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# Outcome von Patienten mit erworbener Hirnschädigung

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# Kapitel 1

## 1.1 Krankheitsbilder

Erworbene Hirnschädigungen, zum Beispiel Schädel-Hirn-Trauma (SHT), zerebrovaskuläre Erkrankungen oder postanoxische Enzephalopathien sind wesentliche Ursachen für schwere Bewusstseinsstörungen, Behinderung und lebenslangen Pflegebedarf. Weltweit führen zerebrovaskuläre Ereignisse wie zum Beispiel ischämischer Schlaganfall oder subarachnoidale Hirnblutungen zu mehr als 35 Millionen Lebensjahren mit Behinderung.[1] Jährlich kommt es in Deutschland bei ca. 27000-40000 Einwohnern zu einem schweren SHT[2,3] bei ca. 130 000 zu einem auf einer stroke unit zu behandelneden Schlaganfall [4], und bei ca. 80000 zu reanimationspflichtigen kardiovaskulären Ereignissen.[5] Mortalitätsraten liegen zwischen 30 - 50% [4,5,6], bei Patienten, bei denen am Unfallort schwerste SHTs diagnostiziert werden, wird sogar eine Letalität von 90-92% angegeben.[7] Von den überlebenden Patienten weisen ca. 30-50% länger anhaltende schwere Störungen des Bewusstseins auf.[5,6,8] Störungen des Bewusstseins reichen von nur leicht herabgesetztem Bewusstsein für die eigene Person, die Umgebung oder beides bis hin zur völligen Bewusstlosigkeit, wie sie beispielsweise während eines Komas vorliegt. Patienten im Koma sind nicht erweckbar, haben kein Wahrnehmungsvermögen und der Schlaf-Wach-Zyklus ist aufgehoben.[9] Patienten mit *schweren* Bewusstseinsstörungen befinden sich meist entweder im *unresponsive wakefulness syndrom (UWS)* oder dem *minimally conscious state (MCS).* Der Begriff UWS wurde erst 2010 geprägt und bezeichnet den Zustand der früher als *vegetative status (VS)* bezeichnet wurde, aber auch in aktuellen Publikationen noch verwendet wird. [10] Patienten im VS öffnen zwar spontan die Augen, nehmen aber sich selbst und ihre Umgebung nicht wahr und zeigen nur motorische Reflexantworten. Patienten im MCS zeigen Reaktionen oder Verhaltensweisen, die auf erhaltenes Bewusstsein hindeuten, wie z.B. Blickfixation, Blickfolgebewegungen oder Befolgen einfacher Aufforderungen.[11] Jährlich sind allein in Deutschland etwa 3000-5000 Patienten von schweren Bewusstseinsstörungen betroffen.[12]

## 1.2 Prognose

Effektivere Systeme des Rettungswesens und intensivmedizinischer Fortschritt haben dazu beigetragen, dass Patienten mit schweren Hirnschädigungen eine bessere Überlebenschance haben. Bedenken bestehen hierbei vor allem, dass eine große Anzahl von Patienten nur mit schweren Bewusstseinsstörungen überlebt.[13] Obwohl das Thema kontrovers diskutiert wird, gibt es die Auffassung, dass es nicht unethisch ist, lebenserhaltende Maßnahmen abzubrechen, wenn ein Koma irreversibel ist. [14] Die Definition von MCS im Jahr 2002 [15] hat ebenfalls die Frage aufgeworfen, ob auch die Entwicklung von VS zu MCS als irreversibel anzusehen ist.[16]

Frühzeitige Prognosestellung hat daher für Angehörigenberatung aber auch für klinische Entscheidungen an Bedeutung gewonnen.[17] Zahlreiche Arbeiten hatten das Ziel, unabhängige Prädiktoren für eine realistische Prognosestellung zu identifizieren; allerdings sind langfristige Studien selten. Die wichtigsten Prädiktoren für negatives Outcome von Patienten, die nach Reanimation schwere Bewusstseinsstörungen aufwiesen, sind fehlende Pupillenreaktionen auf Lichtreize sowie fehlende Cornealreflexe, fehlende Reaktionen auf Schmerzreize nach dem 3. Tag nach Schädigung, beidseitig ausgefallene somatosensorisch evozierte Potenziale (SEP) sowie Konzentrationen des Serummarkers Neuronen Spezifische Enolase (NSE) über 33 µg/L. [18, 19, 20] Zur Messung der SEPs wird der N. medianus am Handgelenk repetitiv elektrisch stimuliert, während auf der Kopfoberfläche gleichzeitig die bioelektrischen Signale mit Hilfe von 5 EEG-Elektroden erfasst werden. Durch die Reizung werden kortikale Potenziale hervorgerufen, deren Ausprägung und zeitliches Eintreffen Aussagen über die somatosensorischen Bahnen bis zur Hirnrinde erlauben.[5] NSE ist ein neuronal exprimiertes Enzym, das im Fall eines erhöhten Spiegels im Blut den Untergang von Hirngewebszellen belegt. [5]

In Fig. 1 ist ein Algorithmus für die Prognose bei Patienten nach Reanimation dargestellt. Schlechtes Outcome wurde dabei definiert als Tod, schwere Bewusstseinsstörung nach 1 Monat oder schwere Behinderung und vollständiges Angewiesen sein auf pflegerische Unterstützung nach 6 Monaten. [18]

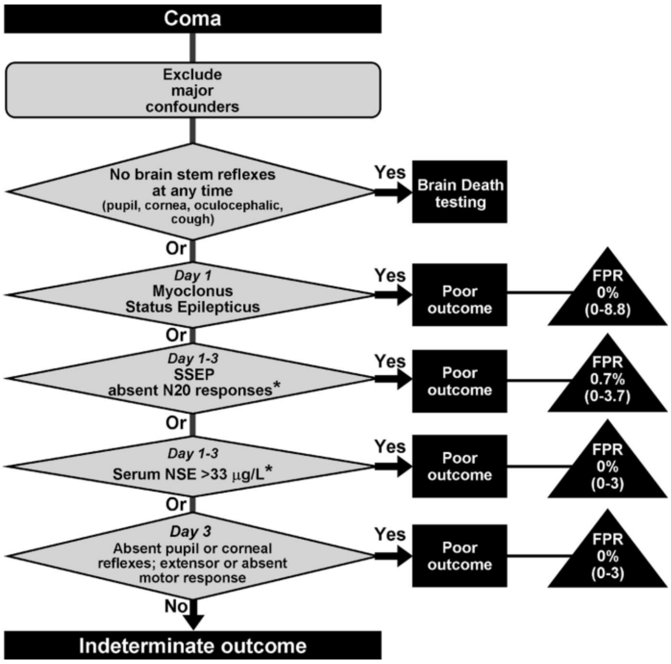


**Abbildung 1.1:** *Algorithmus zur Entscheidungsfindung in der Prognosestellung für komatöse Überlebende nach kardiopulmonaler Wiederbelebung; Zahlen in den Dreiecken geben Prozentsätze an, die Zahlen in Klammern sind das exakte 95% Konfidenzintervall. (übernommen aus Wijdicks et al., 2006)* [18]

**Diese Parameter sind eventuell nicht zur angegebenen Zeit verfügbar.*

*FPR=Falsch-positiv Rate*

In Bezug auf die Diagnose SAB existieren bisher kaum Studien, die explizit das Outcome schwer bewusstseinsgestörter Patienten untersuchen. Die Rate an Patienten, die bei Aufnahme in die Frührehabilitation noch schwere Bewusstseinsstörungen aufweist, liegt hingegen in neueren Studien nur zwischen 0-16%.[21, 22] Die bisherige Datenlage benennt eine Vielzahl an Prädiktoren, in einem aktuellen Review hingegen wurde berichtet, dass Alter, Klassifikation nach Hunt und Hess Skala, Fisher Skala und World Federation of Neurological Surgeons Skala sowie Größe des Aneurysmas die am häufigsten gefundenen Prädiktoren sind.[23] Nach der Hunt und Hess Skala wird der Schweregrad der SAB nach Symptomatik klassifiziert. Die WFNS beurteilt ebenfalls den Schweregrad der SAB, wobei sich diese Skala an der international anerkannten Glasgow Coma Scale (GCS; siehe unten)[24] orientiert. Das Ausmaß der Blutung wird anhand der Fisher Skala beschrieben.

Auf der Basis einer Datenbank mit über 8000 Patienten mit moderatem bis schwerem SHT aus 10 verschiedenen prospektiven Studien hat das IMPACT-Konsortium in den letzten Jahren aktuelle Outcome- und Prognosedaten präsentiert.[25] (siehe Tab. 1)
Außerdem wurde berichtet, dass beidseitig ausgefallene SEPs auch in dieser Patientengruppe mit hoher Spezifität ein schlechtes Outcome vorhersagen.[26]

**Tabelle1.1:** *Beziehung zwischen einzelnen Prädiktoren und dem 6-Monats- Outcome von Patienten mit SHT: Daten des IMPACT-Konsortiums (übernommen aus Steyerberg et al., 2008)* [27]

| Characteristics | Coding | Odds Ratios (95% CI) | | | |
|---|---|---|---|---|---|
| | | Univariate | Core Model (n = 8509) | Extended Model[a] (n = 6999) | Lab Model[b] (n = 3554) |
| **Age, years** | 45 versus 21 years | 2.2 (2.0–2.3) | 2.4 (2.2–2.5) | 2.2 (2.0–2.3) | 1.9 (1.7–2.1) |
| **Motor score** | None | 4.9 (4.3–5.5) | 3.9 (3.4–4.5 ) | 3.4 (2.9–4.0) | 2.8 (2.1–3.7) |
| | Extension | 7.2 (6.3–8.3) | 5.7 (4.9–6.6) | 4.6 (3.9–5.4) | 4.3 (3.5–5.4) |
| | Abnormal flexion | 3.5 (3.1–4) | 3.0 (2.6–3.5) | 2.8 (2.4–3.2) | 2.7 (2.2–3.3) |
| | Normal flexion | 1.8 (1.6–2) | 1.7 (1.5–1.9) | 1.6 (1.4–1.8) | 1.5 (1.3–1.8) |
| | Localizes/obeys | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | Untestable/missing | | | | |
| **Pupillary reactivity** | Both pupils reacted | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) | 1.0 (ref) |
| | One pupil reacted | 2.2 (1.8–2.7) | 2.1 (1.7–2.6) | 2.0 (1.7–2.5) | 1.3 (0.6–2.6) |
| | No pupil reacted | 5.9 (5.3–6.6) | 3.3 (3.0–3.7) | 2.7 (2.4–3.1) | 2.1 (1.6–2.6) |
| **Hypoxia** | Yes or suspected | 2.1 (1.9–2.4) | - | 1.3 (1.1–1.5) | 1.4 (1.2–1.7) |
| | No | 1.0 (ref) | - | 1.0 (ref) | 1.0 (ref) |
| **Hypotension** | Yes or suspected | 2.7 (2.4–3.1) | - | 1.8 (1.6–2.1) | 1.5 (1.2–1.8) |
| | No | 1.0 (ref) | - | 1.0 (ref) | 1.0 (ref) |
| **CT classification**[c] | I | 0.41 (0.33–0.52) | - | 0.64 (0.51–0.82) | 0.65 (0.47–0.89) |
| | II | 1.0 (ref) | - | 1.0 (ref) | 1.0 (ref) |
| | III | 2.6 (2.3–3) | - | 1.7 (1.5–2.0) | 1.7 (1.4–2.0) |
| | IV | - | - | | |
| | V | 2.3 (2–2.6) | - | 1.6 (1.4–1.9) | 1.8 (1.5–2.2) |
| | VI | - | - | | |
| **tSAB**[d] | Yes | 2.6 (2.4–2.9) | - | 1.7 (1.5–1.8) | 1.8 (1.6–2.1) |
| | No | 1.0 (ref) | - | 1.0 (ref) | 1.0 (ref) |
| **Epidural Hematoma** | Yes | 0.64 (0.56–0.72) | - | 0.61 (0.53–0.70) | 0.56 (0.46–0.69) |
| | No | 1.0 (ref) | - | 1.0 (ref) | 1.0 (ref) |
| **Glucose** | 10.4 versus 6.7.mmol/l | 1.7 (1.6–1.8) | - | - | 1.3 (1.2–1.4) |
| **Hb** | 14.3 versus 10.8 g/dl | 0.66 (0.61–0.72) | - | - | 0.78 (0.70 – 0.87) |

[a] Extended Model: Kernmodell und zusätzlich die Parameter postanoxische Enzephalopathie (Hypoxie), Hypotension, und CT Charakteristik als potentiellePrädiktoren.

[b] LabModel: Extended Model und zusätzlich die Laborparameter Glukosespiegel und Hämoglobin (Hb) als potentielle Prädiktoren.

[c] CT Klassifikation: I: kein sichtbarer Defekt; II=Mittellinienverlagerung von 0–5 mm, im zerebralen Computertomogramm (CCT) erfassbare Läsion <25 $cm^3$; III= Zisternen komprimiert oder fehlend mit einer Mittellienienverlagerungvon 0–5 mm, im CCT erfassbare Läsion <25 $cm^3$; IV-=Mittellinienverlagerung > 5 mm, im CCT erfassbare Läsion <25 $cm^3$; V=jegliche Verletzung, bei der eine raumfordernde intrakranielle Blutung operativ entfernt wurde; VI= jegliche Verletzung, bei der eine raumfordernde intrakranielle Blutung nicht operativ entfernt wurde. Für die Analyse wurde Kategorie III und IV sowie V und VI zusammengefasst.

[d] traumatische subarachnoidale Blutung

Veröffentlichte Raten zur Wiedererlangung des Bewusstseins liegen zwischen 20 und 41% innerhalb von 6 Monaten. [28,29] Die meisten initial schwer bewusstseinsgestörten Patienten erlangen ihr Bewusstsein innerhalb von 3 Monaten nach Schädigung wieder. [30] Nur wenige Arbeiten haben sich mit der Identifizierung potentieller Prädiktoren für die Wiedererlangung des Bewusstseins beschäftigt. Bisher gelten der initiale Wert der Disability Rating Scale (DRS; siehe unten), das Vorhandensein einer bilateralen Läsion sowie das Alter als Prädiktoren für die Wiedererlangung des Bewusstseins. [30, 31] Andere Autoren fanden eine Kombination aus Spontanbewegungen, oralen Automatismen und Blickfolgebewegungen als unabhängigen Prädiktor. [32]

Auch zur Evaluation des Langzeit-Outcomes liegen bisher nur sehr wenige Studien vor. Es konnte allerdings gezeigt werden, dass Alter >40 Jahre bei Erkrankung, eine prämorbid bestehende Hirnerkrankung sowie eine soziale Deprivation Prädiktoren für das Versterben der Patienten innerhalb von 5 -7 Jahren waren. [33] In einer weiteren Studie mit einem Beobachtungszeitraum von bis zu 5 Jahren nach Schädigung konnte keiner der 12 Patienten, die nach 1 Jahr noch im VS waren, einen besseren Bewusstseinszustand erlangen. Von den 39 Patienten, die nach 1 Jahr bereits im MCS waren, erlangten 13 Patienten ihr Bewusstsein wieder, allerdings mit schweren Behinderungen. [34]

### 1.3 Häufig eingesetzte Messinstrumente

Messinstrumente, die bei der Charakterisierung dieser Patientengruppe häufig zum Einsatzkommen sind die Glasgow Coma Scale (GCS), die Glasgow Outcome Scale (GOS) [35], der Functional Independence Measure (FIM ) [36], die DRS [37], die JFK Coma-Recovery Scale – Revised (CRS-R) [38] oder die Koma Remissions Skala (KRS) [39]. Die GCS dient der Beurteilung des Schweregrades eines SHTs und umfasst 3 Subskalen: Augen öffnen, verbale Antwort und Motorik. Insgesamt können zwischen 3-15 Punkte erreicht werden. Als schweres SHT gelten Punktwerte von 3-8, mittelschwer 9-12 und leicht von 13-15. Eine der am häufigsten verwendeten Skalen um *funktionelles* Outcome zu erfassen ist die GOS. Funktionell bezieht sich dabei auf den Grad der Selbständigkeit bei der Verrichtung der Aktivitäten des täglichen Lebens. Die GOS ist eine eindimensionale Skala, bei der auf 5 Stufen bewertet wird, welchen Grad an Behinderung ein Patient aufweist. Die einzelnen Stufen sind wie folgt beschrieben: 1=Tod, 2=VS, 3=schwere Behinderung, befolgt Anweisung ohne die Fähigkeit unabhängig zu leben, 4=moderate Behinderung, kann unabhängig leben, allerdings ohne schul- oder berufsfähig zu sein, 5=unabhängiges Leben, schul- und berufsfähig

Beim FIM handelt es sich um ein multidimensionales Messinstrument, mit dem einzelne Aktivitäten des täglichen Lebens (Essen, Fortbewegung, Kontinenz, Kommunikation, Blasen- und Darmkontrolle etc.) beurteilt und erst anschließend zu einem Summenwert zusammengefasst werden. Jedes der 18 Items wird auf einer Skala von 1 bis 7 bewertet, wobei ein höherer Punktwert mehr Unabhängigkeit widerspiegelt.

Die DRS wurde ursprünglich eingesetzt um den klinischen Verlauf während der Rehabilitation bei SHT-Patienten zu evaluieren. Die DRS umfasst 8 Subskalen, wobei die ersten drei Items der GCS entsprechen. Außerdem werden kognitive Fähigkeiten in den Aktivitäten des täglichen Lebens erfasst und die tatsächliche Abhängigkeit von Fremdhilfe sowie die Arbeitsfähigkeit. Der Summenwert reicht von 0-29, ein höherer Wert entspricht einem schlechteren Zustand.

Um den Bewusstseinszustand zu messen wurde 2004 eine revidierte Fassung der JFK Coma Rcovery Scale vorgestellt. Diese Skala besteht aus 6 Subskalen, bei denen die Reaktionen der Patienten nach Qualität und Häufigkeit bewertet werden Es bestehen klare Regeln zur Klassifizierung des Bewusstseinszustandes. Ein Patient hat beispielsweise einen höheren Bewusstseinszustand als MCS erreicht, wenn er funktionellen Objektgebrauch oder funktionell korrekten Sprachgebrauch in mindestens 2 von 4 Versuchen zeigt.

Die KRS wird im deutschen Sprachraum verwendet um die Erholung bei Patienten mit schweren Bewusstseinsstörungen zu evaluieren. Sie besteht aus 6 Subskalen: Erweckbarkeit, motorische Antwort, jeweils Reaktion auf akustische, visuelle und taktile Reize und sprechmotorische Antwort. Aus den Subskalen kann ein Summenscore gebildet werden, erreichbare Wert liegen zwischen 0- 24 Punkten.

### 1.4 Motivation

Obwohl bereits viele Arbeiten zu Outcome und Prognosestellung bei Patienten nach Hirnschädigung vorliegen, haben sich nur wenige explizit auf Patienten mit lang anhaltenden schweren Bewusstseinsstörungen konzentriert. Auch Studien mit längerer Beobachtungszeit sind selten, meist wurde das 6- bzw. 12-Monatsoutcome berichtet. Prädiktoren für eine Prognosestellung wurden meist für das funktionelle Outcome der Patienten evaluiert. Studien, die untersucht haben, welche Faktoren die Wiedererlangung des Bewusstseins begünstigen, sind selten. Die Ergebnisse neuerer Studien haben außerdem Hinweise darauf erbracht, dass bisherige Prädiktoren möglicherweise weniger sicher sind als bisher angenommen.[40,41] Letztlich wurden keine Studien gefunden, die Aussagen darüber treffen, wie der Verlauf des Bewusstseinszustandes sowie der funktionellen Fähigkeiten von Patienten mit schweren lang anhaltenden Bewusstseinsstörungen während der stationären Rehabilitation ist. Daten dazu wären aber in der Lage, den Zeitraum für klinische Verbesserungen konkreter abzustecken sowie eine Aussage darüber zu treffen, ab welchem Zeitpunkt erste Besserungen auftreten.

### 1.5 Vorstellung der Beiträge

In den beiden hier vorgestellten Arbeiten wurde das Rehabilitations- bzw. 6-Monats-Outcome von Patienten mit schweren Bewusstseinsstörungen bei Aufnahme in die Frührehabilitation präsentiert. Zusätzlich wurden Prädiktoren identifiziert und überprüft.

Ein besonderes Augenmerk liegt vor allem auf der Datenerhebung während der stationären Frührehabilitationsphase, die zweiwöchentlich durchgeführt wurde bzw. wird, da die bisherige Datenlage zum klinischen Verlauf der funktionellen Fähigkeiten und des Bewusstseinszustandes sehr eingegrenzt ist. Erhobene Daten decken ein breites Spektrum ab und geben neben den Befunden aus dem Akuthaus, demographischen Parametern und Vorerkrankungen Auskunft über funktionellen Status, Bewusstseinszustand, klinische Befunde, Neurophysiologie, sowie aufgetretene Komplikationen während des Rehabilitationsaufenthaltes.

Diese Arbeit hatte folgende Ziele:

- Prädiktoren zu identifizieren, die bei Patienten mit schweren und anhaltenden Bewusstseinsstörungen nach akuter Hirnschädigung das funktionelle Outcome sowie den Bewusstseinszustand vorhersagen
- den zeitlichen Rahmen bis zur Erlangung eines potentiell positiven Outcomes abzustecken, sowie zu evaluieren, wann bereits erste Besserungen auftreten
- standardisierte Daten zum klinischen Verlauf während der Frührehabilitation zu erfassen und auszuwerten.
- Prädiktoren, die bisher zur Prognose herangezogen wurden, zu überprüfen.

Im Folgenden wird jeweils der Beitrag des Doktoranden zu den verfassten Fachartikeln dargelegt und die Inhalte der einzelnen Veröffentlichungen kurz vorgestellt.

#### *1.5.1 Rehabilitation outcome of unconscious traumatic brain injury patient*

Bei dieser Arbeit handelt es sich um eine retrospektive Kohortenstudie, bei der SHT-Patienten mit schweren, anhaltenden Bewusstseinsstörungen, die zwischen 01.01.2005 und 31.12.2010 zur stationären Frührehabilitation im Therapiezentrum Burgau waren, eingeschlossen wurden. Obwohl es sich um eine retrospektive Studie handelt, wurden die Daten prospektiv erhoben, da die Datenerhebung innerhalb der klinischen Routine im 1- bzw. 2- Wochen-Rhythmus ein Standard ist. Neben der Hauptdiagnose SHT galten auch eine schwere Bewusstseinsstörung sowie eine direkte Verlegung aus dem Akuthaus als Einschlusskriterien.

Outcome wurde sowohl nach funktionellen Fähigkeiten als auch nach Bewusstseinszustand definiert. In Anlehnung an frühere Studien wurde das funktionelle Outcome mit der GOS erhoben, wobei Werte >3 ein positives Outcome definieren. Ein gutes Outcome in Bezug auf Bewusstseinszustand wurde durch eine volle Punktzahl (24 Punkte) in der KRS definiert, was bedeutet, dass der Patient einen höheren Bewusstseinszustand als MCS erreicht hat (MCS+) und damit Dinge wie funktioneller Objektgebrauch bzw. das Erkennen bekannter Personen möglich ist. Um den klinischen Verlauf zu dokumentieren wurde der FIM sowie die KRS genutzt, die 2-wöchentlich erhoben wurden. Mit einem Anstieg der Werte um 10% im Vergleich zum Anfangswert, sollte eine grobe Einschätzung des zeitlichen Beginns der funktionellen bzw. auf den Bewusstseinszustand bezogenen Besserung gegeben werden.

Zur Identifizierung unabhängiger Prädiktoren wurde eine multiple logistische Regressionsanalyse durchgeführt. Potentielle Prädiktoren waren dabei: Alter, Geschlecht, Grund des SHT, VS bei Aufnahme, Schädigung des Kleinhirns, Durchführung einer indizierten Kraniotomie bzw. Anlegen eines ventriculoperitonealen Shunts, Dauer des Aufenthaltes in der Akutklinik, initiale FIM- bzw. KRS-Werte, komorbide traumatische SAB, beidseits ausgefallenen SEPs sowie Dauer bis zum Erreichen des Bewusstseinszustandes MCS+.

Von insgesamt 188 Patienten erreichten 16,5% ein gutes funktionelles Outcome nach ca. 18 Wochen und 37,2% MCS+ nach ca. 9 Wochen Rehabilitationsdauer. 10,1% der Patienten verstarben.

Die gute funktionelle Outcomegruppe hatte ab der 7. Woche signifikant höhere FIM-Werte als die schlechte. Außerdem ergab sich eine signifikante Korrelation zwischen Zeit seit Schädigung und FIM - Werten bei Entlassung ($r = -0,37$; $p<0,01$). Die längste Zeitspanne, die ein Patient der guten funktionellen Outcomegruppe brauchte bis zu einer Verbesserung des initialen FIM-Wertes um 10% betrug 18 Wochen.

Im Gegensatz dazu unterschieden sich die beiden Outcomegruppen, die nach Bewusstseinszustand dichotomisiert wurden, bereits bei der Aufnahme in das Rehabilitationszentrum. Die bessere Outcomegruppe verbesserte sich in der KRS nach ca. 6 Wochen um 10%, wohingegen die andere Gruppe sich nach 7 Wochen verbesserte. Die längste Zeitspanne, die ein Patient der besseren Outcomegruppe benötigte um den KRS-Wert um 10% zu verbessern, betrug 19 Wochen.

Die multiple logistische Regressionsanalyse identifizierte Alter und initiale KRS-Werte als unabhängige Prädiktoren für sowohl das funktionelle Outcome als auch das Outcome nach Bewusstseinszustand. Für das funktionelle Outcome waren die Indikation und Durchführung einer Kraniotomie sowie die Zeitspanne bis zum Erreichen von MCS+ weitere Prädiktoren. Um den Bewusstseinszustand vorherzusagen gingen sowohl die Therapie mit einem VP Shunt als auch Grund für SHT in das finale Mode mit ein.

Besonders anzumerken ist, dass zum Einen in der vorliegenden Studie deutlich weniger Patienten einen höheren Bewusstseinszustand sowie auch funktionellen Status erreichten

als in einer vergleichbaren Studie, die ebenfalls auf schwer betroffene SHT-Patienten fokussierte. [42] Zum Anderen konnte gezeigt werden, dass bei einzelnen Patienten erste klinische Besserungen erst nach einer Zeit von 4-5 Monaten auftreten. Hervorzuheben ist weiterhin, dass beidseitig ausgefallene SEPs in keinem der beiden Modelle als unabhängiger Prädiktor identifiziert werden konnte.
Als Erstautorin dieser Studie war die Doktorandin hauptverantwortlich für die Durchführung, die Analyse und die Formulierung des Manuskripts.

### *1.5.2 Rationale, design and preliminary results of the prospective German registry of outcome in patients with severe disorders of consciousness following acute brain injury (KOPF-R)*

Diese Arbeit präsentiert erste Daten eines prospektiven multizentrischen Registers (**K**oma-**O**utcome bei **P**atienten der neurologischen **F**rührehabilitation – **KOPF**-Register) neurologischer Frührehabilitationszentren. Bei diesem Register werden alle Patienten mit akuten Hirnschädigungen eingeschlossen, die bei Aufnahme in die neurologische Frührehabilitation noch schwere Bewusstseinsstörungen aufweisen. Das Merkmal schwere Bewusstseinsstörung wurde dabei anhand der CRS-R diagnostiziert.
Outcome wurde in dieser Arbeit wiederum nach funktionellen Aspekten (FIM) sowie nach Bewusstseinszustand definiert (CRS-R). Das Protokoll des Registers sieht allerdings vor, Patienten, denen es möglich ist ebenfalls nach Gesundheitszustand, emotionaler Funktionsfähigkeit und Lebensqualität zu befragen, genauso wie die kognitive Funktionsfähigkeit zu überprüfen.
Während des stationären Aufenthaltes in den Rehabilitationskliniken werden von den eingeschlossenen Probanden regelmäßig und prospektiv unterschiedliche Daten aus den Bereichen klinischer Befund, neurophysiologische Diagnostik und Labordiagnostik erhoben und zweiwöchentlich in eine gesicherte, Internet-basierte Datenbank eingegeben.
Von zu dem Zeitpunkt 42 eingeschlossenen Patienten (38% weiblich) wiesen 24% ein SHT auf, 31% eine intracerebrale oder subarachnoidale Blutung und 45% eine postanoxische Enzephalopathie. CRS-R-Werte bei Aufnahme betrugen im Mittel 5,9 und FIM-Werte 18 Punkte. 11 Patienten verstarben innerhalb einer 6-monatigen Beobachtungsdauer. Von den 31 Überlebenden erreichten 9 Patienten MCS+. Insgesamt wiesen 36 Patienten einen oder mehrere Prädiktoren auf, die als stark negativ gelten, 5 davon erreichten MCS+. Nach 3 Monaten verbesserten sich die Patienten um 3 Punkte, nach 6 Monaten um 6 Punkte anhand der CRS-R.
Diese ersten Ergebnisse des Registers weisen daraufhin, dass selbst schwer betroffene Patienten, die außerdem einen oder mehrere negative Prädiktoren im Akuthaus aufweisen,

das Potential haben, ihr Bewusstsein wieder zu erlangen. Ein einzelner Patienten, der über 1 Jahr beobachtet wurde erlangte erst nach 399 Tagen das Bewusstsein wieder, was ein Indikator dafür ist, dass Besserungspotential länger vorhanden sein kann als bisher angenommen.
Die Doktorandin war an der Datenerhebung sowie der Datenanalyse beteiligt, sowie der Endkorrektur des Manuskripts.

### 1.6 Zusammenfassung

Schwere Bewusstseinsstörungen sind mögliche Folgen erworbener Hirnschädigungen und betreffen in etwa 3000-5000 Menschen jährlich allein in Deutschland.
Die Datenlage zu Outcome, klinischem Verlauf und Prognosestellung bei Patienten mit schweren Bewusstseinsstörungen ist sehr eingegrenzt, besonders in Bezug auf Langzeitoutcome, Prädiktoren für den Bewusstseinszustand und Verlauf während der stationären Rehabilitation. Die Ergebnisse neuerer Studien haben außerdem die Spezifität bisheriger Prädiktoren in Frage gestellt.
Ziel dieser Arbeit war es deshalb Rehabilitations- bzw. 6-Monats- Outcome explizit von Patienten mit schweren Bewusstseinsstörungen bei Aufnahme in die Frührehabilitation zu evaluieren sowie potentielle Prädiktoren zu identifizieren und zu überprüfen.
Dazu wurde in einer retrospektiven Studie der klinische Verlauf sowie das Outcome schwer bewusstseinsgestörter Patienten nach SHT während der neurologischen Frührehabilitationsphase (mittlere Dauer 107 Tage) evaluiert. Gutes Outcome wurde dabei sowohl nach dem funktionellen Status als auch dem Bewusstseinszustand definiert. Von 188 eingeschlossenen Patienten erreichten 37,2% MCS+ und 16,5% waren zumindest teilweise funktionell unabhängig bei Entlassung. Mittels multipler logistischer Regressionsanalyse konnten sowohl das Alter der Patienten sowie auch der Bewusstseinszustand bei Aufnahme als unabhängige Prädiktoren für beide Outcomedefinitionen identifiziert werden. Interessanterweise waren beidseits ausgefallene kortikale Reizantworten bei den SEPs in keinem der beiden Modelle ein unabhängiger Prädiktor, obwohl sie als sichere prognostische Marker für die Nicht-Wiedererlangung von Bewusstsein gelten. Der klinische Verlauf der beiden funktionellen Outcomegruppen begann sich in der 7. Woche signifikant zu unterscheiden. Die mittlere Dauer um das bessere funktionelle Outcome zu erreichen betrug 18 Wochen. Erste Verbesserungen in der Gruppe, die MCS+ erreichte, stellten sich nach 6 Wochen ein und die mittlere Dauer MCS+ zu erreichen betrug 9 Wochen. Der jeweils „langsamste“ Patient erreichte dabei die bessere Outcomekategorie jedoch erst nach 18 (funktionell) bzw. 19 (besserer Bewusstseinszustand) Wochen.
Einer der Hauptkritikpunkte dieser Studie ist neben der retrospektiven Datenerhebung die kurze Beobachtungsdauer, die nicht über die Frührehabilitationsphase hinausging. Neuen

Erkenntnissen zu Folge haben Schädel-Hirntrauma-Patienten allerdings ein deutlich länger anhaltendes Potential zur klinischen Besserung als früher angenommen, so dass das abschließende Maß an Verbesserung sicherlich unterschätzt wurde.

Die zweite Studie gibt erste 6-Monats-Ergebnisse einer 2011 initiierten multizentrischen, prospektiven Beobachtungsstudie wieder (KOPF-Register), bei der die Beobachtungszeit auf bis zu 5 Jahren ausgedehnt werden soll. Nach Einschluss ins KOPF-Register werden die Patienten nach einem prospektiven Protokoll während der stationären Neurorehabilitation umfassend klinisch und mit Zusatzdiagnostik (z.B. EEG) charakterisiert und auch nach der Entlassung regelmäßig nachuntersucht. Schwerpunkte liegen hierbei auch auf den Bereichen Lebensqualität, Teilhabe sowie Belastung von Angehörigen und Pflegenden.

Erste Ergebnisse von 42 Patienten zeigten, dass von 31 überlebenden Patienten 9 (29%) das Bewusstsein wieder erlangten. Fünf dieser Patienten wiesen im Vorfeld sogar einen oder mehrere Prädiktoren auf, die herkömmlich für ein negatives Outcome sprechen. Im Falle eines einzelnen Patienten trat die Wiedererlangung des Bewusstseins erst nach über 1 Jahr ein.

Zusammenfassend zeigte sich, dass trotz einer sehr schweren Bewusstseinstörung ein beachtlicher Anteil an Patienten mit erworbenen Hirnschädigungen schon während der Frührehabilitation deutliche klinische Verbesserungen aufweist.

Außerdem ergaben sich Hinweise darauf, dass „sichere“ Prognosefaktoren weniger aussagekräftig sind als bisher angenommen und dass selbst Patienten, die im Vorfeld einen oder mehrere als negativ geltende Prognosefaktoren aufweisen, in der Lage sind ihr Bewusstsein wiederzuerlangen.

Für klinische Entscheidungen und Angehörigenberatung sei darauf hingewiesen, dass in einzelnen Fällen klinische Besserungen erst nach einer Zeitspanne von mehreren Monaten auftreten.

## 1.7 Summary

Severe disorders of consciousness (DOC) are potential consequences of acquired brain injuries and affect approximately 3000-5000 subjects only in Germany annually. Data on outcome, clinical course or prognostication in patients with severe DOC, however, is limited, especially in regard to long-term outcome, prognostication of level of consciousness and clinical course during inpatient rehabilitation. Furthermore, recent results questioned the specifity of previous predictors.

For these reasons, objectives of this thesis were to evaluate rehabilitation outcome and 6-months-outcome, respectively, in patients with severe and prolonged DOC upon admission to early neurorehabilitaion as well as to identify and reasses potential predictors.

Therefore, in a retrospective study the clinical course during early neurorehabilitation phase (mean observation period 107 days) and the outcome in TBI patients with severe DOC was assessed. Outcome thereby was defined in both, functional and behavioral (in respect to level of consciousness) terms. Out of 188 patients 37.2% emerged from MCS and reached at least partial functional independence, respectively. Multiple logistic regression analyses identified age and level of consciousness upon admission as independent predictors for both outcome definitions. Interestingly, bilateral loss of cortical responses of somatosensory evoked potentials (SEP) was not an independent outcome predictor although it is assumed to be a “failsafe” prognostic marker for the failure to regain consciousness (specificity 90-100%).The favorable functional group starts to separate from the corresponding outcome group by week 7. Mean duration to reach the better outcome group was 18 weeks. The favorable behavioral group starts to improve by week 6 and mean duration to emerge from MCS was 11 weeks. The “latest” patient in each favorable outcome group, however, surpassed the threshold after 18 (functional) and 19 (behavioral) weeks, respectively.

One of the main limitations, next to the retrospective design of this study, was the rather short observation period only encompassing the early neurorehabilitation phase. We now know that TBI patients with DOC have a much longer potential for clinically relevant improvement than previously thought so the amount of clinical improvement was certainly underestimated in this cohort.

The second study presents preliminary 6-months follow-up results of a multicenter prospective observation trial initiated in 2011 (KOPF-registry), with a planned observation period up to 5 years. After inclusion into the KOPF-registry patients are characterized clinically and using additionally diagnostic investigations (e.g., EEG) due to a prospective protocol during inpatient neurorehabilitation. After discharge there will be follow-up examinations regularly. Foci thereby also lie on quality of life and participation in these patients as well as on relatives´ and caregivers´ burden.

Preliminary results of 42 patients (mean age 57 years) show that out of 31 ABI survivors 9 patients (29%) emerged from MCS. In 5 of these patients even one or more previously thought strong unfavorable prognostic markers were present. In the case of a single patient recovery of consciousness took more than 1 year.

To sum up it was shown that despite of severe DOC a substantial proportion of TBI patients made significant clinical improvements during early neurorehabilitation. Also there were findings pointing to that “failsafe” prognostic markers are less specific than earlier assumed and that patients are able to recover consciousness even if one or more previously assumed negative prognostic markers are present. In regard to clinical decision making and next-of-kin counseling it must be noted that in individual patients it might take several months before clinical improvements start.

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# Kapitel 2

## Rehabilitation outcome of unconscious traumatic brain injury patients

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**Abstract**

Outcome prediction of traumatic brain injury (TBI) patients with severe disorders of consciousness (DOC) at the end of the intensive care setting is important for clinical decision making and counseling of relatives and constitutes a major challenge. Even the question of what constitutes an improved outcome is controversially discussed. We have conducted a retrospective cohort study for the rehabilitation dynamics and outcome of TBI patients with DOC. Out of 188 patients, 37.2% emerged from MCS (minimally conscious state) and 16.5% achieved at least partial functional independence after a mean observation period of 107 days (range 1-399 days). This reflects that emergence from MCS is much easier to achieve than functional independence. Logistic regression analysis identified age and level of consciousness upon admission to neurorehabilitation as independent prognostic factors for both outcomes. The group who reached at least partial functional independence started to improve significantly more than the corresponding outcome group by post-injury week 7 and the average time to reach this functional status was 18 weeks. In contrast, the group who emerged from MCS started to improve after 6 weeks. The longest delay between brain injury and the beginning of functional improvement (measured by bi-weekly FIM scores) still compatible with reaching at least partial functional independence was 18 weeks.

In conclusion, despite a strong negative selection, a substantial proportion of severe TBI patients with DOC achieves functional improvements or at least emerge from MCS within the inpatient rehabilitation phase. In order to avoid self-fulfilling prophecies in decision making, it is important to be aware of the fact that the beginning of clinical improvement may take several months after brain injury. In this study separation of both of the functional outcome groups started by post-injury 7 weeks.

Keywords: traumatic brain injury, rehabilitation outcome, clinical course, recovery of consciousness

## 2.1 Introduction

Traumatic brain injury (TBI) affects millions of people throughout the world and is a leading cause for morbidity and mortality, especially in young adults.[1] It is estimated that about 10% of TBI cases are severe.[2] Disorders of consciousness (DOC) are the clinical hallmark of severe TBI. While many comatose patients regain consciousness in the first days and weeks after injury, some remain either in a vegetative state (VS; complete unawareness of self and environment; proposed new terminology: unresponsive wakefulness syndrome) or in a minimally conscious state (MCS; limited conscious interaction with the environment).[3, 4, 5, 6]

Predicting the outcome of patients who remain in the VS or MCS at the end of the intensive care setting is a major challenge. It is, however, very important for counseling and expectation management of the affected families and relatives.[7, 8] Based on this prognosis, medical professionals and families may decide to either limit/withdraw life-sustaining therapy or to pursue maximum medical care and neurorehabilitation.[7, 8] This decision-making process carries the risk of self-fulfilling prophecies.[9]

Age, low GCS motor score, absence of pupillary response, and CT characteristics have been established as independent prognostic factors in patients with severe or moderate TBI upon admission to intensive care units (ICU).[10] Also, analogous to patients with anoxic encephalopathy, bilateral absence of cortical responses of early somatosensory evoked potentials (SEP) during the first week post-injury has been shown to have high specificity to predict functional dependence [11,12] When the perspective is shifted from ICU admission to neurorehabilitation admission of TBI patients with DOC, data from the NIDRR TBI Model Systems Programs have shown that patients show functional improvement not only during the early recovery phase but also throughout the following years.[13] An important issue in such prognosis studies are the definitions of outcome categories. It may be too simplistic to base improved outcome solely on functional aspects and independence in activities of daily living (ADL), as quality of life (QOL) comprises many more aspects.[14] For a TBI patient who has remained in the VS for several weeks or months, it may be favorable to regain consciousness and communication skills in order to participate in family life, while functional independence may be out of reach.[15]

We have analyzed the clinical course and rehabilitation outcome of a large cohort of patients with DOC after severe TBI in order to provide further data for expectation management and informed decision making.

## 2.2 Methods

### *2.2.1 Study design and setting*

This is a retrospective cohort study of consecutive severe TBI patients with impaired consciousness, who were discharged from a specialized neurorehabilitation center in southern Germany between January 1st, 2005 and December 31st, 2010. Patients were identified by a review of patient charts. Study data were collected from electronic patient files. Inclusion criteria were acute TBI, sustained DOC upon admission with lack of command following, direct referral from the acute setting ICU to the rehabilitation center, residence in Germany or Austria and German language skills (for follow-up), and availability of bi-weekly, prospectively-collected clinical patient assessments (s. below) throughout the course of the inpatient rehabilitation treatment. The institutional review board of the medical faculty of the

University of Munich approved the retrospective data analysis. The study is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

*2.2.2 Data collection procedures*

All TBI patients at the neurorehabilitation center had bi-weekly standardized clinical assessments by trained hospital personnel. This standard assessment is a requirement of German health insurance companies for the treatment of severely brain injured patients. Data were entered prospectively into the clinical patient management system. As these assessments are standard procedures for all patients, assessors were 'blinded' with respect to the later scientific data use.

*2.2.3 Outcome measures*

We chose to use two different levels of improved outcome, one addressing functional aspects, the other focusing on regaining higher levels of consciousness. Thereby emergence from MCS is more easily to achieve than at least partial functional independence. In fact emerging from MCS is a prerequisite for achieving at least partial functional independence. In the first model, the overall functional outcomes were rated with the Glasgow Outcome Scale (GOS), which is one of the most widely used measures for classifying functioning in TBI survivors, both by acute care and rehabilitation specialists. [16, 17] In this study the GOS was rated for each patient at admission and at discharge retrospectively, using discharge letters of the ICU and the neurorehabilitation center, respectively. The GOS includes five outcome categories: 1=dead; 2=vegetative (cannot interact, unresponsive), 3=severely disabled (can follow commands, cannot live independently), 4=moderately disabled (can live independently, reduced work capacity) and 5=good recovery (can work). In this study, we used a GOS of 4 or 5 to define TBI patients with a good outcome. This cut-off point (GOS ≥ 4) is in accordance with previous studies and addresses the functional aspect of outcome as patients reaching those scores are able to live independently.[8, 18] The GOS has proven its practicability and usefulness to assess outcomes in patients with moderate and severe TBI in several studies.[19]

The German version of the coma remission scale (CRS) is a behavioral test to quantify levels of consciousness and ranges from 0 (deep coma) to 24 (able to use objects purposefully, recognition of familiar people) points comprising six subcategories: alertness and attention, motor response, response to acoustic stimuli, response to visual stimuli, response to tactile stimuli, and verbal response.[20] In contrast to the JFK Coma Recovery Scale –Revised (CRS-R) [4] there are no strictly defined cut-off points in the separate subscales to classify a patient as being in MCS or as emerged from MCS. Nevertheless, both scales encomprise very similar items. So patients reaching a full CRS score of 24 are considered as emerged from

MCS based on meeting at least one of the two criteria proposed for emergence from MCS by the CRS-R. [4] This is a much lower threshold to achieve than at least partial functional independence. In fact, emergence from MCS can be seen as a sequential marker for reaching at least partial functional independence. Even though both outcome measures can be seen as part of a continuous outcome spectrum, we chose to calculate statistical models for each of them separately.

For this further outcome model, the group reaching the better outcome category was defined by the maximum CRS score (24 points). All patients not reaching 24 points in the CRS were categorized into not emerging from MCS. As a consequence, this definition rates also those patients as having an improved outcome in respect to their level of consciousness who remain dependent functionally but who have emerged from the MCS and are able to use objects purposefully. This dichotomization takes into account that a good quality of life (QOL) is not necessarily dependent on functional status as it was shown in the case of patients in the locked-in syndrome.[15] The temporal pattern of CRS improvements were analyzed by determining the week during which the first significant CRS increase occurs (fig. 4b). The start of clinical improvement was defined as an increase of at least 10% of the maximum score, i.e. of ≥ 2 CRS points compared to the initial scores. This definition was chosen only to give a rough estimate of the starting point of increase within the group who emerged from MCS.

*2.2.4 Clinical course of functional abilities*

The Functional Independence Measure (FIM) was developed to uniformly assess severity of patient disability and medical rehabilitation functional outcome.[21] The FIM includes 18 items in 6 subscales: selfcare, sphincters, mobility, communication, psychosocial, and cognition. Each item is rated on a 7-level scale (1 = patient needs total assistance – 7 = patient is completely independent). The minimal clinically important difference (MCID) for the FIM is estimated at 27, i.e. only FIM increases above this threshold are noticed by patients as a relevant functional improvement.[22] For the FIM, good reliability was found. [23] The FIM at discharge has previously been shown to be an independent predictor of the 6-month outcome in TBI patients.[24, 25] According to the CRS, we analyzed the temporal pattern of FIM improvements by determining the week during which the FIM increases 10% of the maximum score, i.e. ≥ 13 FIM points compared to the initial scores (fig. 4a). As in the case of the temporal pattern of the CRS this cutoff point was defined only to give a rough estimate of the starting point of functional recovery within the group who reached at least partial functional independence. Because for the FIM there are no strictly defined cut-off points to identify an improved functional outcome category and the GOS is one of the most widely used measures to assess functional outcome in TBI survivors [8, 18, 19] we used the GOS instead as the functional outcome determinant. The FIM, however, was used to describe temporal patterns of functional abilities during neurorehabilitation.

*2.2.5 Independent variables*

All variables reaching or approaching significance in an univariate logistic regression model were used for multivariate regression modeling. If there were high intercorrelations between specific variables, the G-statistic was used to decide which of the variables were included in the multivariate model to improve the goodness of fit. Potential outcome predictors were: age, sex, cause for TBI (falls, road traffic accident), vegetative state at admission to rehabilitation, infratentorial lesion, need for ventriculoperitoneal (VP) shunting and craniectomy, length of stay in the ICU, FIM and CRS scores at admission, time to emergence from MCS, SEP bilaterally absent, and additional traumatic subarachnoid hemorrhage (SAH).

All patients received median nerve SEP recording within the first two weeks of admission to neurorehabilitation, using a standard clinical protocol. Cortical responses after 20ms (N20) were rated as either bilaterally absent (“malignant”) or not absent (even if only unilaterally present and/ or pathological; “non-malignant”).

*2.2.6 Statistical analysis*

For multivariate logistic regression analyses the sample was dichotomized into patients who emerged from MCS vs. patients who do not, and patients who reached at least partial functional independence and patients who remained functional dependent at the time of discharge from neurorehabilitation.

For description of the temporal patterns during inpatient neurorehabilitation, clinical scores (FIM/ CRS) were analyzed by Kaplan-Meier analysis.

To test for significant differences between the corresponding groups, a Chi Squared test was used for nominal and ordinal variables, and a t-test was used for continuous variables. All statistical tests were 2-sided.

The level of significance was set at $p<0.05$. SYSTAT 11 (SYSTAT Software, Inc., 2004) and SPSS 20 (IBM® SPSS® Statistics 20., 2011) were used for statistical analyses and plotting.

## 2.3 Results

*2.3.1 Patient characteristics and overall outcome*

Out of a total of 687 TBI patients during the 5 year observation period, 41.5 % had TBI as the main diagnosis and severe DOC. Of those, 66.0 % (n = 188) were available for analyses. The remaining patients were not directly referred to our center after ICU (32.3%), lacked clinical scoring data (0.02%), or lived abroad (1.5%).

Demographic and clinical patient characteristics per outcome group are shown in table 1. Out of the 188 patients, 16.5% reached at least partial functional independence (GOS ≥ 4) at the end of inpatient neurorehabilitation (mean observation period: 107 days, range 1-399 days), and 37.2% emerged from MCS (CRS = 24 points). 10.1% of patients died during neurorehabilitation after a mean of 128 days post-injury. In table 1 only the locations the patients were most often discharged to are specified. The remaining patients were discharged to other rehabilitation centers, back to acute care settings in case of complications, or specialized small group housing environments for patients in a vegetative state.

**Table 2.1:** *Patient characteristics for the group as a whole and dichotomized into patients who reached at least partial functional independence and patients who remained functional dependent as well as into patients who emerged from MCS and patients who do not at discharge, respectively.*

| | **All patients** | **Level of functioning** | | **Level of consciousness** | |
|---|---|---|---|---|---|
| **Factor** | | **(GOS ≥ 4)** | **(GOS<4)** | **(CRS=24)** | **(CRS<24)** |
| **n** | 188 | 31 | 157 | 70 | 118 |
| **age** | 53 ± 22 | **40 ± 19*** | **55 ± 22** | **46 ± 22*** | **57 ± 22** |
| **% male** | 72 | 77 | 74 | 77 | 73 |
| **Cause of TBI** | | | | | |
| **falls** | 105 | **11*** | **94** | **29*** | **76** |
| **traffic accidents** | 74 | **20*** | **54** | **38*** | **36** |
| **% VS [a]** | 57 | 48 | 60 | **50*** | **63** |
| **% infratentorial [d]** | 50 | 52 | 52 | 54 | 50 |
| **% VP shunt** | 22 | **6*** | **25** | **9*** | **31** |
| **% craniectomy** | 42 | **19*** | **48** | **30*** | **51** |
| **LOS ICU [b]** | 32 ± 36 | 22 ± 9 | 33 ± 38 | 25 ± 15 | 36 ± 43 |
| **range** | 6-322 | | | | |
| **LOS rehab. [c]** | 107 ± 73 | **128 ± 62*** | **103 ± 74** | **123 ± 63*** | **97 ± 77** |
| **range** | 1-399 | | | | |
| **% Discharge** | | | | | |
| **home** | 28 | **42*** | **28** | **43*** | **21** |
| **nursing facility** | 36 | **13*** | **43** | **19*** | **49** |
| **other/ died in rehab** | 36 | **45*** | **29** | **38*** | **30** |
| **FIM [e] admission** | 18 ± 1 | 18 ± 1 | 18 ± 1 | 18 ± 1 | 18 ± 1 |
| **FIM discharge** | 38 ± 30 | **95 ± 15*** | **27 ± 17** | **67 ± 32*** | **20 ± 5** |
| **CRS [f] admission** | 11 ± 5 | **14 ± 5*** | **11 ± 5** | **14 ± 5*** | **10 ± 5** |
| **CRS discharge** | 18 ± 7 | **24 ± 0*** | **17 ± 7** | **24 ± 0*** | **14 ± 6** |

[a] Vegetative state at admission to neurorehabilitation; [b] Length of stay intensive care unit (days) ;
[c] Length of stay neurorehabilitation (days) ; [d] infratentorial lesion; [e] Functional Independence Measure
[f] German version of the coma remission scale * significantly different from the corresponding group

Changes between GOS scores at admission and at discharge are shown in figure 1.

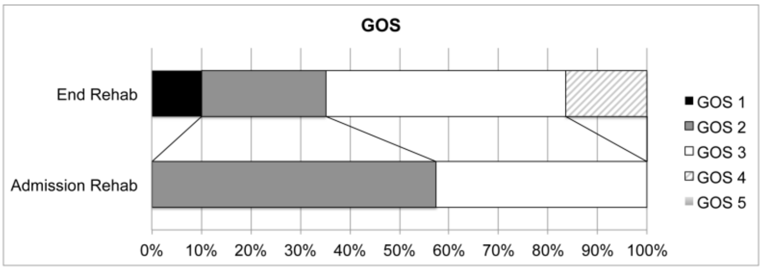


**Figure 2.1:** *Changes in GOS outcome categories between admission to neurorehabilitation and inpatient discharge.*

### *2.3.2 Clinical dynamics during neurorehabilitation*

Patients who were at least partially functional independent at the time of discharge reached this outcome category after 18 ± 7 weeks, those who emerged from MCS after 9 ± 4 weeks ($p < 0.01$; t-test). For both groups reaching the better categories (according to GOS and CRS scores, respectively) Kaplan-Meier plots for the cumulative probability of reaching these categories are shown in figure 2.

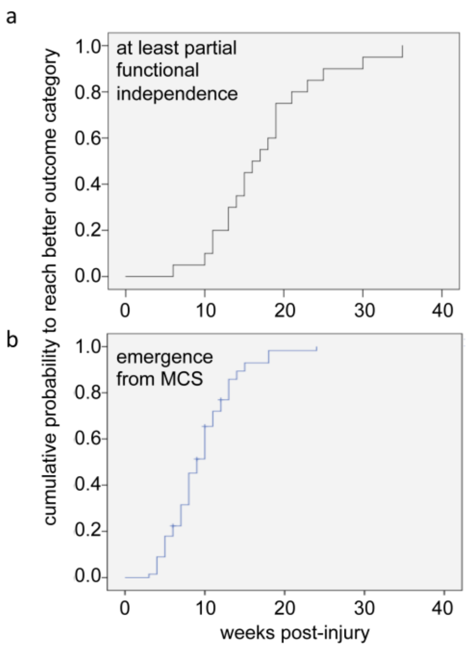


**Figure 2.2:** *Cumulative probability of the groups reaching the better outcome categories for reaching at least partial functional independence (a) and emergence from MCS (b) in dependency of the length of stay during neurorehabilitation.*

Bi-weekly standardized clinical scoring of the FIM showed that the group who reached at least partial functional independence started to separate from the corresponding outcome group by post-injury week 7 (fig. 3). There was a significant correlation between time from injury to improvement and final FIM scores at discharge. The earlier the improvement begins, the higher the discharge FIM scores are (Pearson correlation coefficient $r = -0.37$; $p < 0.01$). The longest delay to the start of FIM improvement in a patient, who surpassed the MCID was 18 weeks after injury (fig. 4a). The longest delay still compatible with at least partial functional independence (GOS ≥ 4) at discharge was also 18 weeks.

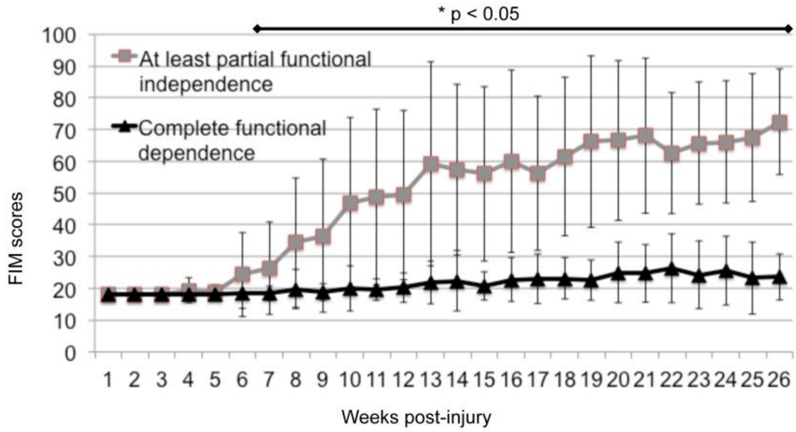


**Figure 2.3:** *Dynamics of functional status measured by the FIM throughout neurorehabilitation.The group reaching at least partial functional independence statistically starts to separate from the corresponding outcome group by week 7 (p < 0.05)*

On the contrary, when looking at the outcome in respect to the level of consciousness, the group who emerged from MCS had already higher CRS scores at admission than the group who did not (14 ± 5 vs. 9 ± 5 points; $p < 0.001$; 2-sided t-test). Yet even, given these different consciousness starting levels, the temporal dynamics of both groups are the same. The group who emerged from MCS starts to improve by at least 10% (i.e. 2 points on the CRS) after 6 ± 3 weeks, while the group not emerging from MCS inclines after 7 ± 4 weeks ($p = 0.1$, t-test). The longest individual delay until CRS improvement still compatible with maximum CRS scores at discharge was 19 weeks (fig. 4b).

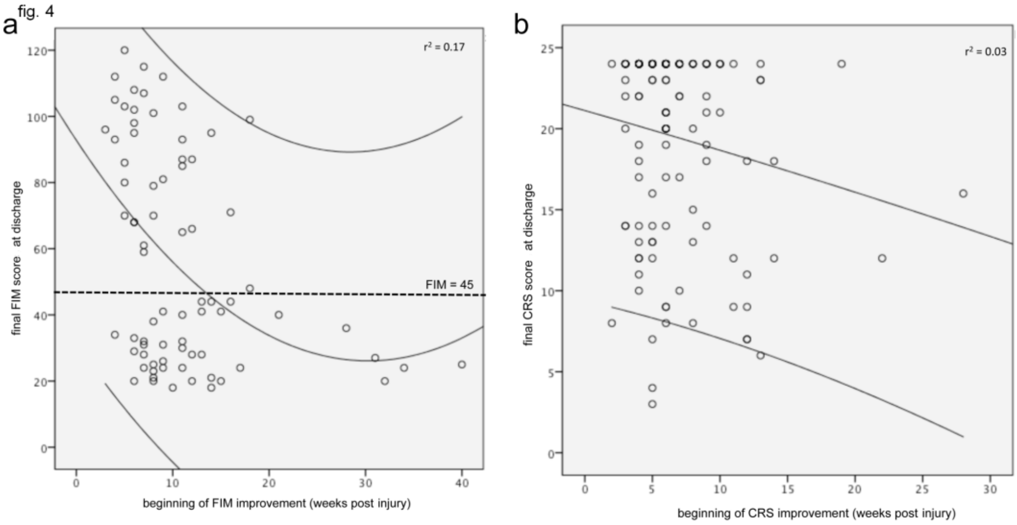


**Figure 2.4a:** *Scatter plot for the correlation between the start of FIM improvement (increase of ≥ 10%) measured in weeks post-injury and final FIM scores at discharge.The quadratic regression line (center curved line; $r^2$ = 0.17) is shown together with the 95% confidence intervals (outer curved lines). The dotted line represents the level of 45 FIM points, which is the minimal clinical important difference (MCID) for the FIM*.

**Figure 2.4b:** *Scatter plot for the correlation between the beginning of CRS improvement (increase of ≥ 10%) measured in weeks post-injury and final CRS scores at discharge from neurorehabilitation. The upper line is the regression line ($r^2$ = 0.03), the lower line represents the lower border of the 95% confidence interval, the upper border is not shown in this figure.*

### *2.3.3 Regression analysis and prognostic markers*

Multivariate binary logistic regression analysis was performed for both outcome measures (GOS and CRS). Age (1.05 odds ratio [OR], 1.02-1.09 95% confidence interval [CI]), CRS scores at admission (0.95 OR, 0.82-1.09 95% CI), time to emerge from MCS (1.35 OR, 1.11-1.65 CI), and previous decompressive craniectomy (4.70 OR, 1.14-19.38 95% CI) were strong functional outcome predictors (see also table 2 for results of the univariate regression model). For the level of consciousness at discharge, age (1.02 OR, 1.00-1.04 95% CI), CRS scores at admission (0.85 OR, 0.79-0.91 95% CI), length of ICU stay (1.02 OR, 1.00-1.05 CI), VP shunting (3.92 OR, 1.37-11.26 95% CI) and falls as cause for TBI (2.01 OR, 1.12-7.58 CI) were independent predictors (see also table 2 for results of the univariate regression model). As table 2 shows, length of ICU stay does not reach but approaches significance in both univariate models (functional: p=0.11; in respect to the level of consciousness: p=0.07). A G-statistic revealed that this variable adds significant improvements to the functional multivariate model (G=14.2, 1 df, p<0.001) but not the model predicting the level of consciousness (G=0.52, 1 df, p>0.50). Interestingly, bilateral absence of N20 cortical SEP responses was not an independent outcome predictor in either of the two models (table 2). The specificity of this malignant SEP test result to predict functional dependence or not emerging from MCS was 83% and 60%, respectively.

**2.4 Discussion**

This cohort study focuses on the inpatient rehabilitation outcome of TBI patients with sustained severe disturbances of consciousness at the time of admission to neurorehabilitation. The better outcome category was defined in terms of both functional aspects and emergence from MCS. It must be noted that emerging from MCS is a prerequisite to reaching at least partial functional independence, i.e. all patients who have reached at least partial functional independence also have emerged from MCS earlier, but not vice versa. Most studies assessing outcome after TBI only focus on the functional status or physical autonomy of patients, possibly ignoring that the definition of a better outcome category depends on the individual perspective. [8, 18] Even very simple communication skills may be of invaluable importance in regaining aspects of QOL like social support.[15] While the analysis was retrospective, clinical scoring data was elicited prospectively. Within a mean observation period of 15.3 weeks, 16.5% of patients achieved at least partial functional independence and 37.2% emerged from MCS. As indicated by the different rates in outcome in respect to functional status and level of consciousness the threshold for emerging MCS is lower for severely affected TBI patients. Average FIM scores at discharge were 38 ± 30 points. To date, the most comprehensive outcome analysis of this patient population stems from the recent report of the NIDRR TBI Model Systems (TBIMS) Program, which prospectively analyzed inpatient rehabilitation and long term outcomes of 396 and 108 patients, respectively.[13] Inclusion criteria of this study were similar to ours, focusing on patients without command-following abilities. Yet, while we used a standardized behavioral assessment tool, the German CRS, this prospective study used a qualitative approach to identify patients. Patients in the TBIMS study had a 47 day rehabilitation length of stay which is considerably shorter than the 107 days in our study. Yet, in their study, 68% of patients regained consciousness. Their median FIM at discharge was 43 points. Despite a shorter rehabilitation treatment period, the functional outcome and the rate of patients regaining consciousness were higher than in our analysis. This underscores the high disease severity in our patients compared to other study populations. This is also reflected by the fact that 57% of our patients were in the VS upon rehabilitation admission and that 42% had to undergo decompressive craniectomy to relieve intractable intracranial hypertension. Other studies report highly variable recovery of consciousness rates between 14% and 95% in TBI patients.[26, 27, 6, 28] This variability is likely to stem from heterogenic inclusion criteria, follow-up periods, and outcome measures used.

In contrast to the recent TBIMS study, we provide bi-weekly information about functional status and consciousness throughout the inpatient treatment phase. This allows for detailed analysis of the temporal patterns and dynamics of clinical improvement. The clinical course of those patients who will go on to reach at least partial functional independence starts to separate from the corresponding group after a mean of 7 weeks post-injury and the average time to reach at least partial functional independence is 18 weeks. No patient who started later than 18 weeks post-injury to significantly improve in his FIM became at least partially functional independent (fig. 4a). Recovery of consciousness begins earlier than functional improvement and maximum CRS scores are achieved after a mean of 9 weeks. Yet, the 'slowest' patient's trajectory within the group who emerged from MCS began to improve by week 19. These results impressively show that the potential for recovery should not be underestimated. In fact, recovery may not start for 4-5 months, especially for younger patients who were not in VS at admission to neurorehabilitation.

It must not be overlooked that inpatient neurorehabilitation may be considered futile by some neurointensivists or insurance regulations in severely brain-injured patients with prolonged coma, VS, or MCS.[13, 29] Given this notion, it is noteworthy that a substantial subgroup of patients improved significantly and even up to the point of functional independence.

The current German DRG catalogue defines the upper limit of the rehabilitation LOS for these patients at 27 days (OPS 8-552; Early neurological rehabilitation complex treatment; www.g-drg.de) for the defined DRGs (longer LOS leads to hospital specific daily rates).

This amounts to about 8-10 weeks post-injury when combined with the average 4 weeks of previous intensive care treatment. Looking at the clinical dynamics of our patients, it becomes evident that a substantial amount of patients begin to improve later than 8-10 weeks after their injury (fig. 4b). This means that at the time when hospitals and health insurance companies must decide about an extension of inpatient rehabilitation and ask for an assessment of the patients´ rehabilitation potential, they may be misguided if relying only on measurable score improvements at that time. Consequently, patients may be discharged prematurely and be deprived of further specialized treatment.[29]

Regression analysis identified age and levels of consciousness upon admission to neurorehabilitation as independent prognostic factors for both outcome definitions (reaching at least partial functional independence and emerging from MCS). It is not surprising that older patients and patients with a higher degree of unconsciousness fare worse during the course of inpatient rehabilitation. This is in line with previous studies and confirms clinical experience and intuition.[10, 18] We additionally found that the need for decompressive craniectomy to treat intracranial hypertension during the ICU phase and the need for introduction of VP shunting are strong negative predictors for functional outcome and the level of consciousness at discharge.

We were especially interested in the role that malignant SEP test results might play in outcome prediction in our cohort, i.e. absence of bilateral cortical N20 responses. In comatose cardiac arrest survivors, this finding predicts an unfavorable outcome with very high specificity, even if this may be a bit lower than previously believed.[9, 30, 31, 32]

In unconscious TBI patients, malignant SEP results have been reported to predict a failure to regain consciousness with high specificity between 90% and 100%.[11,12] To our surprise, bilateral loss of cortical N20 responses of median nerve SEPs was not an independent outcome predictor in our sample (functional: 0.97 OR,0.23-3.28 95%CI; in respect to level of consciousness: 1.14 OR, 0.45-2.90 95% CI). In fact, it only had a specificity of 83% to predict functional dependence and 60% to predict no emergence from MCS. This is an important finding for clinical practice, since such supposedly malignant SEP results may dramatically influence medical decision making on the ICU and often leads to withdrawal of life-sustaining therapy.[7] This carries the potential danger of a self-fulfilling prophecy, which is also relevant for severely affected TBI patients.[33, 34]

Of course, the main limitation of our study is the retrospective analysis design even though we could depend on prospectively elicited data. We have therefore initiated a multicenter prospective observation trial to determine TBI patient outcome using a high methodical standard.[54]

Another weakness of our study design is the fact that the observation period is rather short because we focused on inpatient rehabilitation outcome. We now know that TBI patients with DOC have a much longer potential for clinically relevant improvement than previously thought.[13, 27, 28] Thus, we are almost certain to underestimate the amount of clinical improvement in our cohort, because we were not able to obtain sufficient post-rehabilitation follow-up data.

In conclusion, a significant proportion of patients with very severe TBI and DOC achieve either partial or full functional independence or emergence from MCS during inpatient rehabilitation. Age, the degree of DOC at rehabilitation admission, and the need for neurosurgical procedures are important rehabilitation outcome predictors. For clinical decision making, it is important to be aware of the fact that some patients within the better outcome category may require up to 5 months before showing signs of improvement.

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**Author Disclosure Statement**

No competing financial interests exist for any of the authors.

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# Kapitel 3

## Rationale, design and preliminary results of the prospective German registry of outcome in patients with severe disorders of consciousness following acute brain injury (KOPF-R)

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**Abstract**

Objective: To examine determinants of long-term outcome and functioning of patients with severe disorders of consciousness (DOC) by means of a novel prospective registry (KOPF-R, Koma Outcome von Patienten der Frührehabilitation).

Design: Prospective multicenter neurological rehabilitation registry

Setting: Five specialized neurological rehabilitation facilities

Participants: Patients with DOC in vegetative state (VS) or minimally conscious state (MCS) as defined by the coma recovery scale-revised (CRS-R) following brain injury

Interventions: n/a

Main Outcome Measures: Coma Recovery Scale-Revised (CRS-R), Functional Independence Measure (FIM), emergence from MCS

Results: 42 patients (38% female) with a mean age of 57 years (standard deviation SD 16) have been enrolled so far. Main diagnoses were traumatic brain injury (TBI, 24%), intracerebral or subarachnoid hemorrhage (IAH/SAH, 31%), and anoxic ischemic encephalopathy (AIE, 45%). Mean CRS-R score at admission to rehabilitation was 5.9 (SD 3.3), mean FIM score at admission was 18 (SD 0.4). Eleven patients died within the six months follow-up period (26%). Among the 31 survivors, nine patients emerged from MCS (29%, 2 with TBI, 5 with IAH/SAH, 2 with AIE). 36 patients (86%) had one or more strong negative prognostic factor in the acute phase, five of whom emerged from MCS. Mean CRS-R score difference of first examination to three months was 3 (95% CI 0.4; 4.6), to six months 6 (95% CI 1.5; 9.9).

Conclusions: Prognosis in severe DOC cannot exclusively be based on prognostic markers in the acute care setting. More data on confounding factors and on the actual outcome after full exploitation of all intensive care and rehabilitation options are needed; we hope to be able to narrow this gap with help of data from the KOPFregistry.

Key words: Brain Injuries; Anoxia; Persistent Vegetative State; Disability Evaluation; Registries.

### 3.1 Introduction

Disorders of consciousness (DOC) presenting as coma, vegetative (VS) or minimally conscious state (MCS), are consequences of severe traumatic (TBI) or non-traumatic brain injury (NTBI), e.g. anoxic-ischemic encephalopathy (AIE) or subarachnoid hemorrhage (SAH). The term unresponsive wakefulness syndrome was proposed instead of VS to avoid labeling or a notion of therapeutic nihilism.[1] This state includes patients who are unresponsive to external stimuli but show signs of being wakeful such as eye opening. Patients may evolve from coma to unresponsive wakefulness or to MCS and beyond; however, each state may also persist.

To forecast the long-term DOC outcome is a challenge for health care professionals in the intensive care as well as in the neurological rehabilitation setting. However, reliable prognosis of the long-term outcome of traumatic or non-traumatic brain injury is needed for next-of-kin counseling and medical decision making in the acute phase.

This situation carries an ethical dilemma. Outcome assumptions that are too negative may lead to unjustified withdrawal of life sustaining therapy (LST) resulting in self-fulfilling prophecy. [2] Unrealistically positive expectations may result in prolonged suffering.

For almost two decades now, the 1994 consensus statement of the Multi-Society Task Force on VS has been the basis for prognosis for those patients who do not regain consciousness within one month after acute brain injury.[3] It was concluded that VS can be considered permanent in TBI patients after 12 months and in NTBI patients after 3 months. This view has recently been challenged; patients who had been in VS for more than 6 months can still recover responsiveness. [4]

For AIE following cardiac arrest, the American Association of Neurology has published practice parameters to guide decision making.[5] It was stated that “Pupillary light response, corneal reflexes, motor responses to pain, myoclonus status epilepticus, serum neuron-specific enolase, and somatosensory evoked potential studies can reliably assist in accurately predicting poor outcome in comatose patients after cardiopulmonary resuscitation for cardiac arrest”. This was followed by guidelines from other national associations.[6] However, decision-making based on prognostic markers in the acute setting was challenged; in a prospective study falsepositive prediction rates for mortality were up to 24% for these markers. [7]

Also, complete functional independence is not necessarily a prerequisite for quality of life (QOL), e.g. in locked-in patients.[8] Thus, a decision to continue or withdraw LST and to conduct or withhold specialized neurorehabilitation in vegetative TBI or NTBI survivors cannot merely be based on the prospect of future functional independence.

Based on these limitations of the current data regarding the long-term outcome of unresponsive TBI and NTBI patients, we established a prospective registry for patients, who are either in a VS (the unresponsive wakefulness syndrome) or MCS upon admission to specialized neurorehabilitation centers.

Objective of the registry is to examine determinants of long-term outcome and functioning of patients with severe DOC. We hypothesize that this new prospective database will further our understanding of the rehabilitation potential of the most severely affected DOC patients despite the presence of strong unfavourable prognostic markers. We hope to show, that the actual outcome may be better than previously expected. Here, we present preliminary findings and first experiences with the initial phase of the registry.

## 3.2 Methods

### *3.2.1 Design and setting*

KOPF-R (Koma Outcome von Patienten der Frührehabilitation – Register; registry for coma outcome in patients undergoing acute rehabilitation) is a prospective registry intended as a clinical database on characteristics, management as well as on functional and quality-of-life outcomes of patients with severe DOC (either VS or MCS) following brain injury across the state of Bavaria/Germany. The five participating facilities, Therapiezentrum Burgau, Schön Klinik München-Schwabing, Schön Klinik Bad Aibling, Klinik Kipfenberg, and Neurologische Klinik Bad Neustadt/ Saale are rehabilitation facilities with a special expertise in the rehabilitation of acquired brain damage. The five study sites are among the largest specialized centers for neurological rehabilitation in Bavaria with a total of 420 inpatient beds for early acute rehabilitation. They were selected to represent the major geographic regions of Bavaria and based on their patient intake. Analysis of admission statistics over the past 5 years suggests, that the centers might enroll approximately 300 suitable patients annually.

A positive vote of the local institutional review board was obtained prior to start. Informed consent was obtained from the patient's legal surrogate. Whenever the patient regained consciousness and was formally considered to be contractually capable, he or she was asked for informed consent for further long-term study follow-up.

### *3.2.2 Patients and data collection*

The registry includes patients with acute DOC due to acute brain damage, presenting as coma, VS, or MCS at the time of admission to a participating rehabilitation center immediately after intensive care treatment. Entry into the registry does not depend on specific diagnoses but on the level of consciousness, as defined by the coma recovery scale-revised (CRS-R).[9] Specifically, the registry includes those most severely affected patients where typically discontinuation of specific medical care or life supportive care may have been discussed on the intensive care unit. Patients are admitted for rehabilitation irrespective of results of initial prognostic markers, wherever possible and appropriate. All colleagues who are making transfer decisions in intensive care units of the relevant acute care facilities are encouraged to transfer patients for rehabilitation if this is supported by the families. The enrolled sample is to be representative in this sense. The main exclusion criterion is application of continuous intravenous sedative drugs (e.g. benzodiazepines, propofol) for artificial therapeutic coma. Intermittent applications of lorazepam (maximum dose of 3-12 mg/day) are compatible with study enrollment.

Data is collected prospectively from patients, patient files, and family members. Data collection is carried out by health professionals trained in data collection and data entry in this setting. Data is entered using a web-based electronic data system specifically designed for this purpose. Follow-up will be carried out at 6 and 12 months and yearly thereafter for 5 years. Inclusion of patients started in August 2011.

A steering committee was set up to decide on relevant issues of data collection, changes to the protocol, and data analyses.

*3.2.3 Measures*

Measures include sociodemographic and clinical characteristics (including neurological examinations), course of acute therapy, electrophysiological measures (evoked potentials, electroencephalogram, EEG), laboratory testing (neuron specific enolase, NSE), current medication, functioning, cognition, participation, quality of life, quantity and characteristics of rehabilitation therapy, caregiver burden, and attitudes towards end-of-life decisions. The choice of measures, namely of clinical characteristics, was based on current published practice parameters and guidelines for outcome prediction.[5] The acute care setting contributes data on acute therapy, e.g. cardiopulmonary resuscitation, surgery, medication, complications, and on the results of clinical examinations and investigations, e.g. electrophysiological, biochemical and radiologic findings. Because study enrollment is located in the rehabilitation setting, data from the intensive care units is retrospective in nature; there is no general standard of care in the primary hospitals.

An overview of all measures and the timeline for their collection is shown in table 1.

NSE, EEG, and cortical responses of median nerve evoked potentials (SEP) are tested upon enrollment at the neurorehabilitation centers as well as regularly throughout the inpatient treatment period. Median nerve SEPs are recorded with a standard four canal protocol (supraclavicular fossa, spinal C7 and cortical C3 and C4) within the first week after study enrollment at the centers. Cortical responses after 20ms (N20) are rated as either bilaterally absent or at least unilaterally present (even if pathologic).[5, 10]

EEG recordings are performed according to the international 10-20-system. EEG analysis criteria contain reactivity to stimuli (acoustic, touch/light pain), dominating frequency, presence of burst-suppression patterns, presence of epileptic activity, and special graphoelements (e.g. triphasic waves).

NSE levels are analyzed from serum samples, which are drawn on the mornings (8-9 am) following study enrollment as well as every other week, thereafter. Samples are centrifuged at the study site immediately and sent for standard laboratory tests within 2 hours. NSE is measured using a standard sandwich immunoassay on a Modular E170 module with the normal range at < 16.3 µg/L. In accordance with current guidelines, NSE levels > 33 µg/L are considered a marker for poor prognosis.[5, 10]

Functioning and participation are assessed based on the acute and post-acute Core Sets of the International Classification of Functioning, Disability and Health[11, 12], integrating patients' short- and long-term perspective on disability.

The main outcome measures reported here are state of consciousness and emergence from MCS as assessed by CRS-R, [9] and functioning as assessed by the Functional Independence Measure. [13]

The CSR-R is the recommended behavioral assessment scale for disorders of consciousness. [13] The six subscales are scored from 0 to 3 (oromotor, communication, arousal), 0 to 4 (auditory function), 0 to 5 (visual function), or 0 to 6 (motor function), where smaller values indicate worse states. A total score is calculated by summing up the subscale values. Using the CRS-R, patients can be categorized into one of the following groups: vegetative state (VS), minimally conscious state (MCS), and emergence from minimally conscious state (MCS+). MCS+ is reached if the patient is capable of functional object use (maximum score on the motor function scale) and/or of accurate functional communication (maximum score on the communication scale).

The FIM is widely used to measure disability. Its 18 ordinal scaled items refer to self care, bowel and bladder continence, mobility and ambulation, communication, social functioning, and cognition, yielding scores from 18 to 126. Higher scores indicate better functioning. The FIM has been positively evaluated regarding its psychometrical properties of reliability[15], validity and sensitivity to change.[16] Its appropriateness among rehabilitation patients has been shown.[17]

**Table 3.1:** *Measures and assessments integrated into the registry*

| Domain | Operationalization instrument/measure | Timing and frequency |
|---|---|---|
| **Pre-hospital findings** | initial ECG rhythm, characteristics of resuscitation, Glasgow Coma Scale (GCS), time to hospital admission | retrospective on admission |
| **Findings from acute care ICU** | EEG, SEP, NSE, GCS, complications (such as intracranial hypertension), procedures (such as decompressive craniectomy), length of hospital stay, medication | retrospective on admission |
| **Clinical characteristics** | neurological exam, modified Rankin Scale | on admission |
| | EEG, SEP, NSE | on admission |
| | medication, complications, level of care | weekly |
| | neuroimaging (CT/MRI) | biweekly |
| | level of post rehabilitation care | weekly |
| | | when clinically necessary |
| | | follow-ups |
| **State of consciousness** | Coma Recovery Scale - revised (CRS-R)[8] | weekly within first 4 weeks, then biweekly |
| | Koma Remissions Skala (KRS) [21] | weekly within first 4 weeks, then biweekly |
| **Functioning** | Barthel Index | biweekly |
| | Functional Independence Measure (FIM) [13] | biweekly |
| | Early Functional Abilities (EFA) [22] | biweekly |
| **Depression/cognition** | Beck Depression Inventory [23] | Patients: discharge, follow-ups; Caregivers: admission, discharge, follow-ups |
| | Montreal Cognitive Assessment (MoCA) [24] | discharge, follow-ups |
| **Quality of life** | EuroQOL (EQ5D) [25] | Patients: discharge, follow-ups; Caregivers: admission, discharge |
| | Quality of life after Brain Injury (QOLIBRI) [26] | discharge, follow-ups |
| | Health Questionnaire SF-12 [27] | Patients: discharge, follow-ups; Caregivers: admission, discharge |
| | World Health Organization Disability Assessment Schedule II (WHO-DAS-II) | follow-ups |
| **Caregiver´s burden and attitudes** | Modified Caregiver Strain Index [28] | Caregivers: follow-ups |
| | Burden Scale for Family Caregivers (BSFC) [29] | Caregivers: follow-ups |
| | Ethics questionnaire on attitudes of care-givers towards DOC and end-of-life decision (own development) | Caregivers: admission, discharge, follow-ups |

ECG = Electrocardiogram

EEG = Electroencephalogram

NSE = Serum neuron-specific enolase

SEP = Somatosensory evoked potentials

*3.2.4 Statistical analysis*

We used means for continuous variables and percentages for categorical variables. Explorative t-tests for paired observations were used to compare CRS-R scores at admission to rehabilitation with scores at three and at six months. We present preliminary results of the first patients included in the registry starting from August 2011 until January 2012. Due to the small sample size all longitudinal analyses are of exploratory nature. Significance tests were two tailed, with a p-value of 0.05 to indicate statistical significance. SAS V9.3 (Cary, NC) was used for all analyses.

## 3.3 Results

*3.3.1 Study population*

Because of the registry run-in phase, almost all patients (38 of 42) were included at the Burgau study site. Mean age was 57 years (standard deviation SD 16 years, median 58). Sixteen women (38%) were included. Main diagnoses responsible for DOC were traumatic brain injury (24%), stroke (31%), and anoxic-ischemic encephalopathy (45%). Mean delay between injury and admission to neurorehabilitation and thus study enrollment was 28 days (SD 18, median median 24). Mean observation time since injury was 146 days (SD 111.7, median 96; table 2).

**Table 3.2:** *Characteristics of included patients stratified by diagnosis*

| | Diagnosis | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Traumatic brain injury | | Stroke | | Hypoxic brain injury | | Total | |
| | n | % | n | % | n | % | n | % |
| **Total** | 10 | 24 | 13 | 31 | 19 | 45 | 42 | 100 |
| **female** | 2 | 13 | 5 | 31 | 9 | 56 | 16 | 38 |
| **Consciousness state at last assessment** | | | | | | | | |
| **emerge MCS** | 2 | 22 | 5 | 55 | 2 | 22 | 9 | 21 |
| **MCS** | 0 | 0 | 2 | 40 | 3 | 60 | 5 | 12 |
| **VS** | 8 | 29 | 6 | 21 | 14 | 50 | 28 | 67 |
| **SEP N20 absent n=18** | 1 | 12 | 2 | 25 | 5 | 63 | 8 | 44 |
| **age (years) (mean/sd)** | 58.1 | 16.5 | 58.7 | 14.1 | 54.2 | 16.4 | 56.5 | 15.5 |
| **CRS-R score at admission to rehab** | | | | | | | | |
| **(mean/sd)** | 5.0 | 3.3 | 7.0 | 3.9 | 5.6 | 2.9 | 5.9 | 3.3 |
| **CRS-R score (last available value) n=42 (mean/sd)** | 7.6 | 6.4 | 11.5 | 8.7 | 6.5 | 5.7 | 8.3 | 7.1 |
| **CRS-R score (three months after injury) n=31 (mean/sd)** | 9.4 | 9.1 | 8.3 | 7.3 | 7.6 | 4.9 | 8.2 | 6.3 |
| **CRS-R score (six months after injury) n=9** | | | | | | | | |
| **(mean/sd)** | 11.7 | 4.9 | 14 | - | 12.4 | 6.4 | 12.3 | 5.2 |
| **first NSE (mean/sd)** | 37.4 | 14.3 | 25.1 | 11.3 | 41.9 | 13.7 | 36.5 | 14.7 |
| **time from event to rehabilitation onset (days) (mean/sd)** | 28.8 | 8.9 | 26.5 | 11.1 | 29.1 | 25.4 | 28.2 | 18.4 |

emerge MCS = emergence from minimally conscious state

MCS = minimally conscious state

VS = vegetative state

CRS-R = Coma Recovering Scale-Revised

NSE = serum neuron-specific enolase

SEP = somatosensory evoked potentials

### *3.3.2 Adherence to guideline recommendations by acute care hospitals* [5, 6]

For the subpopulation of 19 anoxic patients, SEPs and EEGs were available in 38% of cases, NSE in 24%, and complete neurological assessment of brain stem reflexes in 85% of cases. Therapeutic hypothermia according to the guidelines had been induced in 38% of AIE patients, two of whom evolved to MCS+ during the course of the study.

3.3.3 C*linical course of consciousness and functioning*

Mean CRS-R score at admission to rehabilitation was 5.9 (SD 3.3), mean FIM score at admission was 18 (SD 0.4, minimum 18, maximum 20). Eleven patients died within the follow-up period (26%). Mean time to death since brain injury was 177 days (SD 10.7 days, figure 1). Among the 31 survivors, nine patients reached MCS+ (29%), five patients with ICH/SAH, two with AIE, and two with TBI. 11 patients (26% of all) gained at least one level of consciousness as denoted by the CRS-R, i.e. improved from VS to MCS or from MCS to MCS+. Three patients experienced a sustained decline in the level of consciousness, i.e. they were enrolled while in MCS and deteriorated to VS. One of them was a TBI-patient, the other two suffered from AIE.

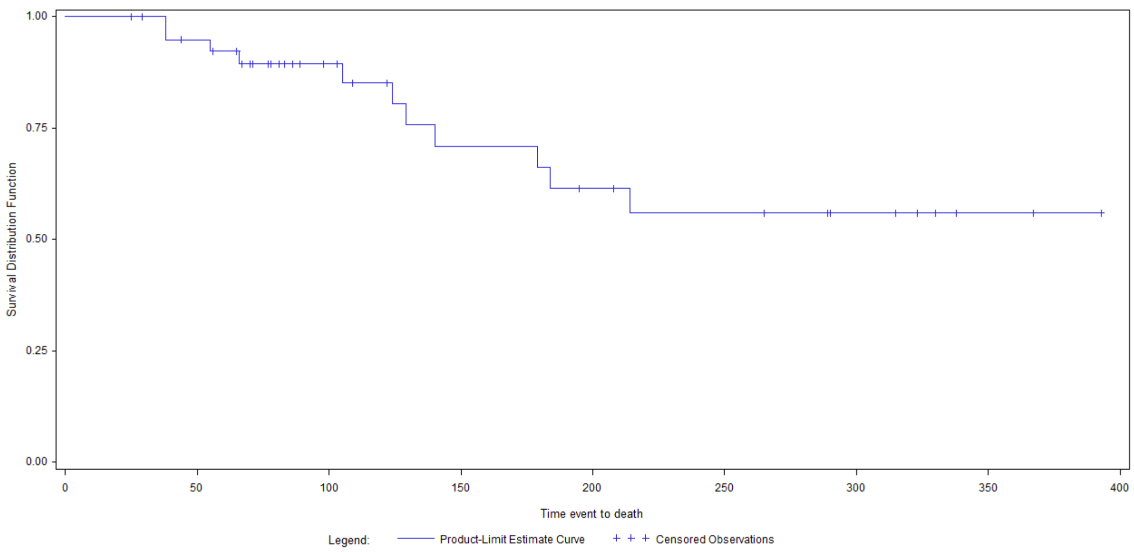


**Figure 3.1:** *Kaplan Meyer plot of time from injury to death (n=42).*

Time for emergence from MCS is shown in figure 2. Figure 3 shows the linearized trajectories of all patients stratified for diagnosis. Mean CRS-R score at last examination was 8 (SD 7.1, minimum 1, maximum 23). Mean FIM score at last examination was 22 (SD 10.6, minimum 18, maximum 75). Mean CRS-R score difference of first examination to three months was 3 (95% Confidence Interval CI 0.4; 4.6), to six months 6 (95% CI 1.5;9.9). The difference between the first and the three months examination was significant ($p = 0.021$), as was the difference of first and six months examination ($p = 0.02$).

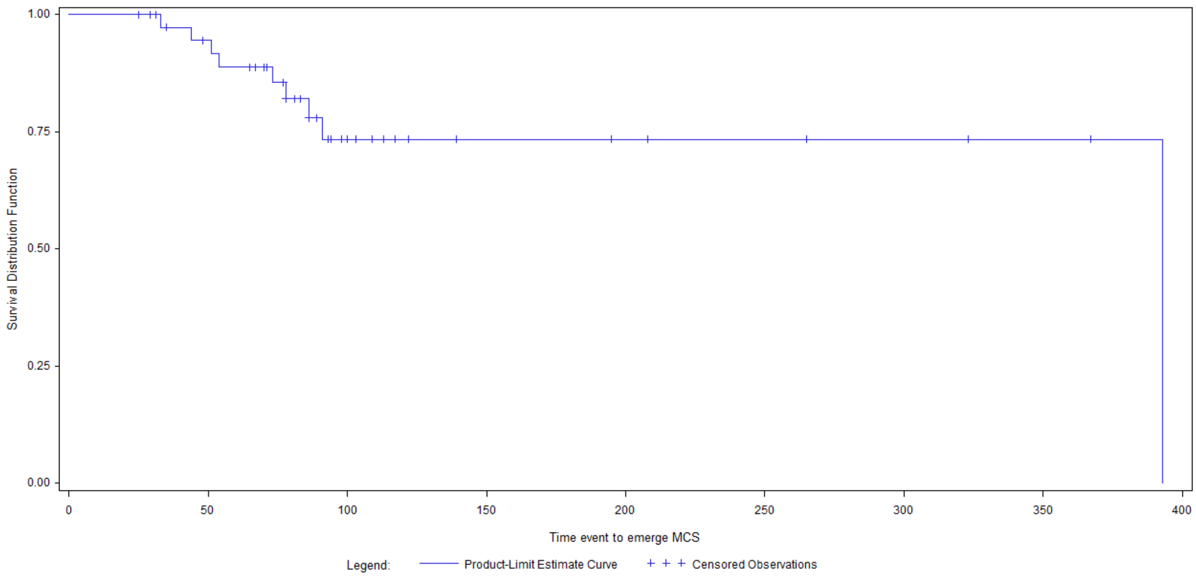


**Figure 3.2:** *Kaplan Meyer plot of time from injury to emergence from MCS (MCS+, n=42). One patient emerged as late as day 393.*

*3.3.4 Prognostic markers during neurorehabilitation*

In total, 36 patients (86%) had one or more negative prognostic factors at the time of admission to neurorehabilitation. Eight patients (19%) showed bilateral absence of the SEP N20 component; one of those eight emerged 1 from MCS and was discharged home with good communication skills but is still dependent regarding activities of daily living (FIM total score of 34). 54% of patients showed no EEG reactivity to external stimuli; three of those emerged from MCS. Pupillary response was bilaterally absent in 10 patients, corneal reflex was bilaterally absent in 12 patients. Twenty patients showed either no motor response or only extensor response to pain, 24 had NSE-levels > 33µg/L. Of the nine patients who emerged from MCS, one had initially shown no pupillary response, did not react to pain and had elevated NSE, one had shown neither pupillary response nor cortical N20 response and had elevated NSE, three had critically elevated NSE levels above the 33µg/L threshold alone.

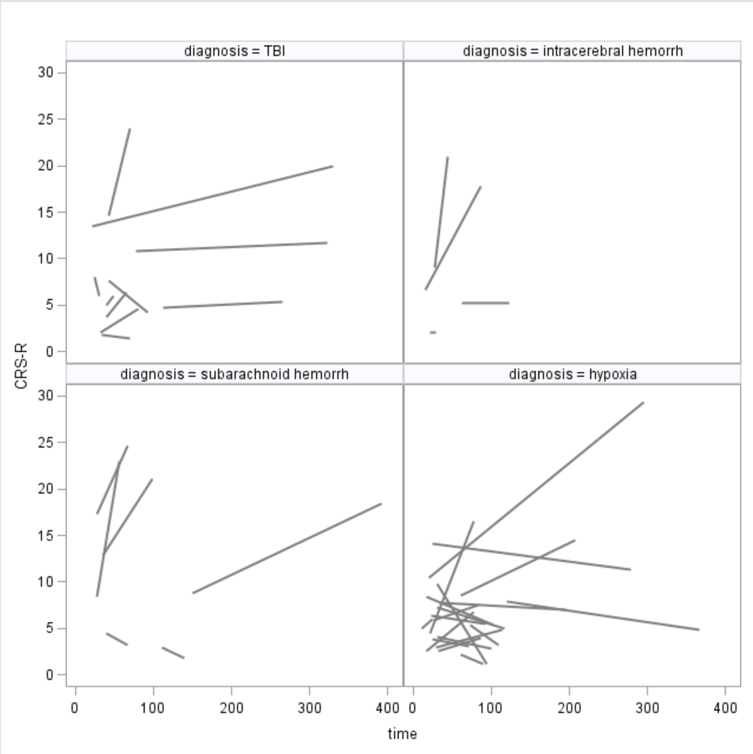


**Figure 3.3:** *Individual growth trajectories of Coma Recovery Scale-Revised (CRS-R) scores of individual patients by time since event (days) stratified by diagnosis. Each line represents one patient with linear regression as the interpolation method.*

## 3.4 Discussion

We present a novel prospective German registry on the outcome of severely affected patients with TBI and NTBI, and its results of the first 6 months. These preliminary results indicate that patients with severe DOC might have a chance to recover consciousness even in the presence of strong predictors for poor prognosis.

All patients were admitted for neurological rehabilitation either in VS or MCS and included consecutively. This is not a selection of favorable cases. Thus it is not surprising that approximately one fourth of all patients died during inpatient rehabilitation or follow-up, despite full LST. Also, only about 30% of our patients emerged from VS/MCS. A similar study on the natural history of traumatic and non-traumatic acute brain injury survivors reported 69% of patients emerging from MCS within 8 to 10 weeks, depending on diagnosis.[18] This highlights indeed the severity of illness in our patients.

We observed that important diagnostic information, namely SEP and NSE, from the acute setting hospitals, i.e. the intensive care units where patients were admitted first, was missing in 70% of patients with AIE, although defined diagnostic guidelines for this group of patients have been published for several years.[5] However, we envision that proactive communication with the acute care wards will improve diagnostic standards.

Partially, our data confirm recent reports about the potential for late recovery from VS/MCS. [4] We followed one patient for more than one year. This patient with a severe SAH emerged from MCS after 393 days, which is considerably late. Future analyses of our data will show which percentage of severely affected patients show late recovery.

As regarding prognostic markers, even patients whose technical findings precluded recovery might have potential to regain consciousness. One of 8 patients with bilateral loss of cortical N20, and 3 of 13 patients with loss of reactivity in the EEG emerged from VS/MCS. This is a dramatic finding since current guidelines and practice parameters currently do not encourage rehabilitation for those patients.[5, 6, 19]

It has recently been shown that especially the alleged “failsafe” SEP test results (bilateral loss of cortical responses) may indeed have a lower specificity than previously assumed.[20, 21] To give an example, patient TZB-0015 of our study, a man of 46 years with AIE after ventricular fibrillation, absent pupillary reflexes, bilaterally absent N20 responses and an initial NSE value of 64 µg/L evolved to MCS+ within three months after the event. Especially on the intensive care units, prognostication may be subject to confounding factors such as multiple organ damage, therapeutic hypothermia, medication, and shock.[5] This underlines the need for prospective studies systematically examining potential confounders.

Initial enrollment was slow in most study centers. It is understood that integrating data collection for study or registry purposes poses specific challenges to clinical routine. Additional training and motivation met these challenges. It will be of utmost importance to closely monitor enrollment and act upon arising problems. Regular meetings of the steering committee have to decide if the number of variables has to be reduced, or if there are other methods to improve enrollment.

*3.4.1 Study limitations*

We are aware that the strategy of creating a patient registry based on the admission of rehabilitation facilities will bias the results towards positive outcomes. However, the present structure of the registry, which is based on already established excellent collaboration in a regionally well-defined area will help to minimize or avoid this kind of selection bias. While a lack of appropriate diagnostic tests, e.g. in patients with AIE, may be considered a procedural quality management issue, it is a valuable opportunity for our registry to obtain an unbiased sample. The potential danger of clinical nihilism and thus self-fulfilling prophecies arising from supposedly fail-safe prognostic tests within the first days following severe acute brain damage is known. [2]

Lack of statistical power, another limitation of the presented data, will be overcome by the continuous inclusion of patients. In fact, at the time of submission of this manuscript, the number of enrolled patients is already at 109.

### *3.4.2 Conclusion*

Our first preliminary results suggest that forecasting the outcome might not be possible based on findings from the first days in acute care. Nevertheless, if the registry is able to overcome initial challenges of enrollment and incompleteness in data collection it will be the first to provide representative data on long-term outcomes and prognosis of patients with severe DOC following brain injury during and after rehabilitation care. Results are likely to have an impact on treatment decisions in the acute situation and in rehabilitation facilities, on treatment guidelines, and on the definition of clinical pathways.

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„Am Ende wird alles gut, und wenn es nicht gut ist, dann ist es auch nicht das Ende“

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