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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 PRISMA guidelines. The three medical databases Medline, EMBASE, and Web of Sciences were searched. 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 1,393 identified records, 31 studies including 1,110 Noma patients were analysed. NOITULP and Montandon/WHO were the most commonly used classification systems. Mouth opening and complication rates were the two most often reported outcomes. Overall mean complication rate was 44%, reported by 24 studies. Postoperative mouth opening ("MO") was reported by 8 publications, of which, five reported long-term outcomes (> 12 months). Mean mouth improved by 20 mm when compared to 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 rigor. Surgeons should be mindful during patient examination by using a classification system that allows to compare pre- 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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Keywords: "Noma", "cancrum oris", "ulcerative necrotizing gingivitis", "facial reconstructive surgery", "global developmental surgery", "mission surgery", "classification", "outcomes", "complications", "trismus", "follow-up"

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 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.

1 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. in 2019.(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.

2 METHODS

A comprehensive, structured literature search of published articles was conducted. This was designed by the authors S.S. and W.R. 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.

2.1 Data sources

The literature search was performed using the electronic databases MEDLINE (PubMed), EMBASE and Web of Science. The keywords used in the search were selected from key papers and can be found in ***Supplementary 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.

2.2 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 ***Supplementary material- Part A***. Study selection was independently assessed by 2 reviewers (S.S. and M.B.).

2.3 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.

2.4 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-randomized studies (MINORS) criteria, both tools are explained in detail in ***Supplementary material- Part B.***(11)

2.5 Statistical analysis

Data were analysed using IBM SPSS statistics version 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 Heterogenous study design and outcome reporting. Averages were represented as a mean and range for normally distributed data and median with IQR for non-normally disributed data. Outcomes were weighted for size of study population, as some studies had larger population sizes and therefore higher weighting.

2.6 Patient and public involvement

Neither patients nor the public were involved in this research.

3 RESULTS

3.1 Selection of Studies

In total, the systematic literature search identified 1,393 records. In addition, 7 records were identified through bibliography review. After excluding duplicates; titles and abstracts of 1,113 articles were screened, with 1,049 being excluded. 64 studies were fully assessed for eligibility according to the criteria previously established. 33 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 (M.B. and S.S), using a data extraction sheet designed a priori. The selection process was performed according to the PRISMA flow chart, as seen in ***Supplementary material- Part C***.

3.2 Details of the Studies

In total, data were available for articles published in the period 1983-2020. The methodology, diagnostic approach and surgical treatment varied significantly between the studies. In total, published data for 1,244 patients from 31 studies were analysed, out of which 1,110 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. 29 studies were case series, four 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 criteria(11) were used to rate quality of methods of the included studies. The overall MINORS scores ranged from 1 to 8 points, as seen in ***Supplementary 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 13-75% 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.

3.3 Patient Characteristics

Median age for operation was 17 years, reported by 23 studies and ranged from 4.5-35.7 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%).

6 studies had a malnutrition rate ranging from 25-100%, with an average of over 56% (median (IQR)) (53.5 (25-81%)) of patients being severely malnourished upon 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 5 pre-screened patients, and only included HIV seronegative patients.(16, 20-23)

3.4 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) in 1991, 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 0-4, 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 localized 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 was available on 376 patients. Out of these, 147 patients (39%) were classified as Montandon Type I, 53 (14%) presented as Montadon Type II, 15 (4%) were rated as Montandon Type III, and 161 patients (43%) 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 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 mouth opening was 7 mm (5-15 mm).

3.5 Surgical Interventions

Hospital duration ranged from 2-140 days, with a mean of 5.5 days. 255 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%).

3.6 Outcomes and Follow-up Time

Objective outcomes were further subdivided into four 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%-200%. The 200% complication rate was seen in a study by Hartman et al.(30), where six complications occurred in three patients.

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/hematoma	12 (6)
Donor site dehiscence	12 (6)
Recurrent fistula	11 (5)

Others	20 (10)

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) 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 (mouth opening) as outcome

Trismus release, stated as a postoperative mouth opening (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 8 publications and ranged from 23-35 mm. Population- weighted mean postoperative MO was 27 mm.(24-27)

Mean MO at long-term follow up was available for 5 publications and ranged from 10.3-35.0 mm. Population weighted mean mouth opening at long-term follow up was 20 mm (median (IQR)) (19 (15-21)). ***Figure 4*** shows population weighted mean mouth opening preoperatively, postoperatively and at long-term follow-up.

Subjective Outcome Measures

Subjective postoperative outcomes included cosmetic/aesthetic improvement, reported by 3 studies, and overall improvement (aesthetic and functional), reported by 8 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.

Median length of follow up was reported by only 8 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 Mahova, all patients were HIV seropositive. One patient developed severe pneumonia and died before reconstructive surgery, another patient died one month after admission, no further detail on the cause of death was given. A third patient died one 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%.

4 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 1,110 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. in 2016 (34). Over half the studies we included reached 50% or less in the MINORS score. Non-randomized 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. Challenges of performing rigorous studies in the developing world include limited resources and the short time frame of two to three 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) in 1998 and Montandon/WHO, first described by Montandon et al.(24) in 1991.

Montandon et al.(24) based their system on two publications by Cariou(35) in 1986 and Raynaud et al.(36) in 1978. The approach Montandon suggested was rating the defect based upon 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 pre- to postoperative state of the patients and ideally use it as a control system for disease relapse or progression. 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. If the patient does not feel that they have benefited from the operation, then it is entirely irrelevant how the surgeon rates the postoperative outcome. Validated questionnaires are one possible way to report patient-reported outcomes.(37)

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 two to three 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 mouth opening as an outcome of trismus release was reported by eight studies, and long-term follow up data were available for five publications. Underreporting of outcomes and limited follow-up suggest a potential risk of reporting bias, leading to overestimation of the beneficial impact of these missions. Nevertheless, population-corrected mean postoperative mouth opening at long-term follow up (>12 months) was 20 mm, which represents a 13 mm increase compared to 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 mouth opening 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.

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 losses 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.

Ruegg 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 wellbeing 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

programs, financial support, research training, academic partnerships and equipment for surgery.

This sustainable treatment strategy was further promoted by Hendriks et al. (8) in 2019. 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 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 pre- 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 mouth opening 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.

Abbreviations:

CEBM- Center of evidence-based medicine

IQR- Interquartile range

MINORS- Methodological index for non-randomized studies

MO- Mouth opening

NOITULP- anagram as classification system for Noma disease

PRISMA- Preferred reporting items for systematic reviews and meta-analyses

WHO- World Health Organization

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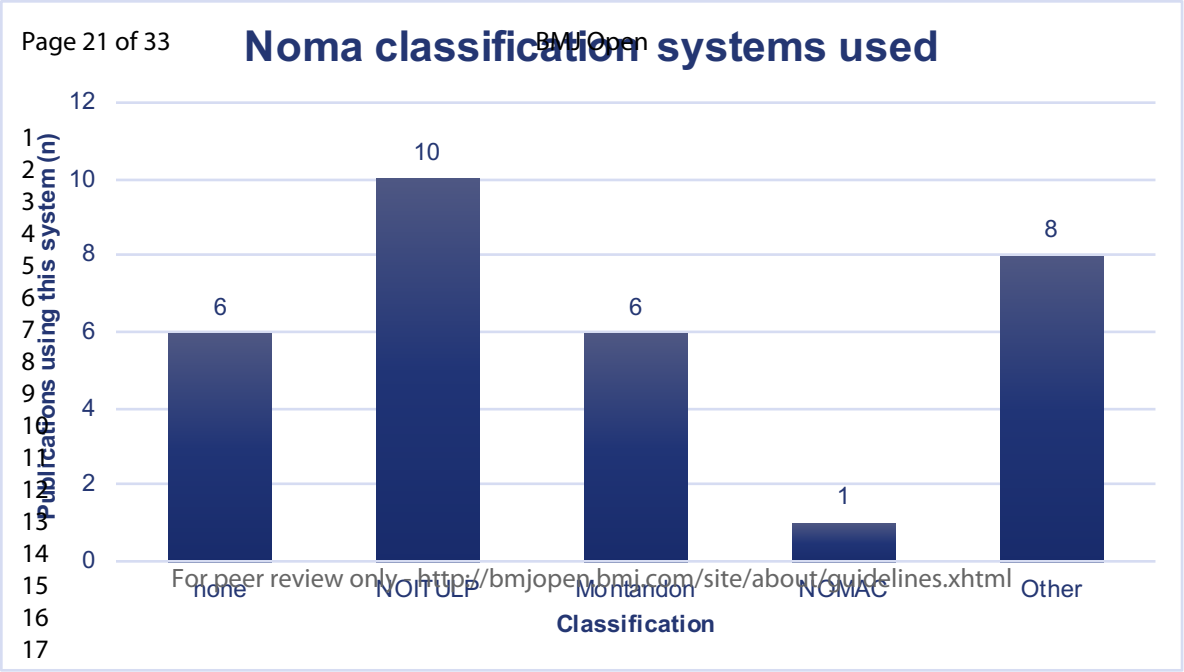
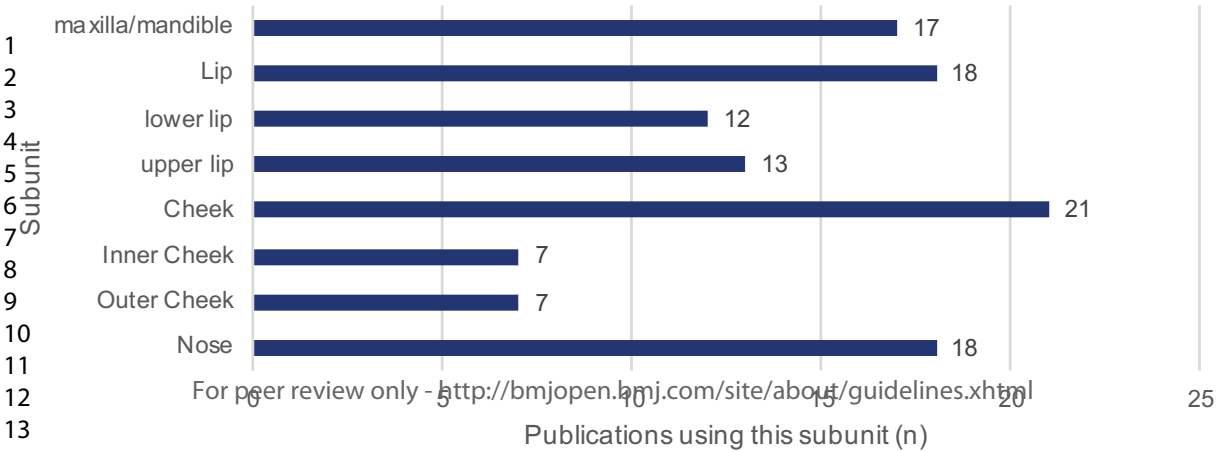
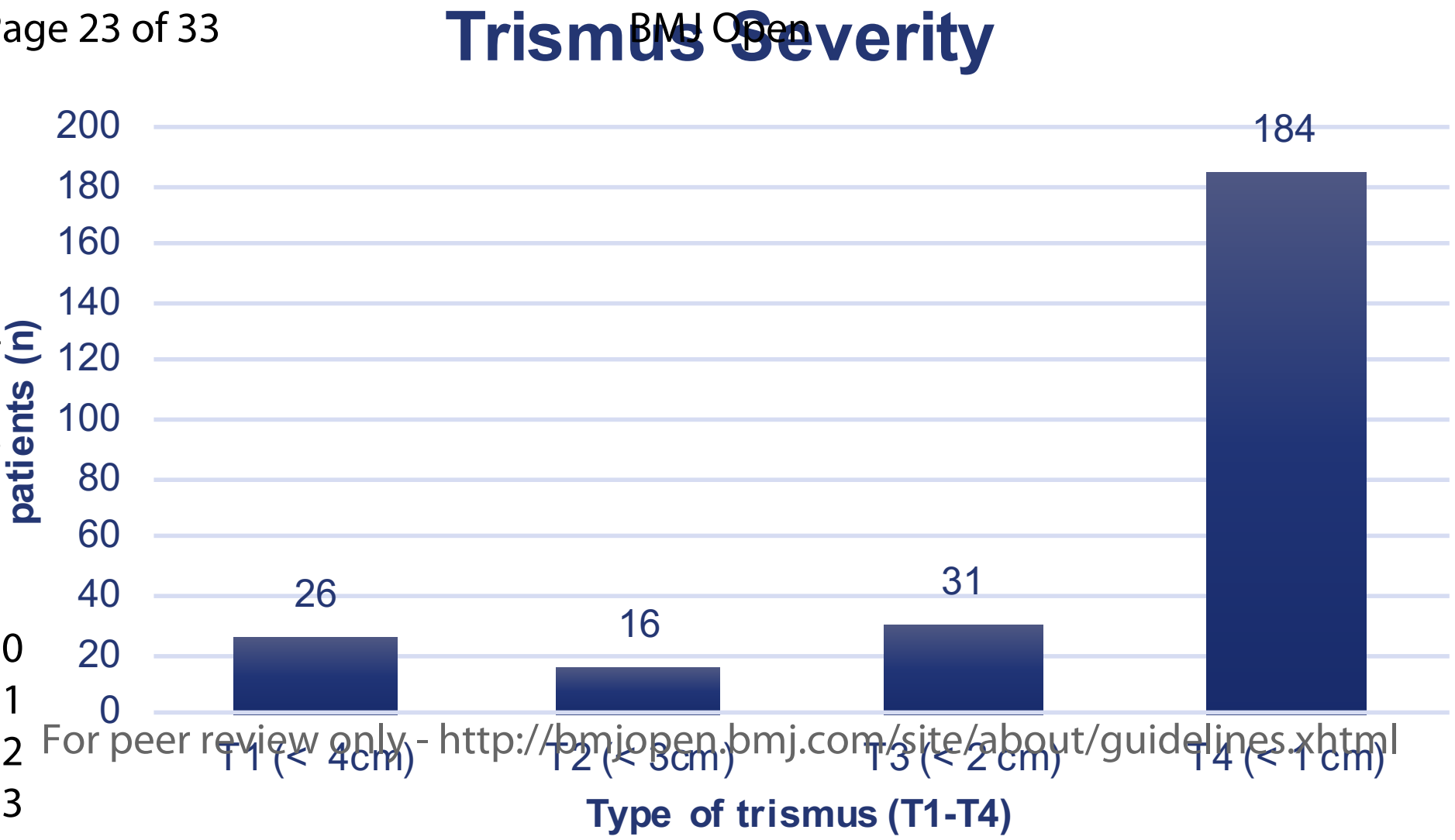
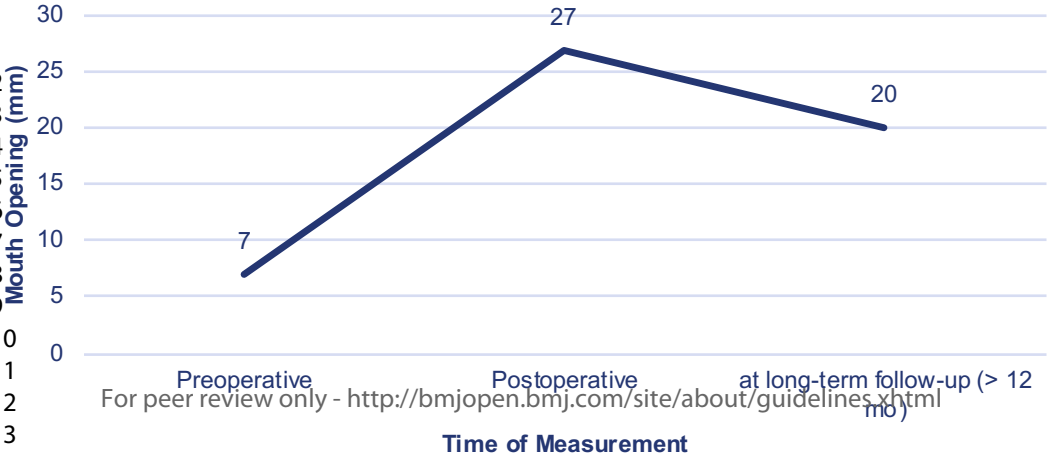
FIGURES AND TABLES









SUPPLEMENTARY MATERIAL

PART A- SEARCH STRATEGY

Keywords

Search strategy for Embase.com (15.04.2020)

/exp = EMtree keyword with explosion
.tw = The Textword field in EMBASE includes Title (TI) and Abstract (AB).

Number	Search terms	Results
#1	exp plastic surgery/ OR exp surgeon/ OR exp plastic surgeon/ OR exp esthetic surgery/ OR exp skin transplantation/ OR exp microsurgery/ OR exp tissue flap/ OR exp Z plasty/ OR exp surgical flaps/ OR exp reconstructive surgery/ OR exp face surgery/ OR exp maxillofacial surgery/ OR exp oral surgery/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. or FTG.tw OR axial flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR exp free tissue graft/ OR free flap*.tw. OR regional flap*.tw. OR exp skin flap/ OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment.tw	8557452
#2	Exp Vincent stomatitis/ OR acute necrotizing ulcerative gingivitis.tw OR acute necrotising ulcerative gingivitis.tw OR acute ulcerative gintivitis.tw OR Noma.tw OR cancrum oris.tw	1401
#3	#1 AND #2	639
Limits: Publication prior to final search, April 15th, 2020		

Search strategy for MEDLINE (PubMed) (15.04.2020)

/exp = MEDLINE keyword with explosion/ Mesh terms
.tw = The Textword field in MEDLINE includes Title (TI) and Abstract (AB).

Number	Search terms	Results
#1	exp Reconstructive Surgical Procedures/ OR exp Surgery, Plastic/ OR exp Tissue Transplantation/ OR exp Surgical Flaps/ OR exp Skin Transplantation/ ORexp Free Tissue Flaps/ OR exp Microsurgery/ OR exp Surgery, Oral/ OR exp Surgical Procedures, Operative/ OR exp "Oral and Maxillofacial Surgeons"/ OR exp Surgeons/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. OR FTG.tw. OR axial flap*.tw.	8167413

	OR pedicle flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR free flap*.tw. OR regional flap*.tw. OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment*.tw	
#2	exp Noma/ OR cancrum oris.tw. OR exp Gingivitis, Necrotizing Ulcerative/ OR acute necrotizing ulcerative gingivitis.tw. OR acute necrotising ulcerative gingivitis.tw.	1664
#3	#1 AND #2	568
Limits: Publication prior to final search, April 15th, 2020		

Search strategy for Clarivate Analytics/Web of Science (15.04.2020)

TOPIC = words in title, abstract or keywords
ndexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Number	**Search terms**	**Results**
#1	TS= (surger* OR surgical* OR surgeon* OR operation* OR operative* OR incisi* OR extracti* OR excisi* OR management* OR treatment*)	9,621,445
#2	TS= (reconstructi* OR cosmetic* OR esthetic* OR aesthetic* OR plastic OR corrective* OR oral* or *maxillofacial* OR facial OR face* OR "head and neck" OR flap* OR skin* or micro*)	8,095,337
#3	TS= (Noma OR "cancrum oris" OR "necrotizing ulcerative gingivitis" OR "acute necrotizing ulcerative gingivitis" OR "acute necrotising ulcerative gingivitis")	3,515
#4	#2 AND #1	1,821,209
#5	#4 AND #3	186
Limits: Publication prior to final search, April 15th, 2020		

Inclusion/exclusion criteria

Inclusion Criteria
1. Original publications 2. Human subjects 3. Case Series, Retrospective Data Analyses, Clinical Trials, Controlled Clinical Trials, Prospective Studies

Exclusion Criteria
1. Publication type does not match inclusion criteria (Review articles, Mixed methodology studies without subgroup data, Animal studies, Conference Articles) 2. Conditions other than Noma, Cancrum Oris, or Necrotizing Ulcerative Stomatitis not related to Noma 3. The paper is about conditions located at sites other than the Maxillofacial and Head and Neck region 4. The paper is not about treatment 5. The paper is not about a surgical intervention (but included if terms such as reconstruction or rehabilitation, or flap or graft, are mentioned). 6. The paper is about prevention rather than treatment of Noma

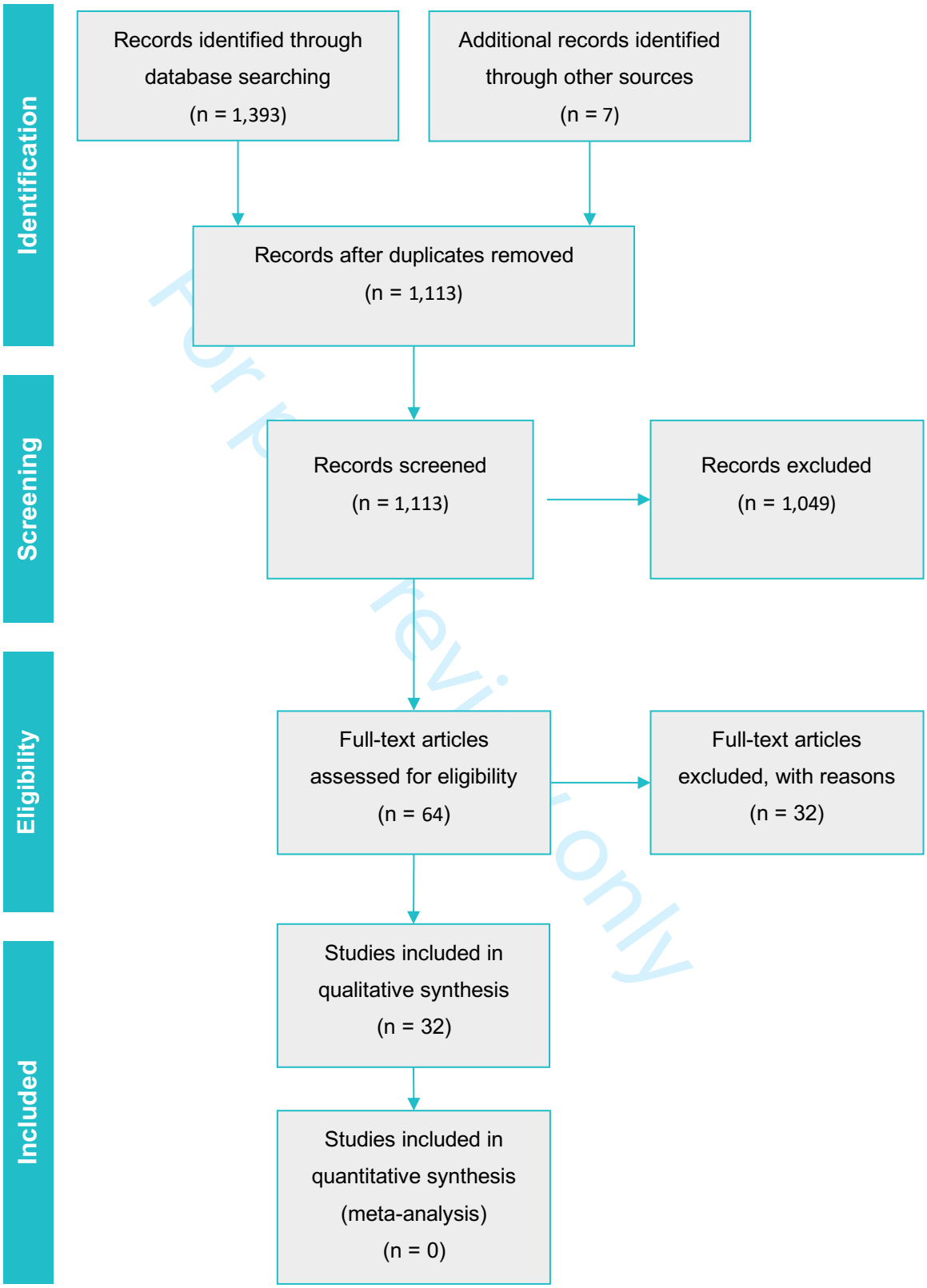
PART B- MINORS CRITERIA

Level of Evidence	Types of Studies
I	SR (with homogeneity) of RCTs, Individual RCT (with narrow Confidence Interval),
II	SR (with homogeneity) of cohort studies, Individual cohort study (including low quality RCT; e.g., <80% follow-up), "Outcomes" Research; Ecological studie
III	SR (with homogeneity*) of case-control studies, Individual Case-Control Study
IV	Case-series (and poor-quality cohort and case-control studies)
V	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

MINORS criteria
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes
Additional criteria in the case of comparative study
9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data
10. Contemporary groups: control and studied group should be managed during the same time period (no historical comparison)

11. Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results
12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk

PART C- PRISMA FLOW CHART



PART D- MINORS CRITERIA FOR INCLUDED STUDIES

First Author	Year	Type	Level of Evidence	1	2	3	4	5	6	7	9	10	11	12	Total	%
Adams-ray	1992	case series (RS)	4	1	1	0	1	0	0	1					4	50%
Adekeye	1983	case series (RS)	4	1	1	0	1	0	0	0					3	38%
Adekeye	1986	case series (RS)	4	1	0	0	1	0	0	1					3	38%
Bisseling	2010	case series (RS)	4	1	1	0	1	1	1	0					6	75%
Bouman	2010	case series (PS)	4	1	1	1	1	0	1	1					6	75%
Chidzonga	2008	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Dammer	2005	case series (PS)	4	1	1	1	1	0	1	0					5	63%
Erdmann	1998	case series (RS)	4	1	1	1	0	0	0	0					3	38%
Giessler	2003	case series (RS)	4	0	1	0	0	0	1	0					2	25%
Giessler	2005	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Giessler	2007	case series (RS)	4	0	1	0	0	0	0	0					1	13%
Giessler	2011	case series (RS)	4	1	0	0	0	0	0	0					1	13%
Hartman	2006	case series (RS)	4	1	0	0	0	0	0	0					1	13%
Heitland	2004	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Holle	2020	case series (RS)	4	1	1	0	1	1	1	0					5	63%
Holle J.	2009	case series (RS)	4	1	1	0	1	1	1	1					6	75%
Honeyman	2019	cohort study (RS)	3	1	1	1	1	1	1	1	0	0	0	1	8	67%
Huijing	2011	cohort study (PS)	3	1	1	1	1	0	1	0	0	0	0	1	6	50%
Kuehnel	2003	case series (PS)	4	1	1	1	0	0	1	1					5	63%
Marck	1998	case series (PS)	4	0	1	1	0	0	0	0					2	25%
Montandon	1991	case series (RS)	4	0	1	0	0	0	0	0					1	13%
Nath	1997	case series (RS)	4	1	1	0	1	1	1	1					6	75%
Oluwasanmi	1976	case series (RS)	4	1	1	1	1	0	0	1					5	63%
Pittet	2001	case series (RS)	4	1	1	1	0	0	1	1					5	63%
Rodgers	2015	case series (RS)	4	1	1	1	1	0	0	0	0	0	0	0	4	50%
Rüegg	2016	case series (RS)	4	1	1	0	1	0	1	1					5	63%
Ruegg	2018	case series (RS)	4	1	1	0	1	0	1	1					5	63%
Saleh	2013	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Shaye	2018	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Simon	2015	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Vinzenz	2008	case series (RS)	4	1	1	0	1	0	1	1					5	63%

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7/8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7/8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10/11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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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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Primary Subject Heading:	Global health
Secondary Subject Heading:	Paediatrics, Surgery, Public health, Dentistry and oral medicine
Keywords:	Nutrition < TROPICAL MEDICINE, Public health < INFECTIOUS DISEASES, SURGERY, Community child health < PAEDIATRICS, PLASTIC & RECONSTRUCTIVE SURGERY, Paediatric oral & maxillofacial surgery < PAEDIATRIC SURGERY

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

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Word Count: 3775

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 PRISMA guidelines. The three medical databases Medline, EMBASE, and Web of Sciences were searched, articles published between 1st of January 1983-15th of 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 1,393 identified records, 31 studies including 1,110 Noma patients were analysed. NOITULP and Montandon/WHO were the most commonly used classification systems. Mouth opening and complication rates were the two most often reported outcomes. Overall mean complication rate was 44%, reported by 24 studies. Postoperative mouth opening ("MO") was reported by 8 publications, of which, five reported long-term outcomes (> 12 months). Mean mouth opening improved by 20 mm when compared to 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 rigor. Surgeons should be mindful during patient examination by using a classification system that allows to compare pre- 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.

PROSPERO registration number: CRD42020181931

Keywords: "Noma", "cancrum oris", "ulcerative necrotizing gingivitis", "facial reconstructive surgery", "global developmental surgery", "mission surgery", "classification", "outcomes", "complications", "trismus", "follow-up"

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.

1 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. in 2019.(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.

2 METHODS

A comprehensive, structured literature search of published articles was conducted. This was designed by the authors S.S. and W.R. 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.

2.1 Data sources

The literature search was performed using the electronic databases MEDLINE (PubMed), EMBASE and Web of Science, including articles published between 1st of January 1983-15th of April 2020. The keywords used in the search were selected from key papers and can be found in ***Supplementary 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.

2.2 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 ***Supplementary material- Part A***. Articles were eligible in German and English language. Study selection was independently assessed by 2 reviewers (S.S. and M.B.).

2.3 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.

2.4 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-randomized studies (MINORS) criteria, both tools are explained in detail in ***Supplementary material- Part B.***(11)

2.5 Statistical analysis

Data were analysed using IBM SPSS statistics version 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 Heterogenous study design and outcome reporting. Averages were represented as a mean and range for normally distributed data and median with IQR for non-normally disributed data. Outcomes were weighted for size of study population, as some studies had larger population sizes and therefore higher weighting.

2.6 Patient and public involvement

Neither patients nor the public were involved in this research.

3 RESULTS

3.1 Selection of Studies

In total, the systematic literature search identified 1,393 records. In addition, 7 records were identified through bibliography review. After excluding duplicates; titles and abstracts of 1,113 articles were screened, with 1,049 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 (M.B. and S.S), using a data extraction sheet designed a priori. The selection process was performed according to the PRISMA flow chart, as seen in ***Supplementary material- Part C***.

3.2 Details of the Studies

In total, data were available for articles published in the period from 1st of January 1983-15th of April 2020. The methodology, diagnostic approach and surgical treatment varied significantly between the studies. In total, published data for 1,244 patients from 31 studies were analysed, out of which 1,110 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, four 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 criteria(11) were used to rate quality of methods of the included studies. The overall MINORS scores ranged from 1 to 8 points, as seen in ***Supplementary 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 13-75% 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.

3.3 Patient Characteristics

Median age for operation was 17 years, reported by 23 studies and ranged from 4.5-35.7 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%).

6 studies had a malnutrition rate ranging from 25-100%, with an average of over 56% (median (IQR)) (53.5 (25-81%)) of patients being severely malnourished upon 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 5 pre-screened patients, and only included HIV seronegative patients.(16, 20-23)

3.4 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) in 1991, 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 0-4, 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 localized 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 was available on 376 patients. Out of these, 147 (39%) patients were classified as Montandon Type I, 53 (14%) presented as Montadon 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 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 mouth opening was 7 mm (5-15 mm).

3.5 Surgical Interventions

Hospital duration ranged from 2-140 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%).

3.6 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%-200%. The 200% complication rate was seen in a study by Hartman et al.(30), where six complications occurred in three patients.

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/hematoma	12 (6)
Donor site dehiscence	12 (6)
Recurrent fistula	11 (5)

Others	20 (10)

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) 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 (mouth opening) as outcome

Trismus release, stated as a postoperative mouth opening (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 8 publications and ranged from 23-35 mm. Population- weighted mean postoperative MO was 27 mm.(24-27)

Mean MO at long-term follow up was available for 5 publications and ranged from 10.3-35.0 mm. Population weighted mean mouth opening at long-term follow up was 20 mm (median (IQR)) (19 (15-21)). ***Figure 4*** shows population weighted mean mouth opening preoperatively, postoperatively and at long-term follow-up.

Subjective Outcome Measures

Subjective postoperative outcomes included cosmetic/aesthetic improvement, reported by 3 studies, and overall improvement (aesthetic and functional), reported by 8 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.

Median length of follow up was reported by only 8 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 Mahova, all patients were HIV seropositive. One patient developed severe pneumonia and died before reconstructive surgery, another patient died one month after admission, no further detail on the cause of death was given. A third patient died one 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%.

4 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 1,110 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. in 2016 (34). Over half the studies we included reached 50% or less in the MINORS score. Non-randomized 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 two to three 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) in 1998 and Montandon/WHO, first described by Montandon et al.(24) in 1991.

Montandon et al.(24) based their system on two publications by Raynaud et al. (35) in 1978 and Cariou (36) in 1986. The approach Montandon suggested was rating the defect based upon 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 pre- 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 pre- 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 pre- 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 two to three 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 mouth opening as an outcome of trismus release was reported by eight studies, and long-term follow up data were available for five publications. Underreporting of outcomes and limited follow-up Underreporting of outcomes and lack of follow-up could lead to underestimation or overestimation of benefits to the patients. Nevertheless, population-corrected mean postoperative mouth opening at long-term follow up (>12 months) was 20 mm, which represents a 13 mm increase compared to 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 mouth opening 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 2-7 years old, and the median age of the reconstruction was 17 years (range from 4.5-35.7), 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 losses 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.

Ruegg 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 wellbeing 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 programs, financial support, research training, academic partnerships and equipment for surgery.

This sustainable treatment strategy was further promoted by Hendriks et al. (8) in 2019. 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-centered outcome evaluation system including PROM's in the form of validated and standardized questionnaires could lead to a sustainable, patient-centered 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 pre- 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 mouth opening 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.

Abbreviations:

CEBM- Center of evidence-based medicine

IQR- Interquartile range

MINORS- Methodological index for non-randomized studies

MO- Mouth opening

NOITULP- anagram as classification system for Noma disease

PRISMA- Preferred reporting items for systematic reviews and meta-analyses

WHO- World Health Organization

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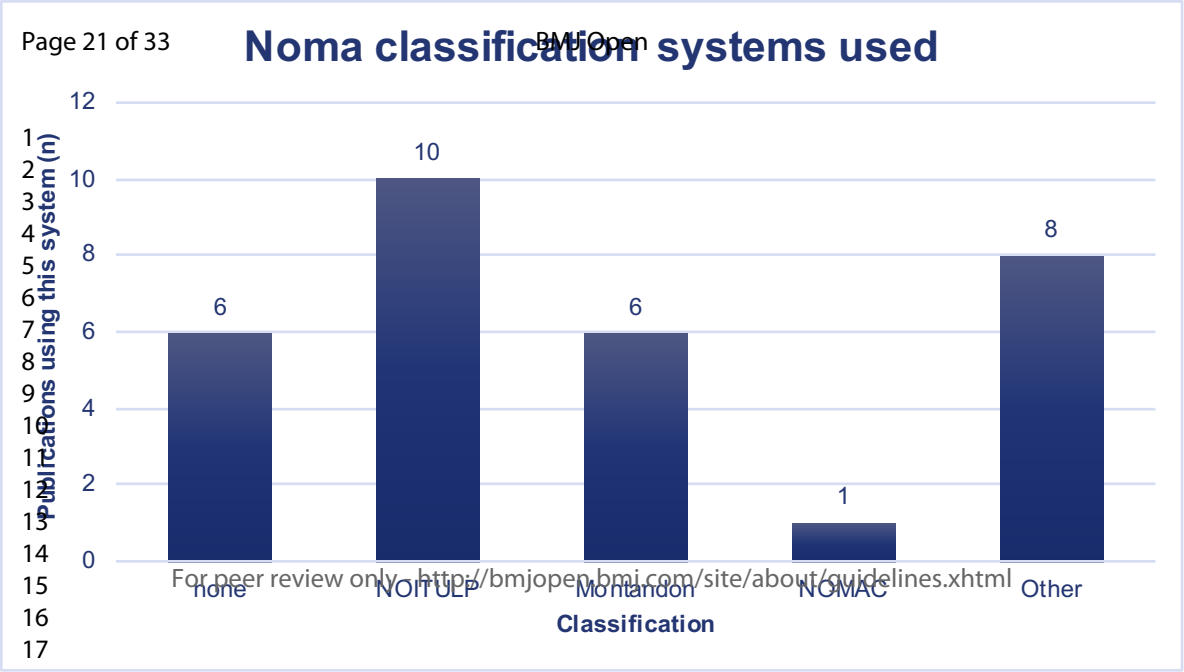
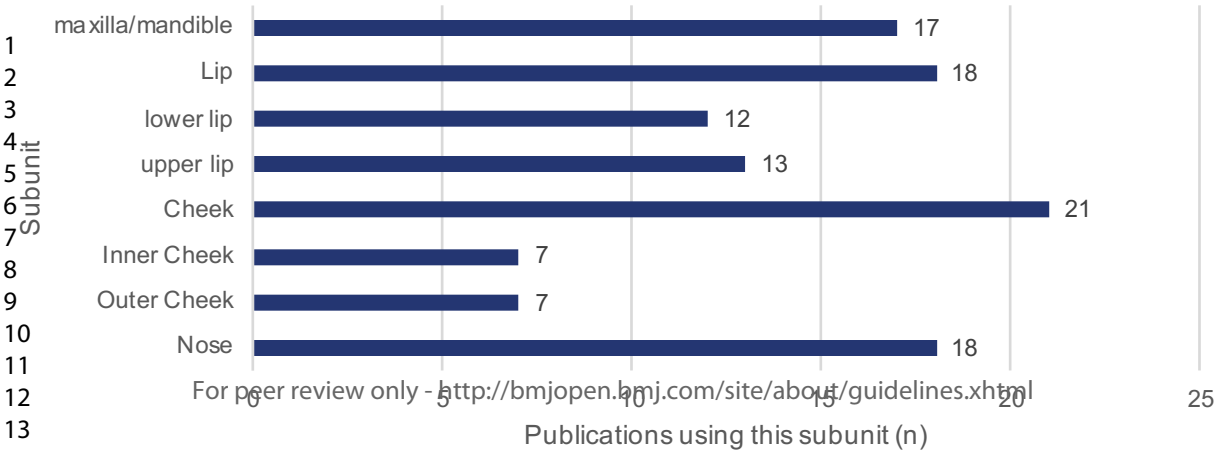
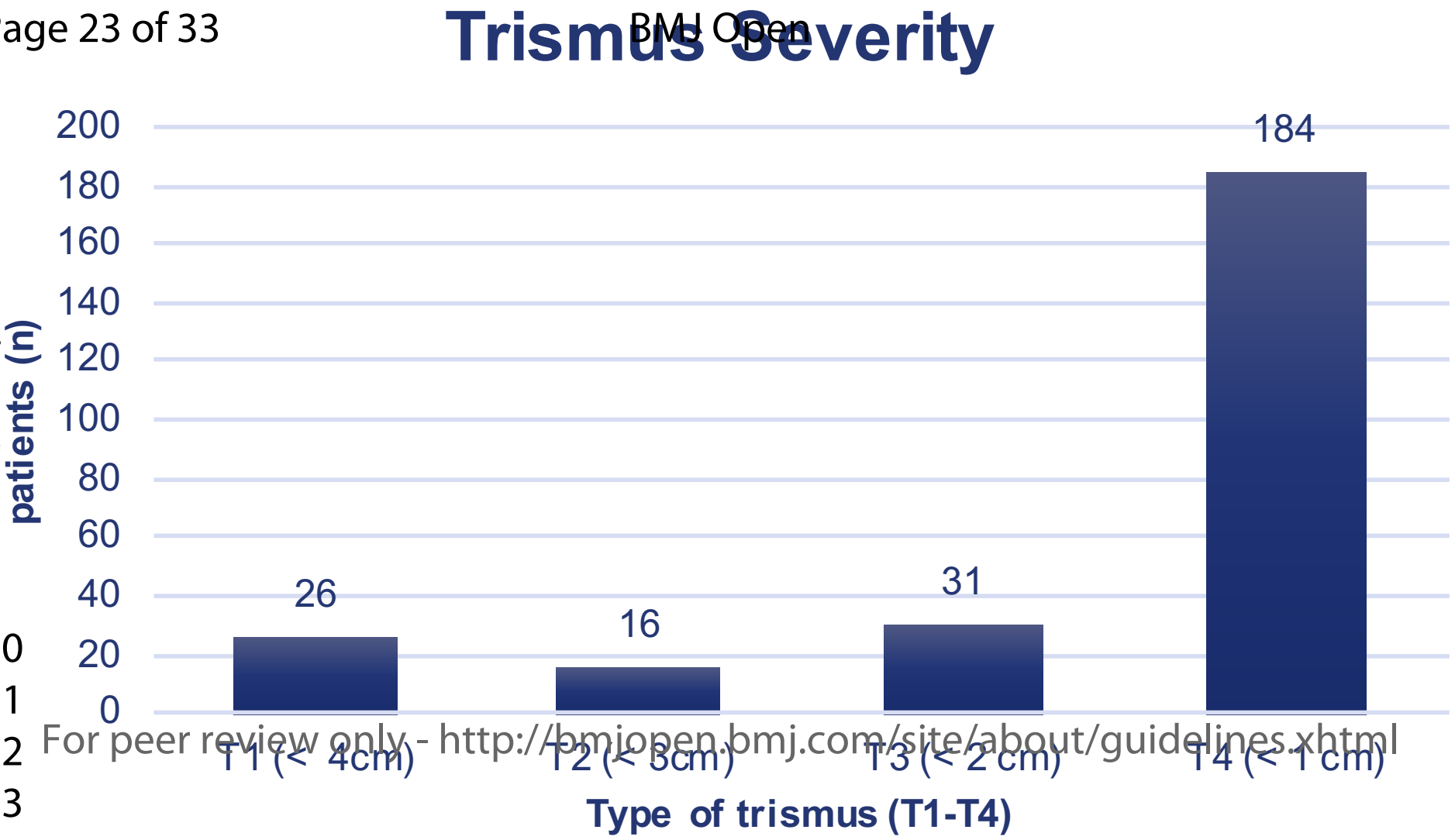
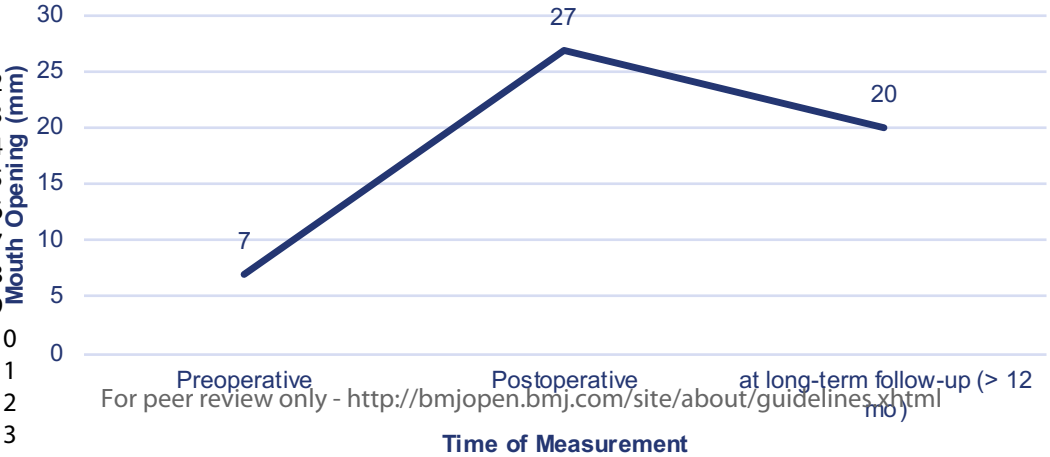
FIGURES AND TABLES









SUPPLEMENTARY MATERIAL

PART A- SEARCH STRATEGY

Keywords

Search strategy for Embase.com (15.04.2020)

/exp = EMtree keyword with explosion
.tw = The Textword field in EMBASE includes Title (TI) and Abstract (AB).

Number	Search terms	Results
#1	exp plastic surgery/ OR exp surgeon/ OR exp plastic surgeon/ OR exp esthetic surgery/ OR exp skin transplantation/ OR exp microsurgery/ OR exp tissue flap/ OR exp Z plasty/ OR exp surgical flaps/ OR exp reconstructive surgery/ OR exp face surgery/ OR exp maxillofacial surgery/ OR exp oral surgery/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. or FTG.tw OR axial flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR exp free tissue graft/ OR free flap*.tw. OR regional flap*.tw. OR exp skin flap/ OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment.tw	8557452
#2	Exp Vincent stomatitis/ OR acute necrotizing ulcerative gingivitis.tw OR acute necrotising ulcerative gingivitis.tw OR acute ulcerative gintivitis.tw OR Noma.tw OR cancrum oris.tw	1401
#3	#1 AND #2	639
Limits: Publication prior to final search, April 15th, 2020		

Search strategy for MEDLINE (PubMed) (15.04.2020)

/exp = MEDLINE keyword with explosion/ Mesh terms
.tw = The Textword field in MEDLINE includes Title (TI) and Abstract (AB).

Number	Search terms	Results
#1	exp Reconstructive Surgical Procedures/ OR exp Surgery, Plastic/ OR exp Tissue Transplantation/ OR exp Surgical Flaps/ OR exp Skin Transplantation/ ORexp Free Tissue Flaps/ OR exp Microsurgery/ OR exp Surgery, Oral/ OR exp Surgical Procedures, Operative/ OR exp "Oral and Maxillofacial Surgeons"/ OR exp Surgeons/ OR skin graft*.tw. OR full thickness graft*.tw. OR SSG.tw. OR FTG.tw. OR axial flap*.tw.	8167413

	OR pedicle flap*.tw. OR pedicled flap*.tw. OR surgical flap*.tw. OR contracture release*.tw. OR free flap*.tw. OR regional flap*.tw. OR local flap*.tw. OR surger*.tw. OR surgical*.tw. OR operation*.tw. OR operative*.tw. OR incisi*.tw. OR excisi*.tw. OR management*.tw. OR treatment*.tw	
#2	exp Noma/ OR cancrum oris.tw. OR exp Gingivitis, Necrotizing Ulcerative/ OR acute necrotizing ulcerative gingivitis.tw. OR acute necrotising ulcerative gingivitis.tw.	1664
#3	#1 AND #2	568
Limits: Publication prior to final search, April 15th, 2020		

Search strategy for Clarivate Analytics/Web of Science (15.04.2020)

TOPIC = words in title, abstract or keywords
ndexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan=All years

Number	**Search terms**	**Results**
#1	TS= (surger* OR surgical* OR surgeon* OR operation* OR operative* OR incisi* OR extracti* OR excisi* OR management* OR treatment*)	9,621,445
#2	TS= (reconstructi* OR cosmetic* OR esthetic* OR aesthetic* OR plastic OR corrective* OR oral* or *maxillofacial* OR facial OR face* OR "head and neck" OR flap* OR skin* or micro*)	8,095,337
#3	TS= (Noma OR "cancrum oris" OR "necrotizing ulcerative gingivitis" OR "acute necrotizing ulcerative gingivitis" OR "acute necrotising ulcerative gingivitis")	3,515
#4	#2 AND #1	1,821,209
#5	#4 AND #3	186
Limits: Publication prior to final search, April 15th, 2020		

Inclusion/exclusion criteria

Inclusion Criteria
1. Original publications 2. Human subjects 3. Case Series, Retrospective Data Analyses, Clinical Trials, Controlled Clinical Trials, Prospective Studies

Exclusion Criteria
1. Publication type does not match inclusion criteria (Review articles, Mixed methodology studies without subgroup data, Animal studies, Conference Articles) 2. Conditions other than Noma, Cancrum Oris, or Necrotizing Ulcerative Stomatitis not related to Noma 3. The paper is about conditions located at sites other than the Maxillofacial and Head and Neck region 4. The paper is not about treatment 5. The paper is not about a surgical intervention (but included if terms such as reconstruction or rehabilitation, or flap or graft, are mentioned). 6. The paper is about prevention rather than treatment of Noma 7. The paper is written in a language other than German or English

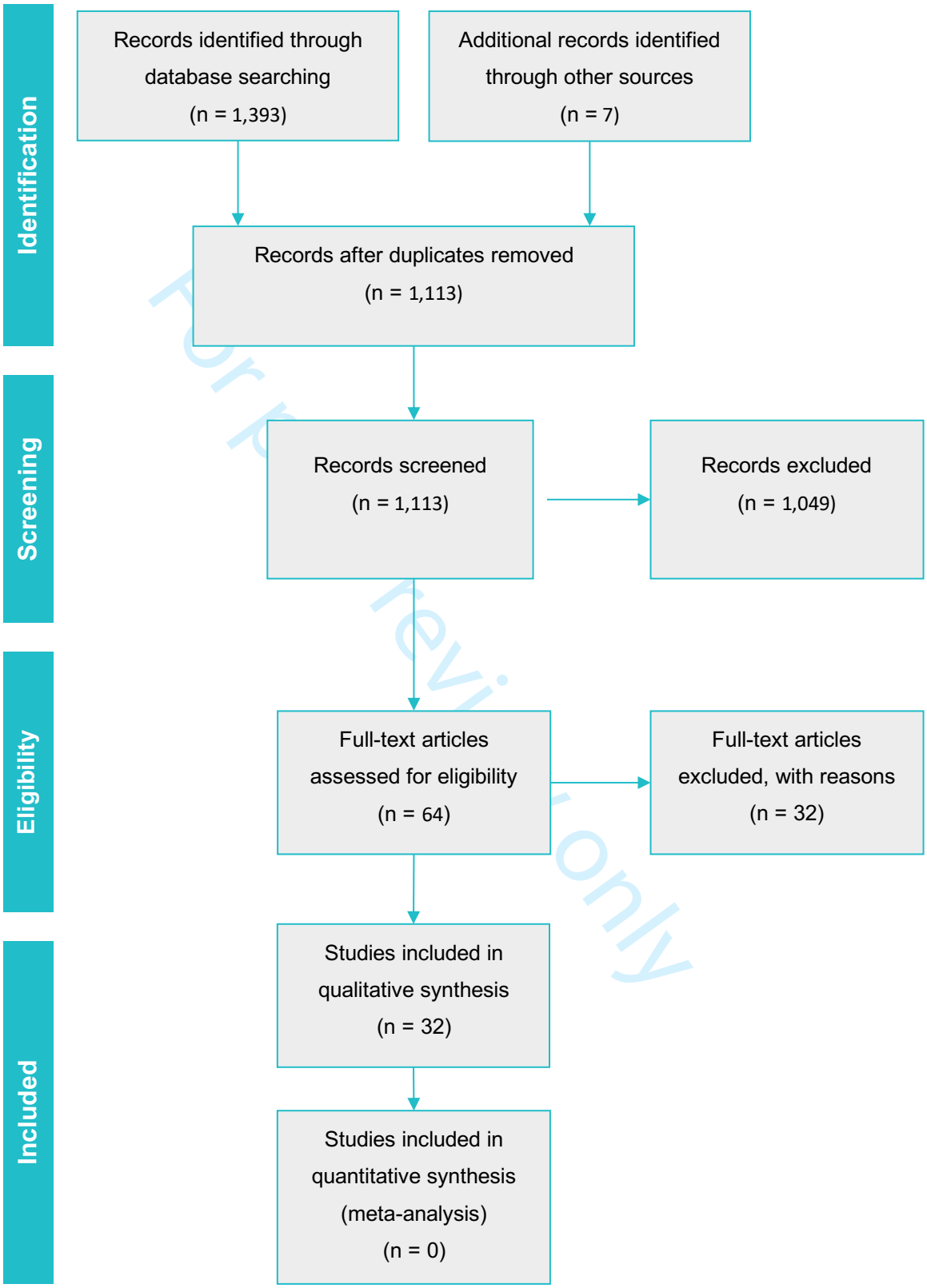
PART B- MINORS CRITERIA

Level of Evidence	Types of Studies
I	SR (with homogeneity) of RCTs, Individual RCT (with narrow Confidence Interval),
II	SR (with homogeneity) of cohort studies, Individual cohort study (including low quality RCT; e.g., <80% follow-up), "Outcomes" Research; Ecological studie
III	SR (with homogeneity*) of case-control studies, Individual Case-Control Study
IV	Case-series (and poor-quality cohort and case-control studies)
V	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

MINORS criteria
1. A clearly stated aim: the question addressed should be precise and relevant in the light of available literature
2. Inclusion of consecutive patients: all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)
3. Prospective collection of data: data were collected according to a protocol established before the beginning of the study
4. Endpoints appropriate to the aim of the study: unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.
5. Unbiased assessment of the study endpoint: blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated
6. Follow-up period appropriate to the aim of the study: the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events
7. Loss to follow up less than 5%: all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint
8. Prospective calculation of the study size: information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes
Additional criteria in the case of comparative study
9. An adequate control group: having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data
10. Contemporary groups: control and studied group should be managed during the same time period (no historical comparison)

11. Baseline equivalence of groups: the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results
12. Adequate statistical analyses: whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk

PART C- PRISMA FLOW CHART



PART D- MINORS CRITERIA FOR INCLUDED STUDIES

First Author	Year	Type	Level of Evidence	1	2	3	4	5	6	7	9	10	11	12	Total	%
Adams-ray	1992	case series (RS)	4	1	1	0	1	0	0	1					4	50%
Adekeye	1983	case series (RS)	4	1	1	0	1	0	0	0					3	38%
Adekeye	1986	case series (RS)	4	1	0	0	1	0	0	1					3	38%
Bisseling	2010	case series (RS)	4	1	1	0	1	1	1	0					6	75%
Bouman	2010	case series (PS)	4	1	1	1	1	0	1	1					6	75%
Chidzonga	2008	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Dammer	2005	case series (PS)	4	1	1	1	1	0	1	0					5	63%
Erdmann	1998	case series (RS)	4	1	1	1	0	0	0	0					3	38%
Giessler	2003	case series (RS)	4	0	1	0	0	0	1	0					2	25%
Giessler	2005	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Giessler	2007	case series (RS)	4	0	1	0	0	0	0	0					1	13%
Giessler	2011	case series (RS)	4	1	0	0	0	0	0	0					1	13%
Hartman	2006	case series (RS)	4	1	0	0	0	0	0	0					1	13%
Heitland	2004	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Holle	2020	case series (RS)	4	1	1	0	1	1	1	0					5	63%
Holle J.	2009	case series (RS)	4	1	1	0	1	1	1	1					6	75%
Honeyman	2019	cohort study (RS)	3	1	1	1	1	1	1	1	0	0	0	1	8	67%
Huijing	2011	cohort study (PS)	3	1	1	1	1	0	1	0	0	0	0	1	6	50%
Kuehnel	2003	case series (PS)	4	1	1	1	0	0	1	1					5	63%
Marck	1998	case series (PS)	4	0	1	1	0	0	0	0					2	25%
Montandon	1991	case series (RS)	4	0	1	0	0	0	0	0					1	13%
Nath	1997	case series (RS)	4	1	1	0	1	1	1	1					6	75%
Oluwasanmi	1976	case series (RS)	4	1	1	1	1	0	0	1					5	63%
Pittet	2001	case series (RS)	4	1	1	1	0	0	1	1					5	63%
Rodgers	2015	case series (RS)	4	1	1	1	1	0	0	0	0	0	0	0	4	50%
Rüegg	2016	case series (RS)	4	1	1	0	1	0	1	1					5	63%
Ruegg	2018	case series (RS)	4	1	1	0	1	0	1	1					5	63%
Saleh	2013	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Shaye	2018	case series (RS)	4	1	1	0	0	0	0	0					2	25%
Simon	2015	case series (RS)	4	1	1	1	1	0	0	0					4	50%
Vinzenz	2008	case series (RS)	4	1	1	0	1	0	1	1					5	63%

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7/8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7/8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10/11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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