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## Publish

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# Coverage and Knowledge Regarding Human Papillomavirus Vaccination Among Female Medical Students at Pelita Harapan University

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## Abstract

**Citation :** Lukman L. Coverage and Knowledge Regarding Human Papillomavirus Vaccination Among Female Medical Students at Pelita Harapan University. *Medicus*. 2025 June; 14(3):182-188.

**Keywords:** Coverage; Knowledge; Human papillomavirus vaccination; Female students; Faculty of medicine.

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**Online First :** June 2025

**Background:** Cervical cancer is the fourth most common cancer among women worldwide. Human papillomavirus (HPV) is the primary cause of cervical cancer. One of the key preventive measures to reduce the incidence of cervical cancer is immunization. According to the data from the World Health Organization year 2020, the national HPV vaccination coverage in Indonesia was only 5% for the complete dose and 6% for the first dose. Lack of knowledge is one of the contributing factor of HPV vaccination coverage.

**Methods:** This study was conducted with cross-sectional design. This study used primary data which was collected using questionnaires. The questionnaire has been tested for validity and reliability in previous study. The subjects were female students of Faculty of Medicine University of Pelita Harapan.

**Results:** Our of 770 subjects with mean age of 20.3 years old, 490 subjects (63.6%) never got HPV vaccination, 102 subjects (13.3%) were not fully vaccinated and 178 subjects (23.1%) were fully vaccinated. Age at first dose of HPV vaccination was 9-14 years old in 123 subjects (43.9%) and > 15 years old in 157 subjects (56.1%). From all of the HPV vaccinated subjects, 18 subjects (6.4%) got bivalent vaccine, 52 subjects (18.6%) got quadrivalent vaccine and 64 subjects (22.9%) got nonvalent vaccine. Majority of the subjects (354 subjects, 46%) had good knowledge regarding HPV vaccination, 271 subjects (35.2%) had sufficient knowledge and 145 subjects (18.8%) had poor knowledge.

**Conclusions:** Despite sufficient knowledge regarding HPV vaccination among majority of female medical students at Pelita Harapan University, HPV vaccination coverage remained suboptimal.

## Introduction

Cervical cancer is the fourth most common cancer among women worldwide. According to data from the World Health Organization (WHO), there were 660,000 new cases of cervical cancer in 2022, with 350,000 resulting in

death.<sup>1</sup> In Indonesia, the data from 2021 showed cervical cancer as the second most common cancer among women. A total of 36,633 cases were reported, accounting for approximately 17.2% of all cancers in women. Cervical cancer is the leading cause of cancer-related deaths

among Indonesian women, with a mortality rate of 21,003 deaths, or 19.1% of all cancer deaths. The incidence of cervical cancer in Indonesia has doubled compared to the data reported in 2008.<sup>2,3</sup>

Human papillomavirus (HPV) is the primary cause of cervical cancer, identified in 99.7% of cervical cancer cases worldwide.<sup>4</sup> Human Papillomavirus can be classified into two major groups: non-oncogenic types and oncogenic types. One of the key preventive measures to reduce the incidence of cervical cancer is immunization. Currently, there are three types of HPV vaccines available: bivalent, quadrivalent, and nonavalent. All of these vaccines have been proven to be highly effective in preventing HPV types 16 and 18 infections, which are responsible for approximately 70% of cervical cancer cases globally.<sup>5-7</sup> The World Health Organization recommends the inclusion of the HPV vaccine in national immunization programs. The goal of the HPV vaccination program is to achieve 90% coverage among 15-year-old girls by the year 2030.<sup>8</sup>

In Indonesia, the HPV vaccination program was first introduced in 2016 in the Special Capital Region of Jakarta and was expanded nationwide in 2023. The HPV immunization program consists of two doses administered to female students in the 5th and 6th grades of elementary school. According to WHO data from 2020, the national HPV vaccination

coverage in Indonesia was only 5% for the complete dose and 6% for the first dose.<sup>9-</sup>

<sup>10</sup> Several factors contribute to the low coverage of HPV immunization in Indonesia, including limited availability of the HPV vaccine and lack of knowledge about the vaccine. Studies have shown that acceptance of the HPV vaccine is associated with levels of knowledge about the virus and vaccination, degree of sexual promiscuity and sexually transmitted infections, as well as perceptions of the vaccine's safety and efficacy.<sup>11-13</sup>

A systematic review conducted in the United States, Europe, Canada, Australia, and Africa found that women's knowledge regarding the link between HPV infection and cervical cancer remains low.<sup>14</sup> According to a study by Monteiro et al., HPV vaccination rates among university students are generally low but are comparatively higher among medical students. This is attributed to their greater understanding of cervical cancer and its association with HPV infection.<sup>15</sup> Therefore, the researcher is interested to study the coverage and level of knowledge regarding HPV vaccination among female medical students at Pelita Harapan University.

## Material And Methods

This study was conducted with cross-sectional design. The target population was female medical students of Pelita

Harapan University. Sample size was calculated with single proportion formula ( $d = 0.05$ ) with minimal sample of 140 subjects. Inclusion criteria including registered female medical students of Pelita Harapan University who consented to take part in this study. Exclusion criteria was incomplete data.

Primary data was collected with questionnaire distributed via google form including age, HPV vaccination status, age at first dose of HPV vaccination, type of HPV vaccination and knowledge regarding HPV vaccination. The questionnaire to assess the knowledge regarding HPV vaccination has been tested for validity and reliability in previous study. The questionnaire consisted of 11 questions with three options of answer: true, false or I do not know. Every correct answer will be scored 2, wrong answer will be scored 1 and unanswered will be scored 0. The score will be summed up and classified into good knowledge (score 17-22), sufficient knowledge (score 12-16) and poor knowledge (score 0-11). The data was then tabulated and univariate analysis was done using Microsoft Excel. This study was approved by the Institutional Review Board of Pelita Harapan University, Tangerang, Banten, Indonesia.

## Result

From March to April 2025, there were 770 subjects who met all inclusion and

exclusion criteria. The mean age was 20,3-year-old with the oldest was 28-year-old and the youngest was 17-year-old. The characteristics of subjects were shown in **Table 1**.

**Table 1.** Subject Characteristics

| Subject Characteristics                | N (%)      |
|----------------------------------------|------------|
| Age, mean (year)                       | 20,3       |
| HPV vaccination status*                |            |
| None                                   | 490 (63,6) |
| Not fully vaccinated                   | 102 (13,3) |
| Fully vaccinated                       | 178 (23,1) |
| Age at first dose of HPV vaccination** | 123 (43,9) |
| 9-14 years old                         | 157 (56,1) |
| >15 years old                          |            |
| Type of HPV vaccination**              | 18 (6,4)   |
| Bivalent                               | 52 (18,6)  |
| Quadrivalent                           | 64 (22,9)  |
| Non-a-valent                           |            |

\*From total 770 subjects

\*\*From total 280 vaccinated subjects

The knowledge regarding HPV vaccination were shown in **Table 2**.

**Table 2.** Knowledge regarding HPV vaccination

| Knowledge regarding HPV vaccination | N (%)      |
|-------------------------------------|------------|
| Good                                | 354 (46,0) |
| Sufficient                          | 271 (35,2) |
| Poor                                | 145 (18,8) |

## Discussion

In our study, the majority of study subjects had sufficient-good knowledge regarding HPV vaccination (81.2%) and only small proportion had poor knowledge (18.8%). This result indicates a high level of awareness regarding the HPV vaccine among the study population. Knowledge regarding HPV vaccination is linked with

educational background. A study from Khatiwada M et al showed that university students have a good knowledge of HPV vaccination. The study also found out that there was significant association between knowledge and faculty.<sup>16</sup> A study done by Adnyana et al with economics university students as subjects found that majority had sufficient-good level of knowledge (78%) and only 22% had poor level of knowledge regarding HPV vaccination.<sup>17</sup> Another study by Putri et al also found that 74% of medical students have a good knowledge regarding HPV vaccination.<sup>18</sup>

Despite sufficient-good knowledge regarding HPV vaccination, majority of our study subjects do not receive HPV vaccine (63.6%). This finding is concerning, particularly within a population expected to show proactive health-seeking behavior and serve as future advocates for preventive care. The disparity between knowledge and vaccine acceptance suggests that factors other than awareness play a critical role in influencing students' decisions. A study by He et al showed factors influencing HPV vaccination in university student including trust in vaccine efficacy, perception of HPV infection risk, price considerations and constraints like distance or time. Educational background of the parents also shown to contribute to HPV vaccine hesitancy.<sup>19</sup> The importance of parent support toward HPV vaccination is also found to be significant factor influencing va

in a study by Wahidin and Febrianti also point out the.<sup>20</sup>

The Indonesian government incorporated the HPV vaccine into the national immunization program across Indonesia in 2023. The HPV vaccines are administered to girls in 5th and 6th grade of elementary school. The youngest subject in our study was 17 years old, and therefore had not participated in the national HPV immunization program. As a result, HPV vaccination had to be paid out-of-pocket, which may be one of the reasons for the low HPV vaccination rate in the population.

In a study conducted in Southern Italy, medical students cited issues such as inconvenient vaccination schedules, lack of time due to academic commitments, and inadequate access to vaccination services as significant deterrents. These logistical challenges are compounded by the absence of institutional initiatives to facilitate vaccination, such as on-campus clinics or coordinated vaccination campaigns.<sup>21</sup> Medical students may perceive themselves as at low risk for HPV infection, especially if they are not sexually active. This perception diminishes the perceived need for vaccination. Studies have shown that individuals who do not recognize themselves as being at risk for HPV are less likely to seek vaccination, despite understanding its importance.<sup>16,22,23</sup>

Cultural and social influences also may play a role. Cultural attitudes towards sexuality and preventive health can influence vaccination decisions. In some contexts, discussions about HPV vaccination may be stigmatized, leading to reluctance in seeking vaccination. Additionally, misinformation and myths about the vaccine, such as misconceptions about its association with infertility or sexual promiscuity, can deter individuals from getting vaccinated.<sup>21,24</sup> Future studies are expected to further investigate factors influencing HPV vaccination coverage in the particular population. By tackling these barriers, vaccination rates among medical students particularly in Pelita Harapan University

can be improved, ultimately contributing to broader public health goals.

## Conclusion

This study showed that despite sufficient knowledge regarding HPV vaccination among majority of female medical students at Pelita Harapan University, HPV vaccination coverage remained suboptimal

## Limitation

This study has several limitations. Data were self-reported, which may affect accuracy and reliability. The findings may not be generalizable due to the specific sample characteristics. Additionally, causal relationships were not assessed, making this a preliminary study.

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Leni Lukman

# The Impact of Attitude and Knowledge on Consent Decisions for Cataract Surgery: A Study at Siloam Hospitals Lippo Village, Building B

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## Abstract

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**Keywords:** Cataract; Cataract surgery; Knowledge level; Attitude; Decision; Cataract patients.

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**Introduction:** Cataracts account for 77.7% of blind cases in Indonesia, indicating that many cataract patients have not had surgery. Low levels of knowledge, attitude, and decision-making among cataract patients regarding surgery may limit the number of procedures performed in Indonesia. Therefore, this study aims to assess cataract patients' knowledge, attitude, and decision-making concerning surgery at Siloam Hospitals Lippo Village in Tangerang. Objective: To determine the relationship between knowledge, attitude, and decision-making regarding cataract surgery among Siloam Hospitals Lippo Village Building B patients.

**Methods:** This cross-sectional study involves 64 cataract patients visiting Siloam Hospitals Lippo Village Building B. The collected data were analysed using SPSS Statistics bivariate analysis.

**Results:** Out of the 64 respondents, 7 (10.9%) demonstrated low knowledge, 4 (6.3%) displayed a negative attitude, and 4 (6.3%) indicated unwillingness to undergo surgery. A significant relationship exists between knowledge and attitude, attitude and decision, and knowledge and decision regarding cataract surgery, with a p-value of 0.000 as determined by the Pearson Chi-Square test.

**Conclusion:** A significant relationship exists between knowledge, attitude, and the decision to undergo cataract surgery.

## Introduction

Cataract is a degenerative process that causes cloudiness in the eye's lens of resulting in blurred vision. Lens cloudiness can be caused by degenerative processes that change the nature and coagulate proteins in the eye's lens through various mechanisms, resulting in loss of

transparency and, ultimately forming cataracts. Cataracts can cause multiple complications, one of which is blindness.<sup>1</sup> Based on data from the World Health Organization (WHO), globally, there are at least 2.2 billion people who experience near or far vision problems with the main cause of visual impairment being cataracts with a prevalence of 94 million out of 1

billion people.<sup>2</sup> In Indonesia, cataracts cause 77.7% of blindness cases. In population aged  $\geq 50$  years, the prevalence of blindness caused by cataract has reached 1.9%. Results of the Rapid Assessment of Avoidable Blindness (RAAB) survey conducted by the Indonesian Ophthalmologist Association (PERDAMI). The high prevalence of blindness caused by cataracts in Indonesia suggests that there are still many cataract sufferers who have not undergone surgery. This is also supported by the Cataract Surgical Rate (CSR) data, namely the number of cataract surgeries per million population per year in Indonesia which is calculated using data from *JKN/BPJS Kesehatan*.<sup>3</sup> Lack of knowledge regarding cataract disease and treatment is still a major Obstacle in developing countries. However, research regarding awareness, knowledge about cataracts and their surgery, and public attitudes towards cataract surgery has yet been carried out. Therefore, this study aims to assess patients' knowledge, attitudes, and decisions of patients towards cataract surgery at Siloam Hospitals Lippo Village, Tangerang

## **Material And Methods**

### ***Research Design and Variables***

This study is a cross-sectional study. The independent variable in this study is the level of knowledge of cataract patients regarding cataract surgery with the

dependent variable being attitude and patient decision toward cataract surgery. Confounding variables include the level of education and income level.

### ***Research Subjects***

Cataract patients at Siloam Hospitals Lippo Village Building B who were 50 years old and over in 2024 were included in this study. This study excluded patients who could not speak Indonesian and patients who were diagnosed with memory or mental disorders. A minimum of 60 samples were required in this study. A total of 64 subjects were obtained.

### ***Research Materials and Methods***

Informed consent sheets, research subject identity sheets, cataract surgery knowledge level questionnaire, and attitude toward cataract surgery questionnaire were utilized. Cataract knowledge was evaluated using a questionnaire consisting of 20 questions with true or false answer choices. Attitude questionnaire towards cataract surgery consisting of 15 questions with answer choices strongly agree, agree, disagree, or strongly disagree. These questionnaires have been previously validated to cataract patients at the Siloam Hospitals Lippo Village Eye Clinic Building B.

### ***Research Ethics***

This study adhered to the principles of the Declaration of Helsinki and was approved by the ethics committee of Pelita

Harapan University (Ethics number 116/K-LKJ/ETIK/II/2024).

### **Data Processing and Statistical Analysis**

The collected data were tabulated into Microsoft Excel 2022 and analyzed using the Statistical Package for the Social Sciences 26 (SPSS 26) using the chi-square analysis.

## **Result**

### **Characteristics of Research Subjects**

**Table 1.** Characteristics of Research Subjects

|                                | Variable            | Frequency (n) | Percentage (%) |
|--------------------------------|---------------------|---------------|----------------|
| Gender                         | Male                | 29            | 45.3%          |
|                                | Female              | 35            | 54.7%          |
| Age <sup>a</sup><br>(In years) | 50-59               | 5             | 7.8%           |
|                                | 60-74               | 50            | 78.1%          |
|                                | 75-90               | 9             | 14.1%          |
| Recent Education               | Elementary School   | 7             | 10.9%          |
|                                | Junior High School  | 18            | 28.1%          |
|                                | High School         | 21            | 32.8%          |
| Occupation                     | Undergraduate       | 3             | 4.7%           |
|                                | Bachelor            | 15            | 23.4%          |
|                                | Employee            | 1             | 1.6%           |
|                                | Housewife           | 32            | 50%            |
|                                | Unemployed          | 2             | 3.1%           |
|                                | Self-employed       | 4             | 6.3%           |
| Monthly Income (IDR)           | Retiree             | 25            | 39.1%          |
|                                | ≥ 3.500.000         | 25            | 39.1%          |
|                                | 2.500.000-3.500.000 | 22            | 34.4%          |
|                                | 1.500.000-2.500.000 | 12            | 18.8%          |
|                                | ≤ 1.500.000         | 5             | 7.8%           |

<sup>a</sup> Age categories based on WHO, **44-60: middle age, 60-75: elderly age, 75-90: senile age.**<sup>4</sup>

Of the 64 respondents, there were more female respondents than male respondents, where there were 35 (54.7%) female respondents and 29 (45.3%) male respondents. The oldest respondent was

80 years old and the youngest was 50 years old with most respondents being 67 years old, which was 13 (20.3%) respondents. The last level of education undertaken by most respondents was high school / vocational school with a result of 21 (32.8%) respondents, then junior high school, which was 18 (28.1%) respondents, bachelor's degree with 15 (23.4%) respondents, elementary school with 7 (10.9%) respondents, and finally diploma with 15 (23.4%) respondents. A total of 32 (50%) respondents were housewives, 25 (39.1%) respondents were retirees, 4 (6.3%) respondents worked as entrepreneurs, 1 (1.6%) respondents were private employees, and 2 (3.1%) respondents were unemployed. Most of the respondents, namely 25 (39.1%), had a very high income level, 22 (34.4%) respondents had a high income level, 12 (18.8%) had a medium income level, and 5 (7.8%) had a low income level.

## **Research Results**

**Table 2.** Respondents' Level of Knowledge, Attitude, and Decisions Regarding Cataract Surgery

| Parameter                                            | Frequency (n) | Percentage (%) |
|------------------------------------------------------|---------------|----------------|
| Level of Knowledge                                   |               |                |
| <b>Level of Knowledge Regarding Cataract Surgery</b> |               |                |
| High                                                 | 57            | 89.1%          |
| Low                                                  | 7             | 10.9%          |
| Attitude                                             |               |                |
| <b>Attitude towards Cataract Surgery</b>             |               |                |
| Good                                                 | 60            | 93.8%          |
| Bad                                                  | 4             | 6.3%           |
| Decisions                                            |               |                |
| <b>Decisions towards Cataract Surgery</b>            |               |                |
| Willing                                              | 60            | 93.8%          |
| Not willing                                          | 4             | 6.3%           |

Of the 64 respondents, 57 (89.1%) respondents had a high level of knowledge, while 7 (10.9%) respondents had a low level of knowledge regarding cataract surgery. Most respondents had a good attitude towards cataract surgery, namely 60 (93.8%), while 4 (6.3%) others had a bad attitude towards cataract surgery. For the respondents' decision regarding cataract surgery, 60 (93.8%) respondents were willing, and 4 (6.3%) respondents were not willing to undergo cataract surgery.

**Table 3.** The Relationship between Attitudes and Decisions regarding Cataract Surgery

| Willingness to Undergo Cataract Sugery |         |      |             |     |       |         |
|----------------------------------------|---------|------|-------------|-----|-------|---------|
| Attitude                               | Willing |      | Not willing |     | Total | P value |
|                                        | n       | %    | n           | %   |       |         |
| Good                                   | 57      | 89,1 | 0           | 0   | 57    | 0,000   |
| Bad                                    | 3       | 4,7  | 4           | 6,2 | 7     |         |
| Total                                  | 60      | 93,8 | 4           | 6,2 | 64    |         |

A P value of 0.000 was obtained after analyzing attitude with patient decision. This value indicates the presence of a significant statistical relationship between attitudes and decisions regarding cataract surgery. (Table 3)

**Table 4.** The Relationship between Knowledge Level and Decisions Regarding Cataract Surgery

| Willingness to Undergo Cataract Surgery |         |      |             |     |       |         |
|-----------------------------------------|---------|------|-------------|-----|-------|---------|
| Level of Knowledge                      | Willing |      | Not willing |     | Total | P value |
|                                         | n       | %    | n           | %   |       |         |
| High                                    | 60      | 93,8 | 0           | 0   | 60    | 0,000   |
| Low                                     | 0       | 0    | 4           | 6,2 | 4     |         |
| Total                                   | 60      | 93,8 | 4           | 6,2 | 64    |         |

A P value if 0.000 was also obtained after analyzing knowledge with patient decision, indicating presence of a significant statistic relationship between the two variables. (Table 4)

**Table 5.** The Relationship between Recent Education and Decisions on Cataract Surgery

| Recent Education   | Willingness to Undergo Cataract Surgery |             |       | P Value |
|--------------------|-----------------------------------------|-------------|-------|---------|
|                    | Willing                                 | Not willing | Total |         |
| Elementary         | 6                                       | 1           | 7     | 2,777   |
| Junior High School | 16                                      | 2           | 18    |         |
| High School        | 20                                      | 1           | 21    |         |
| Undergraduate      | 3                                       | 0           | 3     |         |
| Bachelor           | 15                                      | 0           | 15    |         |
| Total              | 60                                      | 4           | 64    |         |

Table 5 shows the relationship between the last level of education and the decision on cataract surgery. A P Value of 2.777 was obtained from the indicating no significant relationship between level of education and patient decision on cataract surgery.

**Table 6.** The Relationship between Income Level and Decisions on Cataract Surgery

| Level of Income | Willingness to Undergo Cataract Surgery |             |       | P Value |
|-----------------|-----------------------------------------|-------------|-------|---------|
|                 | Willing                                 | Not willing | Total |         |
| Very High       | 25                                      | 0           | 25    | 3,672   |
| High            | 20                                      | 2           | 22    |         |
| Average         | 11                                      | 1           | 12    |         |
| Low             | 4                                       | 1           | 5     |         |
| Total           | 60                                      | 4           | 64    |         |

Table 6 discusses the relationship between income level and the decision on cataract surgery. A P Value of 3.672 was obtained, indicating that there is no significant relationship between income level and the decision on cataract surgery.

## Discussion

This research showed that majority of cataract patients in Siloam Hospitals Karawaci Building B had high knowledge and good attitude regarding cataract. This study also found a significant relationship between patient attitudes towards the decision to undergo cataract surgery which can be seen from the P value of 0.000. This indicates that patient attitudes have an important role in their decision to undergo or refuse cataract surgery. Thus it can be said that a bad attitude towards cataract surgery significantly increases the likelihood of patients being unwilling to undergo cataract surgery.

A significant relationship was found between the level of patient knowledge about cataracts and their willingness to undergo surgery. According to the theory of knowledge-attitude-behavior, information and knowledge about health are the foundation for developing active and appropriate beliefs and attitudes towards a disease, this attitude can be a motivation to change behavior.<sup>5</sup> Respondents in this study had educational backgrounds ranging from elementary school, junior high school / MTs, high school/vocational school, diploma, and bachelor's degree. The results of the analysis showed no significant correlation between the level of education and the decision to undergo cataract surgery. The results of the analysis showed no

significant relationship between income level and the decision to undergo cataract surgery. Access to medical information is not always directly correlated with education level, particularly in Indonesia. Regardless of their level of formal education, patients are frequently given additional information on the advantages of cataract surgery through programs like BPJS Kesehatan, which cover the expenses of the treatment. Healthcare professionals, family members, or community-based navigators such as BPJS Watch, Jaminan Kesehatan Watch, and POSKO JKN-KIS also plays a role in assisting patients in understanding and utilizing BPJS Kesehatan services and also help to spread awareness among patients regarding their benefits and entitlements, which may help patients with lesser educational backgrounds to make educated decisions according to a research done in Jakarta in 2022.<sup>6</sup>

This study was conducted in Tangerang, Banten, with a population of cataract patients residing in the area. The Regional Minimum Wage (UMR) of Banten in 2024 was set at IDR 2,995,421 per month.<sup>7</sup> With this level of income, patients living under the Banten UMR standard may face financial constraints that limit their access to healthcare facilities. However, the availability of financial assistance, such as cataract surgery covered by BPJS, is one of the factors influencing these outcomes. This

assistance enables respondents to adopt positive attitudes and make favorable decisions regarding cataract surgery, as they are not burdened by the cost of the procedure. These findings align with a study conducted by Darius Erlangga, Shehzad Ali, and Karen Bloor in 2018, which found that the JKN/BPJS Kesehatan program increases patients' willingness to undergo outpatient and inpatient treatments, including surgeries.<sup>8</sup>

The decision of cataract patients towards cataract surgery as a whole can be influenced by various factors outside of their level of knowledge and attitude. One of the factors is the social support factor where it was found that the role of the patient's family and environment is very important in providing motivation and reducing patient anxiety before undergoing surgery, this will also influence the patient's final decision to undergo surgery.<sup>9</sup>

The limitation of this study is that it was implemented using interview techniques rather than filling out questionnaires by respondents themselves, making it prone

to risk of biased or inaccurate respondent answers.

## Conclusion

There is a significant relationship between the level of knowledge and attitude, attitude and decision, and the level of knowledge and decision of cataract patients at Siloam Hospitals Lippo Village Building B towards cataract surgery. By conducting this study, health services are expected to improve educational efforts to the community regarding cataracts and cataract surgery in order to increase public knowledge and desire for cataract surgery as a preventive measure for blindness due to cataracts. For further researchers, it is hoped that they can reconsider the techniques used in the sample collection process.

## Acknowledgment

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**Atria Puspitaloka Wibisono**

# The Relationship of Body Mass Index with Length of Stay in Symptomatic Cholelithiasis Patients Who Have Undergoing Open Cholecystectomy at RSUS Lippo Village Karawaci Hospital

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## Abstract

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**Keywords:** Cholelithiasis; Open cholecystectomy; Length of stay; Body mass index

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**Background:** Gallstones, also known as cholelithiasis, are hardened deposits of digestive fluids that develop in the gallbladder. A serious medical condition called cholelithiasis is frequently managed with general surgery. One of the treatments for cholelithiasis is an open cholecystectomy. It will take some time to recover from this surgical procedure at the hospital. The period of hospitalization will depend on the patient's weight. Numerous research findings continue to conflict with this study. As a result, this study was carried out to examine the connection between BMI and the length of hospital stay in the open cholecystectomy technique.

**Methods:** This study used a cross-sectional study design with a sample population of cholelithiasis patients at Siloam Hospital. The sample size of 51 was selected using a purposive sampling technique. Data is taken from the patient's medical record and the data collected will be analyzed using *Mann-U Whitney*.

**Result:** From 51 samples, the mean length of stay for subjects with BMI < 23 kg/ m<sup>2</sup> was 3 days, with the lowest value being 1 day and the highest value was 5 days. Meanwhile, the mean length of stay for subjects with BMI > 23 kg/ m<sup>2</sup> was 3 days with the lowest value was 2 days and the highest value was 6 days. From the Mann-U Whitney test, it was found that the results of the comparison were not significant ( $p > 0.05$ ).

**Conclusions:** This study shows there is no relationship between BMI and duration of hospitalization in cholelithiasis symptomatic patients undergoing open cholecystectomy surgery

## Introduction

Cholelithiasis or gallstones are deposits of digestive fluid that harden and form in the gallbladder. Cholelithiasis is a health problem that affects the population significantly because it can be found in 10% to 15% of the general population<sup>1</sup>, specifically 6% in men and 9% in women.<sup>2</sup>

The prevalence of cholelithiasis varies by country. In Asia, Gallstone prevalence rates range from 3.2% to 15.6%. In Indonesia, cholelithiasis receives minimal attention because it has asymptomatic symptoms, so it is difficult to detect. Based on studies conducted at RSUP Prof. Dr. R.D. Kandou

Manado in the period from October 2015 to October 2016, 113 cases of cholelithiasis were found.<sup>3</sup> Cholelithiasis can be caused by many factors such as age, gender, estrogen, and body mass index (BMI).<sup>4</sup>

BMI is a measure of body fat which is measured by dividing body weight by the square of body height on a meter scale. 6 Based on the Asia Pacific classification, BMI is categorized into 3 groups, namely: underweight (BMI <18.5 kg/m<sup>2</sup>), overweight individuals normal (18.5-22.9 kg/m<sup>2</sup>), and overweight ( $\geq 23$  kg/m<sup>2</sup>).<sup>5</sup> With each increase in BMI, the possibility of cholelithiasis increases. Based on studies, it was found that the risk of gallstone disease increases by 7% for every increase in BMI. The incidence of cholelithiasis occurs in 5% of the general population and this percentage increases significantly in the obese population to reach 45%.<sup>6</sup>

Based on a study conducted in New South Wales in 2016, it was concluded that an increase in BMI was positively correlated with an increase in the duration of hospital stay.<sup>7</sup> This contrasts with the results of research by Bulian (2018) which states that there is no relationship between BMI and the length of hospitalization. This research is supported by other research by Bowling et al which states that obesity does not affect the duration of hospital stay.<sup>8</sup>

In addition, the authors found a gap in literature because similar previous research was only conducted on patients who

underwent laparoscopic cholecystectomy techniques. Based on the explanation of the problem above, the author wants to conduct research looking for the relationship between BMI and length of stay in patients undergoing surgery using the open cholecystectomy technique.

## Material And Methods

This study combines a cross-sectional study with an unpaired numerical comparative analytical study. Conducted from January to June of 2023.

Patients with symptomatic cholelithiasis, aged 18 to 60, who had open cholecystectomy at RSUS Lippo Village Karawaci were the subjects of this study. Data gathered from medical records is used in sampling. Purposive sampling was used to acquire data from the patient's medical record.

The study will not include samples that match the exclusion criteria, such as patients who did not undergo open cholecystectomy at Siloam Hospitals Lippo Village, patients with a history of abdominal surgery, patients with a history of liver disease

The Statistical Package for the Social Sciences (SPSS) software version 25 was used to process and analyse the research data that had been obtained. When the data distribution was not normal, the Man-U Whitney test was used for statistical analysis; when it was normal, the T-test was used. The University of Pelita Harapan's Faculty of Medicine ethical committee approved this study under the reference 010/SHLV/HA/II/23.

## Result

According to Table 1, there were 37 female individuals and 14 male subjects among the 51 processed subjects, according to the collected characteristics. Following the calculation of each patient's body mass index, it was discovered that 25 (49%) of the patients fell into the Asia-Pacific criteria's ideal body weight category (BMI <23 kg/m<sup>2</sup>), while 26 (51%) fell into the overweight category (BMI >23 kg/m<sup>2</sup>). The results of the data analysis showed that the subjects who had open cholecystectomy had a median age of 47 years, with the youngest being 19 years old and the oldest being 60 years old.

After doing the calculations, the number of patients with comorbid hypertension was 4 people in the BMI <23 kg/m<sup>2</sup> and BMI >23 kg/m<sup>2</sup> categories. Meanwhile, 2 patients who had comorbid diabetes were in the BMI <23 kg/m<sup>2</sup> category and 1 person was in the BMI >23 kg/m<sup>2</sup> category.

**Table 1.** Demographic of samples

| Variable                     | BMI <23 (%)   | BMI >23 (%)   |
|------------------------------|---------------|---------------|
| <b>Total</b>                 | 25 (49)       | 26 (51)       |
| <b>Sex</b>                   |               |               |
| Male                         | 5 (20)        | 9 (34,61)     |
| Female                       | 20 (80)       | 17 (65,38)    |
| <b>Age</b>                   |               |               |
| Median (min/max)             | 51 (19/60)    | 44 (22/60)    |
| Mean ± SD                    | 48,2 ± 10,972 | 43,1 ± 11,838 |
| <b>Comorbid Hypertension</b> |               |               |
| Yes                          | 4 (16)        | 4 (15,38)     |
| No                           | 21 (84)       | 22 (84,61)    |
| <b>Diabetes</b>              |               |               |
| Yes                          | 2 (8)         | 1 (3,84)      |
| No                           | 23 (92)       | 25 (96,15)    |

The results obtained show a significance value of  $p < 0.05$ , which states that the data distribution is not normal. Therefore, the analysis used the Mann-U Whitney method. A bivariate analysis of the data was then conducted.

The results of the SPSS analysis showed that the subjects with a BMI <23 kg/m<sup>2</sup> had a median length of stay of 3 days, with the lowest value of 1 day and a maximum value of 5. This is consistent with research by Muqim et al. showing that patients stayed in the hospital for three days following cholecystectomy surgery.<sup>9</sup> For participants with a BMI >23 kg/m<sup>2</sup>, the median duration of stay was 3 days, the lowest value was 2 days, and the maximum value was 6 days. The comparison results, according to the Mann-U Whitney test, were not significant ( $p > 0.05$ ).

**Table 2.** Demonstrated bivariate analysis of Independent Variable toward Length of Stay

| Variable | n  | Median | Min/Max | P Value |
|----------|----|--------|---------|---------|
| BMI      |    |        |         |         |
| <23      | 25 | 3      | 1/5     | 0.431   |
| >23      | 26 | 3      | 2/6     |         |

## Discussion

The purpose of this cross-sectional, unpaired numerical comparative analytical study was to find out if there was a connection between patient's duration of stay following open cholecystectomy surgery and their BMI. In February and March of 2023, data from medical records were gathered at Siloam Hospital Lippo Village Pavilion B. 51 samples were gathered for this investigation, and every

person met the inclusion and exclusion requirements to be included in the research.

Based on the results of the research that has been carried out, it was found that the research subjects were dominated by women (72.5%) compared to men (27.5%). This is in line with the theory that women naturally have higher estrogen levels than men, resulting in higher cholesterol gallstone formation. The results of the Mann-U Whitney test showed that the comparison results were not significant ( $p > 0.05$ ) between BMI and the length of stay in patients who underwent open cholecystectomy surgery.

The findings of this study contrast those of a 2016 study conducted by New South Wales, which found that increased BMI was positively connected with increasing length of hospital stay.<sup>7</sup>

Nonetheless, the findings of my investigation align with the findings of Bowling et al.'s study, which found no relationship between obesity and hospital stay length. According to the study, there was no significant difference in the length of hospital stay or fatality rates between the obese and

non-obesity groups, however, complications occurred more frequently in the obese group.<sup>10</sup>

According to Simopoulus et al, the presence of inflammation or a combination of obesity and abdominal surgery previously was a major detrimental factor for patients. It can be concluded that the increase in the duration of hospitalization is multifactorial, especially with a history of abdominal surgery. As many as 35% of obese patients undergoing surgery may experience wound healing problems. This is due to the risk of adhesion formation in patients who have a history of abdominal surgery. The formation of these adhesions affects the patient's recovery process.

## Conclusion

Based on the results and discussion presented using a cross-sectional study design in symptomatic cholelithiasis patients who underwent open cholecystectomy surgery at Siloam Hospital Lippo Village, it can be concluded that there is no statistically significant comparison ( $p > 0.05$ ) between the length of stay in patients with a BMI of 23 kg/m<sup>2</sup> and patients with a BMI of >23 kg/m<sup>2</sup>.

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**Chellya Fanny Alvionitan**

# Anesthetic Management in Obese Patients Undergoing Laparoscopic Cholecystectomy: A Case Report

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## Abstract

**Citation:** Pakardian IA, Dewi DAMS. Anesthetic management in obese patients undergoing laparoscopic cholecystectomy: a case report. *Medicinus*. 2025 June; 14(3):201-212.

**Keywords:** Anesthesia management in laparoscopy; Laparoscopic complications; Laparoscopy; Obesity.

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**Background:** Obesity is associated with various complications during general anesthesia, including apnea, hypoventilation, and challenges in intubation. In obese patients, these factors increase the anesthetic risks associated with laparoscopic cholecystectomy, a minimally invasive surgery performed to remove the gallbladder. This procedure is often indicated for gallstones causing inflammation, pain, or infection. Laparoscopic cholecystectomy involves small incisions, allowing most patients to recover quickly, return home the same day, and resume normal activities shortly thereafter. Compared to open cholecystectomy, the laparoscopic approach offers advantages such as faster recovery, reduced postoperative pain, and lower risk of complications.

**Methods:** A 43-year-old female patient with a body weight of 120 kg, height of 155 cm, and a BMI of 49.9 kg/m<sup>2</sup> (classified as obesity) was initially scheduled for an open cholecystectomy. However, intraoperative evaluation by the surgeon led to a decision to switch to laparoscopic cholecystectomy. Anesthesia was induced using a propofol syringe pump, fentanyl (150 mcg), and atracurium (40 mg) as a muscle relaxant. Intubation was performed with video laryngoscopy, using an endotracheal tube (ETT) with a cuff size of 7.

**Result:** During the operation, the patient's end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) levels increased to 40 mmHg due to CO<sub>2</sub> insufflation, leading to worsening respiratory acidosis. Complications such as these are common during laparoscopic procedures in obese patients and require timely management to prevent further deterioration.

**Conclusions:** The patient's condition was stabilized by employing specific intraoperative strategies, including positioning in reverse Trendelenburg, mild hyperventilation, and applying positive end-expiratory pressure (PEEP). These measures successfully reduced ETCO<sub>2</sub> levels, demonstrating the importance of tailored anesthetic and ventilatory management in obese patients undergoing laparoscopic cholecystectomy.

## Introduction

The global rise in obesity prevalence poses a significant health challenge for both developed and developing nations. Obesity is defined as an excessive accumulation of body fat that negatively impacts health. It is quantified using the

body mass index (BMI), calculated by dividing an individual's weight by the square of their height, with a BMI of 30 or higher indicating obesity. This issue is widespread, affecting nearly every country, with the exception of certain regions in sub-Saharan Africa and Asia.<sup>1</sup> In 1997, this

condition was officially recognized as a global health issue by the World Health Organization (WHO). By 2016, over 1.9 billion adults worldwide were classified as overweight or obese.<sup>1,2</sup> The prevalence of obesity has risen dramatically across both genders and all age groups, with higher rates observed among older adults and women.<sup>1</sup> A systematic review conducted in 2020 revealed that the prevalence of obesity in Indonesia reached 16.9% among men and 28.6% among women. Across all Southeast Asian countries, women were found to have a higher tendency toward obesity, attributed to lower energy expenditure and reduced physical activity.<sup>3</sup>

Obesity is a significant risk factor for various non-communicable diseases (NCDs) and is associated with higher risks of morbidity, mortality, and disability. It affects nearly all organ systems and increases the likelihood of developing conditions such as diabetes mellitus, cardiovascular diseases, osteoarthritis, hyperlipidemia, sleep apnea, mobility disabilities, a shorter lifespan, and vulnerability to nerve injuries during sedation. These comorbidities contribute to an elevated rate of perioperative mortality.<sup>4,5</sup> In the context of general anesthesia, obesity is linked to several complications, such as apnea, hypoventilation, challenges in intubation, a heightened risk of aspiration, and changes in the pharmacokinetic properties of medications.<sup>4,6,7</sup>

## Material And Methods

A 43-year-old female patient with a body weight of 120 kg, height of 155 cm, and a BMI of 49.9 kg/m<sup>2</sup> (classified as obesity) was initially scheduled for an open cholecystectomy. However, intraoperative evaluation by the surgeon led to a decision to switch to laparoscopic cholecystectomy. Anesthesia was induced using a propofol syringe pump, fentanyl (150 mcg), and atracurium (40 mg) as a muscle relaxant. Intubation was performed with video laryngoscopy, using an endotracheal tube (ETT) with a cuff size of 7.

## Result

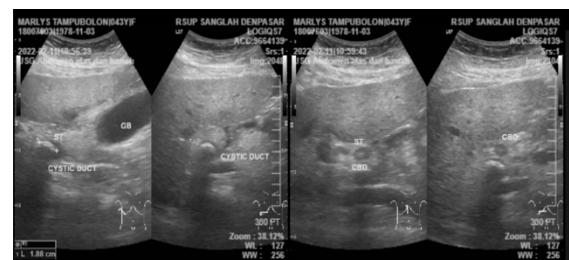
A 43-year-old Balinese woman (155 cm in height, 120 kg in weight, BMI 49.3 kg/m<sup>2</sup>) was admitted to our hospital for a planned laparotomy cholecystectomy (LC). She presented with a one-year history of intermittent abdominal pain localized to the right upper quadrant, radiating to the epigastrium and back. The patient reported a history of snoring but denied experiencing nocturnal dyspnea, fatigue, or excessive daytime sleepiness. She was diagnosed with diabetes mellitus four years ago and is currently managed with a regimen of subcutaneous glargine insulin (20 units daily) and subcutaneous Novorapid insulin (14 units administered with each main meal). Her medical history is unremarkable for prior surgeries, hypertension, cardiovascular disease, or

asthma. However, she has a 10-year history of smoking 12 cigarettes per day. As a homemaker, she is able to engage in light to moderate physical activities without symptoms of dyspnea or chest discomfort.

Physical examination revealed a blood pressure of 140/90 mmHg, heart rate of 84 beats per minute, respiratory rate of 18 breaths per minute, and an axillary temperature of 36.2°C. The numeric rating scale (NRS) for pain was 0/10 at rest, 0/10 during movement, and 3/10 during exacerbations. The APFEL score was 2/4, and the patient's estimated metabolic equivalent of task (MET) was 5–6. Abdominal examination showed normal bowel sounds, tenderness in the right upper quadrant, absence of palpable masses, and a positive Murphy's sign without evidence of jaundice. Airway management was anticipated to be challenging due to the presence of severe obesity (BMI 49.3 kg/m<sup>2</sup>), incomplete upper incisors, a history of snoring, a mentohyoid distance of less than three fingers, stage I hypertension, and a neck circumference of 45 cm. The patient's risk assessment included a MOANS score of 3/5, a LEMON score of 1/10, and a STOP-BANG score of 4, indicating a moderate risk of obstructive sleep apnea.

Laboratory evaluations, including a complete blood count, coagulation studies, blood chemistry, arterial blood gas analysis, electrocardiography (ECG), and

chest radiography, were within normal limits, except for an elevated HbA1c level of 7.1%. Abdominal ultrasonography of the upper and lower quadrants revealed findings consistent with calculous cholecystitis and choledocholithiasis. The gallbladder was of normal dimensions but demonstrated wall thickening of approximately 0.5 cm. Multiple irregular hyperechoic lesions with posterior acoustic shadowing were identified in the neck of the gallbladder, cystic duct, and common bile duct, with the largest lesion measuring approximately 2.6 × 0.6 cm in the gallbladder neck.



**Figure 1.** Gallbladder ultrasonographic findings.

The patient was administered amlodipine 5 mg once daily, mefenamic acid 500 mg as needed, and lactated Ringer's solution for fluid maintenance in the ward. Preoperative management included administering amlodipine 5 mg at 22:00, monitoring blood glucose levels at 22:00 and 06:00 the following day, and providing a 500 mL loading dose of lactated Ringer's solution during fasting. Anticipating challenges with airway management, preparations were made for a long bougie, laryngeal mask airway

(LMA), video laryngoscope, and fiberoptic bronchoscope. Emergency medications, EtCO<sub>2</sub> capnography, arterial line placement, inotropic agents, and vasopressors were also readily available. Prior to induction of general anesthesia, the patient received dexamethasone 10 mg IV, diphenhydramine 10 mg IV, and midazolam 1.5 mg IV as premedication. Analgesia was provided with fentanyl 150 mcg IV, followed by induction using propofol at a dose of 2–3 mg/kg body weight to achieve hypnosis. Atracurium 40 mg IV was administered to facilitate intubation. The patient was positioned in a ramped posture for intubation, which was performed using a size 7 cuffed endotracheal tube (ETT). An epidural catheter was inserted at the L1–L2 level and advanced 6 cm into the epidural space, targeting the T9–T10 vertebral levels to achieve a dermatomal block from T6 to T12 and a viscerotomal block from T6 to T9. A total of 10 mL of 0.25% plain bupivacaine was administered epidurally. Maintenance anesthesia consisted of oxygen, compressed air, and sevoflurane, with additional doses of atracurium 0.2 mg/kg body weight administered every 30–45 minutes. Intermittent doses of 10 mL of 0.2% plain bupivacaine were given via the epidural catheter every 120–180 minutes.

During re-evaluation by the surgeon in the operating room, the surgical plan was revised to a laparoscopic procedure. LC was performed over a duration of 120

minutes. During the surgery, ETCO<sub>2</sub> levels increased to 50 mmHg due to CO<sub>2</sub> insufflation, exacerbating respiratory acidosis. The patient was subsequently placed in the reverse Trendelenburg position. To reduce ETCO<sub>2</sub> levels, hyperventilation was initiated, and positive end-expiratory pressure (PEEP) was increased to 7 cmH<sub>2</sub>O during insufflation. After these adjustments, ETCO<sub>2</sub> levels decreased and were maintained within acceptable limits throughout the CO<sub>2</sub> insufflation period.

## Discussion

Obesity is defined as an excess of body fat, typically associated with an increase in body weight relative to height. BMI is the most commonly used method to measure obesity, allowing comparisons between populations and countries.<sup>8</sup> Obesity is defined as a BMI  $\geq 30$  kg/m<sup>2</sup>. The WHO classifies obesity into Class I (30–34.9 kg/m<sup>2</sup>), Class II (35–39.9 kg/m<sup>2</sup>), and Class III ( $>40$  kg/m<sup>2</sup>). Class III obesity is also referred to as morbid obesity, severe obesity, or extreme obesity.<sup>9</sup> However, BMI values for Asian populations are classified differently. According to the Asia-Pacific cut-off points, obesity is defined as a BMI of 25 kg/m<sup>2</sup>, with Class I (25–29.9 kg/m<sup>2</sup>) and Class II ( $\geq 30$  kg/m<sup>2</sup>).<sup>10</sup> The rate of obesity is increasing in both genders and across all age groups, with a higher prevalence among older adults and women.<sup>1</sup> Considered a major contributor to

metabolic syndrome, obesity plays a role in the etiology of various disorders. Adipose tissue, particularly when centrally located, acts as an endocrine and paracrine organ, releasing bioactive chemicals such as chemokines and cytokines. This leads to metabolic dysfunctions associated with obesity, including atherosclerotic events, hypertension, respiratory depression, insulin resistance, and a pro-inflammatory state.<sup>11</sup> Obesity is associated with an increased risk of morbidity, disability, and mortality. Its mortality risk is comparable to that of smoking.<sup>2</sup> Individuals who smoke are 1.73 times more likely to experience obesity compared to non-smokers. It has been observed that exposure to cigarette smoke increases insulin resistance and is associated with central fat accumulation.<sup>3</sup> According to the Asia-Pacific classification, our patient falls into Class II obesity. The patient has a history of smoking 12 cigarettes per day and has had diabetes for the past four years. Random blood glucose levels are within the normal range (73 mg/dL), but there is a slightly elevated HbA1C of 7.1%. Therefore, the patient was treated with 20 units of glargine every 24 hours and 14 units of novorapid for each major meal. The patient was admitted with complaints of upper right quadrant abdominal pain and was diagnosed with calculous cholecystitis and choledocholithiasis based on investigations. The patient's upper abdominal pain is likely due to

cholelithiasis, which can be identified using the mnemonic "fat, female, fertile, and forty." One study showed that the incidence of cholelithiasis is significantly higher in women, with 150/198 (75%) of cholelithiasis patients being female ( $\chi^2 = 18.8$ ,  $p < 0.001$ ). The cholelithiasis group had 56/198 (28.3%) obese patients compared to 19/200 (9.5%) in the control group ( $p = 0.005$ ). The mean age of the cholelithiasis group was  $45.3 \pm 1.01$  years, while the control group had a mean age of  $46.1 \pm 1.02$  years.<sup>12</sup>

Most preoperative issues are related to respiratory function due to excess adipose tissue stored in various areas, including the chest wall, ribs, diaphragm, and abdomen. Obese patients are more likely to experience reduced lung capacity, lung collapse, abnormalities in lung and chest wall compliance, and varying degrees of hypoxemia.<sup>13</sup> Obesity is a major risk factor for obstructive sleep apnea (OSA), as it leads to upper airway collapse and episodes of apnea. The metabolic activity of fat results in significantly higher oxygen consumption in obese individuals compared to those with normal weight, nearly three times higher. Consequently, airway management can be challenging due to faster oxygen desaturation times and issues with excess fat complicating ventilation and intubation.<sup>14</sup> Predictors of difficult intubation are described by the mnemonic "LEMON," and predictors of difficult bag-mask ventilation are described

by the mnemonic "MOANS."<sup>15</sup> In this patient, the MOANS score is 3/5 (BMI 49.3 kg/m<sup>2</sup>, incomplete incisive teeth, history of snoring), and the LEMON score is 1/10 (mentohyoid distance of 2 finger widths). In a cohort study, the LEMON features were found to be poor predictors of intubation failure. The tendency to administer paralytic drugs decreases as the number of positive LEMON features increases.<sup>15</sup> A positive STOP-BANG (SB) score is also correlated with a higher incidence of hypoxemia and the need for airway maneuvers such as chin lift or nasopharyngeal airway placement.<sup>5,16</sup> Our patient has a history of snoring, hypertension, and a neck circumference of 45 cm, meeting the intermediate risk criteria for OSA. Several studies have shown that patients with OSA are at significantly higher risk for postoperative respiratory complications (respiratory failure, aspiration pneumonia, increased emergency postoperative endotracheal intubation, and the need for postoperative ventilation), atrial fibrillation, neurological complications, and prolonged hospital stays.<sup>17</sup> Excess adipose tissue increases total blood volume, which subsequently increases cardiac output. As cardiac output continues to rise, left ventricular hypertrophy occurs, leading to diastolic dysfunction. Left ventricular enlargement can also cause systolic dysfunction, potentially resulting in atrial hypertrophy and pulmonary hypertension.<sup>13</sup> In our

patient, the blood pressure is 140/90 mmHg (grade I hypertension), with both the ECG and chest X-ray results within normal limits.

In a meta-analysis comparing LC and open cholecystectomy, there was no significant difference in mortality. All trials revealed that the LC group experienced fewer complications, shorter hospital stays, and faster recovery times compared to the open cholecystectomy group.<sup>18</sup> Historically, obesity has been regarded as a relative contraindication for laparoscopic surgery, with technical challenges thought to be associated with increased morbidity, mortality, and higher rates of conversion to open surgery. The thickened abdominal wall, along with elevated levels of intraperitoneal and visceral fat in overweight and obese patients, can impair visualization and limit the ability to maneuver within the abdominal cavity.<sup>19</sup> However, the use of LC in obese patients has evolved due to advancements in equipment and experience. Tiong et al. compared the safety of LC in obese patients and found a significant difference in the average duration of surgery across three BMI groups: BMI <26 (64 minutes), BMI 26-40 (72 minutes), and BMI >40 (82 minutes). However, there were no statistically significant differences in length of hospital stay, perioperative complication rates, open conversion, or bile duct injury among the three groups. This study

suggests that LC can be safely performed in morbidly obese patients.<sup>20</sup>

In LC, the predominant anesthetic technique is GA with endotracheal intubation.<sup>21</sup> In the case of our patient, a combined approach of general anesthesia and epidural anesthesia (CEGA) was utilized. Due to its high lipophilicity, propofol exhibits a large volume of distribution and is quickly cleared from the circulatory system. Propofol is considered the drug of choice for induction in obese patients.<sup>13</sup> A study by Bandewar et al. found that the CEGA approach required a lower dose of propofol after induction compared to general anesthesia (GA) alone, with an average propofol requirement of 0.503 mg/kg versus 1.717 mg/kg ( $p < 0.01$ ). During the post-pneumoperitoneum period, heart rate and systolic blood pressure were statistically lower in the CEGA group.<sup>22</sup> In line with previous findings, Zhu et al. also observed lower systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate in the CEGA group in patients with gallbladder cancer.<sup>23</sup> The Steward recovery score for the CEGA group showed significantly better scores at 4 minutes ( $4.5 \pm 0.6$  vs.  $2.8 \pm 0.4$ ,  $p < 0.05$ ) and 6 minutes ( $5.7 \pm 0.2$  vs.  $4.1 \pm 0.5$ ,  $p < 0.05$ ). Based on these results, the authors concluded that patients receiving CEGA typically experience faster, pain-free recovery. Additionally, the visual analog scale (VAS) pain score was lower in the

CEGA group compared to GA ( $1.7 \pm 0.5$  vs.  $3.4 \pm 0.6$ ,  $p < 0.01$ ), suggesting that the use of an epidural catheter provides adequate pain control.<sup>22</sup> The epidural catheter should be inserted at least 5 cm into the epidural space to reduce migration. Neuraxial anesthesia in obese patients must be performed with caution, as they are prone to hypotension due to decreased tolerance to being in a supine position.<sup>24</sup>

The supine position and anesthesia can negatively affect functional residual capacity (FRC), potentially leading to airway closure.<sup>8</sup> To mitigate this, our patient was positioned in the ramp position, as previous studies have indicated that this positioning extends the safe apnea duration before significant hypoxemia occurs and improves the view for direct laryngoscopy.<sup>24,25</sup> During the procedure, the patient's end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) level increased to 50 mmHg following the creation of pneumoperitoneum. Laparoscopic surgery requires CO<sub>2</sub> insufflation to achieve pneumoperitoneum, which can lead to CO<sub>2</sub> absorption into the circulation, resulting in hypercapnia and respiratory acidosis. However, PaCO<sub>2</sub> levels typically return to baseline after desufflation.<sup>26</sup> A study by Hassan et al. demonstrated an increase in PaCO<sub>2</sub> levels following CO<sub>2</sub> pneumoperitoneum, rising from 35 mmHg to a peak of 47 mmHg at 180 minutes. Both PaCO<sub>2</sub> and ETCO<sub>2</sub> levels showed significant increases after insufflation, but returned to baseline post-

desufflation, with an average postoperative PaCO<sub>2</sub> of 39.4 mmHg. PaCO<sub>2</sub> increases can be minimized by enhancing minute ventilation throughout the procedure.<sup>27</sup> The Trendelenburg position in patients undergoing pneumoperitoneum can exacerbate atelectasis, particularly in obese individuals with poor health. Mazinari et al. found that setting PEEP at 2 cmH<sub>2</sub>O above the intraperitoneal pressure reduced transpulmonary pressure compared to the standard PEEP setting of 5 cmH<sub>2</sub>O.<sup>28</sup>

Before extubation, patients should be positioned in reverse Trendelenburg to enhance functional residual capacity (FRC) and optimize oxygenation. Obese patients may experience delayed recovery due to the accumulation of lipophilic drugs in adipose tissue, necessitating careful monitoring to ensure adequate respiration, full muscle strength, and complete recovery of airway reflexes.<sup>9</sup> Obese individuals have higher oxygen consumption and an increased respiratory depressant response to opioids.<sup>9,14</sup> Therefore, a multimodal approach to pain management is preferred for these patients. In our case, a combination of epidural bupivacaine 0.1% and morphine 1 mg was administered every 10-12 hours, intravenous ibuprofen 400 mg every 8 hours, and oral paracetamol 500 mg every 6 hours for postoperative analgesia.

## Conclusion

The rising incidence of obesity among patients is influencing various fields of medicine. Managing obesity and morbid obesity is expected to become a more frequent scenario in the future. Contrary to previous reports, laparoscopic procedures can now be performed safely and effectively in obese individuals. When compared to laparotomy, minimally invasive surgery leads to lower pain scores, faster recovery, and fewer postoperative complications. Obese patients face an increased risk of intraoperative and postoperative complications, such as respiratory and cardiovascular issues, as well as heightened sensitivity to sedative medications. Consequently, it is essential to carry out a comprehensive preoperative evaluation to minimize the risk of potential anesthetic complications. This assessment should include a review of the patient's comorbidities, airway, and possible drug interactions. Research indicates that a combination of general anesthesia and epidural anesthesia is preferable to general anesthesia alone, offering benefits such as more stable hemodynamic parameters, reduced opioid consumption, improved recovery scores, and effective pain management. Multimodal pain control is also employed postoperatively to prevent respiratory depression in obese patients.

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**(Insan Aqid Pakardian)**

# Forensic Examination in a Homicide Case Due to Suffocation: A Case Report

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## Abstract

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**Background:** Smothering is a form of death due to asphyxia which is caused by obstruction of air flow from the mouth and nose which can be caused by various things such as hands, air-tight paper or textiles. Homicide smothering often occurs in infants, children, vulnerable adults and individuals with limited mobility. Smothering will cause a person to die from suffocation.

**Case Description:** The body of a 4 year 9 months old female was found smothered. On external examination, bruises resembling grips were found on both left and right upper arms, bruises resembling grips were also found on both left and right thighs. There were blackish purple bruises on the back. On internal examination, petechial bleeding was found in the heart.

**Discussion:** Smothering is a form of asphyxia caused by obstruction of the external respiratory opening, either by hand or by other means. Apart from that, it can also be caused by blockage of the nasal and oral cavities due to the entry of foreign objects. Based on the facts obtained from the examination, injuries were found due to blunt force in the form of bruises on the upper and lower lips, back area, upper and lower arms. So it can be concluded that the victim died from suffocation due to the closure of the respiratory tract.

**Conclusions:** External examination and autopsy of the body are very important things to do, especially in crucial cases where there is done to help seek justice for the victim.

## Introduction

Asphyxia is a condition in which the body experiences a lack of oxygen caused by the disruption of supply and transportation between the environment and the organs. Death due to asphyxia can occur as a result of homicide, accidents, or suicide.<sup>1</sup> Mechanically, death from

asphyxia occurs in two ways. First, it can be caused by pressure applied to the neck, chest, or other parts of the body that halts respiratory activity. Second, it can result from certain positions that make breathing difficult. The first mechanism is commonly used to kill someone, while the second is often associated with suicide.<sup>2</sup>

Smothering is one form of death due to asphyxia caused by the obstruction of airflow from the mouth and nose, which may be caused by various means such as hands, airtight paper, or textiles. Smothering as a result of homicide often occurs in infants, children, vulnerable adults, and individuals with limited mobility. Smothering leads to death by suffocation.<sup>3</sup>

Asphyxia ranks third in forensic medicine cases after traffic accidents and mechanical trauma.<sup>4</sup> The most common cause of death by asphyxia in forensic medicine is mechanical asphyxia. Several causes of asphyxia include suffocation, smothering, strangulation, and choking. A study by Siskha Sabilla et al. (2022) reported 44 cases (7%) of deaths due to asphyxia out of 575 cases documented at Dr. Moewardi General Hospital from 2010 to 2020.<sup>4</sup> The latest data from the Centers for Disease Control (CDC) from 1999–2004 reported 20,000 cases of various types of death caused by asphyxia, including drowning, hanging, ligature strangulation, and smothering. Additionally, in 2012 in India, 343 autopsy cases were reported at Citradurga General Hospital, with 36 cases of death caused by asphyxia (10.50%).<sup>5</sup> In this case, a 4-year-9-month-old female was found smothered.

### **Case Description**

A postmortem examination was conducted on the remains of a female child estimated to be approximately 4 years and

9 months of age. The body was discovered wrapped in a black plastic body bag labeled “BASARNAS” (National Search and Rescue Agency) and a batik-patterned sarong with an orange base color and floral motifs in white, black, and brown. The sarong was observed to be damp and exhibited a tear on its lower portion. A second piece of clothing, a long batik fabric with a brown background and abstract pattern in light brown and black, was also present.

The child was wearing a short-sleeved cotton T-shirt in turquoise green, bearing an image of Donald Duck and the text “little point” printed beneath, in size M. The garment appeared saturated with decomposition fluid. Additionally, a pair of light blue cotton underwear was found; it was moist and stained with fecal matter. Jewelry included a silver ring shaped like Mickey Mouse on the middle finger of the right hand and a pair of silver earrings, each adorned with two pearls, on both ears.

External examination revealed no foreign objects in proximity to the body. Due to advanced decomposition, neither rigor mortis nor livor mortis could be assessed. The deceased was identified as ethnically Indonesian of Mongoloid descent. Her body length measured 103 cm. Assessment of skin condition and nutritional status was not feasible due to decomposition.

Ocular findings included partial opening of the right eye (approximately 0.5

cm), with redness observed in the sclera, while the left eye remained closed. The conjunctiva of the left eye measured 0.4 in transparency. The left iris was brown, and the right iris was reddened. Pale conjunctiva was noted on the left eyelid, while reddish bubbles were visible on the right. The face from the nasal bridge to the chin was obscured by black adhesive tape. Upon removal, a flattened nasal profile and oval-shaped auricles were evident.

The oral cavity was partially open (approximately 2 cm), with protrusion of the tongue and evidence of biting injury measuring 1.5 cm in length. Clear fluid was noted emanating from the vaginal opening, and brownish fecal matter was observed exiting the anal region.

Multiple contusions were documented across various anatomical regions. On the anterior aspect of the right thigh extending to the knee, a bruise measuring 18 × 12 cm was identified. This lesion exhibited irregular borders and a curved imprint at its inferior margin consistent with fingerprint-like markings, suggestive of manual compression or gripping (see Image 1).

A comparable contusion was observed on the left thigh, extending from the lateral to medial aspect toward the knee, measuring 22 × 14 cm. It similarly displayed a curvilinear contour at the lower edge, indicative of possible contact with human digits (Figure 1). A widespread bruise extended from the upper right arm to the

forearm, measuring 22 × 20 cm in dimension. Two distinct circular bruises were noted within this area, exhibiting morphology consistent with digital pressure marks (Figure 2).

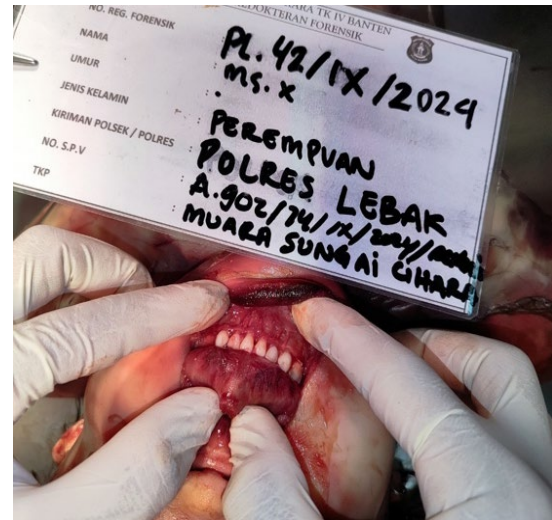
On the left upper extremity, from the upper arm to the forearm, a longitudinal contusion measuring 24 × 15 cm was recorded on the anterior surface. This bruise contained two round impressions resembling fingertip impressions, further supporting the possibility of manual force application (Figure 3).

Facial injuries included dark blackish discoloration affecting both the upper and lower lips (Figure 4). Additionally, a 10 × 5 cm bruise of purple-black hue was identified on the dorsal region. This lesion was irregular in shape, with no palpable fractures detected upon bony assessment (Figure 5).

The body was subsequently transported to Bhayangkara Hospital under the jurisdiction of the Serang City Police Department for full autopsy in order to determine the precise cause and manner of death. Histopathological and toxicological analyses are recommended to complement macroscopic findings and support a comprehensive forensic evaluation.



**Figure 1.** Bruising pattern on both thighs resembling hand-grip impressions.



**Figure 4.** Dark blackish bruising observed on both upper and lower lips.



**Figure 2.** Bruising on the right arm consistent with manual compression.



**Figure 5.** Purple-black contusion located on the dorsal region, irregular in shape.



**Figure 3.** Contusion on the left arm exhibiting fingerprint-like markings suggestive of gripping force.

During internal examination, subcutaneous adipose tissue was noted to be yellow in color, measuring 2 cm in thickness over the thoracic region and 1 cm in the abdominal area. Skeletal musculature appeared uniformly red throughout. The diaphragm on the right side was located at the level of the fifth intercostal space, while the left hemidiaphragm was also situated at the same level. The sternum was intact, with no

rib fractures identified. Both pleural cavities contained decomposition fluid.

The pericardial sac was located one fingerbreadth between the lungs and was empty. Subcutaneous connective tissue and musculature of the neck were reddish in appearance. The parietal peritoneum exhibited a yellowish hue, while the abdominal wall musculature remained red. Decomposition fluid was also present within the abdominal cavity.

The tongue was brown in color with a light brown cross-section. The hyoid bone was intact. Thyroid and cricoid cartilages were preserved without damage. The thyroid gland appeared reddish, with elastic consistency upon palpation and a brown-colored cut surface. No abnormalities were detected in the submandibular glands. The esophagus was empty, with a reddish-brown mucosal lining. The trachea was empty as well, with similar reddish-brown mucosa observed internally.

The heart measured approximately the size of the subject's clenched right fist, weighing 100 grams. It exhibited a reddish-brown color and elastic texture. The circumference of the right atrioventricular valve measured 4 cm, the left 4 cm, the pulmonary artery 3 cm, and the aorta 4.3 cm. The thickness of the right ventricular wall was 0.7 cm and the left ventricular wall was 0.9 cm. The interventricular septum showed no abnormalities. Hemorrhagic

spots were visible on the epicardium, indicating early stages of decomposition.

The right lung consisted of two lobes (congenital variation), was reddish in color, elastic on palpation, and displayed a dark red cross-section. Squeezing of the tissue yielded dark fluid. The weight of the right lung was 150 grams. The left lung also had two lobes, appearing darker with a blackish-red hue, elastic consistency, and dark red cut surface. Expression of the tissue similarly released dark fluid, and the organ weighed 120 grams. The left lung was larger than the right. Both lungs exhibited petechial hemorrhages.

The spleen appeared blackish in color, with a smooth surface and soft consistency. The cut surface revealed a brown hue, consistent with postmortem autolysis. It weighed 80 grams and exuded black fluid upon incision. The liver was pale brown, with a smooth surface and blunt edges. It was firm on palpation, with a brownish cut surface. Normal anatomical structure was obscured due to decomposition. The organ weighed 600 grams. The gallbladder was empty, with greenish mucosa; no obstruction was found in the bile ducts.

The pancreas was yellow in color, with a lobulated surface and soft texture. The cut surface was yellow, with clear glandular architecture. It weighed 100 grams. The stomach was empty, with a brownish mucosal lining. No pathological findings

were observed in the duodenum, small intestine, or large intestine.

The right adrenal gland was triangular in shape, purplish-brown in color, with a dark brown cut surface. The left adrenal gland was crescent-shaped, similarly purplish-brown with a dark brown cross-section. Both kidneys were easily removable, with smooth surfaces and brown coloring. Cut sections revealed dark brown tissue. Morphological detail was obscured by decomposition, and no urinary tract obstruction was noted. Each kidney weighed approximately 80 grams. The bladder was empty, with a yellowish-brown mucosal lining.

No signs of blood infiltration were observed in the skin. The skull was intact, with an undisturbed dura mater. The cerebrum, cerebellum, and brainstem exhibited liquefactive changes with a reddish-brown appearance. Ventricular structures could not be assessed due to advanced decomposition.

## **Discussion**

### **Blunt Force Trauma**

Trauma represents a leading cause of morbidity and mortality among individuals under 35 years of age and ranks as the sixth most common cause of death globally. Blunt force trauma, in particular, constitutes a significant mechanism of injury and must be considered when specific injury patterns

are observed. Impact from blunt objects can result in a wide range of injuries, typically classified into four categories: contusions (bruises), abrasions, lacerations, and fractures. These injuries are frequently encountered in forensic autopsy practice, and accurate interpretation is essential for reliable medicolegal reporting.<sup>6</sup>

In the present case, postmortem examination revealed multiple contusions consistent with blunt force trauma. These included bruises on the upper and lower lips, accompanied by loosening of all lower dental structures. Additional bruising was observed on the back, both upper arms, and both thighs, suggesting that the victim had been physically restrained by hand.

### **Asphyxia Due to Smothering**

Smothering is a form of mechanical asphyxia caused by the obstruction of the external airway, either through manual compression using hands or other means, such as soft or rigid materials. It may also occur due to the introduction of foreign bodies into the nasal or oral cavities. Smothering can occur in various contexts including homicide, accidental suffocation, or suicide. In cases of homicidal smothering, the victim is often vulnerable—such as an intoxicated individual, a frail elderly person, or a child who lacks the capacity to resist.<sup>7</sup>

Autopsy findings suggestive of smothering include bruising around the lips and gums, contusions on the neck or part of it, pressure marks on the posterior neck, upper chest, or arms, scratch marks from fingernails around the face and neck, and the presence of foreign bodies within the nasal passages or trachea. Notably, smothering may occur without leaving visible external signs, and even comprehensive postmortem examinations may fail to detect conclusive evidence.<sup>8</sup>

The obstruction of the mouth and nose—whether by hand, soft or hard materials, or solid objects—can prevent oxygen intake. In many instances, autopsy findings may be minimal or entirely absent. However, in cases of homicidal smothering, particularly involving children, the elderly, or incapacitated individuals, signs such as lacerations and abrasions of the labial, buccal, and gingival mucosa, epistaxis (nosebleeds), nasal bone fractures, facial excoriations, or injuries indicating active resistance may be identified.<sup>9</sup>

Skin lesions on the face or neck may result from direct manual compression or choking. These often manifest as ecchymoses caused by thumb pressure and/or fingernail scratches along free nail edges. Such injuries may not be present if the perpetrator had short nails or wore gloves. Additional skin findings, especially in combined forms of asphyxia involving chest compression, choking, or suffocation,

include counter-pressure lesions located on the posterior body surfaces. These arise from mechanisms such as pressure, sliding, or friction against hard surfaces and are more evident when the victim actively interacts with the assailant, presenting as bruises or abraded areas on the back, buttocks, or posterior elbows.

During smothering, the lips may be forcibly pressed against the teeth, resulting in blunt-force injuries to adjacent tissues, which can appear as ecchymosis or lacerations on the inner lip surface. Additionally, fractures of the thyroid cartilage and hyoid bone have been reported in 70–80% of smothering cases. Hemorrhagic infiltration into the anterior and lateral aspects of the larynx may also be observed, with thyroid cartilage fractures being most commonly detected.<sup>10</sup>

Hemorrhage or blood infiltration in the anterior neck musculature and upper chest may occur due to alternating compressive forces exerted by the assailant and the victim's attempts to resist. These findings reflect the dynamics of struggle and defense. The hemorrhages may be more pronounced across various layers of the anterior and lateral neck musculature, with variable intensity depending on the degree of resistance offered by the victim. Petechial hemorrhages may also be observed on the pleural and epicardial serosa during autopsy.<sup>11</sup> These petechiae typically result from acute increases in

venous pressure, which damage small venules. They are most commonly seen externally on the conjunctiva, oral mucosa, and facial skin, and internally on the epicardium and visceral pleura.

Examination of the laryngeal structures should include identification of the hyoid bone with its minor and major cornua, the thyroid cartilage with its superior and inferior horns, the cricoid cartilage, and any separation of the arytenoid cartilages from the cricoid. The presence of "gas bubble signs" within adjacent tissues or bones, fractures, structural deformities, or dislocations of the thyrohyoid membrane or hyoid/thyroid cartilages should also be assessed. In cases of suspected asphyxia, the presence of gas within adjacent laryngeal structures, fractures, and morphological abnormalities or dislocations of the larynx are evaluated.<sup>12</sup>

## Conclusion

Forensic examination plays a crucial role in identifying the cause, mechanism, and manner of death. Based on findings from the postmortem investigation, the remains were identified as those of a female child, reported to be four years and nine months of age. Blunt force trauma was observed in the form of bruises on the upper and lower lips, accompanied by loosening of all teeth in the mandible. Bruising was also found on the back, as well as on both upper arms and both thighs, suggesting that the victim had been physically restrained by hand. Signs of suffocation were detected. The cause of death was determined to be asphyxia due to airway obstruction. External examination and autopsy of the body are essential procedures, particularly in critical cases, as they serve to support the pursuit of justice for the victim.

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(Donald Rinaldi Kusumaningrat)

# Perioperative Management of Craniotomy for Clipping Aneurysm: A Case Report

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## Abstract

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**Background:** Ruptured cerebral aneurysm is the most common cause of spontaneous subarachnoid hemorrhage (SAH). Anesthesiologists play a critical role in recognizing these complications to ensure thorough pre-anesthetic evaluation and appropriate perioperative management. However, there remains a limited number of case reports detailing the perioperative care of patients undergoing craniotomy for aneurysm clipping.

**Case Description:** We present the case of a 66-year-old woman diagnosed with acute non-communicating hydrocephalus, pan-ventricular intraventricular hemorrhage, and subarachnoid hemorrhage involving the basal cistern, bilateral sylvian fissures, and temporal lobes following ventriculoperitoneal (VP) shunt placement. The hemorrhage was attributed to a ruptured aneurysm. A craniotomy for aneurysm clipping was planned, and the procedure was performed under general anesthesia. Intraoperatively, the patient's hemodynamic parameters were successfully maintained within stable limits. Postoperatively, the patient was closely monitored in the intensive care unit, where no neurological deficits or major complications were observed during the hospital stay.

**Discussion:** This case highlights the complexity of managing patients with aneurysmal subarachnoid hemorrhage, particularly those presenting with multiple complications such as hydrocephalus and intraventricular extension of bleeding.

**Conclusions:** The successful management of this case demonstrates that a well-structured perioperative plan is crucial in the surgical treatment of ruptured aneurysms. Despite the high-risk nature of subarachnoid hemorrhage and its associated complications, favorable outcomes can be achieved with careful preoperative preparation, intraoperative vigilance, and postoperative monitoring. Further case reports and studies are needed to expand the evidence base and refine best practices in the perioperative management of patients undergoing craniotomy for aneurysm clipping.

## Introduction

Stroke is the first common cause of disability and the third leading cause of death in the world after heart disease and cancer, both in developed and developing

countries. According to National Basic Health Research, the prevalence of stroke in Indonesia increased by 56% from 7 per 1000 population in 2013 to 10.9 per 1000 population in 2018.<sup>1</sup> Ruptured aneurysm is

the most common cause of nontraumatic or spontaneous subarachnoid hemorrhages. The clinical manifestation of aneurysmal subarachnoid hemorrhage is rapid onset of the worst headache in the patient's life. Some of the patients may lose consciousness and an unusual headache may be present several weeks prior. The patients also often have nausea and/or vomiting, nuchal rigidity, or photophobia. Patients may be comatose and hypertensive at presentation. Craniotomy and clipping or endovascular intervention involving coils and stents is the definitive treatment of intracranial aneurysm.<sup>2,3</sup> There are several main goals of perioperative management of craniotomy in aneurysmal subarachnoid hemorrhage. A more detailed explanation on these main goals will be discussed later.

### **Case Description**

A 66-year-old female patient with acute non-communicating hydrocephalus, intraventricular hemorrhage pan-ventricle and subarachnoid hemorrhage in basal cistern, right and left sylvian fissure, right and left temporal due to aneurysm rupture post VP was referred to our hospital complaining severe headache and projectile vomiting for three times two days prior admission. Afterward, the patient experienced decreased consciousness which improved on its own. Complaints of seizures, slurred speech and weakness in half of the body were denied. Physical

examination was performed and found high blood pressure and a ruptured brain blood vessel. The patient underwent VP Shunt on December 28<sup>th</sup> 2023 and after the VP Shunt procedure was done, the patient was unable to communicate. The patient underwent DSA on December 29<sup>th</sup> 2023 and the result of anterior communicating artery aneurysm was obtained.

On physical examination, the patient's body weight was 60 kg, height was 160 cm, and measured BMI was 23,4 kg/m<sup>2</sup>. Patient was apathetic (E3VaphasiaM6), with respiratory rate of 15 x/min, heart rate of 95 beats/min, blood pressure of 110/60 mmHg and oxygen saturation of 98% on room air. Other physical examination was within normal limits. A complete blood count examination found leukocytosis (20,70 x 10<sup>3</sup>/μL) and hemoglobin was within normal limit. An electrolyte examination found hyponatremia (131 mmol/L) and hypokalemia (3,10 mmol/L). Other laboratory examinations, including liver and renal function test and urinalysis were within normal limits. Chest x-ray showed a catheter placed from the right neck into the abdomen with non-visualized distal tip suggesting VP shunt. DSA examination was performed and found a small wide neck anterior communicating artery aneurysm with size of 2.3x1.3 mm. CT angiography showed no visibility in A1 segment of right anterior communicating artery and rupture was suspected with intraventricular hemorrhage in right and left

lateral ventricle, third and fourth ventricle; subarachnoid hemorrhage in the sulcus and gyrus of the right and left frontal, temporal, parietal region and right occipital region, anterior inter-hemisphere, basal cistern, right and left sylvian cistern dan sylvian fissure. Aneurysm clipping was planned. We concluded the patient with ASA physical status IV. Surgery was done under general anesthesia.

The patient was not given any pre-medications. Allen test was performed and continued with arterial line insertion and administration of 2% Lidocaine as local anesthetic. Induction was done with target-controlled infusion (TCI) Propofol for Ce target of 3.5-5 mcg/ml. The patient was given Fentanyl 200 mcg (3-4 mcg/kg) intravenously for analgesia and Rocuronium 50 mg (0,6-1,2 mg/kg) intravenously to facilitate intubation. Intubation was performed with a 7.5 endotracheal tube. Anesthesia was maintained using O<sub>2</sub> compressed air, TCI Propofol Ce target effect of 3-4 mcg/ml, Fentanyl 0,5 mcg/kg every 45 minutes IV, and Rocuronium 0,15 mg/kg every 30 minutes IV, dexmedetomidine 0.2 – 0.7 mcg/kg/hour.

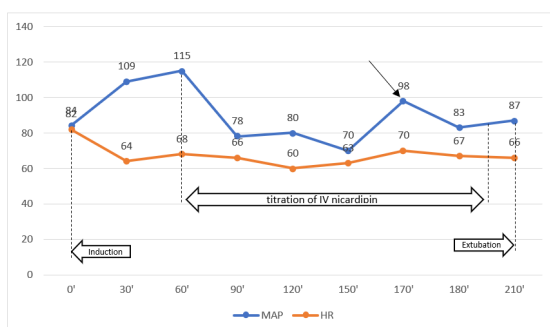
After the surgery, the patient was admitted to the intensive care unit and mechanically ventilated. The patient was given Fentanyl 500 mcg in 50 mL NaCl 0,9% with rate of 2,1 mL/hour and

Paracetamol 1000 mg every 8 hours intravenously for pain control.

During the maintenance phase, the depth of anesthesia was maintained at BIS 40-50. A urinary catheter was placed to monitor urine output. She was then placed in a supine position and blood pressure baseline values at 118/65 mmHg (83 mmHg), pulse rate 63 beats/min without intervention. Before incision, the patient was given mannitol 1 g/kg. The blood pressure change was found 30 minutes later when the surgeon had dissected the multifidus muscle, obtaining an arterial monitoring of 163/81 mmHg (111 mmHg) with no change in pulse rate (64 beats/min). This condition persisted even after craniotomy of the suboccipital bone and opening of the dura via Y-incision (figure 1) with a duration of 30 minutes after the onset of hypertension. We concluded that she had intraoperative neurogenic hypertension after confidently excluding other causes (hypercarbia, desaturation, pain, light anesthesia, and drug interactions). We decided to give her intravenous nicardipine titrated at a dose of 1-3 mcg/kg/min with a target mean arterial pressure return to baseline of 80-90 mmHg. Intraoperative arrhythmia was not found.

There was another blood pressure fluctuation during the Valsava maneuver for the evaluation of cerebrospinal fluid leakage after the duraplasty process. However, it was maintained stable until the

neurosurgeon completed suboccipital decompression and cranioplasty with an upside down-inside out approach to the suboccipital bone. The need for antihypertensive agents was significantly reduced and discontinued before extubation (pre-discontinuation dose 0.4 mcg/kg/min). The surgery lasted 3 hours and 30 minutes.



**Figure 1.** Intraoperative hemodynamic fluctuation: the blue graph represents mean arterial pressure; the red graph represents heart rate. Asterisk (\*) represents time and hemodynamics during suboccipital craniotomy. Arrow (→) represents time and hemodynamics during breath-holding (Valsava) maneuver.

We gave 1700 mL ringer fundin intraoperatively with total bleeding of 350 mL and urine production of 500 mL. Rocuronium was stopped 1 hours before the end of the surgery. We reversed the paralyzed muscle with sugammadex. Fentanyl 25 mcg was given 5 minutes before extubation and dexmedetomidine infusion was maintained at 0.3 mcg/kg/min to prevent coughing. After the anesthetic drugs were stopped, we extubated her when she was easily arousable in the operating room.

She was observed in the recovery room with an Aldrete score of 9/10. Blood pressure was 115/74 (90) mmHg with a pulse rate of 72 beats/minute, axillary temperature was 35.9°C. Urine output was 0.7 mL/kg/hour. She was then admitted to the intensive care unit for monitoring. Neurological examination showed the patient remained with aphasia without other neurological deficits. Recurrent headache symptoms were absent and there were no episodes of hemodynamic instability. The patient was discharged from ICU on postoperative day 3. We continued to follow up on her condition after 1 month postoperatively. She had no complaints and showed resolution of headache and ataxia.

## Discussion

Various studies have reported that eighty percent of spontaneous SAH are caused by aneurysm rupture. There are several risk factors that contribute the formation and rupture of intracranial aneurysms and one of them is poorly controlled hypertension. Hypertension causes increased transmural pressure gradient in the aneurysm wall and changes the thickness of the vessel wall.<sup>4</sup> SAH predominantly occurred at the age of 50-60 years old and the incidence was found 1.6 times higher in females than males.<sup>5</sup> Middle cerebral artery (MCA) and internal carotid artery (ICA) are the arteries that most often form aneurysms, whereas aneurysm in the

anterior and posterior communicating arteries have a high risk of rupture.<sup>6</sup> Craniotomy and clipping or endovascular coiling are the definitive treatment of intracranial aneurysm. A previous study compared the outcome of craniotomy and endovascular intervention and found that craniotomy has poorer outcome due to the surgery process itself rather than rebleeding.<sup>7</sup> In this case, a 66-year-old woman was referred to our institution complaining severe headache and projectile vomiting for three times two days prior admission. The patient also experienced decreased consciousness which improved on its own. The patient has no history of diagnosed hypertension, but high blood pressure was found on physical examination. DSA examination was performed and found a small wide neck anterior communicating artery aneurysm with size of 2.3x1.3 mm. Therefore, craniotomy for aneurysm clipping with general anesthesia was planned.

Pre-operative evaluation should be more focused on pathophysiological sequelae of intracranial aneurysm that needs to be anticipated. Neurologic complication including increased intracranial pressure, decreased cerebral blood flow, cerebral autoregulation disturbance, and delayed cerebral ischemia.<sup>8</sup> Ruptured aneurysm, inflammation, and direct irritation of brainstem stimulate the sympathetic system which leads to neurogenic

pulmonary edema. Sympathetic hyperactivity also leads to myocardial dysfunction. Cardiac arrhythmia and electrocardiography changes such as sinus bradycardia, sinus tachycardia, ST segment depression, T-wave inversion, U-waves, and prolonged QT interval are commonly found.<sup>9</sup> Intracranial aneurysm is also associated with fluid and electrolyte imbalance such as hypokalemia, hyperglycemia that may require insulin administration, and hyponatremia caused by cerebral salt wasting due to raised secretion of brain natriuretic peptide followed by suppressed aldosterone synthesis.<sup>10</sup> Prompt correction of these fluid, glucose and electrolyte imbalance need to be done by the anesthesiologist prior surgery. Monitoring electrolytes and osmolality of blood and urine serially are also required when mannitol or hypertonic saline is administered. In this case, the electrolyte examination showed hyponatremia (131 mmol/L) and hypokalemia (3,10 mmol/L). The patient was not given any mannitol or hypertonic saline by the neurosurgeon. One of the clinical grading that can be used in pre-operative evaluation is Hunt and Hess grading system. Patients with worse neurologic status are associated with increased intracranial pressure, intraoperative brain edema, cerebral autoregulation disturbance, and impaired cerebrovascular reactivity to carbon dioxide.<sup>10</sup>

The main goal for induction of anesthesia is preventing hypertension induced by laryngoscope and tracheal intubation. A study has reported that 8 out of 404 patients had ruptured aneurysm during anesthetic induction or induced by coughing and bucking during tracheal intubation.<sup>12</sup> Airway manipulation stimulates the sympathetic system which results in hypertension. Hypertension could cause rebleeding and increased aneurysmal transmural pressure which leads to sudden rupture. Therefore, blood pressure should be monitored after induction of anesthesia, before laryngoscopy and immediately after tracheal intubation. In this case, the patient's blood pressure after induction of anesthesia is 130/63 mmHg, before laryngoscopy is 103/55 mmHg and after tracheal intubation is 110/58 mmHg.

The anesthesiologist should also be aware of the signs of possible re-bleeding, such as persistent hypertension, bradycardia and sudden anisocoria. Arterial line placement can also cause pain and anxiety which leads to hypertension. Preinduction arterial line placement for monitoring blood pressure is not necessary unless the patient has cardiac dysfunction including increased troponin and hemodynamic instability.<sup>13</sup> In this case, arterial line placement was done before the induction of anesthesia. Allen test was performed and continued with arterial line insertion and administration of 2%

Lidocaine as local anesthetic. The patient's blood pressure was within normal limits (122/61 mmHg) after the arterial line placement. Bag-mask ventilation can accidentally cause hypo- or hypercarbia. Hypercarbia causes vasodilatation resulting increased intracranial pressure and disturbing cerebral perfusion whereas hypocarbia caused by hyperventilation results in reduced intracranial pressure which leads to increased aneurysmal transmural pressure.

The goal for hemodynamic is decreasing of blood pressure by 20% from baseline or systolic blood pressure less than 160 mmHg. However, aggressive treatment in lowering blood pressure could cause secondary ischemia.<sup>14</sup> In this case, the patient's systolic blood pressure was maintained by 120-140 mmHg. Several actions to prevent hemodynamic responses are needed, such as increasing the anesthetic depth; analgesics agents, such as boluses of fentanyl or remifentanyl and short-acting antihypertensive agents, such as esmolol and nicardipine.<sup>13</sup> In this case, the patient was given [hypertensive drugs] to maintain target blood pressure and Fentanyl 150 mcg (2-3 mcg/kg of body weight) intravenously for sedation. The placement of a temporary clip before the placement of the permanent clip may decreased the brain oxygenation. Therefore, raising the blood pressure by 10-20% from preinduction baseline for a short period of time is needed to increase

blood flow to the region at risk of ischemia. The blood pressure can be normalized after the procedure is done.

Herniation and rapid increased in intracranial pressure could result in dilated pupil, arrhythmias and ischemia. The surgeon may also notice increased blood flow at the incision site or sudden bulging of the brain.<sup>16</sup> Reduction of intracranial pressure and neuroprotection are the main goals before the opening of dura mater. The use of propofol bolus, continuous infusion or bolus of short acting opioids, or thiopentone sodium is useful to maintain intracranial pressure, cerebral perfusion pressure, and mean arterial pressure.<sup>17</sup> Intravenous anesthetics is also useful in reducing cerebral metabolic rate. In this case, anesthesia was maintained by administering TCI Propofol Ce target effect of 2-3 mcg/kg/min, Fentanyl 0,25 mcg/kg every 45 – 60 minutes IV, and Rocuronium 0,15 mg/kg every 45 – 60 minutes IV. Other strategies like short period of moderate hyperventilation and hypothermia may also reduce intracranial pressure. Several studies found that mild hypothermia (32–35°) showed benefit in decreasing intracranial pressure in good grade patients.<sup>18</sup>

Hypertension may also occur during extubation due to stimulation of sympathetic nerve.<sup>14</sup> In this case, the patient's blood pressure after extubation was 125/68 mmHg. Clinical manifestations

of intra operative aneurysmal rupture may be shown post operatively, such as delayed return of consciousness, rapid onset of neurological deterioration, hemodynamic instability, focal neurological deficits, or seizures.<sup>19</sup> In this case, after the surgery the patient was admitted to the intensive care unit and mechanically ventilated. Neurological examination showed the patient remained with aphasia without other neurological deficits. Recurrent headache symptoms were absent and there were no episodes of hemodynamic instability. The patient was discharged from hospital on postoperative day 5. We continued to follow up on the patient's condition after 1 month postoperatively. The patient had no complaints and showed resolution of headache and ataxia.

## Conclusion

Hemorrhagic stroke due to a ruptured intracranial aneurysm is life-threatening and requires prompt treatment, either by craniotomy with clipping or endovascular coiling. Anesthesiologists must recognize the sequelae of subarachnoid hemorrhage for thorough pre-anesthesia evaluation and optimal perioperative management. This includes preventing rebleeding, maintaining systolic blood pressure per guidelines, neurophysiological monitoring, controlling intracranial pressure, providing neuroprotection, and preventing postoperative pain and complications.

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**Damatus Try Hartanto Taopan**

# Tuberculoma With Visual and Vestibular Symptoms in A $\beta$ -Thalassemia Patient: A Case Report

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## Abstract

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**Keywords:** TB infection; Intracranial mass; Extrapulmonary TB; Tuberculoma.

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**Online First:** June 2025

**Background:** Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, which can affect the lungs (pulmonary TB) as well as other organs (extrapulmonary TB), including the central nervous system (CNS). The number of TB cases in Indonesia remains high, with 969,000 cases reported in 2021. Tuberculoma is a manifestation of TB in the CNS, presenting as an intracranial mass due to the spread of TB from other organs. It is a rare and serious form of CNS TB infection. The presence of congenital  $\beta$ -thalassemia adds complexity to the pathogenesis, diagnosis, and treatment of tuberculoma.

**Case Description:** A 25-year-old female with a history of  $\beta$ -thalassemia HbE intermedia with a major phenotype presented with the main complaint of blurred vision in the lower right visual field. The patient also experienced vertigo, headache, and a history of seizures. Examination revealed inferior right quadrantanopia, anemia, leukopenia, and thrombocytopenia. Imaging and CSF analysis supported a diagnosis of intracranial tuberculoma. The patient was treated with anti-TB medication and intravenous dexamethasone.

**Discussion:** Patients with thalassemia may have an increased risk of TB infection, including CNS TB. Tuberculoma involves granuloma formation in the brain, often in the meninges and cerebrum. Its manifestations vary and can include headaches and seizures. Diagnosis is based on clinical history, radiological findings, and laboratory results. The patient's symptoms and imaging findings supported a diagnosis of tuberculoma, for which anti-TB and neurorestorative therapy was administered.

**Conclusions:** Tuberculoma, as a manifestation of CNS TB, presents with variable and non-specific symptoms. Visual field disturbances can be one of the presenting symptoms that aid in diagnosis. Clinical, radiological, and laboratory evaluations are necessary for prompt and accurate diagnosis. Treatment involves anti-TB therapy and dexamethasone. This case highlights the importance of early diagnosis and comprehensive management of complex extrapulmonary TB infections.

## Introduction

Tuberculosis (TB) is a contagious infectious disease caused by the bacterium *Mycobacterium tuberculosis*, which can

affect the lungs (pulmonary TB) and other organs (extrapulmonary TB).<sup>1</sup> TB remains one of the major public health issues in Indonesian society due to its high morbidity and mortality rates. In 2021, there were

969,000 reported TB cases in Indonesia, according to the Global TB Report 2022.<sup>2</sup>

Tuberculoma is a manifestation of tuberculosis in the central nervous system, characterized by the presence of solid and multiple intracranial masses.<sup>3</sup> These intracranial masses form as a secondary process resulting from the spread of TB from organs other than the lungs.<sup>4</sup> Tuberculoma is a serious and rare form of central nervous system TB infection, alongside abscesses and meningitis. Dispositional factors such as age and immunosuppressive conditions play an important role in the development of extrapulmonary TB infections.<sup>5</sup> Thalassemia is one of the congenital diseases that can increase the risk of TB infection.<sup>6</sup>

### Case Description

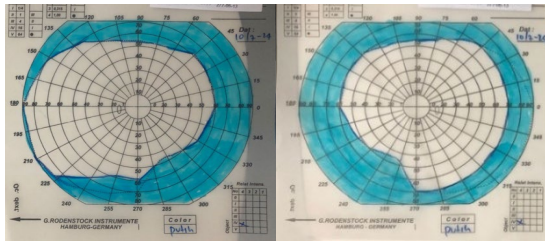
A 25-year-old woman presented to the outpatient clinic at Dr. Cipto Mangunkusumo Hospital (RSCM) with a chief complaint of blurred vision in the lower right visual field that had been occurring intermittently for two weeks prior to hospital admission. The patient reported experiencing double vision and seeing rainbow-like shadows when exposed to sunlight. The symptoms were intermittent, lasting about five minutes each episode. Over the past week, the patient also complained of episodes of vertigo lasting 2–3 minutes, followed by pressing headaches on all sides of the head. These

symptoms typically occurred while sleeping or lying down. The vertigo occurred once every two days and was not always accompanied by headaches. The patient denied any specific triggers.

The patient had a history of seizures, first occurring two years ago. The seizures were characterized by unknown preictal symptoms, ictal upward gaze to the right, head turning to the right, tonic-clonic movements in all four extremities, loss of consciousness for approximately five minutes, followed by postictal confusion for about 15 minutes before returning to baseline consciousness. The patient experienced several more seizures afterward but never took anti-epileptic medication. Additionally, the patient had a history of numbness throughout the body, including the face, and stiffness with pain in both hands. She had a known diagnosis of beta thalassemia HbE intermedia with a major phenotype and had been receiving regular transfusions every two weeks since the age of five. The patient had experienced gradual weight loss over the past three years, with a significant decrease of 10 kg in the past six months. She denied any history of fever, chronic cough, shortness of breath, asthma, or allergies.

On physical examination, the patient had a Glasgow Coma Scale (GCS) of E4M6V5, with stable vital signs (BP: 100/82 mmHg, HR: 108 bpm, RR: 20 bpm, Body temperature: 36.5°C). Neuro-

ophthalmological examination revealed visual field disturbances with blurred vision in the lower right visual field.



**Figure 1.** Campimetry Examination of Both Eyes (ODS)

Campimetry showed lower right quadrantanopsia in both eyes. Fundus examination (fundoscopy) revealed normofundus in both eyes. Neuro-otological examination did not yield significant findings to support the patient's complaint of vertigo.



**Figure 2.** Fundoscopy Examination of Both Eyes (ODS)

Additional investigations included blood laboratory tests. Results showed decreased hemoglobin (Hb) at 11.1 g/dL, hematocrit at 31.6%, leukocyte count of 3,200/ $\mu$ L, and platelet count of 43,000/ $\mu$ L. Cerebrospinal fluid (CSF) analysis showed cyto-protein dissociation and reduced CSF

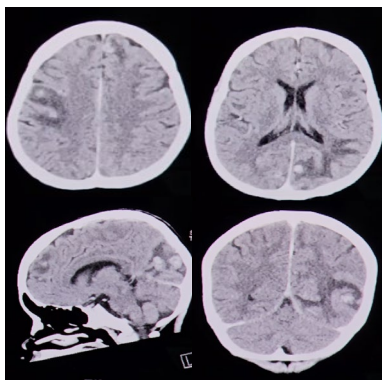
glucose compared to serum glucose. Gen Xpert CSF MTB was not detected, Acid-Fast Bacilli (AFB) smear was negative, and LAM TB was also negative.

Contrast-enhanced brain MRI revealed multiple intra-axial nodules with ring enhancement in the cortical regions of both cerebral and cerebellar hemispheres, as well as in the left mesencephalon, accompanied by perifocal edema and calcifications. A cystic lesion with CSF intensity was observed in the right middle cranial fossa, consistent with an arachnoid cyst. There were no signs of hydrocephalus, infarction, or intracranial hemorrhage. Compared to previous imaging, there was improvement in the left temporal rim-enhancing lesion, although perifocal edema remained. The patient was treated with first-line anti-tuberculosis therapy consisting of 2 months of RHZE followed by 4 months of RH, along with intravenous dexamethasone administered at a dosage of 5 mg three times daily.

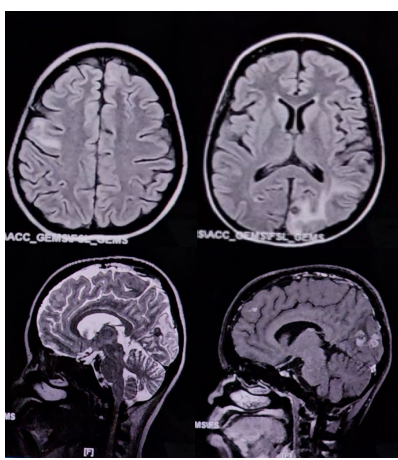
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The patient was treated with first-line anti-tuberculosis drugs: 2 months of RHZE followed by 4 months of RH. Additionally, intravenous dexamethasone therapy was administered at a dosage of 5 mg three times daily.



**Figure 3.** Contrast-Enhanced CT Scan of the Brain (Axial, Sagittal, and Coronal Views).



**Figure 4.** Contrast-Enhanced Brain MRI (Axial and Sagittal Views)

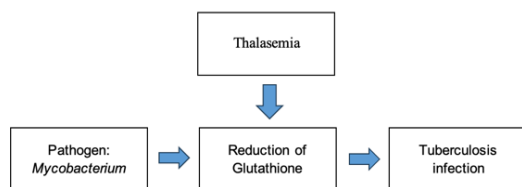
## Discussion

Tuberculoma is a mass lesion in brain tissue formed from granulomas consisting of tuberculous cells and other inflammatory tissues. Tuberculomas frequently occur in the meninges and cerebrum, and more rarely in the cerebellum. They can present as either solitary or multiple lesions in the brain.<sup>7</sup> Extrapulmonary TB infections that can affect the central nervous system (CNS) include tuberculoma, TB meningitis, TB encephalopathy, TB vasculopathy, TB brain abscess, Pott's disease, and spinal meningitis. The incidence of extrapulmonary TB infection in the CNS is approximately 6.3%.<sup>8</sup>

Tuberculoma does not present with specific symptoms. Its manifestations result from mass effect and elevated intracranial pressure, and they depend on the size, number, and location of the lesions. In adults, lesions are commonly found in supratentorial regions, while in children, infratentorial locations are more typical. Clinical symptoms can vary widely, including headache, seizures, cranial nerve paresis, and other neurological signs. Diagnosis of tuberculoma requires a comprehensive approach that includes patient history, radiological imaging, and laboratory investigations.<sup>9</sup>

This patient has a congenital condition— $\beta$  thalassemia HbE intermedia with a major phenotype—requiring regular blood transfusions, which may be a risk

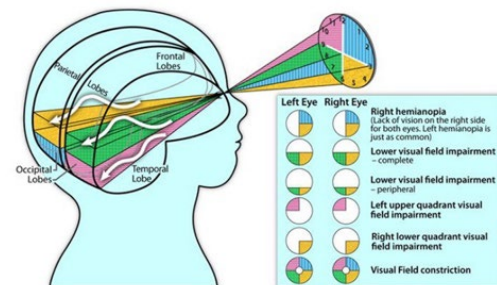
factor for TB infection. The link between thalassemia and TB infection lies in the antioxidant system, a critical biological process for protecting against various health issues. The antioxidant system contributes to TB prevention through antimicrobial and immune-enhancing effects mediated by the glutathione pathway. In thalassemia, this pathway is clinically significant as glutathione levels are reduced, increasing the patient's susceptibility to medical conditions, including infection.<sup>6</sup>



**Algorithm 1.** Antioxidant Pathways Involved in Thalassemia and TB Infection.

In this patient, multiple clinical diagnoses were established: contralateral inferior right quadrantanopia with macular sparing due to an upper occipital brain lesion, spontaneous episodic vestibular syndrome (EVS), and a history of seizures. The patient's subacute and progressive focal neurological symptoms suggest an infectious etiology. The lesion in the upper occipital brain due to tuberculoma manifested as right inferior contralateral quadrantanopia with macular sparing, as shown in the visual field map in Figure 5. The spontaneous EVS can also be explained by a tuberculoma lesion in the left mesencephalon. Radiological findings,

together with clinical history and laboratory results, supported the diagnosis of tuberculoma.



**Figure 5.** Occipital Visual Field Map

This case report emphasizes the patient's visual field disturbance. A lesion in the left occipital lobe caused right inferior quadrantanopia with macular sparing. Macular sparing indicates that the damage in the occipital region is incomplete and that the primary visual cortex is still functioning. This differs from visual field disturbances caused by temporal lobe lesions (involved in the "what" pathway of visual information processing), which typically present with superior quadrantanopia ("pie in the sky") with macular involvement and may include visual agnosia. In contrast, parietal lobe damage (involved in the "where" pathway) can cause inferior quadrantanopia ("pie on the floor") with macular involvement, optokinetic nystagmus impairment, and optic ataxia.

Current patient management includes pharmacological treatment with dexamethasone and anti-tuberculosis therapy, and non-pharmacological

intervention through neurorestorative transcranial magnetic stimulation (TMS) once no contraindications remain.

## Conclusion

Tuberculoma, as a manifestation of TB in the central nervous system, can cause diverse and non-specific symptoms, as seen in this 25-year-old patient. She presented with visual disturbances, seizures, and other neurological symptoms, leading to a tuberculoma diagnosis based on clinical, radiological,

and laboratory findings. Her  $\beta$  thalassemia may have contributed as a risk factor for TB infection through compromised antioxidant mechanisms. Treatment involved anti-TB drugs and dexamethasone, with referral for neurorestorative therapy. This case highlights the importance of recognizing symptoms and risk factors for early diagnosis and comprehensive management of complex and rare extrapulmonary TB infections such as tuberculoma.

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**Evlyne Erlyana Suryawijaya**

# Comparative Effectiveness of SGLT2 Inhibitors and GLP-1 Receptor Agonists in Heart Failure: A Systematic Review

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## Abstract

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**Keywords:** Cardiovascular outcomes; Glucagon-like peptide-1 receptor agonists; Heart failure; SGLT2 inhibitors

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**Background:** Heart failure (HF) affects over 64 million individuals globally and is associated with high morbidity and mortality, particularly in patients with type 2 diabetes mellitus (T2DM). Sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are emerging therapies with reported cardiovascular benefits. However, their comparative efficacy in HF-specific outcomes remains unclear. This systematic review aimed to assess and compare the safety and efficacy of SGLT2 inhibitors and GLP-1 RAs in patients with HF.

**Methods:** We systematically searched PubMed, EMBASE, and Scopus up to 1 May 2025 for randomized controlled trials (RCTs) evaluating SGLT2 inhibitors or GLP-1 RAs in adults with HF. Primary outcomes included all-cause and cardiovascular mortality; secondary outcomes included HF hospitalization and major adverse cardiovascular events (MACE). Risk of bias was assessed using the Cochrane RoB 2 tool and certainty of evidence with the GRADE approach.

**Result:** Fourteen RCTs comprising 30,867 patients (52.2% female; 63.2% with T2DM) were included. SGLT2 inhibitors significantly reduced cardiovascular mortality (RR: 0.85, 95% CI: 0.78–0.93,  $p < 0.001$ ,  $I^2 = 14\%$ ), all-cause mortality (RR: 0.88, 95% CI: 0.81–0.95,  $p = 0.002$ ,  $I^2 = 21\%$ ), and HF hospitalizations (RR: 0.72, 95% CI: 0.67–0.77,  $p < 0.001$ ,  $I^2 = 0\%$ ). GLP-1 RAs did not demonstrate significant effects on these outcomes. Overall risk of bias was low to moderate; GRADE certainty ranged from moderate to high.

**Conclusions:** SGLT2 inhibitors provide consistent reductions in mortality and hospitalization in HF patients across glycemic statuses. GLP-1 RAs showed limited benefit in HF-specific outcomes, supporting the preferential use of SGLT2 inhibitors in HF treatment strategies.

## Introduction

Heart failure (HF) is a progressive clinical syndrome that affects an estimated 64 million individuals worldwide, posing a substantial burden on global healthcare

systems.<sup>1</sup> In the United States, over 6.7 million adults are living with HF, and projections indicate a 46% increase in prevalence by 2030, underscoring the need for effective, scalable therapeutic strategies. HF is associated with high rates

of hospitalization and mortality, with a 5-year survival rate of approximately 50%, making it a leading cause of death and a major contributor to healthcare expenditures.<sup>2</sup> HF is two to four times higher than in non-diabetic populations, due to shared pathophysiological mechanisms including endothelial dysfunction, systemic inflammation, and atherothrombosis.<sup>3</sup> These comorbidities contribute to a complex clinical phenotype that often requires multifaceted treatment approaches.

In this context, sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have emerged as antidiabetic therapies with notable cardiovascular benefits. Beyond glycemic control, SGLT2 inhibitors have demonstrated consistent reductions in HF hospitalization and cardiovascular mortality in both diabetic and non-diabetic patients.<sup>3</sup> Randomized controlled trials (RCTs) such as DAPA-HF, EMPEROR-Reduced, and EMPEROR-Preserved have shown relative risk reductions of 30–35% in HF hospitalizations and significant improvements in mortality and symptom burden.<sup>4–6</sup> These benefits have led to their incorporation into HF management guidelines across the spectrum of ejection fraction, irrespective of glycemic status. In contrast, GLP-1 RAs have primarily demonstrated efficacy in reducing major adverse cardiovascular events (MACE),

including myocardial infarction and stroke, as evidenced in trials such as LEADER, SUSTAIN-6, and PIONEER-6.<sup>7–9</sup> However, their impact on HF-specific outcomes has been inconsistent, with neutral or potentially adverse effects observed in some studies involving HFrEF patients.

Pharmacologically, the divergence in therapeutic profiles between these drug classes is attributable to their distinct mechanisms of action. SGLT2 inhibitors exert multiple HF-relevant effects, including osmotic diuresis, reduction in preload and afterload, attenuation of myocardial fibrosis, improvement in ventricular remodeling, and favorable alterations in myocardial energetics and renal hemodynamics.<sup>10</sup> These mechanisms act synergistically to modify disease trajectory in both HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF).<sup>10</sup> In contrast, GLP-1 RAs primarily exert metabolic effects—enhancing insulin secretion, reducing glucagon levels, promoting weight loss, and exerting anti-inflammatory and anti-atherosclerotic actions.<sup>11</sup> While these properties confer benefit in atherosclerotic cardiovascular disease (ASCVD), their limited influence on volume status and myocardial stress may explain the lack of consistent benefit in HF endpoints. Notably, some GLP-1 RAs have been associated with increased heart rate, a potential concern in HFrEF management.<sup>11</sup>

Despite the growing evidence base for each drug class individually, direct comparisons of their effectiveness in HF remain limited. Both classes are now commonly co-prescribed or considered as alternative options in patients with T2DM and cardiovascular disease, raising critical questions about therapeutic prioritization, sequencing, and HF phenotype-specific efficacy. Understanding the comparative clinical effectiveness of SGLT2 inhibitors versus GLP-1 RAs in HF is essential to inform individualized treatment strategies, guide multidisciplinary care decisions, and optimize long-term outcomes. This systematic review aims to comprehensively evaluate and compare the impact of SGLT2 inhibitors and GLP-1 receptor agonists on patients HF.

## Material And Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.<sup>12</sup> A comprehensive literature search was performed in PubMed, EMBASE, and Scopus databases to identify relevant studies published up to 1 May 2025. The search strategy was designed to capture randomized controlled trials (RCTs) evaluating the effects of SGLT2 inhibitors or GLP-1 receptor agonists in patients with heart failure, regardless of ejection fraction status or presence of type 2 diabetes mellitus. The search combined terms and

Medical Subject Headings (MeSH) related to heart failure, SGLT2 inhibitors (e.g., empagliflozin, dapagliflozin), GLP-1 receptor agonists (e.g., liraglutide, semaglutide), and randomized controlled trials. No language or publication date restrictions were applied. Reference lists of included studies and relevant reviews were manually screened for additional eligible trials.

Eligible studies were randomized controlled trials (RCTs) involving adult participants ( $\geq 18$  years) with a clinical diagnosis of heart failure, irrespective of ejection fraction or diabetes status. Trials were included if they evaluated any sodium-glucose co-transporter 2 (SGLT2) inhibitor or glucagon-like peptide-1 receptor agonist (GLP-1 RA), compared against placebo, standard care, or each other. Studies were required to report on safety outcomes as the primary endpoint, including all-cause mortality and cardiovascular death. Secondary outcomes of interest included efficacy endpoints, such as heart failure hospitalization rate and major adverse cardiac events (MACE). Only full-text articles published in peer-reviewed journals were considered. Studies were excluded if they were observational, non-randomized, lacked HF-specific data, or did not report relevant safety or efficacy outcomes.

All retrieved articles were imported into reference management software, and

duplicates were removed. Titles and abstracts were screened, followed by full-text review, conducted independently by three authors. Relevant data—including study design, population characteristics, interventions, comparators, outcomes, and follow-up duration—were extracted using a standardized form. Disagreements at any stage were resolved through discussion and consensus among the authors.

Risk of bias for each included trial was independently assessed by three reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain and the overall judgment were rated as low risk, some concerns, or high risk. Conflicts were resolved through group discussion.

The certainty of evidence for each outcome was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The evidence was rated as high, moderate, low, or very low, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

All statistical analyses were performed using RStudio (version 2024.03.1+402). For dichotomous outcomes, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated. Meta-analyses were

conducted using a random-effects model, regardless of heterogeneity, to accommodate clinical and methodological variability across studies. Between-study heterogeneity was quantified using  $\text{Tau}^2$ , calculated via the DerSimonian and Laird method, and Wald-type methods were used to derive confidence intervals. Statistical significance was set at  $p < 0.05$ . Subgroup analyses were restricted to comparisons of SGLT2 inhibitors versus placebo and GLP-1 receptor agonists versus placebo. Forest plots were generated to visually present effect estimates for each outcome. To assess potential publication bias, funnel plots were constructed for each pooled outcome. Additionally, Egger's regression test and Begg's rank correlation test were performed to statistically evaluate small-study effects. Results from these tests were interpreted in conjunction with visual asymmetry of the funnel plots.

## Result

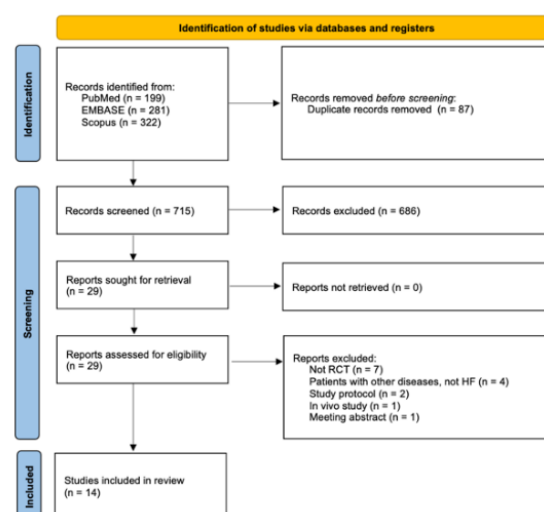


Figure 1. PRISMA flow diagram.

A total of 802 records were initially identified through database searches, including 199 from PubMed, 281 from EMBASE, and 322 from Scopus. After removing 87 duplicates, 715 records remained for screening. Of these, 686 were excluded based on titles and abstracts, leaving 29 full-text reports assessed for eligibility. No reports were excluded due to retrieval issues. Among the 29 full-text articles reviewed, 15 were excluded for the following reasons: not being randomized controlled trials ( $n = 7$ ), involving patients with conditions other than heart failure ( $n = 4$ ), being study protocols ( $n = 2$ ), in vivo studies ( $n = 1$ ), or meeting abstracts ( $n = 1$ ). Ultimately, 14 studies met the inclusion criteria and were included in the final systematic review.<sup>4–9,13–21</sup>

Among these, SGLT-2 inhibitor studies included DAPA-HF, DELIVER, EMPEROR-Reduced, EMPEROR-Preserved, and SOLOIST-WHF, with follow-up durations ranging from 9 to 28 months. These studies enrolled patients with heart failure characterized by varying left ventricular ejection fractions and NYHA classes II–IV, including: DAPA-HF (II = 3203, III–IV = 1541), DELIVER (II = 4713, III–IV = 1549), EMPEROR-Reduced (II = 2800, III–IV = 930), and EMPEROR-Preserved (II = 4883, III–IV = 1101), while SOLOIST-WHF did not report NYHA classification. GLP-1 agonist studies included FIGHT, LIVE, Lepore 2016, LEADER, EXSCEL, HARMONY,

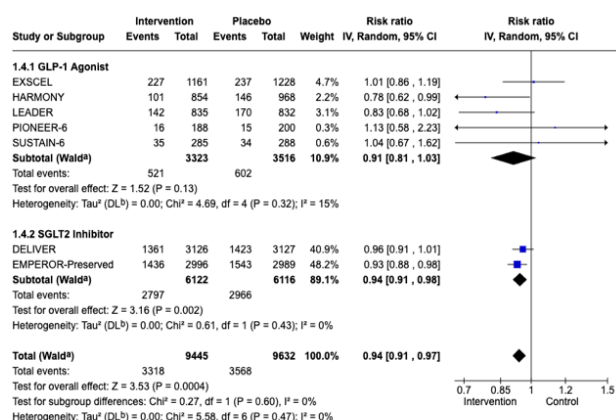
SUSTAIN-6, PIONEER-6, and ELIXA, involving patients with a history of heart failure or reduced ejection fraction. Reported NYHA class distributions were: FIGHT (II = 87, III = 189, IV = 15), LIVE (I = 71, II = 129, III = 33), LEADER (I = 348, II = 1091, III = 214, IV = 14), and EXSCEL (I = 738, II = 1333, III = 303, IV = 13), while other GLP-1 studies did not provide NYHA data. Interventions used included liraglutide, albiglutide, exenatide, semaglutide, and lixisenatide, with follow-up durations ranging from 3 months to 3.8 years. Across all studies, the total cohort included 30,867 participants, with 19,525 having diabetes mellitus as a comorbidity and 16,118 being female.

In patients with heart failure, from our meta-analysis, the overall effect estimate for major adverse cardiac events following treatment with GLP-1 agonists or SGLT-2 inhibitors was a risk ratio (RR) of 0.94 (95% CI: 0.91 to 0.97;  $p = 0.0008$ ;  $I^2 = 0\%$ ) (Figure 2). For all-cause mortality, the RR was 0.94 (95% CI: 0.89 to 1.00;  $p = 0.05$ ;  $I^2 = 0\%$ ) (Figure 3). For cardiovascular death, the RR was 0.89 (95% CI: 0.83 to 0.97;  $p = 0.005$ ;  $I^2 = 0\%$ ) (Figure 4). The hospitalization rate due to heart failure showed an RR of 0.86 (95% CI: 0.76 to 0.97;  $p = 0.02$ ;  $I^2 = 69\%$ ) (Figure 5).

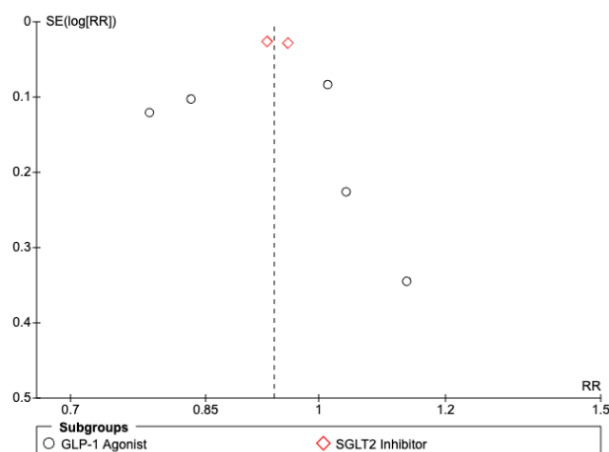
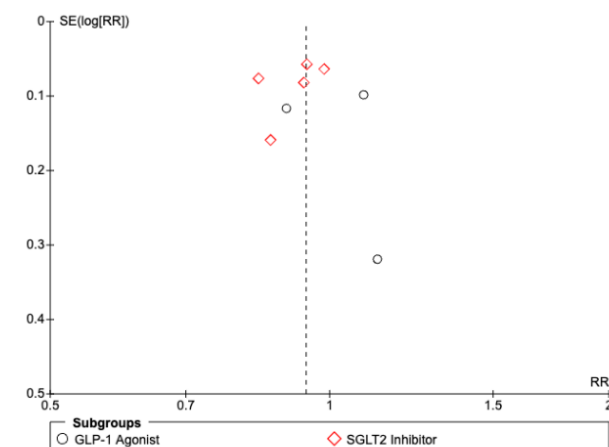
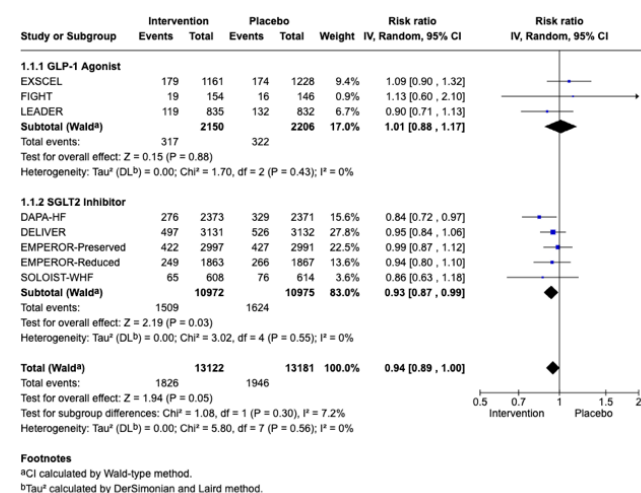
**Table 1.** Demographic characteristics of included studies.

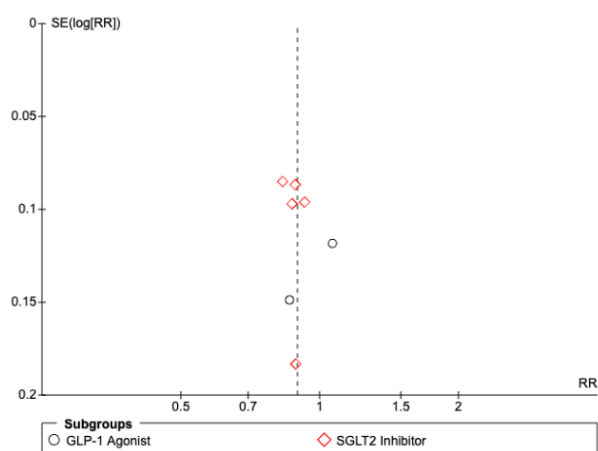
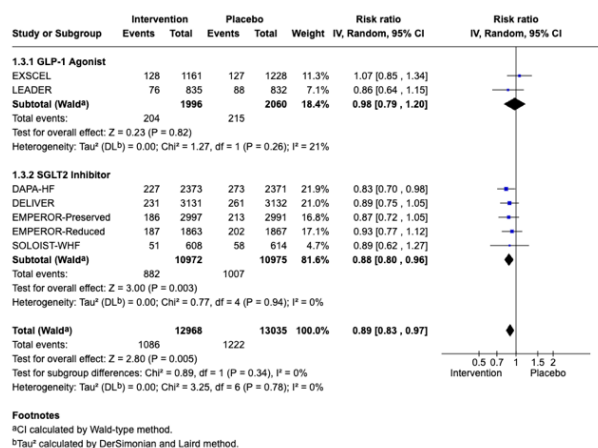
| Study ID                             | Patients details                                                                                                                                                                                                                                                                                                                         | Age, years  | Female, n | LV EF, NYHA, n                            | Intervention details | Follow up duration |
|--------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-----------|-------------------------------------------|----------------------|--------------------|
| <b>SGLT2 Inhibitor</b>               |                                                                                                                                                                                                                                                                                                                                          |             |           |                                           |                      |                    |
| DAPA-HF, (n = 4744)                  | LV EF <50%; elevated NT-proBNP; NYHA functional class II-IV                                                                                                                                                                                                                                                                              | 66.3 ± 10.9 | 3635      | 31.1% II = 1205                           | Dapagliflozin        | 18 months          |
| DELIVER, (n = 4263)                  | LV EF <40% and evidence of structural heart disease; elevated NT-proBNP; NYHA functional class II-IV; ambulatory or hospitalized patients                                                                                                                                                                                                | 71.7 ± 9.4  | 3516      | 54.2% II = 4713                           | Dapagliflozin        | 28 months          |
| EMPEROR-Reduced, (n = 3730), 00000   | LV EF <50%; elevated NT-proBNP; NYHA functional class II-IV                                                                                                                                                                                                                                                                              | 66.5 ± 11.2 | 2937      | 27.2% II = 2880                           | Empagliflozin        | 16 months          |
| EMPEROR-Preserved, (n = 3988), 00000 | LV EF <40%; evidence of structural heart disease or history of heart failure hospitalization within 12 months; elevated NT-proBNP; NYHA functional class II-IV                                                                                                                                                                           | 71 ± 9.6    | 3312      | 54.3% II = 4083                           | Empagliflozin        | 26 months          |
| SOLOIST-WHF, (n = 1223), 00000       | Type 2 diabetes, admitted to the hospital, or urgent heart failure visit for worsening heart failure; previous treatment with loop diuretic for >30 days; previous diagnosis of heart failure (>3 months); elevated BNP or NT-proBNP; undischarged when haemodynamically stable, before hospital discharge or within 3 days of discharge | 70 (64-76)  | 810       | 35% NA                                    | Semagliflozin        | 9 months           |
| <b>GLP-1 agonist</b>                 |                                                                                                                                                                                                                                                                                                                                          |             |           |                                           |                      |                    |
| FIGHT, (n = 300), 0000               | Advanced HF EF (<50%)                                                                                                                                                                                                                                                                                                                    | 61          | 64        | 25% II = 87, III = 118, IV = 15           | Lingulate            | 6 months           |
| LIFE, (n = 241), 00000               | Chronic HF EF (<40%)                                                                                                                                                                                                                                                                                                                     | 65          | 26        | 34.5% I = 71, II = 120, III = 13          | Lingulate            | 24 months          |
| Lapin 2016, (n = 82), 00000          | Chronic HF EF (<40%)                                                                                                                                                                                                                                                                                                                     | 56          | 21        | <40% NA                                   | Abiglate             | 3 months           |
| LEADER, (n = 1667), 0000             | History of HF (NYHA class I-III)                                                                                                                                                                                                                                                                                                         | 64          | 684       | 31.5% I = 348, II = 1091, III = 214       | Lingulate            | 3.8 years          |
| EXSCCEL, (n = 2189), 00000           | History of congestive HF                                                                                                                                                                                                                                                                                                                 | 64          | 849       | NA I = 738, II = 1333, III = 303, IV = 13 | Exanlate             | 3.2 years          |
| HARMONY, (n = 1022), 00000           | History of congestive HF                                                                                                                                                                                                                                                                                                                 | NA          | NA        | NA NA                                     | Abiglate             | ≥1.5 years         |
| SUSTAIN-6, (n = 373), 00000          | Prior HF (NYHA class II or III)                                                                                                                                                                                                                                                                                                          | 64          | 246       | NA NA                                     | Semaglate            | 2.1 years          |
| PIONEER-6, (n = 388), 00000          | Prior HF (NYHA class II or III)                                                                                                                                                                                                                                                                                                          | 65          | 118       | NA NA                                     | Semaglate            | 1.3 years          |
| ELIXA, (n = 1358), 00000             | Prior HF                                                                                                                                                                                                                                                                                                                                 | NA          | NA        | NA NA                                     | Lixianlate           | 25 months          |

The pooled effect estimate for OS demonstrated a HR of 0.81 (95% CI: 0.65 to 1.00;  $p = 0.05$ ;  $I^2 = 0\%$ ) across five studies (Figure 3). For progression-free survival (PFS), the combined HR was 0.80 (95% CI: 0.62 to 1.05;  $p = 0.07$ ;  $I^2 = 0\%$ ) based on three studies (Figure 4). The analysis of grade  $\geq 3$  adverse events showed a RR of 0.31 (95% CI: 0.02 to 6.09;  $p = 0.23$ ;  $I^2 = 90\%$ ), also from three studies (Figure 5).

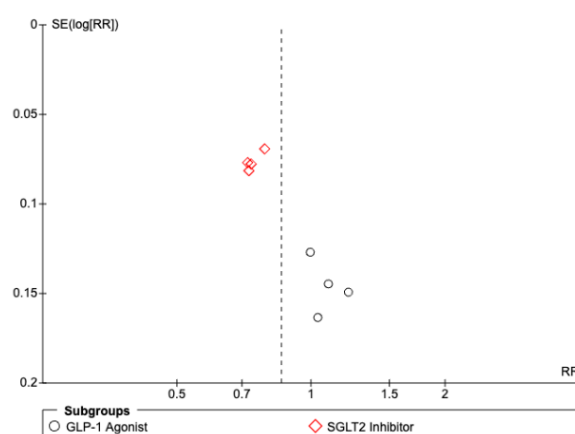
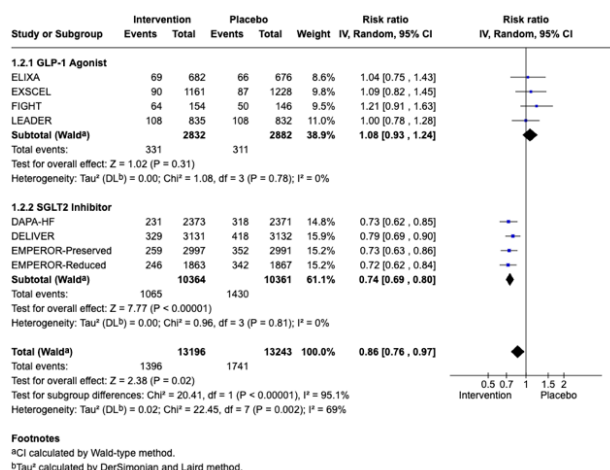


Footnotes  
<sup>a</sup>CI calculated by Wald-type method.  
<sup>b</sup> $\tau^2$  calculated by DerSimonian and Laird method.

**Figure 2.** Meta-analysis for major adverse cardiac events following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.**Figure 3.** Meta-analysis for all-cause mortality following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.

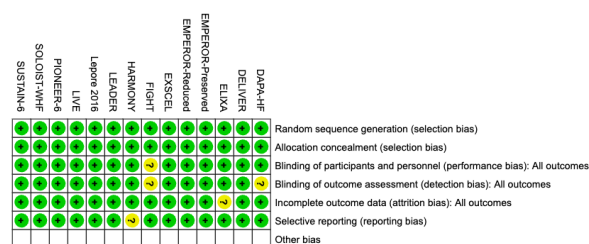


**Figure 4.** Meta-analysis for cardiovascular death following GLP-1 agonists or SGLT-2 inhibitors in patients with HF.



**Figure 5.** Meta-analysis for hospitalization rate due to HF following GLP-1 agonists or SGLT-2 inhibitors.

Risk of bias assessment (figure 6) across the included randomized controlled trials indicated a low to moderate risk of bias overall, with most studies having adequate randomization and outcome reporting. According to GRADE criteria, the certainty of evidence was rated as moderate to high for the major outcomes. This reflects consistency across studies, precise estimates, and direct applicability to the patient population with heart failure.



**Figure 6.** Risk of bias assessment using the Cochrane RoB version 2.

## Discussion

This meta-analysis adds to the growing body of evidence supporting the use of SGLT-2 inhibitors in heart failure, showing consistent benefits across major cardiovascular outcomes. Previous trials such as DAPA-HF and EMPEROR-Reduced have already established SGLT-2 inhibitors as effective therapies in HFrEF. In DAPA-HF, dapagliflozin led to a 26% relative risk reduction in the composite of cardiovascular death or worsening heart failure (HR: 0.74; 95% CI: 0.65–0.85), while EMPEROR-Reduced demonstrated a 25% risk reduction in the same composite outcome with empagliflozin (HR: 0.75; 95% CI: 0.65–0.86). These benefits were observed regardless of diabetic status, indicating a mechanism of action beyond glycemic control.

The clinical utility of SGLT-2 inhibitors in heart failure is supported by their multifaceted pharmacological effects. By promoting glycosuria and natriuresis, they reduce intravascular volume and lower both preload and afterload.<sup>22</sup> This directly addresses the hemodynamic burden in heart failure. Additionally, SGLT-2 inhibitors have been associated with favorable myocardial remodeling, reduced fibrosis, and improved cardiac efficiency through shifts in substrate utilization toward ketone metabolism.<sup>23,24</sup> These effects are particularly relevant in patients with symptomatic heart failure, where volume management and metabolic efficiency play

key roles in disease progression and quality of life.

While GLP-1 receptor agonists have proven cardiovascular benefits in patients with type 2 diabetes and established atherosclerotic cardiovascular disease—as seen in the LEADER trial (liraglutide reduced cardiovascular death by 22%, HR: 0.78; 95% CI: 0.66–0.93)—their role in heart failure remains uncertain.<sup>7,8</sup> Some trials have reported neutral or even adverse effects on heart failure outcomes. For instance, the FIGHT trial found no significant benefit of liraglutide on post-hospitalization outcomes in HFrEF patients and noted a trend toward increased heart rate.<sup>17</sup> These findings suggest that GLP-1 receptor agonists may not confer the same cardiac-specific advantages and should be used selectively, especially in patients with established heart failure.

In routine practice, the reduction in heart failure hospitalizations observed with SGLT-2 inhibitors is particularly impactful, given the high rates of readmission and associated morbidity.<sup>25</sup> Real-world data from registries and observational studies have echoed these trial findings, showing improvements in functional status, reductions in NT-proBNP levels, and fewer HF-related emergency visits.<sup>26</sup> Given these effects, SGLT-2 inhibitors are increasingly regarded not just as antidiabetic agents, but as integral components of comprehensive heart failure management strategies.

A potential limitation of this study lies in the heterogeneity of patient populations across the included trials, particularly in terms of heart failure subtype, background therapies, and comorbid conditions such as diabetes and chronic kidney disease, which may have influenced treatment responses and obscured subgroup-specific effects. Additionally, differences in study design, follow-up duration, and outcome definitions—especially regarding hospitalization for heart failure—introduce variability that may impact the pooled estimates. The inclusion of trials with varying baseline risk and inconsistent reporting of functional class limits the precision of clinical applicability. While efforts were made to assess methodological quality, some studies still carried a moderate risk of bias due to open-label designs or incomplete outcome data. Finally, although the GRADE assessment indicated moderate to high certainty for key outcomes, the reliance on trial-level data rather than individual patient data restricts more nuanced exploration of effect

modifiers such as age, sex, or ejection fraction.

## Conclusion

This meta-analysis reinforces the cardiovascular benefits of SGLT-2 inhibitors in patients with heart failure, demonstrating consistent reductions in hospitalization and cardiovascular mortality, regardless of diabetic status. The findings align with established clinical trial data and support the incorporation of SGLT-2 inhibitors into standard heart failure management. While GLP-1 receptor agonists have shown cardiovascular benefit in patients with diabetes and atherosclerotic disease, their role in heart failure remains less clear, warranting further investigation. Overall, these results emphasize the importance of tailoring pharmacologic therapy to individual patient profiles, with growing evidence supporting the cardioprotective effects of certain glucose-lowering agents beyond glycemic control.

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**Evira Agustina Putri**

# The Therapeutic Potential of Neural Stem Cell in Ischemic Stroke: A Systematic Review

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## Abstract

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**Keywords:** Ischemic stroke; Neural stem cells; Preclinical models; Regenerative therapy.

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**Background:** Ischemic stroke remains a leading cause of disability and mortality worldwide, with over 12 million new cases annually and limited treatment options confined to narrow therapeutic windows. Neural stem cells (NSCs) have emerged as a promising therapeutic avenue due to their ability to self-renew, differentiate into all neural lineages, and exert paracrine effects that modulate inflammation and promote neurogenesis. Preclinical studies have demonstrated functional improvements of up to 60% in animal stroke models, but a systematic evaluation of these findings is needed to inform future clinical applications.

**Methods:** A systematic review was conducted following PRISMA 2020 guidelines. Databases searched included PubMed, EMBASE, and Scopus, covering literature up to May 8, 2025. Inclusion criteria comprised in vivo preclinical studies investigating NSC transplantation in animal models of ischemic stroke with at least one neurological, infarct, or histological outcome. Data extraction and risk of bias assessment (ROBINS-I) were independently performed by three reviewers. Due to study heterogeneity, a narrative synthesis was undertaken.

**Result:** Eight studies met the inclusion criteria. NSC therapy improved neurological recovery in over 80% of cases, reduced infarct volume by up to 40%, and downregulated pro-inflammatory and apoptotic markers. Benefits were dose- and timing-dependent, with intracerebral and intravenous routes demonstrating variable efficacy. One study reported tumorigenicity, highlighting the need for safety profiling.

**Conclusions:** Preclinical evidence supports the therapeutic potential of NSCs in ischemic stroke through neuroprotective and neurorestorative mechanisms. High-certainty findings justify continued investigation in clinical trials to refine dosing, delivery, and safety protocols.

## Introduction

Ischemic stroke is a major global health burden, accounting for approximately 87% of all stroke cases and

ranking among the leading causes of death and long-term disability worldwide. According to the World Health Organization, over 12 million new strokes occur globally each year, with nearly 7

million of these resulting in lasting disability.<sup>1</sup> Despite the implementation of acute-phase therapies such as intravenous thrombolysis and endovascular thrombectomy, these interventions are limited by narrow therapeutic windows—typically 4.5 hours for tissue plasminogen activator and up to 24 hours for selected patients undergoing mechanical thrombectomy—and are only applicable to a minority of patients.<sup>1</sup> As a result, more than 70% of stroke survivors are left with persistent neurological deficits, underscoring the need for restorative therapies that extend beyond the acute phase.<sup>1</sup>

Neural stem cells (NSCs) have emerged as a promising therapeutic candidate in this context due to their intrinsic capacity for self-renewal, multipotency, and targeted migration to injured brain regions.<sup>2,3</sup> Unlike mesenchymal stem cells or hematopoietic stem cells, NSCs possess the unique ability to differentiate into all major neural lineages—neurons, astrocytes, and oligodendrocytes—making them particularly suited for central nervous system repair.<sup>2</sup> Preclinical studies have shown that NSC transplantation can significantly improve functional outcomes in animal models of ischemic stroke, with some reports indicating improvements in neurological scores by up to 40–60% compared to control groups.<sup>4</sup> In addition to structural integration, NSCs are known to

exert potent paracrine effects, including the release of neurotrophic factors, modulation of inflammation, and stimulation of endogenous neurogenesis. These mechanisms collectively contribute to enhanced recovery in both acute and subacute phases of stroke.

Despite encouraging outcomes in early-phase clinical trials—such as the PISCES studies using CTX0E03 human NSCs, which demonstrated safety and preliminary functional gains in chronic stroke patients—the translation of NSC therapy into routine clinical practice remains limited.<sup>5</sup> Key challenges include optimizing dosing strategies, determining the ideal timing and route of administration, and ensuring long-term safety and efficacy. A comprehensive evaluation of preclinical data is essential to bridge this translational gap and guide future clinical application. Therefore, the objective of this systematic review is to critically assess the therapeutic potential of neural stem cell therapy in preclinical models of ischemic stroke.

## Material And Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.<sup>6</sup>

A comprehensive literature search was performed using three electronic databases: PubMed, EMBASE, and Scopus. The search strategy combined

controlled vocabulary terms and free-text keywords related to neural stem cells and ischemic stroke. The search terms included variations and combinations of the following: "neural stem cell", "NSC", "ischemic stroke", "cerebral ischemia", "preclinical", and "animal model". The search covered all articles published up to 8 May 2025, without restriction on publication year. Reference lists of relevant articles were also screened manually to identify any additional studies not captured by the initial database search.

Studies were included if they met the following criteria: (1) *in vivo* preclinical studies using animal models of ischemic stroke; (2) administration of neural stem cells as the primary therapeutic intervention; (3) outcomes assessed included at least one measure of neurological recovery, infarct size, or histological analysis; and (4) published in English in peer-reviewed journals. Studies involving other types of stem cells (e.g., mesenchymal, hematopoietic), *in vitro* models, hemorrhagic stroke, or human clinical trials were excluded.

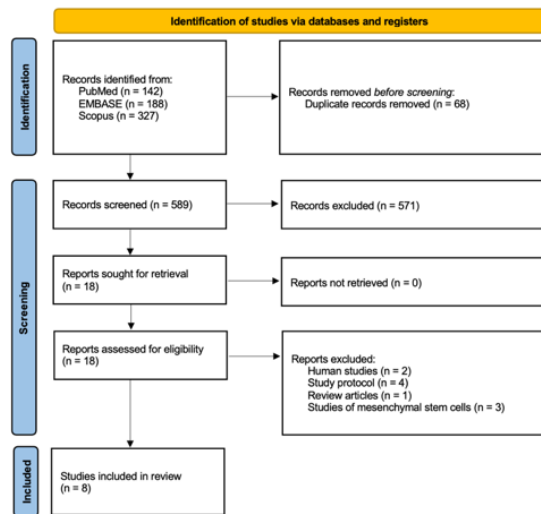
Three reviewers independently screened titles and abstracts, followed by full-text review of potentially eligible studies. Data extraction was conducted independently by the same reviewers using a standardized data collection form. Extracted data included animal species and stroke model, NSC source and type, dose

and timing of administration, route of delivery, outcome measures, and key findings. Any discrepancies in study inclusion or data extraction were resolved through discussion until consensus was reached.

Risk of bias in the included studies was assessed using the ROBINS-I tool, which evaluates non-randomized interventions across seven domains including confounding, selection bias, and outcome measurement; each study was independently rated by three reviewers, with discrepancies resolved through discussion. To assess the overall certainty of evidence, the GRADE framework was applied, considering factors such as risk of bias, inconsistency, indirectness, imprecision, and potential publication bias, with certainty ratings assigned as high, moderate, low, or very low.

Due to the heterogeneity in study design, NSC sources, dosing regimens, outcome measures, and reporting formats, a quantitative meta-analysis was not performed. Instead, the findings were synthesized narratively and summarized in tabular form to provide a comprehensive overview of the therapeutic potential and clinical relevance of NSC therapy in preclinical ischemic stroke models.

## Result



**Figure 1.** PRISMA flow chart for the study selection process.

A total of 657 records were identified through database searches: 142 from PubMed, 188 from EMBASE, and 327 from Scopus. After removing 68 duplicate entries, 589 records remained for screening. Of these, 571 records were excluded based on titles and abstracts, leaving 18 reports for full-text retrieval and assessment. No reports were excluded due to unavailability. Upon full-text evaluation, 10 studies were excluded for the following reasons: human studies ( $n = 2$ ), study protocols ( $n = 4$ ), review articles ( $n = 1$ ), and studies focusing on mesenchymal stem cells rather than neural stem cells ( $n = 3$ ). Ultimately, 8 preclinical studies met the inclusion criteria and were incorporated into this systematic review.<sup>7–14</sup>

Preclinical studies investigating NCS therapy for ischemic stroke have consistently demonstrated functional

improvements in various rodent models, with some variability in infarct volume reduction. Across models such as transient or permanent middle cerebral artery occlusion (MCAO) in rats and mice, NSCs derived from different sources—including immortalized mouse lines (e.g., C17.2), human fetal brain tissue, and conditionally immortalized human NSCs like CTX0E03—were administered via routes such as intravenous, intracerebral, and occasionally intra-arterial injection. Doses typically ranged from  $1 \times 10^5$  to  $5 \times 10^6$  cells, with most studies applying a single dose between 24 hours to several weeks post-stroke.

Timing of administration influenced the mechanisms of action observed. Early post-stroke delivery often correlated with reduced inflammatory cytokine levels and protection of blood-brain barrier integrity, whereas delayed delivery (up to four weeks) enhanced neurogenic activity and endogenous cell proliferation. Behavioral improvements were commonly measured through rotarod, beam-walk, and neurological severity score assessments, with many studies reporting dose-dependent recovery. Some studies found significant upregulation of neuroprotective genes and downregulation of pro-apoptotic signals following NSC transplantation. Others observed migration of NSCs toward ischemic regions, partial differentiation into neural lineages, and modulation of microglial activity.



contributing to an environment conducive to functional recovery.

Pharmacologically, NSCs modulate multiple pathophysiological pathways involved in ischemic brain injury. Studies reported reductions in infarct volume by up to 40% and significant decreases in markers of oxidative stress and inflammation.<sup>16</sup> In one study, NSC transplantation reduced interleukin-1 $\beta$  (IL-1 $\beta$ ) and TNF- $\alpha$  expression by over 50% while upregulating anti-inflammatory cytokines like IL-10.<sup>17</sup> This modulation of the inflammatory milieu also reduced glial scarring and preserved the integrity of the blood-brain barrier. Furthermore, NSCs were shown to inhibit apoptosis through increased expression of Bcl-2 and downregulation of caspase-3, thereby preventing secondary neuronal loss. These data suggest that the pharmacological profile of NSCs supports both acute neuroprotection and long-term regeneration.

From a physiological perspective, the timing and route of NSC delivery are crucial determinants of therapeutic efficacy. Early transplantation (within 72 hours post-stroke) showed greater efficacy in limiting infarct progression, while delayed administration (7 to 28 days post-injury) was associated with enhanced endogenous repair mechanisms such as neurogenesis and axonal sprouting.<sup>18</sup> Intracerebral injection, used in

approximately 60% of preclinical studies, ensures localized delivery but carries procedural risks.<sup>19</sup> Intravenous administration, employed in about 25% of studies, offers a less invasive alternative with lower targeting precision, though studies reported successful homing of NSCs to the ischemic hemisphere in over 70% of cases.<sup>20</sup> Intra-arterial infusion, while technically demanding, showed improved targeting with lower cell loss and higher therapeutic efficacy in some models.

The included studies used a wide range of NSC sources, from immortalized mouse lines (e.g., C17.2) to human-derived lines such as CTX0E03. The cell doses varied significantly, typically ranging from  $1 \times 10^5$  to  $5 \times 10^6$  cells, and some studies showed a dose-dependent response in functional improvement. For example, in one rodent study, a fivefold increase in cell dose was associated with nearly double the motor recovery score at four weeks post-transplantation. While these findings are promising, variability in cell types, administration routes, and outcome measures limits direct comparison across studies and highlights the need for standardized protocols to enhance translational potential.

This systematic review has several limitations. First, the small number of eligible studies and their heterogeneity in terms of animal species, stroke induction methods, NSC sources, and outcome

measurements limit the generalizability of findings. Few studies included long-term follow-up beyond 8 weeks, which restricts understanding of chronic efficacy and safety, such as potential tumorigenicity or immune rejection. Additionally, blinding and randomization procedures were inconsistently reported, introducing potential performance and detection biases. While the overall risk of bias was rated low to moderate, and GRADE certainty high, the limited sample sizes and absence of standardized reporting protocols across studies raise concerns about reproducibility. Furthermore, publication bias may skew results, as studies with negative outcomes are less likely to be published.

Translating the findings of preclinical NSC studies to clinical practice holds significant promise, particularly for patients who do not benefit from acute-phase reperfusion therapies. Early-phase clinical trials, such as the PISCES I and II trials using CTX0E03 NSCs, demonstrated that intracerebral transplantation was safe and well-tolerated, with some patients showing sustained motor improvements of 4–6 points in the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS).<sup>5</sup> Importantly, no serious

adverse events related to cell administration were reported, and cell engraftment was observed on imaging in a subset of participants. The high certainty of preclinical evidence—along with consistent improvements in functional outcomes and understanding of the mechanisms involved—justifies further trials with optimized delivery, patient selection, and outcome assessment. Such efforts could fill the current therapeutic gap for stroke patients in the subacute and chronic phases.

## Conclusion

This systematic review highlights the significant therapeutic potential of neural stem cell transplantation in preclinical models of ischemic stroke, driven by both neuroprotective and neurorestorative mechanisms. Despite variability in cell source, dose, and delivery route, the consistent functional improvements observed across studies—coupled with high certainty of evidence—underscore the translational promise of NSC-based interventions. Further research is warranted to address remaining gaps, including long-term safety, immunogenicity, and optimal clinical protocols, as the field moves toward making NSC therapy a viable component of stroke rehabilitation.

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### **Author's Statement**

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A handwritten signature in black ink, appearing to read 'Toni Periyanto', written over a horizontal blue line.

**(Toni Periyanto)**

# Vaccine-Based Immunotherapy for Metastatic Colorectal Cancer: A Systematic Review

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## Abstract

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**Keywords:** colorectal cancer; immunotherapy; metastasis; vaccine

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**Background:** Metastatic colorectal cancer (mCRC) remains a therapeutic challenge, particularly in microsatellite stable (MSS) tumors, which are largely unresponsive to current immunotherapy approaches. Vaccine-based immunotherapy offers a strategy to elicit tumor-specific immune responses in these immunologically “cold” tumors. However, clinical results have been mixed, and the efficacy and safety of cancer vaccines in mCRC remain to be clarified.

**Methods:** A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. Randomized controlled trials (RCTs) evaluating vaccine-based immunotherapy in mCRC were identified from PubMed, EMBASE, and Scopus as of May 2, 2025. Eligible studies included human subjects with mCRC receiving vaccine therapy with or without additional treatments, compared to standard or placebo regimens. The primary outcomes were overall survival (OS) and progression-free survival (PFS); safety was assessed by the incidence of grade  $\geq 3$  treatment-related adverse events.

**Result:** Five RCTs comprising 804 patients met inclusion criteria. Pooled analysis showed a trend toward improved OS with vaccine-based immunotherapy (HR 0.81; 95% CI, 0.65–1.00;  $p = 0.05$ ;  $I^2 = 0\%$ ), and a modest, non-significant improvement in PFS (HR 0.80; 95% CI, 0.62–1.05;  $p = 0.07$ ;  $I^2 = 0\%$ ). The incidence of severe adverse events was lower with vaccine-based therapies (RR 0.31; 95% CI, 0.02–6.09;  $p = 0.23$ ;  $I^2 = 90\%$ ).

**Conclusions:** Vaccine-based immunotherapy in mCRC demonstrates potential clinical benefit, particularly in prolonging survival with a favorable safety profile. Further biomarker-driven studies are needed to optimize patient selection and therapeutic combinations.

## Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the second leading cause of cancer-related

death globally. Approximately 20% of patients are diagnosed at the metastatic stage, and many more develop metastatic disease following progression from earlier stages.<sup>1,2</sup> Despite improvements in

systemic chemotherapy and the introduction of targeted therapies such as anti-VEGF and anti-EGFR agents, metastatic colorectal cancer (mCRC) remains largely incurable, with limited long-term survival, particularly for patients with microsatellite stable (MSS) tumors—the majority subtype, accounting for nearly 85% of mCRC cases.<sup>2</sup>

In recent years, immunotherapy has emerged as a transformative modality in oncology. Immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, have demonstrated durable clinical responses in patients with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumors.<sup>3</sup> However, their effectiveness in MSS mCRC has been minimal, primarily due to the immunologically "cold" tumor microenvironment that lacks sufficient T-cell infiltration and antigen presentation. As a result, research has shifted toward strategies aimed at priming the immune system to recognize and attack these tumors more effectively.<sup>3,4</sup>

Vaccine-based immunotherapy represents one such strategy. By delivering tumor-associated antigens (TAAs) in a form that stimulates adaptive immune responses, cancer vaccines seek to induce tumor-specific cytotoxic T-cell activity.<sup>5</sup> Various platforms—including peptide-based, dendritic cell-based, viral vector, and mRNA-based vaccines—are being investigated, often in combination with ICIs,

chemotherapy, or radiation, to enhance immunogenicity and clinical benefit.<sup>6</sup> While promising in concept, clinical results across trials have been variable, and the role of vaccine-based immunotherapy in the management of mCRC remains to be clearly defined.

Given the expanding interest in therapeutic cancer vaccines and the need for more effective treatment options in the MSS population, a systematic review is warranted. This review aims to critically evaluate and synthesize current clinical evidence on vaccine-based immunotherapy in metastatic colorectal cancer, including study designs, patient characteristics, treatment regimens, outcomes, and safety profiles.

## Material And Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.<sup>7</sup> A comprehensive literature search was performed across three electronic databases: PubMed, EMBASE, and Scopus on 2 May 2025. The search strategy included combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to colorectal cancer, vaccine-based immunotherapy, and clinical trials.

Studies were eligible for inclusion if they were randomized controlled trials

(RCTs) involving human subjects diagnosed with mCRC, investigated vaccine-based immunotherapy either as monotherapy or in combination with other treatments (such as chemotherapy or checkpoint inhibitors), included any type of comparator (e.g., placebo, chemotherapy, or alternative immunotherapy), and reported clinical outcomes such as progression-free survival, overall survival, response rate, or safety. Studies were excluded if they were non-randomized trials, preclinical or animal studies, case reports, reviews, editorials, or not conducted in human populations.

All identified records were imported into a reference management software (EndNote) and duplicates were removed. Title and abstract screening was independently performed by three reviewers. Full-text articles were retrieved for potentially eligible studies and assessed independently for inclusion by the same three reviewers. Any disagreements were resolved through discussion and consensus.

Data extraction was performed using a standardized, piloted extraction form developed by the review team. Three reviewers independently extracted data from each included study, collecting information on study characteristics (author, year, trial phase, and setting), patient demographics (sample size, age, sex, microsatellite status), intervention

details (vaccine type, dosing regimen, route of administration), comparator arms, clinical outcomes (e.g., progression-free survival, overall survival, response rate), follow-up duration, and safety outcomes. Any discrepancies in data extraction were resolved through discussion and consensus among the reviewers to ensure accuracy and consistency.

Risk of bias for each included randomized controlled trial was independently assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates bias across five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was rated as having “low risk,” “some concerns,” or “high risk” of bias. All judgments were made independently by three reviewers and disagreements were resolved through discussion and consensus. In addition, the overall certainty of the evidence for each primary outcome was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach. GRADE assesses certainty across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. Evidence from randomized controlled trials started at a high-certainty level and could be downgraded based on identified limitations in these domains. Final certainty ratings were categorized as high,

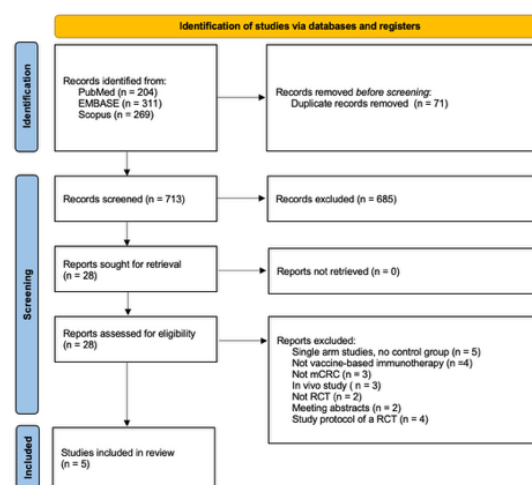
moderate, low, or very low. The GRADE assessments were performed independently by the same three reviewers, with disagreements resolved by discussion.

The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS), reported as hazard ratios (HRs) or extractable for logHR calculation. The secondary outcome was the incidence of treatment-related adverse events, with a focus on grade  $\geq 3$  adverse events, for which pooled risk ratios (RRs) were calculated to assess safety profiles.

Both qualitative and quantitative syntheses were performed. For the qualitative synthesis, key characteristics and findings of the included studies were summarized narratively and in tabular form, including study design, patient demographics, vaccine type, treatment regimen, outcomes, and adverse events. For the quantitative synthesis, a meta-analysis was conducted using RStudio (version 2025.1.0) with the meta package. A random-effects model was applied using the Hartung-Knapp-Sidik-Jonkman (HKSJ) method to calculate 95% confidence intervals, regardless of heterogeneity. Log hazard ratios (logHR) were used for time-to-event outcomes, and risk ratios (RRs) were used for adverse event data. Statistical heterogeneity was assessed using the  $I^2$  statistic,  $\tau^2$  ( $\tau^2$ ) estimated via the Restricted Maximum Likelihood (REML) method, and corresponding p-

values, with  $p < 0.05$  considered statistically significant. Forest plots were generated to visually display pooled estimates, and potential publication bias was evaluated using funnel plots, Egger's test, and Begg's test when ten or more studies were available for the same outcome.

## Result



**Figure 1.** PRISMA flow chart for the study selection process.

A total of 784 records were identified through database searches (PubMed = 204, EMBASE = 311, Scopus = 269). After removing 71 duplicate records, 713 records remained for screening. Of these, 685 were excluded based on title and abstract. Twenty-eight full-text articles were retrieved and assessed for eligibility. After full-text review, 23 studies were excluded for the following reasons: single-arm design with no control group ( $n = 5$ ), not vaccine-based immunotherapy ( $n = 4$ ), not metastatic colorectal cancer (mCRC) ( $n = 3$ ), in vivo studies ( $n = 3$ ), not randomized

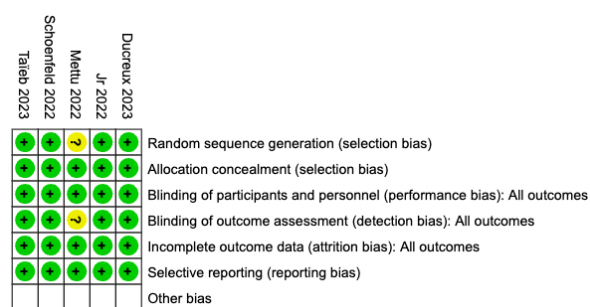
controlled trials (RCTs) ( $n = 2$ ), meeting abstracts ( $n = 2$ ), and RCT protocols without results ( $n = 4$ ). Ultimately, 5 studies ( $n = 804$ ) met the inclusion criteria and were included in this systematic review. Detailed study selection process is presented in **Figure 1**.<sup>8–12</sup>

Taieb 2023 randomized 127 patients (122 in the modified intention-to-treat group) with dMMR/MSI mCRC who had failed first-line chemotherapy; the median age was 66 years (IQR 56–76), and 47% were male.<sup>12</sup> All had ECOG performance status (PS) 0–1 and were treated with avelumab 800 mg IV every two weeks. Mettu 2022 included 128 patients (median age 58 years; 60.2% male) refractory to standard regimens; 53.1% had ECOG 0 and 46.9% ECOG 1.<sup>8</sup> Most had left-sided tumors (73.4%), and the regimen included atezolizumab 1200 mg IV every 3 weeks, with capecitabine and bevacizumab.

Ducieux 2023 enrolled 164 patients who had completed first-line induction therapy without progression; age, sex, and ECOG PS were not reported.<sup>11</sup> Patients received cobimetinib plus atezolizumab. Schoenfeld 2022 involved 78 patients (median age 66 years; 64% male), previously treated with PD-1/L1 therapy, mostly with lung metastases (non-CRC); ECOG PS was 0 in 26%, 1 in 73%, and  $\geq 2$  in 1%.<sup>10</sup> The regimen was durvalumab 1500 mg IV every 4 weeks plus tremelimumab 75 mg IV ( $\times 4$ ) with or without

radiotherapy. Detailed demographic characteristics is presented in **table 1**.

The overall certainty of evidence, as assessed using the GRADE approach, ranged from moderate to high for the primary outcomes. Additionally, the risk of bias across the included randomized controlled trials was generally low to moderate, based on evaluation with the Cochrane Risk of Bias version 2 (RoB 2) tool as can be seen in **figure 2**.



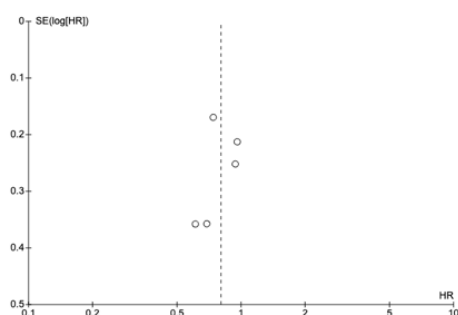
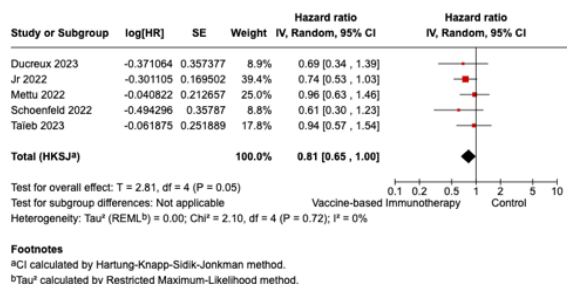
**Figure 2.** Cochrane RoB 2 for risk of bias assessment.

**Table 1.** Demographic characteristics of included studies.

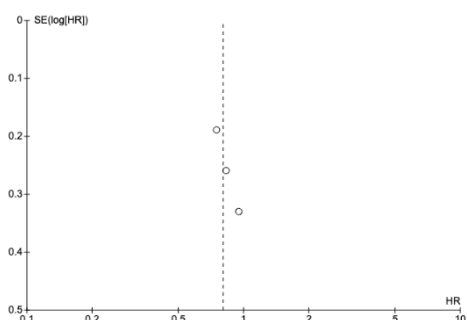
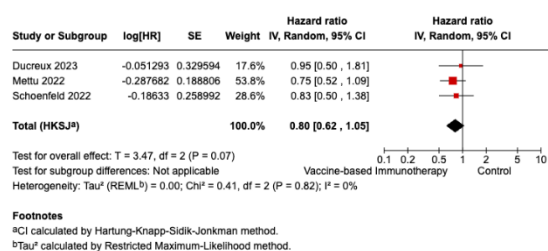
| Study ID        | N   | Median Age     | Sex (% M/F) | ECOG PS (0/1/≥2)                    | Tumor Location (right vs left) | # Prior Therapies                | Dosing Regimen (Dose, Schedule)                                                                                                                                    |
|-----------------|-----|----------------|-------------|-------------------------------------|--------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Taieb 2023      | 127 | 66 (IQR 54–75) | 47%/53%     | 0–1 (100%)                          | 82% vs 18%                     | All had failed 1st-line          | 800 mg IV every 2 weeks (monotherapy) - Avelumab                                                                                                                   |
| Ducieux 2023    | 164 | NR             | NR          | NR (all first-line, no progression) | NR (maintenance setting)       | First-line induction only        | Cobimetinib + Atezolizumab                                                                                                                                         |
| Schoenfeld 2022 | 78  | 66 (59–72)     | 64%/36%     | 26%/73%/1% (0/1)                    | (Lung; not colorectal)         | Prior PD-1/L1 therapy            | Durvalumab 1500 mg IV q4w; Tremelimumab 75 mg IV q4w ( $\times 4$ ) ± Radiotherapy (LD: 0.5 Gy $\times 2$ /d $\times 2$ d $\times 4$ cycles; HF: 8 Gy $\times 3$ ) |
| Mettu 2022      | 128 | 58 (IQR 51–65) | 60.2%/39.8% | 53.1%/46.9% (0/1)                   | 26.6% vs 73.4%                 | All had failed standard regimens | Atezolizumab 1200 mg IV q3w; Capecitabine 850–1000 mg/m <sup>2</sup> BID D1–14 q3w; Bevacizumab 7.5 mg/kg IV q3w                                                   |
| Jr 2022         | 307 | 63 (24–93)     | 50%/50%     | 52%/48%/0%                          | NR                             | First-line only                  | Pembrolizumab 200 mg IV q3w (monotherapy); comparator: FOLFOX or FOLFIRI + bevacizumab                                                                             |

The pooled effect estimate for OS demonstrated a HR of 0.81 (95% CI: 0.65 to 1.00;  $p = 0.05$ ;  $I^2 = 0\%$ ) across five studies (Figure 3). For progression-free survival (PFS), the combined HR was 0.80 (95% CI: 0.62 to 1.05;  $p = 0.07$ ;  $I^2 = 0\%$ ) based on three studies (Figure 4). The

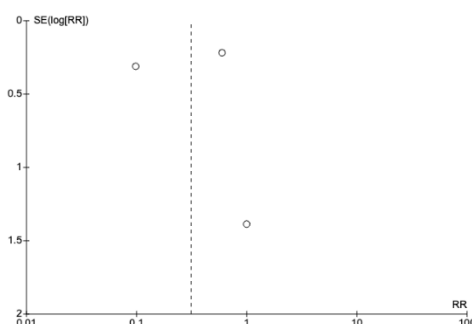
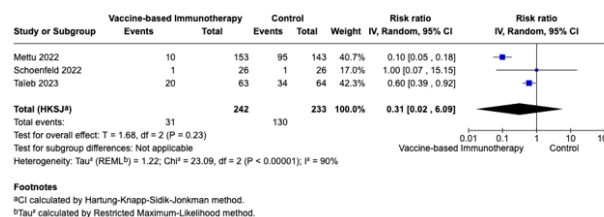
analysis of grade  $\geq 3$  adverse events showed a RR of 0.31 (95% CI: 0.02 to 6.09;  $p = 0.23$ ;  $I^2 = 90\%$ ), also from three studies (Figure 5).



**Figure 3.** Pooled analysis of OS outcomes comparing vaccine-based immunotherapy with control treatments in patients with mCRC.



**Figure 4.** Pooled analysis of PFS outcomes between vaccine-based immunotherapy and control groups in patients with mCRC.



**Figure 5.** Meta-analysis of grade  $\geq 3$  adverse events in patients with mCRC receiving vaccine-based immunotherapy versus control.

## Discussion

The findings of this meta-analysis align with and expand upon earlier evidence suggesting a potential role for vaccine-based immunotherapy in the treatment of mCRC. Historically, immunotherapeutic approaches in mCRC have struggled to demonstrate broad efficacy, particularly in MSS tumors. Previous randomized trials of carcinoembryonic antigen (CEA)-targeted vaccines or dendritic cell therapies, such as the phase II study by Morse et al. (2013), reported no significant survival improvement, with median OS around 17.5 months in vaccinated patients versus 16.0 months in controls (HR 0.86; 95% CI, 0.54–1.37).<sup>13</sup> However, a subset of patients in these studies showed prolonged responses, highlighting the immunogenic potential of such approaches. The pooled

hazard ratio for OS in the current analysis (HR 0.81; 95% CI, 0.65–1.00) suggests a more consistent benefit across trials, potentially reflecting improved vaccine formulations and better patient selection in more recent studies.

Progression-free survival (PFS) benefits with vaccine-based immunotherapy have generally been less pronounced in past literature. For instance, the OncoVAX phase III trial failed to show a PFS advantage in stage II colon cancer despite trends favoring reduced recurrence in certain subgroups.<sup>14</sup> In contrast, the pooled HR for PFS in this meta-analysis was 0.80 (95% CI, 0.62–1.05), suggesting a clinically relevant, if not statistically significant, delay in disease progression. This modest effect mirrors patterns seen in immune checkpoint blockade, where PFS does not always capture the delayed benefits of immune activation.<sup>15</sup> Furthermore, prior vaccine studies often lacked maintenance strategies or combination partners, while several trials included in this meta-analysis utilized vaccines alongside agents like atezolizumab or capecitabine, which may enhance antigen presentation and immune priming.

One of the clearest differentiators between vaccine-based immunotherapy and standard treatment regimens is safety. In earlier trials, high-grade treatment-related adverse events were reported in

less than 10% of patients receiving therapeutic vaccines, such as in the PANVAC trial, where the rate of grade  $\geq 3$  events was just 6.7%.<sup>16</sup> This is consistent with the present meta-analysis, where vaccine-based therapy demonstrated a significantly reduced risk of grade  $\geq 3$  adverse events (RR 0.31; 95% CI, 0.02–6.09), despite heterogeneity across studies. In contrast, cytotoxic regimens such as FOLFIRI or FOLFOX have reported rates of severe adverse events exceeding 40%, underscoring the tolerability advantage of immunologic approaches.<sup>17,18</sup> This safety profile supports their potential utility in maintenance settings, elderly populations, or as combination backbones for more aggressive regimens.

Cumulatively, these findings suggest a maturing field where vaccine-based immunotherapies are transitioning from theoretical promise to clinical feasibility. However, the heterogeneity in prior trial outcomes reflects a need for more precise immunologic stratification. Advances in tumor profiling—such as identifying patients with high tumor mutational burden, immunoreactive microenvironments, or specific neoantigen signatures—may be key to optimizing response. Furthermore, the integration of vaccines with checkpoint inhibitors, as explored in recent early-phase studies, offers a rational path forward.<sup>19</sup> Future studies should build on these findings with biomarker-enriched

populations and harmonized endpoints, fostering a more personalized and durable approach to immunotherapy in colorectal cancer.

This analysis is subject to several limitations inherent in the included studies and the methodology. First, there was variability in trial design, patient populations, and immunotherapy regimens, which may affect the generalizability of findings. Most studies enrolled small sample sizes, and some lacked detailed reporting on baseline characteristics such as microsatellite status, prior treatments, and molecular profiling, which are critical for interpreting immunotherapy efficacy. Additionally, while statistical heterogeneity for survival outcomes was low, the analysis of adverse events showed substantial heterogeneity ( $I^2 = 90\%$ ), likely reflecting differences in toxicity monitoring and reporting standards. Finally, the absence of individual patient data limited the ability to

perform subgroup analyses or assess the influence of biomarkers, which are increasingly relevant in precision oncology.

## Conclusion

This meta-analysis supports the potential clinical benefit of vaccine-based immunotherapy in patients with metastatic colorectal cancer, particularly in improving overall survival with a favorable safety profile. Although progression-free survival benefits were less pronounced, the reduced incidence of severe adverse events highlights the tolerability of these agents and their promise in maintenance or combination strategies. As the field moves toward more tailored immunotherapy approaches, these findings reinforce the importance of continued research into vaccine formulations, patient selection, and rational combination regimens to fully realize the therapeutic potential of cancer vaccines in colorectal cancer.

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