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52

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## Original Articles

Short-Term Training of Family Medicine Teams on Cardiovascular Risk Assessment and Management - Effects on Practice and Outcomes

Determination of ELISA Reactive Mumps IgG Antibodies in MMR Vaccine Recipients in Comparison with MMR Vaccine Naive Children: a Cross Sectional Study

Team Based Learning in Pathology: Lessons Learned From a Pilot Study

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## Original Articles

- Short-Term Training of Family Medicine Teams on Cardiovascular Risk Assessment and Management - Effects on Practice and Outcomes** ..... 165-173  
Savka Štrbac, Nataša Pilipović Bročeta, Nevena Todorović, Vesna Vujić Aleksić, Siniša Stević, Amela Lolić, Alen Šeranić, Duško Vulić, Dubravko Bokonić, Ranko Škrbić
- Determination of ELISA Reactive Mumps IgG Antibodies in MMR Vaccine Recipients in Comparison with MMR Vaccine Naive Children: a Cross Sectional Study** ..... 174-180  
Riya Gupta, Naveen Saxena, Parul Gupta
- Team Based Learning in Pathology: Lessons Learned From a Pilot Study** ..... 181-186  
Shruti Bhargava, Mohnish Grover, Neeraj Verma, Monica Jain
- Effects of the Ultra-Short-Acting Beta-Blocker Esmolol Infusion on Cardiovascular Parameters and Quality of Postoperative Recovery in Patients Scheduled for Elective Plastic Surgery** ..... 187-192  
Dragana Lončar-Stojiljković
- Role of Multidetector Computed Tomography (MDCT) in Evaluation of Lung Nodule with Histopathological Correlation** ..... 193-198  
Jagmohan Gupta, Parul Gupta, Suresh Chandra Gupta, Amit Tak
- The Effect of Presence of *Helicobacter pylori* on the Severity and Clinical Course of Rosacea** ..... 199-204  
Đuka Ninković Baroš, Vesna Gajanić, Nevena Kutlija, Igor Sladojević, Svetozar Krivokuća
- The Clinical and Pathological Characteristics and Survival of Patients With Advanced Ovarian Cancer** ..... 205-210  
Miroslav Popović, Tanja Milić-Radić, Arnela Cerić-Banićević
- Effect of Cardiovascular Training on Functional Capacity in Post-Acute Rehabilitation of COVID-19 Patients** ..... 211-214  
Dragana Dragičević-Cvjetković, Drinka Stevandić

## Review Article

- Faecal Transplantation and *Clostridioides difficile* Infection** ..... 215-223  
Darija A Knežević, Miroslav Petković

## Professional Articles

- A Step Today Can be a Giant Leap Tomorrow - COVID-19 Management Lesson From the Developing World** ..... 224-229  
Sudhir Bhandari, Mohnish Grover, Shruti Bhargava
- Analysis of the Emergency Medical Service Call Centre Actions in Patients with Cardiac Arrest** ..... 230-234  
Radojka Jokšić-Mazinjanin, Aleksandar Đurićin, Milena Jokšić Zelić, Predrag Šaponja, Siniša Saravolac, Zoran Gojković, Velibor Vasović, Momir Mikov

## Case Report

- Rare Concomitant Myxoid and Cystic Degeneration of Uterine Leiomyoma - Case Report** ..... 235-238  
Igor Samardžiski, Gordana Petrushevska, Slagjana Simeonova Krstevska, Iva Paneva, Vesna Livrinova, Irena Todorovska, Maja Pejkovska Ilieva, Sasho Dimitrovski, Katerina Nikoloska

- Instructions to Authors** ..... i - ii



# Short-Term Training of Family Medicine Teams on Cardiovascular Risk Assessment and Management - Effects on Practice and Outcomes

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## Abstract

**Background/Aim:** The prevention of cardiovascular risk factors and cardiovascular disease management contributes to the cardiovascular mortality reduction. The effects of these activities have been measured by quality indicators. The aim of this study was to determine the effects of family medicine team training workshop and implementation of clinical guidelines on the cardiovascular risk factors and diseases management in primary health care in the Republic of Srpska/Bosnia and Herzegovina.

**Methods:** The “CardioVascular Risk Assessment and Management” study included a sample of 373 teams from 41 primary health care centres trained to provide adequate services and to compare the quality of cardiovascular risk management before and after the training workshop and implementation of clinical guidelines. The comparison was based on nine project defined performance indicators related to hypertension, type 2 diabetes mellitus, hyperlipidaemia, tobacco smoking and obesity.

**Results:** Significant improvements were observed in six indicators after the training workshop and implementation of guidelines. Target values for blood pressure and HbA1c were achieved in over 80 % of patients (82.12 ± 15.81 vs 84.49 ± 12.71 and 84.49 ± 12.71 vs 85.49 ± 24.55; before and after the training workshop, respectively), while the target values for LDL cholesterol were achieved in 54.98 % ± 20.33 before and 57.64 % ± 16.66 after the training workshop. The number of teams that had less than 20 % of recorded data significantly decreased after the training workshop and guidelines implementation, and adequate recording of all indicators was improved.

**Conclusion:** The training workshop of family medicine teams and implementation of clinical guidelines resulted in significant quality improvement of cardiovascular diseases management in primary health care.

**Key words:** Family medicine team; Clinical guidelines; Cardiovascular risk factors; Quality indicators; Prevention.

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## Introduction

Chronic non-communicable diseases account for 74 % of deaths worldwide, of which 31 % has been caused by cardiovascular diseases (CVD).<sup>1,2</sup>

In the Republic of Srpska (RS), Bosnia and Herzegovina (B&H), the CVDs cause 47.3 % of total mortality.<sup>3</sup> The RS is one of the two constitutive

entities in B&H with the total population of 1 170 342 people.<sup>4</sup> Based on Low on Health Protection of the RS, the primary health care (PHC) is the foundation of health care system which is organised on municipality level and regulated, controlled and conducted by Ministry of Health and Social Welfare of the RS and financed by Health Insurance Fund of the RS.<sup>5</sup> Measures of health promotion, disease prevention, early detection and timely treatment at PHC level should be able to solve most of health problems and address most of population health requirements. The main pillar of PHC in the RS is family medicine team (FMT). FMT is the basic organisational form of delivering PHC, and basic organisational structure that holds most activities at the PHC level. FMTs can be organised as freestanding FMT (independent legal entity; public or private), group practice or FMT within a PHC Centre (PHCC) as its internal organisational unit. FMT consists of a general practitioner with specialisation in family medicine, or specialist in other branches of medicine who have completed program of additional education in family medicine and two nurses who have completed program of additional nursing education in family medicine. FMTs are primary “gateway” for citizens/patients or entry points into the health system. FMT works in family medicine ambulance which is a PHC setting integrated into and operate within PHCC. PHCC (*Dom Zdravlja*) - is a public health institution that organises its work according to FM model on municipality level. So, the total number of PHCC in is 54 corresponding to the number of municipalities in the RS. First contact with health system or an entry point for citizens is operated through FMT. The total number of FMT in RS is 698, and one FMT can register from 500 to 830 families, representing between 1,500 and 2,500 inhabitants. The FMT's are locally organised and its number and composition, as well as the corresponding municipality population, remain rather stable over the long period of time.

The association of family practitioners has played a great role in the education and implementation of clinical guidelines as two most important activities for achieving better health outcomes.<sup>6,7</sup> Cardiovascular risk factors are classified as modifiable and non-modifiable risk factors.<sup>8</sup> It is well known that prevention of modifiable risk factors and management of patients with CVD contribute to the reduction of CVD mortality. The effects of

these activities have been measured by quality indicators.<sup>7,8</sup> A systematic review of 38 studies showed the role of educational intervention in improvement of CVD prevention, guideline implementation and clinical outcome.<sup>6</sup> Audit based education in the United Kingdom and multimodal intervention in the United States of America and Italy has resulted in better achieving of target values for blood pressure and cholesterol. The analysis recognised a need for complex approach in preventing multiple risk factors in patients since guidelines dissemination alone had not improved adherence nor clinical.<sup>6</sup>

The project “Reducing Health Risk Factors in Bosnia and Herzegovina – Developing and Advancing Modern and Sustainable Public Health Strategies, Capacities and Services to Improve Population Health in Bosnia and Herzegovina” was developed jointly by the Swiss Agency for Development and Cooperation (SDC), the World Health Organisation (WHO) Regional Office for Europe, the WHO Country Office in B&H and the health authorities in B&H (2013-2019).<sup>9</sup> The main goal of this project was a comprehensive intervention for improving CVD prevention and standardisation of “CardioVascular Risk Assessment and Management” (CVRAM) in FM. The project activities included the development of clinical guidelines, short term training workshop and determination of indicators for evaluation of educational effects (baseline assessment and post CVRAM training evaluation). There have been several clinical guidelines developed within the project: Guideline for Prevention and Treatment of Hypertension, Guideline for Prevention and Treatment of Diabetes Mellitus and Cardiovascular Diseases, Guideline for Prevention and Treatment of Hyperlipidaemia, Guideline for Prevention of Child Obesity, Guideline for Prevention of Adult Obesity, Guideline for Promotion of Physical Activity, and Guideline for Smoking Cessation. After the development and full adoption, the guidelines were used as educational tools for FMT training workshop process.

The aim of this study was to evaluate the effects of short training workshop of FMTs and implementation of clinical guidelines on the management of patients with modifiable cardiovascular risk factors, CVDs and type 2 diabetes mellitus (T2DM) in primary health care centres in the RS/B&H.

## Methods

### Study participants

The study included 373 FMTs from 41 primary healthcare centres (367 FMTs from 35 public PHCC and 6 FMTs from 6 private healthcare centres). The inclusion criteria for FMTs participation in the project were as follows: completed CVRAM training, implementation of clinical guidelines, population registered to FMT before 1 July 2015, and all data available in patient electronic medical records.

There were no ethical issues in this research, so there was no need for formal approval by the ethics committee. The values of the quality indicators were extracted from the electronic database of the primary health care. The data on FMTs and observed registered population were anonymous.

### Intervention

The CVRAM training workshop of FMTs was implemented by Departments of Family Medicine of two faculties of medicine in RS; Banja Luka Faculty of Medicine, University of Banja Luka, and Foča Faculty of Medicine, University of Eastern Sarajevo. The trainings consisted of two days educational program on the implementation of clinical guidelines for cardiovascular risk assessment, planning of prevention activities and education on appropriate recording of data in electronic medical records. The CVRAM training workshops were held in the three teaching cities, Banja Luka, Doboje and Foča, representing adequate territorial coverage of the country, in a period of one year; from 30 June 2016 to 1 July 2017. The training workshop was conducted by a defined number of trained family medicine teaching experts to ensure standardisation.

### Data collection

Medical documentation of all patients in family medicine was kept as a patient electronic medical records in a web based information system for family medicine and stored centrally in the electronic database. For the purpose of this study specific data of female and male patients were extracted: the average of the last two measured values of blood pressure (BP) in patients with hypertension, last measured glycated haemoglobin (HbA1c) value in patients with T2DM, last measured low-density lipoprotein (LDL) cholesterol

value in patients with hyperlipidaemia (LDL cholesterol  $\geq 4.1$  mmol/L), body weight in patients with body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup> and history of tobacco smoking. The data on diagnosis for hypertension, T2DM, hyperlipidaemia and obesity were based on physician diagnosis according to ICD10 coding.

The reliability of the data was ensured by comparison with the data from the registers for chronic diseases at the level of the FMT: (1) Registry of patients with hypertension, (2) Registry of patients with T2DM (3) Registry of patients with hyperlipidaemia, (4) Registry of obese patients (BMI  $\geq 30$  kg/m<sup>2</sup>), (5) Registry of patients with hyperlipidaemia and T2DM who were prescribed statin therapy, (6) Registry of patients  $\geq 18$  years of age with a recorded tobacco smoking status.

Existing data information system was designed for primary healthcare system of the Republic of Srpska and it can easily provide the extraction of all needed data for further analysis including the data which can serve as specific indicators for this study.

### Measures

Before FMT training workshop nine quality indicators were developed by the project. The evaluation was based on these previously identified indicators that were measured as process indicators and outcome indicators (Table 1).

### Observation period

The baseline assessment was performed one year before the CVRAM training workshop and guidelines implementation (1 July 2015 – 30 June 2016) and post training and guidelines implementation evaluation was performed one year after the CVRAM training workshop was finished (1 July 2017- 30 June 2018).

### Statistical analysis

The statistical analysis was done by means of statistical software package, SPSS Statistics v. 18, USA. Most of the variables were presented as frequency of certain categories, while statistical significance of differences was tested with the Chi-squared test or two sample t-test of proportion. The most important results were presented by mean percent values  $\pm$  standard deviations (SD). The relationship between the two variables was established by using a Pearson correlation analysis. Probability ( $p < 0.05$ ) was chosen as a limit for statistical significance between two groups.

**Table 1:** The list of CVRAM indicators

No	Indicator	Type	Calculation formula
1.	Percentage of hypertensive patients with BP measurements recorded within the last 12 months	process	Nominator is the number of patients with hypertension who had a record of BP measurement in last 12 months. Denominator is the number of patients with hypertension.
2.	Percentage of patients with hypertension with recorded value of BP $\geq$ 140/90 mmHg in last 12 months	outcome	Nominator is the number of patients with hypertension who had a record of BP measurement in last 12 months and the value of that BP was $\geq$ 160/100 mmHg. Denominator is the number of patients with hypertension who had a record of BP measurement in last 12 months.
3.	Percentage of HbA1c measurements among T2DM patients in last 12 months	process	Nominator is the number of patients with T2DM who had a record of HbA1c measurement in last 12 months. Denominator is the number of patients with T2DM.
4.	Percentage of patients with T2DM with measured HbA1c level $\geq$ 7 % in last 12 months	outcome	Nominator is the number of patients with T2DM who had a record of HbA1c measurement in last 12 months and value of HbA1c was $\geq$ 9.0 %. Denominator is the number of patients with T2DM who had a record of HbA1c measurement in last 12 months.
5.	Percentage of patients with hyperlipidaemia with recorded LDL cholesterol measurement in the last 12 months	process	Nominator is the number of patients with hyperlipidaemia who had a record of LDL cholesterol measurement in last 12 months. Denominator is the number of patients with hyperlipidaemia.
6.	Percentage of patients with hyperlipidaemia with recorded LDL cholesterol $\geq$ 3 mmol/L in the last 12 months.	outcome	Nominator is the number of patients with hyperlipidaemia who had a record of LDL cholesterol measurement in last 12 months and value of LDL cholesterol $\geq$ 4.1 mmol/L. Denominator is the number of patients with hyperlipidaemia who have a record of LDL cholesterol measurement in last 12 months.
7.	Percentage of patients with T2DM with recorded LDL cholesterol $\geq$ 3 mmol/L who were prescribed statin therapy in the last 12 months	process outcome	Nominator is the number of patients with T2DM who had measured LDL cholesterol greater than 4.1 mmol/L in the last 12 months and who were prescribed statins. Denominator is the number of patients with T2DM whom had measured LDL cholesterol $\geq$ 4.1 mmol/L in the last 12 months
8.	Percentage of patients older than 18 with recorded tobacco smoking status	process	Nominator is the number of patients older than 18 with recorded tobacco smoking status. Denominator is a number of patients older than 18.
9.	Percentage of body weight measurements recorded in the last 12 months with obese patients (BMI $\geq$ 30 kg/m <sup>2</sup> )	process	Nominator is the number of patients with obesity who had a record of body weight in the last 12 months. Denominator is the number of obese patients (BMI $\geq$ 30 kg/m <sup>2</sup> )

\*All indicators were calculated in relation to the registered population in FMT, older than 18 years. CVRAM: Cardiovascular Risk Assessment and Management, BP: blood pressure; LDL: low-density lipoprotein, T2DM: type 2 diabetes mellitus, BMI: body mass index.

## Results

Out of a total of 698 FMTs, 483 of them completed the CVRAM training workshop. However, only 373 FMTs (53.44 %) were included in the evaluation due to the accuracy of data provided from their data electronic system.

### Baseline assessment

The baseline assessment showed that many of process indicators were not accomplished in a great percentage of measures. Monitoring of hypertensive patients and recording of BP values were neither properly recorded nor recorded at all in the patient's electronic medical records.

Monitoring of T2DM patients was poor in more than a half of the FMTs, with inadequate recording of HbA1c and LDL values. There was a small percentage of recorded body weight values of obese patients in the majority of FMTs. The same was confirmed for recording the patient's tobacco smoking status. The values of these indicators are shown in Table 2.

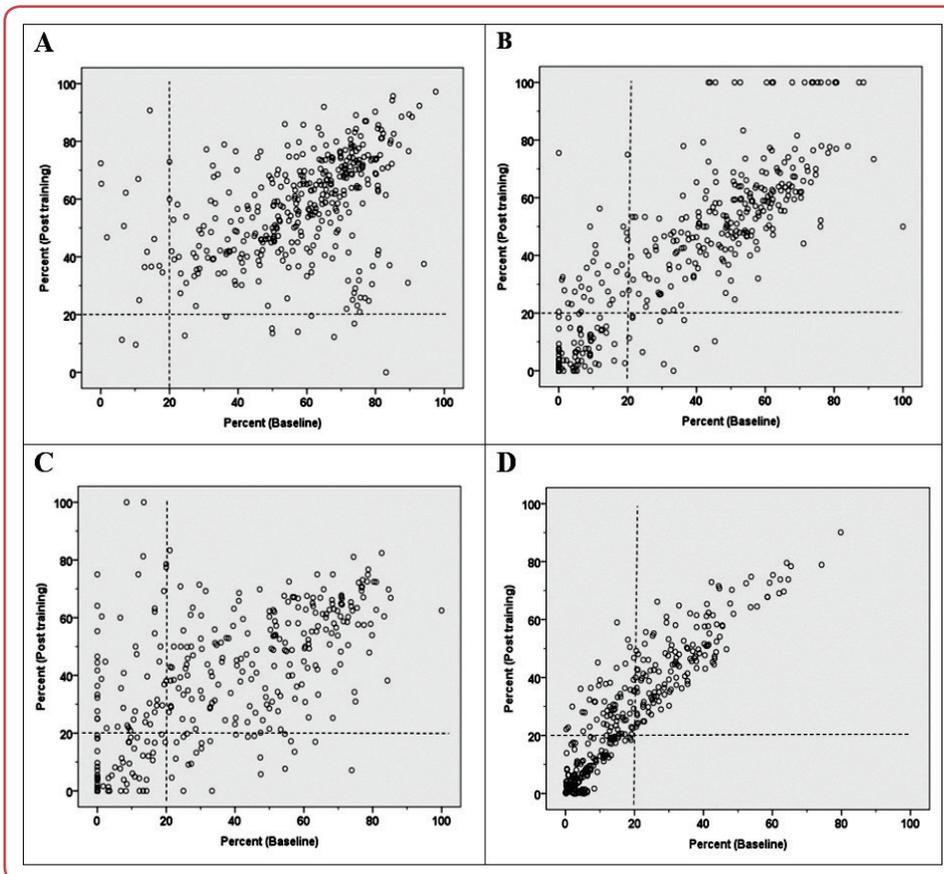
### Post training evaluation

The significant improvement was confirmed for six out of nine analysed indicators. A slight comparative difference in terms of deterioration was

**Table 2:** Trend of indicators before and after CVRAM training workshop

No	Indicator	Baseline N (%)	Post training N (%)	Improvement	p value
1.	Percentage of hypertensive patients with BP measurements recorded within the last 12 months	124931 (57.40)	125655 (57.06)	NO	0.001
2.	Percentage of hypertensive patients with recorded value of BP $\geq$ 160/100 mmHg in last 12 months	74112 (17.88)	77687 (15.51)	YES	0.001
3.	Percentage of HbA1c measurements among T2DM patients in last 12 months	26966 (36.43)	30316 (41.39)	YES	0.001
4.	Percentage of patients with T2DM with measured HbA1c level $\geq$ 9.0 % in last 12 months	10709 (17.36)	13408 (14.51)	YES	0.001
5.	Percentage of patients with hyperlipidaemia with recorded LDL cholesterol measurement in the last 12 months	36905 (34.09)	55496 (36.50)	YES	0.001
6.	Percentage of patients with hyperlipidaemia with recorded LDL cholesterol $\geq$ 4.1 mmol/L in the last 12 months	16448 (45.02)	24687 (42.36)	YES	0.001
7.	Percentage of patients with T2DM with recorded LDL cholesterol $\geq$ 4.1 mmol/L whom were prescribed statin therapy in the last 12 months	1433 (64.48)	1797 (62.76)	NO	0.320
8.	Percentage of patients older than 18 with recorded smoker's status	567732 (17.92)	570874 (26.70)	YES	0.001
9.	Percentage of body weight measurements recorded in the last 12 months with obese patients (BMI $\geq$ 30 kg/m <sup>2</sup> )	26997 (36.79)	34432 (29.19)	NO	0.001

CVRAM: CardioVascular Risk Assessment and Management, BP: blood pressure; LDL: low-density lipoprotein, T2DM: type 2 diabetes mellitus, BMI: body mass index.



**Figure 1:** The number of FMTs that recorded the BP (A), HbA1c (B), LDL cholesterol (C) and tobacco smoking status (D) in a range less than 20 % before and after CVRAM training. FMT: family medicine team; BP: blood pressure; LDL: low-density lipoprotein; CVRAM: CardioVascular Risk Assessment and Management.



**Table 3:** The achievement of target values for outcome indicators - comparison before and after CVRAM training workshop

Indicator	% of patients with target values ( $\pm$ SD)		p value
	Baseline	Post training	
BP < 140/90 mmHg	82.12 $\pm$ 15.81	84.49 $\pm$ 12.71	0.001
HbA1c < 7 %	82.64 $\pm$ 26.75	85.49 $\pm$ 24.55	0.001
LDL cholesterol < 3 mmol/L	54.98 $\pm$ 20.33	57.64 $\pm$ 16.66	0.001

CVRAM: CardioVascular Risk Assessment and Management, BP: blood pressure; LDL: low-density lipoprotein, BMI: body mass index

found for statin prescribing in group of T2DM patients with high LDL values (indicator 7), but this difference was not statistically significant ( $p = 0.320$ ).

The BP recording for hypertensive patients has been confirmed in approximately equal percentage before and after CVRAM training (57.40 % vs 57.06 %). Recording of HbA1c for T2DM patients was improved by 4.96 %, the LDL recording was improved by 2.42 %, while the body weight measurement recording for obese patients was decreased by 7.6 % (Table 2).

### Process indicators

In order to get more precise insight on process improvement the focus of analysis was put on the number of FMTs that had less than 20 % of recorded data. Having done so, the number of FMTs that had recorded BP values in less than 20 % at the baseline was 18 (5.36 %), but after the training that number decreased to 11 (2.94 %). The rest of FMTs remained within the values above 20 % (Figure 1A). The HbA1c recording in patients with T2DM was improved in 22 (5.9 %) FMTs. There were 124 (33.24 %) FMTs in the range from 0 to 20 % before the training, and 102 (27.34 %) FMTs after the training (Figure 1B). The LDL cholesterol recording values in patients with hyperlipidaemia was improved in 24 (6.43 %) FMTs; as many as 139 (37.26 %) FMTs had less than 20 % of recorded data at the baseline, but after the training the number of FMTs in this range decreased to 115 (30.83 %; Figure 1C). The recording rate of tobacco smoking status in the adult population was improved after education in 62 (16.62 %) FMTs; before education 228 (61.12 %) FMTs had recorded this values in less than 20 %, and after the training that number decreased to 166 (44.50 %; Figure 1D).

## Discussion

The cardiovascular risk factors mentioned in this study have been listed by the American Society for Preventive Cardiology as ten essential things to be known about CVD risk factors, emphasising the key activities for health professionals at primary health care level who are facing the fact that many patients have multiple cardiovascular risk factors.<sup>10</sup> Based on official documents issued by healthcare authorities in our country, the FMTs were obligated to register their patient population into an electronic medical record system.<sup>11</sup> This prompted the need for assessment of the extent of control and quality of care of CVD risk factors in the registered population and keep registries according to CVD risk factors as well. These registries have provided the first check up and follow up of patients who were informed adequately about healthy lifestyles leading to better CVD risk factors control. Registries of patients with hypertension, DM and CVD risk factors have been included and automatically updated in electronic medical records, serving as a tool for follow up of those patients.

The implementation of clinical guidelines on non-communicable chronic diseases in RS started in 2004.<sup>11</sup> Since that time there have been several updates of clinical guidelines based on latest recommendations issued by relevant professional associations. The CVRAM training workshop launched additional update of guidelines on hypertension, DM and hyperlipidaemia.<sup>12-14</sup> The importance of guidelines implementation at primary and secondary level in RS/B&H was investigated in the past as well.<sup>7,15</sup>

The results of this study showed a decreasing number of hypertensive patients with irregular BP level after CVRAM training workshop. Majority of hypertensive patients had a well-controlled BP and the percentage of those with achieved target values was significantly increased after the training workshop of FMTs. Similarly, Aguilar-Palacio et al found in their study that more than a half of patients had a regular BP, but the increase in BMI worsened the BP control.<sup>16</sup>

The target value for HbA1c was achieved in over 80 % of patients. The percentage of patients with hyperlipidaemia with recorded LDL cholesterol measurement in the last 12 months increased

and the percentage of patients with hyperlipidaemia with recorded LDL cholesterol  $\geq 4.1$  mmol/L in the last 12 months decreased after the training workshop. These improvements showed that the CVRAM training workshop encouraged the FMTs to implement guidelines, making a unique approach to patients with cardiovascular risk. Nonetheless, the percentage of patients treated in accordance with the guideline on hyperlipidaemia was below expectation. Klimchak et al found that more than a half of sample population was not receiving statin therapy despite of very high burden of atherosclerotic CVD in the United States.<sup>17</sup> In another study dyslipidaemia was confirmed as the most prevalent risk factor for diabetic patients with consequently increased number of those on statin therapy, but normal LDL and HbA1c levels had been achieved in about one third of patients, suggesting the high correlation between DM diagnosis and low dyslipidaemia control.<sup>16</sup> This is a challenging task for family physicians worldwide. Low income countries have been facing low socioeconomic status, urbanisation process, specific cultural context and social determinants such as poverty, illiteracy, and ignorance as well as the challenges of traditional medicine. Majority of population in high income countries have urban lifestyles, facing multiple modifiable risk factors and CVD. There is a global need for better compliance with recommendations and improved guidelines adoption.<sup>18-20</sup>

Concerning body weight measurement in this study, a need for improvement in recording of obese patients with measured body weight values has been recognised before and after the training workshop. Training strategies should be adjusted to different capabilities of the FMTs, following the obesity guideline implementation.<sup>21</sup>

Educational activities had an important role in the recording of tobacco smoking, much like in Spain where primary health professionals improved screening of cardiovascular risk factors after educational intervention. They increased the recording of risk factors and thus improved clinical outcomes.<sup>22</sup> It is necessary to continue with the education on smoking cessation including both professionals and patients according to the guidelines.<sup>23</sup>

The CVRAM training resulted in better implementation of guidelines and this finding is similar to the results of the systematic review of 38 randomised control trials showing better professional adherence to CVD guidelines.<sup>6</sup> Gil-Guillén et al found improvement in cardiovascular risk factors screening after educational intervention at primary health care level.<sup>22</sup> This study clearly showed that educational intervention with full implementation of clinical guidelines was particularly effective for the FMTs with low achievements of indicators at baseline assessment. These FMTs really gained from this intervention and it has significantly influenced their approach to cardiovascular risk factors and chronic diseases management. The results of Egan et al showed improved BP control after medical staff training in hypertension management. The BP values in their sample declined in the six months period and 74.3 % of patients had better hypertension control.<sup>24</sup> The recording of BP, HbA1c, LDL, and BMI values, tobacco smoking status, as well as the implementation of training programmes and clinical guidelines are a good basis for planning of preventive actions and improvements in the management of cardiovascular risk factors and CVDs.<sup>25</sup> Continuing medical education has been implemented widely, but modifications of the training design should be considered.

The major limitation of this study is that not all of the observed FMTs were trained at the same time. The training process lasted one year and the FMTs that were trained at the beginning of training process had almost two years for the implementation of the acquired knowledge and recommendations, while the FMTs that were trained at the end of the training period had only one year for those activities. Comparison between subgroups was not performed in this study. The study was conducted without control group which was another limitation. A different study design, such as a quasi-experimental study with control group, could improve the strength of these findings. However, the study has several strengths: this is the first study, to our knowledge, to evaluate the effects of FMT short training workshop on the cardiovascular risk assessment and management of patients in primary healthcare centres in the RS/B&H, and second, the study sample size was large enough to enable generalisation of study findings.

## Conclusion

The CVRAM training workshop and the implementation of clinical guidelines significantly contributed to the better recording of process indicators, as well as to achieving the target values for BP, HbA1c and LDL. The training workshop has primarily helped the poorly organized FMTs, those that had low indicators values before CVRAM training workshop. Short-term training workshop of FMTs on cardiovascular risk assessment and management can improve their practice and healthcare outcomes for patients with CVD and cardiovascular risk factors.

Training programs should be targeted and tailored according to the needs and achievements of specific groups of FMTs and based on updated guidelines. Universal education for all FMTs as a solely intervention, can lead to small changes in quality assurance, but for more effective results, it may require the combination of different approaches for considerable quality improvement.

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## Conflict of interest

None.

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# Determination of ELISA Reactive Mumps IgG Antibodies in MMR Vaccine Recipients in Comparison with MMR Vaccine Naive Children: a Cross Sectional Study

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## Abstract

**Background/Aim:** Mumps is a vaccine preventable infectious disease characterised by parotitis. In India mumps vaccines are not currently used under National Immunisation Programme (NIP). Waning of vaccine-induced immunity is considered to play a central role in the re-emergence of mumps. The comprehensive data on the seroepidemiology of measles, mumps, and rubella (MMR) as well as studies which compare the antibody titre among mumps vaccine naive and mumps vaccinated children are lacking. The aim of this study was to estimate and compare mumps specific antibody titre in children with and without MMR vaccine.

**Methods:** In 2019/2020, blood samples were collected from 100 healthy children attending immunisation clinic in Government Medical College Kota and associated J K Lon Maternal and Child care hospital Kota. The samples were investigated for MMR IgG antibodies using ELISA.

**Results:** Out of total 100 children included in the study, 32.27 % vaccinated and 4.83 % non-vaccinated children were positive for mumps IgG antibody in the age group of 6 months to 6 years of age. Children aged 6 to 12 years, vaccinated and non-vaccinated, had 31.57 % and 26.57 % positivity, respectively. The seroprevalence of measles, mumps and rubella antibodies among 50 MMR vaccinated children were 94 %, 64 %, and 96 %, respectively. A high measles and rubella seroprevalences were observed among all children age groups, suggesting an effective control program, while the mumps seroprevalence decreased significantly with age.

**Conclusion:** The maximum vaccine effectiveness against mumps for 2 doses of MMR vaccine is  $\approx 96$  %. The herd immunity threshold to block mumps virus transmission is  $\geq 86$  %. In this study only 64 % of the vaccinated children were found to have IgG mumps antibodies. In view of morbidity following mumps infection there is a need to incorporate mumps vaccine along with measles and rubella vaccine in the NIP instead of MR.

**Key words:** Antibody; Measles; Mumps; Vaccination.

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## Introduction

Mumps is a contagious disease characterised by parotitis. Although perceived as a benign childhood disease, mumps was the leading cause of viral meningitis and encephalitis, as well as perma-

nent deafness in children before the widespread vaccination.<sup>1</sup> It is a vaccine-preventable disease that is endemic in most parts of the world.<sup>2</sup>

The burden of mumps remains high (100-1,000 cases/100,000 population) in countries that do not supply routine mumps vaccination, with epidemic peaks each 2-5 years.<sup>3,4</sup> However, mumps disease outbreak have occurred even in countries using mumps vaccination in their National immunisation programs (NIPs).<sup>5-7</sup> According to World Health Organisation (WHO), Southeast Asia Region (SEAR) reported 36,352 cases of mumps in 2013,<sup>8</sup> however there is no information on the cases reported from India.

Mumps, despite being a widely prevalent disease everywhere in the country, is taken into account as associate degree insignificant public ill health in India, primarily due to poor documentation of clinical cases and lack of published studies. There is no across the nation representative knowledge on incidence of the illness.<sup>9</sup>

Although the illness is sometimes mild, its burden should not be underestimated. Up to 10 % of mumps patients developed aseptic meningitis; a less common however more serious complication is encephalitis, which might end in death or disability; and permanent deafness, orchitis and pancreatitis are other untoward effects that may be prevented by vaccination.<sup>10</sup> There is no specific treatment and vaccination is the solely effective way to forestall the disease.<sup>11</sup>

Measles is the most common cause of vaccine-preventable death in children and the eighth leading reason of death worldwide.

In India, measles-rubella vaccination was introduced in 2017.<sup>12</sup> Measles cases in India have dropped considerably by banging 43 % between 2015 and 2016 for the first time, as India builds on its acute anterior poliomyelitis obliteration campaign experience to eliminate measles by 2020. By 2018, India planned to achieve 40 crore children with the measles vaccine, that is predicted to significantly scale back the illness burden and facilitate India meet its 2020 elimination target.<sup>13</sup>

Prior to introduction of vaccination program, rubella was endemic worldwide. Epidemics still occur in developing and tropical countries each four to seven years, however the lack of monitoring programs, along with the absence of severe clinical symptoms, has created them troublesome to assess.<sup>14</sup>

## Vaccination

The mumps vaccine was first licensed in the US in 1967. Since the initiation of the mumps vaccine, reported cases of mumps have decreased by 99 % from 185,691 cases in 1968 to only 906 cases in 1995.<sup>11</sup>

Mumps vaccination has been incorporated into the regular vaccination schedule of the many countries, usually with measles and rubella vaccines in triple formulation (MMR)<sup>15</sup> at nine months, fifteen months, and four to six years of age;<sup>16</sup> or as two doses at twelve to fifteen months with the second dose between four to six years of age.<sup>17</sup> These vaccines have enabled the WHO to ascertain worldwide strategies for the advanced management of measles and rubella resulting in an elimination target in some regions. However, in contrast to rubella and measles, secondary vaccine failure happens oftentimes within the case of mumps and circulation of mumps virus inside highly immunised populations has been frequently reported.<sup>16</sup>

There are lower clinical attack rates among immunised populations; however, epidemics occur much within the second and third decade usually with severe complications.<sup>18</sup> The monovalent measles vaccine is not offered for normal use. Measles-containing immunising agent (MMR/MR) ought to be administered once at nine months of age under NIP of India.

Rubella vaccine is usually given together with measles and mumps as MMR vaccine between twelve and fifteen months of age, with a succeeding booster shot before school entry or in adolescence.<sup>19</sup> Rubella vaccination ought to be given to all women of child bearing age found to possess low or undetectable antibody titre, preferably one month before conception or postnatal. Immunisation during pregnancy should be avoided because of risk of congenital rubella syndrome (CRS).<sup>21</sup>

Government of India has recently introduced some modifications within the NIP supporting the recommendation of National Technical Advisory Group on Immunization (NTAGI) where four new immunising agents were introduced<sup>22</sup> and recommended conversion of MMR vaccine to MR vaccine (measles-rubella). As a result of it, it is felt that the disease burden of mumps is not very

significant in India. Only a few studies are conducted to search out the seroprevalence of antibodies against mumps in Indian children. Indian Academy of Paediatrics (IAP), however, recommends the continuation of this vaccine since incidence of mumps remains high in Indian children.

### Aims and objectives

Aim of this study was to compare mumps specific antibody titre in children vaccinated and not vaccinated with MMR vaccine. Primary objective was estimation of mumps specific IgG antibody in children, MMR naive and MMR vaccinated. Secondary objective was comparison of mumps specific IgG antibody level in above-mentioned children after quantitative estimation.

## Methods

The study was conducted in the Department of Microbiology, Government Medical College, Kota and Department of Paediatrics of associated J K LON Maternal and Child Care Hospital, Kota, Rajasthan. This was a cross sectional observational study, for a period of 1 year (May 2019 - May 2020), in which 100 children between age group of six months to twelve years were investigated. They were divided into two groups. Fifty MMR vaccine naive and fifty MMR vaccinated children between six months to twelve years of age were included. Immunocompromised children, children presenting with acute febrile illness, children who have received blood products or immunoglobulins 3-11 months back, children above 12 years of age were not included in the study. IgG antibodies against measles, mumps, and rubella were measured in the serum by enzyme-linked immunosorbent assay (ELISA) using specific commercially available kits (DIESSE ENZYWELL, Italy). For each test run, control and standard sera were included independent of the number of micro-test strips used. The standard sera were set up in duplicate. All tests were performed and interpreted as per kit manufacturer's instructions.

The assay utilises the microtiter plate-based enzyme immunoassay technique by coating highly purified antibody onto the wall of microtiter well. The purified and inactivated mumps/ measles virus antigen was bound to the solid phase (8-well strip). The specific immunoglobulins were

bound to the antigen through incubation with diluted human serum. After washing, incubation was performed with the conjugate, composed of human IgG monoclonal antibodies labelled with peroxidase enzyme which was detected colourimetrically by adding an enzyme substrate. The optical density of the resulting dye complex was read spectrophotometrically at single wavelength of 450 nm. The colour which was developed was proportional to the concentration of specific antibodies present in the serum sample. The average absorbance for each pair of duplicate test results was calculated.

The continuous data was described as mean and standard deviation, while discrete data was described as proportions. The association between qualitative variables was measured by Chi-squared test. The level of significance was considered at 5 % ( $\alpha = 0.05$ ). The MATLAB 2016 and JASP 0.11.1.0 statistical package was used for statistical analysis.

## Results

Among the 100 children included in the study mean age was 6.7 years (SD = 3.7 years) with male to female ratio of 57:43. Most of the children were from urban area (86 %) and literate families (85 %). Among all the children percentage of children vaccinated with MMR and MR vaccines were 50 % and 78 %, respectively.

Out of 50 vaccinated children 68 % (n = 34) were from 6 months to 6 years of age and 32 % (n = 16) were from 6 year to 12 years of age. While among non-vaccinated children 56 % (n = 28) and 44 % (n = 22) were from 6 months to 6 years and 6 years to 12 years of age group, respectively (Table 1).

**Table 1:** Age distribution of MMR- vaccinated and non-vaccinated children

MMR vaccination	Age		Total
	6 months – 6 years	6 years – 12 years	
Vaccinated	34 (68 %)	16 (32 %)	50
Non-vaccinated	28 (56 %)	22 (44 %)	50
Total	62	38	100

Age distribution showed significant association between MMR vaccination and antibody status in

6 months to 6 years age group ( $\chi^2 = 13.31$ ;  $p < 0.001$ ) but association in 6 year to 12 year age group ( $\chi^2 = 3.81$ ;  $p = 0.05$ ) was less significant.

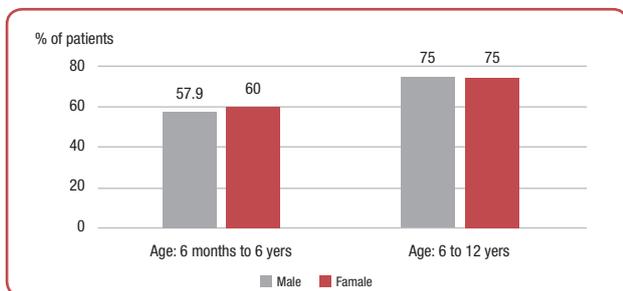
In this study 62.96 % (n = 17) males and 65.22 % (n = 15) females were positive for mumps IgG antibody among vaccinated children. While among non-vaccinated children only 30 % (n = 9) males and 20 % (n = 4) females were positive for IgG mumps antibody (Table 2).

**Table 2:** IgG mumps antibodies in MMR vaccinated and non-vaccinated children related to gender

MMR vaccination	Male			Female		
	Positive	Negative	Total	Positive	Negative	Total
Vaccinated	17 (62.96 %)	10 (37.04 %)	27	15 (65.22 %)	8 (34.78 %)	23
Non-vaccinated	9 (30 %)	21 (70 %)	30	4 (20 %)	16 (80 %)	20
Total	26	31	57	19	24	43

This data showed that there was significant association between MMR vaccination and mumps IgG antibody status ( $\chi^2 = 14.59$ ;  $p < 0.001$ ).

There was 32.27 % and 4.83 % positivity in vaccinated and non-vaccinated children respectively in the age group of 6 months to 6 years. While in the age group from 6 years to 12 years there was 31.57 % and 26.57 % positivity, respectively. This data showed that there was significant association between MMR vaccination and antibody status in 6 months to 6 years age group ( $\chi^2 = 13.31$ ;  $p < 0.001$ ) but in 6 years to 12 years age group ( $\chi^2 = 3.81$ ;  $p = 0.05$ ) was not significant as shown in Figure 1.



**Figure 1:** Age- and gender- wise distribution of positive IgG mumps antibodies among MMR vaccinated children

In MMR non-vaccinated children total positivity for IgG mumps antibody was 26 % (n = 13) while 74 % (n = 37) were negative for all the age groups and gender. This data showed insignificant seropositivity among non-vaccinated group.

Out of 50 vaccinated children included in the study 100 % (n = 19) males and 93.33 % (n = 14) females were positive for measles IgG antibody in the age group of 6 months to 6 years. While among 6 to 12 year age group 100 % (n = 8) males and 75 % (n = 6) females were positive for IgG measles antibodies. This data showed there was significant association between MMR vaccination and measles antibody status in all the age group irrespective of gender.

Out of 50 vaccinated children included in the study 89.47 % (n = 17) males and 80 % (n = 12) females were positive for rubella IgG antibody in the age group from 6 months to 6 years. While among 6 year to 12 year age group 100 % (n = 8) males and 75 % (n = 6) females were positive for IgG rubella antibodies showing significant association between MMR vaccination and rubella antibody status in all the age group irrespective of gender.

Total 78 % children were MR vaccinated. Among 50 MMR vaccinated children 90 % (n = 45) also received MR vaccination. While among non-vaccinated children only 66 % (n = 33) received MR vaccination as shown in Table 3.

**Table 3:** Percentage distribution of MR vaccination among MMR vaccinated and MMR non-vaccinated children

MMR vaccination	MR vaccinated	MR non-vaccinated	Total
Vaccinated	45 (90 %)	5 (10 %)	50
Non-vaccinated	33 (66 %)	17 (34 %)	50
Total	78	22	100

This represents that rate of MR vaccination is high in country to that of MMR vaccination. As in the current schedule of NIP, MMR vaccination is not recommended while private institutions give only MMR vaccines.

## Discussion

The use of vaccine in developed countries successfully reduced mumps virus infection, though outbreaks are often reported. In developing countries, due to absence of effective vaccination due to various reasons such as illiteracy, poor reach to health care services, poor economy, mumps is still a major health issue. The burden of disease in India has still not been clearly defined because of very few studies over it. The present study rep-



resents the current scenario of MMR vaccination in India.

As per WHO, MMR vaccine has been included in NIP of 121 countries.<sup>22</sup> In India it is not a part of NIP. Recently measles and rubella elimination program has been launched by WHO in India which targets 95 % coverage of measles immunisation in community with 2 doses of MR vaccine given, first dose at 9-12 months and second dose at 16-24 months of age.<sup>23</sup> Mumps is not a part of this schedule as it is believed that mumps is a disease of moderate morbidity and mortality in Indian setup.<sup>9</sup> Numerous studies both from India and other countries have reported many outbreaks of mumps in children and young adults both unvaccinated and vaccinated,<sup>24</sup> mostly occurring in age group of 5-10 years. In a prospective study conducted at Finland, where mumps is almost eradicated, antibody titre of measles, mumps and rubella vanished within 20 years, but antibody titres of mumps decreased the most, suggesting poor immunogenicity of the vaccine.<sup>25</sup>

In the present study among the 100 children 50 % were MMR vaccinated and 50 % were not. Out of 50 vaccinated children 68 % (n = 34) were from 6 months to 6 years of age and 32 % (n = 16) were from 6 to 12 years of age. While among non-vaccinated children 56 % (n = 28) and 44 % (n = 22) were from 6 months to 6 years and 6 years to 12 years age group, respectively. Similarly, in a study done by Wang et al,<sup>26</sup> where 42.25 % children were younger than 6 years of age and 57.75 % were from 6-12-year age group. In contrast to a prospective study done by Rout et al,<sup>27</sup> where 33.33 % of children included in the study were younger than 6 years in compare to 61.11 % from 6-12-year age group.

Sixty-four percentage (n = 32) of the 50 vaccinated children had IgG mumps antibodies. Out of these, 62.5 % (n = 20) belong to age group from 6 months to 6 years. This denotes that antibody response declines with increasing age and booster vaccination is required to maintain immunity against mumps. Also it can be due to low seroconversion rate of mumps antibody leading to low immunity. Exact time of vaccination cannot be estimated in India as in India most people belong to rural population and does not maintain records. For prevention of a disease outbreak of mumps at least 90 % of vaccine coverage of the population should be present to maintain and ef-

fective herd immunity as supported by previous studies.<sup>28</sup> In this study only 64 % of vaccinated population had immunity against mumps which is inadequate to prevent an outbreak. Similarly, in a study done by Wang et al<sup>26</sup> among all positive children 70.39 % belong to younger than 6 years age group for IgG mumps antibodies. In contrast, in study done by Adam et al<sup>29</sup> 63.6 % of children were positive for IgG mumps antibody, 34.01 % of them belong to younger than 6 years age group and 65.99 % belong to older than 6 years age group. In their study the mumps and rubella seroprevalence increased significantly with age documenting active wild type circulation.

Among the 50 non-vaccinated children, 26 % (n = 13) of children had presence of IgG mumps antibodies. It was seen that children aged 6-12 years had higher IgG mumps seroconversion as compared to younger children. This could be possibly due to prior exposure to a case of mumps or boosting of natural immunity with age. These results may be an overstatement of the current scenario within the community since the study was conducted on a limited number of participants due to various constraints; also the distribution of participants according to their age and gender was not uniform in each age group. Also it can be due to more chances of accounting an infection in later ages so mumps vaccination is necessary for these children.

Studies from other countries where two doses of MMR vaccination are recommended have reported seroconversion rate of 63-95 % after second dose.<sup>30</sup> Low seroconversion rate were also expected in communities reporting mumps outbreaks.

Among the 50 MMR vaccinated children 94 % (n = 47) were positive for IgG measles antibodies. This shows high seroconversion rate of measles among the vaccinated individuals. Similarly, in study done by Adam et al<sup>29</sup> and Wang et al,<sup>26</sup> among the MMR vaccinated children 93.5 % and 95 % were positive for IgG measles antibodies, respectively.

In the present study 96 % (n = 48) out of 50 MMR vaccinated children were positive for IgG rubella antibody, 60.42 % (n = 29) of which are from 6 months to 6 years of age while rest, 39.58 % (n = 11) were older than 6 years of age. Similarly, in a study done by Poethko-Muller et al<sup>31</sup> 75 % were from 6 months to 6 years of age. In contrast a

study done by Adam et al<sup>29</sup> only 17 % were from 6 months to 6 years of age. This data showed that the seroconversion for rubella is also high among MMR vaccinated children.

Out of 50 MMR vaccinated children only 64 % have IgG mumps antibodies in compare to 94 % IgG measles and 96 % IgG positivity of rubella. Overall, mumps seroconversion is poor due to one dose of vaccine, so another booster of MMR is required to complete coverage of mumps and prevent infection.

In present study, 78 % of all children were MR vaccinated. Among 50 MMR vaccinated children 90 % (n = 45) also received MR vaccination. Among non-vaccinated children only 66 % (n = 33) received MR vaccination. This showed that rate of MR vaccination is high in country due to MMR vaccination, as MR vaccine is currently not available in the private sector in India. In view of morbidity following mumps infection, it has been recommended by IAP that MMR is administered instead of MR. Irrespective of previous vaccination status, additional dose of MR vaccine during MR campaign for children 9 months to 15 years, is to be administered, keeping in mind the need to support national programs.<sup>32</sup>

In view of these results the decision of Government of India and NTAGI on replacing MMR with MR vaccine may require reconsideration since mumps rivals - measles and rubella in its ability to cause outbreak and possible congenital malformations in children. Removing mumps vaccine from states with < 70 % of MMR vaccine coverage can also lead to potential outbreak in future once MR vaccine completely replaces MMR vaccine.

The results of this study were in concordance with previous reports that a single dose is not sufficient to prevent clinical mumps and natural immunity in Indian children and it is not sufficient enough to offer protection upon exposure to the agent. Also, poor efficacy in vaccinated children causes a rightward shift in the epidemiology and affects older children and young adults. This widens the clinical severity of disease. Blanket withdrawal of mumps component of MMR cannot be a final decision without a strong backup of long-term epidemiological data.

## Conclusion

The maximum vaccine effectiveness against mumps for 2 doses of MMR vaccine is  $\approx 96\%$ . The herd immunity threshold to block mumps virus transmission is  $\geq 86\%$ . In present study, only 64 % of the vaccinated children were found to have IgG mumps antibodies. This concludes firstly low seroconversion rate of mumps antibody leading to low immunity and secondly, the antibody response declines with increasing age and booster vaccination is required to maintain immunity against mumps. High seroconversion rate of measles and rubella among vaccinated group was found. Hence in view of morbidity following mumps infection, the results highlight the need to incorporate mumps vaccine along with measles and rubella vaccine in the NIP instead of MR. Irrespective of previous vaccination status, additional dose of MR vaccine during MR campaign for children 9 months to 15 years, is to be administered, keeping in mind the need to support national programs. By preventing measles, rubella and mumps together, significant savings for our country and communities could be provided.

## Acknowledgements

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## Conflict of interest

None.

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# Team Based Learning in Pathology: Lessons Learned From a Pilot Study

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## Abstract

**Background/Aim:** Team based learning (TBL) is an approach where students are organised in groups where they learn from each other. TBL is a student centric approach, which ensures active participation of each member and also promotes teamwork and learning ability. Looking at the teacher centric approach of the conventional teaching learning methods in medical education, where the students are mere passive learners and the sessions can be monotonous, TBL seems to be extremely relevant today as a more student centric teaching learning method. Aim of this study was to compare TBL with conventional teaching learning method (CTL).

**Methods:** This randomised crossover study was conducted in the Department of Pathology, SMS Medical College, on 224 third semester medical students, wherein they were exposed to TBL session and their learning outcome and perception was compared to CTL. The data was analysed using Primer version 6 software.

**Results:** In this study, there was a statistically significant improvement ( $p < 0.001$ ) in the score of students after exposure to TBL. Also, there was a significant difference in the learning outcome of students of TBL (mean assessment score 7.21) as compared to CTL (mean assessment score 6.09). The student perception trends revealed a positive tilt towards TBL, wherein 70.98 % students agreed that TBL was a better learning strategy as compared to lectures.

**Conclusion:** This pilot study concluded that TBL can be used as a supplement to the conventional lectures for improving the learning as well as team work and leadership skills of students.

**Key words:** Team based learning; Team work; Perception of students; Learning outcome.

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## Introduction

Team based learning (TBL) is an approach where the students are organised in groups where they learn from each other.<sup>1</sup> Looking at the teacher-centric approach of the conventional teaching/learning methods in medical education, where the students are mere passive learners and the sessions can be monotonous, today the need for a more student-centric teaching learning method is felt by all. TBL is a student centric approach, which

ensures active participation of each member and also promotes teamwork and learning ability.<sup>2, 3</sup>

Pathology is one of the most important subjects taught in second year in Indian medical schools and is the basis of medicine later on. It is a vast subject which requires in depth knowledge by the students to be able to solve problem-based scenarios, which can be successfully dealt with a

team-based approach, as emphasised by previous authors.<sup>1</sup>

The traditional method of teaching can be improved by introducing the TBL approach for better learning and outcome.<sup>4,5</sup> TBL is a cost-effective teaching learning method which uses the principle of small group learning to a class comprised of large number of students.<sup>5</sup> This method requires just one teacher to manage multiple groups simultaneously in a large classroom setting.<sup>6</sup>

TBL uses strategies that ensure the effectiveness of small groups working independently with high student-to-faculty ratios, without losing the benefits of faculty-led small groups.<sup>6</sup> It also enables the students to have profound insights into their strengths and weaknesses and thus become more self-directed in learning.<sup>5</sup> This innovation generates interest in learning in students, increases interaction, team work, develop better communication skills as well as improve the overall learning ability of the students.<sup>5</sup>

The objective of this study was to introduce the concept of TBL in Pathology and evaluate the perception of students regarding this innovative teaching learning method and then compare the learning outcome of students exposed to TBL versus conventional teaching learning method (CTL).

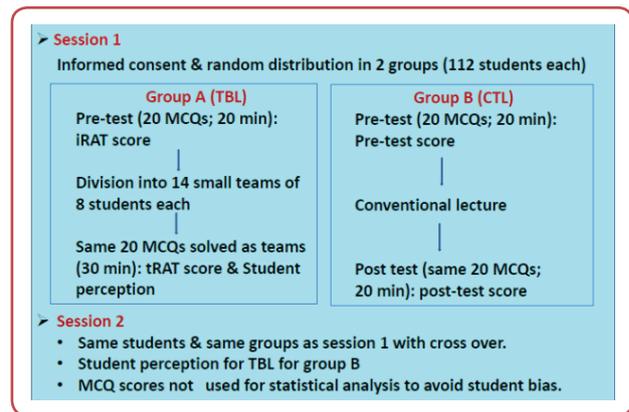
## Methods

This randomised crossover study for TBL was conducted at SMS Medical College in the Department of Pathology for third semester (II MBBS) students, of the academic year 2018-19, after obtaining approval from the Institutional Ethics Committee. Two sessions were conducted of 2-hour duration each, as shown in Figure 1.

### First session

For the first session, at the onset, all third semester students were given a week's time to read the topic of thromboembolism, as a pre-class preparation. Then, on the day of the first session, all students who were present and gave informed consent were randomly divided into two groups (Group A – TBL and Group B – CTL) by chit box method.

Group A (TBL) was taken for TBL session for thromboembolism. This began with a pre-test of



**Figure 1:** Workflow of team based learning (TBL) sessions  
CTL: conventional teaching learning; TBL: Team based learning; tRAT: team readiness assurance test; iRAT: individual readiness assurance test;

20 multiple choice questions (MCQs), which the students solved individually, within 20 minutes.

After their responses were collected, all the students were divided into 14 teams, each having 8 students. Now each of these 14 teams were given the same set of MCQs for solving, together as a group, within the next 30 min. During this time, team members were encouraged to collaborate, discuss and reach a consensus. While this team test was in progress, the individual pre-test responses were evaluated, with each correct answer scoring 0.5 (the total score being 10), and this was called individual readiness assurance (iRAT) score.

Once all the 14 teams had completed their group test, each was provided with four different coloured placards each, showing responses/options namely A (red), B (green), C (yellow) and D (blue). The facilitator posed the given MCQs one by one and all teams were told to respond by raising the placard corresponding to their answer simultaneously (to avoid cheating). These scores of all the teams were recorded and called the team readiness assurance test (tRAT) score.

Thus, all 8 members of one particular team had same tRAT score. During this activity, the teacher also acted as a facilitator and cleared the doubts of these student groups. When the correct answers were provided by the instructor, teams that did not agree were allowed to appeal and the facilitators immediately clarified any misconceptions regarding their answers. After the session the students were given a pre-validated questionnaire to find out their perception for this new innovative teaching learning method, using a 5-point Likert scale.

Simultaneously in a second classroom, group B (CTL) was taken for a conventional lecture for thromboembolism. For this, as with the TBL group, the students were individually given a pre-test of same 20 MCQs initially. After 20 minutes, their responses were collected. Then, a faculty took a conventional lecture on thromboembolism for 30 min. After the lecture the students were again individually given the same set of MCQs for solving (post-test) in 20 min. Their pre-test and post-test scores were recorded.

### Second session

After one week, the second session was conducted on the same students who participated in the first session and the students who were absent during this second session were excluded from the study. The group A of first session (TBL group) was crossed over with the group B of first session (CTL group). Thus, group A was exposed to CTL and group B to TBL. The topic covered this time was shock. Similar procedure was followed, as in session 1. However, the MCQ scores from this session were not used for statistical analysis to avoid students bias, although, the student perception was included in the final analysis in the study.

Comparison of the learning outcomes of TBL and CTL was done after the first session only, in the form of:

- a) Intra-group (group A - TBL group) - The iRAT and tRAT scores of group A (TBL) were compared using paired t-test.
- b) Intra-group (group B - CTL group) - the pre-test and post-test scores of group B (CTL) were compared using paired t-test.
- c) Inter-group (group A and B) - the tRAT score of group A (TBL group) was compared to the post-test score of group B (CTL group) using unpaired t-test.

The data was analysed using the Primer Version 6 software. The data analysis included percentage and proportion and a p value of < 0.05 was considered significant.

## Results

Out of the total 250 students enrolled in the course, 224 students participated in this study

and were randomly distributed into two groups, namely group A and group B, comprising of 112 students each. The rest of the students were excluded as they were absent during one or the other session.

On comparing the iRAT scores and tRAT scores of group A (TBL) students, it was found that the mean score of students significantly increased from  $3.70 \pm 1.84$  to  $7.21 \pm 0.86$  after the TBL session ( $p < 0.001$ ) (Figure 2).

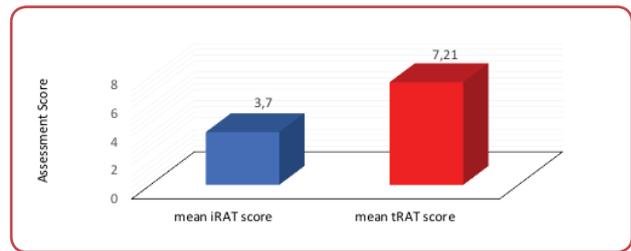


Figure 2: Comparison of mean iRAT and tRAT score of Group A - TBL (n = 112)

TBL: Team based learning; iRAT: individual readiness assurance test; tRAT: team readiness assurance test;

On comparing the pre-test and post-test score of group B (CTL) students, who were exposed to the conventional lecture, it was observed that the mean score of students significantly increased from  $3.59 \pm 1.92$  to  $6.09 \pm 1.65$  after the lecture ( $p < 0.001$ ) (Figure 3).

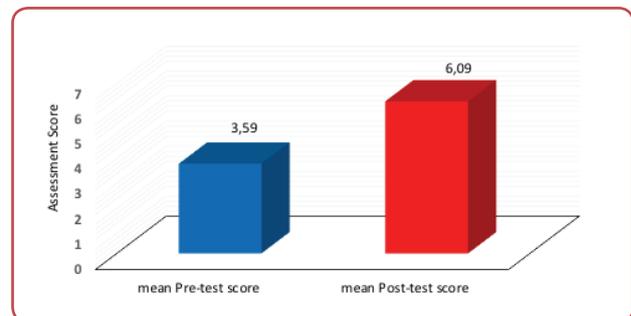


Figure 3: Comparison of pre-test and post-test score of Group B - CTL (n = 112)

CTL: conventional teaching learning;

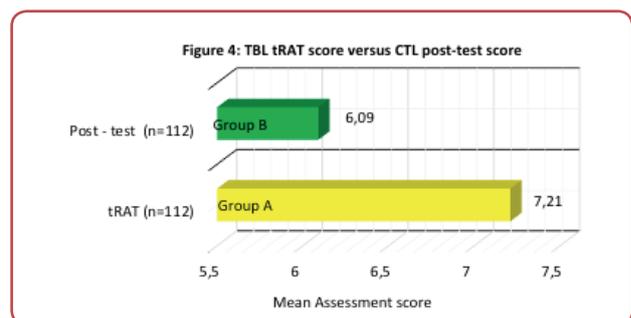


Figure 4: Comparison of final scores of both groups

CTL: conventional teaching learning; TBL: Team based learning; tRAT: team readiness assurance test;



**Table 1:** Perception of students of team based learning (TBL) (n = 224)

Question	Score 1: strongly disagree N (%)	Score 2: disagree N (%)	Score 3: neutral N (%)	Score 4: agree N (%)	Score 5: strongly agree N (%)
TBL was better learning strategy as compared to lecture	1 (0.45)	1 (0.45)	21 (9.38)	42 (18.75)	159 (70.98)
TBL was more effective in achieving learning objectives	1 (0.45)	2 (0.89)	18 (8.04)	54 (24.1)	149 (66.5)
I was more focussed during TBL as compared to lecture	0	1 (0.45)	35 (15.60)	37 (16.52)	151 (67.41)
TBL method improved my motivation to learn	1 (0.45)	3 (1.34)	29 (12.95)	28 (12.50)	163 (72.77)
I think the knowledge I gained in TBL session will be more permanent as compared to lecture	1 (0.45)	2 (0.89)	16 (7.14)	34 (15.18)	171 (76.34)
I enjoyed the TBL session	0	0	15 (6.7)	35 (15.63)	174 (77.68)
I have developed interpersonal and group interaction skills	1 (0.45)	3 (1.34)	19 (8.49)	44 (19.65)	157 (70.09)
With TBL, I have gained profound insights into my strengths and weaknesses as a learner	1 (0.45)	3 (1.34)	29 (12.95)	53 (23.66)	138 (61.61)
TBL session has enabled me to develop healthy personally rewarding relationship with the teachers	1 (0.45)	1 (0.45)	43 (19.20)	37 (16.52)	142 (63.40)
I recommend more TBL sessions in future	1 (0.45)	1 (0.45)	11 (4.91)	34 (15.18)	177 (79.02)

On comparing the tRAT score of group A (TBL) with the post test score of group B (CTL), it was found that the mean score of group A was more than that of group B, with a significant p-value (Figure 4). The final scores of students of both the groups increased from their respective pre-test scores, but the improvement was slightly more in the TBL group as compared to the CTL group.

The perception of students regarding TBL was taken as per the pre-validated feedback questionnaire comprising of ten questions and all the 224 students graded each question on a five-point Likert scale. (Table 1).

The findings clearly indicate the positive feedback of students about this innovation. As depicted, majority of the students (70.98 %) totally

agreed that TBL was a better learning strategy as compared to lectures, whereas 66.5 % were in total agreement that TBL was more effective in achieving learning objectives. Most of the students were more focussed and motivated during the TBL session as compared to lectures, and also felt that the knowledge that they gained by TBL was likely to be more permanently retained.

Most of the students stated that the TBL session was an excellent opportunity for them to gain insight about their weaknesses and strengths and helped them to develop interpersonal skills as well as a good rapport with the facilitator. More than 77 % students thoroughly enjoyed the TBL session and have recommended the use of this innovative teaching learning method in future also.

## Discussion

This pilot study reveals a statistically significant improvement in the learning of students after exposure to TBL, as indicated by an increase in the mean tRAT score as compared to their iRAT score. The studies by Alwahab et al, Brandler et al and Chhabra et al have also shown similar findings.<sup>1,3,5</sup>

A statistically significant increase in the post test

score of students who were exposed to the conventional lecture, as compared to their pre-test score was found. This has also been documented by Du et al and Punja et al.<sup>2,4</sup> So, the importance of lectures cannot be undermined and lectures cannot be totally replaced by TBL.

Although, in this study, the final scores of students

of both the TBL and CTL groups increased from their respective pre-test scores, the improvement was slightly more in the TBL group as compared to the CTL group. This was also observed by previous researchers.<sup>6-11</sup> Devi et al have concluded that the TBL actually helped the academically weaker students to succeed.<sup>8</sup>

Regarding the perception of students, this study infers that most of the students have a positive feedback for this innovative teaching learning method. Majority of the students totally agreed that TBL was a better learning strategy as compared to lectures and was more effective in achieving learning objectives. Most of the students were more focussed and motivated during the TBL session as compared to lectures and also felt that the knowledge that they gained by TBL was likely to be more permanently retained by them. Maximum students realised that the TBL session was an excellent opportunity for them to gain insight about their weaknesses and strengths and also helped them to develop interpersonal skills as well as a good rapport with the facilitator. Almost all the students thoroughly enjoyed the TBL session and have recommended the use of this innovative teaching learning method in future. These findings corroborate with almost all the previous authors except Frame et al, who have found an almost equal perception score for conventional lecture and TBL.<sup>12</sup> Thus, a synergistic approach between TBL and traditional lectures should be followed and TBL should be used as a supplement to conventional lectures for improvement of students' performance, as mentioned by other researchers.<sup>4,7</sup>

There were few limitations of this study. Since this innovation required at least two hours for completion of each session, it would not be possible to conduct it in 1-hour lecture time allotted routinely, as per the presently laid undergraduate timetable.

Though there was a statistically significant documented short-term positive change in learning of undergraduate students exposed to TBL as compared to CTL in this pilot study, it is necessary to carry out more sessions to generate data before a final conclusion about a lasting improvement in learning outcome and change in behaviour can be authentically drawn. Also, since this study was conducted in one department only and for a sin-

gle topic, it would be difficult to draw generalised conclusions about advantages, limitations and feasibility of TBL.

It is planned to carry out this pilot study further by having more sessions in pathology and further start this innovation in other departments as well. Through the Medical Education Unit, plan is to sensitise other Faculty departments regarding this innovative teaching learning method as well.

## Conclusion

This preliminary study clearly reflects that TBL can be a better teaching learning method, as compared to conventional didactic lectures, wherein the principles of effective small group teaching can be easily applied to a large group of 250 undergraduates without needing too many teachers at one time. Improvement in the final scores indicate an increase in the learning of students. Trends in the student perception questionnaire very clearly point towards the fact that this method can be used to motivate students towards studies, learning communication skills and collaborating as teams as well as provide insight into its implementation further at a larger scale.

Also, since TBL requires fewer faculty members compared to other active learning strategies (eg, self-directed learning and problem-based learning), and because it promotes greater student accountability in learning, it could serve as a useful alternative to other active learning strategies.

The high student satisfaction as well as improvement in the learning outcome observed in this study implies that it is necessary to incorporate such newer innovations for better teaching learning in medical colleges. However, CTL cannot be totally replaced by TBL, but, a combination of TBL approach and CTL methods should be used to improve students learnings.

## Conflict of interest

None.

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None.

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# Effects of the Ultra-Short-Acting Beta-Blocker Esmolol Infusion on Cardiovascular Parameters and Quality of Postoperative Recovery in Patients Scheduled for Elective Plastic Surgery

Dragana Lončar-Stojiljković<sup>1, 2, 3</sup>

## Abstract

**Background/Aim:** Esmolol is an ultra-short-acting, easily titratable  $\beta$ -adrenergic receptor antagonist used for urgent treatment of hypertension and tachycardia in non-surgical and surgical settings. Aim of this clinical study was to investigate its cardiovascular effects and quality of the emergence from anaesthesia in patients scheduled for elective plastic surgery under general balanced anaesthesia.

**Methods:** A total of 30 ASA I/II patients were randomised in two groups of similar demographic characteristics and baseline values of cardiovascular parameters. Esmolol group received esmolol dissolved in glucose 5 % as an intravenous infusion, 0.3 mg/kg/min during the first 5 min and at a rate of 0.1 mg/kg/min thereafter. Control patients received the solvent only, at the same rate and volume. General balanced anaesthesia was induced with thiopentone sodium and fentanyl and maintained with nitrous oxide and oxygen. Neuromuscular relaxation was assured with pancuronium bromide and was antagonised at the end of operation with atropine and neostigmine. Systolic and diastolic blood pressure and heart rate were registered at all critical phases: (1) immediately prior to the induction (baseline value), (2) induction to anaesthesia, (3) tracheal intubation, (4) first skin incision, (5) surgical manipulation with organs, (6) suture of the surgical wound and (7) tracheal extubation. Drug consumption and quality of postoperative recovery were monitored.

**Results:** In most of the critical phases of anaesthesia and operation, patients from the Esmolol group had significantly lower values of cardiovascular parameters than the patients from the Control group. Esmolol-treated patients needed less fentanyl, droperidol and pancuronium and had faster and smoother emergence from anaesthesia than the control patients.

**Conclusion:** Esmolol improved haemodynamics and post-anaesthesia recovery in patients undergoing elective plastic surgery under general balanced anaesthesia.

**Key words:** Esmolol; Beta-blockers; Anaesthesia; Plastic surgery; Cardiovascular parameters.

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## Introduction

Laryngoscopy, tracheal intubation, first incision, manipulations with organs, suture of the surgi-

cal wound and tracheal extubation constitute the so-called surgical trauma and represent a source

of very strong painful stimuli.<sup>1</sup> As a consequence, the activation of the sympatho-adrenal response occurs, resulting in hypertension, tachycardia, arrhythmia, lacrimation, diaphoresis and twitches of skeletal muscles.<sup>2</sup> These phenomena are especially dangerous in patients with serious cardiovascular diseases.<sup>3</sup>

The concept of general balanced anaesthesia was developed in order to suppress painful stimuli and ensure best operating conditions, however avoiding use of large doses of intravenous or high concentrations of inhalation anaesthetics and high doses of opioid analgesics to avoid the depression of cardiovascular system, delayed postoperative recovery and respiratory depression.<sup>4</sup> Adjuvant therapy such as short-acting opioid analgesics, local anaesthetics,  $\alpha_2$ -adrenergic receptor agonists, regional neural blocks and  $\beta$ -adrenergic receptor antagonists have been tried as supplements to the usual technique of general balanced anaesthesia.<sup>5</sup>

Esmolol is a hydrosoluble, selective  $\beta_1$ -adrenergic receptor antagonists. It has a unique pharmacokinetics, since it is metabolised by the esterase located in the cytosol of human erythrocytes.<sup>6</sup> It is therefore administered exclusively intravenously (iv), in the form of boluses or infusion, with elimination half-time ( $t_{1/2}$ ) of 10-12 min.<sup>7,8</sup> This short kinetics is responsible for the titratability of esmolol boluses and infusion when administered to treat episodes of hypertension and tachycardia in various indications, including those arising from perioperative painful stimuli.<sup>9,10</sup> All these properties make esmolol a logical choice of supplement to the concept of the general balanced anaesthesia.<sup>11-13</sup>

The aim of this clinical trial was to investigate the effect of esmolol on cardiovascular parameters and quality of anaesthesia in patients scheduled for elective plastic surgery.

## Methods

This clinical trial was performed at the Military Medical Academy and approved by the local Ethics Committee. A total of 30 American Society of Anesthesiologists (ASA) class I or II patients aged 18 or above, scheduled for elective plastic surgery were randomly divided into two equal groups – Control and Esmolol. Patients from the

Esmolol group received esmolol solution in glucose 5 %, as an iv infusion. Its rate was 0.3 mg/kg/min during the first 5 min and 0.1 mg/kg/min thereafter. This maintenance dose was chosen based on the finding that esmolol, when infused at rates up to 0.15 mg/kg/min, was practically hypotension-free.<sup>14</sup> Patients from the Control group received the same volume and rate of the plain glucose 5 % solution iv.

All patients received anaesthesia according to the same protocol. They were premedicated 30-45 min before anaesthesia with diazepam 10 mg intramuscularly (im). Induction to anaesthesia was performed by injecting thiopental sodium 3-5 mg/kg iv and fentanyl 1.5  $\mu$ g/kg iv. Neuromuscular blockade was assured by injecting an iv bolus of pancuronium bromide 0.07 mg/kg. The desired level of neuromuscular blockade was maintained by incremental boluses of 0.01 mg/kg. Mixture of oxygen and nitrous oxide ( $O_2/N_2O$  2 : 1) was used for maintenance of general anaesthesia.

According to the study protocol, every episode of increase of systolic and diastolic blood pressure or heart rate by more than 20 % of its pre-induction (baseline) value was treated with fentanyl 1.5  $\mu$ g/kg alone or in combination with droperidol 1:50 (Thalamonal®). After the end of operation, atropine 0.5 mg iv bolus was injected and neostigmine 1.5 mg iv was used for decurarisation. Atropine 0.5 mg iv was used during the operation to treat episodes of bradycardia. It was defined as a decrease of heart rate below 60 beats/min<sup>15</sup> or by more than 20 % of the baseline values.

Systolic and diastolic blood pressure and heart rate were registered in the following phases of anaesthesia and operation: (1) immediately prior to the induction (baseline value), (2) induction to anaesthesia, (3) tracheal intubation, (4) first skin incision, (5) surgical manipulation with organs, (6) suture of the surgical wound and (7) tracheal extubation. In addition to it, total consumption of fentanyl, droperidol, atropine and pancuronium was registered. Quality of the post-anaesthesia recovery was evaluated based on the registration of times needed to regain ability to open eyes on command, to open eyes spontaneously and to regain full orientation. Overall assessment of the quality of anaesthesia was performed by the experienced anaesthesiologist, with the scale: 1 – poor, 2 – good and 3 – excellent.

Statistical analysis was performed by using parametric or non/parametric tests, depending on the nature of the parameters observed and the normality of their distribution. Software IBM SPSS 18.0 was used for these analyses.

## Results

There were no significant differences between the Control and Esmolol groups of patients regarding their age, weight, gender ratio and the baseline values of the cardiovascular parameters (Table 1).

**Table 1: Demographic data and preinduction (baseline) values of cardiovascular parameters in patients undergoing elective plastic surgery under general balanced anaesthesia**

Parameter (unit)	Control (mean ± SEM)	Esmolol (mean ± SEM)	Statistical significance
Age (years)	41.33 ± 5.33	37.33 ± 7.57	n.s.
Body weight (kg)	75.67 ± 8.29	74.00 ± 6.66	n.s.
Gender (male/female)	8/7	6/9	n.s.
Systolic blood pressure	125.00 ± 10.41	131.67 ± 6.01	n.s.
Diastolic blood pressure	81.67 ± 4.41	88.33 ± 13.02	n.s.
Heart rate (beats per min)	76.76 ± 10.14	80.00 ± 11.55	n.s.

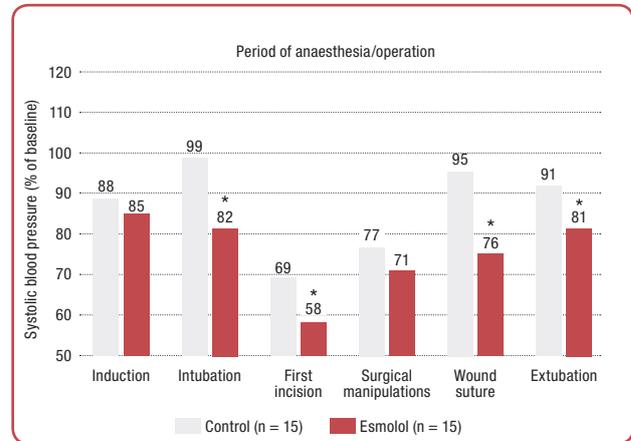
SEM – standard error on the mean; n.s. – not significant

Figure 1 contains data on the values of systolic blood pressure in the critical phases of anaesthesia and operation, expressed as percentages of their baseline values. In both Control and Esmolol group induction to anaesthesia resulted in decrease in systolic blood pressure, which continued well into the operation. When comparing the values in the two groups in all the critical phases of anaesthesia and operation, it was evident that they tended to be lower in the Esmolol group and this difference reached statistical significance at intubation, first skin incision, suture of the surgical wound and extubation.

Similar results were registered with diastolic blood pressure (Figure 2). Esmolol values of diastolic blood pressure were significantly lower in all critical phases of anaesthesia and operation, except during the first incision.

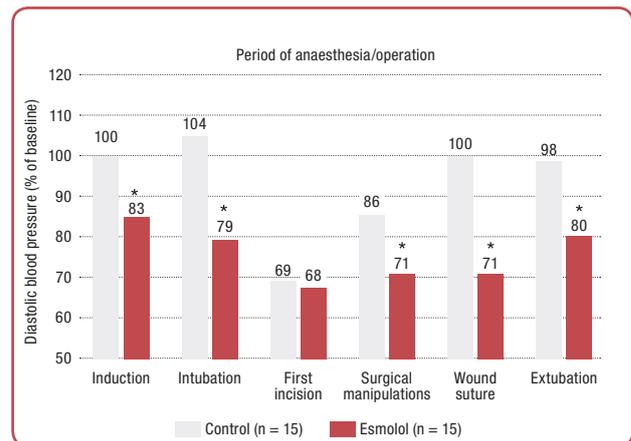
Results for heart rate values are contained in Figure 3. While the values of the systolic in diastolic blood pressure in the Control group were during most phases of anaesthesia and operation below

their baseline values, the Control group values of heart rate were constantly above the baseline ones. At the same time, in the Esmolol group sig-



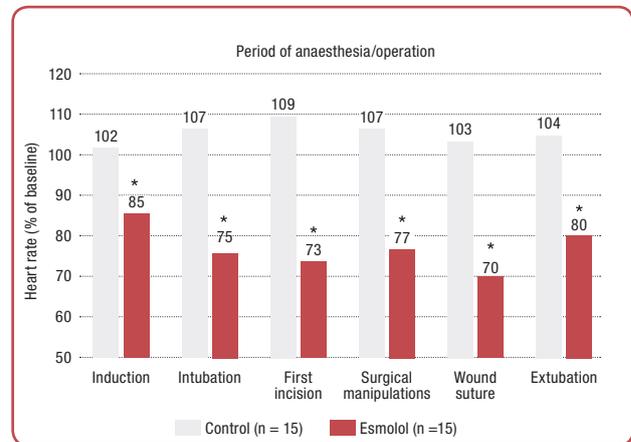
**Figure 1: Effect of esmolol on systolic blood pressure in patients undergoing elective plastic surgery under general balanced anaesthesia**

\*p < 0.05 versus Control



**Figure 2: Effect of esmolol on diastolic blood pressure in patients undergoing elective plastic surgery under general balanced anaesthesia**

\*p < 0.05 versus Control



**Figure 3: Effect of esmolol on heart rate in patients undergoing plastic surgery under general balanced anaesthesia**

\*p < 0.05 versus Control



nificantly lower heart rate values, ranging 70-85 % of baseline, were registered.

Table 2 contains data on the total drug consumption. Only atropine was used in a similar dosage in both groups, while in the Esmolol group a significantly lower consumption of fentanyl, droperidol and pancuronium was registered.

**Table 2:** Consumption of drugs in patients undergoing elective plastic surgery under general balanced anaesthesia

Parameter (unit)	Control (mean ± SEM)	Esmolol (mean ± SEM)	Statistical significance
Fentanyl (mg)	0.38 ± 0.04	0.13 ± 0.03	p < 0.05
Droperidol (mg)	6.67 ± 1.67	0.83 ± 0.83	p < 0.05
Atropine (mg)	1.00 ± 0.29	1.03 ± 0.09	n.s.
Pancuronium (mg)	14.00 ± 3.06	3.67 ± 0.88	p < 0.05

SEM – standard error on the mean; n.s. – not significant

**Table 3:** Speed and quality of postoperative recovery in patients undergoing elective plastic surgery under general balanced anaesthesia

Parameter (unit)	Control (mean ± SEM)	Esmolol (mean ± SEM)	Statistical significance
Duration of anaesthesia (min)	131.67 ± 15.90	123.00 ± 33.21	n.s.
Opening of eyes on command (min)	11.67 ± 1.67	2.67 ± 1.20	p < 0.05
Spontaneous opening of eyes (min)	16.67 ± 4.41	4.50 ± 1.61	n.s.
Regaining of full orientation (min)	25.00 ± 2.89	7.33 ± 1.76	p < 0.01
Extubation possible (% of patients)	100	100	n.s.
Evaluation of quality of anaesthesia*	2.00 ± 0.00	2.67 ± 0.33	n.s.

SEM – standard error on the mean; n.s. – not significant; Quality of anaesthesia: 1 - poor, 2 - good, 3 - excellent;

Although the duration of anaesthesia and operation were similar in both groups, all the times registered – time until regaining ability to open eyes on command, time until regaining ability to open eyes spontaneously and time until regaining full orientation – were significantly shorter in the Esmolol group.

## Discussion

The obtained results are generally in accordance with some other reports. Esmolol proved to be very efficacious in antagonising haemodynamic changes that accompany laryngoscopy and tracheal intubation.<sup>10, 16-19</sup> Like in the present study, esmolol prevented increases in blood pressure

and heart rate during the phase of tracheal intubation.<sup>20-22</sup> Esmolol also assured a more stable haemodynamics during the non-cardiac<sup>23-25</sup> and cardiac surgery.<sup>26, 27</sup>

Esmolol-induced continuous  $\beta$ -adrenergic receptor blockade leads to a more sparing use of opioid analgesics, which was demonstrated in the present study and other clinical trials alike.<sup>28-30</sup> In the current study, a very significant sparing of fentanyl and droperidol were registered.

As a consequence, the patients infused with esmolol had much faster and smoother emergence from anaesthesia than those ones in whom the increases in blood pressure and heart rate were treated with incremental doses of opioid analgesics.<sup>31, 32</sup> The quality of this recovery includes the postoperative nausea and vomiting – a very frequent consequences of opioid administration.<sup>32</sup> Rarely, opposite results were published – in patients undergoing gynaecologic laparoscopic surgery esmolol did not assure better recovery from anaesthesia, as compared with the saline infusion.<sup>33</sup> When compared with lidocaine bolus and infusion, esmolol nevertheless also assured better recovery from anaesthesia.<sup>34</sup>

There are some reports that esmolol, similarly like local anaesthetic lidocaine, decreases pain and withdrawal movements after the administration of non-depolarising neuromuscular relaxant rocuronium, via yet unclear mechanisms.<sup>35, 36</sup> It is possible that such mechanisms are responsible for the decreased consumption of pancuronium noted in the present study.

## Conclusion

Esmolol acts as a useful supplement to the other components of the general balanced anaesthesia technique. It blunted the cardiovascular responses to nociceptive stimuli during the critical phases of anaesthesia and operation in patients undergoing elective plastic surgery, assured less consumption of fentanyl, droperidol and pancuronium, leading to faster and smoother emergence from anaesthesia.

## Acknowledgements

None.

## Conflict of interest

None.

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# Role of Multidetector Computed Tomography (MDCT) in Evaluation of Lung Nodule with Histopathological Correlation

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## Abstract

**Background/Aim:** Lung cancer is the most common and lethal cancer around the world. Computed tomography (CT) is an integral imaging technique for staging the lung cancer. Aim of this study was to correlate the multidetector CT (MDCT) findings of lung nodule with histopathological examination, as well as to assess the diagnostic accuracy of MDCT in evaluation of suspected lung nodule.

**Methods:** One hundred patients with clinical or radiological suspicion of lung nodule referred for CT scan of thorax were included in the study. Histopathological analysis was performed. The location of the lesion was analysed and nodules were classified. Fine needle aspiration cytology (FNAC) was done with spinal needle under all aseptic precautions. The results obtained by MDCT were analysed and compared with histopathological findings done by CT guided FNAC.

**Results:** Average age of patients was 65 years, 25 % were females and 75 % were males. Among all the patients 66 % of lesions were located in right side lung and 34 % of lesions were left in location. Of all, 2 % patients had lesions less than 3 cm, 11 % patients had lesion between 3-4 cm, 19 % patients had lesion between 4-5 cm, 26 % patients had lesion between 5-7 cm and 42 % patients had lesion greater than 7 cm. Many of these patients also presented with enlarged lymph nodes, most commonly mediastinal (73 %) followed by subcarinal (51 %), hilar (44 %) and supraclavicular (4 %) lymph nodes. The most common histological findings of lung nodules analysis were adenocarcinoma (41 %). Among the 100 patients 58 % had lesions located peripherally while 42 % had central lesions. CT was a highly sensitive (95.45 %) and moderately specific (75 %) test and also had a high positive predictive value (96 %) to diagnose malignant lung nodule.

**Conclusion:** CT guided FNAC of lung nodule is a safe, minimal invasive procedure with a high diagnostic accuracy. The use of CT - guided FNAC in hilar and mediastinal nodules can avoid unnecessary exploratory surgery for staging and also diagnosis could be made with lesser cost.

**Key words:** MDCT; Fine needle aspiration cytology; Lung cancer; Sensitivity; Positive predictive value.

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## Introduction

Lung cancer is among the most common and lethal cancer around the world. It represents about 13 % of the new cancer cases and up to 28 % of the cancer deaths.<sup>1</sup> Most lung cancers are direct-

ly attributed to smoking. Lung is also the most common site of metastatic involvement from other extra thoracic malignancies; 20 to 54 % of extra-thoracic malignancies have pulmonary

metastatic disease. A wide variety of imaging techniques are currently available for detection, diagnosis and management of lung cancer. Chest imaging is the primary modality for detection of lung nodules and masses. Computed tomography (CT) and positron emission tomography (PET) are most commonly used imaging modalities for further characterisation and to define extent of malignancy. Along with non-radiological modalities, CT is used for pre-treatment staging of the lung malignancies. Imaging is also required to assess the response to non-surgical treatment and for follow up in treated patients.

CT is more accurate for detection of a small lung nodule and it is a modality of choice for evaluation and classification of lung cancer.<sup>2</sup> CT is an integral imaging technique for staging the lung cancer. Multidetector CT (MDCT) accurately stages the tumour due to the superior multiplanar reformatted images.<sup>3</sup> Till now there is no state sponsored lung screening program in India. This is partly attributed to high prevalence of granulomatous disease (tuberculosis - TB) in India, in which imaging finding may mimic early cancers resulting in significant anxiety and consequently usage of more invasive tests to prove the nature of these nodules; and also due to lack of availability of sufficient imaging, pathology and surgical facilities.

The merits of CT in intrathoracic scanning are innumerable. The most important among them, is the ability to evaluate lung lesions on its own and to differentiate them in terms of benign and malignant with reasonably high degree of accuracy. With this background the present study was undertaken to establish the role of CT in comprehensive evaluation of lung neoplasia, especially in Indian set-up and to study the efficacy and safety of CT-guided biopsy.

Aim of this study was to correlate the MDCT findings of lung nodule with histopathological examination, as well as to assess the diagnostic accuracy of MDCT in evaluation of suspected lung nodule.

## Methods

This was a hospital based observational study. One hundred patients with clinical or radiologi-

cal suspicion of lung nodule referred for CT scan of thorax to the Department of Radio-Diagnosis, Mahatma Gandhi Medical College and Hospital, Jaipur (Rajasthan) were included in the study. Histopathological analysis was performed. Study was approved by Ethic committee of the Hospital.

Data was collected from all cases of suspected lung nodule in a specified form. X-ray was done by X-ray machine Allenger-500/800 MA and a contrast enhanced CT was performed with a 128 slice GE Optima 660 scan machine.

For CT evaluation, the standard protocol involved scanning the entire thorax from the lung apices to the costophrenic angles in supine position. Further thin sections were taken in the region of interest to eliminate partial volume averaging depending on the size of the lesion.

Both non-contrast and contrast enhanced scans were performed in most cases. Used contrast was non-ionic, water soluble, Iohexol 350 mg I/mL. The dose of contrast was 1-2 mL/kg body weight administered by rapid intravenous bolus injection. Scanning began immediately after administration of the contrast injection.

The location of the lesion was analysed and nodules were classified. Fine needle aspiration cytology (FNAC) was done with Spinocan<sup>®</sup> spinal needle under all aseptic precautions. The lesion identified on CT and the site of entry was noted. Two to four mL of local anaesthesia was injected at the site after 2-3 min Spinocan<sup>®</sup> needle (18-20 inches) was used and introduced. The tip of the needle, identified within the lesion with the help of CT. FNAC was taken and both dry and wet slides were prepared and sent to the pathology department. The results obtained by MDCT were analysed and compared with histopathological findings done by CT guided FNAC.

## Results

Among the 100 patients included in this study, the maximum age distribution was between the age group of 40-89 years with a mean age of 65 years. Gender-wise, 25 % of patients were females and 75 % were males. Most common presenting symptom was cough with expectoration (79 %), weight loss (63 %), dyspnoea (55 %),

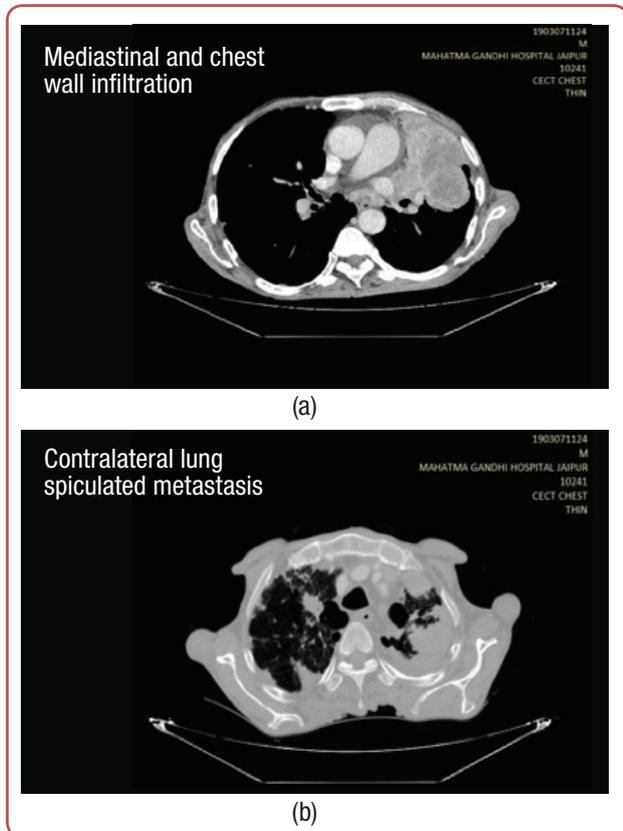
chest pain (54 %), anorexia (39 %) and haemoptysis (36 %) followed by fever (16 %), hoarseness of voice (12 %) and dysphagia (1 %). The distribution of different test modalities is shown in Table 1. Among all the patients 66 % of lesions were located in right side lung and 34 % of lesions were left in location. Of all, 2 % patients had lesions less than 3 cm, 11 % patients had lesion between 3-4 cm, 19 % patients had lesion between 4-5 cm, 26 % patients had lesion between 5-7 cm and 42 % patients had lesion greater than 7 cm. Many of these patients also presented with enlarged lymph nodes, most commonly mediastinal (73 %) followed by subcarinal (51 %), hilar (44 %) and supraclavicular (4 %) lymph nodes.

**Table 1: Diagnostic methods and test results**

Diagnostic Method	Malignant	Benign
X-Ray	77	23
CT-Scan	87	13
FNAC	88	12

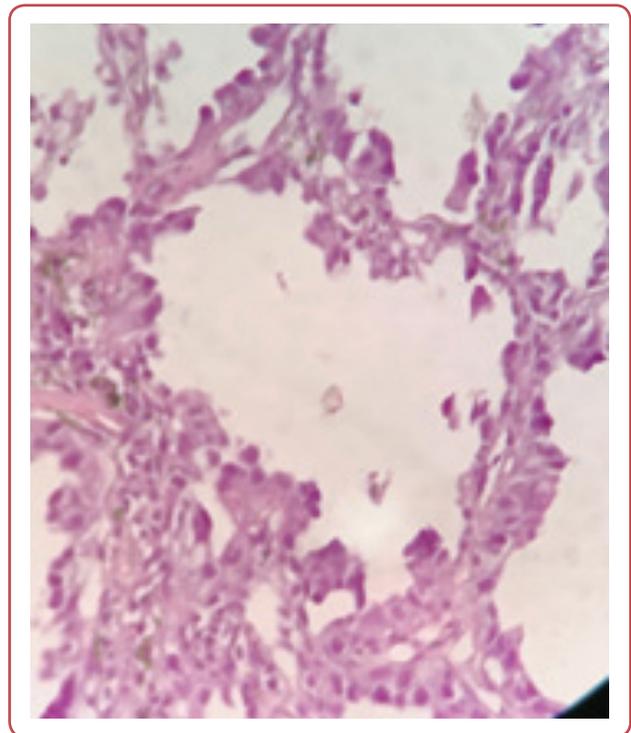
CT: computed tomography; FNAC: Fine needle aspiration cytology;

Patients also presented with complications and mediastinal and nodal involvement of nodules as shown in Figure 1.



**Figure 1:** (a) Contrast enhanced computed tomography (CECT) chest axial scan showing chest wall and mediastinal invasion by mass. (b) CECT chest axial view lung window showing contralateral lung metastasis as spiculated nodular margins.

In this study the most common histological findings of lung nodules analysis were adenocarcinoma (41 %) (Figure 2) followed by others as shown in Table 2. Among the 100 patients 58 % had lesions located peripherally while 42 % had central lesions. Among the central lesions, 45.23 % were squamous cell carcinoma (n = 19), 19.04 % were adenocarcinoma as well as small cell carcinoma respectively (n = 8), 4.76 % cases were of undifferentiated large cell carcinoma and metastatic nodule, respectively (n = 2) while 7.14 % were benign nodules (n = 3). Among the peripherally situated lesions 56.89 % were adenocarcinoma (n = 33), 8.62 % were metastatic nodule (n = 5), 6.89 % (n = 4) were squamous cell carcinoma and undifferentiated large cell carcinoma, 5.17 % were small cell carcinoma (n = 3), while 15.51 % of lesions were benign (n = 9). Histopathological findings related to gender are shown in Table 3.



**Figure 2:** Histopathological findings of lung nodule - adenocarcinoma

**Table 2: Histopathological findings of lung nodules**

Malignant pathology	N	Benign pathology	N
Adenocarcinoma	41	Tubercular granuloma	5
Squamous cell carcinoma (SCC)	23	Adenoma	4
Small cell carcinoma	11	Hamartoma	3
Metastasis	7		
Undifferentiated large cell carcinoma (LCC)	6		



**Table 3: Histopathological findings related to gender**

Histopathological findings	Male		Female	
	N	%	N	%
Adenocarcinoma	29	38.67	12	48.00
Squamous cell carcinoma (SCC)	21	28.00	2	8.00
Small cell carcinoma	7	9.33	4	16.00
Metastatic nodules	4	5.33	3	12.00
Undifferentiated large cell carcinoma (LCC)	6	8.00	0	0
Benign lesions	8	10.67	4	16.00
Total	75	100.00	25	100.00

In presented study, 31 % of patients were non-smokers, and 69 % were smokers. Histopathological findings related to smoking status is shown in Table 4.

**Table 4: Histopathological findings related to tobacco-smoking status**

Histopathological findings	Non-smokers		Smokers	
	N	%	N	%
Adenocarcinoma	17	54.84	24	34.78
Squamous cell carcinoma (SCC)	3	9.68	20	28.99
Small cell carcinoma	3	9.68	8	11.59
Metastatic nodules	2	6.45	5	7.25
Undifferentiated large cell carcinoma (LCC)	0	0	6	8.69
Benign lesions	6	19.35	6	8.69
Total	31	100.00	69	100.00

The comparative evaluation of CT and CT guided FNAC for diagnosis of lung nodules is shown in Table 5.

**Table 5: Comparison of computed tomography (CT) diagnosis with histopathological diagnosis of lung nodules**

	Histopathological diagnosis for lung cancer		
	Yes	No	Total
CT diagnosis for lung cancer	Yes 84 (True positive)	3 (False positive)	87
	No 4 (False negative)	9 (True negative)	13
	88	12	100

**Table 6: Sensitivity, specificity, positive predictive value, negative predictive value and accuracy of computed tomography (CT) to diagnose lung nodules**

Validity Test	Percent
Sensitivity	95.45 %
Specificity	75.00 %
Positive predictive value	96.00 %
Negative predictive value	69.00 %
Accuracy	93.00 %

CT was a highly sensitive (95.45 %) and moderately specific (75 %) test and also had a high positive predictive value (96 %) to diagnose malignant lung nodule as shown in Table 6.

## Discussion

Lung masses whether asymptomatic or presenting with various symptoms have always been challenging entities for both clinicians and radiologists. Many diagnostic modalities and various techniques and approaches have been put forward from time to time. MDCT in the present scenario opened a new horizon for evaluation of intrathoracic masses without any invasive procedure. The present study was undertaken to establish the role of CT and CT guided fine needle aspiration cytology in lung masses.

In this study mean age of the patients was in concordance with study by Gangopadhyay et al,<sup>4</sup> Dharmaraj et al,<sup>5</sup> Ahmed et al,<sup>6</sup> Gupta et al,<sup>7</sup> Indiranarayan et al,<sup>8</sup> Saha et al,<sup>9</sup> Singh et al,<sup>10</sup> while it was contrary to study done by Mundal et al<sup>11</sup> and Mukherjee et al.<sup>12</sup> In the present study there were 75 % male patients out of 100 patient. That result is similar to findings of Gangopadhyay et al,<sup>4</sup> Gadodiya et al<sup>13</sup> and Saha et al,<sup>9</sup> while in some studies<sup>5, 7, 8</sup> the preponderance is very high ie more than 80 % were male patients. In this study 61 % of males and 92 % of females were smokers. High level of association between smoking and occurrence of lung nodules was observed. Similar findings were seen in study done by Meena et al,<sup>5</sup> Narayan et al,<sup>8</sup> where 71.36 % and 65 % patients were smokers, respectively. The most common presentation of patient was cough with expectoration. Some other symptom like anorexia, fever, haemoptysis, hoarseness of voice and dysphagia were also present in some patients but to a lesser extent. Similar findings were observed in studies by other researchers.<sup>5, 14, 15</sup> Out of 100 patients with lung nodule - with X-ray 77 %, with CT scan 87 % and with FNAC 88 % cases were reported malignant and rest were benign. Also, 66 % of lung nodules were found in the right lung and only 34 % were present in left lung. Similar findings were seen in study done by Ahmed et al<sup>6</sup> (45 % right, 31 % left lung), Mundal et al<sup>11</sup> (72 % right, 52 % left lung) and Saha et al.<sup>9</sup> Fifty-eight percent of nodules had peripheral location while 42 % were located centrally. This is in concordance with the study done by Adaikkalavan et al,<sup>16</sup> Biswas et al,<sup>17</sup> Narayanswami et al.<sup>8</sup> Maximum lung nodules in this study were more than 7 cm in size. This suggest that most of the lung nodules express symptoms in patient in their later stages of life, when the size of the lung nodule have already

been increased. Similar findings were found in literature.<sup>7, 9, 12, 13</sup> Patients with lung nodules also had various types of lymphadenopathy. Out of all patients 73 % patient had enlarged mediastinal lymph nodes, 51 % had subcarinal and 44 % had hilar lymph node involvement. There were similar findings seen in study done by Yadav et al.<sup>18</sup> The amount of enhancement of 100 lung nodules were studied by measuring the CT numbers of both benign and malignant nodules on both pre contrast scan and post contrast scan showing maximum enhancement. There was no statistically significant difference between heterogeneity of contrast enhancement. In the present study contrast enhancement was only showed by malignant lesion that helps in identification of lesion easily. The most common histopathological subtype was adenocarcinoma which accounted for 41 % cases. This is in concordance with studies done by Shad et al,<sup>19</sup> Modi et al,<sup>20</sup> Babu et al,<sup>21</sup> Gangopadhyay et al<sup>4</sup> that showed that there was an increasing trend in the incidence of adenoma, contrary to the studies done by Adaikkalavan et al,<sup>16</sup> Rawat et al,<sup>15</sup> Saha et al,<sup>9</sup> Ahmed et al,<sup>6</sup> Narayan et al.<sup>8</sup> In all these studies squamous cell carcinoma was the most predominant subtype. Adenocarcinoma was seen more at peripheral location (56.84 %), than central (19.04 %). Small cell carcinoma was also more in central location (9.04 %) while large cell carcinoma was seen both in central (4.76 %) and peripheral location (6.89 %) equally. Similar findings were seen in the study done by Narayan et al.<sup>8</sup> In this study there is evidence of strong association between smoking and occurrence of adenocarcinoma and squamous cell carcinoma. Similar results were obtained in study by Krishnamurthy et al,<sup>22</sup> Arora et al<sup>3</sup> and Meena et al.<sup>5</sup> The present study showed that MDCT is highly sensitive (95.45 %) and moderately specific (75 %) and also has a high positive predictive value (0.96) in diagnosis of lung nodules accurately. In a study done by Mukherjee et al<sup>12</sup> there was 97.7 % sensitivity and 100 % specificity for CT guided FNAC as a diagnostic procedure. Overall occurrence for cytological subtyping was 95 %. Similarly in study done by Meena et al<sup>5</sup> there was 96.23 % sensitivity and 87.50 % specificity for CT as a diagnostic procedure.

## Conclusion

CT is a highly sensitive and moderately specific diagnostic modality and also has a high positive predictive value to diagnose lung nodules accurately. In addition to morphological evaluation, CT provides information about staging of the disease. CT guided FNAC of lung nodule is a safe, minimal invasive procedure with a high diagnostic accuracy. The use of CT – guided FNAC in hilar and mediastinal nodules can avoid unnecessary exploratory surgery for staging and also diagnosis is made with lesser cost. It provides very early diagnosis and exact sub classification of various lung nodules on the basis of histopathology. Benign lesions like tuberculosis, lung cyst, pneumonitis etc can also be diagnosed with certainty by this technique. The shortcomings in the diagnosis can be prevented by proper clinical and radiological correlation.

## Acknowledgements

None.

## Conflict of interest

None.

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# The Effect of Presence of *Helicobacter pylori* on the Severity and Clinical Course of Rosacea

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## Abstract

**Background/Aim:** Rosacea is manifested by erythema and telangiectasias limited to the regions of cheeks, nose, chin and forehead. Data from the literature indicate a possible causal relationship between *Helicobacter pylori* infection in the gastrointestinal tract and rosacea, which is confirmed by the improvement of symptoms and clinical picture of rosacea after administered *Helicobacter pylori* eradication therapy. The aim of the paper was to determine the frequency of *Helicobacter pylori* infection in patients with rosacea and to examine the effect of the therapy for eradication of infection of this microorganism on the clinical course of rosacea.

**Methods:** Sixty patients with a diagnosis of rosacea who were treated in 2018 at the Clinic for Skin and Venereal Diseases of the University Clinical Centre of Republic of Srpska were analysed. Patients were examined during their visit to a dermatologist (first week) and after applied therapy (sixth week). Subjects were divided into two groups - group I consisted of subjects in which, in addition to rosacea, the presence of *Helicobacter pylori* was registered and for whom the topical therapy and triple therapy for eradication of *Helicobacter pylori* were administered, and group II, which included subjects in which, in addition to rosacea, the presence of *Helicobacter pylori* was not registered and for whom only topical therapy was administered. Statistical processing was performed in the IBM SPSS Statistics 21 software package.

**Results:** *Helicobacter pylori* infection was registered in 45 % of patients. Statistical significance was determined between the presence of *Helicobacter pylori* infection and the presence of pustules in patients with rosacea ( $p = 0.027$ ), with an occurrence of pustules significantly more frequent in patients belonging to group I (55.6 %) than in patients belonging to group II (24.2 %).

**Conclusion:** Therapy for eradicating *Helicobacter pylori* infection improves the clinical course of rosacea, especially in the stage of papules and pustules.

**Key words:** Rosacea; Clinical course; *Helicobacter pylori*, effect of medications;

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## Introduction

Rosacea (lat. *Acne rosace*) is a chronic skin disease the basic characteristics of which include erythema of the central face regions with the appearance of papules and pustules as well as hyperplasia of the connective tissue of the skin and sebaceous

glands.<sup>1</sup> It attacks both sexes equally, although in women, aged 40-50 years, the disease occurs more often with milder symptoms.<sup>2</sup> Several factors play a role in the development of the pathological process in this disease: skin vasculature, digestive

tract disorders, endocrine factors, immune and psychosomatic disorders. The available literature points at a potential link between the *Helicobacter pylori* (HP) infection and rosacea.<sup>3</sup> The first report of a possible link between HP and rosacea dates back to 1994. Thirty-one patient with rosacea participated in that study, and 84 % of them were found to have HP infection. After metronidazole therapy, the symptoms of rosacea either receded or disappeared completely.<sup>4</sup> In the sample of a study by Agnolleti et al, HP infection was present in 88 % of patients with rosacea,<sup>5</sup> while a study by Bhattarai et al, gastric HP infection in patients with rosacea was present in 65.4 % of patients.<sup>6</sup> Since HP infection is associated with the symptoms and skin changes in patients with rosacea, several studies proved the improvement in the symptoms and clinical picture of rosacea following HP eradication therapy.<sup>7-9</sup>

The clinical picture of rosacea is characterised by persistent erythema and telangiectasias limited to the regions of cheeks, nose, chin and forehead, involving, rarely, the entire surface of the face with oedema or erythematous papules and/or pustules.<sup>10, 11</sup> The diagnosis of rosacea is established on the basis of a well-taken anamnesis and clinical picture. Digital dermatoscopy is also used in the diagnostics with an obligatory test for the presence of *Demodex folliculorum* mites and a test for the presence of HP infection.<sup>12</sup> Non-invasive methods in the diagnostics of HP include the detection of its specific activity (urease enzyme - urease breath test), the presence of specific antibodies in the saliva and/or serum of an infected person or the detection of HP antigen in the patient's stool. Invasive methods reveal the presence of HP (microbiological examination, histological examination) or its activity (rapid urease test) in biopsy samples of gastric mucosa obtained by endoscopic examination.<sup>13</sup> The differential diagnosis largely depends on the form of rosacea, with the exclusion of seborrheic dermatitis, lupus erythematosus and other photodermatoses, carcinoid syndrome and mitral valve insufficiency, acne, bromoderma and iododerma, perioral dermatitis and pustular folliculitis, lupus vulgaris and cutaneous sarcoidosis.<sup>14, 15</sup> Classic therapy of rosacea is based on the use of antibacterial drugs from the group of macrolides and metronidazole and topical therapeutic agents, and in more severe forms, also, of synthetic retinoids or combined therapeutic modalities, as in the case of eradication of *Demodex folliculorum* mites with anti-inflammatory therapy and phys-

iotherapy, low-power and high-power laser methods, and photodynamic therapy.<sup>16-19</sup>

The aim of this study was to determine the frequency of HP infection in patients with rosacea as well as to examine the effect of the therapy for HP infection eradication on the clinical course of rosacea.

## Methods

In a prospective study, 60 patients diagnosed with rosacea who were treated in 2018 at the Clinic for Skin and Venereal Diseases of the University Clinical Centre of Republic of Srpska were analysed. Only patients diagnosed with rosacea over the age of 18 were included in the study, while patients under the age of 18 and patients who did not adhere to the treatment protocol and did not come for weekly follow-up examinations were excluded from the study.

Patients were referred to a dermatologist for purposes of assessment of the subjects' skin phototype according to Fitzpatrick<sup>20</sup> and the presence of general symptoms in the region of the affected skin (burning, itching and pain). The dermatological status of the skin affected by the changes was determined, ie, the gradation of the intensity of the disease was performed, from the mildest to the most severe stages: erythema, papules, pustules and phyma, respectively. Patients were examined during their visit to a dermatologist (first week) and after applied therapy (sixth week). The severity of the clinical picture was presented in three categories: moderate symptoms, occasional outbreak of changes in rosacea and worsening of rosacea. Following an examination by a dermatologist, the subjects were referred to the Central Laboratory of the University Clinical Centre of Republic of Srpska, where a single blood test was performed for presence of HP infection, and tests for qualitative *in vitro* detection of IgG antibodies to HP (enzyme-linked immunosorbent assay, ELISA test) were used for this purpose. Laboratory blood analyses were performed by one laboratory technician, and the interpretation, examination and monitoring of the patient were performed by one dermatologist. Based on the positivity of the results concerning the presence of antibodies to HP, the subjects were divided into two groups. Group I consisted of subjects

in whom, in addition to rosacea, as a primary disease, the presence of HP was registered, while group II consisted of subjects in whom, in addition to rosacea, as a primary disease, no presence of HP was registered, which was also the control group. Topical therapy (metronidazole cream 2 times a day for six weeks, with regular skin hydration using neutral creams) as well as triple therapy for eradication of HP (azithromycin tablets 500 mg 1 x 2, for three days, metronidazole tablets 400 mg 3 x 1, for seven days, pantoprazole tablets 20 mg 2 x 1, for seven days, followed by 1 x 20 mg, for 15 days) were administered for group I patients. Only the topical therapy (metronidazole cream 2 x daily for six weeks, with regular hydration using neutral creams) was administered for group II patients.

Statistical processing was performed in the IBM SPSS Statistics 21 software package. The results were presented numerically and tabularly. The  $\chi^2$  test and the two-sided two-sample test were used for statistical analysis, and the reliability value of 0.05 was taken for the margin of statistical significance.

## Results

The sample of this study consisted of 60 patients diagnosed with rosacea. All subjects were familiar with the study concerned and signed an informed consent. With regard to gender distribution, 52 subjects (86.7 %) were female and 8 subjects (13.3 %) were male. The age of the subjects ranged from 18 to 79, with the average age of 45.88. The majority of subjects had skin type according to Fitzpatrick III (91.7 %) and 8.3 % of patients had type IV. The duration of rosacea was measured in months and ranged from one month to 360 months (30 years), with the average duration of the disease being about 30 months. The general symptoms in the region of the affected skin, included, most frequently, burning (35 subjects or 58.3 %), itching in 20 subjects (33.3 %) and pain was present in 12 subjects (20 %). Erythema was present in 59 subjects (98.3 %). Papules were present in 47 subjects (78.3 %). Erythema and erythematous papules were observed in 55 subjects (91.7 %), while the pustular stage was registered in 23 subjects (38.3 %). Stage 4 or phymatous rosacea was observed in 6 subjects (10 %).

A qualitative *in vitro* analysis of IgG antibodies to HP from the blood of patients, registered the presence of HP in 27 patients (45 %), in addition to rosacea as the primary disease (group I), while in 33 patients (55 %) no presence of these antibodies was registered (group II). As regards the gender distribution, in both examined groups there were more female subjects - 77.7 % in group I and 93.9 % in group II. When it comes to age distribution, a difference was observed, because the majority of patients from group I (55 %) were 18 to 30 years old, while in group II the largest percentage were persons of older age (51-80 years of age). Use of the  $\chi^2$  test revealed no statistically significant relationship between the frequency of HP infection and the age of the subjects (Table 1).

**Table 1:** Frequency of *Helicobacter pylori* infection in relation to the age of the subjects ( $\chi^2$  test)

Age (years)	N	<i>Helicobacter pylori</i>				P
		No		Yes		
		N	%	N	%	
18-30	20	9	45	11	55	0.405
31-50	17	9	52.9	8	47	
51-80	23	15	65.2	8	34.8	

N: number of patients;

It was noticed, based on a comparison of the presence of skin changes in the examined groups, that erythema was present in all patients of group I (100 %), and in 32 subjects in group II (96.9 % of cases). Papules were present in 26 subjects (96.3 %) of group I, and in group II papules were observed in 27 (87.9 %) subjects. Pustules were present in 15 subjects of group I (55.6 %), and in 8 subjects (24.2 %) in group II. No statistical significance was observed between the presence of erythema and papules in relation to the presence of HP infection in the present subjects. However, the application of the  $\chi^2$  test revealed a statistically significant relationship between the presence of HP infection and the presence of pustules in patients with rosacea ( $p = 0.027$ ), with the incidence of pustules being significantly higher in group I patients than in group II patients. Phyma was present in 1 subject of group I (3.7 %) and in 5 subjects of group II (15.2 %).

The three registered stages of severity of rosacea symptoms were analysed. It can be noticed that moderate symptoms were more common in group II patients. Worsening of rosacea symptoms was much more common in subjects in the group with HP infection presence (40.7 %). There was no statistically significant difference in the clinical picture severity in relation to the presence of HP infection (Table 2).

**Table 2:** Severity of the clinical picture of rosacea in relation to HP infection ( $\chi^2$  test)

Helicobacter pylori	N	Rosacea severity						p
		Moderate symptoms		Occasional outbreak		Worsening of rosacea		
		N	%	N	%	N	%	
Negative	33	21	63.6	7	21.2	5	15.2	0.083
Positive	27	12	44.4	4	14.8	11	40.7	

N: number of patients;

Of the total number of subjects, erythema regression occurred in 59 subjects (98.3 %), and regression of papules occurred in 53 subjects (88.3 %). Regression of pustules occurred in 23 subjects (38.3 %), and a decrease in phyma was observed in 3 subjects (5 %).

The applied triple therapy for HP infection eradication and the topical therapy for rosacea led to a more pronounced regression of skin changes in group I subjects. Regression of erythema occurred in all 27 subjects (100 %). Papules that were present in 26 group I subjects also receded in all 26 subjects (100 %). In group I, pustules were observed in 15 subjects in the first week, and regression of pustules occurred in 13 subjects (86.7 %). Regression of skin changes in subjects with phyma was reported.

In group II subjects, erythema regression occurred in all 32 subjects (100 %) in whom erythema was observed in the first week. Also, all subjects with the presence of papules reported regression of changes. During the first week, pustules were observed in 8 subjects, while regression occurred in 5 subjects (62.5 %). Regression of skin changes was observed in 2 subjects (40 %) with phyma.

**Table 3:** Effectiveness of the applied therapy on pustule and phyma regression (two-sided two-sample test)

Skin changes	Group I (27 subjects)	Group II (33 subjects)	p value
Pustules 1 <sup>st</sup> week	15	8	p = 0.209
Regression of pustules 6 <sup>th</sup> week	13 (86.7 %)	5 (62.5 %)	
Phyma 1 <sup>st</sup> week	1	5	p = 0.006
Regression of phyma 6 <sup>th</sup> week	1 (100 %)	2 (40 %)	

Group I: patients with rosacea and Helicobacter pylori infection;

Group II: patients with rosacea without Helicobacter pylori infection;

Regression of erythema and papules occurred in all subjects of both groups. Table 3 shows the effectiveness of the applied therapy solely with regard to the regression of pustules and phyma.

A comparison of the therapy effectiveness between group I and group II subjects, using a two-sided two-sample test, showed no statistically significant difference in the therapeutic response in pustule regression ( $p = 0.209$ ). As regards the regression of the phyma, there is statistical significance ( $p = 0.006$ ) in favour of group I. However, due to the small number of subjects with the presence of the phyma, these data cannot be considered as valid.

## Discussion

In this study, of the total number of patients, 86.7 % were female patients and 13.3 % were male patients, while their age ranged from 18 to 79 years, with the average age of 45.88. Of the total 27 number of subjects, who were positive for HP infection most of which were women (77.7 %), while only 6 subjects (22.3 %) were men. HP infection was somewhat more frequent in younger subjects, ie, the presence of HP infection was observed in 55 % of subjects aged 18-30.

Szlachcic established a close link between HP infection and the appearance of rosacea. He states that HP can cause skin inflammation in two ways: by increasing the concentration of nitric oxide (consequently vasodilation) and by inducing a specific cytotoxic reaction, ie, the expression of cytotoxic genes and initiation of a series of inflammatory reactions.<sup>3</sup> On the other hand, based on a quantitative analysis of fourteen studies involving 928 patients and 1527 controls, Jørgensen et al<sup>21</sup> concluded that there was a weak link between HP infection and rosacea, just like that the application of the triple therapy to eradicate HP infection does not result in a significant regression of rosacea symptoms, which is contrary to the results obtained in this studied sample. Yang recommends that all patients with rosacea should be tested for the presence of HP infection in order to achieve the desired therapeutic effects<sup>22</sup> by eradicating the infection, which would be the recommendation of the present study's result, too.

There are theories suggesting that HP infection is a predisposing factor for the appearance of rosacea. Hong observed a more frequent rate of HP infection (Urase-IgG antibodies and HP CagA-IgG antibodies) in the peripheral blood of 39 patients

with rosacea. The incidence rate in patients with rosacea and digestive tract symptoms was 86.7 %, and in patients with rosacea without digestive tract symptoms the incidence rate was 16.7 %.<sup>23</sup>

The dominant symptom in these patients include burning (58.3 %), itching in 33.3 % and pain as a general symptom of rosacea in 20 %. Given the present skin changes, erythema was most common (98.3 % of subjects), followed by erythema papules in 91.7 %, while the third stage or pustular stage was registered in 38.3 % of subjects, and the fourth stage or phymatous rosacea in 10 %.

Skin changes in these subjects show that there is a statistically significant relationship between the presence of HP infection and the presence of pustules in patients with rosacea, with the incidence of pustules being significantly higher in patients with HP infection (55.6 %) than in patients without infection (24.2 %). The severity of the clinical picture of rosacea with regards to HP infection shows that moderate symptoms are more common in patients without HP infection (63.6 %) compared to positive subjects (44.4 %), while worsening of rosacea symptoms is much more common in subjects with present HP infection (40.7 %) than in subjects with rosacea without HP infection (15.2 %).

The applied triple therapy for eradicating HP infection and topical therapy for rosacea in the group I patients led to a more pronounced regression of skin changes, compared to the application of topical therapy in group II patients, but without confirmed statistical significance. The results are in accordance with the data from the literature.<sup>21-23</sup> Piri showed the success of standard triple therapy for eradicating the bacterium but emphasises that due to the high resistance of the bacterium to antibiotics, a better and more effective antibiotic therapy is needed to fight HP.<sup>24</sup>

Authors Saleh et al attempted, in a clinical study, to evaluate the effect of a standard HP eradication protocol on the clinical course of rosacea. In this clinical trial, patients diagnosed with HP infection based on serological studies were evaluated as patients that should be tested for rosacea presence, underwent standard HP eradication therapy. Rosacea was evaluated using the Duluth rosacea grading score at the beginning, 2 months later and at the end of the trial (day 180). Of 872

patients positive for HP, 167 patients (19.15 %) manifested the clinical features of rosacea. The patients with concomitant rosacea and the presence of HP were younger and predominantly female, as was the case in the presented sample. Of 167 patients, 150 received HP eradication therapy, demonstrating a 92 % cure rate. The rosacea Duluth score grading on day 0, 60, and 180 among 138 patients significantly decreased in most criteria, except for telangiectasias ( $p = 0.712$ ) and phymatous changes ( $p = 0.535$ ). This study concluded that eradication of HP leads to improvement in rosacea.<sup>25</sup> The results of the present study are in line with the data of this study.

Contrary to the majority of studies, Herr states that he did not observe a significant improvement in skin changes in rosacea applying triple therapy. Namely, he examined 100 patients with rosacea, but 50 of them received triple therapy, while the other 50 patients received placebo. It was observed that after 2 months the intensity of regression of changes in both groups was approximately the same.<sup>26</sup> The results of this study are consistent with the conclusions of Jorgensen et al.<sup>21</sup>

However, it is necessary to emphasise that there are limitations to the test for HP presence using blood analysis (tests for qualitative *in vitro* detection of IgG antibodies to HP). Namely, this test does not detect the difference between the current and a previous infection. For purposes of accuracy of testing, the new recommendations refer to the method of detection of HP from a stool sample, rather than a blood sample, as a more reliable one.

## Conclusion

In this study sample, the presence of HP infection was registered in 45 % of patients, more frequently in younger subjects and females. The pustular form of rosacea was more common in patients who tested positive for HP. Worsening of rosacea symptoms was much more common in subjects with HP infection. Therapy for eradicating HP infection improves the clinical course of rosacea, especially in the stages of papules and pustules.

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## Conflict of interest

None.

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# The Clinical and Pathological Characteristics and Survival of Patients With Advanced Ovarian Cancer

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## Abstract

**Background/Aim:** Ovarian cancer has the highest mortality rate of all gynaecologic malignancies. The aim of this study was the evaluation of the clinical pathological characteristics and survival analysis of primarily operated patients with advanced stages of malignant epithelial ovarian tumour.

**Methods:** The research was conducted as a cohort study with 59 patients with FIGO stage III and IV, which were primarily operated between 1 January 2008 and 31 December 2010 (three years). Age, comorbidities, BMI, presence of ascites, the level of the marker CA-125, histopathology and FIGO stage were analysed. The survival rate was estimated at the level of 1, 3 and 5 years.

**Results:** The median age was 53 years (range 29-86). The most common histopathological type was serous (66.1 %) and the most common FIGO stage was 3a (49.2 %). Optimal cytoreduction was performed in 35.5 % of patients, 84.7 % of patients survived for one year, 44.1 % three years and 37.3 % for five years. The median survival was 26.25 months (range 0-91). Chi-square test showed significant difference between the number of months of survival and: the value of CA-125 ( $t = 2.004$ ,  $p = 0.050$ ), cytoreduction ( $p < 0.001$ ) and FIGO stage ( $p < 0.01$ ).

**Conclusion:** According to the results of this study, optimal cytoreduction and FIGO stage significantly influence survival ( $p < 0.001$ ). Optimal cytoreduction (< 2 cm of residual disease) had the highest prognostic value for survival. A total five-year survival in this study was 37.3 %.

**Key words:** Ovarian cancer; Radical surgery; Survival rate; Clinical features; Pathological features.

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## Introduction

Ovarian cancer makes 5 % of all malignant tumours in women and has the highest mortality rate of all gynaecological malignancies.<sup>1</sup> Ovarian cancer in the early stages of the disease is characterised by non-specific symptomatology which can easily be misinterpreted.<sup>2</sup> Therefore, the disease is, in 60-70 % of cases, detected in advanced stages, which partly explains the high mortality.<sup>3</sup>

The aetiology of ovarian cancer is multifactorial. A number of factors increase the risk of ovarian cancer: a family history of ovarian cancer, previ-

ous breast or endometrium cancer, lower parity or infertility, late menopause, age, genetic background, obesity and smoking, and exposure to chemical and biological agents from the environment.<sup>4,5</sup> Marker, cancer antigen 125 (CA-125) is elevated in about 80 % of patients with advanced disease stadiums. However, it is a non-specific marker which can be elevated in some benign conditions as well.<sup>6</sup> The definitive diagnosis is based on histopathologic examination of tumour tissue after surgery (laparoscopy or laparotomy).

The standard surgical treatment of ovarian cancer involves a maximum reduction of the tumour mass, ie a hysterectomy with bilateral adnexectomy and omentectomy, and in some cases appendectomy and pelvic and/or para-aortic lymphadenectomy are done.<sup>7</sup> In advanced stages of ovarian cancer cytoreductive surgery with the aim of a greater reduction of tumour mass is done, due to better effect of chemotherapy.<sup>8,9</sup>

The two most important prognostic factors for further postoperative course and outcome of disease are the stage of tumour disease at the moment of diagnosis (FIGO stage) and the volume of residual tumour tissue.<sup>10</sup> Vergote and colleagues have shown that the mass of residual tumour expressed in grams and the age of the patient are the only two independent prognostic factors.<sup>11</sup> Although the prognosis of patients with advanced ovarian cancer has improved in recent decades, the long-term survival remains low and is, despite all therapeutic measures, less than 50 % for 5 years overall.<sup>12</sup> Therefore, there is a tendency to develop more effective therapeutic procedures, especially for patients whose tumours cannot be treated by initial optimal cytoreduction.<sup>13</sup> A significant issue in the treatment of advanced ovarian cancer concerns the assessment of surgical cytoreduction, which has not proved reliable even by visual inspection methods, serum biomarkers, and even with the help of molecular biology. Although there are still few studies on the role of laparoscopy in valuating resectability in advanced ovarian cancer, it proved to be a promising approach.<sup>14</sup>

The aim of this study was to evaluate the clinical pathological characteristics and survival analysis of primarily operated patients with advanced stages of malignant epithelial ovarian tumours at the Clinic of Gynaecology and Obstetrics, University Clinical Centre of the Republic of Srpska, Banja Luka, Bosnia and Herzegovina (Clinic).

## Methods

The research was conducted as a cohort study in the Clinic. It included 59 patients who were primarily radically operated in the period from 1 January 2008 to 31 December 2010 (three years), in which the changes to adnexa were preopera-

tively diagnosed and malignant epithelial ovarian tumour of the third and fourth (FIGO III and IV) stage was postoperatively histopathologically confirmed. Prospective part of the study observed the five-year survival of all operated patients and the state of their vital status until 31 December 2015. The basic epidemiological data, personal, family, gynaecological history and the results of laboratory tests [blood count, level of tumour markers (CA 125, HE 4, Roma index)] were taken from all the patients from medical archives of the Clinic for Gynaecology and Obstetrics of University Clinical Centre of Banja Luka.

In patients in whom it was preoperatively estimated that the tumour was resectable, the disease stage was determined by laparotomy and radical surgery was made and in accordance with current protocols. The decision as to whether the patient will be primarily operated or will go to neoadjuvant chemotherapy was based on a clinical review, general condition, age, performance status and results of the CT scan. In all operable patients, and depending on the stage of the disease, the total hysterectomy with bilateral adnexectomy, total supracolic omentectomy, appendectomy, pelvic and/or para-aortic lymphadenectomy and multiple biopsies of macroscopically unchanged peritoneum were done.

Postoperatively, histopathological findings (HP) of removed tumours were analysed in order to establish a definitive diagnosis and staging of disease. From operating protocols, and HP reports, the extent of the surgery and the existence and size of possible residual tumour was determined. Based on the size of residual tumour tissue, patients were divided into 2 groups: patients with the largest diameters of residual tumour < 2 cm - complete and optimal cytoreduction, and patients with the largest diameters of residual tumour  $\geq$  2 cm - suboptimal cytoreduction. Postoperative chemotherapy was determined based on these data.

The survival rate (of 1, 3 and 5 years) was determined and all the factors that affect the survival rate were analysed for the patients who had been operated from one to five years before. Survival data were obtained in personal contact with patients (interview by telephone) or families of deceased patients, then from registry offices, municipality of residence of the patient and the Statistical Office of Bosnia and Herzegovina.

Data was compared with Chi-squared test, using IMB SPSS version 16.0 statistical software. Statistical significance was set up at  $p < 0.05$ .

## Results

The study included 59 patients with malignant epithelial ovarian tumour of stage III and stage IV (FIGO III and IV) who were primarily radically operated in the three-year time period. There were a total of 75 patients with epithelial ovarian tumours who were treated in the Clinic in that time period, but this study only included 59 (79 %) patients who were primarily operated. In 16 patients (21 %) only a biopsy was performed, ei-

**Table 1:** Clinical and pathological features of patients

Parameters	Values	N	%
Year of starting treatment	2008	17	128.8
	2009	23	39.0
	2010	19	32.2
Age groups	< 65 years	43	72.9
	≥ 65 years	16	27.1
Family history	Negative	53	89.8
	Positive	6	10.2
Chronic diseases	No	38	64.4
	Yes	21	35.6
Body Mass Index BMI (kg/m <sup>2</sup> )	≥ 25	28	47.5
	< 25	31	52.5
Ascites	No	18	31.6
	Yes	39	68.4
	Missing	2	
Tumour marker CA-125 (U/dL)	< 500	37	62.7
	≥ 500	22	37.3
Pathological diagnosis	Serous	39	66.1
	Mucinous	7	11.9
	Other	13	22.0
FIGO stage	3a	29	49.2
	3b	6	10.2
	3c	14	23.7
	4a	7	11.9
	4b	3	5.1
Chemotherapy	No	8	13.8
	Yes	50	86.2
	Missing	1	
Number of months of survival	< 12	10	16.9
	12-36	23	39.0
	> 36	26	44.1
Alive October 2015	Yes	22	37.9
	No	36	62.1
	Missing	1	59.0
Patients	Total	59	100.0

ther by laparotomy or laparoscopy, and they were directed to neoadjuvant chemotherapy, and they were not included in this study. Table 1 shows the clinical and pathological features of patients, while Table 2 shows mean values and dispersion measures for continuous numerical variables.

**Table 2:** Mean values and dispersion measures of clinical features

Parameter	Age (Years)	Body Mass Index - BMI (kg/m <sup>2</sup> )	Tumour marker CA-125 (U/dL)	Months of survival
Mean	56.03	25.55	563.66	39.90
Median	53.00	25.40	230.00	26.00
Mode	51	24.10	85.00	13.00
Std. deviation	12.72	3.20	826.56	29.92
Minimum	29	19.60	10.00	0
Maximum	86	35.40	4200	91

Most of patients (n = 43) were ≥ 65 years (72.9 %), and most of patients did not have a history of gynaecological and breast malignancies (89.8 %). Median age was 53 ± 17.7 years. Most patients (38), had no chronic diseases (64.4 %) and 31 of them had a body mass index (BMI) ≥ 25 (52.5 %). The median BMI was 25.4 ± 3.1 kg/m<sup>2</sup>.

Thirty-nine patients (66.1 %) had ascites and 36 of them had tumour marker values CA-125 ≥ 500 U/dL (62 %). Tumour marker below 500 have been reported among the 17 patients who survived less than 3 years, which makes 51.5 % of all patients who survived less than 3 years. Tumour markers below 500 have been reported among the 20 patients who survived more than 3 years, which makes 76.9 % of all patients who survived over three years. The difference between these percentages (ratio) was statistically significant (t = 2.004, p = 0.050). Thus, statistic shows that there are significantly more patients with tumour markers below 500 among the patients who survived 3 years and more, than among the patients who survived less than 3 years.

Optimal cytoreduction was performed in 21 patients (35.5 %) while 38 patients (64.4 %) were sub-optimally operated. The most common HP stage was serous type (66.1 %), while 29 patients (49.2 %) had the most common FIGO stage 3a. Fifty patients (84.7 %) received postoperative chemotherapy.

In the first postoperative year 10 patients (16.9 %) died. In the period from 12 months to 36 months 23 patients (39 %) died, and other 26 patients



died in the period after 36 months (44.1 %). Table 3 shows the number of the surviving patients after one, three and five years.

**Table 3:** The number of the surviving patients after one, three and five years

Number of years of survival	N	%
Up to 1 year (up to 12 months)	50	84.70
Up to 3 years (36 months)	26	44.10
Over 5 years (over 60 months)	21	35.60

In this research, 50 patients (84.7 %) survived for one year, 26 patients (44.1 %) survived for three years, 21 patients survived for five years (37.3 %). Median survival was  $26 \pm 29.9$  months (Table 2). Table 4 mostly show nominal variables and their correlation with the number of months of survival, which was tested using Chi-square tests, whose results are reported in Table 4.

**Table 4:** Variables and their correlation with the number of months of survival (Chi-squared test)

Variables in contingency table	N	X <sup>2</sup>	df	p
Age groups	59	1.544	2	0.462
Family history	59	1.961	2	0.375
Chronic diseases	59	0.273	2	0.872
Body Mass Index - BMI (kg/m <sup>2</sup> )	59	2.600	2	0.873
Ascites (Yes/No)	57	2.976	2	0.226
Tumour markers	59	4.456	2	0.108
Pathohistological diagnosis	59	9.934	4	0.042
Cytoreduction	59	22.949	2	< 0.001
FIGO stage	59	42.791	8	< 0.001
Chemotherapy	58	0.660	2	0.719
The year of the start of treatment	59	6.979	4	0.137

*Red colour: statistical significance;*

Statistically significant relationship was found between HP diagnosis and months of survival (classified in three groups). Interpretation of the association is the following: in patients with serous histologic type of diagnosis survival was the longest (54 % of patients survive over 3 years with this diagnosis). In patients with mucinous histologic type survival is the shortest, since 42 % of them survived up to a year. Statistically significant association ( $p < 0.001$ ) was found between the level of cytoreduction and the number of months of survival. Significant correlation was found between FIGO stage and the number of months of survival ( $p < 0.01$ ).

## Discussion

This research included 59 patients with malignant epithelial ovarian tumour of stages III and IV (FIGO III and IV) which were primarily radically operated in the three-year time period, in which there were a total of 75 patients with epithelial ovarian tumours who were treated in the Clinic. As is noted, this research included only the patients who were primarily operated and that is 59 patients (79 %). In 16 patients (21 %), only a biopsy was done, either by laparotomy or laparoscopy, and they were directed to neoadjuvant chemotherapy, and were excluded from this study. One of the reasons for exclusion of these patients was that researchers were unable to track and identify women treated with neoadjuvant chemotherapy before surgery because of the absence of data during the entire period of the study.

In 2016, Dahm-Kähler and colleagues from Sweden have posted a multicentre study, similar to this, in which they had 81 % primarily operated, optimum cytoreduction in 37 % to 49 % of patients and the relative rate of the three-year survival ranged between 44 % and 65 %.<sup>15</sup> In this study 85 % of patients survived for one year after operation, 44 % of patients survived for three years, and a five-year survival was 35.5 %. Median survival for the 59 patients followed was 26.25 months, which showed that the results of this study are similar to presented results.

This study examined the clinical pathological characteristics of tumour and survival of patients with advanced stage of epithelial ovarian cancer. Median age was 53 years, which is significantly lower than in other similar studies. In the research of Mueller et al median age was 62 years, while in the study Fotopoulou and associates, median age was 63.<sup>16, 17</sup> The difference and much earlier occurrence of advanced ovarian cancer in presented population is disturbing. Some studies show the impact of age on survival, which was not confirmed in this study.<sup>24</sup>

The results presented also identified the three most important factors affecting the survival of patients: HP type of tumour, tumour FIGO stage and the level of cytoreduction. Two independent prognostic factors, FIGO stage and histological type of tumour, have shown a great impact on survival. The most common histological type was

serous epithelial ovarian cancer, which was also shown as the best prognostic factor with longer survival compared to other histological types. Also, nearly half of the patients were with FIGO stage IIIa, where the results of survival were better compared to other stages. These results are correlated with the results of other authors.<sup>18-20</sup>

Results also showed the importance of optimal cytoreduction and a great significance of residual tumour < 2 cm on the survival of patients with stage III and IV resectable ovarian cancer. Size of residual tumour after primary surgery is one of the most important prognostic factors according to most studies.<sup>21-23</sup> Results clearly demonstrate the importance of surgical intervention and optimal cytoreduction on survival of our patients, and they are in correlation with other studies and in particular with study of Mette Ørsk and associates, where they concluded that the most important predictors of mortality within one year after

surgery are residual tumour tissue > 2 cm (0-180 days after surgery) and advanced FIGO stage of the disease.<sup>24</sup> However, optimal cytoreduction was performed in only 35 % of patients who had a significantly longer survival compared to patients treated with suboptimal operation, which showed the prognostic importance of optimal cytoreduction in this study as well.

This study has certain limitations, lack of information on smoking, alcoholism or use of drugs to stimulate ovulation and their impact on survival. Then, some treated patients were not acceptable for evaluation. Also, data on possible reoperations and data on neoadjuvant chemotherapy were not available. And finally, even if the exact time of death of the deceased patients was available, the information about the exact cause of death of patients was not, so, these data may have influenced the results of our research.

## Conclusion

According to the results of this study, two important independent prognostic factors were found; the benefit of optimal cytoreduction (< 2 cm of residual disease) that had the greatest prognostic value on survival and pathohistological type of tumour (serous histological type proved to be the most favourable). FIGO stage of the disease and the value of CA-125 markers were inversely correlated with the survival of patients. According to this results, patient survival was not significantly associated with age, family history of gynaecological malignancies and breast malignancies, comorbidities, or with the values of the BMI.

## Conflict of interest

None.

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# Effect of Cardiovascular Training on Functional Capacity in Post-Acute Rehabilitation of COVID-19 Patients

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## Abstract

**Background/Aim:** In the overall strategy of developing the optimal treatment of patients after COVID-19 infection, recommended by the World Health Organization, rehabilitation plays one of the key roles in improving the functional capacity of these patients and thus their quality of life. The aim of this study was to investigate the effect of cardiovascular training during post-acute rehabilitation on the functional capacity of patients after moderate COVID-19 pneumonia.

**Methods:** The prospective study included 84 patients of both sexes, mean age  $57.92 \pm 11.79$  years, who were hospitalised at the Institute of Physical Medicine and Rehabilitation "Dr Miroslav Zotović" Banja Luka due to moderate pneumonia caused by the COVID-19 virus and after they finished acute rehabilitation. All patients underwent cardiovascular training three times per week and occupational therapy during 28 days of stationary post-acute rehabilitation. The follow-up parameter was a six-minute walk (6-MWT) test at admission and discharge from post-acute rehabilitation. Student t-test for paired samples was used for statistical analysis, and the value of  $p < 0.05$  was taken as statistical significance.

**Results:** The functional capacity of the cardiovascular and respiratory system was statistically significantly improved at discharge compared to admission ( $p < 0.05$ ).

**Conclusion:** Targeted cardiovascular training during post-acute rehabilitation leads to improvement of functional capacities of patients after moderate COVID-19 pneumonia.

**Key words:** Cardiovascular training; Post-acute rehabilitation; COVID-19.

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## Introduction

Conducting rehabilitation during the COVID-19 pandemic is a major challenge. On the one hand, the need for rehabilitation has increased, but the way of organisation and timing of its implementation required the reorganisation of rehabilitation systems around the world.<sup>1,2</sup> The World Health Organization (WHO) has integrated rehabilitation as one of the key links in the chain of the

overall treatment of COVID-19 patients, whether it is acute or post-acute rehabilitation.<sup>3</sup> The main goals of post-acute rehabilitation of these patients are reduction of current problems, training in breathing techniques and improvement of lung function, improvement of general fitness status, and ultimately improvement of quality of life. A 6-MWT was used as a test to assess the effect

of post-acute rehabilitation. This test was introduced in 2020 according to the recommendations of the American Thoracic Association as a test to assess aerobic capacity and endurance.<sup>4</sup> However, this test can also be used to assess functional capacity in amputees, patients with neurological and muscular diseases.<sup>5</sup>

The aim of this study was to investigate the effect of cardiovascular training in post-acute rehabilitation on the functional capacity of patients after moderate COVID-19 pneumonia.

## Methods

A prospective study followed 84 patients who, after hospitalisation due to moderate pneumonia caused by the COVID-19 virus and finished acute rehabilitation, underwent post-acute rehabilitation at the Institute for Physical Medicine and Rehabilitation "Dr Miroslav Zotović" Banja Luka in period from October 2020 to March 2021. Criteria for admission to post-acute rehabilitation was inpatient treatment of patients with COVID-19 pneumonia. Criteria for inclusion in the study were hospitalised patients of both sexes with moderate pneumonia caused by COVID-19 virus with no other comorbidities except hypertension. The exclusion criteria were patients younger than 30 years and patients with associated chronic diseases except hypertension. All patients underwent cardiovascular training three times per week and occupational therapy during 28 days of inpatient post-acute rehabilitation. Cardiovascular training included the implementation of the following rehabilitation interventions: breathing gymnastics, muscle strength training, endurance training, ergometer, back gymnastics, pelvic floor muscle training. Through the modalities of occupational therapy, patients underwent progressive muscle relaxation, practicing daily life activities, and educating patients about self-help measures. Patients were tested using 6-MWT on admission and discharge from post-acute rehabilitation. The walk distance as a result of test used for evaluation of cardio-respiratory capacity. Student t-test for paired samples was used for statistical analysis, and the value  $p < 0.05$  was taken as statistical significance.

## Results

The investigated sample of patients consisted of 84 patients, with a mean age of  $57.92 \pm 11.79$  years (Figure 1, Figure 2).

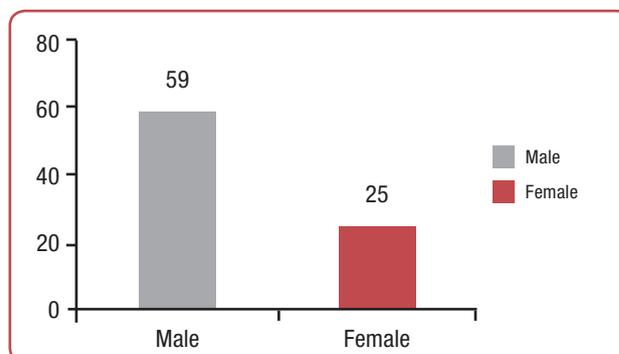


Figure 1: Distribution of patients by gender

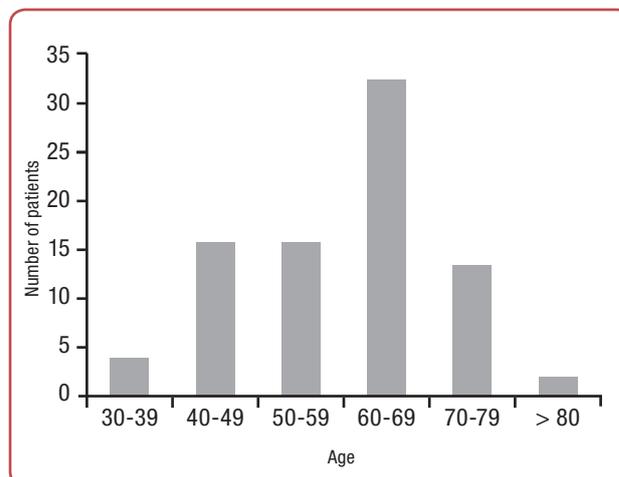


Figure 2: Distribution of patients by age

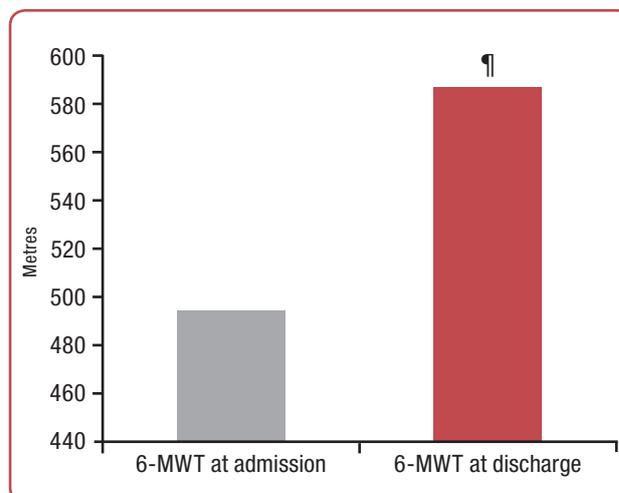


Figure 3: Mean value 6-minute walk test (6-MWT) in post-COVID-19 patients at admission and discharge from post-acute rehabilitation (metres)

†  $p < 0.05$

The average time from completion of primary hospital treatment and acute rehabilitation to admission to post-acute rehabilitation was 50 days.

The values of the 6-MWT on admission and discharge from post-acute rehabilitation were taken as average values. At admission, the average value of the 6-MWT was 493 m. At discharge, the value of the monitored parameter was statistically significantly better at 583 m ( $p < 0.05$ ) (Figure 3).

## Discussion

This study was based on the evaluation of the effects of the applied modalities of post-acute rehabilitation in patients suffering from moderate pneumonia caused by the COVID-19. Since most patients complain of fatigue, shortness of breath, palpitations, and loss of muscle mass after suffering from COVID-19 pneumonia, the goal of this rehabilitation is to minimise these symptoms. Rehabilitation was performed in accordance with the basic principles of cardiovascular and respiratory rehabilitation.<sup>5</sup> The average time from completion of primary hospital treatment and acute rehabilitation to admission to post-acute rehabilitation was 50 days. Patients underwent cardiovascular training three times per week with occupational therapy for a total of 28 days. A 6-MWT as a parameter to assess the effect of the applied therapy was used. Positive effects of applied aerobic training in patients on functional cardio-respiratory capacity were observed, which was shown in a statistically significant improvement in the average value of the 6-MWT on discharge from post-acute COVID-19 rehabilitation. During the post-acute rehabilitation, side effects of the applied therapeutic interventions were not determined.

Although these are the challenges of the “new disease” there are many studies that testify to the benefits of cardiovascular training on the financial capacity of patients after COVID-19 pneumonia.<sup>6-13</sup> These positive effects can be explained by understanding the mechanisms of action of applied therapeutic interventions in the plan of cardio-respiratory rehabilitation. Cardiovascular training improves the functional capacity of patients after COVID-19 pneumonia in several ways. By improving the strength and endurance of the

respiratory muscles, additional ventilation is improved. Combining aerobic capacity reduces free radical production and oxidative damage, reduces cough and improves airway clearance. Conducting aerobic training improves the immune response.<sup>14-17</sup>

One of the limiting factors is the short follow-up period, although there are studies that report positive short-term effects of applied cardiovascular training in post-COVID-19 patients.<sup>8-11</sup>

Besides, the period of time between the end of acute rehabilitation and starting post-acute rehabilitation is a parameter that should be considered in the future. This is especially important from the aspect of the found average values of the 6-MWT at admission. In this study, the average values of this parameter were in the range recommended for the age of 20-50 years.<sup>4</sup> If patients were admitted earlier for post-acute rehabilitation, the effect could be even better and clinically more significant. Of course, it is indisputable that the criteria for admission to post-acute rehabilitation are primarily met. This means it is necessary to conduct the post-acute rehabilitation at the right time and with the right effect, without side effects and complications, that criteria for admission of patients must be clearly defined and fulfilled. Surely this will happen in the future connectivity of scientific truth in the field of treatment and rehabilitation of patients after COVID-19 pneumonia. The criteria will be changing and supplementing within the overall management of these patients and improve their functional capacity and quality of life.

## Conclusion

The positive effects of cardiovascular training were verified in patients after post-acute rehabilitation after COVID-19 moderate pneumonia in the short-term follow-up period. It is indisputable that that this is a dynamic clinical and scientific field and that in the future numerous reports will define the optimal components of post-acute rehabilitation, the dynamics of its implementation, and tools for monitoring its outcome.

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## Conflict of interest

None.

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# Faecal Transplantation and *Clostridioides difficile* Infection

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## Abstract

Faecal microbiota transplantation (FMT), known equally well as faecal transplantation or faecal bacteriotherapy, is the process of implanting the faecal suspension containing balanced microbiota from a healthy donor to the colon of a recipient patient. Excessive growth of *Clostridioides difficile* (*C difficile*) in the intestinal microbiota resulting from antibiotic consumption is currently a rising threat to public health. FMT is one of the most important, newer approaches to treating *C difficile* infections. Since *C difficile* is regarded as an opportunistic bacterium triggering disease in conditions of disturbed homeostasis of the intestinal microbiota, restoration of healthy intestinal microflora facilitates suppression of toxic strain of *C difficile* by anaerobic bacteria of normal intestinal microflora with concomitant cure. Nurses have important role in caring for patients after faecal transplantation.

**Key words:** Faecal microbiota transplantation; *Clostridioides difficile* infection; Microbiota.

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## Introduction

Faecal microbiota transplantation (FMT), also called faecal transplantation or faecal bacteriotherapy, is the transfer of a faecal suspension from a healthy donor into the colon of a recipient patient. The goal of FMT is to achieve the restoration of the intestinal flora of an infected person by transmitting the intestinal flora bacteria of a healthy donor. FMT is one of the more important, newer approaches for the treatment of *Clostridioides difficile* (*C difficile*) infections (CDI).<sup>1-3</sup> As a method of treatment, FMT was used long before modern medicine. Ancient civilisations did not know the concept of microbiota but talked about the healing effect of faeces. The first recorded case of ingestion of faecal material for medical reasons dates from the traditional Chinese medicine that in the 4<sup>th</sup> century used this procedure for the treatment of severe diarrhoea, food poisoning and malaria (recorded in the book *Prescription Collection of Emergency*). This treatment is also mentioned by Li Shizhen in the 16<sup>th</sup> century in his famous book

*Ben Cao Gang Mu (Compendium of Materia Medica)* for the treatment of gastrointestinal diseases as a “yellow soup”.<sup>4,5</sup> In modern medicine, the first published study in English literature of the use of FMT dated from 1958 and talked about the use of faecal enema, as an additional procedure for pseudomembranous colitis caused by antibiotics. It is rarely mentioned later, until in 2010 when FMT has been increasingly recognised as a successful therapeutic procedure for recurrent cases of CDI, but also the treatment of ulcerative colitis, Crohn’s disease, irritable bowel syndrome, metabolic syndrome, and even chronic fatigue syndrome.<sup>6-9</sup>

## Microbiota and microbiome

More than 100 billion symbiotic microorganisms are found in and on humans, which is on average

ten times more than the estimated number of cells in the human body. Most of these microorganisms inhabit the gastrointestinal tract (GT), which contains about 150 times more genes (microbiome) than are identified in the human genome, so this complex community of GT is called the intestinal microbiota. More than 1,000 separate species of bacteria have been discovered in the human microbiota using molecular diagnostic techniques, many of which cannot be cultured.<sup>10-13</sup> Humans live with their microbiota forming a complex symbiotic system in which balance (eubiosis) and microbiota disorder (dysbiosis) favour the development of some chronic diseases (eg, allergic diseases, obesity, diabetes mellitus, metabolic syndrome, atherosclerosis, malignant diseases, inflammatory bowel disease).<sup>14, 15</sup>

The physiological microbiota of an individual is rapidly formed during the first months of life. By the end of the second year, it achieves a composition that remains stable throughout life. Interaction with the intestinal microbiota in infancy plays an essential role in health and disease in later life, creating immune and metabolic pathways. During birth and after birth, the newborn's body is being quickly inhabited by microorganisms with which it comes into contact.<sup>16-18</sup> Data from epidemiological studies have shown that caesarean section, preterm birth, early exposure to antibiotics, and supplementation with adapted milk harm the development of the intestinal microbiota and contribute to some diseases later in life, for example obesity, asthma and inflammatory bowel disease.<sup>19</sup>

Although no two humans with the same microbiota exist, there are more remarkable similarities in their composition among members of the same race, ethnic groups and related individuals.<sup>20, 21</sup> The type and function of the human microbiota differ depending on the anatomical localisation, age, sex, race and diet of the host. Bacteria are primarily present in a healthy human microbiota. However, in addition to them, some viruses (primarily bacteriophages), fungi, archaea (mainly of the genus *Methanobrevibacter*) and some eukaryotes are also present. The most significant number of microorganisms of the human microbiota is found in the intestines, greatly influencing the formation of the metabolic phenotype, the epithelium's development, and innate immunity.<sup>22-24</sup> Bacteria that predominate in the colon are *Bacteroidetes* (including the genus *Bacteroides*) and *Firmicutes* (including the genera *Clostridioides* and

*Eubacterium*). *Actinobacteria*, *Verrucomicrobia*, *Proteobacteria* and *Fusobacteria* appear as well in smaller numbers.<sup>25, 26</sup> Intestinal commensals prevent colonisation by pathogenic microorganisms by occupying living space and utilising food and in several indirect ways, such as stimulating a local immune response or producing various compounds with an antimicrobial role. Thus, for example, lactic acid produced by the species of the genus *Lactobacillus* participates in the degradation of the bacterial wall, and the constitution of bile acids, which reflects the overall metabolism of the intestinal microbiota, significantly affects the intergrowth of *C difficile* spores.<sup>27</sup>

Bacteria, human symbiotes, aid in the metabolism of difficult-to-digest compounds by providing the host with essential nutrients, prevent expansion of opportunistic microorganisms and add to the creation of intestinal architectures. Foods that are difficult to digest, such as dietary fibre xyloglucan, usually found in vegetables, can be broken down by bacteria from the genus *Bacteroides*. Bacteria from the genera *Lactobacillus* and *Bifidobacterium* enable the digestion of difficult-to-digest fibres, for instance fructooligosaccharides. The gut flora alters the metabolism of carbohydrates, proteins and lipids. With its enzymes, it affects the host enzymes by fermentation. Around 50-100 mmol/L of the short chain fatty acids (SCFA), notably acetic, propionic and butyric acid, are produced daily by intestinal microbiota, thus providing the source of energy for the intestinal epithelium.

The microbiota carries an indispensable role in the synthesis of folate, vitamin K and some B vitamins, such as biotin (B1), riboflavin (B2) and cobalamin (B12). It also participates in the metabolism of bile acids, polyphenols, xenobiotics and drugs. In addition, bacteria that colonise the intestine promote the proper development of the mucosal immune system.<sup>28, 29</sup> Alterations in the intestinal microbiota have been observed in obesity, irritable bowel syndrome, ulcerative colitis, Crohn's disease, inflammatory bowel disease, colorectal cancer, non-alcoholic fatty liver, and some other diseases.<sup>30-32</sup> Since most primary bacterial pathogens have been successfully brought under control by vaccination or improved living conditions, today, the onset of bacterial disease is more associated with disruption of a complex human ecosystem than with the pathogenic power of a single microorganism. Given the high variability of the human microbiota, it is difficult to deter-

mine what a normal or healthy microbiota is. The ability to treat or prevent disease by altering an individual's microbiota is a significant challenge in many areas of medicine.<sup>33</sup>

## Intestinal microbiota and infectious diseases

The intestinal microbiota is made up of microorganisms, which inhabit various regions of the gastrointestinal tract. The number of bacteria increases towards the end of the digestive tract. The stomach and duodenum are settled by a small number of microorganisms, less than 10<sup>3</sup> colony-forming units (CFU) per gram of intestinal contents. Infectious disease is most often the result of microbiota dysbiosis. Then again, infection and its treatment directly influence the intestinal microbiota, which determines the outcome of infection in the human population. The spread of some opportunistic (*Enterococcus faecalis*, *Enterococcus faecium*, and bacteria of the *Enterobacteriaceae* family) and pathogenic bacteria (*Salmonella enterica*, *C difficile*) results in a robust inflammatory response, followed by a change in the intestinal microbiota.<sup>34-36</sup> Numerous studies have demonstrated an association between infection and microbiota dysbiosis. The intestinal microbiota of patients with CDI was significantly altered.<sup>37, 38</sup> Also, microbiota disorders lead to the advancement of infection with viruses such as hepatitis B virus (HBV) or human immunodeficiency virus (HIV).<sup>39-41</sup>

## *Clostridioides difficile* infection

Excessive growth of *C difficile* bacterium in the intestinal microbiota gives rise to diarrhoea. It is one of the most common complications that occur after the administration of antibiotics, currently presenting the rising threat to public health. Antibiotics disrupt the homeostasis of the intestinal mucosa, thus reducing resistance to the effect of *C difficile* toxin and leading to the progression of CDI. The higher incidence of these infections in recent years has been closely related to the development of highly virulent strains, such as those with ribotype 027 (NAP1 / 027 / BI).<sup>42, 43</sup> *C difficile* is an anaerobic, sporogenic, rod-shaped, Gram-positive bacterium. It was discovered in 1935 in newborns

and was named *Bacillus difficilis* (lat. *Difficilis* - heavy) due to its difficult cultivation. Later, due to the phenotypic similarity with bacteria from the genus *Clostridium*, it was named *Clostridium difficile*. Since 2016, based on the sequence analysis of 16S rRNA gene, it has been called *Clostridioides difficile*.<sup>44-46</sup> It is omnipresent in nature, inhabiting the intestines of humans and animals as well. The proliferation of toxigenic strains of this bacterium leads to various clinical conditions, from asymptomatic carriers, through diarrhoea and self-limiting colitis to serious situations just as fulminant colitis and toxic megacolon.<sup>47</sup> CDI transmission is horizontal, faecal-oral. In healthcare facilities, it is usually transmitted by contaminated hands (healthcare workers, patients and their families) and objects from the environment (stethoscopes, thermometers, surfaces and space near the patient).<sup>48</sup> Although it can be found in meat and meat products, seafood, and fresh vegetables and fruits, no food-borne epidemic disease is directly related to *C difficile*.<sup>49, 50</sup> Thanks to the resistance of its spores (they tolerate most antiseptics), *C difficile* can persist for a long time in the external environment, which allows it to stay in the patient's vicinity for a long time. It can be found on various surfaces in the hospital with which patients come into contact and on the hands, clothes, and shoes of medical staff, which according to research, has one of the essential roles in the spread of infection.<sup>51</sup> Risk factors for the occurrence of the disease are old age, severe chronic diseases, long-term hospitalisation, as well as staying in institutions for the elderly and the chronically ill. However, the most critical factor of risk contributing to the expansion of infection is the change in the intestinal microbiota due to antibiotic therapy. The highest risk is therapy with clindamycin, cephalosporins, penicillins and fluoroquinolones. Moderate risk involves therapy with macrolides and sulphonamides, while treatment with tetracyclines carries no risk.<sup>52</sup>

*C difficile* is ubiquitous and is statistically present in 15-70 % of neonates and in 2-5 % of the adult population, who are mostly colonised by its community. For example, in most neonates colonisation with *C difficile* is temporarily, and colitis does not develop.<sup>53</sup> The observed transient asymptomatic colonisation might result from *C difficile* toxin-binding receptors, a disorder of antibody production against *C difficile* toxins, and the development of protective mechanisms associated with breastfeeding or intestinal bile acid me-

tabolism.<sup>54, 55</sup> It is recommended not to perform diagnostic procedures, nor therapy treatments in patients who are asymptomatic, as antimicrobial agents may cause unwanted changes in composition of gut microbiota.<sup>56, 57</sup> Recognition of the symptoms of CDI in adult patients is critical for timely initiation of therapy. Wide range of CDI symptoms are documented, from mild diarrhoea as a the most common symptom, to severe form of ulcerative colitis leading to toxic megacolon or to the perforation of the colon.<sup>58</sup> Usually patients with confirmed CDI do not have diarrhoea with blood (bloody diarrhoea), which can be found in patients with inflammatory bowel disease.<sup>59</sup> The rate of first recurrent CDI cases is between 10 % and 20 %. A recurrent case of CDI is identified as an infection that reoccurs within eight weeks after the end of the last episode of the disease. With each subsequent repetition of CDI, the repetition rate increases significantly. After the first relapse, the cash recurrence rate increases to 40 % and then to more than 60 % for each subsequent period.

Patients with recurrent CDI have a deficiency of bacteria prevalent in the colon, leading to multiple relapses.<sup>60, 61</sup> When repeated CDI is diagnosed, it is recommended to treat the first CDI relapse with the same therapy as the one used for the initial case of infection (metronidazole or vancomycin). Nevertheless, many authors suggest vancomycin for the treatment of the first relapse after initial infection with CDI was treated with metronidazole. If the first case of CDI was treated orally with vancomycin, fidaxomicin is the next choice of therapy for the first relapse, although it is often budget limited. Since there are concerns about the occurrence of neurotoxic effects with long-term use, metronidazole is not recommended as a therapy for the second relapse. Moreover, the effect of metronidazole is reduced after repeated infections. Thus, for any subsequent relapse, the therapy with antibiotics for a more extended period, even longer than four weeks, often with reduced or increased doses of vancomycin, is considered.<sup>62</sup> Due to the limited possibilities of medical treatment of recurrent cases of CDI, the pursuit of other possible treatments has intensified over the last years. FMT is one of the potential therapies, which has been used quite often since 2010, primarily due to its good efficacy (in some studies, it has been successful in over 90 % of cases).<sup>63, 64</sup>

## FMT as a therapy for CDI

The concept of FMT implies the restoration of the altered microbiota in the intestines (dysbiosis) of the diseased person to a healthy microbiome (symbiosis). This regeneration is performed by transmitting the intestinal flora of a healthy donor to the intestine of an infected person.<sup>65</sup> As an opportunistic pathogen, *C difficile* promotes disease when microbiota homeostasis is disrupted. Thus, restoration of balanced intestinal microflora enables suppression of toxic strain of *C difficile* by anaerobic bacteria of normal intestinal microflora with accompanying cure.<sup>66</sup>

There are three primary indications for FMT in the case of CDI: (1) CDI that reoccurs repeatedly, (2) restrained CDI resistant to standard antibiotic therapy (vancomycin or fidaxomicin) during minimum one week, and (3) serious form of ulcerative colitis (fulminant CDI) not responding to standard antibiotic therapy during 48 hours.<sup>67</sup> In some cases of CDI, antibiotic therapy is unsuccessful due to increased formation of *C difficile* toxins, delayed response of immune system or conditions such as ileus or diverticulum, preventing the antibiotic from reaching the colon. FMT can be used as a therapeutic option in these cases, especially if the patient is not a candidate for surgery.<sup>68</sup> In addition to CDI, this method is used as a therapy for metabolic syndrome, irritable bowel syndrome and inflammatory bowel disease. Research on FMT use in some other diseases, such as Parkinson's disease, multiple sclerosis, autism and obesity, is underway.<sup>69, 70</sup> FMT leads to a more robust immune response, faster healing but also improves the overall quality of life and the FMT procedure is straightforward.<sup>71</sup>

To perform FMT, it is necessary to provide a healthy donor, the equipment of the laboratory required for processing and storage of faeces and medical equipment for the transfer of faeces into the small or large intestine of the patient. Research has shown that donor selection, processing and storage of faeces differ somewhat, but standardized procedures already exist.<sup>72</sup> FMT providers can be older than 18 years, known to the patient (family members or friends) or unknown, ie those who want to give faeces (volunteers). Family members, especially immediate family, share the most significant amount and content of microorganisms with the recipient. While family members share the risk

factors for infection diseases as well, the factors of risk are minimised with unknown donors, as they go through the same procedure as blood donors.<sup>73</sup> In any case, all faecal donors for FMT must undergo rigorous screening to reduce the possibility of transmitting infectious diseases. Current FMT guidelines advise employing a donor questionnaire analogous to the one required for voluntary blood donors, serological testing, or faecal examination for infectious agents.<sup>74</sup> The donor cannot be a person if he has any of the gastrointestinal diseases (inflammatory bowel disease, irritable bowel syndrome, constipation, chronic diarrhoea, history of major gastrointestinal surgery, gastrointestinal cancer or polyposis) or conditions that may influence the intestinal microbiota setup (metabolic syndrome, systemic autoimmune diseases, atopic diseases). Also, donors should not use antibiotics and immunosuppressive drugs for three months before faecal administration.

After answering the questions from the questionnaire, serological testing for syphilis, hepatitis A, hepatitis B, hepatitis C, human immunodeficiency virus (HIV), and human T lymphotropic virus (HTLV) I and II is performed. Donor faeces should be tested for bacteria, viruses, protozoa, and parasites: *C difficile*, *Helicobacter pylori*, *Listeria spp*, *Salmonella spp*, *Shigella spp*, *Vibrio spp*, *Yersinia spp*, *Campylobacter spp*, *Escherichia coli (E coli) O157 H7*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and Gram-negative bacteria producing extended-spectrum  $\beta$ -lactamases and carbapenemases (ESBL), rotavirus, norovirus, adenovirus.<sup>75</sup> Some authors recommend a short screening protocol for the donor that is a close relative or intimate partner. In contrast, others suggest that all tests should be performed regardless of the donor's choice.<sup>76,77</sup> The faecal sample for transplantation can be prepared as fresh, frozen or in the form of gelatine capsules. If it is fresh faeces, it is recommended to be transplanted within six hours of defecation. To preserve anaerobic bacteria, some research also suggests automated preparation of faeces, so that the time of preparation itself is reduced to one hour. Faeces can also be stored at - 80 °C. Before the application, the stool suspension should be heated to 37 °C in a water bath, and the transfer should be performed within six hours.<sup>78,79</sup>

## Processing of donor faeces for FMT

The faecal sample must be properly taken from an appropriate donor, must not encounter contaminated water, urine or blood, has to be in the amount of at least 50 grams and delivered to the laboratory at shortest convenience. The faeces are homogenised in the laboratory by centrifugation in sterile 0.9 % saline, filtered and resuspended.<sup>80</sup> How FMT will be performed depends on the clinical presentation but also on the patient's requirements. The methods of faecal transplantation currently used are: 1) endoscopy, via a nasoduodenal probe or by swallowing a gelatine capsule, for the upper part of the gastrointestinal tract, 2) colonoscopy, for the initial part of the colon, 3) sigmoidoscopy, rectal probe or enema, for the final part of the colon. The combined route of administration is preferred for more complex conditions, as for example ileus or anatomical disorders of the gastrointestinal tract.<sup>81,82</sup>

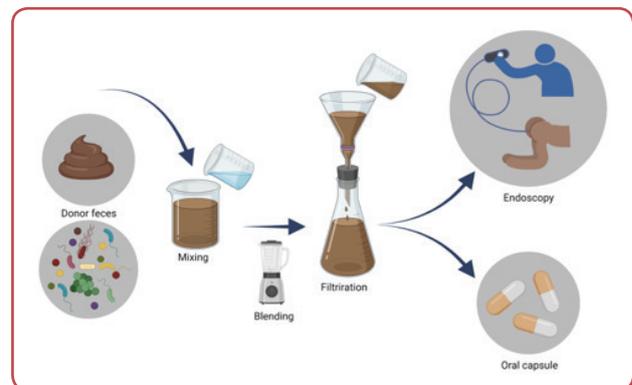


Figure 1: Schematic presentation of faecal microbiota transplantation [Wang et al, 2019]

Although, in general, the FMT procedure is considered safe, possible complications have not been well studied as large cohort studies are still missing. After colonoscopic faecal transplantation, stomach pain, diarrhoea, distension with nausea and vomiting, obstipation and mild fever may occur. Such symptoms are usually temporal and subside after several hours.<sup>84</sup> Complications of FMT are associated with risks associated with FMT itself, eg exposure to pathogens. Although the overall risk of exposure to pathogens is considered low, pathogens that can be transmitted include *E coli* and norovirus.<sup>85</sup>

## The role of the nurse

Nurses play an essential role in caring for patients with CDI, after they have been subjected to FMT, primarily if those patients are housed in an intensive care unit. Enteric preventive measures and proper isolation of patients with CDI are crucial care procedures.<sup>86</sup> According to the CDI prevention guidelines, contact isolation must be applied for the duration of the disease. The prescribed protective equipment is used: gloves, surgical mask, protective coat during care, PVC apron during other minor interventions. Protective equipment should also be used by those visiting the patient. Hygienic handwashing with soap after each direct contact with the patient is essential, and disinfectants with alcohol must not be used because they do not have a sporicidal effect. Equipment used to access a patient with suspected CDI or confirmed infection should be disposable or intended for these patients only (stethoscopes, thermometers, sphygmomanometer cuffs). The patient area is thoroughly cleaned and disinfected. Nurses should inform the patient about CDI, and his family and visitors about the importance of implementing prescribed hygiene measures.<sup>87</sup>

Patients prone to developing CDI have often used antimicrobial drugs in the recent past (eg, as a surgical prophylaxis, due to hospitalisation caused by long-term infection, following immunosuppressive therapy or older age). In case the antibiotic therapy is necessary even after FMT, it will again cause a change in the patient's intestinal microbiota. After FMT procedure, nurses should monitor patients who use antibiotics for possible recurrent CDI.<sup>88</sup> Patients who have undergone FMT are often bedridden and need special care. Since the patient's environment is most likely contaminated with *C difficile* spores, the patient's room must be thoroughly cleaned with a chlorine-containing agent immediately before performing FMT. If technically feasible, the patient should be placed in a new or thoroughly cleaned bed with clean bedding. Reducing the number of *C difficile* spores improves the success of FMT administration in patients with CDI. The patient should be asked not to defecate for at least 4 hours, if he can endure, after performing FMT, and if he can go for longer, he must be placed in a semi-sitting position for 24 hours and given diarrhoea medication.<sup>89</sup>

## Conclusion

By modulating an individual microbiome, many diseases can be prevented and treated. One of the latest approaches to treating recurrent CDI cases is the FMT method. It is a simple method during which the faeces of a healthy donor is being transplanted to a patient. Several faecal transplant procedures are used, and the most important thing is to perform safe preparation. Nurses apply specific prevention measures during the care of patients who have undergone FMT. In order to improve the effectiveness of FMT in patients with CDI, it is necessary to ask them not to defecate by placing them in a semi-sitting position.

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## Conflict of interest

None.

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# A Step Today Can be a Giant Leap Tomorrow - COVID-19 Management Lesson From the Developing World

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## Abstract

**Background/Aim:** Although India is relatively better resourced as compared with other low middle income countries in several aspects, it shares several challenges and vulnerabilities like high population, resource constraints (limited number of hospital beds, skilled healthcare personnel, intensive care units) and socioeconomic milieu, and it is important that these resources are spent wisely to maximise lives saved and minimise disruption to health services for all COVID-19 patients. Hence for dealing with this pandemic quickly and efficiently, a centre which could be set up urgently at a low cost for efficient oxygen triage was needed and thus cater to the sudden enormous load of patients who were unnecessarily occupying oxygen beds in hospitals.

**Methods:** This study describes the setting up, management and outcome of seven hundred bedded COVID-19 care centre at Jaipur, India, within three days, at low cost, by multidisciplinary efforts of the Government of Rajasthan for efficient triage of patients and to share the excessive patient load of the biggest Government medical college of the state.

**Results:** More than 700 patients were successfully managed at the centre within a period of one month with a favourable outcome. The perceptions of patients assessed via questionnaire also establish the success of this endeavour in sharing the load of hospitals at the peak of the pandemic.

**Conclusion:** This paper describes the positive impact of setting up this COVID-19 care centre, and experience presented in this paper can be utilised as a novel and future oriented solution to address effectively the unprecedented pressure on the healthcare systems, created by the COVID-19 pandemic.

**Key words:** COVID-19; Resource limited setting; Triage; COVID-19 care centre.

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## Introduction

The World Health Organization (WHO) declared the coronavirus disease (COVID-19) as a pandemic on 11 March 2020.<sup>1</sup> What arose from Wuhan City in China, is probably the worst pandemic in recent history and has led to panic and global public health emergency.<sup>2</sup>

After the reporting of the first case of COVID-19 in

India on 30 January 2020, cases started increasing in early March and the first wave peaked around September 2020.<sup>3,4</sup> However, subsequently the COVID-19 case numbers started to drop after a high of around 100,000 daily infections and the country was fortunate in successfully crushing the first wave of COVID-19 due to strict contact tracing, institutionalised quarantine and

provision of care for all PCR-positive individuals. The current existing healthcare facilities in Jaipur include a Government sector medical college with 1,200 beds reserved for COVID-19 patients and the Government is responsible for the treatment of these patients.

The cases began to rise again in March 2021 and currently India is experiencing the second wave of COVID-19, which has hit India more like a tsunami, with a deadly toll. The available healthcare resources got overwhelmed due to the sudden and enormous rise of cases in April in the state. There arose a shortage of hospital beds and oxygen support as more and more patients with varying severity of the disease started filling up the already overwhelmed infrastructure of the health care services. Unnecessary admissions due to panic or some high-profile patients or mild lung involvement caught on a CT scan, some abnormal lab tests or the fear that beds would not be available later became rampant also. This scenario where there was immense shortage of oxygen was extremely heartburning as people started dying in necessity of oxygen cylinders.

As there was extreme shortage of beds in the hospitals for those actually needing them, a need was felt to urgently develop a low cost COVID-19 care centre, which could act as a connecting link between home and hospital and could cater the less serious patients thereby contributing to an efficient triage system wherein those actually needing ICU beds could get the same.

This paper presents authors' experience of developing and managing such a COVID-care centre in a resource limited setting, within a short span of just three days and suggests strategies which would aid in tiding over any future waves of this pandemic effectively in a resource limited setting.

## Methods

This descriptive study was conducted for duration of one month from 28 April 2021 to 27 May 2021, during which 1846 COVID-19 patients reported in the outpatient department at the COVID-19 centre, and 740 of these were admitted for management in the inpatient department.

Keeping in view the increasing number of COVID-19 patients and the overwhelmed capacity of Government run COVID-19 hospitals, a seven hundred bedded facility for care of mild COVID-19 cases was set up in Jaipur within three days. The aim of opening this centre was to create a link between home and hospital and to decrease the panic driven unnecessary load on the Government hospitals. This facility was developed and managed as a multidisciplinary effort which involved various segments of the Government, namely the Jaipur development authority, municipal corporation, Police and the Department of Medicine and Health.

The temporarily created COVID-19 care facility was developed in an open area, which was composed of a roofed but open from sides premises in a one million square feet property owned by Radha Swami Satsang charitable trust and accommodated 768 beds. The heights of tents were approximately 6 to 9 feet so that there was enough open space above the tent wall and below the dome roof, which made the centre well ventilated. The entire tented area was divided into blocks. Each block had 4 wards of 16 beds each. One nursing station was set up for each block with round the clock trained and dedicated doctors, nursing and support staff working there. The beds were equipped with oxygen concentrators and cylinders. However, no ICU or ventilators were set up. An outpatient department and pharmacy were set up in another tent, 500 metres away from the isolation ward area. Arrangement was also made for attendants stay for people coming from remote areas.

Local guidelines were developed for different aspects of COVID-19 management keeping in view the latest available evidence, national and international recommendations. These included guidelines for patient management workflow, PPEs, staff roster, sampling, admission criteria, isolation, treatment of cases, bed allocation and management, disinfection, transport of referred patients and dead body management. Policy for bed allocation and management of patients was ensured.

Standard disinfection guidelines were followed and standard operating procedures (SOPs) for isolation, personal protection and patient information brochures were created and distributed.

All patients reporting to the outpatient depart-

ment at the main entrance were screened. Hand sanitisers were provided at main gate and at entrances of all blocks. There was open and rapid communication between the administration and the clinical staff.

Strict criteria were laid down for admission in the COVID-19 care centre. This included a symptomatic RTPCR positive / negative COVID-19 patient with high resolution computed tomography (HRCT) score of less than 13 and peripheral oxygen saturation (SpO<sub>2</sub>) ranging between 85 and 92 % on room air. This was done to ensure that seriously ill patients, who needed ventilator support were excluded, since this centre was acting as a link between home and hospital but did not have facility to manage serious patients.

The patients reporting to outpatient department, who could not maintain their oxygen saturation at room temperature and fit into the above admission criteria, were admitted. The patients who were admitted from the outpatient department were received by trained staff working in full personal protective equipment (PPE). They were examined by the doctor on duty and put on the type of oxygen support needed.

About 150 health care workers were catering to these patients round the clock. An inhouse laboratory was set up in the centre premises with facilities for routine investigations like complete blood count, blood sugar, renal function tests, liver function tests and special investigations like D-dimer assay, serum ferritin and C-reactive protein, which are required for proper management of the COVID-19 cases. Facility for collection of RTPCR sample of attendants and staff was also given.

A two-way referral system was developed where this centre was linked to the biggest Government run COVID-19 dedicated hospital in the city. Bidirectional transfer of patients, as per requirement was ensured between the COVID-19 care centre and the tertiary care COVID-19 dedicated hospital, so that the hospital burden of less serious patients could be shared by the care centre while the patients who developed a need of higher centre treatment during their stay could easily get it. Efficient and timely transport of the patients was ensured.

The charitable organisation employees served as helpers for the admitted patients and round the clock food and water was provided by the organisation.

For spiritual and mental wellbeing of the patients, light music in the form of bhajans was played in the inpatient area, and the ambient temperature was kept pleasant with the use of sprinkler system on the dome.

Majority of the patients managed in this centre were earlier previously managed with oxygen lines or cylinders in various hospitals. However, in this care centre, they were being managed by 5 and 10 L oxygen concentrators. Wise use of oxygen cylinders was done for patients who could not maintain their saturation levels on concentrators and actually needed them, to combat the current oxygen shortage.

On discharge, the perception of patients was assessed using a pre-validated questionnaire and scoring was done on a five-point Likert scale. The questionnaire comprised of questions related to the facilities and treatment provided at the centre and the overall satisfaction of the patients, and it was pre-validated by getting it filled and checked by other doctors of the team. All participants gave written consent for participation in the study and this was cleared by institutional Ethics Committee.

## Results

Out of the 740 admitted patients, there were 502 (67.8 %) men and 238 (32.2 %) women, of age group ranging from 21 years to 84 years (Table 1), average age of the patients was 50.1 years. The biggest number of patients were from the age group of 41 – 60 years (n = 338; 45.7 %).

Among these patients, the lowest HRCT score encountered was 4 and the highest HRCT score was 13 (out of 25).

Out of these 740 admitted patients, majority (73.9 %) were managed on 5 to 10 L oxygen concentrators while only 9.3 % required oxygen cylinders

*Table 1: Age- and sex-wise distribution of the admitted patients (n = 740)*

Age group	No of male	No of female	Total	Percentage of all patients
21-40 years	144	72	216	29.2
41-60 years	230	108	338	45.7
61-80 years	121	53	174	23.5
> 80 years	7	5	12	1.6
Total patients	502	238	740	100

**Table 2: Mode of oxygen support in admitted patients (n = 740)**

Type of oxygen support	No of patients	Percentage
Oxygen concentrators	547	73.9
Oxygen cylinders	69	9.3
None	124	16.8
Total	740	100.0

**Table 3: Outcome of admitted patients (n = 740)**

Outcome	No of patients	Percentage
Discharged	578	78.1
Referred to higher centre	135	18.3
Death	27	3.6
Total	740	100.0

**Table 4: Feedback of discharged patients (n = 578)**

S. no	Parameter	Score 1: strongly disagree (%)	Score 2: disagree (%)	Score 3: neutral (%)	Score 4: agree (%)	Score 5: strongly agree (%)
1	I am totally satisfied by the ambience of the centre	2 (0.3 %)	3 (0.5 %)	27 (4.7 %)	319 (55.2 %)	227 (39.3 %)
2	I am totally satisfied by the treatment given at the centre	2 (0.3 %)	4 (0.7 %)	24 (4.2 %)	315 (54.5 %)	233 (40.3 %)
3	I am totally satisfied by the behaviour of the staff at the centre	2 (0.3 %)	4 (0.7 %)	26 (4.5 %)	345 (59.7 %)	201 (34.8 %)
4	I am totally satisfied by facilities (promised on arrival) provided, at the centre	1 (0.2 %)	3 (0.5 %)	29 (5.0 %)	244 (42.2 %)	301 (52.1 %)
5	Overall, I am totally satisfied during my stay at the centre	2 (0.3 %)	3 (0.5 %)	26 (4.5 %)	239 (41.4 %)	308 (53.3 %)

while 16.8 % did not require oxygen support and could maintain their oxygen saturation on room air (Table 2). Table 3 depicts the final outcome of patients during the one month of study. Out of 740 patients admitted during this period, 578 (78.1 %) were discharged after recovery while 135 (18.3 %) had to be referred to higher centre as they could not maintain their oxygen levels or had other comorbid conditions like uncontrolled diabetes which could not be managed at this COVID-19 care centre and required hospital

setup. Unfortunately, there were 27 casualties during this period.

The feedback gathered from the patients who were discharged after recovery is shown in Table 4. Majority of the patients (94.7 %) were satisfied by the ambience of the centre, facilities provided, the treatment given, behaviour of the staff of the COVID-19 care centre and gave a positive feedback.

## Discussion

The COVID-19 pandemic, caused by SARS-CoV2, is of unprecedented global public health concern.<sup>5</sup> India is currently passing through a critical phase of the second wave of COVID-19 and ranks second globally in total infections and fourth in total mortality.<sup>6</sup> With a population of ~1.4 billion, India's response to COVID-19 directly affects 17.7 % and 21.8 % of the global and low middle income countries (LMIC) populations, respectively.<sup>7</sup> As per the constitution of India, as a semi federal democratic governance system, the responsibility of 'health' and prevention of disease spread is concurrently vested with the Government of India (GoI) and the states.<sup>8</sup>

This COVID-19 pandemic has stressed healthcare systems across the globe, irrespective of the development status of the countries. Even the high-income countries with a well-developed healthcare system were overwhelmed with this pandemic

within the first few weeks. However, the developing low- and middle-income countries were awfully hit, due to relatively scarce health care resources.<sup>9</sup> There is a limited number of hospital beds and skilled healthcare personnel per se in these countries, although this may vary from country to country.<sup>10-12</sup>

Also, there is very limited number of intensive care units (ICUs) with access to mechanical ventilation in LMICs as compared to the developed world, and experts had warned of this inadequacy in the wake of a tsunami of COVID-19 cases requiring hospitalisation.<sup>13</sup> This fear proved true during the second wave and within days the ICU ventilators were fully occupied, leading to an acute shortage of medical oxygen in major hospitals in Jaipur, as well as in other places across the country.<sup>14</sup>

However, not all the patients that filled up the hos-



pitals really needed ICU beds, interventions or mechanical ventilation. This clinical spectrum has been proven by other studies worldwide.<sup>15,16</sup> This scenario led to exhaustion of the already overwhelmed infrastructure similar to the global trends.<sup>17</sup> A number of oxygen supply systems have been described but, there is, per se, a lack of needed oxygen supply in resource limited areas and hence the importance of proper oxygen supplies management.<sup>18-21</sup>

At the present centre, patients were initially put on 5 to 10 L oxygen concentrators at the time of admission and maintained it unless there arose a need to shift to oxygen cylinders. This endeavour helped in reducing the wastage of oxygen and an optimal triage for oxygen when the supply was limited.

The urgent need to clearly understand the likely burden of infection requiring hospital care and to develop locally appropriate triage and clinical care centre to overcome this problem led to the successful establishment and running of the COVID-19 care centre by a multidisciplinary Government team. This has been supported by WHO, who have concluded that opening field hospitals or care centres in large public spaces (eg, stadiums) allows for triaging and managing stable patients and decongest other hospitals.<sup>22</sup>

Local guidelines and standard operating procedures were developed for different aspects of COVID-19 management keeping in view the latest available evidence and international and national recommendations.<sup>23-25</sup> No compromise was done for safety of the staff working there and measures for infection prevention and reduction of exposure risk to staff were strictly integrated, as advocated by other studies.<sup>26,27</sup>

Stringent guidelines were formed and followed for rapid referral of patients to higher centre if they developed symptoms corresponding to severe disease or complications during treatment. The patients who could not be managed at this COVID-19 care centre were referred as and when required to the largest Government sector hospital. This was done in accordance to the guidelines issued by the WHO.<sup>23</sup>

Research has shown that the spiritual care provider plays an important role when families are faced with challenging health risks and the prospect of palliative care.<sup>28</sup> The psychological wellbeing of those admitted was also well taken care of at this centre with continuous bhajans and availability

of books. This made the patients feel relaxed and decreased their anxiety levels. Moreover, the open tents were a better option to do away with the claustrophobic environment of the hospital, which may have an adverse effect on the mental health of already stress out patient.

The feedback gathered from the patients who got discharged after recovery, tells us that most of the patients were fairly satisfied by the ambience and facilities of the COVID-19 care centre apart from the treatment rendered. To the best of our knowledge, no previous literature is available regarding the patients' perception after establishment of such a COVID-19 centre.

## Conclusion

The coronavirus disease 2019 (COVID-19) pandemic is putting health-care systems under unprecedented stress to accommodate unexpected numbers of patients forcing a quick reorganisation. Developing and successfully managing a Government sector COVID-19 care centre in a resource limited country was a big challenge. It involved coordination and cooperation between departments of the state Government along with creating guidelines and out of the box solutions on a day-to-day basis pertaining to the problems encountered.

This low-cost endeavour can act as a role model for countries who are relatively poor in resources and where it is nearly impossible to scale up the development of health infrastructure. And also, can act as a strong pillar in the preparation of the impending third wave.

Such centres may act as saviours in third wave for the children, who would need such open centres for recovery where they can get the treatment without feeling stressed out or claustrophobic in a hospital setting. These can also alleviate the panic of the parents who can stay in a socially pleasant atmosphere with their diseased child. Therefore, present experience may be utilised by the decision makers world over who must prioritise resourcing and capacity development for such care and simple oxygen therapy that most hospitalised COVID-19 patients will need – not the high-end clinical care that may well be impossible to scale up in time in countries with limited resources.

## Acknowledgements

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## Conflict of interest

None.

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# Analysis of the Emergency Medical Service Call Centre Actions in Patients with Cardiac Arrest

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## Abstract

**Background/Aim:** Cardiac arrest (CA) is a leading cause of mortality in the last forty years worldwide. Immediately initiated cardiopulmonary resuscitation (CPR) improves chances for survival. Aim of this study was to determine the efficiency of the Emergency medical service (EMS) dispatch centre in the absence of the uniform emergency medical dispatch assessment protocols in the management of cardiac arrest.

**Methods:** The retrospective and observational study was conducted in Institute for Emergency Medical Service Novi Sad (IEMS Novi Sad) Serbia during a one-year follow-up. The study included patients with out-of-hospital cardiac arrests who underwent CPR.

**Results:** EMS teams of the IEMS Novi Sad had 198 CPRs in the follow-up period. In 142 (71.72 %) calls, the EMS dispatcher got information that the patient was unconscious. The reported reaction time I by the dispatchers for the unconscious patients was  $1.37 \pm 1.27$  minutes, actual duration of the conversation between the dispatcher and a caller – was longer:  $138.21 \pm 103.02$  seconds ( $p < 0.001$ ). The average conversation time with a caller was  $61.37 \pm 31.13$  seconds. In 6 (4.22 %) cases, the EMS team was dispatched to a patient before the phone call was terminated. At the moment of arrival, all patients were unconscious, 194 (94.37 %) were pulseless, while the remaining 8 (5.63 %) experienced cardiac arrest during the examination. The cardiac arrest was witnessed by a layman in 120 (84.51 %) cases and CPR was initiated by bystanders, before the arrival of the EMS team, only in 13 (10.83 %) patients. Twenty-seven (19.01 %) patients arrived in a hospital with vital signs.

**Conclusion:** The absence of the uniform EMS dispatch assessment protocols for the triage of incoming calls and phone assisted CPR for lay rescuers decreases the survival rate of patients with cardiac arrest.

**Key words:** Emergency medical service; Dispatcher; Out-of-hospital cardiac arrest; Cardiopulmonary resuscitation; Telephone CPR.

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## Introduction

Cardiac arrest (CA) is defined as a cessation of normal circulation of blood due to failure of the heart to contract effectively during the systole. CA

manifests with loss of consciousness, abnormal or absent breathing and pulselessness. CA occurs at home or in the public places and it is usually

witnessed by laymen. Appropriate, fast intervention by laymen and medical teams significantly increases chance of survival of patients with CA.<sup>1</sup>

Timely treatment of CA improves chances for survival up to three times.<sup>2,3</sup> Delay of cardiopulmonary resuscitation (CPR) measures increases mortality by 10 to 12 % per minute. On the other hand, if CPR measures are undertaken promptly, mortality increases by 3 to 4 % per minute until the defibrillation is delivered.<sup>4</sup>

Emergency Medical Service Call Centre (EMS Call Centre) occupies an important place in the pre-hospital treatment of patients with CA. Operators in the EMS Call Centre are the first responders in such conditions and their timely and adequate reaction may affect the outcome, both by instructing the laymen to start CPR until the arrival of emergency medical staff as well as by assigning such calls as first priorities.<sup>5</sup>

The aim of this study was to determine the efficiency of the EMS Call Centre in dealing with patients with CA in the absence of the standard questioning protocol.

## Methods

The study was retrospective and observational. It was conducted in the Institute for Emergency Medical Service Novi Sad (IEMS Novi Sad), in the one-year period.

The IEMS Novi Sad covers the municipalities of Novi Sad and Sremski Karlovci with 389,130 inhabitants.<sup>6</sup> It is the only health institution capable for prehospital dealing with medical urgencies in this territory. It consists of ambulance squads in each working shift, with a doctor, emergency medical technician and ambulance driver. Every ambulance squad has identical equipment and staff are trained to deliver advanced life support (ALS) measures and to treat urgent medical conditions. In addition to this, there are non-urgent transportation squads, consisting of an emergency medical technician and an ambulance driver.

A doctor and an emergency medical technician work 12-hour shifts in the EMS Call Centre, answer the calls for the medical emergencies and non-urgent patient transport and dispatch the ambulance squads.

The patients enrolled into this study were those with CA recognised by a layman. Data were collected from the recorded conversations data basis in the EMS Call Centre and from the official records written by the Call Centre personnel. Collected data included:

- reaction time I - a period between the moments when the priority I call is answered and when the ambulance squad is dispatched, reported by operators in minutes and measured in seconds from the recorded phone calls
- duration of a phone call, measured in seconds
- reaction time II - a period between the moment when the ambulance squad is dispatched and their arrival to the patient, measured in minutes
- information about a witness of CA
- information about sending the ambulance squad before the phone call is terminated
- information about phone assisted CPR
- initial rhythm on the cardiac monitoring
- information about the return of spontaneous circulation (ROSC) and its maintenance until the arrival to the hospital.

Data were stored in the specially created database. All the data were calculated by using a statistic package SPSS 11. Statistical significance was determined by using Student t-test and  $\chi^2$  test. Influence of a particular factor on the outcome was determined by using univariate logistic regression analysis.

## Results

In the one year, there were 198 prehospital CPRs in the territory covered by IEMS Novi Sad. In most cases, they were witnessed by a layman (Table 1) ( $\chi^2 = 154.758$ ,  $p < 0.001$ ). In 142 cases (71.72 %), EMS Call Centre operator was informed that a patient was unconscious ( $\chi^2 = 39.510$ ,  $p < 0.001$ ). After this information was obtained, the operator asked if the patient breathed in 36 (25.35 %) cases. The patient did not breathe in 30 cases (21.13 %) and was pulseless in 3 cases (2.11 %). In another 3 cases (2.11 %), the operator said to caller that it was necessary to undertake CPR.

Reaction time I, reported by the operators, was 1.37 minutes ( $SD \pm 1.27$ , min 0, max 11, Me 1). On the other hand, the average reaction time I, measured from the recorded phone calls, was a bit longer: 138.21 seconds ( $SD \pm 103.02$ , min 16, max

840, Me 120) ( $t = -5.177$ ,  $p < 0.001$ ). Average phone call duration was 61.37 seconds ( $SD \pm 31.13$ , min 10, max 193, Me 54). In six cases (4.22 %), the urgent ambulance squad was dispatched before the phone call was terminated.

Average reaction time II was 7.18 minutes ( $SD \pm 3.87$ , min 2, max 24, Me 6). All patients were unconscious at the moment of arrival of the ambulance squad, 134 patients (94.37 %) were pulseless, and the remaining 8 patients (5.63 %) experienced cardiac arrest in the presence of the ambulance squad.

**Table 1:** Witnesses of sudden cardiac arrest in relation to the total number of cardiopulmonary resuscitations (CPRs)

CPR witnessed by	N	%
Laymen	148	74.75
Ambulance squad	33	16.67
Health professionals	17	8.58
Total	198	100.00

N: number of patients;

**Table 2:** Witnesses of sudden cardiac arrest and immediately initiated cardiopulmonary resuscitation (CPR)

CPR witnessed by	N	%	CPR	%	p
Laymen	84.51	74.75	13	10.83	$p < 0.001$
Ambulance squad	5.63	16.67	8	100.00	$p = 0.285$
Health professionals	9.86	8.58	9	64.29	$p < 0.001$
Total	100.00	100.00	30	21.13	

N: number of patients;

**Table 3:** Univariate binary logistic regression analysis of predictors determining the early survival (until the hospital admission)

Predictors	OR	95 % CI	p
Reaction time I reported by EMS			
Call Centre operators <sup>1</sup>	1.532	0.721-3.255	0.267
Recorded reaction time I <sup>2</sup>	1.002	0.997-1.006	0.511
Duration of phone calls <sup>3</sup>	1.020	1.001-1.038	0.035
Reaction time II <sup>4</sup>	1.064	0.942-1.203	0.318
Witnessed CA	0.719	0.394-1.313	0.283
Initial cardiac rhythm	2.896	1.383-6.066	0.005
Immediately initiated CPR	3.474	1.396-8.646	0.007
Phone-assisted CPR	0.460	0.040-5.269	0.532

CPR: cardiopulmonary resuscitation; CA: cardiac arrest; EMS: emergency medical service;

Univariate binary logistic regression analysis determines the significance of particular predictors on establishing and maintaining return of spontaneous circulation until the hospital admission.

**Odds Ratio (OR)** - probability of establishing return of spontaneous circulation in a patient with CA and its maintenance to the hospital admission, depending on the presence or absence of a particular predictor.

<sup>1</sup> period of time between the phone call reporting CA and dispatching the ambulance, measured in minutes by EMS Call Centre operators.

<sup>2</sup> period of time between the phone call reporting CA and dispatching the ambulance, measured in seconds, based on the recorded time.

<sup>3</sup> duration of phone calls reporting CA, measured in seconds.

<sup>4</sup> period of time between dispatching the ambulance and its arrival to the patient with CA, measured in minutes.

CA was in most cases witnessed by a layman and CPR measures were initiated before the arrival of the ambulance squad in small number of patients (Table 2). Automatised external defibrillator (AED) was used in one patient (0.70 %). In 3 patients (2.11 %), EMS Call Centre operator gave instructions how to start CPR before the arrival of the ambulance.

The initial cardiac rhythm was non-shockable (pulseless electrical activity or asystole) in 27 patients (19.01 %), while shockable rhythm (ventricular fibrillation or pulseless ventricular tachycardia) was present in 55 patients (38.73 %).

At the hospital admission, ROSC was maintained in 27 patients (19.01 %). The immediate survival was determined by three variables: phone call duration, initial cardiac rhythm and immediately attempted CPR (Table 3).

## Discussion

CA is a leading cause of mortality in the last forty years worldwide.<sup>7</sup> It is experienced by approximately 700,000 people in Europe and 400,000 people in USA every year.<sup>8,9</sup> Prehospital survival of patients with CA is very low and is greatly determined by immediately initiated CPR by CA witnesses.<sup>10</sup> Immediately initiated CPR improves the chances for the initial shockable rhythm, thus improving chances for survival.<sup>11,12</sup> Besides, quality of life is better in CA patients with immediately initiated CPR.<sup>13</sup>

If EMS Call Centre operator asks adequate questions, recognition rate of CA by laymen could rise up to 83 %.<sup>14</sup> Reaction time I for the priority I calls should be less than one minute.<sup>15</sup> After the recognition of CA, the operator should dispatch the ambulance squad without terminating the phone call and also give instructions how to initiate CPR before the arrival of ambulance.<sup>16</sup> In this study, more than 70 % of callers recognised the unresponsiveness. When asked if the patient breathed, all the callers gave correct answer. However, operators asked that question in about 25 % of cases. Another problem was that operators measure reaction time I in minutes, taking into consideration the period between the moments they wrote entry for a new patient and dispatched the ambulance squad. The reported reac-

tion time I is therefore longer than it should be and even the recorded reaction time I is longer than two minutes. There was no standard questioning protocol with adequate questioning techniques in the critical problems, so the EMS operators dealt with the callers according to their best knowledge and experience. This resulted in longer duration of phone calls and omission of relevant information in some cases. The operator usually terminated the phone call in order to dispatch the ambulance squad, which lengthened the reaction time I. Due to the lack of standard questioning protocol and undermanned EMS personnel, operators are not able to deliver phone assisted CPR, so the duration of calls is shorter than reaction time I.

In most European countries, it takes six minutes on average for the ambulance squad to arrive to the patient with CA.<sup>17,18</sup> If CA is in the presence of witnesses, the initial rhythm is shockable in 75 % of cases. If CA is not witnessed at the moment of collapse, the shockable rhythm is initially present in only 40 % of cases.<sup>19</sup> In this study, reaction time II was over 7 minutes. If reaction times I and II are summed up, it turns out that it took more than 9 minutes for the ambulance squad to arrive to the patient with CA. In the presence of witnesses, the initial rhythm was shockable in only 40 % of patients.

Low incidence of the shockable rhythm could also be attributed to the fact that only small number of witnesses attempted CPR before the arrival of the ambulance squad. The percentage of the laymen initiated CPR ranges from 3 % in the undeveloped countries to 45 % in urban areas, or 16-33 % on average.<sup>19-21</sup> A rise in the laymen initiated CPR was observed in the last 15 years due to the Basic life support (BLS) trainings of the non-medical staff and introduction of standard questioning protocols in EMS Call Centres. This study showed that CPR was most often witnessed by a layman and that CPR was initiated before the arrival of the medical staff on every tenth patient. Number of phone-guided CPRs was negligible. All these facts attributed to the small number of initial presentation with shockable rhythm.

It is well known that initiated CPR in patients with CA improves the chances for survival by two or three times. It also improves the probability of finding the patient in the initial shockable rhythm, with the survival rate which is doubly higher than in those with non-shockable rhythm.<sup>2, 3, 19</sup>

Univariate binary logistic regression analysis showed that the survival rate was determined not by the presence of witnesses, but by the attempted CPR. Immediately initiated CPR improves the chances for ROSC to be established and sustained to the hospital admission. However, small rate of patients with immediately initiated CPR attributed to the small survival rate of patients with out-of-hospital CA.

Most studies in the world literature did not take into consideration the period between the collapse and the phone call to the EMS. Most data regarding this period are taken to be unreliable due to the emotional stress on the part of the witnesses. Most witnesses claim that they called EMS in the first minute after the collapse.<sup>11</sup> The same result is found in this study as well.

ERC Guidelines for Resuscitation 2010 recommend the prehospital use of therapeutic hypothermia in comatose survivors of CA.<sup>22, 23</sup> In Serbia, therapeutic hypothermia is currently applied only in the tertiary medical centres. For this reason, IEMS Novi Sad cannot apply this method pre-hospitally.

A drawback of this study is its limitation to the prehospital level. Data regarding the short-term survival (from the admission to the discharge from the hospital) and neurological evaluation of patients after CA were not included.

## Conclusion

CA is one of the most urgent medical conditions and reaction time I should be lower than one minute. EMS operators should quickly interrogate callers with strict protocols to elicit information, focusing on the recognition of unresponsiveness and the quality of breathing. The ambulance squad should be dispatched without terminating the phone call and a protocol for CA should be started. In order to achieve this, standard questioning protocols and up-to-date information technologies in the EMS Call Centres are necessary, as well as regular training of EMS operators in encouraging witnesses to initiate CPR. Work in the modern EMS Call Centre also necessitates employment of the new personnel.

## Ethics Approval

This study was conducted with the approval of the Institute for Emergency Medical Service Novi Sad Ethics Committee.

## Acknowledgements

None.

## Conflict of interest

None.

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# Rare Concomitant Myxoid and Cystic Degeneration of Uterine Leiomyoma - Case Report

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## Abstract

The uterine leiomyomas are monoclonal tumours of myometrial smooth muscle cells that are oestrogen dependent. A 43-year-old patient was referred by her gynaecologist under a suspected diagnosis of ovarian tumour. She complained of prolonged and profuse, regular menstrual bleeding that led to anaemia. The ultrasound examination showed a complex tumour mass with dimensions 68 x 85 mm, with several cystic formations fulfilled with clear fluid, which protrudes from the posterior wall of the uterus. Therefore, the diagnosis of leiomyoma with a cystic degeneration was considered preoperatively. In the case of cystic degeneration of the myoma, the ultrasound shows a combination of cystic and solid components with irregular shape and variable echogenicity. The ovarian malignancy should be ruled out in the presence of a large cystic mass with irregular septa and solid nodular parts filling the small pelvis. Ultrasound characteristics of degenerative myomas should always be considered, so as not to replace it with an ovarian mass, especially if it is subserosal and on the loop.

**Key words:** Leiomyoma; Myxoid degeneration; Cystic degeneration; Ovarian tumour; Differential diagnosis.

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## Introduction

The uterine leiomyoma is the most common pelvic tumour in the female population. The exact incidence is difficult to be determined as all the studies are either based on symptomatic cases or histopathological evaluation of the preparations after hysterectomy. Nevertheless, the leiomyomas are thought to be clinically diagnosed at around 12 % to 25 % of the reproductive female population, and in about 80 % of preparations of hysterectomy.<sup>1</sup> The leiomyomas are monoclonal tumours of myometrial smooth muscle cells that are oestrogen dependent and therefore not seen

at prepubertal girls.<sup>2</sup> There are sporadically described cases in adolescence and most of them shrink in menopause.

## Case History

A 43-year-old patient (G2, P2) was referred by her gynaecologist under a suspected diagnosis of ovarian tumour. Anamnestically, she complained of prolonged and profuse, regular menstrual

bleeding that led to anaemia. On bimanual examination, a motile, soft uterus was found completely enlarged and pushed forward, and a painfully sensitive tumour mass in the recto-uterine pouch (*cavum Douglasi*). The ultrasound examination showed a complex tumour mass with dimensions 68 x 85 mm, with several cystic formations fulfilled with clear fluid, which protruded from the posterior wall of the uterus (Figure 1 and 2). The entire uterus was pushed forward and to the right. The tumour mass was continuous with the rest of the myometrium on the posterior wall of the uterus, indicating uterine origin (Figure 3). The right ovary was displayed separately with a neat morphology and size appropriate for the age. The left ovary was displaced cranially and posteriorly from the tumour mass, but also with neat morphology on ultrasound. Due to the clear ultrasound image of the uterine origin of the tumour, there was no need for MRI preoperatively. Therefore, the diagnosis of leiomyoma with a cystic degeneration was considered preoperatively.

As part of the preoperative preparation, a fractional exploratory curettage of the body and the cervix of the uterus was performed. The histopathological finding was a functional endometrium under prolonged and exclusively oestrogenic action within the anovulatory cycle.



Figure 1: Transabdominal ultrasound - cross sectional imaging of leiomyoma with cystic changes



Figure 2: Transabdominal ultrasound - coronal section of a leiomyoma

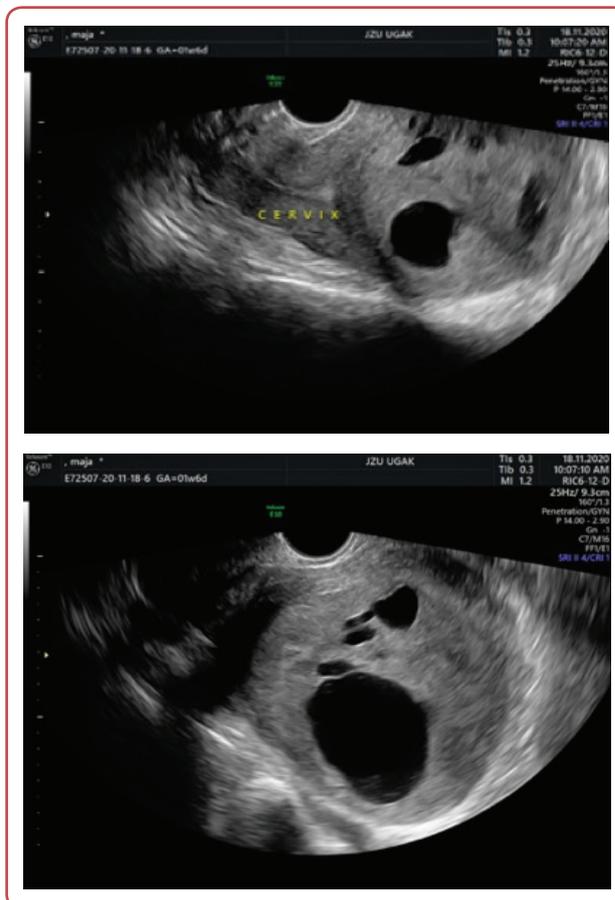


Figure 3: A sagittal, transvaginal ultrasound view of the cervix and the body of the uterus with leiomyoma on the posterior wall



Figure 4: Macroscopic appearance of the specimen from the operation

The patient underwent a laparotomy and large leiomyoma was found originating from the left part of the posterior uterine wall. Both ovaries were with a neat morphology. Total abdominal hysterectomy with a bilateral salpingectomy was carried out (Figure 4).

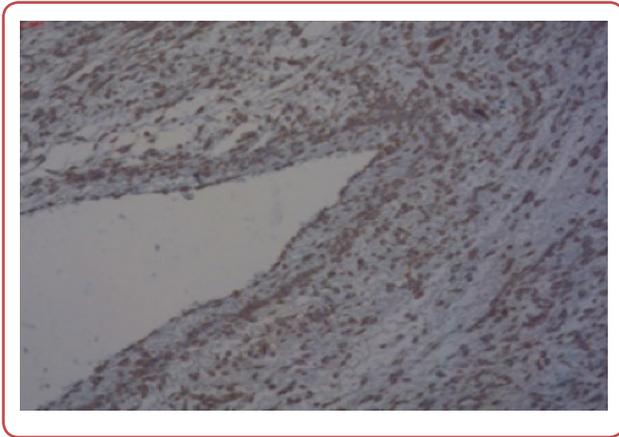


Figure 5: Microscopic specimen after staining with Vimentin

The histopathological analysis showed a leiomyoma with an extensive area of myxoid degeneration and cystic spaces. Immunohistochemical analysis showed that the cystic spaces were coated with smooth muscle actins (SMA) and vimentin positive myocyte cells. Staining for CD34, CD10 and CD31 was negative corresponding to a cystic degenerative leiomyoma (Figure 5).

## Discussion

The leiomyomas are usually diagnosed accidentally during routine gynaecologic examination, or when symptoms appear. The symptoms primarily depend on the location of the myoma (submucosal, intramural or subserosal). Most often it is prolonged and heavy menstrual bleeding and less often pelvic pain or infertility and obstetric complications.

The rapid growth of the myoma<sup>3</sup> can lead to a relative deficiency of its blood supply and result in various types of degeneration: hyaline (most common, in about 60 % of cases), cystic (4 %), red (3 %), calcified (4 %), myxoid (1 - 3 %), sarcomatous degeneration (0.1 - 0.8 %). The combination of myxoid and cystic degeneration is very rare as only case reports were found in the literature.

Clinically, the leiomyoma degeneration can lead to acute pain, fever, uterine tenderness on palpation, or pressure with an ultrasound probe on the fibroid, elevated leucocytes or even peritoneal signs.<sup>4</sup> These symptoms, caused by the degeneration, are usually self-limiting and respond well to non-steroidal anti-inflammatory drugs.

The first imaging method of the leiomyoma diagnosis is the ultrasound. At ultrasound, the leiomyoma is presented as hypoechogenic, well-defined round masses, often with shadows. If it is a cellular leiomyoma, then the ultrasound may be isoechoic (making it difficult to differentiate from the surrounding normal myometrium) or hyperechoic.<sup>5</sup>

In the case of cystic degeneration of the myoma, the ultrasound shows a combination of cystic and solid components with irregular shape and variable echogenicity. Due to this, they can be mistaken with a large ovarian simplex cyst, complex endometrial hyperplasia, or postoperative abscess, and therefore, they present a diagnostic challenge.<sup>6</sup>

The first diagnosis to be ruled out in the presence of a large cystic mass with irregular septa and solid nodular parts filling the small pelvis is ovarian malignancy. The exclusion of the ovarian origin is crucial for a differential diagnosis. This can be achieved by showing both ovaries with normal morphology, and on the other hand, showing the continuity of the leiomyoma with the uterine wall. The absence of ascites and other signs of malignancies also support the diagnosis of myoma with cystic degeneration. Low tumour markers can once again confirm the diagnosis pre-operatively.

The differential diagnosis of leiomyoma with cystic degeneration also includes cystic mesothelioma, cystic teratoma, endometriosis, lymphangioma or mesenteric cyst.<sup>7</sup>

In obscure cases, and when a precise diagnosis of complex pelvic mass preoperatively is needed, MRI may be used. The MRI is the most effective method for diagnosing and classification of myomas given the good resolution of the presented soft tissues.

## Conclusion

Although the myomas are the most common small pelvic tumours in the female population and have a characteristic ultrasound appearance, a diagnostic challenge may occur when degeneration of tumour appears. Ultrasound characteristics of degenerative myomas should always be considered, so as not to replace it with an ovarian mass, especially if it is subserosal and on the loop.

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None.

## Conflict of interest

None.

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Captions for illustrations are typed on a separate page, with Arabic numbers corresponding to the illustrations. If used to identify parts of the illustrations, the symbols, arrows, numbers, or letters should be identified and explained clearly in the legend. The method of staining and magnification in photomicrographs should be explained. Captions should be detailed enough to allow for understanding of the content of the figure without previous reading of the text. The place of the figure in the text should be marked as in the following example: "(Figure 1 near here)".

#### Abbreviations and acronyms

Authors are encouraged to use abbreviations and acronyms in the manuscript in the following manner: abbreviations and acronyms must be defined the first time they are used in the text and thereafter must be consistently used throughout the whole manuscript, abbreviations should be used only for terms that appear more than three times in text; abbreviations should be sparingly used. Use of abbreviations in the titles should be avoided. Even if used after its definition in the abstract, the same definition and repetition of the abbreviation should be performed the first time it is used in the text. In order to assure self-explanatory nature of the tables and figures, abbreviations and acronyms should be defined in the captions and then introduced, irrespective of whether it was done earlier in the text.

#### 4. References

References should be superscripted and numerated consecutively in the order of their first mentioning within the text. All the authors should be listed, but if there are more than 6 authors, the first 6 should be quoted, followed by comma and "et al". Abstracts, secondary publications, oral communications, unpublished papers, official and classified documents should not be used. References to papers accepted but not yet published should be cited as "in press". Data from the Internet are cited with the date of citation. Articles from the e-journals should always contain DOI code.

Examples of references:

Gillespie NC, Lewis RJ, Pearn JH, Bourke ATC, Holmes MJ, Bourke JB, et al. Ciguatera in Australia: occurrence, clinical features, pathophysiology and management. *Med J Aust* 1986;145:584-90.

Hull J, Forton J, Thompson A. Paediatric respiratory medicine. Oxford: Oxford University Press; 2015. Bydder S. Liver metastases. In: Lutz S, Chow E, Hoskin P, editors. Radiation oncology in palliative cancer care. Chichester (UK): John Wiley & Sons, Ltd.; 2013. p. 283-298.

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

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