Contemporary management and outcome of myelomeningocele: the Rotterdam experience

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OBJECTIVE Myelomeningocele (MMC) is the most common form of spina bifida, with a lifelong impact on the quality of life for infants born with this condition. In recent decades, fetal surgery has evolved from an experimental therapy to standard of care for many centers in the world. In this study, the authors aimed to provide an overview of the current management and outcomes for infants with MMC managed at their institution. This then provides a center-specific historical cohort for comparison with future antenatal-treated MMC cases.

METHODS This is a retrospective, single-institution cohort study including all consecutive MMC cases between January 1, 2000, and June 1, 2018, at Erasmus MC. Outcome data included closure of the defect (location, timing, and surgical parameters), hydrocephalus management, Chiari malformation type II (CMTII) management, incidence of spinal cord tethering and outcome, motor outcomes, and continence.

RESULTS A total of 93 patients were included with predominantly lumbosacral lesions. Two patients died during follow-up. Hydrocephalus was present in 84%, with a 71% ventriculoperitoneal shunt reoperation rate. Surgery was performed in 12% for a tethered spinal cord at a mean age of 8 years. Decompression surgery was performed in 3 patients for CMTII. Special education in 63% was significantly associated with hydrocephalus ($p < 0.015$). Nineteen percent of patients were able to walk independently, and 47% were nonambulators. Social continence for urine was obtained in 75% of patients, 4% had fecal incontinence.

CONCLUSIONS This study provides an overview of current MMC outcomes at the authors' center and will serve as a historical cohort for comparison with future fetal surgery cases operated on at the center in the coming years. Apart from a relatively low surgical untethering rate, the authors' outcome data are comparable to those in the literature. Hydrocephalus is highly prevalent in postnatally treated MMC patients; in this study as in much of the literature, hydrocephalus is correlated with a low cognitive function. Fetal surgery for MMC halves the need for shunt treatment in a select group of MMC pregnancies, constituting a major indication for us to undergo the transition to a fetal surgery center. The fetal benefits of open antenatal surgery for MMC are well established, yet long-term data on especially tethered spinal cord are eagerly awaited.

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KEYWORDS spina bifida; myelomeningocele; tethering

MYELOMENINGOCELE (MMC) is the most common form of spina bifida. Patients with MMC face lifelong disabilities such as paralysis of the lower limbs; sensory loss; impaired cognition; and bladder, bowel, and sexual dysfunction. Most cases are identified during routine anomaly scanning around 20 weeks of ges-

tation, and a large proportion of parents opt not to continue the pregnancy (termination of pregnancy). This, in combination with the increased use of folic acid supplementation during pregnancy, has reduced the incidence of neural tube defects in the past decades.³¹ For instance, in the US, the incidence of neural tube defects at birth decreased

ABBREVIATIONS CIC = clean intermittent catheterization; CMTII = Chiari malformation type II; ETV = endoscopic third ventriculostomy; MMC = myelomeningocele; MOMS = Management of Myelomeningocele Study; NSBPR = National Spina Bifida Patient Registry; TSC = tethered spinal cord; VP = ventriculoperitoneal.

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19% following folic acid supplementation between 1990 and 1999.^{9,16} However, more recent data showed that this dramatic decline in incidence has stabilized in later years, with approximately 3.39 per 10,000 children born with spina bifida in 2003–2004.⁴

Management of MMC is complex, and multidisciplinary treatment is warranted. Usually, shortly after birth, the MMC defect will be closed surgically to prevent further damage to the spinal cord and infection. MMC patients are at risk for developing other conditions. A highly prevalent one is the development of hydrocephalus.¹⁴ Diversion of CSF is usually performed by shunting, alternatively by creating an endoscopic third ventriculostomy (ETV).

Another condition associated with MMC is Chiari malformation type II (CMTII).^{2,20,23,24} Even though almost all patients with postnatal MMC repair have a CMTII on imaging, only a proportion present with clinical symptoms. Clinical symptoms may include neck pain, muscle weakness, central apnea, dysphagia, stridor, and opisthotonus. The first-line treatment of CMTII is also ventriculoperitoneal (VP) shunting, whereas foramen magnum decompression with or without duraplasty can be considered when shunting is not providing adequate relief of symptoms.

In addition to CMTII, the majority of patients with MMC have a tethered spinal cord (TSC) on imaging, but only a minority will also present with clinical symptoms. Tethering of the spinal cord can result in back or leg pain, syringomyelia, decline in motor function, progression of scoliosis, and bladder dysfunction. The goal of surgical treatment is to release the spinal cord.¹⁹

In 2011, the results of the Management of Myelomeningocele Study (MOMS) trial were published.¹ In this randomized controlled trial, 183 women before 26 weeks of gestation were randomized between prenatal surgery and conventional postnatal repair. Despite the more frequent occurrence of pregnancy-related complications such as preterm birth, the outcomes of the patients who underwent antenatal repair were favorable. For example, less than half of them required the placement of a shunt. Furthermore, the patients had a reduced rate of CMTII and better cognitive function and motor skills. Although clinically relevant, tethering of the spinal cord is often a late-occurring complication, and long-term data are not available. Fetal closure of MMC seems to be associated with a higher TSC rate, even at a very young age as shown in the MOMS trial.

The purpose of the current study was to evaluate the contemporary management and long-term outcomes of patients with MMC managed at our institution, Sophia Children's Hospital, Rotterdam, the Netherlands. To this end, we assessed the rate of shunting, untethering procedures, and decompression interventions for CMTII in relation to clinical outcome. This series provides a contemporary cohort that could improve counseling parents about the long-term complications and risks of postnatal repair. This also allows comparison to much-awaited long-term outcomes of the MOMS trial, in particular to TSC rates. Furthermore, as our institution is currently transitioning toward the establishment of a fetal surgery center, the

present study provides a center-specific historical cohort to compare with future antenatal-treated MMC cases.

Methods

Management of MMC at the Sophia Children's Hospital

Annually, approximately 15 patients are diagnosed with MMC at the Erasmus MC-Sophia Children's Hospital. The diagnosis is usually suspected at the routine 20-week anomaly ultrasound scan and confirmed with a more detailed scan at our center. The latter also aims to diagnose associated abnormalities and to evaluate the extent of the spinal abnormality (i.e., lesion level, presence of CMTII, hydrocephalus). All women carrying an MMC fetus are counseled by a maternal fetal medicine specialist as well as a pediatric neurosurgeon. Amniocentesis is offered to identify associated genetic abnormalities. If the decision is made to continue the pregnancy, the ensuing pregnancy care takes place at our institution.

Postnatal closure consists of microsurgical freeing of the placode, followed by neurulation of the tube. Next, the dura is dissected and closed around the newly constructed neural tube. A musculofascial flap is used to cover the defect, and the skin is closed. In large skin defects, the plastic surgeon is asked to perform a skin flap.

If the parents opt for fetal surgery, they are currently referred to University Hospitals Leuven, Belgium. Further follow-up and delivery by cesarean section in the current and future pregnancies take place at our institution.

After birth, MMC patients are followed regularly at the MMC outpatient clinic. During these specific consulting visits, patients are seen by a multidisciplinary team of specialists from departments such as neurosurgery, orthopedic surgery, rehabilitation medicine, urology, pediatrics, neurology, social work, and furthermore by dedicated nurses.

Patient Selection and Data Extraction

This is a retrospective, single-institution cohort study. Using a departmental database, a chart review was performed on all patients born between January 1, 2000, and June 1, 2018, who underwent closure of an MMC defect. All surgically treated MMC patients who are currently under treatment at the Sophia Children's Hospital were included. Patients were excluded if they had any other form of spina bifida (such as spina bifida occulta).

The following outcome data were collected: 1) type of surgical closure of the MMC defect, location of defect, timing of repair, and surgical parameters; 2) management of hydrocephalus: shunt procedures, ETVs, and reoperations; 3) management of CMTII and an indication for decompression; 4) management of spinal cord untethering; and 5) long-term quality of life: bowel and bladder function, level of functioning, and the ability to walk according to the Hoffer classification.⁸

Institutional review board approval was not needed since this was an anonymous retrospective study.

Statistical Analysis

IBM SPSS (version 21.0, IBM Corp.) was used for analysis of data; $p < 0.05$ was considered to be statistically sig-

TABLE 1. Baseline characteristics of patients and surgical closure of the MMC

	No. of Patients (%)
Total	93
Sex	
Male	46 (49.5)
Female	47 (50.5)
Gestational age in wks (n = 73)	
<37 wks	14 (19.2)
≥37 wks	59 (80.8)
Mean time of op after birth (n = 80)	
≤48 hrs	17 (21.3)
≥48 hrs	63 (78.8)
≤7 days	58 (92.1)
Defect location (n = 93)	
Thoracic	5 (5.4)
Thoracolumbar	13 (14.0)
Thoracolumbosacral	1 (1.1)
Lumbar	35 (37.6)
Lumbosacral	28 (30.1)
Sacral	11 (11.8)

nificant. The p value and confidence intervals were both determined using the Pearson chi-square test. Categorical data are presented as valid percentages.

Results

Patient Characteristics and Closure of the Defect

A total of 93 patients were included in this study (47 females); 3 patients had been excluded because 2 of them had a meningocele and 1 had a spina bifida occulta. All patients were followed up for a mean duration of 11.8 years (range 1.0–18.2 years). No patients were lost to fol-

low-up. No patients died after delivery or before surgical closure. Two patients died during follow-up, one due to an unrelated infection at the age of 10 months and the other at the age of 17 years who had a short history of deterioration, which ended in asystole. Although this patient had never shown any signs of a clinically relevant CMTII, the deterioration and subsequent death might at least be partly due to CMTII.

Fifty-nine (80.8%, 59/73) patients were born after 37 weeks of gestation, while 14 (19.2%, 14/73) were born between 33 and 37 weeks. Table 1 shows the level of the MMC lesions. Most were located in the lumbosacral area.

The two most recent patients underwent an antenatal repair abroad, while the remaining 91 underwent postnatal closure of the MMC. Postnatal repair was performed within 48 hours after birth in 17 patients (21%, 17/80) and in 63 (79%, 63/80) patients after 48 hours (between day 3 and day 8). In 58 patients (73%, 58/81), the plastic surgeon performed the closure of the skin by the means of a flap. See Fig. 1 for an overview of surgical procedures performed on patients born with MMC at our center.

Hydrocephalus

Hydrocephalus was present in 78 patients (84%), of whom 74 underwent VP shunt placement as initial treatment, 2 underwent ETV as primary treatment, and 2 patients were successfully treated conservatively. See Fig. 2 for a flowchart showing the management of hydrocephalus. Five (7.1%) patients were treated within a week after closure of the MMC, 59 (84.3%) between 1 week and 1 month after closure, and 6 (8.6%) between 1 month and 1 year after closure of the MMC. Of the 2 patients who underwent antenatal repair, 1 needed shunt placement due to hydrocephalus.

Fifty-five of 76 (72%) patients needed at least one revision during follow-up with a mean of 2.9 revisions (range 1–8 revisions). The main reasons were shunt malfunction in 65.5% and infection in 25.5% of cases. In 5 patients, an ETV was performed instead of a shunt revision (Table 2).

FIG. 1. An overview of the number of patients who underwent surgical procedures related to MMC throughout the years.

FIG. 2. Flowchart depicting the treatment of hydrocephalus among MMC patients. VPS = VP shunt.

Hindbrain Herniation

Radiological evidence of CMTII on MRI was present in 79 patients (90%), which was clinically relevant in 5 patients. In 3 patients (4%), posterior fossa decompression was indicated for bulbar symptoms in 2 patients and because of loss of motor function in the remaining patient (Table 3). Two patients improved after surgery; the remaining patient had to undergo reoperation with no clear clinical improvement.

Tethering of the Spinal Cord

Similar to CMTII, almost all patients showed a TSC on MRI. In 11 patients (12%), an untethering procedure was deemed necessary. The mean age at surgery was 8 years (range 3–16 years). The indications for surgery were back and leg pain in 1 patient, progression of scoliosis in 2, bladder dysfunction in 2, and decline in lower-limb motor function in 4 patients.

Since 2009, surgery has been performed using intra-

operative neuromonitoring (IONM), and in the majority of cases a widening nonresorbable dural patch was used.

Long-Term Quality of Life

Cognition

Thirty-two patients (37%, 32/86) attended regular schools, whereas 54 (63%, 54/86) go to special schools, and 4 patients did not reach school age at the time of this study. The presence of radiological hydrocephalus was significantly associated with following special education ($p < 0.015$).

Ability to Walk

Table 4 shows the ability to walk according to the Hoffer scale ($n = 86$; data were missing in 3 patients, and 4 patients were still under the age of walking at the time of the study; 18.6% of patients were able to walk independently at the last time of follow-up and 46.5% were nonambulators).

TABLE 2. Management of hydrocephalus

	No. of Patients (%)
Presence of hydrocephalus (n = 93)	
Yes	78 (83.9)
No	15 (16.1)
Primary treatment w/ a shunt (n = 82)	
Yes	74 (90.2)
No	8 (9.8)
Mean duration until op for hydrocephalus (n = 70)	
<1 wk	5 (7.1)
>1 wk to <1 mo	59 (84.3)
>1 mo to <1 yr	6 (8.6)
Reop during follow-up (n = 78)	
Yes	55 (70.5)
No	23 (29.5)
Reasons for revision (n = 55)	
Overdrainage	2 (3.6)
Infection	14 (25.5)
Malfunction	36 (65.5)
Check & change	2 (3.6)
CSF leakage	1 (1.8)
Eventual reop	
VP shunt	50 (90.9)
ETV	5 (9.1)

Urine Continence

We defined social continence as having no involuntary loss of urine between the clean intermittent catheterizations (CICs). There are various definitions for social continence depending on the purpose of research, but, in general, this term refers to an acceptable situation for the patient without significant disturbance of daily activities.

Sixty-eight patients (75%, 68/91) had social continence. Twenty-one patients (23%, 21/91) reported some degree of involuntary loss of urine in between the CICs.

All patients started with CICs and anticholinergics shortly after birth. In total, 8 patients received a bladder augmentation with or without a continent catheterizable stoma. Nine patients received a continent catheterizable stoma alone. One patient needed a temporary vesicostomy at the age of 2 years in order to protect the upper urinary tract. None of the patients born in our hospital experienced a significant deterioration of renal function.

Bowel Function

Ten patients had undisturbed bowel emptying, whereas 4 patients reported some fecal incontinence. The vast majority of the patients (84%) had severe difficulties in emptying their bowels properly (Table 4).

Discussion

In this study, we describe a contemporary cohort of infants who underwent postnatal repair for MMC. Hydrocephalus remains the main condition requiring surgical

TABLE 3. Management of hindbrain herniation

	No. of Patients (%)
CMTII on imaging (n = 88)	
Yes	79 (89.8)
No	9 (10.2)
Clinical symptoms of CMTII (n = 74)	
Yes	4 (5.4)
No	70 (94.6)
Indication for decompression (n = 4)	
Central apnea	3
Stridor	0
Neck pain	1
Syrinx	0
Swallowing disorders	0
Initial decompression for CMTII (n = 2)	
Bone only	1
Duraplasty	1
No. of reops for CMTII (n = 1)	
1	1
2	0
>2	0
Need for tracheostomy	2

intervention in the first month of life for the majority of cases. Despite radiological diagnoses of CMTII and TSC, these can most often be treated conservatively. Interestingly, the rate of untethering surgery in our series is relatively low. Motor function skills, cognitive capacity, and the occurrence of bladder/bowel dysfunction are comparable to other case series such as the National Spina Bifida Patient

TABLE 4. Quality of life at last follow-up

	No. of Patients (%)
Ambulation according to Hoffer (n = 86)	
Nonambulators	40 (46.5)
Nonfunctional ambulators	7 (8.1)
Household ambulators	9 (10.5)
Community ambulators	14 (16.3)
Independent ambulators	16 (18.6)
Level of education (n = 90)	
Special education	54 (60.0)
Regular education	32 (35.6)
Too young	4 (4.4)
Bowel function (n = 90)	
Constipation	76 (84.4)
Incontinence	4 (4.4)
Normal	10 (11.8)
Urinary continence (n = 91)	
Yes	68 (74.7)
No	23 (25.3)

Registry (NSBPR) consisting of almost 8000 patients (age range 0–89 years). The NSBPR aims to identify variation between institutes and its impact on clinical outcomes, facilitate research, and improve health-related quality of life among patients with spina bifida.²⁸

Hydrocephalus

Our rate of 84% is comparable to that of both the NSBPR and MOMS trial. Kim et al.^{13,14} looked at shunting rates among NSBPR centers⁸ and included 4448 patients with MMC. Eighty percent of patients had undergone at least one procedure for hydrocephalus. Among the 23 centers, the shunt rate varied from 72% to 96%. The shunt rate in the MOMS trial was 82% in the postnatal group and 40% in the prenatal group.¹ Tulipan et al. showed similar outcomes for the entire MOMS trial population in 2015.³⁰

Seventy-one percent of our patients needed at least 1 revision, which is a very significant number but comparable to that reported in the literature, with rates ranging between 64% and 95%. We found a shunt infection rate of 25%, which is rather high compared with that of Bowman et al. (10%) but comparable to that of Tuli et al. (24%).^{5,29} Overall, this demonstrates that hydrocephalus is a significant and very challenging condition in MMC patients, with a profound effect on cognitive function.

In recent years, the role of ETV as a treatment option for hydrocephalus has been reemerging. In a pediatric population of 501 patients with mixed etiologies of hydrocephalus (e.g., tumor, aqueductal stenosis) the success of ETV was 71%;¹⁷ 41.5% of the ETVs failed during follow-up, and 24% of these patients underwent re-ETV and 76% required shunting. Patients 0–6 months old were more likely to have ETV failure, which is also the age category in which most patients in our series undergo a CSF-diverting procedure. Another study consisting of 18 pediatric patients with MMC treated with ETV or VP shunt showed a similar rate of ETV success (37.5%).²⁶ Because of the risk of infection as well as the high reoperation rate in VP shunting, we consider ETV the preferred approach whenever feasible; ETV also shows promising results in patients who underwent prenatal closure.⁶

The rate of shunt infection at our center may be deemed as relatively high (with 14 of the 74 shunts being infected). Throughout the years, multiple recommendations have been proposed to decrease the rate of shunt infections.^{7,15,21,27} Having a specific shunt protocol can help decrease infection rates, as can the use of antimicrobial-impregnated and -coated shunt catheters. Intraoperative irrigation with saline or the use of antimicrobial sutures for wound closure also show positive effects on shunt infection rates.

In a retrospective study of 127 patients with MMC, the concurrent placement of a shunt with the repair of the MMC defect, versus a delayed insertion of the shunt after repair, did not lead to any significant rates of shunt complications.²⁵

CMTII

At our institution, when patients with MMC present with complaints of hindbrain herniation, a thorough assessment including MRI and sleep and swallow studies is

performed. If indeed clinically relevant CMTII is present, we first establish the functioning of the shunt. We only consider a surgical decompression if there is no doubt about shunt function and the Chiari complaints are substantial. The rate of decompression surgery for CMTII in our center (4%) is rather low compared with that of 9.15% in the NSBPR.¹³ Adzick et al.¹ found a 5% decompression surgery rate in the MOMS trial for the postnatal group and a 1% rate for the prenatal group at the 1st year after birth. In our cohort, 2 patients underwent decompression surgery for CMTII before the age of 12 months (at 4 and 8 months). The third patient was 3.5 years old at surgery. It is well known that CMTII can become manifest at older ages, emphasizing that a long follow-up is needed to determine the incidence of CMTII decompression surgery.

Among the 23 NSBPR centers enrolling more than 10 patients, the rate of decompressions varied from 1.28% to 23.57%. Reoperation was performed in 10.8% of the patients who underwent a CMTII decompression. In 2.7% of this group, even a second or third reoperation was needed. At our center, one patient underwent reoperation. Since only 3 patients underwent surgery for CMTII, this constitutes a 33% reoperation rate. Due to these small numbers, a proper comparison is limited.

TSC

The percentage of cases that required surgical intervention for TSC in our series is relatively low. Similar cohort series, however, have reported a long-term risk of surgery for TSC of up to 32%.⁵ On the other hand, the oldest patient in our cohort was 18 years, and the majority are several years younger, which might in part explain our lower rate. Furthermore, the indication for TSC surgery at our institution is based on very stringent criteria; hence, this could also account for differences in surgery rates compared with other single-center series.

The treatment of clinically important TSC is challenging and often requires surgical interventions with not always successful outcomes. As such, an optimal closure technique at the initial surgery seems essential to prevent such long-term complications. With this in mind there is some concern about antenatal repairs. Despite clear benefits on motor skills and CMTII, the MOMS cohort also had a relatively higher need for TSC surgery in infants who underwent prenatal closure. Albeit not significantly different, in 8% of fetal surgery cases an untethering surgery was performed at the age of 12 months compared with only 1% in the postnatal group. This emphasizes the importance of long-term follow-up studies as are currently organized by the MOMS centers. On the other hand, the surgical technique to close the MMC during open fetal surgery is in principle similar to what is used in postnatal repair. Ongoing research on improvement of fetal surgery for MMC, especially of the fetoscopic technique, is therefore of the utmost importance.²²

Ability to Walk

Of our patients, 19% were able to walk independently, which is comparable to the 21% in the postnatal group of the MOMS trial. It is less than half of the 42% of patients who were able to walk independently in the prena-

tal MOMS trial group, showing the clear benefit of fetal MMC closure on this socially important factor.

Cognition

In our cohort only one-third of patients attended regular schools, whereas the majority needed special education. The radiological presence of hydrocephalus was the most important risk factor for cognitive developmental delay. This is similar to what has been published by various groups.^{3,18} Our relatively high rate of shunt infection might also play a role in this. Interestingly, a more recent cohort series consisting of 108 cases from the MOMS trial did not confirm this association. They observed no difference in cognitive function between patients without hydrocephalus, shunt-treated hydrocephalus, or untreated hydrocephalus.¹⁰

Before the MOMS trial, Johnson et al. showed that shunt-treated MMC patients who underwent antenatal MMC closure had lower neurodevelopmental outcome scores at the age of 2 years.¹² A systematic review by Inversetti et al. demonstrated no differences in the risk for neurodevelopmental impairment between antenatal- and postnatal-treated infants.¹¹

Overall, the correlation between hydrocephalus and a higher need for special schools in our cohort of MMC patients represents only part of the literature and may represent the effects of shunt placement and high occurrence of revision surgery.

Strengths and Limitations

The main strength of this study is related to the unique standardized multidisciplinary follow-up clinic at our institution, which results in a low lost-to-follow-up rate. This provides a wealth of information about contemporary outcomes of infants with MMC. Our study is limited by its retrospective design and the inevitable loss of data.

Conclusions

This study provides an overview of current outcomes for infants born with an MMC managed at our center. The overall outcomes are similar to those reported in the literature. However, we did observe a relatively low incidence of surgery for TSC. This study will serve as a historical cohort for comparison with future fetal surgery cases operated on at our center in the coming years. Hydrocephalus is highly prevalent in postnatally treated MMC patients, as is the revision rate for VP shunts, in which infection is a major reason for revision. In our study as in much of the literature, hydrocephalus is significantly correlated with a low cognitive function. Fetal surgery for MMC has been shown to halve the need for shunt treatment in a select group of pregnancies, and this constitutes a major indication for our center to undergo the transition to a fetal surgery center. Since shunt malfunction and shunt infection are frequently seen in shunt-treated MMC patients, we strongly promote ETV to be considered in case the need for a shunt revision is anticipated. The fetal benefits of open fetal surgery for MMC are well established in a select group of MMC pregnancies, yet it is well known and also illustrated by our series that MMC-related complications such as clinically

relevant CMTII and especially TSC often occur years after closure of the MMC. Therefore, multicenter, long-term clinical data, especially regarding TSC in antenatally operated MMC patients compared with postnatally operated MMC patients, are eagerly awaited; an anticipated higher rate may stimulate ongoing research on further improvement of fetal closure techniques.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Spoor, Gadjradj, de Jong. Acquisition of data: Spoor, Gadjradj. Analysis and interpretation of data: Spoor, Gadjradj, Eggink, Scheepe, de Laat, van Veelen. Drafting the article: Spoor, Gadjradj. Critically revising the article: Gadjradj, Eggink, DeKoninck, Lutters, Scheepe, van Meeteren, de Laat, van Veelen, de Jong. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Spoor. Statistical analysis: Spoor. Administrative/technical/material support: Gadjradj.

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