	89.58%
	Harshitha M. Swamy et al.[16](2020)	60%	45%	21.4%	81.8%
	Tushar Priyanka et al. [21](2018)	34.6%	78.7%	52.5%	63.9%
	Present study	72.2%	62.2%	29.5%	91.1%

Table 24: Comparison of Sensitivity, Specificity, PPV, NPV of CRP Levels with Other Studies

Test	Authors	Sensitivity	Specificity	PPV	NPV
CRP levels (>6mg/dl)	Patel U et al.[30] (2014)	81.7%	88%	95.7%	59.5%
	Vinay BS et al. study[9] (2015)	81.2%	50%	86.6%	40%
	Flora Chacha et al.[14] (2014)	40.4%	82.7%	37.5%	84.5%
	Chandna A et al.[29](1988)	83%	42%	57%	-
	Sharma CM et al.[31] (2103)	80%	93%	-	-
	Harshitha M. Swamy et al.[16]	90%	47.5%	30%	95%
	Sucilathangam G et al.[32] (2012)	50%	69.4%	38.8%	78.1%
	Sriram R study[17] (2011)	52.0%	61.5%	91.4%	14%
	Present study	83.3%	9.8%	16.9%	72.7%

In conclusion, it is proved that no single individual test is better than others in detecting neonatal sepsis. So, the conjunction of tests like Total WBC, Platelets and CRP can be utilized for better sepsis screening, timely management and to reduce the duration of hospital stay and to improve appropriate antibiotic utilization.

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Author's Contribution:

Vamseekrishna Polepalli: Definition of intellectual content, Literature survey, Prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article;

Rohini Reddy Vanukuri: Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision;

Nayan Baba Pelala: Design of study, statistical Analysis and Interpretation;

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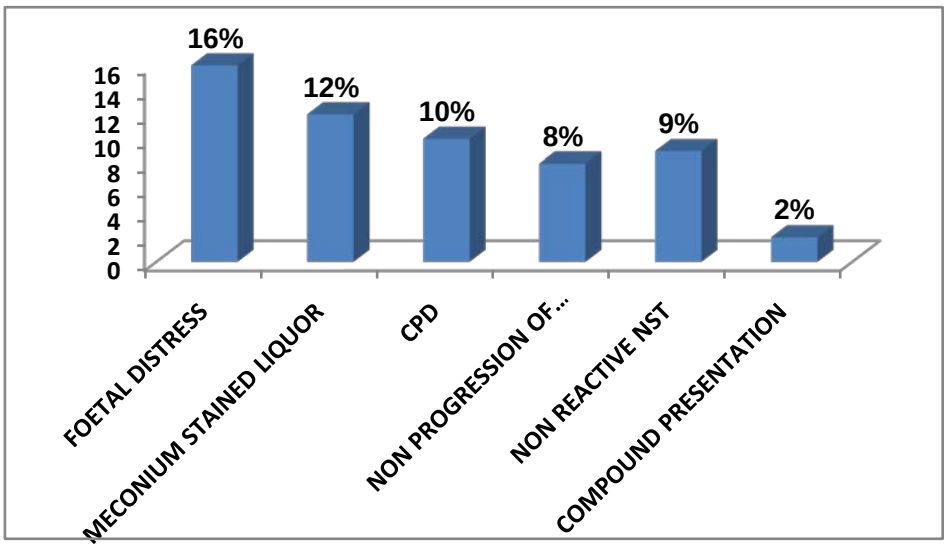

Figure 1: Distribution of Study Population based on Indication for Caesarean

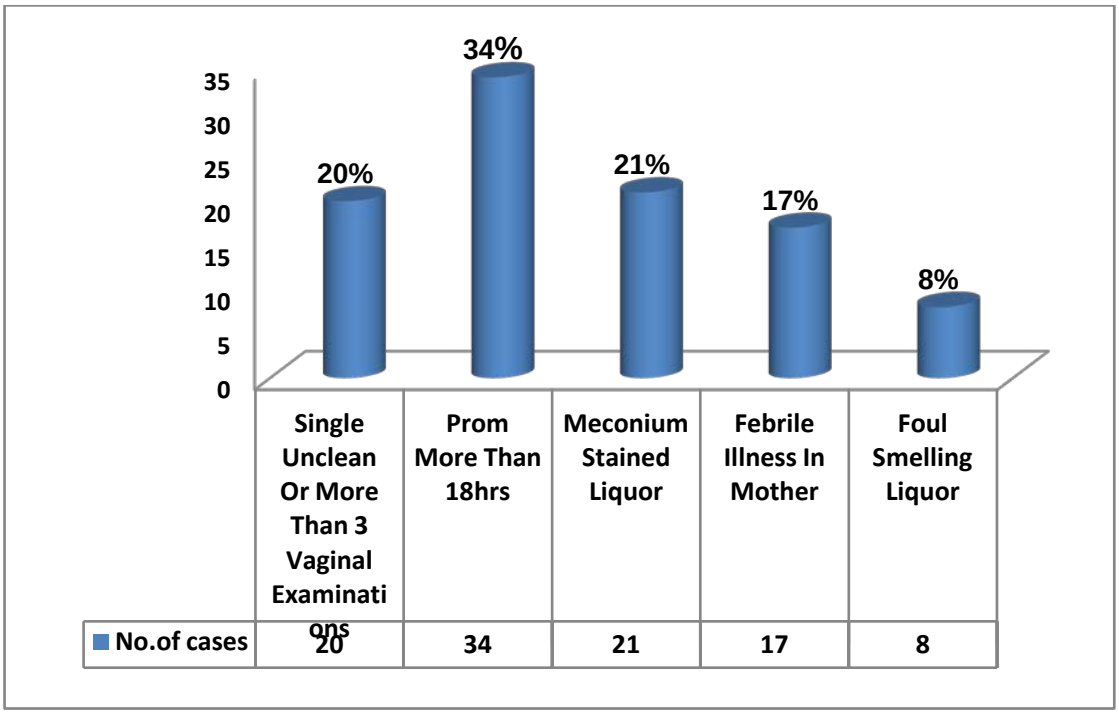

Figure 2: Distribution of Risk Factors for Sepsis

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Lipedema and Postoperative Care

By Dr. Nagila Bernarda Zortea & Eduarda Coan Bis

Abstract- *Introduction:* Liposuction has become one of the main surgical interventions for the treatment of lipedema, being associated with a reduction in clinical symptoms and improvement in patients' quality of life. Postoperative management is recognized as a key factor for maintaining surgical outcomes and preventing complications.

Objective: To review and synthesize strategies used in the postoperative care of liposuction for patients with lipedema, emphasizing the role of compression therapy and manual lymphatic drainage in functional recovery and symptom control.

Methods: A narrative literature review was conducted, considering publications from the past ten years in international scientific databases. Articles addressing postoperative interventions following liposuction for lipedema were included, encompassing physiotherapy protocols, compression therapy, lymphatic drainage, mobilization, and skin care. Studies that did not detail postoperative management or focused on other pathologies were excluded.

Keywords: *lipedema, plastic surgery, liposuction, postoperative care.*

GJMR-I Classification: *NLMC Code: WR 590*



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Lipedema and Postoperative Care

Lipedema E Os Cuidados Pós-Operatórios

Dr. Nagila Bernarda Zortea[α] & Eduarda Coan Bis[σ]

RESUMO- Introdução: A lipoaspiração tem se consolidado como uma das principais intervenções cirúrgicas no tratamento do lipedema, sendo associada à redução dos sintomas clínicos e à melhora da qualidade de vida das pacientes. O manejo pós-operatório é reconhecido como fator determinante para a manutenção dos resultados e prevenção de complicações.

Objetivo: Revisar e sintetizar as estratégias utilizadas no pós-operatório de lipoaspiração em pacientes com lipedema, enfatizando o papel da compressão e da drenagem linfática manual na recuperação funcional e no controle de sintomas.

Métodos: Foi realizada uma revisão narrativa da literatura, considerando publicações dos últimos dez anos em bases de dados científicas internacionais. Foram incluídos artigos que abordassem intervenções de pós-operatório em lipoaspiração para lipedema, contemplando protocolos de fisioterapia, compressão, drenagem linfática, mobilização e cuidados com a pele. Estudos que não detalhavam o manejo pós-operatório ou que tratavam de outras patologias foram excluídos. *Resultados e Discussão:* A análise das publicações evidencia que protocolos integrados de pós-operatório, envolvendo o uso precoce de malhas ou bandagens compressivas, drenagem linfática manual e mecânica, exercícios graduais e cuidados com a pele, promovem redução significativa do edema, da dor, da fibrose e de complicações pós-cirúrgicas. A progressão gradual de mobilizações passivas para ativas, associada à compressão ajustável, potencializa o retorno funcional e favorece a reabsorção de fluidos, diminuindo a dependência de terapias conservadoras.

Conclusão: Apesar da ausência de consenso absoluto sobre o protocolo ideal, a literatura atual demonstra que a integração de compressão e drenagem linfática manual constitui a estratégia mais eficaz no pós-operatório de lipoaspiração em pacientes com lipedema. Protocolos individualizados e multidisciplinares são essenciais para garantir resultados duradouros, alívio dos sintomas e melhoria da qualidade de vida, servindo como referência para a prática clínica e futuras pesquisas.

Palavras-Chaves: Lipedema, cirurgia plástica, lipoaspiração, pós-operatório.

Abstract: Introduction: Liposuction has become one of the main surgical interventions for the treatment of lipedema, being associated with a reduction in clinical symptoms and improvement in patients' quality of life. Postoperative management is recognized as a key factor for maintaining surgical outcomes and preventing complications.

Objective: To review and synthesize strategies used in the postoperative care of liposuction for patients with lipedema, emphasizing the role of compression therapy and manual lymphatic drainage in functional recovery and symptom control.

Methods: A narrative literature review was conducted, considering publications from the past ten years in international scientific databases. Articles addressing postoperative interventions following liposuction for lipedema were included, encompassing physiotherapy protocols, compression therapy, lymphatic drainage, mobilization, and skin care. Studies that did not detail postoperative management or focused on other pathologies were excluded.

Results and Discussion: Analysis of the literature indicates that integrated postoperative protocols comprising early use of compression garments or bandages, manual and mechanical lymphatic drainage, graded exercises, and skin care significantly reduce edema, pain, fibrosis, and postoperative complications. The gradual progression from passive to active mobilization, combined with adjustable compression, enhances functional recovery and promotes fluid reabsorption, reducing dependence on conservative therapies.

Conclusion: Although there is no absolute consensus on the ideal postoperative protocol, current evidence demonstrates that the integration of compression therapy and manual lymphatic drainage is the most effective strategy for postoperative care in patients undergoing liposuction for lipedema. Individualized, multidisciplinary protocols are essential to ensure lasting results, symptom relief, and improved quality of life, serving as a reference for clinical practice and future research.

Keywords: lipedema, plastic surgery, liposuction, postoperative care.

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I. Referencial Teórico

A cirurgia plástica de lipoaspiração em lipedema é crescente e é a cirurgia mais avançada no tratamento da doença. No estudo retrospectivo de 10 anos conduzido por Kruppa et al., que avaliou 106 pacientes submetidas a lipoaspiração multiestágio para lipedema, os resultados evidenciaram melhora clínica significativa após o procedimento. Foram realizados 298 procedimentos com volume médio aspirado de 6.355 ± 2.797 mL, e no seguimento mediano de 20 meses verificou-se redução consistente dos sintomas associados ao lipedema, com diferença estatisticamente significativa ($p < 0,0001$). Além disso, observou-se diminuição relevante na dependência de terapias conservadoras, como a terapia descongestiva complexa, que apresentou queda mediana de 37,5 % na necessidade de utilização ($p < 0,0001$). Essa redução foi mais acentuada em pacientes com índice de massa corporal ≤ 35 kg/m² e nos estádios I e II da doença ($p = 0,0019$), indicando que a cirurgia não apenas atenua sintomas, mas também reduz a

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necessidade de tratamentos conservadores contínuos. Esses achados reforçam a lipoaspiração como uma intervenção eficaz para quebrar o ciclo progressivo do lipedema e melhorar a qualidade de vida das pacientes.[1]

Já no estudo de Kirstein et al., os autores avaliaram auto-relatos de pacientes com lipedema antes e depois da realização de lipossução, com o objetivo de mensurar o impacto da cirurgia na qualidade de vida (QOL) e nos sintomas associados (dor, aspectos psicológicos, sociais). Dos 511 pacientes que responderam ao questionário na apresentação primária, apenas 56 completaram o questionário após a cirurgia, e 34 pacientes preencheram ambos os momentos de avaliação (pré e pós). Os resultados mostram que houve melhora "pertinente" nos sintomas diários da doença, assim como na saúde psicológica dos pacientes após a cirurgia. No domínio da dor, por exemplo, a pontuação média antes da cirurgia era de 6,68 (± 2,29), enquanto no pós-operatório caiu para 4,29 (± 2,16), indicando uma redução importante do desconforto (padrão de desvio incluído no estudo) ^1. Nas escalas de depresión via PHQ-9, a média caiu de 10,84 (± 6,39) no pré para 8,27 (± 6,45) no pós, sugerindo uma melhora no humor ou diminuição do componente depressivo após a intervenção. Quanto aos domínios da qualidade de vida medidos pelo WHOQOL-BREF, os autores relatam ganhos consistentes após a cirurgia. No domínio físico, houve um aumento médio de 54,54 para 60,33; no domínio psicológico, de 51,85 para 57,51; no social, de 63,72 para 68,42; e no ambiental, de 71,85 para 74,50. Esses incrementos sugerem que a lipossução não só alivia sintomas físicos, mas também melhora percepções de bem-estar social, psicológico e de ambiente para os pacientes. Em relação à satisfação, a média obtida entre 56 pacientes após a cirurgia foi de 2,00 (± 0,98) numa escala onde "1 = muito satisfeito" e "5 = piora", o que indica um nível de satisfação entre "muito satisfeito" e "satisfeito" 1. Os resultados globais apontam que a lipossução pode ter um efeito geral positivo na qualidade de vida, tanto na esfera pessoal quanto na profissional, sendo identificada pelos autores como atualmente uma das intervenções mais promissoras no tratamento do lipedema[2].

No estudo retrospectivo de Seefeldt et al. (2023), foram analisados 860 pacientes com diagnóstico de lipedema submetidos à lipoaspiração e comparados com grupo sob tratamento conservador. Os autores observaram redução significativa da dor após o procedimento cirúrgico, com escore médio de NRS de 6,99 no pré-operatório para 2,24 no pós-operatório ($p < 0,05$), enquanto o grupo conservador apresentou média de 6,26, evidenciando superioridade da intervenção cirúrgica. A análise estratificada por estádios da doença mostrou que a intensidade da dor aumentava conforme a progressão do lipedema, porém, a lipoaspiração promoveu melhora significativa em todos os estádios. Além disso, foram relatadas comorbidades frequentes, incluindo queixas menstruais (43%), insônia (36%) e enxaqueca (35%). Os autores destacam que o lipedema não se limita às alterações morfológicas e desproporções corporais, mas associa-se a impactos relevantes na qualidade de vida, especialmente pela dor crônica. Assim, a lipoaspiração demonstrou ser um método eficaz para quebra do ciclo de progressão da doença e alívio sintomático, independentemente do estágio clínico [3].

O estudo de Río-González Á, et al., (2024) focou no período pós-operatório, o protocolo fisioterapêutico adotado no estudo incluiu estímulos cervicais segundo o método de Godoy, com o objetivo de ativar mecanismos de drenagem linfática central e modular o retorno venoso local. Além disso, foi empregada drenagem linfática manual baseada nas manobras de Godoy adaptadas à cirurgia plástica, com ênfase na aplicação suave e sequencial, respeitando as orientações anatômicas e direções de fluxo linfático (proximal para distal) para evitar sobrecarga dos linfáticos remanescentes. Complementarmente, utilizou-se um sistema mecânico de drenagem, com dispositivos intermitentes (pressão sequencial) para estimular o transporte linfático nas regiões operadas, especialmente nas primeiras 24 a 72 horas, quando o edema é mais pronunciado. Esses recursos integrados tinham por finalidade reduzir o acúmulo de fluido intersticial, diminuir o risco de complicações linfáticas e acelerar a normalização tecidual.4

No decorrer dos dias iniciais, o protocolo adotou mobilizações passivas e assistidas de segmentarização leve com o objetivo de evitar aderências cicatriciais, manter a amplitude de movimento articular próxima ao nível funcional e favorecer a movimentação fluida de líquidos nos tecidos subcutâneos. As mobilizações foram graduadas conforme a tolerância do paciente e o tipo de procedimento realizado, respeitando sempre os limites de dor e evitando estiramentos excessivos que pudessem comprometer suturas. Paralelamente, aplicou-se compressoterapia adaptada através de bandagens elásticas de baixa tensão ou malhas compressivas leves, com ajuste progressivo da tensão, para favorecer a reabsorção do edema residual e moldagem dos contornos sem comprometer a perfusão local. A combinação de drenagem manual, mecânica e compressão visa criar um gradiente de pressão que favoreça o fluxo linfático de dentro para fora estratégia que tem respaldo em protocolos de reabilitação pós-cirúrgica e linfática 4.

Em fase intermediária do pós-operatório, assim que permitido pela evolução da cicatrização, introduziram-se exercícios ativos leves e drenagem linfática ativa, com contraturas musculares suaves (por

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exemplo, movimentos cutâneos locais ou contrações isométricas moderadas) para ativar a bomba muscular local como complemento à drenagem passiva. Também se incluíram suas variantes de drenagem com movimento ativo (drainage with movement) para acoplar estímulos mecânicos ao sistema linfático durante a mobilização funcional leve. Durante essa fase, a compressão utilizada foi adaptada para malhas de compressão mais graduadas, sempre sob monitoramento cuidadoso para evitar estrangulamentos ou pontos de isquemia. O objetivo foi transformar o sistema de drenagem passiva predominante para um suporte dinâmico, promovendo remissão gradual do edema residual associado ao movimento e facilitando o retorno funcional precoce 4.

No quarto e último estágio considerado (fase de consolidação), o protocolo enfatizou a transição para drenagem linfática domiciliar, com orientações ao paciente para automassagem suave, uso regular de malhas compressivas levemente graduadas e exercícios ativos funcionais graduais conforme tolerância. A progressão foi guiada por parâmetros objetivos de edema, dor e mobilidade, reduzindo gradualmente a intervenção profissional conforme a melhora evolutiva. Também foi recomendada supervisão fisioterapêutica periódica para ajustes de compressão, técnica de massagem e monitoramento de possíveis complicações linfáticas crônicas. Por meio dessa abordagem escalonada iniciando com drenagem manual, mecânica, compressão e mobilizações passivas, e evoluindo para ativação muscular e cuidados domiciliares o estudo demonstra uma estratégia integrada para otimizar o pós-operatório de cirurgias plásticas, especialmente em relação ao manejo do edema e à preservação da função linfática 4.

Portanto, este estudo fundamenta-se na realização de uma revisão de literatura com o objetivo de evidenciar os principais métodos empregados no pós-operatório de lipoaspiração em pacientes com lipedema, analisando estratégias que contribuem para otimizar a recuperação funcional, reduzir complicações e melhorar a qualidade de vida dessas pacientes. A partir da síntese crítica de publicações recentes, busca-se identificar técnicas fisioterapêuticas, recursos compressivos, protocolos de drenagem linfática e intervenções complementares que têm demonstrado eficácia clínica, oferecendo assim embasamento científico para a prática profissional e direcionando condutas mais seguras e baseadas em evidências.

II. Materiais e Métodos

Esse estudo trata-se de um estudo de revisão de literatura narrativa com enfoque nas intervenções utilizadas no pós-operatório de cirurgias plásticas de lipoaspiração em pacientes com diagnóstico de lipedema. A busca bibliográfica foi realizada entre agosto e setembro de 2025, nas bases de dados PubMed, SciELO, LILACS e Google Scholar, utilizando os descritores controlados em inglês e português, combinados por palavras chaves: “lipedema”, “liposuction”, “plastic surgery”, “postoperative care”. Foram incluídos artigos originais, revisões sistemáticas, ensaios clínicos, relatos de caso e diretrizes publicadas nos últimos 10 anos, em português, inglês e espanhol, que abordassem especificamente os métodos de manejo pós-operatório aplicados a pacientes submetidos à lipoaspiração para tratamento do lipedema.

Como critérios de exclusão, foram retirados da análise artigos duplicados entre as bases, publicações sem acesso ao texto completo, estudos que abordassem apenas aspectos diagnósticos ou cirúrgicos sem detalhamento do manejo pós-operatório, além de trabalhos direcionados a outras patologias que não o lipedema. A seleção inicial dos estudos foi feita pela leitura de títulos e resumos, seguida de análise integral dos textos para verificar a aderência aos objetivos da revisão.

III. Discussão

No estudo de Baumgartner et al., observou-se que os efeitos benéficos da lipoaspiração perduraram por até 12 anos após o procedimento, com manutenção da melhora em parâmetros como dor espontânea, sensibilidade à pressão, edema, equimoses e limitação de movimento.Importante destacar que, no mesmo período, houve uma redução estrutural na utilização de terapias conservadoras, em especial a terapia descongestiva e o uso de roupas de compressão, mantendo-se níveis mais baixos desses tratamentos em comparação aos períodos de 4 e 8 anos pós-cirurgia.Tal achado sugere que a lipoaspiração exerce efeito duradouro não apenas na diminuição dos sintomas associados ao lipedema, mas também na dependência terapêutica convencional (como drenagem linfática e compressão), evidenciando uma possível “liberação” gradual desses pacientes da necessidade contínua desses métodos conservadores. No pós-operatório, a terapia consistiu no uso imediato de malhas compressivas, drenagem linfática manual a partir do segundo dia após a cirurgia e reavaliações com ajuste das vestimentas três semanas depois. Essa abordagem integrada de compressão e drenagem teve papel fundamental na manutenção dos resultados obtidos pela lipoaspiração, proporcionando redução significativa dos sintomas e diminuindo a dependência de terapias conservadoras a longo prazo. 5

De acordo com Río-González et al. (2025), a drenagem linfática desempenha papel fundamental no pós-operatório de cirurgias para tratamento do lipedema, sendo parte central de um protocolo modificado de Terapia Descongestiva Completa

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utilizado pelos autores. Esse protocolo inclui estímulos cervicais, drenagem linfática manual segundo as manobras propostas pelo Método Godoy, drenagem linfática mecânica com o dispositivo RAGodoy®, uso de bandagens compressivas, cuidados com a pele e educação terapêutica. A drenagem linfática manual tem como principal função favorecer a reabsorção do edema cirúrgico, promovendo o desvio do líquido intersticial para vasos linfáticos funcionais e auxiliando na redução da tensão tecidual e na prevenção da fibrose. A associação entre drenagem manual e mecânica intensifica o escoamento linfático, especialmente nos primeiros dias críticos do processo de recuperação. Segundo os achados de Río-González et al., o número de sessões de fisioterapia, nas quais a drenagem é um componente essencial, apresentou relação estatisticamente significativa com a redução da dor ($p = 0,000$), menor ocorrência de complicações ($p = 0,007$) e aumento da mobilidade ($p = 0,003$). Além disso, 47, 24 % das pacientes tornaram-se funcionalmente independentes até o terceiro dia de tratamento. O estudo também destaca que o uso inadequado da terapia compressiva esteve associado ao surgimento de complicações em 36,52 % dos casos, reforçando que a drenagem, quando combinada à compressão, é indispensável para otimizar a recuperação, reduzir seromas e fibroses, minimizar o edema genital e melhorar significativamente a qualidade de vida no pós-operatório 4.

No estudo longitudinal realizado por Dadras et al., intitulado *Liposuction in the Treatment of Lipedema: A Longitudinal Study*, o acompanhamento pós-operatório das pacientes envolveu uma abordagem estruturada e progressiva. Após a lipoaspiração, as pacientes receberam orientações para o uso de roupas de compressão, que foram ajustadas três semanas após o procedimento, quando a redução do edema permitiu a medição adequada. Além disso, a drenagem linfática manual foi autorizada a partir do segundo dia pós-operatório, visando otimizar a reabsorção do edema e prevenir complicações. Essa estratégia terapêutica contribuiu para a redução significativa da necessidade de terapia descongestiva completa (TDC), como evidenciado pela diminuição do escore composto de TDC nas avaliações pós-operatórias. O estudo demonstrou que a lipoaspiração não apenas aliviou os sintomas do lipedema, mas também reduziu a dependência de tratamentos conservadores, melhorando a qualidade de vida das pacientes.6

Amato et al. (2024) discutem a complexidade do lipedema, destacando que o tratamento conservador, especialmente a fisioterapia, desempenha papel central tanto nas fases iniciais quanto no pós-operatório de pacientes submetidas a procedimentos cirúrgicos como a lipoaspiração. Segundo os autores, a Terapia Descongestiva Completa constitui o padrão de cuidado, englobando drenagem linfática manual para estimular o sistema linfático, promover reabsorção do edema e aliviar a dor; bandagens de compressão multicomponente para manter a redução do volume corporal e prevenir o retorno do edema; exercícios terapêuticos que melhoram a mobilidade, fortalecem a musculatura e promovem a circulação; além de cuidados com a pele para prevenir infecções e manter a integridade cutânea. Amato et al. também enfatizam o papel de dispositivos de drenagem linfática mecânica e terapias complementares, como o ultrassom multifocal de baixo índice mecânico, que potencializam a reabsorção de líquidos, aceleram a recuperação pós-operatória e aprimoram os resultados estéticos, destacando a importância de um manejo multidisciplinar, consciente e individualizado para otimizar a qualidade de vida das pacientes.7

IV. Conclusão

Embora ainda não exista consenso absoluto sobre a melhor técnica no pós-operatório de lipoaspiração para pacientes com lipedema, as evidências atuais reforçam a importância da terapia compressiva associada à drenagem linfática manual como estratégias centrais para otimizar a recuperação. Estudos de longo acompanhamento, como os de Baumgartner et al., Dadras et al. e Río-González et al., demonstram que o uso precoce e adequado de roupas de compressão, aliado à drenagem linfática manual e mecânica, contribui significativamente para a redução do edema, da dor, da fibrose e da dependência de terapias conservadoras. Protocolos estruturados, que incluem ajustes progressivos da compressão, sessões regulares de drenagem linfática e acompanhamento individualizado, mostraram-se eficazes em manter os resultados da lipoaspiração a longo prazo e em melhorar a qualidade de vida das pacientes. Dessa forma, mesmo diante da ausência de uniformidade nos protocolos, a literatura aponta que a integração da compressão e da drenagem linfática manual constitui a abordagem mais fundamentada e recomendada para o manejo pós-operatório de pacientes submetidos à lipoaspiração por lipedema.

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Prevalence of Portopulmonary Hypertension in Patients with Chronic Liver Disease; A Cross-Sectional Comparative Study

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Abstract- *Background: Portopulmonary hypertension (PoPH) is an uncommon complication of chronic liver disease (CLD) defined by mean pulmonary artery pressure (mPAP)≥25mmHg at rest, pulmonary vascular resistance (PVR)>240 dyne/sec/cm-5 in the presence of portal hypertension (PoH). Literature on its prevalence amongst CLD patients in Nigeria is scanty.*

Objective: To determine the prevalence of PoPH in patients with chronic liver disease

Methods: Adult patients ⩾18 years) diagnosed of CLD at the University of Calabar Teaching Hospital, Nigeria were recruited over a 10 month period from June 2018- April, 2019. The cases were age and sex matched with controls that had no symptoms or signs of CLD. All patients had trans-thoracic echocardiography (TTE). All parameters for the diagnosis of pulmonary arterial hypertension (PAH) were assessed based on recommendations of the American/ European Echocardiographic Association.

Keywords: *Porto-pulmonary hypertension, chronic liver disease, Trans-thoracic Echocardiography.*

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Prevalence of Portopulmonary Hypertension in Patients with Chronic Liver Disease; A Cross-Sectional Comparative Study

Uchenna Njideofor [α], Uchenna Okonkwo [σ], Victor Ansa [ρ] & Clement Odigwe [ω]

Abstract- Background: Portopulmonary hypertension (PoPH) is an uncommon complication of chronic liver disease (CLD) defined by mean pulmonary artery pressure (mPAP)≥ 25mmHg at rest, pulmonary vascular resistance (PVR)>240 dyne/sec/cm^{-5} in the presence of portal hypertension (PoH). Literature on its prevalence amongst CLD patients in Nigeria is scanty.

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Results: A total of 160 individuals participated in the study (80 cases of CLD and 80 healthy controls). The M: F ratio was 2.8:1. Hepatitis B virus infection was the aetiologic agent of CLD in 73.75% of cases. The mPAP was significantly higher in CLD patients (21.3 ± 10.1mm Hg versus 14.1 ± 7.6mm Hg; p <0.001) although only 5% had estimated mPAP>25mm Hg and 1.25% had PoPH. Thus, the prevalence of PoPH in this study was 1.25%. The estimated PVR and the systolic function of the right ventricle was not significantly different between the cases and the controls (p>0.05).

Conclusion: The prevalence of PoPH is low in our CLD cohort and most of these patients were females with HBV-related CLD.

Keywords: Porto-pulmonary hypertension, chronic liver disease, Trans-thoracic Echocardiography.

I. Introduction

Portopulmonary hypertension (PoPH) refers to the development of pulmonary arterial hypertension (PAH) in the setting of portal hypertension (PoH). This can result in significant right ventricular dysfunction, right heart failure and ultimately death. It is increasingly being recognized in chronic liver disease (CLD) patients because of its associated adverse outcome.[1,2] A study in Romania demonstrated that the prevalence of PoPH in cirrhotic patients was 3.7%.[3] The prevalence of PoPH amongst liver cirrhotic patients in Nigeria has not been formally documented. PoPH is defined by mean pulmonary artery pressure (mPAP)≥ 25mmHg at rest as confirmed by right heart catheterizations, pulmonary vascular resistance (PVR) >240dyne/sec/cm^{-5}, in the presence of PoH.[4,5] However, during the 6th world symposium on pulmonary hypertension (WSPH) in 2018, the value of mPAP was changed to ≥20mmHg.[6] However, mPAP≥ 25mmHg was used for this study. Pulmonary capillary wedge pressure (PCWP) < 15mmHg was previously part of the diagnostic criteria forPoPH but many of these patients may have volume overload and coexisting left ventricular dysfunction associated with cirrhotic cardio myopathy (CCM) which can cause the PCWP to exceed 15mmHg and so, it is no longer included in the diagnostic criteria.[4]

The pathophysio logical mechanism underlying the development of PoPH has not been fully elucidated. It was postulated that PoPH develops because of the increased sheer stress within the pulmonary vascular bed as a result of the hyper-dynamic circulation in CLD patients. In addition, there is increased level of vasoconstrictors such as endothelin-1, angiotensin II and thromboxane B_2 either produced locally within the pulmonary vascular bed or shunted into the pulmonary circulation from the hepatic bed. These substances leads to pulmonary endothelial damage, vascular remodeling and micro thrombosis.[7] PoPH causes increase in right ventricular (RV) afterload leading to RV ischemia, dilatation, and failure.[8] The clinical symptoms of PoPH are non-specific and may include dyspnea, fatigue, chest pain and some patients may not manifest any symptoms.[8]

Transthoracic echocardiography (TTE) is a recommended method to screen for PoPH in CLD.[9,10] Right cardiac catheterization is necessary to confirm the diagnosis but it is invasive and not usually available. Moreover, the procedure requires highly skilled personnel to distinguish PoPH from other cardiovascular derangements associated with CLD.

The impact of PoPH on morbidity and mortality of patients with CLD is independent of the severity of the PoH; while mild PoPH does not significantly influence outcome, moderate to severe PoPH can affect survival in CLD and is considered an absolute contraindication

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to liver transplantation because of increased risk of perioperative mortality.[11] In a study of survival in PoPH, Swanson et al[12] reported that patients who had PoPH and received no treatment for it had a five-year survival of 14% while those who received therapy but no liver transplant had a five-year survival of 45% and amongst patients who had liver transplant, five-year survival for those who received therapy for PoPH was 67% compared to 25% in those who did not receive treatment.

CLD remains one of the leading causes of in-hospital mortality in Nigeria; ranking fifth behind infections, chronic kidney disease, stroke and heart failure.[13,14] However, not much is known about the prevalence of PoPH in these patients.

II. Objective

To determine the prevalence of portopulmonary hypertension in patients with chronic liver disease.

III. Methodology

a) Study Design/Setting

This was a cross-sectional comparative study conducted at the Medical Outpatient Department and Medical wards of the University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria over a 10 month period from June 2018- April 2019.

b) Study Population

Adult patients aged≥ 18 years presenting with features of CLD were consecutively recruited into the study. Subjects with hypertension, diabetes mellitus, retroviral disease and other causes of PoPH such as underlying cardiovascular disease, chronic obstructive pulmonary disease) were excluded from the study. Controls were recruited from members of staff and patient relatives with no evidence of CLD and no underlying risk factor for pulmonary hypertension. The cases were age and sex matched with controls

c) Data Collection

Eighty consecutive adults with diagnosis of CLD (chronic hepatitis, liver cirrhosis and primary liver cell carcinoma) seen at the Gastroenterology unit of UCTH were prospectively recruited from the MOPD and medical wards of UCTH. All patients gave a written informed consent and were assessed with a structured questionnaire (developed for the purpose of this study by the authors) to obtain socio-demographic data (age, gender, alcohol consumption and smoking), symptoms and signs of liver decompensation, symptoms and signs of cardiovascular dysfunction and medication history. The patients were asked to stop medications that might interfere with the study protocol like β-blockers for at least 48 hours before the study. Biophysical, biochemical measurement as well as resting transthoracic echocardiography was done.

d) Diagnostic Criteria for CLD

CLD was diagnosed based on a combination of clinical features such as presence of peripheral stigmata of CLD (palmer erythema, finger clubbing, leuconychia, spider naevi, gynaecomastia in males), jaundice, hepatomegaly, splenomegaly and ascites. Biochemical parameters (deranged liver enzymes, thrombo-cytopenia, hypoalbuminemia and coagulopathy), hepatitis B and C serology, radiological and liver histology if there was no contraindication to liver biopsy. Severity of CLD was assessed using model for end-stage liver disease (MELD) score and categorized into 3 classes; class 1= ≤ 9, class 2 = 10-20, class 3 = > 20.

e) Diagnostic criteria for PoPH using Trans- thoracic Echocardiography

All patients had trans- thoracic echocardiography (TTE). Standard images were obtained through the apical four chamber, parasternal long axis and parasternal short axis views. All parameters were assessed based on recommendations of the American/ European Echocardiographic Association.[15]Right ventricular systolic function was assessed by determination of the tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (PASP) was assessed using tricuspid regurgitation velocity (TRV) and right atrial pressure (RAP)

$$\text{Pulmonary artery systolic pressure} = 4TRV^2 + RAP.$$

Mean PAP was obtained using pulsed wave-doppler study of flow across the pulmonary valve during systole in the parasternal short axis view to determine the right ventricular acceleration time (RV ACT). Mean PAP was calculated using the formula; 79 – (0.45 x RV ACT).

Pulmonary vascular resistance (PVR) was estimated using the TRV and the timed velocity integral of the right ventricular outflow tract (TVI_{RVOT}) in the equation shown below-

$$PVR = TRV/TVI_{RVOT} \times 10 + 0.16.$$

Right ventricular systolic dysfunction was considered present if TAPSE was < 17mm while the normal cut off for TRV was 2.8m/s. The upper limit of PASP was 40mmHg and mPAP was 25mmHg. Increased PVR was considered present when it was greater than 3 Wood units (240dynes.cm/s^2). RV basal dimension was estimated at end-diastole using a RV focused apical 4-chamber view. The RV basal dimension was defined as the maximal short axis dimension in the basal one third of the RV seen on apical 4 chamber view. RV basal dimension greater than 4.2cm was considered abnormal.

f) Sample Size Determination

This was calculated using Cochran's formula[16]n= Z^2Pq/e^2 wheren is the desired sample

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population, Z is the desired confidence interval set at 95%. P is the proportion of patients with PAH in CLD which was 3.7%. [3] d is the desired precision of 5%.The minimum sample size of 54.7 was rounded up 80 after accounting for 10% attrition rate.Eighty patients with CLD and equivalent number of age and sex matched controls were recruited.

g) Statistical Analysis

All data collected were analyzed using the IBM SPSS version 20.0 (SPSS, Inc. Chicago, Illinois, USA). Continuous variables were described using mean and standard deviation while categorical variables were presented as percentages. Chi-square test was used for comparisons between categorical variables while Fishers exact test was used where > 20% of the expected frequencies was <5.The independent sample T-test was used for comparisons between continuous variables. Statistical significance was set at p-value less than 0.05.

IV. Results

a) Demographic Characteristics of Study Population

A total of 160 individuals participated in the study out of which 80 were those with CLD, the remaining 80 were healthy controls. Males were 118 (73.8%) while females were 42 (26.2%) of the population giving a male to female ratio of 2.8:1. The mean age of patients with CLD was similar to the controls (42.0±12.6 years versus 40.8±9.9 years; p = 0.208). Other socio-demographic characteristics are shown in Table 1.

Table 1: Comparison of Socio-Demographic Characteristics of Cases and Controls (N=160)

Variable		Arm of Study			Chi Square Test	p-value
		Cases N=80 n (%)	Controls N=80 n (%)	Total N=160n (%)		
Gender	Male	59(73.8)	59(73.8)	118(73.8)	3.47	0.49
	Female	21(26.2)	21(26.2)	42(26.2)		
Age group/years	18-25	7(8.8)	5(6.3)	12(7.5)	7.430	0.115
	26-34	19(23.8)	19(23.8)	38(23.8)		
	35-44	20(25.0)	22(27.5)	42(26.3)		
	45-54	16(20.0)	19(23.8)	35(21.9)		
	≥55	18(22.5)	15(18.7)	33(20.6)		
Marital status	Single	32(40.0)	27(33.8)	59(36.9)	2.34	0.488
	Married	41(51.3)	49(61.3)	90(56.3)		
	Divorced	1(1.3)	1(1.3)	2(1.3)		
	Widowed	6(7.5)	3(3.7)	9(5.6)		
Education	None	4(5.0)	1(1.3)	5(3.1)	FET,7.435	0.125
	Primary	9(11.3)	3(3.7)	12(7.5)		
	Secondary	29(36.3)	25(31.3)	54(33.8)		
	Post-secondary	34(42.5)	48(60.0)	82(51.3)		
	Post graduate	4(5.0)	3(3.7)	7(4.4)		
Occupation	Unemployed	4(5.0)	5(6.3)	9(5.6)	FET,14.931	0.013*
	Trading	25(31.3)	12(15.0)	37(23.1)		
	Unskilled labour	14(17.5)	9(11.3)	23(14.4)		
	Professional	5(6.3)	14(17.5)	19(11.9)		
	Office worker	21(26.3)	28(35.0)	49(30.6)		
	House wife	0(0.0)	1(1.3)	1(0.6)		
	Student	9(11.3)	5(6.3)	14(8.8)		
	Farmer	2(2.5)	6(7.5)	8(5.0)		
Residence	Urban	51(63.7)	64(80.0)	115(71.9)	5.225	0.022*
	Rural	29(36.3	16(20.0)	45(28.1)		

*SD=Standard Deviation; *=statistically significant FET= Fischer Exact Test*

b) Comparison of RV structure and function amongst CLD patients and Controls

The RV basal dimension was the same in both arms (p = 1.000). The systolic function of the RV was not significantly different in the two arms (p = 0.283). The prevalence of right ventricular systolic dysfunction was 5% among the CLD patients and 1.2% among the

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control subjects and showed no statistically significant difference between the two groups (p=0.124).

Mean PAP was significantly higher among those with CLD compared with the controls (21.3±10.1mmHg versus 14.1±7.6mmHg; p < 0.001). Four (5%) patients among the CLD group had elevated mPAP> 25mmHg with a mean of 26.5 ±3.1mmHg while there was none among the controls. The estimated pulmonary vascular resistance (PVR) was not significantly different between the cases and the controls (p > 0.05). PVR was found to be elevated(285dyne/sec/cm^{-5}) in only one person in the CLD group and none among the controls (Table 2).

Table 2: Relationship between Pulmonary Hypertension and Gender, Age and Aetiology of CLD

Variable	Pulmonary arterial Hypertension			Fisher's exact test	P=value
	Present (4)	Absent (76)	Total (80)		
Gender					
Male	1 (25)	58 (76.3)	59 (73.8)	5.169	0.053
Female	3 (75)	18 (23.7)	21 (26.3)		
Age					
≤ 25	0 (0)	7 (9.2)	7 (8.8)		
26-34	0 (0)	19 (25)	19 (23.8)	4.582	0.188
35-44	0 (0)	20 (26.3)	20 (25)		
45-54	2 (50)	14 (18.4)	16 (20)		
≥ 55	2 (50)	16 (21.1)	18 (22.5)		
Aetiology of CLD					
HBV	3 (75)	56 (73.7)	59 (73.8)		
HCV	1 (25)	12 (15.8)	13 (16.3)	2.061	0.825
Alcohol	0 (0)	7 (9.2)	7 (8.8)		
HBV/HCV	0 (0)	1 (1.3)	1 (1.3)		

c) *Aetiology of CLD in Patients with Elevated mPAP*

Of the 4 patients with mPAP> 25mmHg, the M: F ratio was 1: 3, 75% were HBV positive and 25% were HCV positive. None had significant alcohol use. Three were in MELD class 2 and one in MELD class 1. None was in MELD class 3 (p > 0.05)(Table 3).

Table 3: Comparison of Right Ventricular Structure and Function among Patients with CLD and their Healthy Controls (N=160)

Variable	Cases N=80 (%)	Controls N=80 (%)	Total N=160 (%)	Statistical Test	P-value
RV TAPSE Mean TAPSE±SD (cm)	2.16±0.4	2.2±0.3		T-test,1.663	0.283
RV Systolic function					
Normal	76(95.0)	79(98.8)	155(96.8)	FET	0.124
Abnormal	4(5.0)	1(1.2)	5(3.2)		
mPAP category					
Normal	76(95.0)	80(100.0)	158(97.5)	FET	0.120
Abnormal	4(5.0)	0(0.0)	4(2.5)		
Mean of mPAP±SD (mmHg)	21.3±10.1	14.1±7.6	17.0±12.4	T-test, 3.832	<0.001*
RV basal dimension					
Normal	77(96.3)	76(95.0)	153(95.6)	FET,	1.000
Increased	3(3.6)	4(5.0)	7(4.4)		
Pulmonary vascular resistance					
Normal	79(98.8)	80(100.0)	159(99.4)	FET,1.393	1.000
Elevated	1(1.2)	0(0.0)	1(0.6)		

*SD=Standard Deviation; *=statistically significant; FET= Fischer Exact Test; TAPSE= Tricuspid Annular Plane Systolic Excursion; mPAP= mean Pulmonary Artery Pressure*

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V. Discussion

PoPH is an uncommon component of PAH. In the USA and Europe, the prevalence of PAH ranges from 15-50 per million with PoPH accounting for 5-15% of all cases of PAH.[17] McDonnell et al[18] reported that patients with hepatic cirrhosis had a low prevalence of PAH (0.73%) which corroborates the 1.25% found in this study. However, the prevalence appears to increase with the severity of liver disease and reaches approximately 5% amongst patients on a liver transplantation waiting list.[19]

Although mPAP was significantly higher in patients with CLD compared to those without CLD, the mean PVR showed no significant difference between the two arms of the study. This implies that hyper-dynamic circulation rather than a primary disorder of the pulmonary vessels was the underlying mechanism for the pulmonary hypertension in CLD patients.[7]The most common documented hemodynamic pattern in CLD patients with clinically significant PoH is peripheral vasodilatation and high cardiac output characterized by majorly, an increase in mPAP[8]

HBV is the most common cause of CLD in Nigeria and has been documented in other studies.[20,21] This study showed that more patients with HBV infection compared to HCV infection had PoPH but the difference was not statistically significant. HCV infection has been shown to be associated with decreased risk of PoPH[22] Female gender is associated with increased risk of PoP Hand is similar to findings in this study which documented PAH in more females than males although the difference was not statistically significant. Endogenous sex hormones particularly 17β oestradiol and its metabolites, have been implicated in the development of PAH.[23]

Evaluation of RV systolic function has become increasingly important in CLD patients as detection of subclinical RV dysfunction correlates positively with adverse clinical outcomes.[24]

RV systolic function assessment using TAPSE did not show any significant difference between the study and control groups and is similar to what was previously reported.[25] However, application of a new echo cardiographic modality known as speckle tracking in assessment of RV dysfunction showed significantly reduced RV total longitudinal strain was related to the severity of liver disease.[26]This highlights the usefulness of newer echo cardiographic modalities in evaluation of RV dysfunction in CLD.

Although right atrial catheterization remains gold standard for the diagnosis of PoPH, it is invasive and not readily available in our practice. TTE is a non-invasive, readily available modality for screening PoPH. A Cochrane systematic review and meta-analysis to evaluate the diagnostic accuracy of TTE in patients with PAH reported a sensitivity and specificity of 88% and 90% respectively in those without definitive lung disease.[27]

VI. Conclusion

The prevalence of PoPH was low in our CLD cohort and most of these patients had HBV-related CLD. TTE is a reliable method of screening forPoPHin CLD patients. Further studies are needed to identify symptoms, associations and prognosis of PoPH in our environment where liver transplantation is not readily available

VII. Limitation

Patients without clinically significant portal hypertension were not excluded from the study because of financial constraints in conducting additional investigations necessary to make that diagnosis. Secondly, Right atrial catheterization was not done because of its unavailability.

Declarations

Ethical Approval

Ethical approval was obtained from the Health Research Ethics Committee (HREC) of the University of Calabar Teaching Hospital, Calabar with protocol number UCTH/HREC/33/596

Consent for publication- Not applicable

Data Availability

The data supporting our findings are available from the corresponding author on reasonable request.

Competing interest: The authors declare no competing interests

Funding: None

Clinical Trial Number – Not Applicable.

Authors' Contributions

UN contributed to the design of the study, data collection and analysis and wrote the original manuscript. UO contributed to literature review, discussion and wrote the final draft of the manuscript. VA contributed to concept, study design and supervision of the study. CO contributed to concept and study supervision. All authors read and approved the final manuscript and gave their consent for publication.

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6. Proper permissions must be acquired for the use of any copyrighted material.
7. Manuscript submitted *must not have been submitted or published elsewhere* and all authors must be aware of the submission.

Declaration of Conflicts of Interest

It is required for authors to declare all financial, institutional, and personal relationships with other individuals and organizations that could influence (bias) their research.

Policy on Plagiarism

Plagiarism is not acceptable in Global Journals submissions at all.

Plagiarized content will not be considered for publication. We reserve the right to inform authors' institutions about plagiarism detected either before or after publication. If plagiarism is identified, we will follow COPE guidelines:

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- Words (language)
- Ideas
- Findings
- Writings
- Diagrams
- Graphs
- Illustrations
- Lectures



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- Printed material
- Graphic representations
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- Electronic material
- Any other original work

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1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

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Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

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Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.



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Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.



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6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

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To make a paper clear: Adhere to recommended page limits.



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Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



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Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

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Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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