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Intensivmedizinisches Management von Patienten mit intrazerebraler Blutung

Habilitationsschrift
zur Erlangung der Venia Legendi
der Hohen Medizinischen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn
für das Lehrgebiet
„Anästhesiologie und Operative Intensivmedizin“

vorgelegt von

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Wissenschaftlicher Mitarbeiter
an der Rheinischen Friedrich-Wilhelms-Universität
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Die nachfolgenden Arbeiten liegen der kumulativen Habilitationsschrift zugrunde und werden im Folgenden behandelt und diskutiert:

1.) **Lehmann F**, Schenk LM, Bernstock JD, Bode C, Borger V, Gessler F, Güresir E, Hamed M, Potthoff AL, Putensen C, Schneider M, Zimmermann J, Vatter H, Schuss P, Hadjiathanasiou A.
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2.) **Lehmann F**, Schenk LM, Schneider M, Bernstock JD, Bode C, Borger V, Gessler F, Güresir E, Hadjiathanasiou A, Hamed M, Müller M, Putensen C, Zimmermann J, Vatter H, Schuss P.
Predictive Relevance of Baseline Lactate and Glucose Levels in Patients with Spontaneous Deep-Seated Intracerebral Hemorrhage.
Brain Sci. 2021 May 14;11(5):633.
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3.) **Lehmann F**, Schenk LM, Bernstock JD, Bode C, Borger V, Gessler FA, Güresir E, Hamed M, Potthoff AL, Putensen C, Schneider M, Zimmermann J, Vatter H, Schuss P, Hadjiathanasiou A.
Elevated Red Cell Distribution Width to Platelet Ratio is Associated With Poor Prognosis in Patients With Spontaneous, Deep-Seated Intracerebral Hemorrhage.
Front Neurol. 2021 Nov 15;12:751510.
https://doi.org/10.3389/fneur.2021.751510

4.) **Lehmann F**, Schenk LM, Ilic I, Putensen C, Hadjiathanasiou A, Borger V, Zimmermann J, Güresir E, Vatter H, Bode C, Schneider M, Schuss P.
Prolonged Mechanical Ventilation in Patients with Deep-Seated Intracerebral Hemorrhage: Risk Factors and Clinical Implications.
J Clin Med. 2021 Mar 2;10(5):1015.
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Die oben aufgeführten Arbeiten befassen sich mit der intensivmedizinischen Initialtherapie, Weiter- bzw. Folgebehandlung und Prognoseabschätzung von Patienten mit spontaner intrazerebraler Blutung.

Inhaltsverzeichnis

Abkürzungsverzeichnis

AKI	Akutes Nierenversagen, Acute Kidney Injury
ATACH-II	Antihypertensive Treatment of Acute Cerebral Hemorrhage–II
CCT	cerebrales Computertomogramm
CI	Konfidenz Intervall
CRP	C-Reaktives Protein
DNR	Do-Not-Resuscitate
GCS	Glasgow Coma Scale
eGFR	geschätzte glomeruläre Filtrationsrate
EVB	Erythrozytenverteilungsbreite
Hb	Hämoglobingehalt des Blutes
ICB	Intrazerebrale Blutung
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	Intracranial Hemorrhage
MISTIE	Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation
ml	Milliliter
mRS	Modified Ranking Scale
NICU	Neuro-Intensive-Care-Unit
OR	Odds-Ratio
PCT	Procalcitonin
PMV	Prolongierte mechanische Ventilation
RPR	Red blood cell distribution width to platelet count ratio
rt-PA	gewebespezifische Plasminogenaktivator
SOFA-Score	Sepsis-related organ failure assessment score
STICH	Surgical Trial in Intracerebral Haemorrhage
SWITCH	Swiss Trial of Decompressive Craniectomy versus Best Medical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage
U/Cr	Verhältnisses von Serum-Harnstoff zu Kreatinin

Einleitung

Pathophysiologie

Die spontane, nicht-traumatische intrazerebrale Blutung (ICB) stellt eine intrakranielle Blutung in das unmittelbar umliegende Hirnparenchym dar. Die ICB nimmt im Rahmen der Schlaganfall-Statistik etwa 10 bis 15 Prozent der Gesamtfälle ein und zeigt hierbei aber mit die höchste Mortalität [1].

Die Gesundheitsberichterstattung des Bundes gibt für das Kalenderjahr 2021 eine Gesamtanzahl von 32.836 betroffenen Patienten für die Diagnose der intrazerebralen Blutung in der Bevölkerung der Bundesrepublik Deutschland an (hier: ICD-10-Code I61; letzter Zugriff: 15.10.2023). Obwohl die Fallzahl im Vergleich zu den Vorjahreszeiträumen inklusive des Jahres 2000 für die hiesigen Breiten nahezu identisch bleiben, zeigen neueste Untersuchungen aus den USA eine Häufung von spontanen ICBs insbesondere in der jüngeren, sozio-ökonomisch relevanten Bevölkerungsgruppe [2].

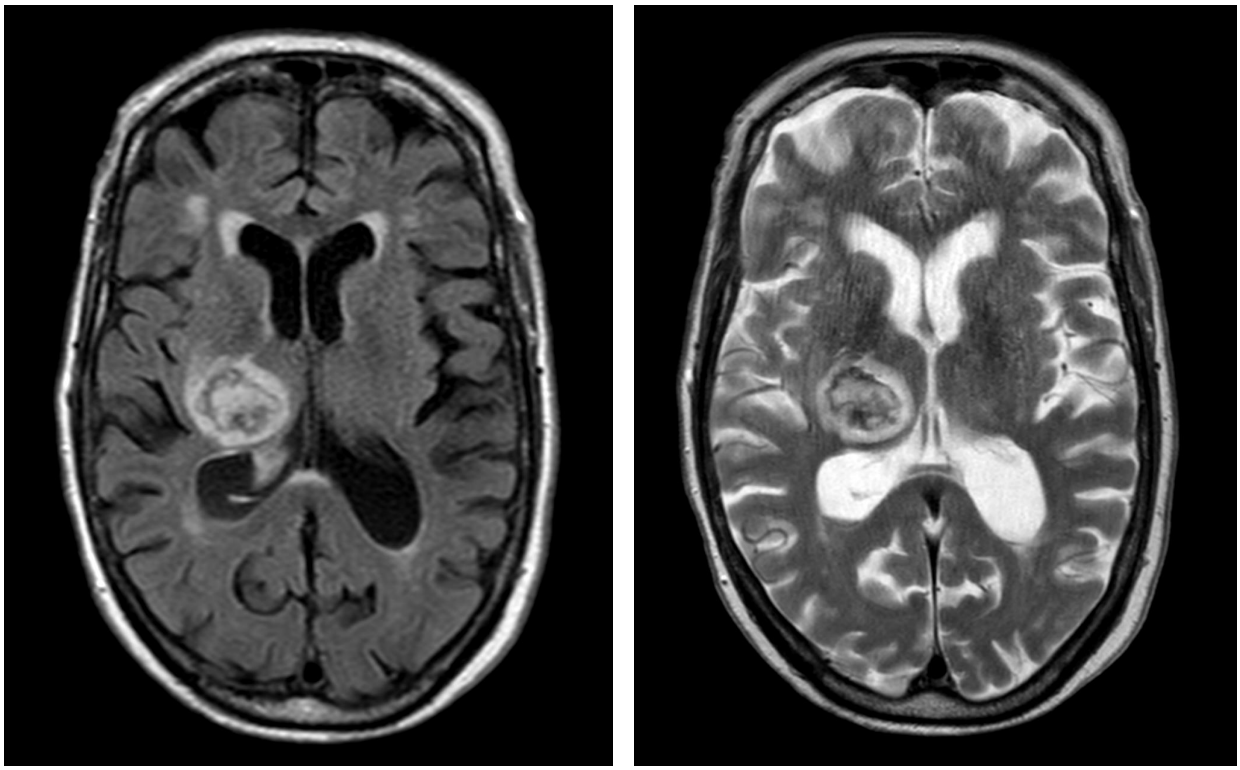

Abbildung 1: Beispiel einer typischen stammganglionären ICB in der CT-Bildgebung (links) und der T2 gewichteten MRT-Bildgebung (rechts). Bilder mit freundlicher

Genehmigung der Klinik für Neuroradiologie, Universitätsklinikum Bonn, Chefarzt Prof. Dr. A. Radbruch

Als Ursache für einen Großteil der spontanen ICBs wird eine Ruptur der lento-striatalen Gefäße angeführt [1]. Durch chronische Schädigung der Gefäße im Rahmen eines (nicht therapierten) arteriellen Hypertonus und/oder einer zunehmenden Arteriosklerose kommt es hierbei zur Entwicklung solcher, oftmals als “typisch” lokalisiert beschriebenen, ICBs (siehe Abbildung 1).

Seltener, aber diagnostisch herausfordernder, sind sogenannte “atypische” ICBs, die ihren Ursprung eher im Zusammenhang mit Gefäßmissbildungen, Hirnaneurysmen, Tumoren und/oder (überschießender) Blutgerinnungshemmung finden [3] (siehe Abbildung 2).

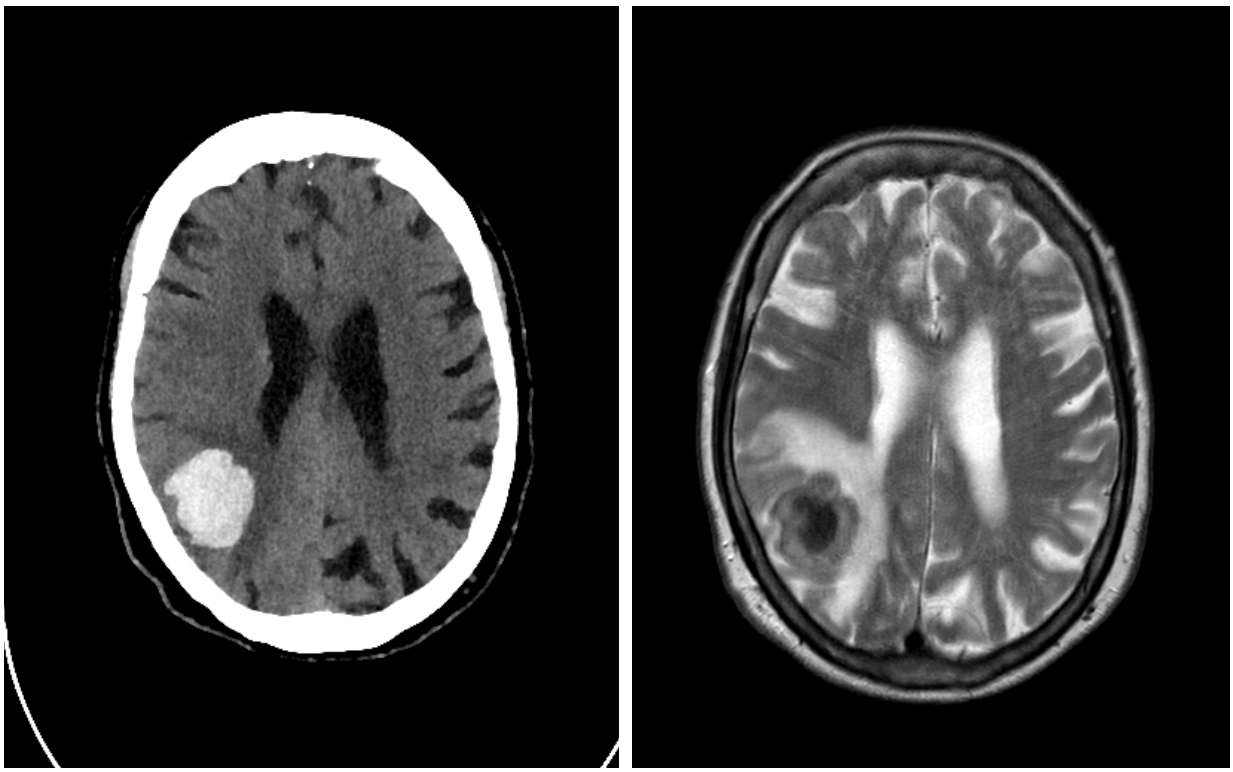

Abbildung 2: Beispiel einer atypischen lobären ICB in der CT-Bildgebung (links) und der T2 gewichteten MRT-Bildgebung (rechts). Bilder mit freundlicher Genehmigung der Klinik für Neuroradiologie, Universitätsklinikum Bonn, Chefarzt Prof. Dr. A. Radbruch

Konservative Therapie

Aufgrund der hohen Mortalität der ICB werden seit langer Zeit unterschiedlichste Bemühungen zur Etablierung/Verbesserung möglicher Therapiekonzepte angestrengt.

Hierbei stehen zum einen konservative Therapieverfahren zur Verfügung. Hauptziel ist hierbei eine weitere Ausbreitung der ICB und eine damit sich fortsetzende Schädigung zu unterbinden [4]. Dies kann neben einer Blutdrucknormalisierung im notwendigen Falle auch durch eine aktive, zeitnahe Gerinnungsoptimierung erfolgen [5,6]. Ergebnisse zweier randomisierter, multizentrischer Studien zeigen hierbei Grenzen hinsichtlich der Aggressivität einer möglichen Blutdrucksenkung und damit die Notwendigkeit einer ausgewogenen Anpassung im Sinne der zeitgleich erforderlichen Aufrechterhaltung eines suffizienten zerebralen Perfusionsdruckes [7,8]. Das Team um Andersen, welches die erste groß angelegte Studie zum Blutdruckmanagement nach ICB durchführten (INTERACT 2), berichtete über einen moderaten Einfluss auf das funktionelle Outcome nach 90 Tagen und die gesundheitsbezogene Lebensqualität [7]. Die Ergebnisse dieser Arbeit flossen danach in die internationalen Leitlinien zur Therapie der ICB ein, die nun eine aggressive frühzeitige Blutdrucksenkung empfahlen. Die zweite Studie jedoch (ATACH-II) konnte diesen Effekt nicht reproduzieren und zeigte keinen Einfluss auf das Überleben oder den Grad an Behinderung an Tag 90. In der Behandlungsgruppe zeigten sich aber gehäufter unerwünschte renale Nebenwirkungen [8]. Diese zunächst widersprüchlichen Signale wurden in einer gepoolten Analyse beider Studienpopulationen relativiert. Es war möglich einen linearen Zusammenhang einer frühen Blutdruck-Reduktion und eines stabilen Blutdrucks in den ersten 24h nach Beginn der Therapie mit einem guten Outcome und einem geringen Risiko für unerwünschte Nebenwirkungen zu zeigen [9]. Hierin lässt sich bereits erkennen, dass neben einer zeitlichen Komponente auch die Intensität/Ausgewogenheit der Therapie eine hohe Relevanz hat. Im Rahmen von ATACH-II ist der Blutdruck aggressiver gesenkt worden, so dass möglicherweise vorteilhafte Effekte durch Nebenwirkungen der antihypertensiven Therapie egalisiert wurden.

Operative Therapie

Neben der rein konservativen Therapie und Vermeidung der Hämatomexpansion sind unterschiedliche Optionen der operativen Therapie wissenschaftlich aufgearbeitet worden. Die International Surgical Trial in Intracerebral Hemorrhage (STICH) war eine randomisierte Studie, die darauf abzielte, bei Patienten mit einer spontanen supratentoriellen ICB eine frühe Operation mit einer konservativen Therapie zu vergleichen. An der Studie nahmen 1033 Patienten aus 83 Zentren in 27 Ländern teil, die nach Randomisierung entweder einer frühen Operation (<24 Stunden nach der Randomisierung) oder einer konservativen Primärbehandlung zugeteilt wurden [10]. Die Ergebnisse erbrachten keinen schlüssigen Beweis für den Nutzen einer Operation bei lobären und typischen ICBs. Eine Subgruppenanalyse zeigte, dass bei Patienten mit einer lobären Blutung ohne intraventrikulären Anteil eine frühzeitige Operation ein günstigeres Outcome zeigte, obwohl der Unterschied statistisch nicht signifikant war. Dieser Umstand führte zu der Folgestudie STICH II, die selektiv die chirurgischen Therapie von lobären Blutungen untersuchte und dies erneut mit einer konservativen Therapie verglich [11]. Auch in dieser Studie konnte nach sechs Monaten kein signifikanter Unterschied im funktionellen Outcome zwischen beiden Gruppen demonstriert werden. Eine Subgruppenanalyse deutete jedoch darauf hin, dass bei Patienten mit einem Glasgow Coma Scale (GCS) unter 9 eine frühzeitige Operation mit einem besseren Outcome im Vergleich zur konservativen Therapie assoziiert war.

Während in den STICH I und II Studien die operative Dekompression und Hämatomevakuation mittels Kraniektomie im Vordergrund stand, wurden auch weniger invasive Verfahren untersucht, deren primäres Ziel die Reduktion des Hämatomvolumens darstellte. Im Rahmen der Minimally Invasive Surgery plus rt-PA for Intracerebral Hemorrhage Evacuation Studie (MISTIE) wurde untersucht, ob minimalinvasiv über einen Katheter in die ICB eingebrachte gewebespezifische Plasminogenaktivator (rt-PA) zu einer Verbesserung des funktionellen Outcomes führt [12]. Es wurden Patienten mit spontaner supratentorieller ICB mit einem Volumen von mehr als 20 Milliliter (ml) eingeschlossen. Es handelte sich um eine multinational randomisierte, kontrollierte Studie, welche die Interventionsgruppe gegen eine rein konservativ behandelte Kontrollgruppe untersuchte. Der primäre Endpunkt war der Anteil der Patienten mit einem modifizierten Rankin-Skalenwert (mRS) von 0-3 nach

einem Jahr. Die Prozedur war zwar sicher anwendbar, allerdings wurde der primäre Endpunkt verfehlt, da eine signifikante Verbesserung des funktionellen Outcomes letztlich nicht demonstrierbar war. Eine standardisierte Anwendung in der Behandlung kann daher gegenwärtig nicht empfohlen werden [13].

Das Ziel solcher chirurgischen Interventionen ist neben der Hirndruck-Reduktion auch die Vermeidung sekundärer Hirnschädigungen, entweder durch den erhöhten Druck oder durch ein periläsionale Schädigung (Penumbra) im Rahmen der postiktalen Ödembildung. Erste Untersuchungen im Sinne der Durchführung einer dekompressiven Hemikraniektomie zur Drucksenkung ohne zusätzliche Evakuation des intrazerebralen Hämatoms zeigen hier ermutigende Ergebnisse, die aktuell in einer multizentrischen, prospektiv-randomisierten Studie (SWITCH-trial; ClinicalTrials.gov-Identifier: NCT02258919) untersucht werden [14,15].

Therapie- Algorithmen

Die Vielschichtigkeit und Komplexität einer ICB und deren Auswirkungen beispielsweise auf das umliegende Hirngewebe, aber auch diverse patientenspezifische Faktoren machen es schwierig einzelne Behandlungsziele zu extrahieren, die alleinig einen vorteilhaften Einfluss auch den Verlauf der Erkrankung nehmen. Die Bündelung von mehreren Maßnahmen bietet hier zusätzliche Vorteile. Die Translation wissenschaftlich evidenter Erkenntnisse in die tägliche Routine stellt hier eine anspruchsvolle Hürde dar [16]. Eng abgestimmte Maßnahmen, die kontinuierlich überprüft werden müssen um möglichst präzise definierte Ziele zu erreichen können hier hilfreich sein, auch teilweise komplexe klinische Routinen zu etablieren. Einen solchen Prozess, bezogen auf die ICB, stellt die Implementation eines “ABC”-Algorithmus dar [17]. Die hier zusammengefassten Maßnahmen beinhalteten eine frühzeitige Normalisierung der Gerinnungsfunktion (**A**nticoagulant reversal), eine standardisierte Behandlung/Kontrolle des systolischen Blutdrucks (**B**loodpressure Control) und eine institutionalisierte Abstimmung mit einem Neurochirurgen (**C**are pathway for referral to neurosurgery). Bereits in einem 1-Jahres Zeitraum konnte nach Einführung dieser pragmatischen Maßnahmen ein Rückgang der Sterblichkeitsrate nach 30 Tagen um 44% gezeigt werden. Obwohl nicht Teil des ABC-Bündels, waren ein Rückgang der Do Not Resuscitate [DNR] Anordnung und ein verbesserter Zugang zu intensivmedizinischer Versorgung für die beobachtete Verbesserung der Überlebensrate mit verantwortlich.

Therapie-Begrenzungen

Bei der Behandlung von Patienten mit einer ICB müssen in einem sehr kurzen Zeitraum teilweise extrem weitreichende Entscheidungen getroffen werden, deren Folgen häufig nur sehr begrenzt absehbar sind. Es existiert Literatur, die zeigt, dass gerade im Rahmen der Therapie einer ICB die Entscheidung für palliative Therapielimitationen (z.B. DNR-Anordnung) häufiger getroffen werden, als bei der Behandlung von ischämischen Schlaganfällen [18]. DNR-Anordnungen sind in der Behandlung von Patienten mit ICB unabhängig mit einem schlechten Outcome assoziiert [19]. Eine zu pessimistische Einschätzung der Krankheitsschwere führt mit einer höheren Wahrscheinlichkeit zu unangemessenen Limitation/Initiation von lebensrettenden Behandlungen. Der Effekt der selbsterfüllenden Prophezeiung ist in diesem Zusammenhang gut beschrieben und schlägt sich beispielsweise in den US-amerikanischen Behandlungsleitlinien nieder, in denen empfohlen wird eben auf diese frühen DNR-Anordnungen zu verzichten und sie frühestens nach dem zweiten Behandlungstag zu treffen[20].

Themenstellung

Nimmt man all diese akademischen Bemühungen, um eine möglichst optimale Therapie von Patienten mit ICB zusammen, so überrascht es dennoch, dass die Mortalität der Patienten mit ICB seit dem Jahr 2000 in der Bundesrepublik keine signifikante Veränderung aufzeigt (Gesundheitsberichterstattung des Bundes; Zugriff: 15.10.2023). Im Jahre 2001 gelang Hemphill et al. die Etablierung eines einfachen Faktoren-Scores zur Einschätzung der 30-Tages-Mortalität nach einer spontanen ICB [21]. Hierbei werden die Variablen Alter, Vigilanz (über Glasgow-Coma-Scale [GCS]), infratentorielle Lage, Blutungsvolumen und Vorhandensein einer intraventrikulären Blutungskomponente in einem Punktesystem abgefragt [21]. Hierbei kann eine maximale Punktzahl von 5 erreicht werden. Dies entspricht einer 30-Tages Mortalität von 100%. Bereits bei einem Punktewert von 3 muss mit einer 30-Tages-Mortalität von 72% gerechnet werden. Dieser sogenannte “ICH-Score” bietet im klinischen Alltag eine wichtige Entscheidungshilfe bei der Initiierung invasiver Therapien (ob

neurochirurgischer oder intensivmedizinischer Art) und wird nach der initialen Akutphase auch für orientierende Angehörigengespräche als Argumentationsgrundlage genutzt.

Die Auswahl der beim ICH-Score verwendeten Variablen jedoch deutet bereits darauf hin, dass das Outcome nach ICB eine multifaktorielle Abhängigkeit aufweisen kann. Die Vermutung, dass die stark betroffenen Patienten multifaktorielle Prädiktoren für ein schlechtes klinisches Outcome aufweisen, führt im Verlauf zu immer intensiveren Bemühungen der interdisziplinären Therapieabstimmung/-umsetzung. Jedoch stellt insbesondere die rechtzeitige Prognosestellung bei neurologisch-schwer beeinträchtigten Erkrankungen wie der spontanen intrazerebralen Blutung eine wichtige Leitschiene für die Kommunikation mit dem betroffenen Patienten bzw. häufiger, den betroffenen Angehörigen/Betreuern dar. Hier gilt es vor langen, aufwändigen, invasiven und ggf. unerwünschten intensivmedizinischen Therapien eine balancierte Risiko-/Nutzen-Abwägung anzustellen und diese auch in ihrer Konsequenz zu kommunizieren.

Aus diesem Grund beschäftigt sich die vorliegende kumulative Habilitationsschrift mit der Identifizierung und so dann der klinischen Bedeutung von möglichen negativen Outcome-Prädiktoren in der unmittelbaren Aufnahmesituation, wie auch im kurz- bis mittelfristigen intensivmedizinischen Verlauf, um in der interdisziplinären Konsensfindung im Rahmen der Prognoseabschätzung und ggf. Eskalations-/Deeskalationsentscheidungen einen entscheidenden Beitrag liefern zu können.

Zusammenfassende Ergebnisdarstellung

Lehmann F, Schenk LM, Bernstock JD, Bode C, Borger V, Gessler F, Güresir E, Hamed M, Potthoff AL, Putensen C, Schneider M, Zimmermann J, Vatter H, Schuss P, Hadjiathanasiou A. (2021). **Admission Dehydration Status Portends Adverse Short-Term Mortality in Patients with Spontaneous Intracerebral Hemorrhage**. *J Clin Med.* 2021 Dec 17;10(24):5939.

Zielsetzung der Arbeit

Die Mortalität der intrakraniellen Blutung ist auch unter Therapie nach wie vor hoch. Neben dem unmittelbaren Einfluss der Blutung auf die Sterblichkeit sind allerdings auch Begleitfaktoren für das intensivmedizinische Überleben relevant. Ziel dieser Arbeit war es zu identifizieren, inwieweit eine Dehydratation bei der Aufnahme Einfluss auf das Überleben haben kann.

Methoden und Ergebnisse

Von 2018 bis 2019 wurden Patienten mit einer typischen ICB in die Studie eingeschlossen. Die Charakteristika jedes Patienten wie die Vorerkrankungen, das Vorhandensein von gerinnungshemmenden Medikamenten oder Thrombozytenaggregationshemmern vor dem Iktus, die Lokalisierung und das Volumen der ICB, der initiale Glasgow Coma Scale (GCS) bei Aufnahme, der ICH-Score, sowie die Laborparameter zum Zeitpunkt der Aufnahme wurden in der Datenbank gesammelt und ausgewertet. Der primäre Endpunkt war die 30 Tages Mortalität. Zur Definition des Dehydratations-Status erfolgte die Verwendung des Verhältnisses von Serum-Harnstoff zu Kreatinin (U/Cr). War das Verhältnis U/Cr >80 lag eine Dehydration vor.

Insgesamt wurden 249 Patienten mit spontaner ICB identifiziert. Bei der Kombination aus Alter und ICB-Volumen wiesen 201 Patienten (81%) einen ICH-Score ≤ 3 und 48 Patienten (19%) einen ICH-Score > 3 auf. Darüber hinaus wiesen 41 Patienten (17%) bereits bei der Aufnahme Anzeichen einer zerebralen Herniation im Sinne einer ein- oder beidseitigen Mydriasis auf. Insgesamt 62 Patienten mit ICB (25%) wiesen in der initialen radiologischen Bildgebung eine Mittellinienverschiebung von >5mm auf. Die 30-Tages Mortalität betrug 41% (101 Patienten) in der gesamten Patientenkohorte. Insgesamt waren zum Aufnahmezeitpunkt 173 (69%) Patienten nicht dehydriert und 76 (31%) dehydriert. Die Patienten mit ICB, die zum Zeitpunkt der Aufnahme

dehydriert waren, waren im Vergleich zu den nicht dehydrierten Patienten deutlich älter. Darüber hinaus befanden sich dehydrierte Patienten mit ICB in einem signifikant schlechteren klinischen Zustand (Höhe des ICH-Scores, Vorhandensein von Dezerebrationszeichen, Ausmaß/Volumen der Blutung) als nicht dehydrierte Patienten. Eine zusätzliche multivariate Analyse identifizierte "Anzeichen einer zerebralen Herniation" (p=0,008, OR 6,6, 95% CI 1,6-26,9), "initiale Mittellinienverschiebung >5mm" (p<0,001, OR 8,2, 95% CI 3,4-19,6), "ICH-Score > 3" (p=0.007, OR 3,9, 95% CI 1,4-10,5) und "Dehydratation bei der Aufnahme" (p=0,007, OR 2,6, 95% CI 1,3-5,3) als unabhängige Prädiktoren für die 30-Tages Mortalität bei Patienten mit spontaner ICB (Nagelkerke's R2 = 0,48).

Schlussfolgerungen

Die Kernaussage dieser Arbeit ist, dass eine Dehydratation bei Aufnahme ein signifikanter und unabhängiger Prädiktor für die 30-Tage Mortalität bei der ICB sein kann.

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Article

Admission Dehydration Status Portends Adverse Short-Term Mortality in Patients with Spontaneous Intracerebral Hemorrhage

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Abstract: The impact of dehydration at admission of patients with spontaneous intracerebral hemorrhage (ICH) on short-term mortality remains ambiguous due to scarce data. All of the consecutive patients with spontaneous ICH, who were referred to our neurovascular center in 2018/19, were assessed for hydration status on admission. Dehydration was defined by a blood urea-to-creatinine ratio > 80. In a cohort of 249 patients, 76 patients (31%) were dehydrated at the time of admission. The following factors were significantly and independently associated with increased 30-day mortality in multivariate analysis: "signs of cerebral herniation" ($p = 0.008$), "initial midline shift > 5 mm" ($p < 0.001$), "ICH score > 3" ($p = 0.007$), and "admission dehydration status" ($p = 0.007$). The results of the present study suggest that an admission dehydration status might constitute a significant and independent predictor of short-term mortality in patients with spontaneous ICH.

Keywords: spontaneous intracerebral hemorrhage; dehydration; mortality; fluid balance

1. Introduction

An intracerebral hemorrhage (ICH) is one of the most fatal forms of stroke. Depending on the localization (deep-seated versus lobar), different causes (e.g., hypertension, arteriovenous malformations, aneurysms, tumors) may account for such hemorrhage [1,2]. Despite a variety of potential therapeutic approaches (e.g., blood pressure control, aspiration, decompressive craniectomy), the outcome (in this case, 30-day mortality) of ICH is often considered poor [3–7]. In addition to the consequences of the hemorrhage on the outcome/mortality of patients with ICH, intensive care therapy addresses additional risk factors/comorbidities unrelated to the hemorrhage [8]. These may include prolonged mechanical ventilation and the need for renal replacement therapy, among other complications of intensive care [9–11].

Dehydration at the time of admission is often an important factor affecting expected short-term mortality in the assessment of other acute illnesses [12–16]. Thus, dehydration status can act as an imminent risk, particularly in elderly, secluded patients with an unclear duration of recumbency and/or eventual lengthy diagnostic procedures [17–19]. To date, there have been only sporadic reports on the influence of admission dehydration status on short-term mortality in patients with ICH [20].

We aimed to assess the potential influence of admission dehydration status on short-term mortality in patients with spontaneous, non-traumatic ICH.

2. Materials and Methods

From 2018 to 2019, all consecutive patients with spontaneous, non-traumatic ICH who were referred to our neurovascular center were recorded in a computerized database. Patients with ICH resulting from a potential underlying source of hemorrhage (e.g., arteriovenous malformation, aneurysm, tumor) were excluded from further analysis using a consistent diagnostic algorithm as previously reported [2]. After the identification of eligible patients, information was retrospectively obtained for each patient, comprising patient characteristics, pre-existing conditions, presence of anticoagulant/antiplatelet medication prior to ictus, localization and volume of ICH, neurological status on admission in terms of initial Glasgow Coma Scale (GCS), ICH score [3], as well as laboratory parameters at the time of admission. The ICH volume was determined using the abc/2 method of initial imaging [21]. Surgical treatment of patients studied consisted of cerebrospinal fluid diversion, ICH aspiration/evacuation, and/or decompressive craniectomy. The primary endpoint used was short-term mortality in terms of 30-day mortality.

Since no distinct definition of the dehydration status has been established, we adopted a definition including laboratory parameters and determined the dehydration status by the ratio of blood urea and creatinine [13–15,22]. In the present study, dehydration was defined as the prevalence of a urea-to-creatinine (U/Cr) ratio of > 80 in the admission laboratory results.

3. Statistics

The computer software package SPSS (version 25, IBM Corp., Armonk, NY, USA) was used for data analysis. To compare continuous variables, the Mann–Whitney U test was selected when data were not normally distributed. An unpaired, two-sided t-test was used for parametric statistics after testing for normal distribution. Categorical variables were analyzed in contingency tables using Fisher's exact test. Results with $p < 0.05$ were considered statistically significant.

To determine the independent predictors that might predict short-term mortality after experienced ICH and would be available at the time of admission, an additional multivariate analysis was performed using a binary logistic regression. A backward stepwise method was used to construct a multivariate logistic regression model with short-term mortality as the dependent variable, with an inclusion criterion for variables with presumed/proven clinical relevance.

4. Results

4.1. Patient Characteristics

A total of 249 patients with spontaneous ICH were identified using the above-mentioned inclusion criteria. The median age of all patients was 76 years (IQR 65–82 years), with 128 patients (51%) being female. Regarding the localization of ICH, supratentorial ICH appeared in 212 patients (85%) while infratentorial ICH was present in 37 patients (15%). At the time of admission, 127 patients (51%) exhibited a GCS ≤ 12, with 114 patients (46%) presenting with an intraventricular hemorrhage (IVH) component. With the combination of age and ICH volume, 201 patients (81%)

demonstrated an ICH score ≤ 3 and 48 patients (19%) indicated an ICH score > 3. Furthermore, 41 patients (17%) presented with signs of cerebral herniation in terms of one or bilateral mydriasis as early as at the time of admission to our neurovascular center. A total of 62 patients with ICH (25%) displayed a midline shift of > 5 mm during baseline radiological imaging. Overall, 92% of the chronologically trackable patients (156/169) received in-hospital imaging within the first h (≤ 1 h) following admission. In total, 32% of patients (n = 80) were referred from external hospitals with existing imaging and were therefore not included in the time data acquisition. A significant correlation between time from admission to first imaging and 30 days mortality was not detected (p = 0.2). As a result of spontaneous ICH, 65 patients (26%) underwent surgical intervention during the course of treatment (Table 1). However, surgical treatment was not associated with short-term mortality in patients with spontaneous ICH (39% of patients without surgical treatment versus 43% of patients with surgical treatment; p = 0.7). The median hospital length of stay was 8 days (IQR 4–18 days). Short-term mortality (30 days) was 41% (101 patients) in the overall patient cohort. Further details are provided in Table 1.

Table 1. Overall patient characteristics. ICH, intracerebral hemorrhage; IQR, interquartile range; GCS, Glasgow Coma Scale; IVH, intraventricular hemorrhage; MLS, midline shift.

	Patients with Spontaneous ICH, n = 249
Median age (years, IQR)	76 (65–82)
Female sex	128 (51%)
Anticoagulation/antiplatelet medication prior ictus	125 (50%)
Pre-existing hypertension	204 (82%)
Pre-existing diuretic treatment	77 (31%)
Initial ICH score > 3	48 (19%)
GCS ≥ 13	122 (49%)
patient age ≥ 80 years	83 (33%)
infratentorial location	37 (15%)
ICH volume ≥ 30 mL	105 (42%)
presence of IVH	114 (46%)
Presence of clinical signs of herniation at admission	41 (17%)
MLS > 5 mm	62 (25%)
Surgical treatment	65 (26%)
Short-term mortality	101 (41%)

4.2. Admission Dehydration Status

Overall, 173 (69%) patients were assigned to the non-dehydrated subgroup and 76 (31%) to the dehydrated subgroup at the time of admission (Table 2). Diuretic drug

treatment before ictus had no significant influence on the dehydration status of a patient with ICH (Tables 1 and 2). The patients with ICH, who suffered from dehydration at the time of admission were significantly older compared with non-dehydrated patients with spontaneous ICH. Furthermore, patients with ICH and a dehydrated admission status were in a significantly deteriorated clinical condition (level of ICH score, presence of signs of decerebration, extent/volume of hemorrhage) compared to non-dehydrated patients with ICH (details are provided in Table 2, see also Figure 1).

Table 2. Patient characteristics in non-dehydrated and dehydrated group with ICH.

	Non-Dehydration U/Cr ≤ 80, *n* = 173	**Dehydration U/Cr > 80, *n* = 76**	
Median age (years, IQR)	75 (63–82)	76 (70–82)	$p < 0.001$
Female sex	77 (45%)	51 (67%)	$p = 0.001$, OR
Anticoagulation/antiplatelet medication prior ictus	86 (50%)	39 (51%)	$p = 0.9$
Pre-existing hypertension	140 (81%)	64 (84%)	$p = 0.6$
Pre-existing diuretic treatment	56 (32%)	21 (28%)	$p = 0.6$
Supratentorial ICH location	151 (87%)	61 (80%)	$p = 0.2$
ICH volume ≥ 30 mL	59 (34%)	46 (61%)	$p < 0.001$, OR 3.0, 95% CI 1.7–5.2
Presence of IVH	66 (38%)	48 (63%)	$p < 0.001$, OR 2.8, 95% CI 1.6–4.9
Initial ICH score > 3	21 (12%)	27 (36%)	$p < 0.001$, OR 3.9, 95% CI 2.1–7.7
Presence of clinical signs of herniation at admission	21 (12%)	20 (26%)	$p = 0.009$, OR 2.6, 95% CI 1.3–5.1
MLS > 5 mm	32 (18%)	30 (39%)	$p = 0.001$, OR 2.9, 95% CI 1.6–5.2
Short-term mortality	53 (31%)	48 (63%)	$p < 0.001$, OR 3.9, 95% CI 2.2–6.8

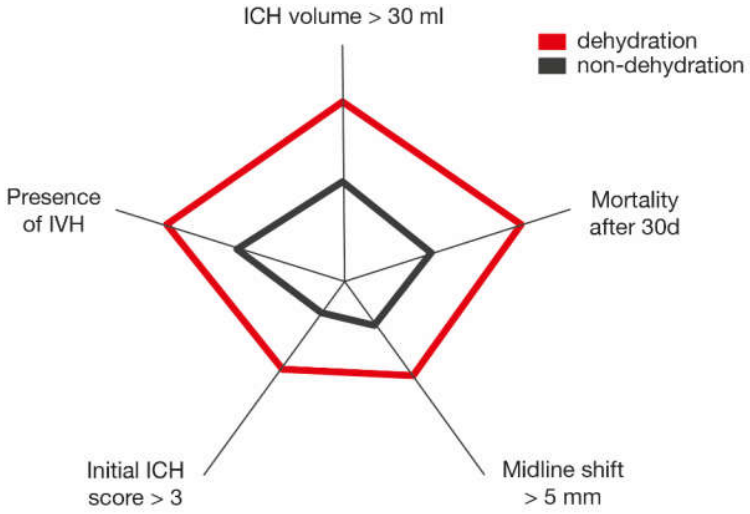

Figure 1. Graphical illustration of selected clinical and radiological conditions in dehydration/non-dehydration group and corresponding impact on mortality after 30 days. ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage.

4.3. Multivariate Analysis

An additional multivariate analysis identified "signs of cerebral herniation" (p = 0.008, OR 6.6, 95% CI 1.6–26.9), "initial midline shift > 5 mm" (p < 0.001, OR 8.2, 95% CI 3.4–19.6), "ICH score > 3" (p = 0.007, OR 3.9, 95% CI 1.4–10.5), and "admission dehydration status" (p = 0.007, OR 2.6, 95% CI 1.3–5.3) as independent predictors of short-term mortality in patients with spontaneous ICH (Nagelkerke's R^2 = 0.48).

5. Discussion

Dehydration represents an important component in the prevention of complications/mortality in a wide variety of diseases [15,23–26]. Dehydration, alongside fever, aspiration, and infection, is a potentially preventable complication of the course of several diseases and frequent in elderly patients [27,28]. Furthermore, initial dehydration at the time of admission seems to be a potential surrogate parameter for the severity in acute disorders and the subsequent clinical course. Especially in acute neurological disorders, which may be associated with reduced vigilance and thus reduced fluid intake, dehydration may have a negative influence on the further clinical course [29]. In this regard, an increased likelihood of thrombotic complications as well as the need for renal replacement therapy have been described repeatedly in patients suffering from ischemic stroke [25,30]. In patients with spontaneous ICH, the influence of dehydration status at the time of admission on the further clinical treatment course/outcome of the disease has not been identified conclusively.

The present study identified dehydration at the time of admission in 31% of patients admitted with spontaneous ICH to the authors' neurovascular center. In this regard, the findings of the present study demonstrated that patients with admission dehydration status were of older age and presented with poorer neurological status. In addition, admission dehydration status was more frequently noted to occur in female patients with ICH than in male patients. As previously reported, this observation might arguably be explained by the lower muscle mass in women, which might lead to lower creatinine, but not urea, levels, thus negating the definition of dehydration utilized herein [31].

Factors associated with greater hematoma volume, such as a higher ICH score, signs of cerebral herniation, as well as increased MLS, were associated with an admission dehydration status in patients with ICH. While the underlying mechanism has not been

clearly elucidated, Qureshi et al. suggested reduced cerebral perfusion due to hypovolemia in dehydrated patients with ICH as a reasonable explanation accounting for increasing perihematomal ischemia [32]. Contradictory theories advocate that hypovolemia-induced reduced blood pressure inhibits hematoma growth and dehydration-related hypernatremia increases intravascular osmolality causing a reduction in perihematomal edema and intracranial pressure [33–36]. Nevertheless, admission dehydration and poor outcome might be a simplified consequence of the fact that patients with lower GCS, greater ICH volume and therefore higher ICH score at admission might also be more neurologically impaired. However, neurologically impaired patients might be unable to adequately hydrate through the acute phase of deterioration, and in the case of increased age, occasionally suffer from an inadequate baseline hydration status already. In addition to dehydration, age might also act as a contributing factor to short-term mortality in patients with ICH, as elderly patients usually exhibit decreased renal function and are frailer compared to younger patients [37,38].

The assessment of a suspected dehydrated patient status using the laboratory values presented here is fast and performed with ease. However, a critique of such a definition, which relies solely on laboratory parameters, is that many additional aspects (especially in older, more frail patients) remain neglected. For example, other clinical parameters, urine analyses, or even ultrasound-based fluid volume analyses might provide a much more accurate impression of potential dehydration [39–41]. However, despite their accuracy, these methods might not be routinely applicable in the regular emergency patient. Nonetheless, the results of the current study might serve as a reason not only to define dehydration as such more precisely, but also to be able to better investigate suspected dehydration with established, more accurate methods after initial detection.

As mentioned previously, data regarding the association of admission dehydration status and short-term mortality in patients with spontaneous ICH remain scarce. To date, only one registry analysis has suggested an association between both parameters [20]. Gao et al. found that dehydration reduces in-hospital mortality in patients with ICH, indicating an inverse effect of admission dehydration status compared with the present cohort analysis [20]. However, as it was a registry analysis, details of ICH (e.g., location, cause, volume) were not accessible in the previous study [20]. Thus, other causes of ICH such as aneurysms, arteriovenous malformations, trauma, and tumors were not excluded, and the generalizability of the results of this previously published work remained limited. In addition, Gao et al. stated, in their limitation section, that neither imaging data nor information on the severity of ICH on admission was available during the registry analysis [20]. Through a meticulous consideration of patients, the results of the present study suggest that admission dehydration status in patients with spontaneous ICH may have a direct or indirect effect on the clinical course and short-term mortality, similarly to other diseases. In line with this reasoning, the multivariate regression analysis of the present study identified admission dehydration status in patients with spontaneous ICH as an independent predictor of short-term mortality.

6. Conclusions

The results of the present study suggest that admission dehydration status might serve as a significant and independent predictor of short-term mortality in patients of spontaneous, non-traumatic ICH.

7. Limitations

Interpretation of the results of the present study must be made in consideration of several shortcomings. In addition to the retrospective data collection method, the present study solely considers clinical factors that were known at admission for an interpretation of results. This may result in the neglection of potential outcome determinants in the further course of treatment (e.g., postoperative and/or intensive care complications).

However, the retrospective aspect of the present study also restricts the informative value of the data on admission parameters. For instance, missing information in medical records limits the validity of data for the exact time course of further diagnostic measures/treatment (e.g., time from admission/ictus to first imaging). Furthermore, the inconsistent definition of dehydration throughout the literature is a significant limitation. The present study used the widely accepted U/Cr-ratio, but this may vary in patients with other medical conditions that were not further assessed in the present study. Nevertheless, this detailed exploration of a selected, but nonetheless consecutive, patient population demonstrates, for the first time, the potentially negative impact of dehydration at admission on outcome in patients with ICH. For a broader interpretation and possible clinical implications, additional studies are needed to supplement this study and improve the dataset in this context.

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Conflicts of Interest: The authors declare no conflict of interest.

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Zielsetzung der Arbeit

Um den potentiellen Erfolg einer intensivmedizinischen Therapie möglichst frühzeitig abschätzen zu können, sind prognostische Parameter, welche die Mortalität nach einer ICB vorhersagen und im Routinebetrieb erhoben werden können, sinnvoll.
Ziel dieser Arbeit war es zu prüfen, inwieweit das Serum-Laktat und der Blutzuckerspiegel die Mortalität der typischen ICB beeinflussen.

Methoden und Ergebnisse

Für diese Arbeit wurden alle auf die neurologisch-neurochirurgische Intensivstation der Universitätsklinik Bonn (NICU) aufgenommenen Patienten zwischen 2014 und 2020, die eine typische ICB erlitten hatten und für mindestens drei Tage behandelt wurden, analysiert. Serum-Laktat Werte und Blutzuckerwerte wurden für die ersten vier Tage evaluiert. Eine Hyperlaktatämie war ab einem Wert von >1,8mmol/l definiert, eine Hyperglykämie ab einem Wert von über 180mg/dL. Unabhängig vom Patienten-Outcome wurden im initialen CCT Hämatomgröße und Vorhandensein einer intraventrikulären Blutung bestimmt. Der initiale Grad der Bewusstseinsstörung wurde mittels GCS dokumentiert und der ICH-Score errechnet. Für die weitere Analyse wurden die Patienten in zwei Gruppen (ICH-Score ≥3 und ICH-Score <3) unterteilt. Die Mortalität wurde drei Monate nach dem Iktus ermittelt und das funktionelle Outcome anhand der mRS dokumentiert.
Unter den 102 Patienten mit typischer ICB war ein erhöhtes Laktat und/oder ein erhöhter Blutzuckerspiegel signifikant mit einer verschlechtern 90-Tage Mortalität assoziiert. Eine multivariate logistische Regressionsanalyse identifizierte "ICH-Score ≥3" (p=0,004) zusammen mit "Hyperlaktatämie bei der Aufnahme" (p=0,025) und "Hyperglykämie bei der Aufnahme" (p=0,029) als unabhängige und signifikante Prädiktoren für die 90-Tage-Mortalität bei Patienten mit typischer ICB.

Schlussfolgerungen

Bereits bei Aufnahme erhöhte Laktat und Blut-Glukose Spiegel sind bei der typischen ICB mit einem schlechten Outcome vergesellschaftet. Zusammen mit dem radiologischen/neurologischen Risikoprofil ermöglichen diese Parameter damit eine frühe und umfassendere Bewertung der individuellen Behandlung.

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Article

Predictive Relevance of Baseline Lactate and Glucose Levels in Patients with Spontaneous Deep-Seated Intracerebral Hemorrhage

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Abstract: (1) Background: As elements of the standard admission blood panel, lactate and glucose represent potential biomarkers for outcome prediction. In patients with intracranial hemorrhage (ICH), data on the predictive value of these blood values is exceedingly sparse. (2) Methods: Between 2014 and August 2020, all patients with deep-seated ICH referred to the neurovascular center at the authors' institution were included in the subsequent study. Serum levels of lactate and glucose at the time of admission were compared with mortality at 90 days. In addition, a multivariate analysis was performed in order to identify independent admission predictors for 90-day mortality. (3) Results: Among the 102 patients with deep-seated ICH, elevated lactate and glucose levels on admission were significantly associated with increased mortality at 90 days. Multivariate logistic regression analysis identified "ICH score ≥ 3" ($p = 0.004$) along with "admission hyperlactatemia" ($p = 0.025$) and "admission hyperglycemia" ($p = 0.029$) as independent and significant predictors of 90-day mortality in patients with deep-seated ICH. (4) Conclusions: Initially elevated lactate and glucose levels after spontaneous intracerebral hemorrhage are associated with poor outcome, suggesting a potential application for future prognostic models when considered in conjunction with other parameters.

Keywords: intracerebral hemorrhage; lactate; glucose; mortality

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) is a potentially devastating neurological emergency in which long-term functional independence is achieved in only a fraction of cases and mortality rates are tremendous, exceeding 50% [1]. Therefore, prognostic factors for mortality after ICH are warranted for early assessment of the potential success/necessity of an often-debilitating intensive care/surgical treatment [2]. Of particular value in this context are clinical predictors that are easily available at

admission after spontaneous ICH and are also not subject to increased interobserver variability (such as measures of ICH size). Promptly available biomarkers on admission may support early risk assessment of a complicated course and provide additional insight into pathophysiological mechanisms if such factors are causally related to the event or its immediate sequelae [3]. In critically ill patients, initially elevated serum lactate levels have previously been identified as associated with an unfavorable outcome [4,5]. In contrast, the prognostic value of blood lactate levels in ICH patients has been studied scarcely. Whereas several studies have indicated that glucose is associated with outcome in ICH [6–9]. Lactate and glucose represent two crucial metabolites that are also interrelated. Glucose constitutes a direct precursor of lactate, and both circulating blood levels of lactate and glucose can be increased by different stress conditions [10]. An issue with studies of spontaneous ICH is the distinct heterogeneity due to the varying location, size, and sequelae of hemorrhage [11]. Therefore, the present study focused exclusively on patients with spontaneous non-traumatic ICH in the area of the basal ganglia (herein: deep-seated ICH). The aim of this study was to determine whether early elevations in circulating lactate and glucose levels are associated with increased mortality after spontaneous deep-seated ICH.

2. Materials and Methods

Patients: For the present retrospective analysis, all patients with spontaneous deep-seated ICH admitted to the neuro-intensive care unit (NICU) of the author's institution between 2014 and August 2020 were considered to be eligible for potential inclusion in the present study. Patients with lobar ICH and/or an underlying source of bleeding (e.g., aneurysm, AVM, trauma) were excluded. Patients who were not treated in the NICU for at least 3 days and those whose disastrous clinical situation (e.g., intractable cardio-/pulmonary instability, brain injury not deemed compatible with survival) precluded further meaningful intensive care were also excluded. Patients with an existing patient wish for withdrawal of life-sustaining treatment were not considered in further study analysis. Baseline demographic and clinical data, including age, sex, vital signs, radiological features, length of stay, and mortality, were retrospectively obtained from medical records. The results of the routine blood tests performed on admission and in the subsequent 4 days of treatment were reviewed with regard to serum lactate level and blood glucose level. Hyperlactatemia at the time of hospital admission was defined as a lactate value of >1.8mmol/l and hyperglycemia as a glucose value of >180 mg/dL according to institutional and described reference values [12]. In addition, the highest values of the first 5 days of treatment were determined and analyzed separately as peak lactate and/or peak glucose levels. Unaware of patient outcome, initial head computed tomography (CT) scans were used to measure both the presence of intraventricular blood and hematoma size (ABC/2 method, [13]). The initial degree of affected consciousness was determined by means of the Glasgow Coma Scale (GCS). With the data collected the ICH score was calculated for each individual patient [14]. For further statistical analysis, patients were divided into two groups based on ICH score: 1) ICH score < 3 and 2) ICH score ≥3. All patients were treated according to the standard guidelines [15], and the primary end point of the present study was all-cause mortality at 90 days. Follow-up was obtained 3 months after ictus. Therefore, functional outcome was assessed at 3 months after ICH using the modified Rankin Scale (mRS). The affected patients were consequently divided into two groups, where, also taking into account the eloquence of the ICH localization, favorable outcome was defined as mRS 0–4, while unfavorable outcome was defined as mRS 5–6. For clarity of presentation, patients were assigned to the non-survivor group or the survivor group according to mortality within 90 days after hemorrhage.

Statistics: All results are presented as medians with interquartile range (IQR) for continuous variables and as numbers with percentages for categorical variables. Fisher's exact test was applied to compare unpaired categorical and binary variables. The Mann–Whitney U-test was chosen to compare continuous variables as the data were largely not

normally distributed. Receiver operating characteristic (ROC) curve analysis was also conducted, and the area under the curve (AUC) values were calculated to evaluate the utilization of serum lactate levels as well as glucose levels for mortality prediction in patients with deep-seated ICH. All statistical analyses were performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY). Results with $p < 0.05$ were considered statistically significant. Furthermore, a multivariate analysis was performed to confirm the independence of the potential outcome predictors studied. The following variables were included in a multivariate logistic regression model applying the events per variable (EPV) 1 to 10 rule of thumb: ICH score ≥ 3, admission hyperlactatemia, admission hyperglycemia, and anticoagulant medication prior ictus.

3. Results

3.1. Patient Characteristics

A total of 1409 patients with the diagnosis of ICH between 2014 and August 2020 were referred to the authors' institution. After implementing the aforementioned inclusion criteria (spontaneous, non-traumatic, supratentorial, deep-seated ICH with NICU stay ≥ 3 days), 102 patients with deep-seated ICH were identified as eligible for further analysis. Median age of patients 66 years (IQR 57–76). Mortality rate after 90 days was 42% (43/102). Overall, 57 patients (56%) achieved a favorable outcome (mRS 0–4), whereas 45 patients with deep-seated ICH (44%) experienced an unfavorable outcome (mRS 5–6). Baseline characteristics of patients with deep-seated ICH are given in Table 1.

Table 1. Baseline patient characteristics.

	Survivors	**Non-Survivors**	***p*-Value**
number of patients	59	43	
median age (IQR, yrs)	63 (53–72)	68 (59–81)	$p = 0.03$
female sex	21 (36%)	16 (37%)	$p = 1.0$
ICH score ≥ 3 at admission	4 (7%)	16 (37%)	$p < 0.0001$
initial GCS ≤ 12	28 (48%)	36 (84%)	$p < 0.0001$
ICH volume ≥ 30ml	24 (41%)	29 (67%)	$p = 0.009$
known diabetes mellitus prior ictus	5 (9%)	7 (16%)	$p = 0.4$
anticoagulant medication prior ictus antiplatelet medication combination	8 (14%) 15 (25%) 1 (2%)	6 (14%) 13 (30%) 0 (0%)	$p = 1.0$
initial SBP (mmHg) mild (<180) moderate (180–219) severe (≥220)	 36 (61%) 17 (29%) 6 (10%)	 27 (63%) 10 (23%) 6 (14%)	$p = 0.7$
median admission lactate (IQR, mmol/L)	1.48 (1.05–1.88)	1.88 (1.49–2.41)	$p = 0.004$
median admission glucose (IQR, mg/dL)	126 (112–132)	143 (120–183)	$p = 0.001$

IQR, interquartile range; yrs, years; ICH, intracerebral hemorrhage; GCS, Glasgow Coma Scale; SBP, systolic blood pressure.

3.2. Influence of Early Serum Lactate on Mortality

Overall, median admission serum lactate level was 1.56 (IQR 1.18–2.16) mmol/l in all patients. Forty-one patients (40%) presented with hyperlactatemia on admission. In detail, 16 patients with deep-seated ICH who survived (27%), compared to 25 patients of the non-survival group (58%), presented with initial hyperlactatemia (p = 0.002, OR 3.7, 95% CI 1.6–8.6). Median admission serum lactate level was 1.48 (IQR 1.05–1.88) mmol/l in the group of patients with deep-seated ICH who survived and 1.88 (IQR 1.49–2.41) mmol/l in the non-survival group (p = 0.004). Patients with deep-seated ICH categorized in the survivor group exhibited a significantly lower median peak lactate value (1.51 mmol/l, IQR 1.19–2.14), compared to patients allocated to the non-survivor group (2.08 mmol/l, IQR 1.59–2.70; p = 0.001). The course of the median serum lactate values of the initial five days after admission are shown in Figure 1.

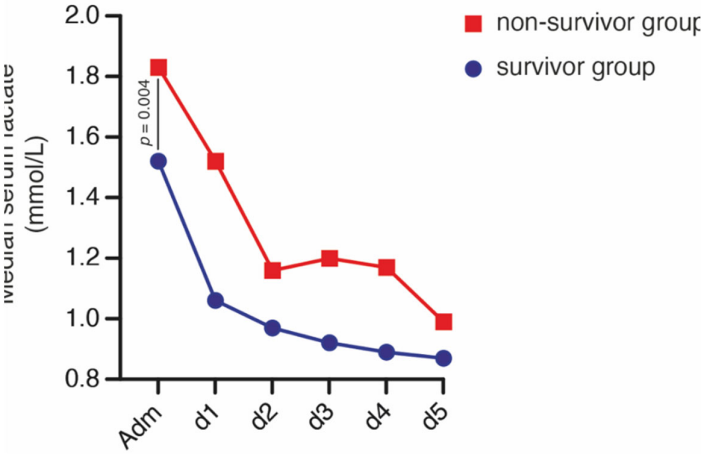
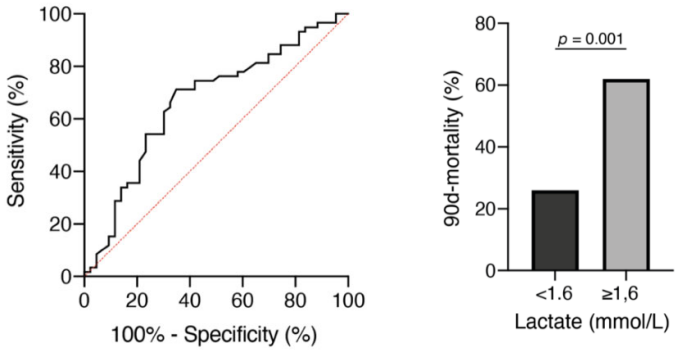


Figure 1. Chronological progression of lactate values distributed according to mortality at 90 days in patients with deep-seated intracerebral hemorrhage within the initial period after admission.

Regarding the initial serum lactate value, the optimal cutoff was 1.6 mmol/L and the AUC was 0.67 (95% CI 0.56–0.78, p = 0.004), with a sensitivity of 67% and a specificity of 71% (Figure 2a). In patients who presented with serum lactate < 1.6mmol/L, mortality rate after 90 days was 26% (15/57) compared to 62% in patients with an initial serum lactate ≥ 1.6mmol/L (28/45; p = 0.001, OR 4.6, 95% CI 1.99–10.7, Figure 2b).



(**a**) (**b**)

Figure 2. Receiver operating characteristic (ROC) curves (**a**) for admission lactate levels and mortality after 90 days in relation to initial lactate levels (**b**).

3.3. Influence of Admission Glucose on Mortality

Overall, median admission glucose level was 130 (112–148) mg/dL in all patients. Hyperglycemia was detected on admission in 15 patients (15%). In detail, three patients with deep-seated ICH who survived (5%) compared to 12 patients of the non-survival group (28%) presented with initial hyperglycemia (p = 0.002, OR 7.2, 95% CI 1.9–27.6). Median admission glucose level was 126 (IQR 112–132) mg/dL in the group of patients with deep-seated ICH who survived and 143 (IQR 120–183) mg/dL in the non-survival group (p = 0.001). Patients with deep-seated ICH categorized in the survivor group exhibited a significantly lower median peak lactate value during the study time period (130 mg/dl, IQR 121–144) compared to patients allocated to the non-survivor group (163 mg/dl, IQR 133–213; $p < 0.0001$). The course of the median glucose values of the initial five days after admission are shown in Figure 3.

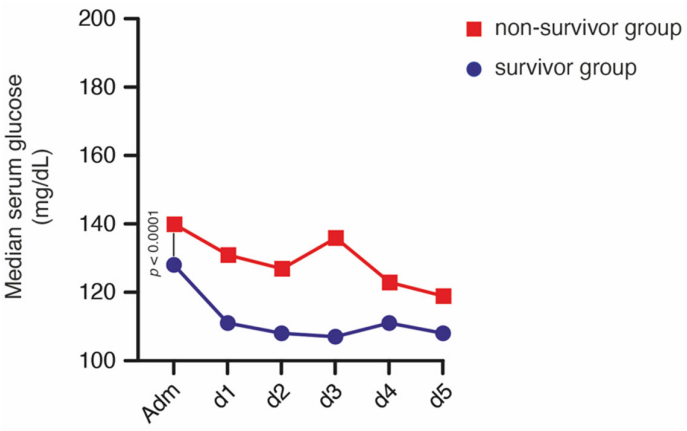
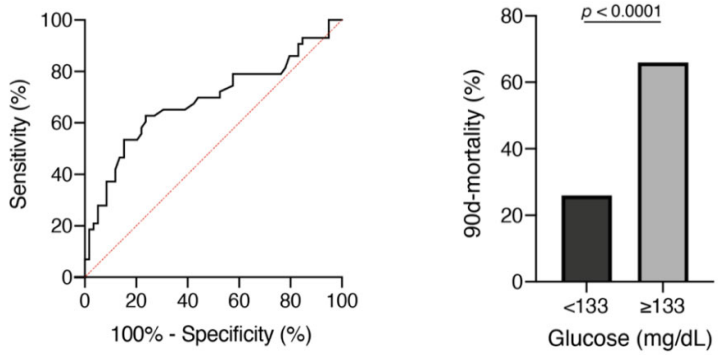


Figure 3. Chronological progression of blood glucose values distributed according to mortality at 90 days in patients with deep-seated intracerebral hemorrhage within the initial period after admission.

Regarding the initial glucose value, the optimal cutoff was 133 mg/dL and the AUC was 0.69 (95% CI 0.58–0.796, p = 0.001), with a sensitivity of 63% and a specificity of 76% (Figure 4a). In patients who presented with admission glucose < 133 mg/dl, mortality rate after 90 days was 26% (16/61), compared to 66% in patients with an initial glucose ≥ 133 mg/dL (27/41; $p < 0.0001$, OR 5.4, 95% CI 2.3–12.8; Figure 4b).



(**a**) (**b**)

Figure 4. Receiver operating characteristic (ROC) curves (**a**) for admission blood glucose levels and mortality after 90 days in relation to initial blood glucose levels (**b**).

3.4. Multivariate Analysis

The additionally performed multivariate logistic regression analysis identified "ICH score ≥ 3" ($p = 0.004$, OR 6.4, 95% CI 1.8–22.7), "admission hyperlactatemia" ($p = 0.025$, OR 2.9, 95% CI 1.1–7.4), and "admission hyperglycemia" ($p = 0.029$, OR 5.0, 95% CI 1.2–21.3) as independent and significant predictors for 90-day mortality in patients with deep-seated ICH (Nagelkerke's R^2 0.329).

4. Discussion

Critically ill patients after spontaneous intracerebral hemorrhage often have to undergo extensive therapies. Early reliable biomarkers to assess mortality might help in the course of this often-sophisticated management of affected patients to support the assessment of benefit and/or necessity of specific intensive medical therapy (organ replacement procedures) or neurosurgical interventions (decompressive hemicraniectomy) [2,3,16]. In patients with deep-seated ICH, the present study demonstrates an association between an initial elevated lactate concentration, as well as an elevated glucose level, with an increased likelihood of mortality at 90 days after the ictus.

In patients with spontaneous ICH, an initially elevated serum lactate level might reflect a multifactorial pathophysiology. These patients often experience a catecholamine response due to hemorrhage-related hypothalamic dysfunction with the possible consequence of tissue hypoxia from pulmonary edema [17,18]. Due to this sudden catecholamine release combined with a sudden increase in intracranial pressure, enhanced renal perfusion may lead to subsequential hypovolemia [17]. In addition, excessive adrenergic stimulation could also induce increased glucose metabolism with rapid output of pyruvate and lactate, the latter being measurable in the systemic circulation. Similar observations have been made in patients with sustained aneurysmal subarachnoid hemorrhage [19,20]. In patients with deep-seated ICH, the results of the present case series indicate that both the existence of hyperlactatemia on admission as well as an exceeded peak level within the first days after hemorrhage seems to be linked to the probability of a decreased survival at 90 days. This spurs the importance of lactate-oriented therapy in critically ill patients, now including patients with deep-seated ICH in the present study [5].

Furthermore, experimental studies suggest that hyperglycemia after ICH may also be triggered by a neuroendocrine stress-mediated response and in turn aggravates subsequent brain tissue damage through metabolic dysregulation, cytotoxicity, and neuronal cell death [21,22]. In an animal experimental approach with induced hyperglycemia, Song et al. found it to result in more severe brain edema and perihematomal cell death [22]. Similarly, studies in the clinical setting-consistent with the present study-demonstrated that patients with elevated blood glucose on admission had significantly higher mortality at 90 days, regardless of preexisting glycemic status prior to hemorrhage [23]. The data of the present study also indicate, within patients with deep-seated ICH, that not only the presence of hyperglycemia on admission but also an excessive peak value occurring within the first days after hemorrhage seems to be associated with a lower probability of survival at 90 days. The guidelines for management of patients with ICH therefore state that hyperglycemia should be avoided due to its impact on outcome, not only during the course of treatment but also during the prehospital/admission period [15]. However, exaggerated correction of blood glucose into hypoglycemia should also be avoided to prevent energy crisis in such a vulnerable stage [15,24,25]. In the present study, only 12 patients (12%) had a history of diabetes mellitus. Similar to the study on initial glucose/lactate concentration in patients with aneurysmal subarachnoid hemorrhage by Ndieugnou Djangang et al., diabetes mellitus as a pre-existing condition did not appear as a decisive factor in the initial determination of mortality in patients with deep-seated ICH [19].

Thus, in a reasonably homogeneous patient population (deep-seated ICH), the present study indicates that an adequate, balanced therapy should be initiated early in response to the initial admission state. Moreover, these easily obtained laboratory parameters provide an early impression of the patient, which together with the radiological and neurological findings allows for an improved evaluation.

This study has several limitations in addition to its retrospective design. The confinement to patients with deep-seated hemorrhage and assignment to a university medical center certainly offer advantages of reduced heterogeneity but do not allow an uncritical generalization of the results of this study to all patients with ICH. Furthermore, lactate and glucose were not measured at specific, predefined time points but were measured after admission. This circumstance neglects the different disease courses ahead of admission. Finally, we relied on systemic lactate and glucose values and had to forgo corresponding values from CSF and/or microdialysis.

5. Conclusions

Hyperlactatemia as well as hyperglycemia in the early phase of deep-seated intracerebral hemorrhage are associated with increased mortality. These findings add to the radiological/neurological risk profile of patients with deep-seated ICH, allowing earlier and more comprehensive assessment of individual management.

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Informed Consent Statement: Patient consent was waived due to the used retrospective study design.

Data Availability Statement: All data are contained within the article.

Conflicts of Interest: The authors declare no conflicts of interest.

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Zielsetzung der Arbeit

Das Verhältnis der Erythrozytenverteilungsbreite (EVB) zur Thrombozytenzahl (Red blood cell distribution width to platelet count ratio; RPR) zeigt in verschiedenen Veröffentlichungen die Schwere einer Inflammation an und wurde zur prognostischen Einschätzung von beispielsweise Brustkrebs oder dem Grad der hepatischen Fibrosierung im Rahmen der chronischen Hepatitis angewandt.
Ziel dieser Arbeit war es, die RPR als möglicherweise einfachen und vor allem unmittelbar verfügbaren Index für eine frühzeitige prognostische Evaluation von Patienten mit spontaner tiefer ICB zu analysieren, um gegebenenfalls die Entscheidungsfindung auf der Intensivstation zu erleichtern.

Methoden und Ergebnisse

Bei allen Patienten mit einer stammganglionären ICB, die zwischen 2014 und 2020 in unserem neurovaskulären Zentrum behandelt wurden, wurden neben den Patientenmerkmalen, der Lokalisation und Ausdehnung der ICB auch die initialen Laborwerte zur Bestimmung der RPR, einer Anämie (Hb <12mg/dl bei Frauen; <13mg/dl bei Männern), CRP und PCT analysiert. Anschließend wurde eine multivariate Analyse durchgeführt, um unabhängige Risikofaktoren für die 90-Tage-Mortalität nach einer tiefen ICB zu ermitteln.
Es wurden insgesamt 102 Patienten mit tiefer ICB identifiziert und weiter analysiert. Patienten mit einer anfänglichen RPR <0,06 wiesen eine signifikant niedrigere Sterblichkeitsrate nach 90 Tagen auf als Patienten mit einer anfänglichen RPR ≥0,06 (27 vs. 57%; p=0,003). Die multivariate Analyse identifizierte "ICH-Score ≥3" (p=0,001), "Anämie bei Aufnahme" (p=0,01) und "erhöhte RPR ≥0,06" (p=0,03) als unabhängige Prädiktoren für die 90-Tage-Mortalität.

Schlussfolgerungen

Diese Studie zeigt erstmals, dass die RPR ein unabhängiger Entzündungsmarker sein könnte, der mit der Prognose bei der typischen ICB in Verbindung gebracht werden kann. Die Ergebnisse zeigen, dass Patienten mit einem erhöhten RPR-Wert im Aufnahmelabor auch eine erhöhte 90-Tage Mortalität aufweisen.

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Elevated Red Cell Distribution Width to Platelet Ratio Is Associated With Poor Prognosis in Patients With Spontaneous, Deep-Seated Intracerebral Hemorrhage

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Object: Inflammatory response is an important determinant of subsequent brain injury after deep-seated intracerebral hemorrhage (ICH). The ratio of red blood cell (RBC) distribution width to platelet count (RPR) has been established as a new index to reflect the severity of inflammation. To the best of our knowledge, no association between RPR and prognosis after spontaneous ICH has yet been reported.

Methods: In all patients with deep-seated ICH treated at our Neurovascular Center from 2014 to 2020, initial laboratory values were obtained to determine RPR in addition to patient characteristics and known risk factors. Subsequent multivariate analysis was performed to identify independent risk factors for 90-day mortality after deep-seated ICH.

Results: Hundred and two patients with deep-seated ICH were identified and further analyzed. Patients with an initial RPR < 0.06 exhibited significantly lower mortality rate after 90 days than those with an initial RPR ≥ 0.06 (27 vs. 57%; $p = 0.003$). Multivariate analysis identified "ICH score ≥ 3" ($p = 0.001$), "anemia on admission" ($p = 0.01$), and "elevated RPR ≥ 0.06" ($p = 0.03$) as independent predictors of 90-day mortality.

Conclusions: The present study constitutes the first attempt to demonstrate that the ratio of RBC distribution width to platelets—as an independent inflammatory marker—might serve for prognostic assessment in deep-seated ICH.

Keywords: spontaneous intracerebral hemorrhage, red blood cell distribution width, platelets, morbidity/mortality, inflammation

INTRODUCTION

Patients that suffer from spontaneous intracerebral hemorrhage (ICH) often display significant morbidity/mortality due to the extent and/or the location of the bleed (1). These devastating injuries occur as a result of primary [i.e., mass effect(s)] and/or secondary (i.e., oxidative stress, inflammation, etc.) injury caused by the hemorrhage (2). Of note,

deep-seated ICH appears to be distinct from lobar ICH, implying different etiologies and ultimately different clinical outcomes (3).

Given the varying degrees and locations of ICH, reliable prognostic aids supporting early clinical decision-making are essential. Accordingly, herein we assessed ICH scores, and a myriad of lab values in effort to develop a tool capable of providing better clinical guidance for neurointensivists, neurosurgeons, ICH patients, and their families (4–7).

Of note, the inflammatory response referenced above is exacerbated via the intracerebral extravasation of blood products (8, 9). Intracerebral hemorrhage-induced inflammation precedes disruption of the blood-brain barrier (BBB) and in patients with spontaneous ICH, concurrent alterations of immune profiles within peripheral blood have been observed (10). Such alterations in peripheral blood have been the target of numerous efforts to establish markers for early ICH prognostication (11–13).

Red cell distribution width (RDW), an indicator of size variability among circulating red blood cells (RBCs), is routinely reported as part of the complete blood count (CBC) and is typically used to identify the etiology of anemia (14). More recently, RDW has gained considerable attention as an inflammatory marker and as a predictive metric for cardiac as well as infectious diseases (15–17). In addition, there is evidence that RDW is a significant prognostic factor in several malignancies (18, 19). A new index, the ratio of RDW to platelet count (RPR), has been reported to reflect the severity of inflammation and has previously been utilized for prognostic prediction in breast cancer or fibrosis in chronic hepatitis (20, 21).

To the best of our knowledge, no association between RPR and prognosis after spontaneous ICH has been reported. Therefore, the aim of the present work was to include the RPR as a simple, readily available index for early prognostic assessment in patients with spontaneous deep-seated ICH to facilitate intensive care decision making.

MATERIALS AND METHODS

This retrospective study includes 102 patients with spontaneous deep-seated ICH who were referred to our Neurovascular Center for further management between 2014 and July 2020. The institutional ethics review board approved this retrospective study (no. 383/20). All procedures used in this study were performed in accordance with the principles of the Declaration of Helsinki and its subsequent amendments. To obtain a more homogeneous patient cohort, patients with traumatic or other bleeding sources (e.g., aneurysm, arteriovenous malformation, tumor) and those with a lobar ICH location were excluded from further analysis. All patients received at minimum a conservative treatment, including blood pressure control, according to current guidelines. Information on patient characteristics, ICH localization, ICH extent, ICH score (4), and intensive care and laboratory values were collected and analyzed in a computerized database. Furthermore, patients were separated into two groups based on the ICH score. Given the experience from previous studies on the clinical significance of the ICH score pertaining to mortality, the groups were divided into patients with an initial ICH score <3 and an ICH score ≥ 3 (4, 22). Blood samples were obtained from peripheral venous blood as part of routine management at the time of hospital admission and thus before any therapeutic interventions. Red cell distribution width and platelet count were routinely obtained. The ratio of RDW to platelets was calculated accordingly at follow-up. Regarding further inflammatory markers, patients were divided into two groups each based on their C-reactive protein (CRP; CRP $\leq$ 3 mg/l vs. CRP $>$ 3 mg/l), procalcitonin value (PCT; PCT $\leq$ 0.5 μg/l vs. PCT $>$ 0.05 μg/l), and peripheral white blood count (WBC; WBC $\leq$ 12g/l vs. WBC $>$ 12g/l) at the time of hospital admission (6). Anemia assessed in the admission laboratory was defined according to the World Health Organization (WHO) definitions [hemoglobin (Hb) $<$ 12 g/dl for women, Hb $<$ 13 g/dl for men] (23).

Mortality at 90 days after the bleeding event was used as the primary end point. Thus, to avoid confounding bias of the results attributable to cases with devastating extent of hemorrhage and/or patient wishes of waiving life-sustaining measures, only patients hospitalized for $>$3 days were included. Data analysis was accomplished using the SPSS computer software package (version 25, IBM Corp., Armonk, NY, USA). The Mann-Whitney U-test was chosen to compare continuous variables because the data were mostly not normally distributed. Categorical variables were analyzed in contingency tables using Fisher's exact test. Results with $p < 0.05$ were deemed statistically significant. To assess the discrimination ability of the ICH score and the RPR in predicting the probability of a case fatality within 90 days, receiver operating characteristic (ROC) curves were constructed for both values within the patient population studied, and the areas under the curves (AUC) were calculated. The optimal cut-off value for each curve was determined for sensitivity and specificity, both being equally important. In addition, to ascertain independent predictors of 90-day mortality in patients with deep-seated ICH, multivariate analysis was performed using binary logistic regression.

RESULTS

Patient Characteristics

Between 2014 and July 2020, 102 patients with deep-seated ICH were referred to the corresponding authors' neurovascular specialty center for management/treatment of ICH. The median age of the patients was 66 years [interquartile range (IQR) 57–76 years]. At the time of admission, 64 patients (63%) presented with a Glasgow Coma Score (GCS) $<$ 13, 63 patients (62%) suffered from additional intraventricular hemorrhage (IVH), 53 patients (52%) had deep-seated ICH with hematoma volume $\geq$30 ml. The 90-day mortality rate was 42% (43/102 patients). Further details on patient characteristics, focusing on availability of data at the time of admission and stratified by 90-day mortality into two groups for survivors and non-survivors, are given in **Table 1**.

Influence of Anemia and Routine Inflammatory Markers on Mortality

Patients with anemia at the time of admission had a significant difference in 90-day mortality compared to patients without initial anemia (69 vs. 32%; $p = 0.001$, OR 4.8, 95% CI 1.9–12.2). No significant difference in mortality was observed in

TABLE 1 | Patient characteristics.

	Survivors ($n = 59$)	Non-survivors ($n = 43$)	
Median age (years, IQR)	63 (53–72)	68 (59–81)	$p = 0.03$
Female sex	21 (36%)	16 (37%)	$p = 1.0$
ICH score > 3	4 (7%)	16 (37%)	$p = 0.0002$, OR 8.1, 95% CI 2.5–26.7
Initial SBP (mmHg)			$p = 0.7$
Mild (<180)	36 (61%)	27 (63%)	
Moderate (180–219)	17 (29%)	10 (23%)	
Severe (≥220)	6 (10%)	6 (14%)	
Admission CRP (median, IQR; mg/l)	3.1 (1.2–9.2)	3.7 (1.5–10.4)	$p = 0.6$
Admission PCT (median, IQR; μg/l)	0.06 (0.04–0.12)	0.09 (0.05–0.27)	$p = 0.01$

TABLE 2 | Distribution of known prognostic factors in patients with deep-seated ICH.

	RPR < 0.06 ($n = 49$)	RPR ≥ 0.06 ($n = 53$)	
ICH score > 3	8 (16%)	12 (23%)	$p = 0.5$
Age ≥ 80 years	4 (8%)	13 (25%)	$p = 0.03$, OR 3.7, 95% CI 1.1–12.1
Baseline GCS < 13	30 (61%)	34 (64%)	$p = 0.8$
Baseline ICH volume ≥ 30 ml	22 (45%)	31 (59%)	$p = 0.2$
Initial IVH	27 (55%)	36 (68%)	$p = 0.2$
CRRT	2 (4%)	8 (15%)	$p = 0.1$
PMV (>7 days)	21 (43%)	25 (47%)	$p = 0.7$
90 day mortality	13 (27%)	30 (57%)	$p = 0.003$, OR 3.6, 95% 1.6–8.3

patients with an initial WBC of >12 g/l compared to patients with a baseline WBC ≤ 12 g/l (47 vs. 39%; $p = 0.5$). Ninety-day mortality following ICH was not significant in patients with a baseline CRP ≤ 3 mg/l compared with patients with an initial CRP > 3 mg/l (38 vs. 45%; $p = 0.6$). Patients with deep-seated ICH and an initial PCT ≤ 0.5 μg/l exhibited significantly lower mortality at 90 days compared to patients with an initial PCT > 0.5 μg/l (39 vs. 78%; $p = 0.03$, OR 5.5, 95% CI 1.1–28.2).

Influence of RPR on Mortality

Neither the median admission laboratory value for RDW nor that for platelet count demonstrated a significant difference between survivors and non-survivors with deep-seated ICH ($p = 0.2$ and $p = 0.07$, respectively). The median RPR for the entire cohort was 0.062 (IQR 0.050–0.078). The optimal cut-off value in terms of RPR was determined to be 0.06 with an AUC of 0.63 (95% CI 0.517–0.739; $p = 0.027$) and a sensitivity of 70% and a specificity of 61%. **Table 2** illustrates the distribution of known and established risk factors for poor outcome in patients with deep-seated ICH. With the exception of age, none of the known prognostic factors are statistically different between the two groups. Patients with an RPR < 0.06 were distinguished by significantly lower case-fatality at 90 days compared to patients with a baseline RPR ≥ 0.06 (27 vs. 57%; $p = 0.003$, OR 3.6, 95% 1.6–8.3).

Multivariate Analysis

Multivariate logistic regression analysis was performed to identify independent initial determinable predictors of 90-day mortality in patients with deep-seated ICH and to clarify the influence of the RPR in this regard. Multivariate analysis identified "ICH score ≥ 3" ($p = 0.001$, OR 8.6, 95% CI 2.4–31.1), "anemia on admission" ($p = 0.01$, OR 3.6, 95% CI 1.3–10.2), and "elevated RPR ≥ 0.06" ($p = 0.03$, OR 2.9, 95% CI 1.1–7.7) as significant and independent predictors of 90-day mortality (Nagelkerke's $R^2 = 0.35$, **Figure 1**).

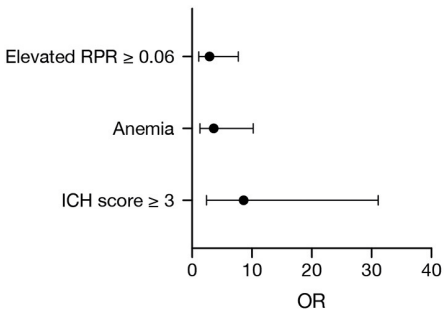

FIGURE 1 | Forest plot of significant and independent predictors of 90-day mortality identified by multivariate logistic regression analysis.

DISCUSSION

The present study evaluated a potential link between RPR and 90-day mortality after deep-seated ICH. The results suggest that patients with an elevated RPR in the admission laboratory are more likely to decease within 90 days after the bleeding.

RPR is calculated from the ratio of RBC distribution width to platelet count. As a potential indicator of inflammatory processes, RPR has already been established as a prognostic factor in numerous other diseases. In patients with ICH, to the best of our knowledge, there have been no such association studies yet. In the context of the initial bleeding, but also in the course of the alteration/depletion processes in the area of the hemorrhage, a number of inflammatory reactions have been detected in ICH (24, 25). Not only via the initial extravasation of cytokines, but also through blood breakdown products, inflammatory reactions may very well have a direct impact on the pathophysiological and clinical course, e.g., on the development of perilesional edema (26). Thus, early and readily available inflammatory markers may provide an important insight into the inflammatory events early in the course of management/treatment of patients with ICH and thereby offer

a reflection of the inflammation-triggered brain injury in the setting of ICH (27, 28).

RPR is derived in part from RDW. Red cell distribution width measures the size distribution of RBCs and indicates in case of strongly elevated values the presence of different types of anemia. Anemia or low hemoglobin have already been identified as influencing factors on outcome but also on hematoma extent after spontaneous ICH (29–31). In the present work, anemia is also associated with increased mortality, and yet the RPR extends beyond a mere determination of hemoglobin by including a platelet count. RPR has been found to be a prognostic marker in various immunological diseases and is also considered to reflect the severity of the inflammatory event by attributing some influence to platelet count (20, 21). In the inflammatory process, in addition to sepsis-related anemic events, inflammatory cytokines may inhibit the maturation of RBCs and thus alter the RDW (32) whereas platelets are known to be placed on the intersection of an immune response and coagulation in infectious diseases (33). Thus, a marker as RPR, which takes into account both potential reflections of the inflammatory process, may be more accurate than non-specific markers such as CRP (34, 35). Also, in the anticipation of further complications in the course of treatment of ICH (e.g., renal replacement therapy), non-specific markers such as CRP have been reported to be less predictive than those that are considered more specific for inflammatory processes, such as PCT (6). Common to non-specific inflammatory markers may be a reflection of just another surrogate parameter as for example, in terms of a stress response of the body to intracranial hematoma volume or aspiration in the context of low GCS.

Nevertheless, when discussing the potential implications of this readily available laboratory marker, it is important to note that the focus of the present study was directed at patients with deep-seated ICH. One reason for this selection lies in the multiple etiologic possibilities in patients with lobar ICH. An underlying disease resulting in lobar ICH (e.g., cancer) seems to be more likely to affect initial laboratory parameters compared to deep-seated ICH (3).

The present study demonstrates the anticipated distribution of known and/or established risk factors for increased mortality after ICH (except for age) in both groups with decreased and increased RPR. This strengthens the suspicion that the RPR could be established as an independent prognostic factor. Despite the association of RPR with mortality after deep-seated ICH reported herein, further exploration of the underlying mechanisms and corroboration of our findings in other study populations is warranted.

LIMITATIONS

In addition to retrospective data collection and analysis with the bias inherent to this study design, our study reveals other shortcomings that need to be carefully considered when interpreting our results. The sample size is comparably small due to a restriction to patients with a deep-seated ICH. This increases the homogeneity of the study population, but also raises the possibility of selection bias. Among these is the exclusion of patients with lobar ICH. However, this might also be considered a potential advantage, as this pre-selection might reduce the variety of underlying ICH etiologies and therefore their potential influence on initial laboratory values. In addition, the retrospective data analysis also precludes a dedicated analysis of potential additional determinants (such as a preexisting chronic inflammatory disease/acute aspiration pneumonia) throughout the complete dataset.

CONCLUSION

This is the first study to provide evidence that RBC distribution width to platelet ratio might constitute an independent marker of inflammation associated with the prognostication of outcome in deep-seated ICH.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Local Ethics Committee at the University of Bonn. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FL, PS, and AH: conceptualization and supervision. FL, LS, PS, and AH: data curation. FL, PS, MS, and AH: formal analysis. FL, JB, FG, MS, PS, and AH: writing—original draft preparation. FL, LS, JB, CB, VB, FG, EG, MH, A-LP, CP, MS, JZ, HV, PS, and AH: writing—review and editing. A-LP and MS: visualization. All authors contributed to the article and approved the submitted version.

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Zielsetzung der Arbeit

Neben der blutungsbedingten Schädigung eloquenter Hirnareale kann eine ICB auch zu einer lang anhaltenden Vigilanzstörung führen, die häufig eine längere maschinelle Beatmungspflichtigkeit (prolongierte mechanische Ventilation; PMV) nach sich zieht. Dennoch sind der Einfluss der PMV bei Patienten mit ICB und die möglichen Risikofaktoren, die zu einer PMV bei diesen Patienten führen, gegenwärtig nicht klar. Daher untersuchten wir in der vorliegenden Studie eine Kohorte von Patienten mit tiefer ICB hinsichtlich Risikofaktoren für die Notwendigkeit einer PMV und deren möglichen Einfluss auf die Mortalität.

Methoden und Ergebnisse

Von Januar 2014 bis Mai 2020 wurden alle Patienten mit typischer ICB, die für mehr als 3 Tage stationär auf der interdisziplinären neurologisch-neurochirurgischen Intensivstation versorgt wurden, in die weiteren Analysen einbezogen. PMV ist definiert als mechanische Beatmung für mehr als 7 Tage. Bei 42 von 94 Patienten (45%) mit typischer ICB war im Verlauf der Behandlung eine PMV notwendig. Die 90-Tage Mortalität war bei diesen Patienten signifikant höher als bei denen ohne PMV (64% gegenüber 22%, p<0,0001). In der multivariaten Analyse wurden "ICB-Volumen >30ml" (p=0,001, OR 5,3) und "SOFA-Score bei Aufnahme >5" (p=0,007, OR 4,2) als signifikante und unabhängige Prädiktoren für PMV im weiteren Verlauf der Behandlung einer tiefen ICB identifiziert.

Schlussfolgerungen

In einer hochselektiven Patientenkohorte konnten wir zeigen, dass bei Patienten mit typischer ICB die Notwendigkeit einer PMV besonders häufig besteht. ICB-Volumen und SOFA-Score bei der Aufnahme auf die Intensivstation wurden hierfür als Prädiktoren identifiziert. Die Kenntnis und Interpretation potenzieller Risikofaktoren ist von entscheidender Bedeutung, um eine adäquate Therapieplanung und Prognostizierung in den frühen Phasen der ICB-Therapie zu ermöglichen.

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Prolonged Mechanical Ventilation in Patients with Deep-Seated Intracerebral Hemorrhage: Risk Factors and Clinical Implications

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Abstract: While management of patients with deep-seated intracerebral hemorrhage (ICH) is well established, there are scarce data on patients with ICH who require prolonged mechanical ventilation (PMV) during the course of their acute disease. Therefore, we aimed to determine the influence of PMV on mortality in patients with ICH and to identify associated risk factors. From 2014 to May 2020, all patients with deep-seated ICH who were admitted to intensive care for >3 days were included in further analyses. PMV is defined as receiving mechanical ventilation for more than 7 days. A total of 42 out of 94 patients (45%) with deep-seated ICH suffered from PMV during the course of treatment. The mortality rate after 90 days was significantly higher in patients with PMV than in those without (64% versus 22%, $p < 0.0001$). Multivariate analysis identified "ICH volume >30 mL" ($p = 0.001$, OR 5.3) and "admission SOFA score > 5" ($p = 0.007$, OR 4.2) as significant and independent predictors for PMV over the course of treatment in deep-seated ICH. With regard to the identified risk factors for PMV occurrence, these findings might enable improved guidance of adequate treatment at the earliest possible stage and lead to a better estimation of prognosis in the course of ICH treatment.

Keywords: prolonged mechanical ventilation; intracerebral hemorrhage; intensive care

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1. Introduction

Spontaneous intracerebral hemorrhage (ICH) is a major contributor to mortality and morbidity in stroke patients [1–3]. Despite ongoing efforts to improve surgical and medical management, advances in mortality and morbidity of this disease are modest [1,4,5]. Even with the best medical management and/or surgical treatment, functional outcomes remain poor, with less than 20% of all ICH patients regaining functional independence after 6 months [6]. Depending on the localization, ICH is differentiated into deep-seated ICH—involving the basal ganglia and/or thalamus—and superficial, lobar ICH. The different localizations of ICH may have various causes [6]. Thus, deep-seated ICH is often associated with hypertensive long-term damage, while lobar ICH may have other bleeding sources (aneurysm, arteriovenous malformation (AVM), cerebral amyloid angiopathy (CAA), tumor, infection) [2]. The resulting heterogeneity in these cases makes ICH generally difficult to study.

Along with the bleeding related damage that often occurs to eloquent brain tissue, ICH might also lead to a long-lasting impairment of vigilance, which often results in subsequent prolonged dependence on a ventilator [7]. The condition known as prolonged mechanical

ventilation (PMV) has already been identified as an important factor influencing mortality in numerous other etiologies/specialties [8–11]. Nevertheless, the influence of PMV in patients with ICH and the possible risk factors for PMV in these patients remains to be clarified.

Therefore, in the present study we investigated a cohort of patients with deep-seated ICH only—also in terms of minimized heterogeneity—for risk factors for the necessity of PMV and its potential impact on mortality.

2. Materials and Methods

Clinical records of patients who were admitted to the neurosurgical department of the University Hospital Bonn between January 2014 and May 2020 for non-traumatic intracerebral spontaneous hemorrhages were retrospectively evaluated. After study approval by the local institutional review board (IRB), patients with lobar ICH and/or ICH with associated cause of bleeding (e.g., aneurysm, arteriovenous malformation, trauma) were excluded from further evaluation. Only patients with deep-seated ICH were considered for further analysis. ICH localization was deemed deep-seated if the hemorrhage originated predominantly in or involved the basal ganglia or thalamus [12–14]. Information collected for each patient included patient characteristics, pre-existing conditions, ICH location, ICH volume [15], neurological status at admission, ICH score [3], Intensive Care Unit (ICU) and laboratory admission parameters, admission SOFA/SAPS scores [16,17], necessity of prolonged mechanical ventilation (PMV), 30-day mortality, and 3-month outcomes/mortality and treatment strategies chosen during hospitalization.

The best medical treatment was provided to all patients suffering from deep-seated ICH according to the hospitals internal standard operating procedures, which are in accordance with the guidelines of the American Heart Association/American Stroke Association [1]. Best medical treatment included, among other procedures, rapid resolution of severe coagulation factor deficiencies or severe thrombocytopenia, normalization of blood pressure, implementation of general monitoring, and management of any elevated intracranial pressure.

The first spontaneous breathing trial was performed within at least 5 h after arrival at the ICU. Patients were evaluated as eligible for extubation if they presented adequate oxygenation and ventilation indices, sustained hemodynamic stability and demonstrated minimum neurological function including logopedic evaluation of dysphagia. The final decision to extubate, re-intubate or perform percutaneous tracheostomy was based on the independent discretion of the treating intensive care physician. PMV was defined as the inability to wean from the ventilator more than 7 days after admission. The cut-off at 7 days was chosen in accordance with the definition proposed by the Task Force of the European Respiratory Society and respective previous studies [8,18].

Dividing values that could be used to dichotomize patients with respect to the different variables had already been defined previously: ICH volume [3], Glasgow Coma Scale (GCS) [3], ICH score [3], c-reactive protein (CRP) [19], white blood cells (WBC) [19]. The optimal cut-off values for the SOFA and SAPS values were defined separately for the investigated patient population, as described in the following.

The modified Rankin Scale (mRS) was used to assess the functional outcome. Patients were dichotomized after mRS in two groups: (1) favorable outcome (mRS 0–4) versus (vs.) unfavorable outcome (mRS 5–6), as previously defined [20].

Data analysis was performed using the computer software package SPSS (version 25, IBM Corp., Armonk, NY, USA). The Mann–Whitney U-test was chosen to compare continuous variables as the data were mostly not normally distributed. An unpaired *t*-test was used for parametric statistics after testing for normal distribution. Categorical variables were analyzed in contingency tables using Fisher's exact test. Results with $p < 0.05$ were considered statistically significant. Regarding the optimal cut-off values of the SOFA and SAPS scores to differentiate between patients with the need for PMV and those without PMV, an appropriate approximation was attempted after determining the area under the

curve (AUC) using constructed receiver operating characteristic (ROC) curves with the aid of Youden's index.

In addition, in order to determine independent predictors of the necessity of PMV in patients with deep-seated ICH, a multivariate analysis using binary logistic regression was performed. Therefore, a backward stepwise method was used to construct a multivariate logistic regression model in relation to PMV as a dependent variable with an inclusion criterion for variables with presumed/proven clinical relevance. The variables included in the multivariate analysis were the following: ICH volume, SOFA, SAPS, acute kidney injury (AKI).

3. Results

3.1. Patient Characteristics

A total of 94 patients with deep-seated spontaneous ICH were identified and further analyzed, as described below. The median volume of hemorrhage in the studied patients with deep-seated ICH was 31.6 mL (IQR 14.4–68.9). Surgical management of patients with deep-seated ICH in the reported patient cohort included stereotactic aspiration of the hemorrhage in seven patients (7%), decompressive hemicraniectomy (DC) with ICH evacuation in three patients (3%), and DC without ICH evacuation in 19 patients (20%). Cerebrospinal fluid diversion as a sole surgical intervention was performed in 26 patients (28%). Overall, 42 of 94 patients (45%) required prolonged mechanical ventilation > 7 days after admission. With regard to patient age, there was no significant difference observed between patients with and without PMV (Table 1). Additionally, with regard to pre-existing comorbidities and/or the administration of anticoagulant medication prior to bleeding, no significant difference could be identified between the groups with and without PMV. Further details are given in Table 1.

Table 1. Characteristics for patients with deep-seated intracerebral hemorrhage (ICH).

	Patients without PMV (*n* = 52)	**Patients with PMV (*n* = 42)**	
Mean age (years)	65 ± 16	64 ± 11	n.s.
female sex	21 (%)	12 (%)	n.s.
pre-existing hypertension	41 (%)	37 (%)	n.s.
diabetes mellitus	5 (10%)	7 (17%)	n.s.
previous stroke	9 (%)	8 (%)	n.s.
chronic obstructive pulmonary disease COPD	3 (6%)	5 (12%)	n.s.
anticoagulant medication prior ictus	23 (44%)	17 (41%)	n.s.

3.2. Admission Characteristics in Deep-Seated ICH Patients

Patients with subsequent PMV after deep-seated ICU presented with significantly larger intracerebral hematomas compared to patients without PMV ($p < 0.0001$) (Table 2). Furthermore, patients with the necessity of PMV presented with an initial Glasgow Coma Scale (GCS) > 12 significantly less often compared to patients without PMV ($p = 0.0002$, OR 5.8, 95% CI 2.2–15.5). Neither the presence of intraventricular blood nor the results of the initial assessment of the ICH score differed significantly between the two groups of patients with and without PMV (Table 2).

3.3. ICU Admission Parameters

Patients with subsequent PMV after deep-seated ICU suffered significantly more often from early acute kidney injury (AKI; within 48 h after admission) compared with patients without PMV ($p = 0.02$, OR 3.6, 95% CI 1.3–9.9) (Table 2). With a sensitivity of 91% and a specificity of 52%, a cut-off point at 30 was identified for the admission SAPS score (AUC 0.78, $p < 0.0001$). Subsequently, patients with PMV presented significantly more often with a SAPS score >30 compared to patients without PMV during the treatment course ($p < 0.0001$, OR 5.4, 95% CI 2.0–14.3). With a sensitivity of 43% and a specificity of 92%, a

cut-off point at five was identified for the admission SOFA score (AUC 0.79, $p < 0.0001$). Subsequently, patients with PMV presented significantly more often with a SOFA score > five compared to patients without PMV during the treatment course ($p < 0.0001$, OR 16.0, 95% CI 4.9–52.5; Table 2).

Table 2. ICU admission parameters and outcome.

	Patients without PMV (n = 52)	Patients with PMV (n = 42)	Significance
median ICH volume (IQR, mL)	20.3 (9.9–39.6)	51.8 (29.7–93.9)	$p < 0.0001$
ICH volume > 30 mL	18 (35%)	32 (76%)	$p < 0.0001$, OR 6.0, 95% CI 2.4–15.0
admission GCS > 12	28 (54%)	7 (17%)	$p = 0.0002$, OR 5.8, 95% CI 2.2–15.5
ICH score > 3	6 (12%)	11 (26%)	n.s.
admission CRP > 10 mg/L	13 (25%)	11 (26%)	n.s.
admission PCT > 0.5 µg/L	2 (4%)	7 (17%)	n.s.
admission WBC > 12 G/L	16 (31%)	19 (45%)	n.s.
early AKI	7 (14%)	15 (36%)	$p = 0.02$, OR 3.6, 95% CI 1.3–9.9
admission SAPS score > 30	25 (48%)	35 (83%)	$p < 0.0001$, OR 5.4, 95% CI 2.0–14.3
admission SOFA score > 5	4 (8%)	24 (57%)	$p < 0.0001$, OR 16, 95% CI 4.9–52.5
favorable outcome after 3 months (mRS 0–4)	38 (73%)	15 (36%)	$p < 0.0001$, OR 4.9, 95% CI 2.0–11.8
90 d mortality	13 (25%)	27 (64%)	$p < 0.0001$, OR 5.4, 95% CI 2.2–13.2

3.4. Impact of PMV on Length of Stay/Outcome/Mortality

Patients with PMV after deep-seated ICH had significantly longer hospital stays compared to patients without PMV (34 ± 21 days versus 17 ± 37 days, $p < 0.0001$). Patients with PMV developed ventilator-associated pulmonary complications significantly more often compared to patients without PMV (45% versus 14%; $p = 0.001$, OR 5.3, 95% CI 1.9–14.5). Patients with PMV achieved a favorable outcome (mRS 0–4) after 3 months significantly less often when compared with patients without PMV and deep-seated ICH (36% vs. 73%; $p < 0.0001$, OR 4.9, 95% CI 2.0–11.8) (Table 2). Using a more stringent outcome comparison, patients with PMV also experienced a worse outcome (mRS 3–6) compared to patients without PMV ($p = 0.04$). Additionally, the 90-days-mortality rate in patients with PMV and deep-seated ICH was significantly higher compared to patients without PMV and deep-seated ICH (64% vs. 25%; $p < 0.0001$, OR 5.4, 95% CI 2.2–13.2; Table 2).

3.5. Multivariate Analysis

The multivariate analysis identified "ICH volume > 30 mL" ($p = 0.001$, OR 5.7, 95% CI 1.9–16.7) and "admission SOFA score > 5" ($p < 0.0001$, OR 15.2, 95% CI 4.3–54.6) as independent predictors for the necessity of PMV in patients suffering from deep-seated ICH (Nagelkerke's R2 = 0.47; Figure 1).

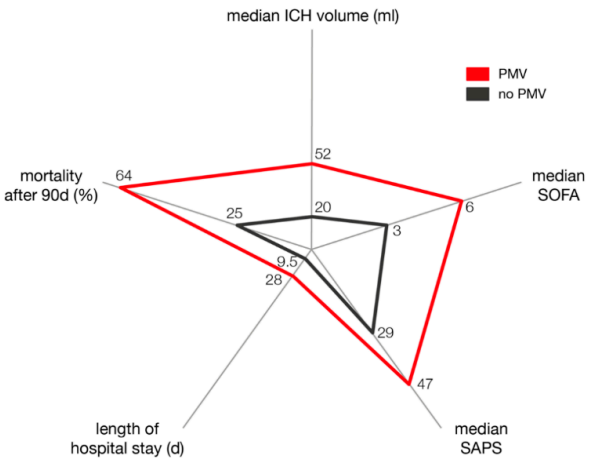

Figure 1. Graphical display of selected ICU admission data in PMV/non-PMV patients and corresponding impact on length of hospital stay and mortality after 90 days.

4. Discussion

The profound impact of intracerebral hemorrhage on both neurological outcome and mortality has been well studied [21,22]. Especially for the initial assessment of patients with ICH, numerous factors as well as scores have been established [3,23,24]. The often irreversible neurological damage caused by the bleeding, however, often confronts the affected patients themselves or their relatives/caregivers with the difficult decision to initiate/conduct the therapeutic process with intensive care measures or to opt for withdrawal of life-sustaining therapy [4,25–27]. Ideally, patients known wishes, personal preferences, value systems, and advance directives—if available—should be considered in such decision-making processes. In everyday clinical practice, however, such decisions are largely dependent on the prognosis assessment of the treating physician team and the derived goals-of-care [28]. Thus, a detailed analysis of possible predictors for unfavorable outcome after ICH is necessary for this prognosis estimation. In addition to the above-mentioned clinical scores and individual factors, prediction models are increasingly being established to provide a basis for decision-making in this process [28]. Therefore, in the present study we were able to illustrate a significant influence of prolonged mechanical ventilation on clinical outcome and/or mortality in our selected cohort of patients with deep-seated ICH.

PMV has been proven to have a negative impact on outcome as well as survival, and is associated with incremental health care costs across various specialties and etiologies [9,11,29–31]. In addition to the extensive implications that prolonged mechanical ventilation might have on the outcome, these are often not due to the actual ventilation, but to its further-reaching complications. For example, in the present patient population, ventilator-associated pulmonary complications (e.g., pneumonia) occurred in 45% of patients who required PMV, but only in 14% of patients without PMV. This circumstance is associated with subsequent further therapy (here: antibiotic therapy), which in turn might lead to further complications. However, to the best of our knowledge, this is the first study that has focused on the predictors and influence of PMV in patients with ICH. In accordance with Saber et al. in the setting of PMV following endovascular stroke therapy, we consider PMV as an important independent clinical outcome, in contrast to previous studies, and therefore, focused on predictors of PMV based on initial clinical characteristics [10].

In the present study, the initial SOFA score is an important predictor for a subsequent need for PMV. The SOFA scoring system has proven to be a useful predictor of ICU mortality, although it was not designed to predict, but rather to describe, a sequence of complications in critically ill patients [17,32]. However, evaluation of a score that measures/monitors organ dysfunction should take into account that organ failure is not an all-or-nothing phenomenon, but rather a continuum of changes in organ function leading to alterations over time [33]. Nevertheless, the initial SOFA score at ICU admission already delivers a good estimate of later mortality of the critically-ill patient [33]. In the present study, an initial SOFA score > five has been identified as a significant and independent predictor of the need for PMV in patients with deep-seated ICH.

Another predictor for the necessity of PMV in the present study was the volume of the intracranial hematoma in patients suffering from deep-seated ICH. As a part of the established ICH score of Hemphill et al., hematoma size is an established measure of mortality in patients with ICH [3]. In addition to pulmonary causes, impairment of consciousness is most likely responsible for a prolonged weaning from mechanical ventilation [7]. The association between reduced consciousness and increased ICH volume has been described previously [7,34,35]. With regard to the necessity of ventilation and thus the timing of tracheotomy, the SETPOINT score of Bösel et al., for example, also considers hematoma size in patients with ICH [36]. In the present study, an initial ICH volume > 30 mL was identified as a significant and independent predictor of the need for PMV in patients with deep-seated ICH.

We aimed at identifying potential predictors of prolonged mechanical ventilation in patients with deep-seated intracerebral hemorrhage. Both ICH volume and SOFA score

at ICU admission are of crucial importance in this context. Therefore, the results of the present study are intended to support physicians in formulating goals-of-care and/or patient-adapted treatment decisions.

The present study has several limitations. The data collection was conducted retrospectively and only includes a single center's experience. Patients were not randomized, but treated according to the preferences of the treating physicians. In addition, the homogeneous, but therefore, small patient population makes it difficult to interpret the multivariate analysis performed, without introducing the risk of bias and increased variability. Nevertheless, the present study investigates an important aspect in a selected, and thus, less confounder-prone patient cohort and therefore provides the basis for the initiation of multicenter registries and/or further studies.

5. Conclusions

The present study in a highly selective patient cohort reveals that patients with deep-seated ICH have a high incidence of PMV. Increased ICH volume and an elevated SOFA score at ICU admission were identified as predictors. Knowledge of potential risk factors is essential to improve early initiation of adequate treatment and prognosis assessment in the early stages of ICH treatment.

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Informed Consent Statement: Patient consent was waived due to the used retrospective study design.

Data Availability Statement: Data are contained within the article.

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Diskussion

Eine spontane, nicht-traumatische intrazerebrale Blutung (ICB) kann aus unterschiedlichsten Gründen entstehen [22–26]. Unabhängig von der Genese ist jeder Hirnblutung aber gemeinsam, dass sie unvorhersehbar auftreten kann und in meist einschneidender Art und Weise Einfluss auf die gesamte Lebenssituation der betroffenen Patienten und deren sozialem Umfeld nehmen kann [27]. Der individuelle Behandlungswunsch des betroffenen Patienten ist nur in seltenen Fällen für das Behandlungsteam initial abzusehen. Bei schweren ICBs, die einer zeitnahen Intervention bedürfen, kommt es oftmals zusätzlich zu schweren Vigilanzstörungen, die eine sofortige Klärung teilweise unmöglich machen [28,29]. Je nach Lokalisation der ICB muss im Falle des Überlebens der Akutsituation mit schweren körperlichen Behinderungen gerechnet werden. Hierdurch kann sich trotz anschließender neurologischer Rehabilitationsmaßnahmen durchaus eine hochgradige Pflegebedürftigkeit mit der eventuellen Unmöglichkeit eines selbstbestimmten Lebens anschließen [12]. Nun gilt es in der Neuro-Intensivmedizin interdisziplinär mit den akut versorgenden Fachdisziplinen zeitnah die möglichen Chancen auf eine neurologische Erholung abzuschätzen, um im weiteren Verlauf der Behandlung durch teils auch wiederholte Gespräche mit Angehörigen und/oder Freunden den Patientenwillen mit der neurologischen Prognose abzugleichen. Durch eine suffiziente Neuro-Prognostizierung ist eine eventuelle Therapie, die womöglich nicht dem Patientenwillen entspricht, vermeidbar [30]. Eine eventuell vorhandene Patientenverfügung kann in solchen Situationen zusätzlich helfen, den mutmaßlichen Patientenwillen zu eruieren, wobei diese schriftlichen Festlegungen häufig nur sehr vage formuliert sind oder durch feste Formulierungen (in der Akutsituation nicht vorhandene) definitive medizinische Erkenntnisse voraussetzen. Zwar urteilte der Bundesgerichtshof bereits 2017, dass Patientenverfügungen in Deutschland ausreichend konkret formuliert sein müssen [31]. Therapien im Rahmen von Schlaganfällen, seien sie blutig oder ischämisch, erfordern aber unmittelbare Entscheidungen, deren Folgen in dem Moment, in dem sie gefällt werden, nicht absehbar sein können und daher auch selten definitiv im Voraus verfügt wurden. In der Praxis sind Patientenverfügungen teilweise veraltet oder fehlen schlicht ganz. [30] In einer eigenen Analyse von Patienten mit spontaner ICB war in einem 2-Jahres

Zeitraum der Patientenwille hinsichtlich einer Therapielimitierung in etwa 50% der Fälle zu ermitteln, wobei der Inhalt einer Patientenverfügung im Rahmen dieser Entscheidungsfindung nur einen Anteil von 21% ausmachte [30]. Einerseits scheinen Intensivmediziner im Rahmen ihrer Behandlungsentscheidung nicht notwendigerweise durch den Patientenwillen beeinflusst zu sein [32], andererseits sind Angehörige im Rahmen von Gesprächen über eine Therapielimitierung häufig misstrauisch [33], so dass in der Praxis Entscheidungen häufig nicht ohne weiteres zu fällen sind. Für das Behandlungsteam sind daher Parameter relevant, die unkompliziert in einem frühen Behandlungsabschnitt ermittelbar sind und sich eignen, besser abschätzen zu können, welche Konsequenz aus verschiedenen Behandlungsentscheidungen resultiert.

Der primäre Hirnschaden, hervorgerufen durch die ICB ist zunächst abhängig von Größe und Lokalisation der Blutung selbst [20]. Dieser initialen Schädigung schließt sich ein sekundärer Prozess an, welcher Schäden durch beispielsweise entstehenden oxidativen Stress oder inflammatorische Prozesse hervorruft [34]. Diesen sekundären Hirnschaden gilt es im Rahmen der akut-medizinischen und damit auch neurointensivmedizinischen Therapie entweder zu verhindern oder zumindest abzumildern. Inflammatorische Prozesse beispielsweise werden wesentlich durch den Austritt von Blut und Blutbestandteilen im Rahmen der ICB sowie deren anschließenden Resorptionsprozess im Hirnparenchym ausgelöst [35]. Das Wissen um solche Prozesse macht diese durch die Identifikation von Surrogatparametern messbar und damit hinsichtlich ihrer Mitwirkung am Outcome als mögliche Vorhersageparameter für das neurologische Outcome relevant.

Im Rahmen der ICB konnte bereits gezeigt werden, dass laboranalytisch unterschiedliche immunologische Profile im peripheren Blutbild existieren [36]. Die Erythrozytenverteilungsbreite (EVB) ist ein Routineparameter des Differentialblutbildes, der zuletzt als inflammatorische Marker und prädiktiver Indikator bei Herz-Kreislauferkrankungen beschrieben wurde [37–39]. Die RPR als neuerer Marker kann letztlich die Schwere einer Inflammation anzeigen und wurde bereits als Prognose-Tool im Rahmen der Behandlung des Mammakarzinoms und der Leberfibrose im Rahmen der Hepatitis beschrieben [27,40]. In einer Arbeit dieser kumulativen Habilitationsschrift gelang die Assoziation einer erhöhten RPR mit einem

schlechten neurologischen Outcome bei intensivmedizinischen Patienten mit ICB. Bei Patienten mit einer Stammganglien-ICB war eine erhöhte RPR bei Aufnahme unabhängig mit einer erhöhten Mortalität nach drei Monaten assoziiert [41]. Die Identifikation der RPR als möglichem Prädiktor für ein schlechtes neurologisches Outcome nach ICB gelang im Rahmen dieser Arbeit erstmals. Da sich in der RPR sowohl der inflammatorisch vermittelte Einfluss auf die Erythrozytenreifung [42], als auch die thrombozytäre Aktivierung abbildet [43], ist es ein insgesamt spezifischerer Marker als beispielsweise das ebenfalls oftmals utilisierte C-reaktive Protein (CRP) [44].

In einer weiteren dieser kumulativen Habilitationsschrift zugrunde liegenden Arbeit konnte das Serum-Laktat und der Blutzuckerspiegel bei Aufnahme ebenfalls als prädiktiver Outcomeparameter identifiziert werden [45]. Eine Erhöhung beider Werte bei Aufnahme und im Verlauf der Behandlung von Patienten mit ICB wirkte sich hier ebenso negativ auf die Mortalität nach drei Monaten aus. Bereits für das Krankheitsbild der aneurysmatischen Subarachnoidalblutung ist eine mit dem Iktus verknüpfte hyperadrenerge Reizantwort des Organismus beschrieben, die katecholaminbedingt zu einem Hypermetabolismus führt, der im steigenden Serum-Laktat messbar wird [46,47]. Darüber hinaus deuten weitere Daten darauf hin, dass auch eine Hyperglykämie nach einer ICB möglicherweise ebenfalls durch eine neuroendokrine, stressvermittelte Reaktion ausgelöst wird, die wiederum die anschließende Schädigung des Hirngewebes durch metabolische Dysregulation, Zytotoxizität und neuronalen Zelltod begünstigt [47,48]. Die Korrektur einer bestehenden Hyperglykämie findet sich daher ebenfalls in den aktuellen Behandlungsempfehlungen der ICB [20]. Die im Rahmen dieser Habilitationsschrift erhobenen institutionellen Daten deuten darauf hin, dass bei einer relativ homogenen Patientenpopulation (stammganglionäre ICB) eine adäquate, balancierte Therapie einer Hyperlaktatämie/Hyperglykämie frühzeitig eingeleitet werden sollte. Zudem bieten diese Parameter zusammen mit der radiologischen und neurologischen Evaluation des Patienten die Möglichkeit einer umfassenderen Einschätzung der Prognose des Patienten in einem frühen Stadium der Therapie(planung).

Die Ergebnisse dieser beiden Arbeiten haben somit frühzeitig messbare Parameter identifizieren können, welche eine initiale, multifaktorielle Prognoseeinschätzung bei Patienten mit ICB zusätzlich zu erleichtern vermögen.

Die weiteren Arbeiten der hier vorliegenden Habilitationsschrift haben sich nunmehr mit der Identifikation von Parametern beschäftigt, die im Laufe der bereits begonnenen intensivmedizinischen Therapie die Reevaluation der Sinnhaftigkeit einer eventuellen Eskalation (Organersatztherapie) unterstützen sollen.

So stellt der arterielle Hypertonus einen der relevantesten Risikofaktoren der spontanen ICB dar, welcher zeitgleich zur Vermeidung einer weiteren Hämatomexpansion o.ä. aggressiv zu behandeln ist [20,49]. Langjährig an einen arteriellen Hypertonus adaptierte Patienten weisen häufig eine Vaskulopathie auf, die nicht nur auf das Gehirn beschränkt ist, sondern vielmehr eine Systemerkrankung darstellt. Denkbar sind daher auch negative Auswirkungen einer bewusst aggressiven antihypertensiven Therapie auf unterschiedliche Organfunktionen. Eine chronische Niereninsuffizienz ist ein starker negativer Outcome-Prädiktor sowohl beim ischämischen, wie auch dem hämorrhagischen Schlaganfall [50]. Insbesondere bei großen, raumfordernden Hirnblutungen stellt die Blutdrucksenkung einen Risikofaktor für eine verringerte geschätzte glomeruläre Filtrationsrate (eGFR) und Mortalität dar [51]. Gerade grenzkompensierte Patienten sind damit dem Risiko der Entwicklung einer akuten Niereninsuffizienz (acute kidney injury, AKI) ausgesetzt [52]. Das alleinige Auftreten eines dialysepflichtigen AKI führt bei Intensivpatienten zu einer gesteigerten Mortalität und häufigerer chronischer Dialysepflichtigkeit [53,54]. Eine dieser Arbeit zugrundeliegende Analyse von Patienten mit ICB konnte die Entwicklung eines AKI mit der Notwendigkeit einer kontinuierlichen Dialyse assoziieren. Dieser Umstand war nicht nur mit einem signifikant verlängerten Krankenhausaufenthalt, sondern auch mit einer signifikant erhöhten Mortalität verbunden [55]. Sowohl ein bei Aufnahme erhöhtes Procalcitonin (PCT), als auch die rasche Entwicklung eines AKI (<48 Stunden nach Aufnahme) stellten hierbei unabhängige Prädiktoren für die Notwendigkeit einer Nierenersatztherapie dar.

Ein weiterer Faktor der das Auftreten eines AKI begünstigen kann ist eine klinisch relevante Dehydratation [56,57] Eine Dehydratation, die häufig im Kontext neurologischer Erkrankungen zu beobachten ist und sich negativ auf den weiteren klinischen Verlauf auswirken kann [58], wurde daher im Rahmen dieser kumulativen Habilitation weiter untersucht. Das im Verlauf der Behandlung einer ICB thromboembolische Komplikationen oder auch eine Dialysepflichtigkeit auftreten [59,60] können wurde bereits beschrieben. Es war uns möglich zu zeigen, dass bei Aufnahme

exsikkierte Patienten mit einer typischen ICB eine signifikant höhere Sterblichkeit nach 30 Tagen aufwiesen [61] und damit dieser Befund einen möglicherweise relevanten Faktor zur Einschätzung der kurzfristigen Sterblichkeit dieser Patienten darstellt.

Die häufig hochgradig eingeschränkte körperliche Exekutivfunktion zusammen mit der Vigilanzstörung macht bei Patienten mit einer ICB in vielen Fällen eine langfristige, teils Monate dauernde Intensivtherapie inklusive aller heutzutage verfügbarer Organersatzverfahren notwendig. Der Verlust der Schutzreflexe zusammen mit damit verbundenen Lungenfunktionsstörungen durch Sekretretention/Infektion führt bei diesen Patienten häufig zu einer PMV. Neben den bereits oben angesprochenen relevanten Nierenfunktionsstörungen hat auch die Notwendigkeit einer PMV erheblichen Einfluss auf das Überleben und die damit verbundenen Kosten der Behandlung von diversen Erkrankungen [62–66]. Hierbei stellt nicht nur die Beatmungstherapie an sich das Problem dar, sondern häufig auch die direkt damit verbundenen Komplikationen. In einer dieser kumulativen Habilitationsschrift zugrunde liegenden Untersuchung der intensivmedizinischen Verläufe von Patienten mit ICB konnte erstmals der Einfluss einer Langzeitbeatmung (Beatmung > 7 Tage) auf das Überleben dargestellt werden [67]. In der analysierten Studienpopulation war als Grund für die prolongierte Beatmung die erhöhte Inzidenz einer (begleitenden) Pneumonie mit 45% gegenüber 14% bei den nicht beatmungspflichtigen Patienten mit ICB nachweisbar. Die Langzeitbeatmung kann aufgrund der im Rahmen der ICB erlittenen neurologischen Defizite (Vigilanzminderung, Schluckstörungen) aber auch durch die Kumulation intensivmedizinischer Komplikationen bedingt sein.

Wie auch die Nierenersatztherapie steht die Langzeitbeatmung im klinischen Alltag häufig als Synonym für die von Angehörigen (und Patienten) oft gefürchtete “Gerätemedizin”. Die in dieser Arbeit identifizierten Risikofaktoren sollen durch die aufgezeigte Assoziation dieser Befunde mit einem ungünstigen Ausgang der Erkrankung die oftmals schwierigen Entscheidungsfindungsprozess der Intensivmedizin aber auch die Arzt-/Angehörigengespräche unterstützen. Idealerweise sollten Wünsche, persönliche Präferenzen, Wertesysteme und Patientenverfügungen - sofern vorhanden - des Patienten in derartigen Entscheidungsprozessen berücksichtigt werden. Im klinischen Alltag sind sie jedoch weitgehend von der Prognoseeinschätzung des behandelnden Ärzteteams und den

daraus abgeleiteten Therapiezielen abhängig [68]. Eine möglichst präzise Analyse von für die Prognose relevanten Prädiktoren eines ungünstigen Verlaufs ist daher notwendig und wünschenswert. Aufgrund der multifaktoriellen Problematik insbesondere akut-neurologischer Erkrankungen werden neben klinischen Scores und Einzelfaktoren [21,69,70] zunehmend auch Vorhersagemodelle etabliert, die eine Entscheidungsgrundlage für diesen Prozess zu verbessern vermögen [68]. Dennoch muss auch stets dem Umstand Rechnung getragen werden, dass ein früher Abbruch der Therapie mit hoher Wahrscheinlichkeit zu einem schlechten Ergebnis führt und damit das Risiko einer sich selbsterfüllenden Prophezeiung bei diesem Krankheitsbild besteht [71].

Aus diesen Gründen war das Ziel der vorliegenden kumulativen Habilitationsschrift auf möglichst vielen Ebenen der neurointensivmedizinischen Behandlung von Patienten mit ICB, Parameter zu identifizieren, die im klinischen Alltag genutzt werden können, jenen schwerwiegenden Entscheidungsprozess zu unterstützen. Es gelang dabei, Laborparameter wie RPR, Aufnahme- Laktat/Glukose und den Dehydratationsstatus, sowie technische Aspekte im Bereich der Organersatztherapie von Niere und Lunge aber auch patientenspezifische Faktoren im Rahmen von Therapie limitierenden Entscheidungen teils erstmalig für dieses facettenreiche Krankheitsbild aufzuzeigen. Damit stellen die Ergebnisse dieser Habilitationsschrift behandelnden neuro-intensivmedizinischen Ärzte-Teams zusätzliche, neue Entscheidungshilfen zur Seite, um im Sinne der Patienten deren Angehörige besser beraten zu können und eine umfassendere Entscheidungsgrundlage zu bieten.

Zusammenfassung

Die spontane intrazerebrale Blutung (ICB) stellt nach wie vor eine der Entitäten des Schlaganfalls mit der höchsten Mortalität dar. Zahlreiche Ansätze, die Behandlung und das Outcome zu optimieren, haben bisher zu keiner deutlichen Reduktion der Sterblichkeit geführt.

Weder rein chirurgische Therapieansätze, die teilweise auf eine reine Entlastung der raumfordernden Komponente abzielten (STICH I und II), oder auch das Hämatom evakuierten (MISTIE), noch konservative Therapien, die beispielsweise eine sekundäre Hämatomexpansion verhindern/reduzieren sollten (ATACH-II, INTERACT 2), zeigten ausgeprägte Effekte in Bezug auf das qualitative Überleben. Hierbei wird deutlich, dass die Prognose nach einer ICB von einer Vielzahl an verschiedenen Faktoren, wie der Blutungslokalistion, Ausdehnung, dem Patientenalter aber auch dem klinischen Zustand des Patienten bei Aufnahme abhängig ist. Im Rahmen einer self-fulfilling prophecy ist die Gefahr im klinischen Alltag die Prognose einer ICB falsch einzuschätzen groß. Auf der anderen Seite ist ein Überleben nicht selten nur mit ausgeprägten körperlichen Behinderungen und erheblich verringerter Lebensqualität möglich. Das Behandlungsteam muss daher häufig unter erheblichem zeitlichen Druck, sehr weitreichende Entscheidungen treffen und kann diese nicht immer mit den Patienten selber abstimmen, sondern muss dies mit den Angehörigen/Betreuern tun, die nachvollziehbarerweise in dieser Situation ebenfalls überfordert sind. Es ist daher von großer Bedeutung, Parameter zu identifizieren, die im klinischen Alltag verfügbar sind und helfen, die Prognose einer ICB besser abschätzen zu können, um die Behandlung der Patienten und die Beratung der Angehörigen so gut wie möglich führen zu können.

Ziel dieser kumulativen Habilitationsschrift war es daher, Parameter in der frühen Phase der Behandlung, unmittelbar nach Aufnahme, aber auch im kurz- und mittelfristigen Verlauf der intensivmedizinischen Versorgung zu identifizieren. Da sich typische von atypischen ICBs hinsichtlich ihrer Genese und auch ihrer Prognose unterscheiden, wurde ein hoch selektives Patientenkollektiv mit rein stammganglionären Blutungen gewählt. Es gelang dabei, Laborparameter wie die RPR, Aufnahme Lactat/Glucose und den Dehydratationsstatus als Prädiktoren einer gesteigerten Sterblichkeit zu identifizieren. Aber auch technische Aspekte im Bereich

der Organersatztherapie von Lunge und Niere konnten identifiziert werden. So führen eine prolongierte Beatmungspflichtigkeit und ein frühes akutes Nierenversagen bei diesen Patienten zu einer Outcome-Verschlechterung. Auch patientenspezifische Faktoren im Rahmen von therapielimitierenden Entscheidungen konnten beschrieben werden. Diese Daten konnten für Patienten mit einer typischen ICB teils erstmalig publiziert werden.

Die Ergebnisse dieser Habilitationsschrift stellen neurointensivmedizinisch tätigen Kollegen damit neue Entscheidungshilfen zur Seite, um Patienten und Angehörige möglichst optimal beraten zu können und eine umfassende und breite Grundlage zur Stratifizierung der Therapie zu bieten.

Überlappung durch geteilte Autorenschaften

Die vorliegende Habilitationsschrift hat vier publizierte Originalarbeiten zur Grundlage. Keine dieser Arbeiten enthält eine geteilte Erst- oder Letzautorenschaft. Eine Überlappung mit anderen Habilitationsschriften ist nicht gegeben.

Zwei der insgesamt 8 geforderten Arbeiten als Erst- oder Letztautor enthalten geteilte Autorenschaften. Die beiden 2021 in Frontiers in Neurology publizierten Arbeiten habe ich gemeinsam mit Herrn Patrick Schuss als Letztautor und mit Herrn Florian Gessler als gemeinsamer Erstautor publiziert. Das untersuchte neurochirurgische Patientenkollektiv im Kontext der intensivmedizinischen Fragestellung erforderte ein hohes Maß an interdisziplinärer Zusammenarbeit. Alle Erst- und Letztautoren steuerten in erheblichem Maße ihre Expertise und Engagement zur Fertigstellung der Manuskripte bei

Die Arbeit „Triage and Allocation of Neurocritical Care Resources During the COVID 19 Pandemic - A National Survey" war eine multizentrisch, national ausgelegte Untersuchung, bei der sowohl Herr Gessler, Herr Schuss und ich maßgenblich mit der Konzeption, Supervision/Koordination aller beteiligten Häuser und Entwicklung des initialen Manuskripts befasst waren, was zur Teilung der Autorenschaft führte.

Die Arbeit „Early Laboratory Predictors for Necessity of Renal Replacement Therapy in Patients With Spontaneous Deep-Seated Intracerebral Hemorrhage" wurde maßgeblich von Herrn Patrick Schuss und mir konzipiert und initiiert. Die Datenakquise und Analyse erfolgte durch Frau Lorena Schenk, Herrn Schuss und mich. Entsprechend des gemeinsamen Engagements wurde die Autorenschaft geteilt.

Köln, den 09.11.2023

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