Sonothrombolysis for novel adjuvant therapy in ST-Elevation myocardial infarction: A Systematic Review

Muhammad Isra Rafidin Rayyan¹, Ichlasul Mahdi Fardhani¹, Hammam Arif Shabri¹*

ABSTRACT

Introduction: Current standard ST-segment elevation myocardial infarction (STEMI) treatments, such as percutaneous coronary intervention (PCI) and thrombolytic agent administration, still have some limitations. Sonothrombolysis is a new therapeutic modality that utilizes ultrasound energy to break up thrombus and is currently considered a promising alternative therapeutic strategy to treat STEMI. This systematic review aims to further review the clinical application of sonothrombolysis as an adjuvant therapy modality in STEMI based on the evidence available in the last ten years.

Main Text: We systematically searched studies on PubMed, Cochrane Library, and ScienceDirect databases. After removing duplicates and screening studies based on inclusion and exclusion criteria, data extraction and critical appraisal were performed by three independent reviewers. Study search and selection resulted in five studies with 614 patients and an additional 273 patients as a reference group. Results showed that patients treated with an intermittent, short pulse, and high mechanical index sonothrombolysis with microbubble infusion had significantly better ST-segment resolution and vessel recanalization rates than the other treatment groups. In addition, there was no significant difference in the safety level among all intervention groups.

Conclusion: Sonothrombolysis is a promising novel therapy that is an adjunct to PCI, which is effective and safe for treating STEMI.

Keywords: Sonothrombolysis, ultrasound, microbubble, STEMI

1. Medical Program, Faculty of Medicine, University of Jember, Jember, Indonesia

* Email: hammam.shabri15@gmail.com
INTRODUCTION

Acute myocardial infarction (AMI) remains one of the leading causes of death in developed countries, with an annual incidence of three million cases worldwide. Most AMI events are associated with atherosclerotic plaque disruption that can lead to thrombosis and acute coronary artery blood flow deterioration (Hajar, 2017; Mechanic et al., 2021). Generally, AMI is divided into two disease spectrums: non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) (Mechanic et al., 2021; Ojha and Dhamoon, 2021). Between the two, STEMI accounts for about 25-40% of all AMI cases (O’Gara et al., 2013). Nevertheless, STEMI is the main indicator of total occlusion of one or more coronary arteries that can cause necrosis of myocardial cells (Akbar et al., 2021).

According to the European Society of Cardiology guidelines, immediate reperfusion therapy with primary percutaneous coronary intervention (PCI) is the most effective way to limit myocardial ischemia, reduce infarct size, and thus reduce the risk of complications after STEMI. If primary PCI cannot be performed within 120 minutes of diagnosis, thrombolysis therapy should be completed within 10 minutes. Despite the therapeutic benefits, thrombolytic agents are still associated with side effects, such as bleeding, hypotension, and gastrointestinal problems (Ibanez et al., 2018; Vogel et al., 2019). The mortality rate due to STEMI is still relatively high, especially in developing countries, which is influenced by various factors, including advanced age, delay in treatment, number of blocked coronary arteries, contraindications to therapy, and comorbid conditions (Jayaraj et al., 2018; Vogel et al., 2019). Based on these limitations, it is necessary to develop new adjuvant therapy strategies that are safer and more effective in treating STEMI patients.

One of the new adjuvant therapies that have the potential to be used as a diagnostic and therapeutic method of STEMI is sonothrombolysis (Roos et al., 2014). Sonothrombolysis is a novel therapeutic modality that utilizes ultrasound energy to break up thrombus and is currently considered a promising alternative therapeutic strategy for STEMI. The primary mechanism by which it enhances thrombus breakdown is by providing thermal effects that increase enzymatic activity as well as through acoustic cavitation (Bader et al., 2016). Its effectiveness can also be further enhanced by adding microbubbles, a common type of contrast used in ultrasound diagnostic applications. The addition of microbubbles can increase the exposure of the thrombus surface to thrombolytic agents, thereby further accelerating the thrombus breakdown process (Nederhoed et al., 2021).

Several systematic reviews have reviewed the efficacy and safety of sonothrombolysis for other diseases (Bor-Seng-Shu et al., 2012; Li et al., 2020; Nederhoed et al., 2021; Ricci et al., 2012; Roos et al., 2014; Saqqur et al., 2014; Shi et al., 2018; Zafar et al., 2019). However, to date, no systematic review has specifically addressed the application of this therapy for STEMI. Therefore, in this systematic review, we are interested in further investigating the clinical application of sonothrombolysis as an adjunctive therapeutic modality in STEMI based on the available evidence over the past ten years.

MAIN TEXT

We performed systematic reviews following the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines for review reporting (JPT et al., 2019; Page et al., 2021).

1. Medical Program, Faculty of Medicine, University of Jember, Jember, Indonesia

*Email: hammam.shabri15@gmail.com
**Literature search strategy**

The literature search was conducted on three electronic databases, namely Pubmed, ScienceDirect, and Cochrane Library, during January 2022 with the following keywords: (“Sonothrombolysis” OR (“Ultrasonography” AND “Thrombolysis”)) AND (“ST Elevation Myocardial Infarction”), combined with known synonyms and Medical Subject Headings (MeSH) terms.

**Study selection**

All citations identified from the database were then pooled in Mendeley Desktop and Rayyan.ai to remove duplicates (Ouzzani et al., 2016). Subsequently, the remaining articles were screened by three independent reviewers based on title and abstract, with any discrepancies resolved through consensus.

**Inclusion and exclusion criteria**

The inclusion criteria were: 1) study design in the form of a randomized clinical trial (RCT) and cohort; 2) published in the last ten years (2012-2022); 3) English language; 4) population: patients diagnosed with STEMI; 5) intervention: sonothrombolysis as adjunctive therapy before and/or after PCI; 6) comparison: standard care or sonothrombolysis in different settings; and 7) study outcomes: degree of ST-segment resolution, degree of vessel recanalization, improvement in left ventricular function, improvement in microvascular flow, infarct size, and degree of safety or reported adverse events. We excluded studies: 1) conducted on non-humans, review articles, conference abstracts, books, research protocols, case reports, case series, and single-arm studies; as well as 2) articles not accessible in full text.

**Data extraction**

The selected studies were independently extracted using Google Sheets by three independent reviewers. Data extracted included the author’s name and year of publication, study design, study location, sample size, interventions given to each group, age, and a summary of the main findings from each study.

**Risk of bias and study quality assessment**

Risk-of-bias assessment for randomized clinical trials was conducted using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2), and observational studies was assessed with the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies by three independent reviewers and any discrepancies were resolved through consensus (NHLBI, 2021; Sterne et al., 2019).

**Study Selection and Characteristics**

We retrieved 792 articles during the initial search in various databases. After title and abstract screening, 21 articles were available for full-text screening. We excluded 16 articles and left five that met the inclusion criteria for qualitative synthesis (Mathias et al., 2019, 2016; Niu et al., 2020; Slikkerveer et al., 2012; Tavares et al., 2016). A flowchart of study selection can be seen in Figure 1. This review included results from four RCTs and one retrospective cohort study conducted in three countries (Brazil, China, and Netherlands) with a total of 614 patients and an additional 273 patients in the reference group. Of the four RCT studies we included, three (75%)
were pilot studies, indicating that they were in the early stages of clinical trials. The sonothrombolysis intervention was delivered in the included studies using a transthoracic ultrasound probe with varied settings. Only one study by Slikkerveer et al. reported using an additional thrombolytic agent as an alteplase before PCI (Slikkerveer et al., 2012). A summary of all included studies can be seen in Table 1.

![Figure 1. PRISMA flow diagram](image)

**Risk of bias and study quality assessment results**

A summary of the risk of bias and study quality assessment results can be seen in Table 2 and Figure 2. Overall, two RCT studies rated as having a low risk of bias (Slikkerveer et al., 2012; Tavares et al., 2016), two rated as having some concerns (Mathias et al., 2019, 2016), and one retrospective cohort study with fair quality (Niu et al., 2020).

![Figure 2. Risk of bias assessment summary](image)
Table 1. Characteristics and main findings of the included studies

<table>
<thead>
<tr>
<th>No</th>
<th>Author(s), Year</th>
<th>Study Design</th>
<th>Study Location</th>
<th>Intervention Given</th>
<th>Sample Size</th>
<th>Age (Years)</th>
<th>Main Findings</th>
<th>Effects of Therapy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Niu et al., 2020</td>
<td>Retrospective cohort</td>
<td>China</td>
<td><strong>HMI + PCI:</strong> frequency 1.8 MHz, MI 1.1 - 1.3, pulse duration 3 µs intermittently every 10 - 20 s with perflutren (Optison®) microbubble 0.5 ml</td>
<td>251</td>
<td>54.71 ± 3.15</td>
<td>Lower number of obstructed vessels in the HMI + PCI group at 48 hours (p = 0.015) and 1 month after therapy (p = 0.043)</td>
<td>No significant difference in heart rate (p = 0.133) and oxygen saturation (p = 0.079)</td>
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<td></td>
<td><strong>LMI + PCI:</strong> frequency 1.8 MHz, MI 0.18, and frame rate 25 Hz for diagnostic purposes</td>
<td>199</td>
<td>54.12 ± 3.45</td>
<td>Higher percentage of ST-segment resolution in the HMI + PCI group at 48 hours before hospital discharge (p &lt; 0.0001) and one-month post-therapy (p &lt; 0.0001)</td>
<td>Higher LVEF in the HMI + PCI group at 48 hours before hospital discharge (p = 0.003) and 1 month post-therapy (p &lt; 0.0001)</td>
<td>Lower number of MVOs in the HMI + PCI group at 48 hours before hospital discharge (p = 0.045) and 1 month post-therapy (p = 0.049)</td>
</tr>
<tr>
<td>2</td>
<td>Mathias et al., 2019</td>
<td>RCT</td>
<td>Brazil</td>
<td><strong>HMI + PCI:</strong> frequency 1.8 MHz, MI 1.1 - 1.3, pulse duration &lt; 5 µs intermittently with 3 ml perflutren (Definity®) microbubble, therapy given before and after PCI for (median = 50 min)</td>
<td>50</td>
<td>59 ± 10</td>
<td>Higher proportion of patients with ST-segment resolution ≥ 50% in the HMI + PCI group before PCI (p &lt; 0.001) and after PCI (p = 0.011)</td>
<td>Not reported</td>
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<td></td>
<td><strong>LMI + PCI:</strong> MI &lt; 0.2 for diagnostic purposes</td>
<td>50</td>
<td>59 ± 11</td>
<td>Higher proportion of patients with vessel recanalization before PCI in the HMI + PCI group (p &lt; 0.001)</td>
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1. Medical Program, Faculty of Medicine, University of Jember, Jember, Indonesia

* Email: hammam.shabri15@gmail.com

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<table>
<thead>
<tr>
<th>No</th>
<th>Author(s), Year</th>
<th>Study Design</th>
<th>Study Location</th>
<th>Intervention Given</th>
<th>Sample Size</th>
<th>Age (Years)</th>
<th>Main Findings</th>
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<td></td>
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<td><strong>Reference group:</strong> standard care for STEMI patients without ultrasound intervention</td>
<td>203</td>
<td>59 ± 11</td>
<td><a href="https://doi.org/10.24815/jks.v23i2.32232">Effects of Therapy</a></td>
</tr>
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<td><strong>LMI + PCI:</strong> MI &lt; 0.2 with 25 Hz frame rate for imaging and 3% Definity® microbubble</td>
<td>9</td>
<td></td>
<td><strong>Safety</strong></td>
</tr>
<tr>
<td>3</td>
<td>Tavares et al., 2016</td>
<td>RCT (pilot study)</td>
<td>Brazil</td>
<td><strong>Long pulse HMI + PCI:</strong> frequency 1.7 MHz, MI &gt; 1, pulse duration 4 - 20 µs with 3% Definity® microbubble, for 50-60 minutes</td>
<td>7</td>
<td>58 ± 9</td>
<td>Higher proportion of patients with TIMI 3 flow grade in the therapy group (p = 0.02)</td>
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<td><strong>Short pulse HMI + PCI:</strong> frequency 1.7 MHz, MI &gt; 1, multiple impulse with pulse duration 2 µs, and 3% Definity® microbubble, for 50-60 minutes</td>
<td>8</td>
<td></td>
<td>Smaller infarct size in the HMI + PCI group at 48-72 hours after PCI (p = 0.026)</td>
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<td><strong>Safety</strong></td>
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<td>No significant difference in the MVO rate of the two groups (p = 0.095). However, there was a trend of ↓ MVO in LAD artery STEMI patients from the HMI + PCI group (p = 0.05)</td>
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<td>Higher LVEF in the HMI + PCI group after PCI (p = 0.032), 1 month (p = 0.018), and 6 months (p = 0.015)</td>
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<td>The proportion of patients with vessel recanalization before PCI was higher in the short pulse HMI + PCI group compared to the long pulse group: HMI + PCI and control group (p &lt; 0.05)</td>
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<tr>
<td>No</td>
<td>Author(s), Year</td>
<td>Study Design</td>
<td>Study Location</td>
<td>Intervention Given</td>
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<td>Main Findings</td>
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<td>4</td>
<td>Mathias et al., 2016</td>
<td>RCT (pilot study)</td>
<td>Brazil</td>
<td><strong>Long pulse HMI + PCI (1):</strong> frequency 1.3 MHz, MI 1.3, frame rate 10 Hz, pulse duration 5 μs, intermittently every 5 - 15 s with Definity® 5% microbubble, for 12 ± 10 min before PCI and 30 min after PCI</td>
<td>10</td>
<td>59 ± 10</td>
<td>Higher proportion of patients with ST-segment resolution ≥ 20% before PCI in the HMI + PCI group compared to the LMI + PCI group (p = 0.03) Higher proportion of patients with TIMI flow grade 2 or 3 before PCI in the HMI + PCI group compared to the LMI + PCI and reference groups (p = 0.002) There was no significant difference in the proportion of patients with TIMI flow grade 2 or 3 among all groups after PCI (p &gt; 1.0) No significant difference in the number of segments experiencing MVO of both groups before PCI (p=0.11) After PCI, the proportion of segments still showing MVO was significantly lower in the HMI + PCI group compared to the LMI + PCI group (p = 0.01)</td>
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<td><strong>Long pulse HMI + PCI (2):</strong> frequency 1.8 MHz, MI 1.3, frame rate 5 Hz, pulse duration 20 μs, intermittently every 5 - 15 s with Definity® 5% microbubble, for 20 ± 8 min before PCI and 30 min after PCI</td>
<td>5</td>
<td></td>
<td>No differences in blood pressure, heart rate, or oxygen saturation parameters before and after PCI among all groups.</td>
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<td><strong>Short pulse HMI + PCI:</strong> frequency 1.8 MHz, MI 1.1 - 1.3, frame rate 25 Hz, pulse duration 3 μs, intermittently every 5 - 15 s with Definity® 5% microbubble, for 19 ± 14 min before PCI and 30 min after PCI</td>
<td>5</td>
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<td></td>
<td><strong>LMI + PCI:</strong> frequency 1.8 MHz, MI 0.18, frame rate 25 Hz, pulse duration 3 μs for diagnostic purposes, for &lt; 2 minutes</td>
<td>10</td>
<td></td>
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<tr>
<td>No</td>
<td>Author(s), Year</td>
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<td>Study Location</td>
<td>Intervention Given</td>
<td>Sample Size</td>
<td>Age (Years)</td>
<td>Main Findings</td>
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<td></td>
<td>Slikkerveer et al., 2012</td>
<td>RCT (pilot study)</td>
<td>Netherlands</td>
<td><strong>HMI + PCI:</strong> frequency 1.6 MHz, MI 1.18, frame rate about 28 Hz, pulse duration 1.25 μs intermittently every 5 s (5 s on - 5 s off) with 1.5 ml Luminity® microbubble and peak smoothing pressure 1.5 MPa and mean intensity at maximum MI 26 mW/cm² + alteplase single bolus 50 mg, therapy was given for 15 min before PCI</td>
<td>5</td>
<td>66 ± 5</td>
<td>No patients had ST-segment resolution ≥ 50% before PCI. However, ST-segment resolution ≥ 50% 60-90 minutes after PCI was obtained in patients of the HMI + PCI group compared with the control group (5/5 vs. 3/5; p = 0.11). A higher proportion of patients with TIMI flow grade 3 in the HMI + PCI group before PCI (3/5 vs. 1/5; p = 0.23) and after PCI (5/5 vs. 4/5; p = 0.29) compared to controls</td>
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<td></td>
<td>Control group: alteplase single bolus 50 mg + PCI</td>
<td>5</td>
<td>65 ± 11</td>
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</tbody>
</table>

**RCT:** randomized clinical trial; **MI:** mechanical index; **HMI:** high mechanical index; **LMI:** low mechanical index; **PCI:** percutaneous coronary intervention; **LVEF:** left ventricular ejection fraction; **MVO:** microvascular obstruction; **STEMI:** ST-elevation myocardial infarction; **LAD:** left anterior descending; **TIMI:** thrombolysis in myocardial infarction; **CK:** creatine kinase; **CK-MB:** creatine kinase-myocardial band
Table 2. Quality assessment of cohort studies with the NHLBI quality assessment tool for observational cohort and cross-sectional studies

<table>
<thead>
<tr>
<th>Author(s), Year</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niu et al., 2020</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>10/14 (Fair)</td>
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<tr>
<td>NA</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>NR</td>
<td>NR</td>
<td>Y</td>
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</table>

Study quality was rated as **Poor** if 0 - 4/14 questions answered "yes", **Fair** (5 - 10/14 questions answered "yes"), or **Good** (11 - 14/14 questions answered "yes"); **CD**: cannot determine; **NA**: not applicable; **NR**: not reported

**Discussion**

In this systematic review, we summarized evidence from four RCTs and one retrospective cohort (involving 887 participants) from 792 studies initially identified in various databases, which considered STEMI treatment with transthoracic sonothrombolysis. Our findings showed that four of the five studies we included reported statistically significant positive outcomes assessed by the degree of ST-segment resolution (Mathias et al., 2019, 2016; Niu et al., 2020), vessel recanalization (Mathias et al., 2019, 2016; Niu et al., 2020; Tavares et al., 2016), LVEF (Mathias et al., 2019; Niu et al., 2020), and MVO (Mathias et al., 2016; Niu et al., 2020). In addition, three of the five studies we included also reported no significant difference in safety parameters between intervention groups (Mathias et al., 2016; Niu et al., 2020; Slikkerveer et al., 2012). Only one study by Slikkerveer et al. showed no significant differences across the evaluated outcomes. This may be due to the lack of sample size and the use of additional thrombolytic agents in that study (Slikkerveer et al., 2012). All of the included studies reported the use of microbubbles in addition to ultrasound. Based on our review, we can also conclude that the use of ultrasound with frequency (1.3 - 1.8 MHz), high mechanical index (1.1 - 1.3), and short pulse duration (< 5 µs) intermittently provides superior therapeutic effects compared to other settings.

Sonothrombolysis is a therapeutic modality that utilizes ultrasound energy to break up a thrombus. This therapy can break the thrombus through three mechanisms, namely thermal effect, primary mechanical effect, and secondary mechanical effect. First, the thermal effect generated by ultrasound can increase the ambient temperature around the thrombus, increasing enzymatic activity and accelerating the thrombolysis process (Bader et al., 2016). Second, the primary mechanical effect, which is by initiating acoustic flow that, can then help thrombolytic agents to penetrate the blood clot. Third, the secondary mechanical effect (acoustic cavitation) refers to the ability of ultrasound to form air bubbles and, when ruptured, can generate energy that can destroy the thrombus (Goel and Jiang, 2020; Porter and Mathias, 2019; Xin et al., 2016).

In addition, the mechanical effect generated by ultrasound can be enhanced by adding microbubbles. Microbubbles can increase the amount of cavitation by lowering the threshold required to create cavitation. In this case, the power generated by ultrasound not only causes microbubble rupture but also serves as a driving force for the microbubble acting on the thrombus surface. Therefore, one of the advantages of using sonothrombolysis is that it can eliminate or significantly reduce the need for thrombolytic agents to break up the thrombus, thereby reducing the risk of bleeding due to the use of such agents (Goel and Jiang, 2020; Guan et al., 2020).

Our review differs from previous reviews as it included all studies with RCT and cohort designs. The previous systematic review by Roos et al., published in 2014, had only three RCT studies and three clinical trials without randomization. In addition, the previous
researchers also evaluated the effects of sonothrombolysis in acute ischemic stroke as part of their review. Another major difference in our review is the addition of microbubbles in all included studies, whereas the previous review included only one study reporting the use of microbubbles for the treatment of STEMI (Roos et al., 2014).

The main strengths of this review include the research methodology, comprehensive eligibility criteria, and strict adherence to the review reporting based on PRISMA 2020. This review also has some limitations that need to be considered. A limited number of studies met the inclusion criteria, and most of the studies included fairly small sample sizes (n < 100). There was considerable variation in follow-up periods, and not all studies reported on the safety and duration of intervention given. Three of the four RCTs we included were pilot studies indicating the need for further research on this topic, and we still advise readers to be cautious in interpreting our findings.

CONCLUSION
This systematic review demonstrates that sonothrombolysis with microbubble infusion as adjuvant therapy may provide promising results for STEMI patients, especially for those with contraindications to thrombolytic agents. This therapy had no safety concerns based on the three studies we included. As most of the studies we included were pilot studies, not all studies reported the safety and duration of therapy, and only a small number of studies met the inclusion criteria; further studies with larger samples on a multi-center scale are needed to verify our findings.

ACKNOWLEDGEMENTS
All praise is due to Allah Subhanahu wa Ta’ala, by whose mercy and grace we were able to complete this review. Also, we would like to thank the Faculty of Medicine, University of Jember, and all those who supported the writing of this review.

REFERENCES


