


BMJ Open Update on Noma: systematic review on classification, outcomes and follow-up of patients undergoing reconstructive surgery after Noma disease

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ABSTRACT

Introduction Noma is a significant yet neglected disease which affects some of the least developed countries in the world. The long-term benefit and safety of Noma surgical reconstructive missions have recently been under scrutiny due to a perceived lack of measurable outcomes and appropriate follow-up. This study analyses and reports on classifications, outcome measurement tools and follow-up for reconstructive surgery after Noma disease.

Methods This systematic review was undertaken following Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. The three medical databases Medline, EMBASE and Web of Sciences were searched, articles published between 1 January 1983 and 15 April 2020 were included. All primary evidence on reconstructive surgery following Noma disease, reporting data on outcome after surgery, follow-up time and complications were included. Extracted data were aggregated to generate overall and population corrected mean outcomes and complication rates.

Results Out of 1393 identified records, 31 studies including 1110 Noma patients were analysed. NOITULP and Montandon/WHO were the most commonly used classification systems. Mouth opening (MO) and complication rates were the two most often reported outcomes. Overall mean complication rate was 44%, reported by 24 studies. Postoperative MO was reported by eight publications, of which, five reported long-term outcomes (>12 months). Mean MO improved by 20 mm when compared with mean population weighted preoperative MO (7 mm). At long-term follow-up, MO decreased to 20 mm.

Conclusions Studies reporting on neglected diseases in developing countries often lack methodological rigour. Surgeons should be mindful during patient examination by using a classification system that allows to compare preoperative versus postoperative state of disease. Short-term mission surgery is a vital part of healthcare delivery to underdeveloped and poor regions. Future missions should aim at sustainable partnerships with local healthcare providers to ensure postoperative care and long-term patient-oriented follow-up. A shift towards a diagonal treatment delivery approach, whereby local surgeons and healthcare staff are educated and empowered, should be actively promoted.

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Strengths and limitations of this study

- Our statistical approach (qualitative synthesis) allowed us to compare different outcome measurement methods and give a recommendation for use of classification systems.
- Evidence on surgical methods, outcome and follow-up after Noma disease is scarce and of low quality, which limits the strength of this systematic review.
- The majority of the studies included in this systematic review were case series, which are considered low-quality evidence and therefore limit the generalisability of the results.
- The publications we found represent only a small part of reconstructive surgical missions conducted for Noma disease, which could lead to potential bias of the results.
- Substantial heterogeneity between studies, including differences in outcome measurement and follow-up, limited our ability to draw clear conclusions about how safe reconstructive missions for Noma surgery are.

INTRODUCTION

Noma is a gangrenous ulcerating bacterial disease of multifactorial origin, mostly prevalent in sub-saharan Africa. Due to the high reported mortality rate of up to 85%–90%, and its frequent occurrence in regions of extreme poverty, the WHO officially declared Noma a public health problem in 1994.¹ The global incidence is reported as 30 000–140 000 new cases per year.^{1 2} There are currently 210 000 Noma survivors worldwide, according to latest estimates.²

Most cases of Noma occur between the ages of 2–7 years old. Malnutrition, poor oral hygiene and poverty are known etiological factors leading to nutritionally acquired immune deficiency syndrome.^{3 4} Children with this syndrome present with lymphatic atrophy and impaired cellular immune responses, as accompanied by increased

vulnerability to infections.⁵ These preconditions lead to pathogen invasion through the gingival mucosa.^{6,7} After opportunistic infections take hold, progression to Noma disease occurs in several stages, starting with a simple gingivitis and ending in sequelae such as trismus, feeding difficulties and facial disfigurement.¹ Surgical reconstructive missions have become an established method to reduce the impact of diseases like Noma. The long-term patient benefit of these missions has come under scrutiny on multiple occasions, most recently by Hendriks *et al.*⁸

The purpose of this systematic review is to analyse the currently used classification systems and compare methods of outcome assessment. In addition, the safety and patient-benefit of these procedures are analysed through comparison of complication rates and long-term outcomes.

METHODS

A comprehensive, structured literature search of published articles was conducted. This was designed by the authors SS and WR and performed in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).⁹ Methods are described in more detail in the following sections.

Data sources

The literature search was performed using the electronic databases MEDLINE (PubMed), EMBASE and Web of Science, including articles published between 1 January 1983 and 15 April 2020. The keywords used in the search were selected from key papers and can be found in online supplemental material-part A. Search strings 1 and 2 were combined using the Boolean term AND, then the limits were applied. In addition, a 'MeSH term' search was conducted, and the reference lists of included articles were reviewed for any additional articles.

Study eligibility criteria

Articles were eligible for inclusion if they provided primary empirical evidence of patient outcomes after Noma surgery. The full inclusion and exclusion criteria are detailed in online supplemental material-part A. Articles were eligible in German and English language. Study selection was independently assessed by two reviewers (SS and MMB).

Data extraction and analysis

Articles were systematically analysed and data extracted using a structured data collection sheet. This data collection template was pilot tested on two selected articles, before being used to assess all included articles. Data extracted included patient demographics (gender, age, comorbidities), and any outcome measurement tools used.

Methodological quality and assessment of bias

Included studies were assigned a level of evidence based on the Oxford Centre for Evidence Based Medicine.¹⁰ In

addition, studies were rated for methodological quality using the methodological index for non-randomised studies (MINORS) criteria, both tools are explained in detail in online supplemental material-part B.11

Statistical analysis

Data were analysed using IBM SPSS statistics V.24. Descriptive statistics were performed where possible to allow for narrative synthesis. Weighted population mean outcomes were calculated for outcomes of interest.

Meaningful meta-analysis was not possible due to heterogeneous study design and outcome reporting. Averages were represented as a mean and range for normally distributed data and median with IQR for non-normally distributed data. Outcomes were weighted for size of study population, as some studies had larger population sizes and therefore higher weighting.

Patient and public involvement

Neither patients nor the public were involved in this research.

RESULTS

Selection of studies

In total, the systematic literature search identified 1393 records. In addition, 7 records were identified through bibliography review. After excluding duplicates, titles and abstracts of 1113 articles were screened, with 1049 being excluded. Sixty-four studies were fully assessed for eligibility according to the criteria previously established. Thirty-three articles were excluded, 23 of which did not report any outcomes of surgery and 6 had duplicate study populations.

Data were extracted from the 31 included articles. Data extraction was pilot tested on two studies and then performed by two independent reviewers (MMB and SS), using a data extraction sheet designed a priori. The selection process was performed according to the PRISMA flow chart, as seen in online supplemental material-part C.

Details of the studies

In total, data were available for articles published in the period from 1 January 1983 to 15 April 2020. The methodology, diagnostic approach and surgical treatment varied significantly between the studies. In total, published data for 1244 patients from 31 studies were analysed, out of which 1110 patients had reconstructive surgery for Noma disease. In cases of mixed disease populations, estimates were made based on population overall descriptive statistics, dividing the total outcome by Noma population proportions. Patient populations ranged from 2 to 148 patients, with an average of 36 Noma patients enrolled per study. Twenty-nine studies were case series, 4 of them were prospective,¹²⁻¹⁵ 25 were retrospective. Two publications had at least two cohorts,¹⁶⁻¹⁸ two were retrospective

cohort studies and one was a prospectively designed cohort study.¹⁷

The overall quality of the studies was low. Three publications^{16–19} were graded with an evidence level III according to the Oxford CEBM. The remaining 28 studies were retrospective case series graded as level IV. The MINORS criteria¹¹ were used to rate quality of methods of the included studies. The overall MINORS scores ranged from 1 to 8 points, as seen in online supplemental material-part D. Proportional scores were calculated as a percentage of the maximum score of 8 for case series and 12 for cohort studies. Scores ranged from 13% to 75% of the maximum amount of points. The quality level was generally low: more than half of the studies did not even reach 50% of the ideal outcome.

Patient characteristics

Median age for operation was 17 years, reported by 23 studies and ranged from 4.5 to 35.7 years. 584 (53%) female and 424 (38%) male patients were included. For 102 (9%) patients the gender was not known. The median percentage of female population was 56% (43%–65%).

Six studies had a malnutrition rate ranging from 25% to 100%, with an average of over 56% (median (IQR)) (53.5 (25%–81%)) of patients being severely malnourished on study inclusion. No specific details were given on how malnutrition was measured in the included studies. HIV status was stated by six studies, of which five prescreened patients, and only included HIV seronegative patients.^{16 20–23}

Classification systems

The two most common classification systems were the NOITULP, introduced by Marck *et al*¹⁵ and the Montandon/WHO, first described by Montandon *et al*,²⁴ as seen in figure 1.

The NOITULP approach uses the letters N-‘nose’, O-‘outer cheek’, I-‘inner cheek’, T-‘trismus’, U-‘upper lip’, L-‘lower lip’ and P-‘particularities’ to describe the anatomical subunits affected and gives them a rating from 0 to 4, depending on the severity of the defect. Nose, cheek, lip and maxilla/mandible involvement were the most commonly mentioned fields, as seen in figure 2.

Six of the included studies used the Montandon classification to rate disease severity.^{14 25–29} Type I represents a

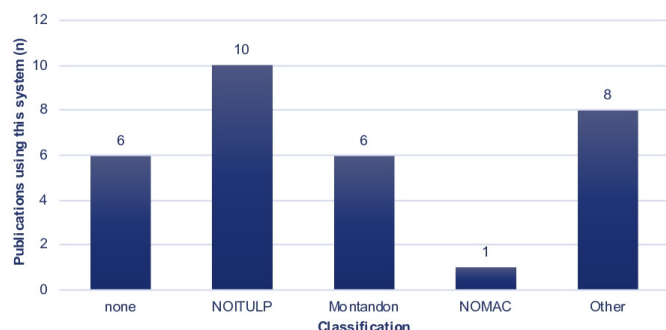


Figure 1 Noma classification systems used 6.

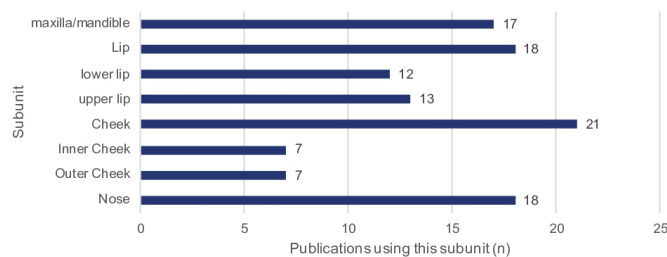


Figure 2 Subunits used for disease classification 6.

localised lip, commissure or cheek defect that normally can be lined by local tissues and covered with a single flap. Type II includes an upper lip and nose amputation. Type III involves a lower lip and mandible amputation, and type IV marks large defects involving the lips, cheek, palate, maxillary bone, orbital floor and other entities.

Montandon classification data were available on 376 patients. Out of these, 147 (39%) patients were classified as Montandon type I, 53 (14%) presented as Montandon type II, 15 (4%) were rated as Montandon type III and 161 (43%) patients had Montandon type IV.

Trismus as a complication of Noma disease was stated by 26 studies. On average, 59.6% (39.2–95.9) of the patient population per study presented with trismus. Trismus was further subdivided into T1–T4 in 257 patients, as seen in figure 3.

The mean preoperative mouth opening (MO) was calculated only for the 257 patients that further divided the trismus classifications into T1–T4. the population weight corrected mean was used as a proxy for comparison where average values were not provided by the original publication. Population weight-corrected median preoperative MO was 7 mm (5–15 mm).

Surgical interventions

Hospital duration ranged from 2 to 140 days, with a mean of 5.5 days. Two hundred and fifty-five patients were treated by local surgeons in six studies (23%) and 855 patients were operated on by mission surgeons in 20 of the studies (77%).

Outcomes and follow-up time

Objective outcomes were further subdivided into two categories, trismus (MO) and complication rate.

Complication rate as outcome

In total, 204 complications were reported in 24 studies. Median complication rate was 24% (13%–53%) per study and ranged between 1% and 200%. The 200% complication rate was seen in a study by Hartman *et al*,³⁰ where six complications occurred in three patients.

The most common short-term complications can be seen in table 1. Long-term complications over 12 months were only stated in two publications. Bisseling *et al*³¹ reported on long-term results of 36 patients undergoing trismus release with mean follow-up of 43 months (12–78). 22% of these patients experienced difficulties eating and 14% had difficulties with speaking. Honeyman *et al*¹⁶

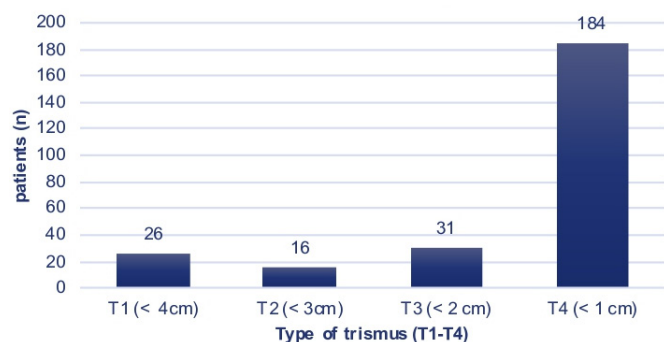


Figure 3 Trismus severity reported preoperatively 6.

reported 15 long-term complications: chronic fistula (n=6), chronic infection (n=3), chronic pain (n=2), keloid scarring (n=2), wound breakdown (n=1), exposed metal work (n=1). In total, 30% of the population (21 patients) experienced long-term complications.

Trismus MO as outcome

Trismus release, stated as a postoperative MO of >3 cm, was achieved in 189 out of 349 patients, reported by 13 publications. Average rate of successful trismus release was 53%. Three publications reported a 100% postoperative trismus release rate.^{23 29 32} Persisting trismus after surgery was reported in eight publications and was present in 83 out of 286 cases (29%).

Mean postoperative MO was reported only by eight publications and ranged from 23 to 35 mm. Population-weighted mean postoperative MO was 27 mm.²⁴⁻²⁷

Mean MO at long-term follow-up was available for five publications and ranged from 10.3 to 35.0 mm. Population-weighted mean MO at long-term follow-up was 20 mm (median (IQR)) (19 (15–21)). **Figure 4** shows population-weighted mean MO preoperatively, postoperatively and at long-term follow-up.

Subjective outcome measures

Subjective postoperative outcomes included cosmetic/aesthetic improvement, reported by three studies, and overall improvement (aesthetic and functional), reported by eight publications. No further details on how improvement was measured was given by the publishers. No information on if this was patient-measured or observer-measured was stated.

Table 1 Most common short-term complications

Complication	Rate n (%)
Infection	37 (18)
Partial flap necrosis	26 (13)
Total flap loss and necrosis	20 (10)
Bleeding/haematoma	12 (6)
Donor site dehiscence	12 (6)
Recurrent fistula	11 (5)
Others	20 (10)

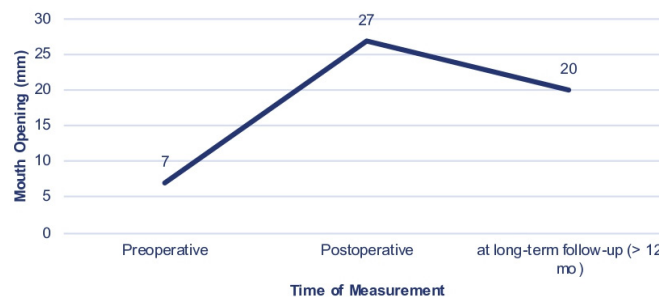


Figure 4 Mouth opening at preoperative, postoperative and long-term follow-up points 7.

Median length of follow-up was reported by only eight publications, which was 24 months (12.7–45) and ranged from 31 days to 324 months (27 years).²⁸ Death was reported in 23 cases (2%).^{25 33} Nath and Jovic reported on 81 patients treated on Noma which were HIV positive in Zambia, out of which 11 patients died during initial medical treatment for infection, and 12 (13.6%) died following minor surgery. No further information on comorbidities or health status of these children was provided. In the study published by Chidzonga and Mahomva, all patients were HIV seropositive. One patient developed severe pneumonia and died before reconstructive surgery, another patient died 1 month after admission, no further detail on the cause of death was given. One-third patient died 1 month after initial soft tissue debridement and sequestrectomy. All patients showed severe facial tissue loss and dentoalveolar necrosis.

Long-term follow-up, which was defined as longer than 12 months, was reported by only six publications (263 patients in total), and mean loss to follow-up was 56%.

DISCUSSION

Noma affects mostly children in the poorest and least developed regions of the world. It causes facial disfigurement and can lead to functional impairment such as loss of oral competency including salivary leakage and trismus. This is the first systematic review specifically analysing the classification, complications and long-term outcomes of Noma surgery, both in local and in mission surgery settings.

Thirty-one studies met the inclusion criteria, with a total of 1110 patients included which had undergone reconstructive surgery for Noma disease. The overall methodological quality of the studies, rated by the MINORS criteria, was poor and reflects similar outcomes of the systematic review on trismus conducted by Bouman *et al.*³⁴ Over half the studies we included reached 50% or less in the MINORS score. Non-randomised studies with high quality are usually rated 83% and higher, according to Slim *et al.*¹¹ Out of the 31 studies included, four of them were prospective, and two of them cohort studies.

The methodological limitations of this study include the low-quality evidence of articles and heterogeneity between studies. This led to the lack of data stratification

towards parameters such as age, first surgery versus revision surgery and type of defect.

Challenges of performing rigorous studies in the developing world include limited resources and the short time frame of 2–3 weeks, which the surgeons typically spend on surgical missions. This can be improved by promoting a system where high-quality research can be provided by local staff with the support of plastic surgeons from more developed countries, advocating an academically profitable partnership, sustainable throughout the year.

Classification systems have been proposed by several authors, the two most commonly used were NOITULP, introduced by Marck *et al*¹⁵ and Montandon/WHO, first described by Montandon *et al*.²⁴

Montandon *et al*²⁴ based their system on two publications by Raynaud *et al*³⁵ and Cariou.³⁶ The approach Montandon suggested was rating the defect based on its severity, taking into account the surgical strategy needed to successfully reconstruct the face.

Marck *et al* found that the previously described classifications lacked in brevity as in conciseness and were not quantifiable in the way NOITULP is.¹⁵ NOITULP covers anatomical subunits and severity of defect, not previously taken into account by any system.

While the Montandon classification has been validated by the WHO in 1994,¹ Noma surgeons are still using both classification systems in parallel. While the Montandon classification is simple and easy to comprehend and apply, it might not fully grasp the disease severity, and it misses one important disease characteristic: trismus. However, the NOITULP classification has a more holistic approach and is more complex in its entirety. The question to be asked is, what do the surgeons want to achieve by using the tool and how can we compare the preoperative to postoperative state of the patients and ideally use it as a control system for disease relapse or progression in trismus patients. In addition, the system must be comprehensible by the surgeon using it, which ultimately shall be a surgeon within the local healthcare system. One suggestion might be to distinguish between a role for a more complex classification to be used predominantly in the research setting, while the other could have a more direct clinical role. In addition, the role of patient-reported outcome measures (PROMs) should be explored with Noma patients for preoperative and postoperative evaluation. If the patient does feel that they have benefited from the operation, this may be more relevant than the surgeons' report or the classification system. Validated questionnaires are one possible way to report patient-reported outcomes.³⁷ They are essential for preoperative and postoperative interviews and evaluation of the patients view on benefit from the operation.

Out of the 31 studies analysed, in only six studies were the operations undertaken by a local surgeon. The majority of operations were undertaken by mission surgeons travelling to the region. This vertical approach to healthcare includes short missions of 2–3 weeks. Unfortunately, these missions are typically characterised

by a higher risk of poor follow-up. They are also often fail to provide a holistic approach to the patient's ongoing treatment after surgery, especially when compared against clinics that include permanent local surgeons and healthcare staff.⁸ This was well reflected in the outcomes and follow-up seen in the 31 publications we analysed. Outcome measurements were inconsistent, and follow-up was incomplete in the majority of publications (81%).

While postoperative complication rates were available for the majority of studies (77%), long-term complications were only reported by two publications. Bisseling *et al*³¹ reported that 22% of patients experienced loss of oral competency and 14% had difficulties with speaking. Honeyman *et al* reported a 30% long-term complication rate. These high long-term complication rates, including severe complications such as loss of oral competency, make the long-term benefit of these short-term missions questionable, as stated previously by Hendriks *et al*.⁸ Reasons for the high complication rates could be lack of postoperative physiotherapy and/or regular follow-up visits. It is therefore important that any surgical missions develop links with the local healthcare system in order to ensure that complications can be managed effectively and to provide training where required for local healthcare workers.

Postoperative MO as an outcome of trismus release was reported by eight studies, and long-term follow-up data were available for five publications. Under-reporting of outcomes and limited follow-up under-reporting of outcomes and lack of follow-up could lead to underestimation or overestimation of benefits to the patients. Nevertheless, population-corrected mean postoperative MO at long-term follow-up (>12 months) was 20 mm, which represents a 13 mm increase compared with the preoperative mean. It is worth mentioning at this point, that there is broad range of ages for the patients included in this review. Whether a 20 mm increase in MO is of any relevance changes based on age as an adult mouth is larger than a young child's mouth. Unfortunately, no further details were given on the ages of the patients measured at long-term follow-up. Also, most cases of Noma occur between the ages of 2 and 7 years old, and the median age of the reconstruction was 17 years (range from 4.5 to 35.7), so the long-term evolution may influence the outcome.

Bisseling *et al*³¹ followed up patients treated in the Noma Childrens Hospital in Sokoto, Nigeria. In this mission hospital, in the majority of patients, contact is lost entirely after discharge and long-term outcome is not known. Therefore, they tried to revisit the patients in their home communities to retrieve patient outcome data. Out of 130 patients documented, only 36 patients were found and included into the study, representing a greater than 70% loss to follow-up rate. Similarly high losses were reported by Pittet *et al*(79%) and Vinzenz *et al*.³⁸ (78%) and slightly less by Dammer *et al* (50%), reflecting the challenges of providing adequate ongoing care in the developing world. Reasons for high lost to



follow-up could be inconsistency in local healthcare provision and lack of infrastructure and long distances that have to be overcome by the parents and the child to reach the local clinics.

Rüegg *et al.*²⁷ lost only 21% of their patients to follow-up, with their patients being treated in Switzerland and repatriated following discharge from hospital. They were followed up by the local healthcare workers of the Swiss charity Sentinelles. They implemented a local complication report and follow-up system, working together with physiotherapists and ensuring local healthcare support and regular controls throughout the year. Whereas it is often not feasible to fly Noma patients to Europe for treatment, their strategy of consistent local care and staff to oversee the postoperative healing process on site helped them stay connected with their patients and ensured their well-being after reintegration.

Transition from a vertical approach, where short-term missions are performed, but no activities throughout the year are supported, to a more diagonal strategy, used for mission surgery in underdeveloped countries, has previously been suggested by Patel *et al.*³⁹ In this model, which was originally developed for cleft lip and palate patients, they combine short-term missions with ongoing measures such as the support of local staff with residency programmes, financial support, research training, academic partnerships and equipment for surgery.

This sustainable treatment strategy was further promoted by Hendriks *et al.*⁸ Working together with local staff and implementing a mutually beneficial partnership helps ensure a holistic approach towards healthcare provision and management in underdeveloped countries.

Advantages of this system include development of a long-term presence in the respective countries with the ultimate goal of building local surgical capacity and treatment independence in a supported setting. Visiting surgeons benefit from experience in global healthcare delivery and have the chance to transfer their knowledge to local surgeons, who gain surgical skills and experience. In addition, other local healthcare workers can be trained including nutritionists, physiotherapists and speech therapists, to support the patients in the perioperative settings.³⁹

Data on how far this has been implemented in hospitals treating Noma patients is scarce. However, given the low long-term follow-up rate and incomplete reporting of outcomes in studies published up to date, implementation of this model is likely limited in Noma patients.

The diagonal treatment strategy combined with a patient-centred outcome evaluation system including PROMs in the form of validated and standardised questionnaires could lead to a sustainable, patient-centred and holistic treatment system for survivors of Noma disease.

The systematic review conducted demonstrates the current most common classification systems used, outcomes and follow-up for reconstructive surgery following Noma disease to date. Consistency in classifying and following up on patients imposes a challenge

for neglected diseases in developing countries, no less so for Noma. When classifying disease severity of Noma patients, surgeons should aim to achieve comparability of the preoperative versus postoperative and long-term status by using a classification system that allows documentation of affected anatomical subunits, as well as to note trismus severity at every point in follow-up.

Tools for measuring surgical outcomes in Noma patients are scarce and need further research and validation. Complication rates and MO were the two most commonly reported outcomes. In general, reported outcomes were often inconsistent and of low quality, as was evidence of follow-up data. Short-term mission surgery is a vital part of healthcare delivery to underdeveloped regions. Future missions should focus on fostering cooperation and forming partnerships with local organisations to ensure postoperative care and long-term patient-oriented follow-up. A shift towards a diagonal treatment delivery approach where local surgeons and healthcare staff are educated and supported should be actively promoted.

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