Prospective observational cohort study on epidemiology, treatment and outcome of patients with traumatic brain injury (TBI) in German BG hospitals


ABSTRACT

Objectives Since 2000/2001, no large-scale prospective studies addressing traumatic brain injury (TBI) epidemiology in Germany have been published. Our aim was to look for a possible shift in TBI epidemiology described in other European countries, to look for possible changes in TBI management and to identify predictors of 1-year outcome especially in patients with mild TBI.

Design Observational cohort study.

Setting All patients suffering from a TBI of any degree between 1 October 2014 and 30 September 2015, and who arrived in one of the seven participating BG hospitals within 24 hours after trauma, were included.

Participants In total, 3514 patients were included.

Outcome measures Initial care, acute hospital care and rehabilitation were documented using standardised documentation forms. A standardised telephone interview was conducted 3 and 12 months after TBI in order to obtain information on outcome.

Results Peaks were identified in males in the early 20s and mid-50s, and in both sexes in the late 70s, with 25% of all patients aged 75 or older. A fall was the most frequent cause of TBI, followed by traffic accidents (especially bicyclists). The number of head CT scans increased, and the number of conventional X-rays of the skull decreased compared with 2000/2001. Besides, more patients were offered rehabilitation than before. Though most TBI were classified as mild, one-third of the patients participating in the telephone interview after 12 months still reported troubles attributed to TBI. Negative predictors in mild TBI were female gender, intracranial bleeding and Glasgow Coma Scale (GCS) 13/14.

Conclusion The observed epidemiological shift in TBI (ie, elderly patients, more falls, more bicyclists) calls for targeted preventive measures. The heterogeneity behind the diagnosis ‘mild TBI’ emphasises the need for defining subgroups not only based on GCS.

Strengths and limitations of this study

► The study population reflects a real-world cohort from multiple centres evenly distributed throughout Germany, which should prevent a regional bias.
► Our study is the first large-scale prospective cohort study since 2000/2001, which addresses traumatic brain injury (TBI) epidemiology in Germany.
► We closely adapted the methodological design to a previous study conducted in two regions of Germany in 2000/2001, in order to facilitate the evaluation of a possible epidemiological shift and improvement in TBI management.
► Our cohort is not population based, that is, some epidemiological parameters such as incidence cannot be calculated.
► Since informed consent to participate in the telephone interview after 3 and 12 months was only obtained from 21.2% of all participants, there might be a selection bias regarding the results of the telephone interview.

INTRODUCTION

Besides stroke, traumatic brain injury (TBI) is one of the most important causes of disability and death in adults. However, in contrast to stroke, epidemiological knowledge on TBI is relatively sparse. The incidence in Western Europe including Germany is estimated between 250 and 350 cases TBI per 100 000 population. There are marked differences not only in incidence rates across the world, but also in other epidemiological parameters such as injury characteristics, making it difficult to transfer results from epidemiological studies on other countries, even...
study adapted methodologically to the above-mentioned criteria defined by Rickels et al in a previous study:

Symptoms defining TBI:
- Nausea and/or vomiting
- Headache
- Loss of consciousness (LOC)
- Anterograde and/or retrograde amnesia
- Impaired consciousness and/or impaired vigilance
- Fracture of skull and/or face
- Focal neurological sign

ICD-10 diagnoses defining TBI:
- S02: Fracture of skull and of facial skull bones, without S02.5: Dental fracture
- S04: Injury of cerebral nerves
- S06: Intracranial injuries
- S07: Crushing of head
- S09: Other, no specified head injuries

Only adult patients were included, that is, patients aged <18 at the time of injury were excluded. No other exclusion criteria were implemented.

Patient and public involvement
Patients or the public were not involved in the design, or conduct, or reporting, or dissemination of this research.

Initial care
Among all patients included in the study, initial care was documented by a standardised documentation form. In those patients who were admitted by an emergency rescue service, details on prehospital care including GCS and neurological findings were documented. For all patients, cause and type of trauma, clinical features and neurological findings including GCS in the emergency room, Injury Severity Score (ISS), diagnostic procedures, diagnosis and the further proceeding/outcome after initial care were reported.

Acute hospital care
Among the patients who were hospitalised in a participating institution after completion of initial care, acute hospital care was documented by a standardised documentation form. The duration of the stay on an intensive care unit (ICU), intermediate care unit (IMC) and/or general ward including clinical findings, diagnostic procedures, therapeutic interventions and medical complications were documented. Clinical findings at the end of the acute hospital care in addition to further proceedings were reported, as well as cause of death, if applicable.

METHODS
Seven hospitals (BG Klinikum Unfallkrankenhaus Berlin, BG Universitätsklinikum Bergmannsheil Bochum, BG Unfallklinik Frankfurt, BG Klinikum Bergmannstrost Halle, BG Klinikum Hamburg, BG Unfallklinik Ludwigshafen and BG Unfallklinik Murnau) and the Department of Medical informatics, Biometry and Epidemiology of the Ruhr-University Bochum participated in the study. Patient recruitment and documentation of initial care, acute hospital care and rehabilitation with standardised documentation forms adapted from the forms used by Rickels et al. were conducted by the participating hospitals. Standardised follow-up telephone interviews after 3 and 12 months and data management were performed by the department of medical informatics, biometry and epidemiology. The three documentation forms and two versions of the telephone interview (self-rating and foreign rating) are provided as supplementary material, translated into English (online supplemental material 1–5). We used the STROBE cohort checklist when writing our report.9
Rehabilitation
For those patients who underwent rehabilitation after termination of acute hospital care, this was also documented by a standardised documentation form. In contrast to initial care and acute hospital care in which the participating hospitals were directly involved, for rehabilitation many patients were referred to an external rehab hospital. In these cases, the rehab hospital was contacted by the participating hospital in order to obtain the information required to fill in the documentation form if written informed consent was provided by the participant. If, for some reason, this was not possible, we strove to extract the relevant information from the final doctor’s report provided by the rehab hospital.

Follow-up telephone interview
In the patients who had provided written informed consent, a standardised telephone interview was conducted 3 and 12 months after TBI, in order to obtain information on the further course, complications, treatment, interventions and outcome after TBI. Two different versions of the interview were available: when possible, a self-rating version of the interview was used. If the patients were too severely handicapped to participate in the interview, an alternative foreign-rating version was used, and questions were asked to the primary caregiver of the patient. In order to assimilate information on the reasons for a lacking consent to participate in the telephone interview, these reasons were assessed by a short questionnaire as of February 2015. The telephone interview was conducted by a call centre located at the Department of Medical informatics, Biometry and Epidemiology of the Ruhr-University Bochum.

Data flow
Documentation forms were filled out in the recruiting hospitals, pseudonymised and sent to the data management. If patients or their legal guardians (if applicable) provided written informed consent for the telephone interviews, their contact data were transferred separately from the documentation form to the Department of Medical informatics, Biometry and Epidemiology of the Ruhr-University Bochum, in order to enable the call centre to contact the patients after 3 and 12 months.

Statistical analysis
Characteristics of participants are presented descriptively with mean and SD for continuous variables and counts and proportions for categorical variables. Association of patients’ age, gender and cause of TBI with severity of TBI was checked in a loglinear model. Besides, in a prognosis model, the presence of TBI-related health reports in patients with mild TBI was investigated. For estimations of outcome predictors, a logistic regression model was used, and the OR and 95% CIs were calculated for each parameter. Statistical analysis was performed using the statistical package SAS, V.9.4 (SAS Institute).

RESULTS
Initial care
Initial care was documented in 3524 patients who were treated in the seven participating hospitals. After exclusion of 10 patients who were aged <18 years and therefore did not meet the inclusion criteria, 3514 patients were included in the analysis (figure 1). Overall, 59.2% were men and 40.8% were women, with a mean age of 54.5 years (SD 22.6, quartile 1 33, quartile 3 75, range 18–103) (figure 2). ICD-10 main diagnosis was S09.9 in 18.6%, S02.9 in 11.2%, S06.0 in 37.4%, S06.1 in 0.4%, S06.2 in 1.7%, S06.3 in 1.6%, S06.4 in 0.9%, S06.5 in 5.6%, S06.6 in 7.5%, S06.7 in 3.3%, S06.8 in 1.2%, S06.9 in 3.3% and other in 0.9%. In 6.6% of all patients, ICD-10 diagnosis was missing.

Prehospital GCS was available in 68.8% of all patients, and in 94.5% of the patients when an emergency physician was present at the accident site. In these patients, initial TBI severity was classified as mild in 85.1%, moderate in 7.2% and severe in 7.7% (table 1). In the emergency room of the treating hospital, GCS was assessed in 93.6% of all patients. Among these patients, 87.3% had mild, 3.3% moderate and 2.3% severe TBI. In 7.1% of these patients, GCS was available, but not usable to classify initial TBI severity due to previous application of sedative drugs (table 1). For most of these sedated patients (209 of 234), prehospital GCS was available and indicated that TBI was severe in 53.1%, moderate in 20.1% and mild in 26.8% of these patients. Overall, 21.3% of all patients presented autonomously at the hospitals’ emergency room, without any prehospital medical contact. In these patients, prehospital GCS generally was not available.

ISS at the emergency room was documented in 72.9% of all patients. In most of them (82.3%), injury was classified as mild to moderate (ISS <16). Patients with mild-to-moderate injury (ISS <16) generally had only mild TBI (97%), whereas this was the case only in 55.9% of the patients with an ISS ≥16.

In 14.4% of all patients, alcohol was a relevant cofactor, in 0.5% illegal drugs, in 0.5% a combination of both. A total of 17.3% of all accidents that led to a TBI were insured by the social accident insurance (occupational or way-to-work accident).

In 71% of all patients, a CT scan of the head was performed in the emergency room, whereas 4.8% of all patients received a conventional X-ray examination of the skull. In patients with GCS<9, 80% received a CT scan of the head within 30 min after arrival.

The most frequent causes of TBI were falls, followed by traffic accidents and external force (figure 3A). Among the traffic accidents, most frequently cyclists without helmet were injured, followed by passenger car occupants (figure 3B). There were marked differences in the causes of TBI with respect to patients’ age: Whereas falls dominated in patients aged >50 (71.3%), the most frequent cause in patients ≤50 was trauma by external force (30.6%), followed by traffic accidents (29.0%) and falls (27.3%).
Looking for a possible association between patients’ age, gender and cause of TBI with TBI severity (classified by GCS at the emergency room or, if then sedated, at the accident site before sedation) using a loglinear model, we found a significant association of age (p=0.019) and cause of TBI (p<0.001), but not of gender (p=0.143) with TBI severity. Moderate-to-severe TBI were more frequent in elderly patients with falls (male and female), and in middle-aged male with falls or traffic accidents (figure 4). After initial care, 27.6% remained in an ambulatory setting, whereas most patients were hospitalised for further treatment. Seven patients (0.2%) died during initial care, after having arrived at the emergency room.

Acute hospital care

In 2375 patients, acute hospital care was documented in addition to initial care (figure 1). Overall, 60.8% were men and 39.2% women, with a mean age of 53.3 years. Overall, 35.5% patients initially were admitted to an ICU, 14.5% to an IMC and 46.4% to a standard ward. In 3.6%, no information was available. During ICU treatment, 23.1% of the patients underwent tracheotomy, and 47.6% at least one surgical intervention. The

### Table 1  TBI severity classified by GCS in the prehospital and emergency room setting (n=3514 patients)

<table>
<thead>
<tr>
<th>TBI severity (classified by GCS)</th>
<th>Prehospital</th>
<th>Emergency room</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (GCS 13–15)</td>
<td>2059 (58.6%)</td>
<td>2871 (81.7%)</td>
</tr>
<tr>
<td>Moderate (GCS 9–12)</td>
<td>174 (5.0%)</td>
<td>108 (3.1%)</td>
</tr>
<tr>
<td>Severe (GCS 3–8)</td>
<td>186 (5.3%)</td>
<td>75 (2.1%)</td>
</tr>
<tr>
<td>Sedated</td>
<td>0 (0%)</td>
<td>234 (6.7%)</td>
</tr>
<tr>
<td>All</td>
<td>2419 (68.8%)</td>
<td>3288 (93.6%)</td>
</tr>
<tr>
<td>GCS missing</td>
<td>1095 (31.2%)</td>
<td>226 (6.4%)</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; TBI, traumatic brain injury.
surgical interventions included extracranial head surgery (30.9%), intracranial pressure (ICP) monitoring via ICP probe/external ventricular drain (16.4%), surgical cerebral decompression (e.g., haematoma evacuation, decompressive craniectomy; 20.6%), conversion of open TBI to closed TBI (3.4%), removal of foreign particles (0.6%) and implantation of a shunt system (1.3%). Most patients spent only 1 day on ICU (figure 5).

Overall, 96.5% received at least one CT scan of the head, 6.4% at least one MRI scan of the head, and 4.5% at least one electroencephalography (EEG).

Regarding rehabilitative treatment during acute hospital care, 46.5% of these patients were treated with physiotherapy, 4.7% with occupational therapy, 5.9% with speech therapy and 3.1% with neuropsychological therapy.

In 19.7% of the patients, at least one medical complication was documented (figure 6). In 2.3% of the patients, epileptic seizures occurred during acute hospital care.

At discharge, 22.3% of the patients complained of subjective symptoms. Most frequent symptoms at discharge were headache (18.6%) and dizziness (10.2%). Neurological deficits at discharge were present in 13.1% of the patients. Overall, 69.6% were discharged at home (with domestic nursing care being necessary in 1.1% of the patients), 12.4% at a rehabilitation unit, 7.5% at
another acute hospital. Overall, 4.1% were discharged at a nursing home.

One hundred and one patients (4.3%) deceased during acute hospital care. Main cause of death was TBI and/or cerebral complications, followed by cardiac and pulmonary causes and infections.

Rehabilitation
In 210 patients, rehabilitation was documented in addition to initial and acute hospital care (figure 1). Mean age of this group was 59.7 years (66.7% male, 33.3% female). Mean duration of rehabilitation was 62.3 (SD ±65.9) days. After rehabilitation, 44.3% were discharged at home, 20.5% at another hospital, 11.9% at a nursing home and 11.0% at a facility for disabled persons. Ten patients (4.8%) deceased during rehabilitation. In only 9.3% of the patients, their working capacity when discharged from rehabilitation was considered to be similar to that before TBI.

Follow-up telephone interview
In total, 748 patients or their primary caregivers gave informed consent to participate in the telephone interview three and 12 months after TBI. At the self-rating interview, 527 patients participated after 3 months and 465 after 12 months, whereas 57 caregivers participated at the foreign rating version after 3 months and 45 after 12 months. In 450 patients, self-rated interview at 3 and 12 months was available (figure 1). Of this group, 62.0% were male and 38.0% female (mean age 54.8 years). Initial TBI severity according to GCS assessed in the emergency room was mild in 81.6% of these patients. The question ‘Do you still have troubles that result from TBI?’ was affirmed by 36.4% at 3 months and 35.3% at 12 months (figure 7A,B). Before TBI, 43.3% of the patients participating in the interviews had a full-time job, 10.9% a part-time job, 37.6% were pensioners. The question ‘Did your occupation change due to TBI?’ was affirmed by 8.7% after 3 months and 7.6% after 12 months (figure 7C,D).

Predictors of outcome after 12 months in mild TBI
Considering only the patients with mild TBI (n=414), that is, with GCS 13–15 when arriving at the emergency room or, if then sedated, with GCS 13–15 at the accident site before sedation, 37.0% answered ‘yes’ when they were asked if they still had troubles that resulted from TBI after 12 months (telephone interview, either self-rating or foreign rating version). Overall, 108 of these patients had an ICD-10 diagnosis defining intracranial bleeding (S06.2, S06.3, S06.4, S06.5, S06.6 or S06.8), and 70 of them a GCS other than 15. Due to missing values, 390 patients comprised the population for the prognosis model. The risk for persisting troubles after 12 months

Figure 5  (A) Duration of intensive care unit (ICU) treatment (n=842). (B) Duration of acute hospital care (n=2375).

Figure 6  Medical complications during acute hospital care. Multiple nominations were permitted (n=2375).
was elevated in patients with an ICD-10 diagnosis defining intracranial bleeding as compared with other ICD-10 diagnoses (OR 2.76), and in patients with a GCS of 13 or 14 as compared with GCS 15 (OR 1.82). The risk was reduced in male versus female patients (OR 0.62) and in patients with specified alcoholic intoxication (OR 0.45).

Age, cause of TBI or insurance state did not significantly predict persisting troubles after 12 months in mild TBI (figure 8).

**DISCUSSION**

**Epidemiology and prevention**

During the past two decades, an epidemiologic shift has been observed in high-income countries, with patients with TBI becoming older and falls surpassing traffic accidents as the main cause of TBI. Our results confirm this trend, with a quarter of all patients being 75 years or older. Looking at the age–gender distribution, a clear qualitative difference can be observed in comparison to the data obtained by Rickels et al in 2000/2001. They found a pronounced peak around the 20th year of age in males, whereas the number of patients with TBI diminished with increasing age in males, and was more or less equally distributed across all ages in females. In contrast, we observed three similar peaks in males in the early 20s, mid-50s and late 70s, whereas females had one clear peak in the late 70s. In this age, the typical male preponderance can no longer be observed, which might be a result of the higher expectation of life in females. An age–gender distribution similar to our study was observed by Maegele et al 2013–2017 in a German registry-based study when looking at moderate-to-severe TBI only. Their possible explanation for the different peaks (‘young male risk takers’, ‘older male risk takers’, ‘falls in elderly’) might also be true for our study population with a high amount of mild TBI. The finding of a peak in the late 70s is in line with observations in other countries, indicating an increase in TBI-related deaths in subjects aged ≥75 years. Our data show an association between TBI severity, age and cause of TBI, with moderate-to-severe TBI occurring more frequently in elderly patients with falls, and therefore provide an explanation for this increase in TBI-related deaths. There is an urgent need to extend and improve evidence-based interventions to prevent falls in elderly persons such as multifactorial and exercise interventions, in order to reduce TBI related morbidity and mortality in this vulnerable group.

Although the portion of traffic accidents did not differ between our study and the study of Rickels et al, there was a shift within the group of traffic accidents: Bicyclists, especially non-helmet wearing bicyclists, now made up the largest group within the traffic accidents. This is in line with another study, which showed a 54% increase in bicycle-related TBI between 1998 and 2012 in the Netherlands. Ironically, this development represents a relapse into challenges concerning motorcyclists which in Europe have already been solved but are still present in Asian countries. It has been demonstrated that helmet...
use is able to reduce TBI incidence and severity not only in young children, where it is widely accepted, but also in elderly subjects. The implementation of mandatory bicycle helmet use, therefore would constitute a cost-effective measure to reduce TBI-related morbidity and mortality in cyclists.

Development of TBI management between 2000/2001 and 2014/2015

Regarding emergency imaging, management in the emergency room has substantially changed compared with the 2000/2001 study by Rickels et al.: CT scans are now performed more often (71% vs 19.3%) and more rapidly (severe TBI: 80% vs 45.2% within 30 min after arrival), whereas the number of conventional X-rays of the skull has remarkably diminished (4.8% vs 82%). A similar shift has also been observed in other countries. Although X-ray of the skull has been considered to be only useful in exceptional cases since the 1980s, it has taken a long time to implement this recommendation in clinical practice, perhaps for medicolegal reasons. Recently, the efficacy of dose reduced CT scan of the whole body in multiply injured patients has been proven. A continuation of this development for cranial CT scans can be expected, since CT is currently considered as the gold standard in patients who have suffered a head injury. However, the available clinical information on the patients who underwent head CT is not sufficient to judge if CT indication was in accordance with current guidelines (see ‘limitations’).

Another problem identified by Rickels et al was the low rate of GCS and/or neurological status recording, despite current guideline recommendations. Neurological assessment including GCS, pupil reaction and signs of asymmetry performed repeatedly in the prehospital and emergency room setting is crucial to assess TBI severity and secondary deterioration due to intracranial complications with the need of a neurosurgical intervention. It is therefore very reassuring that this was also found to be substantially improved in our study, with GCS being recorded in 94.5% of the patients when an emergency physician was present at the accident site.

A third important issue observed by Rickels et al was the low portion of patients (3.7%) who underwent early rehabilitation after TBI. In our study, 12.4% underwent immediate rehabilitation after acute hospital care, and in another 1.6% delayed rehabilitation was documented. Since early rehabilitation is considered to reduce functional deficits and improve long-term quality of life and participation, this is also an important step towards an improved care of patients with TBI.

Persisting health complaints in mild TBI

Regarding the outcome after 12 months, we were especially interested in patients with mild TBI, which is the largest subgroup of TBI. Available literature on prognosis
and outcome of mild TBI is heterogeneous and contradictory: Whereas a large review of the literature in 2004 reported a recovery of symptoms within 3–12 months in most patients,25 there is an increasing number of studies which report persisting symptoms 12 months after mild TBI in up to 58% of patients.26–28 In our study, approximately one-third of these patients complained of troubles related to TBI after 3 and 12 months. Given this consistency of reported symptoms between 3 and 12 months, spontaneous recovery might not be expected if patients still report symptoms 3 months after trauma, which should lead to intensified diagnostic and therapeutic efforts at this time.

GCS 13 or 14 and especially an imaging-based diagnosis of intracranial bleeding were predictors of persistent symptoms after 12 months, whereas male gender and alcoholic intoxication were associated with a more favourable outcome. In previous studies females were reported to more often develop chronic post-traumatic headaches after mild TBI and to report lower health-related quality of life in TBI of all severities.29–30 A disruption of hormone production after injury was discussed as a possible explanation.31 However, the exact mechanism for this finding is not known. Although alcoholic intoxication is an accepted risk factor for TBI, our results suggest a reduced risk of persisting symptoms after 12 months. Similar results have been reported by other groups,32 and a potential neuroprotective effect is discussed.33 Patients with a diagnosis of intracranial bleeding had a higher risk of persistent symptoms after 12 months as compared with other patients in this study, which corresponds with previous observations,26–30 and can easily be explained by the apparent structural damage in these patients. This finding highlights the problem linked to the GCS-based diagnosis of mild TBI, including a heterogenous group of patients ranging from a mild concussion to a potentially life-threatening structural damage revealed by CCT.33 It also supports the opinion that TBI with GCS 13 is substantially different from TBI with GCS 15, although both are classified as ‘mild TBI’.34–35 Recently attempts have been made to subclassify patients with mild TBI (eg, complicated vs uncomplicated mild TBI) according to their prognosis.35–36 Although these subclassifications are not widely accepted so far, our results strongly encourage such a subclassification of mild TBI, including imaging and biomarker findings as well as certain sociodemographic and psychologic factors, which have also been found to predict mild TBI outcome in other studies.35–36

**Limitations**

In our study, we used a very simplified definition of TBI. The main reason for using this definition was to obtain comparability to the 2000/2001 study by Rickels et al.7, the only large-scale prospective epidemiological study conducted in Germany so far. Since we were interested in examining a possible epidemiological shift and a possible change of TBI management as compared with the 2000/2001 study, it was necessary to use the same inclusion criteria as they did. However, this simplified TBI definition allowed the inclusion of patients for example, with head injury and headache only, but without any signs of brain dysfunction, which is an inevitable, but considerable limitation of our study.

Besides, we used a unidimensional classification of initial TBI severity into mild, moderate or severe based on the GCS, which was also used by Rickels et al.7 Although being the most commonly used approach in epidemiological studies,30–32 this unidimensional classification is often criticised since it ignores the mechanistic heterogeneity of TBI, and does not consider brain imaging findings.33 Therefore, studies focusing on mild TBI often use additional parameters such as duration of LOC and duration of amnesia in order to create more homogenous groups.37 However, the use of LOC and amnesia as additional parameters is not undisputed, and both are deemed unreliable when applied to TBI by some authors.39 In order to warrant comparability to the 2000/2001 study, we decided to use the GCS-based classification of TBI severity, despite its limitations.

A further limitation of our study is that the clinical information that was obtained on initial care, acute care and rehabilitation is not sufficient to judge adherence to current guideline recommendations.22 This applies not only to the indication for CT of the head and to rehabilitation, but also to different surgical and non-surgical treatment strategies or to measurement and management of ICP.

Finally, the outcome after 3 and 12 months was assessed by a telephone interview consisting of 14 (foreign-rating version) or 15 (self-rating version) questions addressing subjective complaints, but also treatment and personal situation including changes at the workplace. Again, this telephone interview was designed according to the telephone interview used by Rickels et al.7 Similarly to them, we did not use established TBI outcome questionnaires such as the Glasgow Outcome Scale or the Rivermead Post-Concussion Questionnaire, which hampers the comparability to other studies, and therefore has to be mentioned as further limitation.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Requests for access to extra data will be considered by the corresponding author (peter.schwenkreis@rub.de).

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