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Analysen der Akuttherapie und Komplikationen von ischämischen Schlaganfällen

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1 Inhaltsverzeichnis

2 Einleitung

Die folgenden vier Originalarbeiten liegen dieser kumulativen Habilitationsschrift zugrunde:

1. Stösser, S., Bode, F.J., Dorn, F., and Petzold, G.C. (2022). Workflow Times and Outcome of Endovascular Therapy in Stroke Patients with Initial MRI or CT. Cerebrovascular diseases (Basel, Switzerland) 51, 45-51. https://doi.org/10.1159/000517903.
2. Stösser, S., Ullrich, L., Kassubek, J., Ludolph, A.C., Schocke, M., and Neugebauer, H. (2020). Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis. European journal of neurology 27, 2483-2490. https://doi.org/10.1111/ene.14453.
3. Stösser, S., Gotthardt, M., Lindner-Pfleghar, B., Jüttler, E., Kassubek, R., and Neugebauer, H. (2021). Severe Dysphagia Predicts Poststroke Fever. Stroke 52, 2284-2291. https://doi.org/10.1161/STROKEAHA.120.033396.
4. Stösser, S., Isakeit, J., Bode, F.J., Bode, C., and Petzold, G.C. (2022b). Sepsis in Patients With Large Vessel Occlusion Stroke-Clinical Characteristics and Outcome. Frontiers in neurology 13, 902809. https://doi.org/10.3389/fneur.2022.902809.

2.1 Überblick über die Behandlung von Schlaganfällen

Der Schlaganfall ist weltweit eine der führenden Ursachen für Mortalität und erworbene Behinderungen (Feigin et al., 2021). In Deutschland ereignet sich bei etwa 270.000 Menschen pro Jahr ein Schlaganfall (Heuschmann et al., 2010). Ein bis 2% der Erwachsenen in Deutschland erleidet innerhalb eines Jahres einen Schlaganfall oder leidet an chronischen Beschwerden eines Schlaganfalls. Diese Jahresprävalenz steigt altersabhängig auf bis zu über 6% bei über 75-jährigen an (Robert Koch-Institut, 2017).

Die Behandlung von Patienten mit einem akuten Schlaganfall erfolgt auf einer Stroke Unit (Ringelstein, 1998; Nabavi et al., 2015). Hier erfolgt einerseits die Akuttherapie mittels intravenöser Thrombolysetherapie (IVT) und endovaskulärer Therapie (ET), andererseits

werden die Patienten monitorüberwacht und erhalten weitere Diagnostik, um die Schlaganfallursache zu klären, geeignete sekundärprophylaktische Maßnahmen einzuleiten und Komplikationen vorzubeugen bzw. diese früh zu erkennen und zu behandeln. Des Weiteren wird bereits mit einer frühen Rehabilitation begonnen. Die Behandlung auf der Stroke Unit an sich sowie die genannten medizinischen Maßnahmen sind effektiv und evidenzbasiert (Langhorne and Ramachandra, 2020), jedoch bestehen bei jedem dieser Behandlungsschritte offene Fragen, deren Beantwortung zu einer Verbesserung der Schlaganfallbehandlung führen kann.

In den vier Arbeiten, die dieser kumulativen Habilitationsschrift zugrunde liegen, werden verschiedene Aspekte der Behandlung auf der Stroke Unit mittels klinischer Kohorten- und Registerstudien adressiert. Der Fokus liegt dabei einerseits auf der Optimierung der Akutdiagnostik und –therapie von Hirninfarkten und andererseits auf der Früherkennung der Komplikationen Fieber und Infektionen nach Hirninfarkt.

2.2 Akutdiagnostik und –therapie ischämischer Schlaganfälle

Schlaganfälle zeichnen sich klinisch durch plötzlich auftretende fokal-neurologische Ausfallserscheinungen aus (Sacco et al., 2013). Eine präzise Diagnosestellung ist allerdings nur unter Zuhilfenahme einer radiologischen Schnittbildgebung des Hirns möglich. Diese ist vor allem nötig, um einen ischämischen Schlaganfall, also einen Hirninfarkt, von einem hämorrhagischen Schlaganfall, also einer intrazerebralen Blutung, zu unterscheiden.

Als Bildgebungsmodalitäten stehen die Computertomographie (CT) sowie die Magnetresonanztomographie zur Verfügung (MRT), die sich durch unterschiedliche Vor- und Nachteile auszeichnen (Vert et al., 2017). Das CT bietet im Vergleich zum MRT folgende Vorteile: kürzere Untersuchungszeiten, eine geringere Anzahl an Kontraindikationen sowie eine breitere Verfügbarkeit. Des Weiteren können im CT auch einfacher klinisch instabile Patienten untersucht werden, die auf eine Monitorüberwachung oder künstliche Beatmung angewiesen sind. Der wesentliche Nachteil des CT ist, dass in der Akutphase nur eine intrazerebrale Blutung nachgewiesen werden kann, während ein ischämischer Schlaganfall

lediglich als Ausschlussdiagnose festgestellt werden kann, falls noch keine ischämischen Frühzeichen vorliegen. Dem gegenüber liefert das MRT deutlich mehr klinisch wichtige Informationen: Ein akuter ischämischer Schlaganfall kann mittels Diffusions-MRT direkt nachgewiesen werden, zudem erhält man Informationen über die genaue Lokalisation, das Volumen und das Alter des Infarktkerns. Des Weiteren erlaubt das MRT durch den Positivnachweis des Infarktkerns eine Abgrenzung zu weiteren Differentialdiagnosen von Schlaganfällen wie epileptischen Anfällen oder Migräneattacken mit Aura. Die Nachteile des MRT sind die längeren Untersuchungszeiten, diverse Kontraindikationen, insbesondere das Vorhandensein von Metallimplantaten wie Herzschrittmachern, die geringere Verfügbarkeit und der höhere personelle Aufwand (Muir et al., 2006; Leslie-Mazwi et al., 2018).

Die Akutbehandlung ischämischer Schlaganfälle erfolgt mittels intravenöser IVT und bei Nachweis von Verschlüssen größerer hirnversorgender Arterien in der CT- oder MR-Angiographie zusätzlich mittels ET. Voraussetzung für beide Therapien ist, dass noch Hirngewebe vorliegt, das infolge der Ischämie funktionsgestört, aber noch nicht irreversibel infarziert ist und durch eine Rekanalisation des zugrundeliegenden Gefäßverschlusses vor einem Infarkt bewahrt werden kann.

Bei einem Symptombeginn von 4,5 bzw. 6 Stunden vor Einleitung der Therapie sind die IVT bzw. die ET auf der Basis randomisierter kontrollierter Studien sicher und effektiv (Wardlaw et al., 2014; Goyal et al., 2016b). Bei Patienten, die nur außerhalb diese Zeitfenster behandelt werden können oder bei denen das Zeitfenster unklar ist, muss mittels erweiterter Bildgebung, z.B. einem Perfusions-CT, noch rettbares Gewebe nachgewiesen werden, bevor die Indikation zur IVT oder ET gestellt wird (Albers et al., 2018; Nogueira et al., 2018; Thomalla et al., 2018; Campbell et al., 2019; Tsivgoulis et al., 2020).

2.2.1 Prozesszeiten der endovaskulären Therapie bei initialem MRT oder CT

Für den Erfolg der IVT und ET ist es essentiell, dass diese erfolgen, bevor es zu einer irreversiblen Infarzierung kommt. Dieser Prozess ist zeitkritisch: Je später nach Symptombeginn die Therapie begonnen wird, desto geringer ist die Chance auf ein gutes klinisches Outcome (Saver et al., 2016; Bluhmki et al., 2020). In einer Metaanalyse mehrerer

Thrombektomiestudien stellten Saver et al. fest, dass die Odds Ratio für funktionelle Unabhängigkeit drei Monaten nach dem Schlaganfall durch die ET bei Behandlung drei Stunden nach Symptombeginn 2,83, sechs Stunden nach Symptombeginn 2,32 und acht Stunden nach Symptombeginn nur noch 2,03 beträgt (Saver et al., 2016). Daher ist eine Optimierung des gesamten Arbeitsablaufes von der Erkennung der Symptomatik, der Einleitung der Rettungskette mit Transport ins Krankenhaus, der Untersuchungsschritte im Krankenhaus und schließlich des Therapiebeginns erforderlich.

Die dargestellten Charakteristika der Bildgebung mittels CT oder MRT sorgen vermutlich für Unterschiede im zeitlichen Arbeitsablauf. Daher stellt sich die Frage, ob die Wahl der Bildgebungsmodalität den zeitlichen Arbeitsablauf in der Praxis tatsächlich bestimmt und ob dies einen Einfluss auf das klinische Outcome nach ischämischem Schlaganfall hat. Besonders relevant ist dies für Patienten mit ischämischen Schlaganfall bei Verschluss einer großen hirnversorgenden Arterie, da hier der Arbeitsablauf bis zur Gefäßrekanalisation mittels ET mehr Einzelschritte und somit mehr Potenzial für Störfaktoren aufweist als bei Patienten, die lediglich eine IVT erhalten.

Bisherige Studien zu dieser Fragestellung bei Schlaganfallpatienten, die eine ET erhielten, lieferten widersprüchliche Ergebnisse. Menon et al. stellten in einer Kohorte einer prospektiven Studie von 51 MRT- und 81 CT-Patienten fest, dass die Zeit von der initialen Bildgebung bis zur Leistenpunktion für die ET bei Patienten mit MRT im Mittel 18 Minuten länger war (Menon et al., 2014). Kim et al. berichteten anhand von 986 MRT- und 279 CT-Patienten eines prospektiven multizentrischen koreanischen Registers, dass die untersuchten Zeitintervalle der verschiedenen Prozessschritte mit Beginn bei der Krankenhauseinlieferung bis zur Rekanalisation bei Patienten mit MRT länger waren, jedoch nicht die Zeitintervalle vom Zeitpunkt der initialen Bildgebung bis zur Leistenpunktion und Rekanalisation (Kim et al., 2019). In einer retrospektiven multizentrischen Studie von 80 MRT- und 286 CT-Patienten war das Zeitintervall von Bildgebung zu Leistenpunktion bei MRT-Patienten gegenüber CT-Patienten um 63 Minuten länger (Sheth et al., 2013). In einer Sekundäranalyse der randomisierten Thrombektomiestudie THRACE wurde anhand von 299 MRT- und 102-CT-

Patienten zwar eine längere Untersuchungszeit der Bildgebung (MRT: 13 Minuten, CT: 9 Minuten), jedoch kein Unterschied der weiteren Prozesszeiten und auch ein vergleichbares klinisches Outcome in beiden Gruppen beschrieben (Provost et al., 2019). Simonsen et al. ermittelten in einer Sekundäranalyse der GOLIATH-Studie, die nur MRT-Patienten (n=128) umfasste, vergleichbare Prozesszeiten im Vergleich zu randomisierten Thrombektomiestudien (Simonsen et al., 2018). In einer Sekundäranalyse der randomisierten Thrombektomiestudie SWIFT PRIME wurde anhand von 34 MRT- und 139 CT-Patienten kein signifikanter Unterschied des Zeitintervalls von Aufnahme bis zur Randomisierung beschrieben (Menjot de Champfleur et al., 2017). Eine weitere Sekundäranalyse erbrachte ebenfalls keinen signifikanten Unterschied dieses Zeitintervalls, jedoch wurde nach Adjustierung für mögliche Störfaktoren ein signifikanter Effekt der Bildgebungsmodalität auf dieses Zeitintervall festgestellt (Goyal et al., 2016a).

Zusammenfassend war auf der Basis der bisherigen Studienlage unklar, ob und inwieweit die Bildgebung mittels MRT einen Zeitverlust gegenüber einem CT bedingt. Hinweise, dass sich das klinische Outcome je nach eingesetzter Bildgebungsmodalität unterscheidet, ergaben sich aus den bisherigen Studien nicht. Die bisherigen Studien basierten größtenteils auf Sekundäranalysen prospektiver kontrollierter Studien, die sich durch ein stark selektiertes Patientenklientel auszeichnen, was die Übertragbarkeit der Ergebnisse in die klinische Praxis einschränkt. Zudem war die Aussagekraft dieser Studien mit Ausnahme der Studien von Kim et al. sowie Provost et al. durch die geringe Anzahl an MRT-Patienten limitiert.

Ziel der Arbeit „Workflow Times and Outcome of Endovascular Therapy in Stroke Patients with Initial MRI or CT“ war es daher, die Prozesszeiten und das klinische Outcome nach ET anhand einer großen Kohorte von Schlaganfallpatienten zu untersuchen, die initial mittels MRT oder CT untersucht wurden. Die Daten dieser Arbeit gingen aus dem German Stroke Registry Endovascular Treatment (GSR-ET) hervor. Das GSR-ET ist eine akademische prospektive multizentrische Registerbeobachtungsstudie von 25 Universitätskliniken und nicht universitären Krankenhäusern (Alegiani et al., 2019). Seit Juni 2015 wurden fortlaufend Schlaganfallpatienten mit einem Verschluss großer hirnversorgender Gefäße, die mittels ET

behandelt werden, eingeschlossen. Es erfolgte eine prospektive Datenerhebung von klinischen und radiologischen Parametern während des stationären Aufenthalts sowie ein standardisiertes 3-Monats-Follow-up. Bis Ende 2022 wurden insgesamt über 10.000 Patienten eingeschlossen.

2.2.2 Hämorrhagische Transformation nach intravenöser Thrombolysetherapie

Das wesentliche Risiko der IVT des Hirninfarkts ist das Auftreten einer intrakraniellen Blutung. Das Spektrum intrakranieller Blutungen nach IVT ist breit: Petechiale Einblutungen oder solide intrazerebrale Hämatome im Bereich des Infarktareals sind die häufigste Form und werden als hämorrhagische Transformation bezeichnet. Eine genauere Klassifizierung der hämorrhagischen Transformation in vier Schweregrade erfolgt gemäß den Kriterien der ECASS-II-Studie (Berger et al., 2001). Es können jedoch auch intrazerebrale Blutungen in anderen Hirnarealen, die nicht durch den Infarkt geschädigt sind, auftreten. Des Weiteren kommt es gelegentlich auch zu Subarachnoidalblutungen. Sub- oder epidurale Hämatome werden selten und in der Regel nur in Verbindung mit einem vorangehenden Trauma beobachtet.

Der wesentliche Sicherheitsendpunkt für die IVT ist das Auftreten symptomatischer intrazerebraler Blutungen. Hierbei werden lediglich raumfordernde solide Einblutungen als klinisch relevant betrachtet. Daraus ergibt sich die aktuelle Definition der symptomatischen intrazerebralen Blutung gemäß der SITS-MOST-Kriterien: Diese setzt das Vorliegen einer solchen raumfordernden soliden Einblutung in Verbindung mit einer Verschlechterung des neurologischen Befundes, die klinisch auf die Blutung zurückzuführen ist, voraus (Wahlgren et al., 2007). Bei Anwendung dieser Kriterien wurden symptomatische intrazerebrale Blutungen im Zeitfenster von bis zu 36 Stunden nach IVT in 1,7% der Fälle des SITS-MOST-Registers beobachtet (Wahlgren et al., 2007). Die Häufigkeit aller, inklusive asymptomatischer, intrazerebraler Blutungen nach IVT betrug in der SITS-MOST-Kohorte 14,5%. Bei rein MRT-basierten Studien liegt die Häufigkeit jeglicher hämorrhagischer

Transformation methodenbedingt deutlich höher, wie beispielhaft von Caparros et al. beschrieben (29,7%) (Caparros et al., 2020).

2.2.3 Kontraindikationen für die intravenöse Thrombolysetherapie

Die Entscheidung für eine IVT beinhaltet immer eine Abwägung zwischen der individuellen Chance auf eine erfolgreiche Behandlung des Hirninfarkts und dem Risiko einer Blutungskomplikation. Mit Hilfe von Kontraindikationen werden Patienten, die mutmaßlich ein exzessiv hohes Blutungsrisiko haben, von der Therapie ausgeschlossen. Diese Kontraindikationen basieren auf den Ausschlusskriterien der Phase-3-Studien, die zur Zulassung von Alteplase zur Behandlung des Hirninfarkts geführt haben (Tissue plasminogen activator for acute ischemic stroke, 1995; Hacke et al., 2008). Diese waren aus Sicherheitsgründen sehr konservativ formuliert. In nachfolgenden Studien wurde jedoch gezeigt, dass einige dieser Ausschlusskriterien Patienten von der IVT ausschließen, obwohl diese tatsächlich von der Therapie profitieren. Beispiele dafür sind die obere Altersgrenze von 80 Jahren sowie das Zeitfenster für die IVT, das von anfangs drei Stunden zunächst auf 4,5 Stunden und schließlich unter Zuhilfenahme erweiterter Bildgebung auf bis zu neun Stunden nach Symptombeginn ausgedehnt werden konnte (Sandercock et al., 2012; Thomalla et al., 2018; Ma et al., 2019).

Eine der Kontraindikation für die IVT ist das Vorliegen eines rezenten Schlaganfalls innerhalb der vorangehenden drei Monate. Ein rezenter Schlaganfall kann einerseits durch ein klinisches Ereignis mit plötzlich auftretenden fokal-neurologischen Ausfallserscheinungen, die länger als 24 Stunden anhalten, definiert sein, andererseits aber auch durch den Nachweis eines rezenten Hirninfarkts in der zerebralen Bildgebung ohne Auftreten klinischer Symptome (Sacco et al., 2013). Die letztere Konstellation wird als klinisch stummer Hirninfarkt definiert. Rezente klinisch stumme Hirninfarkte (RSIs) werden mittels MRT wesentlich häufiger festgestellt als mittels CT (Muir et al., 2006; Chalela et al., 2007). Patienten mit RSIs, die nur im MRT, jedoch nicht im CT zu sehen sind, wurden aus den CT-basierten Phase-3-Studien für IVT gemäß Protokoll nicht ausgeschlossen. Daher ist unklar, ob RSIs als Kontraindikation für die IVT betrachtet werden sollten. In bisherigen MRT-basierten Studien wurden RSIs häufig (11,6%

bis 18,3%) festgestellt, zudem wurde beschrieben, dass diese nicht mit einem erhöhten Risiko einer hämorrhagischen Transformation nach IVT einhergehen, jedoch war die Aussagekraft dieser Studien durch eine geringe Fallzahl begrenzt (Tisserand et al., 2011; Gaillard et al., 2012).

Das MRT kommt als primäre bildgebende Diagnostik eines Schlaganfalls zunehmend häufiger zum Einsatz, um die IVT auch bei Patienten mit unklarem oder erweitertem Zeitfenster einzusetzen (Thomalla et al., 2018; Ma et al., 2019). Infolgedessen werden RSIs häufiger als Nebenbefund festgestellt, so dass das klinische Dilemma, ob RSIs eine Kontraindikation für die IVT darstellen, adressiert werden muss, da hierfür eindeutige Evidenz fehlt.

Ziel der Arbeit „Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis" war es daher, ob das Auftreten von RSIs im MRT mit einem erhöhten Risiko einer hämorrhagischen Transformation oder eines schlechteren klinisches Outcomes bei Schlaganfallpatienten, die mittels IVT behandelt wurden, assoziiert ist. Grundlage für diese Arbeit war eine Kohorte konsekutiver Schlaganfallpatienten, die nach initialem MRT mittels IVT behandelt wurden.

2.3 Frühe Komplikationen nach ischämischen Schlaganfällen

Nach ischämischen Schlaganfällen können eine Vielzahl von Komplikationen auftreten (Kumar et al., 2010; Schwarzbach and Grau, 2020; Krishnan et al., 2021). Diese können den klinischen Verlauf nachteilig beeinflussen, so dass deren Vorbeugung, frühe Erkennung und Behandlung auf der Stroke Unit essentiell ist. Die Komplikationen lassen sich folgendermaßen unterteilen:

- Intrakranielle Komplikationen
- Komplikationen der Behandlung mittels IVT und ET
- Primäre Folgeerscheinungen des Schlaganfalls
- Sekundäre internistische Komplikationen

Zu den intrakraniellen Komplikationen zählen eine hämorrhagische Transformation des Infarktareals, die Entwicklung eines Hirnödems mit raumforderndem Effekt und ggf. Liquorzirkulationsstörungen und Rezidiv-Schlaganfälle. Eine hämorrhagische Transformation des Infarktareals kann zudem durch eine IVT und ET begünstigt werden, wie bereits unter 2.2.2 diskutiert. Weitere wichtige Komplikationen der Akuttherapie umfassend das allergische Angioödem nach IVT sowie Schädigungen der hirnversorgenden Gefäße, unter anderem Perforation oder Dissektion, und Komplikationen an der Punktionsstelle, wie z.B. ein Aneurysma spurium, infolge der ET. Bei Implantation eines Gefäßstents im Rahmen der ET kann des Weiteren eine thrombotische Stentokklusion auftreten.

Die folgenden Komplikationen können als eine direkte Folge der Hirnschädigung durch den Schlaganfall auftreten: neurogene Dysphagie mit sekundärer Mangel- oder Fehlernährung, epileptische Anfälle, Urin- und Stuhlinkontinenz, Atemregulationsstörungen, Spastik, Schmerzen und Delir.

Internistische Begleit- und Folgeerkrankungen nach Schlaganfall umfassen Infektionen, Fieber, tiefe Beinvenenthrombosen, Lungenarterienembolien, kardiale Komplikationen wie Myokardinfarkt und Arrhythmien und gastrointestinale Blutungen.

2.3.1 Dysphagie

Die Dysphagie ist eine sehr häufige Folgeerscheinung eines Schlaganfalls. Bei klinischer Diagnosestellung sind etwa 50% der Schlaganfallpatienten betroffen, bei Einsatz apparativer Schluckdiagnostik bis zu 80% (Martino et al., 2005). Ursächlich ist in der Regel eine direkte Schädigung von für den physiologischen Schluckakt essenziellen Hirnarealen im Cortex, Cerebellum und vor allem im Hirnstamm durch den Schlaganfall. Einerseits können Paresen und Koordinationsstörungen der am Schluckakt beteiligten Muskeln zu einer Dysphagie führen, andererseits können auch enorale, pharyngeale und laryngeale Sensibilitätsstörungen den Schluckakt beeinträchtigen. Des Weiteren kann ein Schlaganfall zu Störungen der Vigilanz und Konzentration führen, die ebenfalls mit einer Dysphagie einhergehen können. Als Folge einer Dysphagie kann es zu einer Aspiration kommen, die zu einer Pneumonie führen kann. Des Weiteren kann eine Dysphagie eine Mangel- und Fehlernährung zur Folge haben. Eine

frühzeitige Beurteilung des Schluckens nach Aufnahme auf die Stroke Unit ist daher nötig, um Maßnahmen zur Vorbeugung einer Aspiration sowie zur Behandlung der Dysphagie einzuleiten.

Hierzu stehen drei diagnostische Methoden zur Verfügung: ein Schluckscreening, eine klinische Schluckuntersuchung sowie apparative Untersuchungen des Schluckens (Martino et al., 2005).

Schluckscreenings beinhalten in der Regel einen Schluckversuch mit Wasser, bieten einen ersten Überblick über die Schluckfunktion und können auch mit relativ geringer klinischer Erfahrung durchgeführt werden. Die klinische Schluckuntersuchung ist dem gegenüber deutlich differenzierter und beinhaltet eine Untersuchung der relevanten Hirnnerven sowie Schluckversuche mit Nahrung und Flüssigkeiten unterschiedlicher Konsistenzen. Die Durchführung der klinischen Schluckuntersuchung erfordert spezielle Expertise und wird daher auf den meisten Stroke Units von LogopädInnen vorgenommen. Die in der nachfolgenden Arbeit vorgenommene klinische Schluckuntersuchung basierte auf der Screeningprozedur von Logemann sowie dem Stufenkonzept für neurogene oropharyngeale Dysphagie (Logemann et al., 1999; Ickenstein et al., 2010). Einige wichtige Bestandteile dieser klinischen Schluckuntersuchung werden im Folgenden erläutert: Die Prädiktoren für eine mittel- bis schwergradige Dysphagie nach Daniels umfassen die Beurteilung von Dysarthrie, Dysphonie, abnormen willkürlichen Husten, abnormen Würgereflex, Husten nach Wasserschluck sowie Stimmänderung nach Wasserschluck (Daniels et al., 1997). Das Vorliegen von zwei dieser sechs Prädiktoren spricht mit einer Sensitivität von 92,3% und einer Spezifität von 66,7% für das Vorliegen einer mittel- bis schwergradigen Dysphagie. Das Ergebnis der klinischen Schluckuntersuchung und die daraus resultierende Kostempfehlung können mittels der Functional Oral Intake Scale (FOIS) sowie der Schluckbeeinträchtigungsskala (SBS) angegeben werden. Beides sind Skalen mit sieben Items, die das Spektrum der Kostempfehlung bei Dysphagie von einer Ernährung ausschließlich über eine Magensonde bis hin zu voll-oraler Ernährung ohne Einschränkungen abbilden (Prosiegel et al., 2002; Crary et al., 2005).

Als apparative Verfahren stehen die flexible endoskopische Evaluation des Schluckakts (FEES) sowie die videofluoroskopische Evaluation des Schluckakts (VFSS) zur Verfügung. Die FEES ist auf den meisten deutschen Stroke Units der Standard. Sie erlaubt eine direkte Visualisierung der pharyngealen Phase des Schluckakts, zudem kann während der Untersuchung das Schlucken unterschiedlicher Nahrungskonsistenzen, vor allem in Hinblick auf eine Aspirationsgefahr beurteilt werden. Das Ergebnis der FEES wird üblicherweise mittels der achtteiligen Penetrations-Aspirations-Skala beurteilt, wobei ein Punktwert von zwei bis fünf für eine Penetration, also ein Eindringen von Bolusmaterial in den Aditus laryngis, und ein Punktwert von sechs bis acht für eine Aspiration, also ein Eindringen von Bolusmaterial bis unterhalb der Plicae vocales, steht (Rosenbek et al., 1996). Die VFSS ist eine radiologische Untersuchung mit Schlucken kontrastmittelhaltiger Boli unterschiedlicher Konsistenzen. Gegenüber der FEES bietet sie den Vorteil einer genauen Beurteilung der intradegluttitiven und ösophagealen Phasen des Schluckakts sowie der genauen Bestimmung von Bolustransitzeiten. Nachteil ist, dass die VFSS nicht bettseitig erfolgen kann und die Gabe von Kontrastmittel mit möglichen Nebenwirkungen beinhaltet. Die Diagnostik mit FEES und VFSS kann bei Verdacht auf Funktionsstörung des oberen und unteren Ösophagussphinkters um eine Manometrie ergänzt werden.

Bei der Behandlung von Schlaganfallpatienten mit Dysphagie sind Ziele, Aspirationen sowie eine Fehl- und Mangelernährung zu vermeiden. Dies wird durch Wahl einer geeigneten, in der Konsistenz angepassten Ernährung, die sicher geschluckt werden kann, erreicht. Zusätzlich werden in der logopädischen Therapie kompensatorische Verfahren eingeübt, die das Schlucken sicherer machen können. Falls bei schwerer Dysphagie keine ausreichende orale Ernährung möglich ist, erfolgt die Ernährung kurzfristig über eine nasogastrale Sonde und bei Zeiträumen von über vier Wochen über eine perkutane endoskopische Gastrostomie. Mittels restituierender Verfahren zielt die logopädische Therapie darauf ab, die gestörte Schluckfunktion wiederherzustellen.

2.3.2 Fieber

Fieber ist eine häufige Komplikation nach Schlaganfall und wird bei 4% bis zu 60% aller Schlaganfallpatienten beobachtet (Castillo et al., 1998; Grau et al., 1999; Prasad and Krishnan, 2010; Phipps et al., 2011; Karaszewski et al., 2012; Honig et al., 2015; Gillow et al., 2017). Fieber wird am häufigsten am ersten oder zweiten Tag nach dem Schlaganfall festgestellt (Azzimondi et al., 1995; Grau et al., 1999; Wong et al., 2007; Karaszewski et al., 2012). Die Diagnose von Fieber setzt eine Erhöhung der Körpertemperatur voraus. Dafür kamen in den genannten Studien unterschiedliche Grenzwerte von 37,4°C bis 38,3°C zum Einsatz. Diese heterogene Definition erklärt einerseits die große Spannbreite der Fieberinzidenz nach Schlaganfall, andererseits tragen auch die unterschiedlichen Messmethoden der Körpertemperatur, wie tympanal, oral, rektal, intravesikal und axillär, dazu bei.

Die Hauptursache von Fieber nach Schlaganfall sind Infektionen. Diese sind gemäß der Literatur in 54 bis 83% der Fälle verantwortlich (Reith et al., 1996; Georgilis et al., 1999; Grau et al., 1999; Karaszewski et al., 2012; Honig et al., 2015; Gillow et al., 2017). In den restlichen Fällen ist meist zentrales Fieber infolge einer Schädigung der zentralen Thermoregulationszentren durch den Schlaganfall ursächlich.

In der Literatur beschriebene Prädiktoren für Fieber nach Schlaganfall umfassen den Schweregrad des Schlaganfalls, definiert über den klinischen neurologischen Befund oder bildgebende Verfahren mit Nachweis eines ausgedehnten Infarktareals, hämorrhagische Schlaganfälle, Infektionen, Dysphagie, Invasivitäten wie nasogastrale Sonden und Blasenkatheter, maschinelle Beatmung, höheres Lebensalter, Vorhofflimmern, Diabetes mellitus, Rauchen und chronisch obstruktive Lungenerkrankung (Reith et al., 1996; Ruborg et al., 2017; Wästfelt et al., 2018).

Fieber ist mit einem schlechten klinischen Outcome sowohl nach ischämischem als auch hämorrhagischen Schlaganfall assoziiert (Azzimondi et al., 1995; Castillo et al., 1998; Boysen and Christensen, 2001; Kammersgaard et al., 2002; Prasad and Krishnan, 2010; Hertog et al., 2011; Phipps et al., 2011; Honig et al., 2015; Gillow et al., 2017). Hervorzuheben ist dabei die Metaanalyse von Prasad und Krishnan, die anhand von sechs Studien mit insgesamt 2986

Patienten mit ischämischem Schlaganfall eine adjustierte Odds Ratio von 2,2 für ein Versterben innerhalb von 30 Tagen bei Feststellen von Fieber in den ersten 24 Stunden nach Schlaganfall bestimmte. Die Grenzwerte für Fieber in den sechs eingeschlossenen Studien reichten dabei von 37,4°C bis 37,9°C.

In der aktuellen Leitlinie der Deutschen Gesellschaft für Neurologie wird die Überwachung der Körpertemperatur, eine entsprechende diagnostische Abklärung von Fieber sowie eine medikamentöse Fiebersenkung mit einem Antipyretikum, wie z.B. Paracetamol, empfohlen (Ringleb et al., 2021). Eindeutige Evidenz aus klinischen Studien für ein verbessertes Outcome bei Fiebersenkung gibt es jedoch nicht. In einem Cochrane-Review von 2009 wurde anhand acht Studien zur Fiebersenkung mittels medikamentöser oder physikalischer Temperatursenkung kein statistisch signifikanter Effekt hinsichtlich der Mortalität bzw. einen kombinierten Endpunkt von Mortalität und Pflegebedürftigkeit festgestellt (Hertog et al., 2009a). In der Paracetamol in Stroke (PAIS) Studie wurde anhand einer Kohorte von 1400 Schlaganfallpatienten die prophylaktische Gabe von Paracetamol untersucht. Dies hatte gegenüber Placebo keinen positiven Effekt auf das klinische Outcome, jedoch zeigte eine Post-Hoc-Analyse, dass zumindest Patienten mit erhöhten Temperaturen von 37 bis 39°C ein besseres Outcome hatten (Hertog et al., 2009b). Die Quality in Acute Stroke Care Studie erbrachte den Nachweis, dass eine kombinierte pflegerische Intervention zum Management von Fieber, Hyperglykämie und Dysphagie das Outcome von Schlaganfallpatienten verbessern kann, allerdings ließ sich aufgrund des Studiendesigns nicht nachvollziehen, welchen Effekt die einzelnen Interventionen hatten (Middleton et al., 2011).

2.3.3 Zusammenhang von Fieber und schwerer Dysphagie

Ein Zusammenhang von Fieber und Dysphagie ist aus theoretischen Überlegungen naheliegend. Eine Dysphagie mit Aspirationsrisiko kann zu unteren Atemwegsinfektionen wie Pneumonie oder Bronchitis führen, die wiederum häufig mit Fieber einhergehen. Während die Assoziation von Dysphagie und Pneumonie gut untersucht ist, gab es bisher nur wenige Arbeiten zur Assoziation von Dysphagie und Fieber. Lediglich Ruborg et al. erhoben den Parameter Dysphagie direkt und zeigten eine unabhängige Korrelation von Dysphagie und

Körpertemperatur (Ruborg et al., 2017). Allerdings erfolgte in dieser Arbeit lediglich ein nicht näher spezifiziertes Schluckscreening und keine vollständige klinische Schluckuntersuchung oder eine apparative Diagnostik. In zwei weiteren Studien wurde das Vorliegen einer nasogastralen Sonde als Prädiktor für Fieber beschrieben, ohne dass in diesen Studien eine detaillierte Dysphagiediagnostik erfolgte (Muscari et al., 2015; Wästfelt et al., 2018). Da nasogastrale Sonden in der Regel bei Patienten mit schwerer Dysphagie oder Vigilanzminderung eingesetzt werden, stellt deren Verwendung vermutlich lediglich einen Surrogatparameter für ein erhöhtes Aspirationsrisiko dar.

Es war anzunehmen, dass eine gründliche Dysphagiestufendiagnostik mit klinischer Schluckuntersuchung unterstützt von apparativer Diagnostik bei der Prädiktion von Fieber hilfreich ist, und außerdem, dass eine frühe Erkennung von schwerer Dysphagie dabei helfen kann, Fieber nach einem Schlaganfall zu vermeiden und so möglicherweise das klinische Outcome zu verbessern. Ziel der Arbeit „Severe Dysphagia Predicts Poststroke Fever“ war es daher, Risikofaktoren von schlaganfallassoziiertem Fieber zu untersuchen und dabei insbesondere die Assoziation von Dysphagie und schlaganfallassoziiertem Fieber genauer zu prüfen.

2.3.4 Infektionen

Nach etwa einem Drittel aller akuten Schlaganfälle werden Infektionen beobachtet (Westendorp et al., 2011). Die häufigsten Infektionen sind dabei Pneumonien und Harnwegsinfekte.

Zu einer Pneumonie kommt es gemäß einer aktuellen Metaanalyse bei 12% aller Schlaganfallpatienten (Badve et al., 2019). Die in die Metaanalyse eingeschlossenen Studien zeichnen sich allerdings durch eine große Varianz der Pneumonieinzidenz aus (1,4 bis 56,8%). Dafür lassen sich verschiedene Gründe finden: Einerseits unterschieden sich die untersuchten Patientenkohorten hinsichtlich des Pneumonierisikos, z.B. allgemeine Schlaganfallkohorten gegenüber schwer betroffenen intensivpflichtigen Patienten, andererseits gab es Unterschiede in den Behandlungsstandards, wie z.B. der Implementation eines Dysphagiemanagements. Zudem kommt noch hinzu, dass hinsichtlich einer Pneumonie uneinheitliche Definitionen

genutzt werden. Um die Diagnose einer schlaganfallassoziierten Pneumonie zu harmonisieren, entwickelte die Pneumonia in Stroke Consensus Group (PISCES) 2015 standardisierte Kriterien zur Pneumoniediagnose bei Schlaganfallpatienten (Smith et al., 2015). Die Pneumonie hat einen maßgeblichen Einfluss auf das klinische Outcome: In einer Metaanalyse wurde für die Mortalität eine adjustierte Odds Ratio von 3,62 bei Vorliegen einer Pneumonie bestimmt; ebenso zeigte sich ein erhöhtes Risiko für ein schlechteres funktionelles Outcome (Westendorp et al., 2011). Hauptursache für die schlaganfallassoziierte Pneumonie ist die Dysphagie mit Aspirationsgefahr (Martino et al., 2005; Badve et al., 2019), jedoch gibt es auch Arbeiten, die auf eine schlaganfallinduzierte Immunodepression als Risikofaktor für eine Pneumonie hindeuten (Hoffmann et al., 2017).

Die Häufigkeit von Harnwegsinfekten nach Schlaganfall wird mit 8 bis 19% angegeben (Yan et al., 2018; Badve et al., 2019). Auch hier gibt es unterschiedliche Definitionen. Eine spezielle Definition für schlaganfallassoziierte Harnwegsinfekte existiert nicht. Die häufig herangezogenen Diagnosekriterien des amerikanischen Centers for Disease Control and Prevention sind für den klinischen Alltag nicht gut geeignet, da sie zu Surveillancezwecken für das öffentliche Gesundheitswesen entwickelt wurden (Centers for Disease Control and Prevention, National Healthcare Safety Network, 2022). In der bereits genannten Metaanalyse wurde keine erhöhte Mortalität in Verbindung mit schlaganfallassoziierten Harnwegsinfekten, jedoch ein schlechteres funktionelles Outcome festgestellt (Westendorp et al., 2011). Ursächlich sind in der Regel katheterassoziierte Infektionen, da transurethrale Blasenkatheter aufgrund einer neu aufgetretenen Urininkontinenz infolge des Schlaganfalls häufig zum Einsatz kommen.

Die Behandlung schlaganfallassoziierter Infektionen unterscheidet sich nicht im Wesentlichen von der Behandlung nicht schlaganfallassoziierter Infektionen. Einen Unterschied stellt jedoch das Keimspektrum bei der Pneumonie dar: Aufgrund der zugrundeliegenden Aspiration als Pathomechanismus sind meist Bakterien der oropharyngealen Flora ursächlich und nur sehr selten atypische Erreger, was bei der Antibiotikaauswahl Berücksichtigung findet. Aufgrund des häufigen Auftretens schlaganfallassoziierter Infektionen wurde in mehreren Studien

untersucht, ob eine prophylaktische Antibiotikatherapie Infektionen verhindern und das Outcome von Schlaganfallpatienten verbessern kann (Kalra et al., 2015; Westendorp et al., 2015). Ein relevanter Effekt der prophylaktischen Antibiotikagabe wurde jedoch nicht nachgewiesen, so dass diese nicht zum Behandlungsstandard gehört.

2.3.5 Sepsis

Schlaganfallassoziierte Infektionen können zu einer Sepsis führen. Unter einer Sepsis versteht man nach der aktuellen Sepsis-3 Definition eine lebensbedrohliche Organdysfunktion infolge einer Infektion, die mit einer hohen Morbidität und Mortalität einhergeht (Singer et al., 2016). Im Gegensatz zu Pneumonien und Harnwegsinfektionen wurde die schlaganfallassoziierte Sepsis bisher nur in einer Studie untersucht. Berger et al. stellten anhand einer Kohorte intensivpflichtiger Schlaganfallpatienten inklusive hämorrhagischer Schlaganfälle eine Sepsis in 12,6% der Fälle und eine Assoziation der Sepsis mit einem schlechten Outcome fest (Berger et al., 2014). Diese Ergebnisse sind allerdings nur begrenzt auf die klinische Praxis übertragbar, weil einerseits eine spezielle Patientenkohorte untersucht wurde und eine mittlerweile überholte Definition der Sepsis Anwendung fand.

Nach der Sepsis-3 Definition wird die für die Diagnose zentrale Organdysfunktion mit Hilfe des Sequential Organ Failure Assessment (SOFA)-Score festgestellt. Der SOFA-Score bewertet die Funktion von sechs Organsystemen (zentrales Nervensystem, Atmung, Herz-Kreislauf-System, Leber, Gerinnung, Niere) auf einer Skala von 0 bis 4 (Vincent et al., 1996). Ein Anstieg des SOFA-Scores von zwei Punkten über das Ausgangsniveau spricht bei Patienten mit einer Infektion für eine Sepsis (Singer et al., 2016). Der SOFA-Score wurde für intensivpflichtige Patienten entwickelt und beinhaltet mehrere Parameter, die in der Regel nur auf der Intensivstation erhoben werden, wie arterielle Blutgase oder die inspiratorische Sauerstofffraktion.

Als Screeninguntersuchung für eine Sepsis bei Patienten außerhalb der Intensivstation wurde der quick SOFA (qSOFA)-Score entwickelt (Seymour et al., 2016). Er beinhaltet mit der Bewusstseinslage, der Atemfrequenz und dem systolischen Blutdruck klinisch einfach bestimmbare Parameter. Da bei Schlaganfallpatienten insbesondere der Parameter

Bewusstseinslage durch den Schlaganfall selbst beeinträchtigt sein kann, war aber bisher unklar, inwieweit der qSOFA-Score die Diagnose einer schlaganfallassoziierten Sepsis valide unterstützen kann.

Ziel der Arbeit „Sepsis in Patients With Large Vessel Occlusion Stroke – Clinical Characteristics and Outcome“ war es daher die Häufigkeit, klinische Charakteristika sowie das Outcome der schlaganfallassoziierten Sepsis zu untersuchen und die prädiktive Validität des qSOFA-Scores nach Schlaganfall zu prüfen. Grundlage für diese Arbeit war eine Kohorte von Patienten mit einem Schlaganfall mit Verschluss eines großen hirnversorgenden Gefäßes, die am Universitätsklinikum Bonn mittels ET behandelt und in das GSR-ET-Register eingeschlossen wurden.

3 Ergebnisteil

3.1 Stösser et al., Cerebrovascular diseases 51: 45-51

In der Arbeit “Workflow Times and Outcome of Endovascular Therapy in Stroke Patients with Initial MRI or CT” wurden die Daten von 4638 Patienten, die aufgrund eines Schlaganfalls mit einem Verschluss eines großen Gefäßes mittels endovaskulärer Therapie behandelt und zwischen 2015 und 2019 in das multizentrische GSR-ET-Register eingeschlossen worden waren, analysiert. Davon wurden 370 (8,0%) Patienten vor der endovaskulären Therapie primär mittels MRT untersucht und die restlichen 4268 (92,0%) Patienten mittels CT.

Die MRT- und CT-Kohorten wurden hinsichtlich der Prozesszeiten von der Aufnahme des Patienten bis hin zur Rekanalisation des verschlossenen Gefäßes analysiert. Der Arbeitsablauf wurde dabei in folgende Zeitintervalle unterteilt: Aufnahme-Bildgebung, Bildgebung-Ankunft in der Angiographie, Ankunft in der Angiographie-Leistenpunktion, Leistenpunktion-Rekanalisation mit Flusswiederherstellung. Im Vergleich zu den CT-Patienten hatten MRT-Patienten eine signifikant längere mediane Zeit von Aufnahme bis zum Beginn der Bildgebung (23 versus 14 min, $p<0,001$). Die nachfolgenden Arbeitsschritte waren in nicht adjustierten Analysen bei MRT-Patienten ebenfalls verzögert, jedoch war in multivariablen Analysen festzustellen, dass nicht die Bildgebungsmodalität, sondern andere Störfaktoren die Unterschiede bei den nachfolgenden Arbeitsschritten zwischen beiden Gruppen bedingten. Das klinische Outcome nach 24 Stunden, bei Entlassung aus dem Krankenhaus sowie nach 90 Tagen unterschied sich in multivariablen adjustierten Analysen nicht signifikant zwischen MRT- und CT-Patienten.

Zusammenfassend verzögerte eine initiale Untersuchung mit MRT statt CT die Zeit von Aufnahme bis zum Beginn der Bildgebung im Arbeitsablauf der endovaskulären Schlaganfalltherapie, jedoch ohne Verzögerung der nachfolgenden Arbeitsschritte und ohne nachteiligen Effekt auf das klinische Outcome.

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Short title: Workflow and outcome of endovascular therapy after initial MRI

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Introduction: Treatment of patients with acute large vessel occlusion (LVO) stroke is highly time-dependent. Magnetic resonance imaging (MRI) and computed tomography (CT) are both used as primary neuroimaging modalities in these patients, which may be associated with differences in workflow times of endovascular therapy (ET), thus potentially affecting clinical outcome. We here aimed to compare workflow times and clinical outcome in a large cohort of patients initially examined by MRI or CT.

Methods: We analyzed patients who underwent ET between 2015 and 2019 and were enrolled into the prospective multicenter German Stroke Registry–Endovascular Therapy (GSR–ET). Patients who had an MRI prior to ET were compared to patients with a pretreatment CT regarding baseline data, in-hospital workflow times and clinical outcome.

Results: 370 out of 4638 patients were examined with an initial MRI (8.0%). Compared to patients with an initial CT, MRI patients had a longer median time from hospital admission to imaging acquisition (23 versus 14 min). All consecutive workflow times did not significantly differ between both groups after adjustment for confounders. Moreover, the clinical outcome did not differ between MRI and CT patients after adjustment for confounders.

Conclusion: In LVO stroke patients undergoing ET, pretreatment imaging with MRI instead of CT leads to a delay of imaging acquisition after hospital admission without having a measurable impact on consecutive workflow steps and clinical outcome.

Treatment of patients with LVO stroke is highly time-dependent [1]. Neuroimaging modalities provide information on infarct localization, volume and age, tissue at risk and vascular status reliably and rapidly [2–4]. These data are used to assign treatment with intravenous thrombolysis (IVT) and endovascular therapy (ET). MRI and CT can both be used as the primary neuroimaging modality in acute stroke patients, but they are both associated with different advantages und disadvantages [3]. CT has shorter scanning times, fewer contraindications and allows easier monitoring of unstable patients, while MRI provides more details on the localization, volume and age of the ischemic core [5, 6], but takes considerably longer than CT. These inherent characteristics of MRI and CT might be associated with differences in workflow times and clinical outcome in acute stroke patients.

Previous studies comparing workflow times and outcome of ET patients based on the initial imaging modality showed conflicting results: some studies reported longer in-hospital workflow times in MRI patients [7–9], while other studies reported only minor differences [10–13]. A difference in clinical outcome of MRI and CT patients was not observed in those studies. However, most of these studies were post-hoc analyses of prospective controlled ET trials featuring highly selected patient cohorts and relatively few MRI patients, potentially hampering the generalizability of these results to daily clinical practice.

The aim of this study was to compare workflow times and clinical outcome in a large cohort of patients initially investigated by MRI or CT.

All data analyzed in this study were derived from patients included in the German Stroke Registry–Endovascular Therapy (GSR-ET) between June 2015 and December 2019. The GSR-ET is an ongoing, open-label, prospective registry of 25 university and community hospitals in Germany enrolling consecutive patients with LVO stroke undergoing ET. A detailed description of the GSR-ET study design and a report of the main outcome of the patients included between June 2015 and April 2018 study have been published [14, 15].

Patients who had received either MRI or CT prior to treatment at the ET providing center (ETC) were included. Patients who were transferred to an ETC from another hospital and did not receive any pretreatment imaging at the ETC were excluded. Patients who had received both MRI and CT consecutively before ET at the ETC were also excluded, as were patients with missing data on the time of hospital admission and the modality and time of the qualifying neuroimaging study.

Workflow times were calculated based on the recorded time points of hospital admission, start of imaging acquisition, start of IVT and workflow steps of ET for each patient. In patients in whom the time of symptom onset to hospital admission (onset–admission) was not known, the estimated onset was defined as the halfway point of time between the time of last seen well and the time of recognition of symptoms. The MRI and CT cohorts were compared regarding baseline data, workflow times and clinical outcome parameters as described previously [14, 15]. Primary outcome measure was the proportion of patients with a score of 0 to 2 on the modified Rankin Scale (mRS) after 90 days. Secondary outcome measures included National Institutes of Health Stroke Scale (NIHSS) scores, the length of hospitalization, median mRS scores and mortality. mRS and NIHSS scores were prospectively collected by trained observers. Symptomatic intracranial hemorrhage was evaluated retrospectively according to the European Cooperative Acute Stroke Study (ECASS) II definition [16].

Statistical analyses were performed using the Statistical Package for Social Sciences version 25.0.0.0 (IBM SPSS Statistics, Armonk, N.Y., USA). Differences in metric data were assessed using Mann-Whitney U tests. Differences in frequencies were assessed using Pearson chi-square tests. Regression analyses were conducted using multivariable linear, logistic and ordinal models where appropriate. Multivariable analyses were adjusted for variables that showed significant differences between both cohorts in univariate analyses. All tests were 2-tailed. Statistical significance was determined at an α level of 0.05 in uni- and multivariate tests and at 0.01 for identifying independent predictors in multivariable regression analyses.

The data of 6635 patients enrolled into the GSR-ET between June 2015 and December 2019 were available. 1997 patients were excluded from the analysis according to the exclusion criteria (shown in Supplemental Fig. 1). Of the remaining 4638 patients, 370 (8.0%) were imaged by MRI before treatment at the ETC. 4268 (92.0%) patients had a pretreatment CT.

The baseline data of the MRI and CT cohorts are shown in Table 1. MRI patients were younger (median: 74 versus 76 years), less frequently had a history of dyslipidemia (27.6% versus 39.1%), atrial fibrillation (35.1% versus 41.8%) and smoking (19.3% versus 25.5%), and were on oral anticoagulation less often (16.4% versus 23.4%). At hospital admission, MRI patients had lower median NIHSS scores (13 versus 15). Onset-to-admission times were longer in MRI patients (median: 165 versus 78 min). In cases without known onset of symptoms, MRI patients had a significantly longer time of last seen well to admission (604 versus 372 min). The composite measure combining known onset–admission and estimated unknown onset–admission times was also significantly longer in MRI patients (247 versus 120 min). This difference may be overestimated as the MRI group

included significantly less patients with a known onset (42.2% versus 56.8%). Moreover, MRI patients were less often admitted primarily to the ETC (61.5% versus 75.4%). The neuroimaging protocols included angiography slightly less often in the MRI than CT group (91.4% versus 94.3%), while MR perfusion was performed more frequently than CT perfusion (76.1% versus 59.2%). The median Alberta stroke programme early CT (ASPECT)-score was lower in MRI patients (7 versus 9), which was expected based on the inherent differences of MRI- and CT-based ASPECT-scores [17]. IVT was initiated less often in MRI patients (45.2% versus 50.7%), and also less often at the ETC (47.2% versus 63.2%). Stroke etiology was more often due to large artery atherosclerosis (35.6% versus 23.8%) and less often due to cardioembolism (42.7% versus 52.7%) in MRI patients.

The workflow times are shown in Table 2 and illustrated in Supplemental Figure 2. All workflow times were significantly longer in MRI patients in univariate analyses except for the time of groin puncture to flow restoration. Multivariable adjusted linear regression analyses confirmed that workflow times depending on the time from admission to imaging were significantly longer in MRI patients except for the time of admission to IVT. In contrast, all workflow times that did not depend on the time of admission to imaging did not significantly differ between MRI and CT patients in multivariable analyses.

The influence of an initial MRI and other significant independent predictors on critical workflow times in multivariable analyses are reported in Figure 1. Primary MRI (instead of CT) was the main predictor of the time of admission to imaging (non-standardized β 11.13 min), whereas the only other significant predictor was the time of onset to admission (β 8.55 min per 5 h). The time of imaging to IVT was predicted by previous anticoagulation only (β 7.72 min). The time of imaging to arrival in the angio suite was predicted by the admission NIHSS (β -5.45 min per 10 points) and primary admission in the ETC (β 15.09 min). The time of arrival in the angio suite to groin puncture was predicted by primary admission in the ETC (β 3.12 min), general anesthesia (β 6.92 min) and a history of dyslipidemia (β -4.15 min). The time of groin puncture to flow restoration was predicted by atrial fibrillation only (β -5.17 min).

272 (73.5%) of all MRI patients were included by 3 out of 25 study sites. These centers each examined 57.2%, 19.6% and 12.1%, respectively, of their patients primarily by MRI. These patients had a shorter time from imaging to IVT (median: 16 versus 23 min), but a longer time from imaging to groin puncture (72 versus 61 min) and from arrival in the angio suite to groin puncture (30 versus 15 min; Supplemental table 1) when compared to centers that used MRI less often.

Clinical outcome parameters are shown in Table 3. In a multivariable adjusted logistic regression analysis, the proportion of patients with good functional outcome after 90 days was not significantly

different between MRI and CT patients (42.8% versus 37.2%). Further, there were no significant differences regarding secondary outcome parameters.

In this cohort of 4638 patients with LVO stroke undergoing ET, imaging with MRI prior to treatment led to a delayed time between hospital admission and imaging acquisition when compared to CT imaging, but did not delay subsequent workflow steps of IVT and ET after adjustment for confounders. The initial imaging modality did not have an impact on clinical outcome after adjustment for confounders.

The use of MRI for patients with suspected LVO stroke has potential advantages including more detailed information about the ischemic core than CT and may facilitate treatment of patients with an unknown or extended time of stroke onset [5, 6, 18]. In some countries, such as France, MRI is recommended as the primary imaging modality for patients with suspected stroke in national guidelines [10]. In our cohort reflecting the standard of stroke care in German university and community hospitals, MRI was used primarily in only 8.0% of patients. These patients were younger, had lower NIHSS scores and longer or unclear times of stroke onset to admission. This likely reflects an effort to subject these patients to a more informative imaging modality and to select patients with an unknown or extended time window for ET.

Our data show that MRI delayed the time from admission to imaging acquisition, but not the subsequent workflow steps of IVT and ET. Previous studies did not analyze each single workflow step, so the comparability to our data is limited. A registry-based analysis of patients treated from 2008 to 2015 also observed that the admission to imaging time was longer in MRI patients [8]. A post-hoc analysis of the THRACE trial demonstrated longer scanning times for MRI, but no delay of the later workflow steps [10]. The time of admission to imaging, however, was not investigated in that analysis.

There is evidence that ETCs with a high case volume may perform better in terms of workflow, reperfusion rate and even clinical outcome [19, 20]. Accordingly, centers with a higher MRI utilization rate had a shorter time from imaging to IVT than centers with a lower MRI utilization rate in our cohort.

Our analysis identified multiple other factors delaying ET after the initial imaging. The start of IVT was delayed in patients on oral anticoagulation, reflecting the time needed to perform coagulation tests or obtain a detailed history. The arrival at the angio suite after imaging took longer in patients who were primarily admitted to an ETC and who had lower NIHSS scores at admission; this likely reflects that more time to make a decision for ET is needed in those patients, consistent with previous

studies [13, 21–23]. The most important predictor of anesthesia time (represented by the time of angio suite arrival to groin puncture) was the type of anesthesia used (general versus conscious sedation) confirming previous studies [23, 24]. The ET procedure time (time of groin puncture to flow restoration) was shorter in patients with atrial fibrillation. A previous analysis of GSR-ET patients demonstrated that patients with atrial fibrillation had a higher rate of successful reperfusion and a lower number of retrieval attempts [25], consistent with our observation that atrial fibrillation is associated with shorter procedure times.

Importantly, the observed delays of workflow in MRI patients did not translate into a difference in clinical outcome. However, only a randomized trial would provide definitive evidence to the question if the delayed workflow in MRI patients impairs clinical outcome and how the potentially better selection of patients suitable for EVT by MRI affects clinical outcome.

The strengths of this study are a large cohort representing acute stroke care in German university and community hospitals. The main limitation is a potential selection bias as standards of care, decision making and workflow may differ between centers even if national guidelines are applied consistently.

In this registry-based cohort of 4638 patients with LVO stroke undergoing ET in German university and community hospitals, pretreatment imaging with MRI instead of CT led to a delayed time between admission and imaging acquisition, but did not delay subsequent workflow steps of IVT and ET and did not have an impact on clinical outcome after adjusting for confounders. Hence, MRI and CT can both effectively enable ET for patients with LVO stroke in routine stroke care if all relevant workflow steps are optimized.

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Data collection was centrally approved by the Ethics Committee of the Ludwig-Maximilian University Munich (689-15) and ethics committees or institutional review boards according to local regulations. Written consent was obtained from patients, if capable.

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S.S. and G.C.P. conceptualized and designed the study; all authors acquired and analyzed data; S.S. and G.C.P. drafted the manuscript, and all authors approved the final version.

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Supplemental Figures 1 and 2

Supplemental Table 1

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Fig. 1. Influence of initial magnetic resonance imaging (MRI) and other significant independent predictors of workflow times in multivariable analyses. The workflow steps and corresponding predictors are given on the left side; beta-coefficients for each predictor are represented in the diagram and given numerically on the right side. IVT indicates intravenous thrombolysis; OAC, oral anticoagulation; NIHSS, National Institutes of Health Stroke Scale score; ETC, endovascular therapy center; AF, atrial fibrillation.

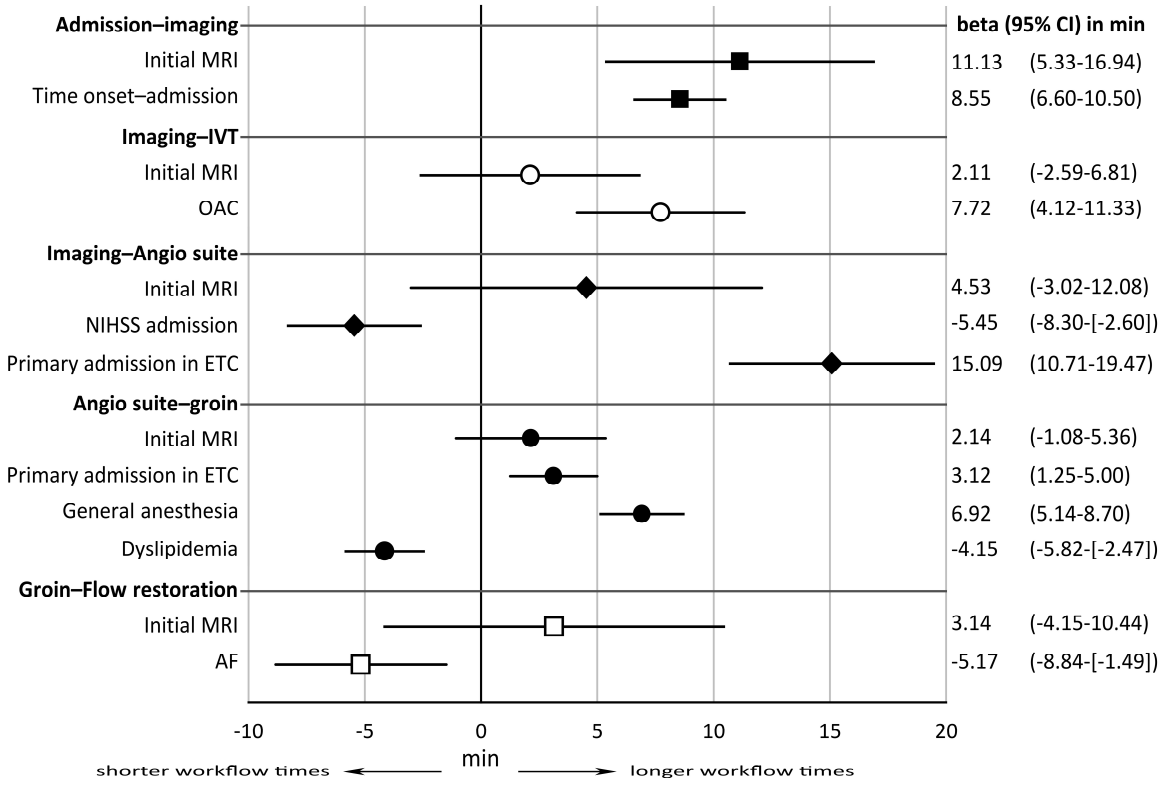

Table 1. Baseline data of endovascular therapy patients with an initial magnetic resonance imaging (MRI) or computed tomography (CT).

	MRI group % (n/N)	CT group % (n/N)	p
Demography and medical history			
Age, years, median (Q1-Q3)	74 (63-81)	76 (66-82)	0.001
Sex, female	49.5% (182/368)	50.8% (2167/4268)	0.628
Arterial hypertension	74.9% (263/351)	77.4% (3125/4038)	0.292
Diabetes mellitus	19.0% (67/353)	21.6% (870/4029)	0.251
Dyslipidemia	27.6% (97/351)	39.1% (1576/4026)	<0.001
Atrial fibrillation	35.1% (124/353)	41.8% (1683/4030)	0.015
Smoking	19.3% (65/337)	25.5% (957/3754)	0.012
Previous anticoagulation	16.4% (57/347)	23.4% (940/4010)	0.003
Premorbid modified Rankin Scale, median (Q1-Q3)	0 (0-1)	0 (0-1)	0.336
Admission status			
Admission National Institutes of Health Stroke Scale, median (Q1-Q3)	13 (8-17)	15 (9-19)	<0.001
Systolic blood pressure, mmHg	150 (134-170)	150 (133-170)	0.898
Diastolic blood pressure, mmHg	80 (70-92)	80 (72-93)	0.548
Onset of symptoms known	42.2% (156/370)	56.8% (2425/4268)	<0.001
Time onset–admission, minutes (median, Q1-Q3)	165 (64-274)	78 (50-168)	<0.001
Time last seen well–admission	604 (337-790)	372 (192-710)	<0.001
Time known/estimated unknown onset–admission	247 (135-403)	120 (60-251)	<0.001
Stroke Etiology			
Cardioembolism	42.7% (150/351)	52.7% (2113/4012)	<0.001
Large artery arteriosclerosis	35.6% (125/351)	1.6% (66/4012)	<0.001
Arterial dissection	2.6% (9/351)	0.1% (5/4012)	0.204
Small vessel occlusion	0% (0/351)	23.8% (954/4012)	0.509
Other determined	4.8% (17/351)	4.7% (190/4012)	0.879

Undetermined	14.2% (50/351)	17.0% (684/4012)	0.178
Pretreatment imaging			
MR or CT angiography	91.4% (309/338)	94.3% (3993/4234)	0.030
Perfusion imaging	76.1% (166/218)	59.2% (2500/4226)	<0.001
Occlusion: Middle cerebral artery	72.4% (268/370)	74.0% (3159/4268)	0.506
Intracranial internal carotid artery	20.0% (74/370)	19.9% (851/42689	0.978
Basilar Artery	9.7% (36/370)	10.0% (426/4268)	0.877
Other	7.8% (29/730)	6.6% (281/4268)	0.354
Occluded vessel side left	47.0% (174/370)	47.4% (2024/4268)	0.884
Alberta stroke program early CT score, median (Q1-Q3)	7 (6-8)	9 (7-10)	<0.001
Treatment			
Intravenous thrombolysis (IVT)	45.2% (166/367)	50.7% (2157/4251)	0.043
IVT in endovascular therapy center (ETC)	47.2% (102/216)	63.2% (1627/2573)	<0.001
Primary admission to ETC	61.5% (184/299)	75.4% (3035/4025)	<0.001
General anesthesia	72.2% (260/360)	73.3% (2982/4068)	0.657
Successful recanalization (final modified Thrombolysis In Cerebral Infarction scale 2b to 3)	82.8% (298/360)	84.1% (3516/4183)	0.527

Caption: n = absolute frequency, N = number of patients with available data.

Table 2. Workflow times from admission to flow restoration of endovascular therapy patients with initial magnetic resonance imaging (MRI) or computed tomography (CT).

Time interval in minutes	MRI group median (Q1-Q3)	CT group median (Q1-Q3)	p	adjusted p
Workflow times from admission				
Admission to imaging	23 (15-35)	14 (10-22)	<0.001	<0.001
Admission to IVT	40 (30-52)	29 (22-40)	<0.001	0.717
Admission to angio suite	69 (51-96)	48 (33-71)	<0.001	0.035
Admission to groin puncture	99 (75-128)	75 (57-102)	<0.001	0.016
Admission to flow restoration	148 (117-183)	125 (96-161)	<0.001	0.007
Workflow times from imaging				
Imaging to IVT	19 (12-29)	15 (9-24)	0.003	0.378
Imaging to angio suite	41 (30-56)	32 (20-52)	<0.001	0.239
Imaging to groin puncture	69 (54-94)	59 (42-82)	<0.001	0.082
Imaging to flow restoration	120 (94-154)	107 (81-141)	<0.001	0.053
Workflow times in angio suite				
Angio suite to groin puncture	28 (16-40)	25 (15-36)	0.002	0.193
Groin puncture to flow restoration	42 (27-69)	41 (26-65)	0.344	0.398

Caption: p-value adjusted for age, history of dyslipidemia, atrial fibrillation, smoking, previous anticoagulation, admission NIHSS, time (estimated) onset-admission, primary admission in ETC, IVT in ETC and general anesthesia.

Table 3. Clinical outcome of endovascular therapy patients with initial magnetic resonance imaging (MRI) or computedy tomography (CT).

	MRI group % (n/N)	CT group % (n/N)	adjusted p
24 hours follow up			
National Institutes of Health Stroke Scale (NIHSS), median (Q1-Q3)	9 (4-16)	10 (4-19)	0.815
Any intracranial hemorrhage	10.5% (39/370)	11.4% (487/4268)	0.732
Symptomatic intracranial hemorrhage	3.0% (11/370)	3.7% (158/4268)	0.473
Discharge follow up			
NIHSS, median (Q1-Q3)	5 (2-12)	5 (2-13)	0.947
Length of hospitalization, days, median (Q1-Q3)	9 (6-14)	9 (6-14)	0.546
Death	12.4% (43/304)	17.6% (700/3287)	0.271
90 days follow up			
Good outcome (modified Rankin Scale 0-2)	42.8% (131/306)	37.2% (1334/3583)	0.364
modified Rankin Scale, median (Q1-Q3)	3 (1-5)	4 (1-6)	0.502
Death	19.9% (61/306)	29.8% (1069/3583)	0.056

Caption: n = absolute frequency, N = number of patients with available data. p-value adjusted for age, admission NIHSS, time (estimated) onset–admission, IVT, primary admission in ETC, history of atrial fibrillation and previous anticoagulation.

3.2 Stösser et al., European journal of neurology 27, 2483-2490

In der Arbeit „Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis" wurde eine Kohorte von 891 Patienten, die aufgrund eines Hirnfarkts initial mittels MRT untersucht worden waren und anschließend eine IVT erhalten hatten, analysiert. Davon wurde bei 113 Patienten (11,3%) neben dem akuten Indexinfarkt zusätzlich ein rezenter klinisch stummer Hirninfarkt nachgewiesen (RSI+ Patienten). Bei den verbleibenden 868 Patienten zeigte sich lediglich der akute Indexinfarkt (RSI– Patienten).

In der Verlaufsbildgebung, die im Median 23 Stunden nach IVT erfolgte, zeigte sich eine hämorrhagische Transformation bei 32 (28,3%) der RSI+ Patienten und bei 56 (25,8%) der RSI– Patienten (p = 0,499 nach Adjustierung für bekannte Risikofaktoren einer hämorrhagischen Transformation). Die Verteilung der verschiedenen Schweregrade der hämorrhagischen Transformation nach der ECASS-II-Klassifikation unterschied sich ebenfalls nicht signifikant zwischen beiden Gruppe (p = 0,079 nach Adjustierung). Insbesondere traten relevante raumfordernde solide Einblutungen („parenchymal haemorrhage grade 2" gemäß der ECASS-II-Klassifikation) bei lediglich 2 (1,8%) der RSI+ Patienten und 11 (5,1%) der RSI– Patienten auf. Eine symptomatische intrazerebrale Blutung gemäß der SITS-MOST-Kriterien war bei 2 (1,8%) der RSI+ Patienten und bei 5 (2,3%) der RSI– Patienten festzustellen (p = 0,866 nach Adjustierung). Die klinischen Endpunktparameter National Institutes of Health Stroke Scale nach 24, 48 und 72 Stunden, modifizierte Rankin-Skala und Barthel-Index bei Entlassung sowie die Krankenhaussterblichkeit wiesen keine signifikanten Unterschiede zwischen beiden Gruppen auf.

Zusammenfassend war das MR-tomographische Vorliegen von rezenten klinisch stummen Hirninfarkten bei Patienten, die aufgrund eines akuten Hirninfarkt mittels IVT behandelt wurden, nicht mit einem erhöhten Risiko einer hämorrhagischen Transformation oder einem schlechteren klinischen Outcome assoziiert.

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Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis

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Short Title: Recent infarcts and haemorrhage after IVT

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Abstract

Background: Haemorrhagic transformation (HT) is one of the main risks of intravenous thrombolysis (IVT) for acute ischemic stroke. Contraindications serve to exclude patients at high risk of HT after IVT. One of these contraindications is a stroke within the preceding 3 months. It is unclear if this contraindication should include recent clinically silent infarcts (RSI). The aim of this study was to investigate whether RSI are associated with a higher risk of HT and a worse clinical outcome after IVT for acute ischemic stroke.

Methods: In a retrospective monocentric cohort study, all patients who received IVT for acute ischemic stroke based on magnetic resonance imaging (MRI) were assessed over 5 years. RSI were defined as lesions with diffusion restriction and positive signal on fluid attenuated inversion recovery sequences (FLAIR). Patients with RSI (RSI+) were compared to patients without RSI (RSI–) regarding HT after IVT and clinical outcome.

Results: 981 patients who had received IVT for acute ischemic stroke demonstrated by MRI were identified. RSI were detected in 115 patients (11.5%). HT after IVT was observed in 32 (28.3%) RSI+ and 56 (25.8%) RSI– patients (p=0.624). Symptomatic intracerebral haemorrhage was noted in 2 (1.8%) RSI+ and 5 (2.3%) RSI– patients (p=1.000). No differences in clinical outcome were observed.

Conclusions: The detection of RSI in patients treated with IVT for acute ischemic stroke was not associated with a higher risk of HT or a worse clinical outcome. The results of this study argue against considering RSI as a contraindication for IVT.

Introduction

Intravenous thrombolysis (IVT) is the standard therapy for acute ischemic stroke[1,2]. The main risk of this therapy is intracranial haemorrhage. Contraindications for IVT are supposed to exclude patients with an excessively high risk of haemorrhagic transformation. One of these contraindications is a recent stroke in the preceding 3 months, based on pathophysiological considerations and on the exclusion criteria of phase III trials for IVT[3,4]. A recent stroke can either be confirmed by a clinical event with overt symptoms lasting longer than 24 hours (i.e. stroke in the strict sense) or by the evidence of a recent ischemic infarct on cerebral imaging without a history of overt symptoms, a so-called silent infarct[5]. Recent ischemic lesions are observed more often on magnetic resonance imaging (MRI) than on computed tomography[6–8]. Patients with small recent ischemic lesions that may be detected on MRI, but not on computed tomography were not excluded from CT based IVT trials per protocol. It is, therefore, unclear if the presence of recent clinically silent infarcts (RSI) on MRI should be considered as a contraindication for IVT. Previous MRI-based studies suggested that RSI are frequent (11.6% to 18.3%) and that their presence does not increase the risk of haemorrhagic transformation after IVT, but those studies were limited by small study populations[9,10].

The use of MRI for acute stroke patients might increase in the future. Compared to computed tomography, MRI offers more information about lesion localisation and age as well as a higher sensitivity for smaller, silent or posterior circulation infarcts[6,7]. Furthermore, the use of MRI might increase to provide IVT to patients with wake up stroke or stroke with an extended time window[11,12]. Following a higher utilization of MRI in acute stroke treatment, detection of RSI will become increasingly frequent and neurologists will more often have to face the dilemma whether IVT is safe in these patients. However, conclusive evidence for this situation is lacking.

The aim of this study was to investigate whether the presence of RSI on MRI was associated with an increased risk of haemorrhagic transformation or worse clinical outcome in acute stroke patients who received IVT.

Materials and Methods

Study cohort

All patients with a diagnosis of ischemic stroke who received IVT at the Department of Neurology, University Hospital of Ulm, RKU, Germany, between January 2013 and September 2018 were retrospectively identified via diagnostic and procedural code. MRI was the principal neuroimaging

modality in all stroke patients. Patients who had received an MRI immediately after admission before IVT and follow-up neuroimaging after IVT (MRI or CT) were included into the study. Exclusion criteria were missing imaging data, motion artefacts confounding imaging analysis, no evidence of an acute infarct on the initial MRI (to exclude patients with potential stroke mimics) and clinically symptomatic ischemic stroke or transient ischemic attack within the last three months prior to admission. Medical history was carefully reviewed to ensure recent ischemic lesions were clinically silent. In patients who were not able to give a reliable medical history a third party medical history by a caretaker was taken into account. IVT was conducted with alteplase at a standard dosage of 0.9 mg per kg bodyweight in all cases. The study protocol was approved by the local Ethics Committee of the University of Ulm, Germany (protocol number 38/19).

Clinical and laboratory data

Clinical and laboratory data and medical history were collected by chart review. The National Institutes of Health Stroke Scale (NIHSS) after 24, 36 and 72 hours, the modified Rankin Scale (mRS) and the Barthel Index (BI) at hospital discharge as well as death during hospitalization were used as clinical outcome measures[13–15]. The NIHSS and BI scores had been evaluated by a trained clinician and trained nurse respectively during the hospitalization of each patient and were collected by chart review. The mRS grades were evaluated retrospectively based on the neurological status documented at discharge and the scores on relevant categories of the Barthel Index (e.g. walking).

Imaging analysis

MRI were acquired using a clinical 1.5 Tesla MR scanner (Magnetom TIM Symphony, Siemens, Erlangen, Germany) equipped with a standard 12-channel head coil. Follow-up CT imaging was acquired using a clinical 16 slice CT scanner (Somatom Emotion 16, Siemens, Erlangen, Germany). The MRI protocol included transversal diffusion weighted imaging (DWI), transversal or coronal fluid attenuated inversion recovery sequences (FLAIR) and a transversal gradient recalled echo sequence (T2*w) in all cases. Imaging analysis was conducted using an in-house PACS system (Centricity PACS-IW, version 3.7.3.9078, General Electrics Healthcare, Milwaukee, USA). Recent infarcts were identified on MRI as lesions with restricted diffusion (i.e. hyperintense signal on isotropic b1000 and hypointense signal on ADC maps) and hyperintense FLAIR signal, distinct from the acute index infarct with restricted diffusion and no signal change on FLAIR. This MRI signal pattern is usually observed between 6 hours to 10 days after the onset of an ischemic infarct[16–18].

Localisation of ischemic lesions and haemorrhagic transformation were determined. Haemorrhagic transformation was classified using established criteria[19]. Symptomatic intracranial haemorrhage

(sICH) was determined using several definitions according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST), the European Cooperative Acute Stroke Study II (ECASS-II), the National Institutes of Neurological Disorders and Stroke (NINDS) trial and the Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) trial[4,20–22]. RSI lesion volumes were estimated using the ABC/2 formula[23]. Imaging analysis was conducted by a board-certified neurologist with experience in stroke imaging (S.S.) The detection of RSI and the classification of haemorrhagic transformation was reviewed by an experienced board-certified senior neuroradiologist (M.S.) The first 20 cases were analysed together, the remaining cases were analysed independently and in a blinded fashion by both observers.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences version 25.0 (IBM SPSS Statistics, Armonk, N.Y., USA). Differences in metric data between groups were assessed using Mann–Whitney U tests. Differences in frequencies between groups were assessed using Pearson chi-square or Fisher's exact test where appropriate. Multivariate analyses were performed using binominal, multinominal or ordinal regression analyses where appropriate. Interrater agreement was assessed using Cohen's Kappa coefficient. All tests were 2-tailed. Statistical significance was determined at an α level of 0.05. In case of multiple testing a Bonferroni correction was used to determine the level of significance.

Results

A total of 1276 patients who received IVT for acute ischemic stroke in the study period were identified. 146 patients were excluded because the pretreatment imaging modality was CT. 28 patients were excluded due to recent symptomatic stroke or TIA. 96 patients were excluded because no acute infarct was identified on neuroimaging (potential stroke mimics). 19 patients were excluded due to motion artefacts. 4 patients were excluded due to missing data. 2 patients were treated twice in the study period, the former admission was excluded for each of those patients. Thus, a total of 981 patients who received IVT for acute ischemic stroke demonstrated by MRI remained according to the inclusion criteria. Among those, 113 patients (11.3%) were observed to have had a recent silent infarct in addition to the acute index infarct. These patients constituted the cohort RSI+. The remaining 868 patients had one acute index infarct (or more) on MRI, but no evidence of recent infarcts on MRI. Among those, every fourth patient (by admission date) was included into the control cohort RSI– (n=217).

The clinical and laboratory baseline data as well as procedural data of the treatment of the two study cohorts are shown in table 1. Significant differences in baseline data between the two cohorts were observed for the following parameters: First, systolic blood pressure after IVT was higher in RSI+ compared to RSI– patients (2 hours after IVT, mmHg: RSI+ 150 (145-165), RSI– 145 (130-160), p=0.025; after 4 hours: RSI+ 150 (135-165), RSI– 145 (126-160), p=0.009; after 6 hours: RSI+ 145 (135-160), RSI– 140 (125-155), p=0.001). Mean arterial pressure was higher in RSI+ patients after 6 hours (RSI+ 100 (90-110), RSI– 95 (87-107), p=0.010). Second, serum glucose at admission was significantly higher in RSI+ than in RSI– patients (median (IQR), mmol/l: RSI+ 6.97 (5.80-8.63), RSI– 6.50 (5.68-7.86), p=0.022). A history of diabetes mellitus was significantly more frequent in RSI+ than in RSI– patients (RSI+ n=27 (23.9%), RSI– n=32 (14.7%), p=0.040).

The distribution of acute index ischemic infarcts according to vascular territory was significantly different for both cohorts (p<0.001). Multiple comparisons revealed that index infarcts in RSI+ patients were significantly more often localised in both anterior and posterior circulation as compared to anterior or posterior circulation alone than in RSI– patients (p<0.001 for anterior circulation and p=0.01 for posterior circulation). The distribution of lesions according to vascular territory was significantly different for RSI compared to index infarcts (p=0.002). Multiple comparisons revealed that RSI were significantly more often localised in the posterior than in the anterior circulation (p<0.001). Detailed data on infarct localisation are reported in supplemental table 1. RSI lesion volumes were small indicated by a median diameter of 0.92 cm (IQR: 0.64-1.39) and a median estimated volume of 0.20 ml (0.07-0.60).

Follow-up imaging was conducted after a median of 23:00 hours:minutes (IQR: 16:25-26:54) after the start of IVT in RSI+ and after a median of 23:02 hours:minutes (IQR: 17:24-25:48) in RSI– patients (p=0.644). The imaging modality for the follow-up was MRI in 101 (89.4%) RSI+ and in 179 (82.5%) RSI– patients (p=0.098). The remaining patients received a CT scan for follow-up imaging.

The characteristics of the follow up imaging and the clinical outcome are reported in table 2. Haemorrhagic transformation on follow-up imaging after IVT occurred in 32 (28.3%) RSI+ patients and in 56 (25.8%) RSI– patients (p=0.624). Analysis of the subtypes of haemorrhagic transformation according to the ECASS-II study revealed no significant differences between RSI+ and RSI– patients (p=0.247). The interrater reliability for the raters was observed to be Kappa=0.72. Haemorrhagic transformation occurred mainly into the acute index infarct (RSI+ n=19 (59.4%), RSI– 43 (76.8%), p=0.078). It should be noted that only one RSI+ patient suffered from haemorrhagic transformation of the recent infarct (3.1% of all RSI patients).

Taking the clinical outcome into account, symptomatic intracranial haemorrhage (sICH) according to the SITS-MOST definition was observed in 2 (1.8%) RSI+ and 5 (2.3%) RSI– patients, which did not constitute a significant difference (p=1.000). The rates of sICH according to the ECASS-II, NINDS and PROACT-II definitions were also similar in RSI+ and RSI– patients (ECASS-II: RSI+ 2 (1.8%), RSI– 6 (2.8%), p=0.720; NINDS: RSI+ 10 (8.8%), RSI– 16 (7.4%), p=0.637; PROACT-II: RSI+ 3 (2.7%), RSI– 8 (3.7%), p=0.683).

NIHSS scores after IVT did not differ significantly between both cohorts (median (IQR), after 24 hours: RSI+ 3.5 (2-9), RSI– 4 (1-11), p=0.899, after 36 hours: RSI+ 3.5 (1-7), RSI– 3 (1-10), p=0.707; after 72 hours: RSI+ 2 (1-6), RSI– 3 (1-8), p=0.898). No significant differences were noted for mRS scores (RSI+ 3 (3-4), RSI– 3 (3-4), p=0.625) and Barthel index at hospital discharge (RSI+ 62.5 (15-95), RSI– 65 (15-95), p=0.733). In-hospital mortality was similar in both groups (RSI+ n=6 (5.3%), RSI– n=13 (6.0%), p=0.808). Multivariate analyses adjusted for age, admission NIHSS, endovascular treatment, history of diabetes mellitus, serum glucose at admission, systolic blood pressure after 6 hours were performed for each imaging and clinical outcome parameter to account for possible confounders. The clinical outcome parameters did not differ significantly between both cohorts in multivariate analyses (see adjusted p values in table 2).

Imaging and clinical outcome parameters were analysed separately for the subgroup of patients who received endovascular therapy. The data are shown in supplemental table 2. Briefly, no significant differences in outcome were observed between both cohorts, but the analysis was limited by small numbers of patients (RSI+ n=17, RSI– n=41).

Discussion

Multiple contraindications for IVT, which originated from the exclusion criteria of the phase III IVT trials[4,20], have been challenged by recent studies, such as age and onset-to-treatment time[11,12,24]. With an increased use of MRI in the diagnostics of acute stroke, recent silent infarcts accompanying the acute index stroke are frequently observed. Although “stroke within previous 3 months” is a contraindication for IVT, the results of this retrospective cohort study show that patients with RSI do not seem to have a higher risk of haemorrhagic transformation or a worse clinical outcome when treated with IVT for acute ischemic stroke as compared to patients without RSI.

The medical history, the clinical and laboratory baseline data as well as the procedural data of neuroimaging and acute stroke treatment were overall similarly distributed between the two cohorts. Significant differences, however, were noted for serum glucose at admission, history of

diabetes mellitus and systolic blood pressure, which were higher or more frequent, respectively, in RSI+ patients. Hyperglycemia and high blood pressure are associated with an increased risk of haemorrhagic transformation after IVT[25–29]. According to this, the risk of haemorrhagic transformation should have been higher in the RSI+ cohort. Since a higher risk of haemorrhagic transformation was not observed in RSI+ patients compared to RSI– patients, the differences in serum glucose and blood pressure are unlikely to cause a bias with regard to the primary hypothesis of this study.

The rate of RSI in our screening sample was 11.8%, which is similar to the study of Gaillard et al. (11.6%), but lower than in the study of Tisserand et al. (18.3%)[9,10]. Furthermore, the MRI analysis revealed that the acute index infarct was more often characterized by multiple lesions and localised in multiple arterial territories in RSI+ patients than in RSI– patients. Thus, ischemic events were more disseminated temporally and spatially in RSI+ patients than in RSI– patients. This could reflect a more active source of ischemia, e.g. an active cardiac embolic source or active instable arteriosclerotic plaques[30,31], even though large artery atherosclerosis and cardioembolism were not observed more frequently in RSI+ patients than in RSI– patients. On the other hand, RSI were more often localised in the posterior than in the anterior circulation. Posterior circulation stroke has been associated with diabetes mellitus, arterial hypertension and small-vessel occlusion[32–35]. Corresponding to that, diabetes mellitus and higher blood pressure at admission was observed more frequently in the RSI+ cohort, and the lesion volume of RSI was small, which would point to small vessel disease as most common aetiology of RSI.

The rates of sICH after IVT were not significantly different between both cohorts. This confirms the observation of Tisserand et al. and Gaillard et al., who observed low frequencies of sICH after IV in similar, but significantly smaller cohorts[9,10]. The rate of sICH in this study cohort were very similar to the one reported in the SITS-MOST registry (1.7%)[20]. The rate of any HT in this study cohort was 26.7% as expected from previous studies using MRI as principal follow up neuroimaging, e.g. Caparros et al. observed an HT rate of 29.7% in a cohort of 944 IVT patients[36].

The radiographic severity based on the ECASS-II imaging criteria and the localisation of haemorrhagic transformation after IVT did not differ between RSI+ and RSI– patients. Haemorrhagic transformation was most often localised in the acute index infarct. Interestingly, haemorrhage into an RSI was observed in only one case. Infarcts localised in the posterior circulation and caused by small-vessel disease seem to have a lower risk of haemorrhagic transformation[37,38]. As RSI were more often localised in the posterior circulation and potentially caused by small-vessel disease as discussed

above, this might explain why haemorrhage into an RSI was observed in only case. This emphasizes that RSI do not seem to convey a high risk of haemorrhage after IVT.

The main limitation of this study is the lack of information about how many patients with acute ischemic stroke and RSI were not treated by IVT. This subgroup might reflect patients who were not treated by IVT because it was clinically suspected that the individual risk of haemorrhagic transformation outweighed the potential benefit of IVT. As these patients were not included in our analysis, the observed low risk of haemorrhagic transformation after IVT in RSI+ patients might be biased. Thus, conclusions from this study about the entirety of RSI+ patients have to be drawn carefully.

The strengths of this study are a sizeable sample size of unselected "real life" patients and that MRI was the principal neuroimaging modality for all patients with suspected stroke, which minimizes selection bias for an MRI based study.

In summary, the results of this retrospective study suggest that RSI are not associated with a higher risk of haemorrhagic transformation or a worse clinical outcome after IVT for acute ischemic stroke. As a consequence, the contraindication "recent stroke in the preceding 3 months" for IVT needs to be questioned. Based on the results of this study and the two smaller preceding studies[9,10], IVT should not be withheld from patients with acute ischemic stroke and evidence of RSI on neuroimaging. Randomized trials are needed to prove this assumption and determine if IVT is of favor in unselected patients with RSI. The contraindication "recent stroke in the preceding 3 months" also excludes patients with recent clinically symptomatic stroke from IVT. This subgroup of patients was not addressed in the current study and might potentially have a higher risk of haemorrhagic transformation than stroke patients with RSI. Another important subgroup are patients with silent, but radiographically extensive infarcts. Although large infarcts are rarely clinically silent, this subgroup might have a higher risk of haemorrhagic transformation than the present study cohort[39,40]. Further studies are needed to address these groups of patients.

Conclusions

In this retrospective study, the detection of recent silent infarcts in 981 patients treated with IVT for acute ischemic stroke was not associated with a higher risk of haemorrhagic transformation or a worse clinical outcome. Recent silent infarcts should not be considered a contraindication for IVT based on the results of this study. Randomized trials are needed to prove this assumption and determine if IVT is of favor in unselected patients with recent silent infarcts.

Statements

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Statement of Ethics

The study protocol was approved by the local Ethics Committee of the University of Ulm, Germany.

Disclosure Statement

The authors have no conflicts to declare.

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Author contributions

S.S.: design of the study, interpretation and analysis of data, writing the manuscript. L.U.: acquisition, analysis and interpretation of data. J.K.: interpretation of data, revising the manuscript. A.C.L.: revising the manuscript. M.S.: analysis of data, revising the manuscript. H.N.: design of the study, interpretation of data, revising the manuscript.

Data availability statement

Data available on request from the authors.

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Tables

Table 1. Clinical and laboratory baseline data of patients

	RSI+ n=113	RSI− n=217	p value
Age, years, median (IQR)	75 (68-83.5)	76 (66-84)	0.954
Sex, female, n (%)	52 (46)	103 (47.5)	0.803
Medical History, n (%)			
Arterial Hypertension	85 (75.2)	162 (74.7)	0.910
Diabetes mellitus	27 (23.9)	32 (14.7)	**0.040**
Hypercholesterolemia	26 (23)	50 (23)	0.995
Smoking	25 (22.1)	33 (15.2)	0.117
Atrial fibrillation	35 (31.0)	81 (37.3)	0.251
Coronary artery disease	19 (16.8)	40 (18.4)	0.716
Peripheral artery disease	9 (8.0)	8 (3.7)	0.095
Previous cerebral ischemia	21 (18.6)	45 (20.7)	0.643
Previous intracerebral haemorrhage	0 (0)	2 (0.9)	0.548
Antiplatelet use	41 (36.3)	94 (43.3)	0.217
Anticoagulant use	7 (6.2)	15 (6.9)	0.804
Statin use	38 (33.6)	57 (26.3)	0.161
Vital signs on admission, median (IQR)			
Systolic blood pressure, mmHg	160 (145-175)	155 (140-170)	0.168
Diastolic blood pressure, mmHg	85 (70-95)	85 (70-95)	0.582
Mean blood pressure, mmHg	110 (98-123)	107 (97-119)	0.274
Heart rate, bpm	80 (68-88)	80 (70-88)	0.830
Body temperature, °C	36.4 (36.1-36.8)	36.6 (36.2-36.8)	0.472
After 1 hour			
Systolic blood pressure, mmHg	155 (135-165)	150 (130-165)	0.121
Diastolic blood pressure, mmHg	80 (70-90)	80 (70-90)	0.595
Mean blood pressure, mmHg	103 (93-115)	103 (93-113)	0.289
After 2 hours			
Systolic blood pressure, mmHg	150 (140-165)	145 (130-160)	**0.025**
Diastolic blood pressure, mmHg	80 (70-90)	80 (70-85)	0.366
Mean blood pressure, mmHg	103 (94-113)	102 (90-110)	0.073

After 4 hours			
Systolic blood pressure, mmHg	150 (135-165)	145 (126-160)	**0.009**
Diastolic blood pressure, mmHg	75 (70-85)	75 (65-84)	0.432
Mean blood pressure, mmHg	100 (92-112)	98 (87-108)	0.065
After 6 hours			
Systolic blood pressure, mmHg	145 (135-160)	140 (125-155)	**0.001**
Diastolic blood pressure, mmHg	78 (70-85)	75 (65-85)	0.148
Mean blood pressure, mmHg	100 (90-110)	95 (87-107)	**0.010**
Stroke assessment and treatment			
NIHSS on admission, median (IQR)	5 (3-10)	6 (3-13)	0.697
Door-to-needle-time, min	36 (27-50)	35 (25-49)	0.515
Onset-to-needle-time, min	120 (93.5-180)	120 (90-180)	0.913
IVT within 4.5 h after onset, n (%)	106 (93.8)	192 (88.5)	0.121
IVT after 4.5 h after onset or unknown onset, n (%)	7 (6.2)	25 (11.5)	0.121
Endovascular treatment, n (%)	17 (15)	41 (19)	0.374
Aetiology: symptomatic stenosis or occlusion	19 (16.8)	25 (11.5)	0.179
Aetiology: cardioembolism	43 (38.1)	86 (39.6)	0.780
Laboratory characteristics on admission, median (IQR)			
Leukocyte count, G/l	7.7 (6.6-9.7)	8.0 (6.4-9.4)	0.694
Thrombocyte count, G/l	224 (195-292)	231 (193-285)	0.835
International normalized ratio (INR)	1.03 (0.96-1.11)	1.03 (0.98-1.09)	0.427
activated partial thromboplastin time (aPTT), s	28.2 (25.5-31.4)	28.5 (26.1-30.9)	0.532
C-reactive protein, mg/l	4.4 (1.9-10.1)	4.0 (1.8-10.7)	0.828
Creatinin, µmol/l	85 (73-106)	82 (71-102)	0.372
Urea, mmol/l	6.78 (5.33-8.79)	6.39 (5.18-8.16)	0.291
Serum glucose, mmol/l	6.97 (5.80-8.63)	6.50 (5.68-7.86)	**0.022**
Haemoglobin A1c, %	5.7 (5.4-6.2)	5.6 (5.4-6.0)	0.230

Caption Table 1: cohorts with (RSI+) and without (RSI−) recent silent infarcts, IQR = interquartile range, NIHSS = National Institutes of Health Stroke Scale, IVT = intravenous thrombolysis. Bold value indicates $p<0.05$.

Table 2. Characteristics of the follow up imaging and clinical outcome

	RSI+ n=113	RSI− n=217	p value / adjusted p value
Haemorrhagic transformation present, n (%)	32(28.3)	56 (25.8)	0.624 / 0.499
Classification of HT (ECASS-II), n (%)			overall 0.247 / 0.079
None	81 (71.7)	161 (74.2)	
Haemorrhagic infarction grade 1	13 (11.5)	21 (9.7)	
Haemorrhagic infarction grade 2	10 (8.8)	19 (8.8)	
Parenchymal haemorrhage grade 1	2 (1.8)	3 (1.4)	
Parenchymal haemorrhage grade 2	2 (1.8)	11 (5.1)	
Subarachnoid haemorrhage	5 (4.4)	2 (0.9)	
Localisation of HT, n (%)	N=32	N=56	overall 0.078 / 0.262
Index infarct	19 (59.4)	43 (76.8)	
RSI	1 (3.1)	0 (0)	
Remote	4 (12.5)	9 (16.1)	
Multiple sites	3 (9.4)	2 (3.6)	
Subarachnoid haemorrhage	5 (15.6)	2 (3.6)	
sICH present, n (%)			
SITS-MOST definition	2 (1.8)	5 (2.3)	1.000 / 0.866
ECASS-II definition	2 (1.8)	6 (2.8)	0.720 / 0.724
NINDS definition	10 (8.8)	16 (7.4)	0.637 / 0.682
PROACT-II definition	3 (2.7)	8 (3.7)	0.683 / 0.583
NIHSS, median (IQR)			
After 24 hours	3.5 (2-9)	4 (1-11)	0.899 / 0.244
After 36 hours	3.5 (1-7)	3 (1-10)	0.707 / 0.148
After 72 hours	2 (1-6)	3 (1-8)	0.898 / 0.386
mRS at discharge, median (IQR)	3 (3-4)	3 (3-4)	0.625 / 0.836
Barthel index at discharge, median (IQR)	62.5 (15-95)	65 (15-95)	0.733 / 0.822
Death during hospitalization, n (%)	6 (5.3)	13 (6)	0.808 / 0.413

Caption Table 2: cohorts with (RSI+) and without (RSI−) recent silent infarcts, adjusted p values according to multivariate logistic regression analyses (adjusted for age, admission NIHSS, endovascular treatment, history of diabetes mellitus, serum glucose at admission, systolic blood

pressure after 6 hours), HT = haemorrhagic transformation, ECASS-II = European Cooperative Acute Stroke Study II, sICH = symptomatic intracranial haemorrhage, SITS-MOST = Safe Implementation of Thrombolysis in Stroke-Monitoring Study National Institutes of Neurological Disorders and Stroke (NINDS), PROACT II = Prolyse in Acute Cerebral Thromboembolism II, NIHSS = National Institutes of Health Stroke Scale, IQR = interquartile range, mRS = modified Rankin Scale.

3.3 Stösser et al., Stroke 52: 2284-2291

In der Arbeit “Severe Dysphagie Predicts Poststroke Fever“ wurde eine monozentrische Kohorte von 923 Patienten, die innerhalb eines Jahres aufgrund eines akuten ischämischen oder hämorrhagischen Schlaganfalls stationär behandelt wurden, untersucht. In der Kohorte wurde bei 127 (13,8%) der Patienten Fieber (>38,0°C) festgestellt. Die Fieberinzidenz war am zweiten Tag der Behandlung am höchsten. Eine Infektion lag dem Fieber bei 78 (61.4%) der Patienten zugrunde.

Eine detaillierte Analyse der Items der klinischen Schluckuntersuchung zeigte, dass Patienten mit Fieber im Vergleich zu Kontrollen ohne Fieber häufiger eine Dysphagie aufwiesen. Beispielhaft sind die medianen Werte der Schluckbeeinträchtigungsskala (Patienten mit Fieber: 6 [Q1-Q3: 4-6]; Kontrollen ohne Fieber: 0 [0-6]) sowie das Vorliegen von zwei oder mehr Dysphagieprädiktoren nach Daniels (Patienten mit Fieber: 78,8%; Kontrollen ohne Fieber: 42,2%) zu nennen. Eine Untergruppe von 264 Patienten, bei denen die klinische Schluckuntersuchung keine eindeutige Klassifikation des Aspirationsrisikos erlaubte, wurden mittels FEES untersucht. Hier wurde bei Fieberpatienten signifikant häufiger eine Aspiration nachgewiesen (22,2% gegenüber 10,0% der Kontrollen).

Mittels multivariabler logistischer Regressionsanalysen wurde untersucht, welche der in der Literatur beschriebenen Prädiktoren, das Auftreten von Fieber in der Kohorte unabhängig vorhersagten. Eine mittel- bis schwergradige Dysphagie in der klinischen Schluckuntersuchung war dabei der stärkste unabhängige Prädiktor für Fieber (Odds Ratio 3,05 [95% Konfidenzintervall: 1,65-5-66]). Weitere unabhängige Prädiktoren waren das Vorhandensein eines Blasenkatheters (2,03 [1,13-3,65]) sowie ein höherer Wert auf der National Institutes of Health Stroke Scale, die die Schlaganfallschwere widerspiegelt, zum Aufnahmezeitpunkt (1,06 pro Punkt [1,01-1,11]). Andere vorbeschriebene Prädiktoren wie das Vorhandensein einer Magensonde, Vorhofflimmern und Alter sagten in der Analyse Fieber nicht unabhängig vorher. Zusammenfassend wurde in dieser Arbeit der Zusammenhang von Dysphagie und Fieber erstmalig anhand eines detaillierten Schluckassessments gezeigt.

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Severe dysphagia predicts post-stroke fever

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Abstract

Background and Purpose: Fever is a common observation after ischemic or hemorrhagic stroke and is associated with a worse clinical outcome. Infections, stroke severity, preexisting medical conditions, insertion of catheters and dysphagia have been implicated in causing post-stroke fever. Given that dysphagia has not been evaluated in detail yet, the aim of this study was to investigate if the severity of dysphagia assessed by a detailed swallowing assessment predicts post-stroke fever.

Methods: In this retrospective monocentric cohort study, all patients admitted for ischemic or hemorrhagic stroke within 12 months were included. Patients underwent a detailed standardized swallowing assessment including a clinical exam by a speech therapist and fiberoptic endoscopic evaluation in a subset of patients. Patients who developed fever within 5 days were compared to patients without fever regarding swallowing parameters and other clinical characteristics relevant for the prediction of post-stroke fever.

Results: 923 patients with acute ischemic or hemorrhagic stroke were included. 127 (13.8%) patients developed fever. In multivariable analyses, fever was independently predicted by moderate-to-severe dysphagia in clinical assessments (odds ratio [95% confidence interval] 3.05 [1.65-5.66]) and also by dysphagia with proven risk of aspiration as a combined endpoint of clinical and instrumental assessments (1.79 [1.07-3.00]). Other independent predictors were stroke severity (odds ratio 1.06 per point on the National Institutes of Health Stroke Scale [1.01-1.11]) and the presence of an urinary catheter (odds ratio 2.03 [1.13-3.65]).

Conclusions: Severe dysphagia evaluated by a detailed clinical assessment complemented by instrumental testing predicts the development of post-stroke fever. Early identification of patients with severe dysphagia after stroke followed by consequent monitoring and treatment might be effective in reducing post-stroke fever.

Non-standard abbreviations and acronyms

CSA: clinical swallowing assessment

FEES: fiberoptic endoscopic evaluation of swallowing

FOIS: Functional Oral Intake Scale

NIHSS: National Institutes of Health Stroke Scale

Introduction

Fever is common after ischemic or hemorrhagic stroke and is associated with a worse clinical outcome. Previous studies observed fever in 4 to 60% of patients after ischemic stroke or intracerebral hemorrhage using cut-off temperatures ranging from 37.4°C to 38.3°C[1–7]. The onset of fever usually occurred on day 1 or 2 after stroke[1,3,8,9]. Fever was associated with a worse clinical outcome in both ischemic and hemorrhagic stroke[2,4–8,10–12]. Previously observed predictors of post-stroke fever were heterogenous between the studies and included more severe stroke – indicated by worse neurological status, larger lesion volume and hemorrhagic rather than ischemic stroke – infections, dysphagia, placement of nasogastric tubes or urinary catheters, mechanical ventilation, higher age, atrial fibrillation, diabetes, smoking, and chronic obstructive pulmonary disease[13–15]. Infections were established as cause of fever in the majority of patients (54-83%)[1,3–5,16,17].

Pneumonia is the most common focus of infection after stroke and is strongly linked to dysphagia and in particular aspiration[18,19]. While the association between dysphagia and pneumonia is well established, only one study addressed the association of dysphagia and post-stroke fever directly[14]. In that study, dysphagia was evaluated by a not further specified swallowing screening test and not by a formal clinical swallowing assessment or instrumental testing. The insertion of nasogastric tubes was established as a predictor of fever in multiple studies without detailed assessment of dysphagia[13,15]. Nasogastric tubes are usually used in patients with severe dysphagia or impaired consciousness and their use most likely represents a surrogate marker for an increased risk of aspiration.

It may be hypothesized that the thorough detection and classification of the severity of dysphagia assessed by a detailed clinical swallowing assessment (CSA) complemented by instrumental testing predicts post-stroke fever and that the early recognition of severe dysphagia is helpful in preventing post-stroke fever, which may improve outcome after

stroke. Previous trials on prevention of post-stroke fever by admission of antipyretics such as paracetamol failed to demonstrate a positive effect on clinical outcome[20]. As the study cohorts were relatively unselected in these trials, this raises the question if selection of patients at high risk of post-stroke fever could improve the power of future trials on prevention of post-stroke fever.

Thus, the aim of this study was to identify risk factors of post-stroke fever and to evaluate the association of dysphagia and post-stroke fever in detail.

Materials and Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

All patients admitted to the Department of Neurology, University Hospital of Ulm, RKU, Germany, between January 2016 and December 2016 for acute ischemic or hemorrhagic stroke were included. The patients were identified as cases documented in the Baden-Württemberg stroke registry, a database for monitoring of stroke care at the regional office for quality assurance in health care ("Qualitätssicherung im Gesundheitswesen Baden-Württemberg")[21]. Inclusion of all stroke patients admitted to a hospital into the registry is mandatory and is ensured by a centralized monitoring of diagnostic codes in the hospital information system. The following inclusion criteria were used: diagnosis of acute stroke as indicated by the diagnostic codes (International Classification of Diseases-10) I63.* (cerebral infarction) or I61.* (intracerebral hemorrhage), admission within 7 days after stroke onset and age of 18 years or older. Patients with transient ischemic attack, acute traumatic brain injury, subarachnoid hemorrhage and cerebral infarction due to intracranial neoplastic disease were not included. The study protocol was approved by the local Ethics Committee of the University of Ulm, Germany (protocol number 211/18). An informed consent of patients was not required due to the retrospective design.

Data on demographics, medical history, diagnostics and the therapeutic course during hospitalization were collected by review of case reports forms of the stroke quality monitoring registry as well as individual medical records. Fever was defined as at least a single temperature reading >38.0°C documented in the hospital chart within five days after admission. Temperature readings were acquired by tympanic measurements every 4 hours as a standard procedure. Laboratory data were collected by review of the medical records; the results of the first laboratory analysis within 24 hours after admission are reported. All patients received a neuroimaging study to confirm the stroke. Magnetic resonance imaging was the primary imaging modality in most patients. Items on swallowing function were collected from CSA reports by speech therapists and reports of fiberoptic endoscopic evaluation of swallowing (FEES). CSA was conducted by a speech therapist on the day of admission or on the following day as a standard of care in all stroke patients, using a standardized in-house protocol as reported previously[22,23]. Briefly, this protocol is based on the screening procedure by Logemann et al. and the stepwise concept for examination of neurogenic oropharyngeal dysphagia[24,25]. It includes the assessment of dysphagia predictors according to Daniels as a screening tool for moderate-to-severe dysphagia[26,27]. As outcome parameter of CSA, the Functional Oral Intake Scale (FOIS) and the Swallowing Impairment Scale are reported[28,29]. Patients received the complete CSA if they were awake and responsive. Patients who were not awake and responsive were ordered “nil per os” and were provided with a nasogastric tube. Data on CSA was not available in some patients due to missing reports in medical records, no order of speech therapy by the treating physician in mildly affected or asymptomatic patients or decline of the exam by the patient. In order to assess severity of dysphagia and risk of aspiration, patients were investigated by FEES if they were awake and responsive and had at least two aspiration predictors according to Daniels or a clinical suspicion of dysphagia with risk of aspiration. Patients with clinically proven risk of aspiration demonstrated by evidence of aspiration in CSA or by impaired consciousness with

impairment of airway protective reflexes were not investigated by FEES. Thus, only patients with an uncertain risk of aspiration due to suspected moderate-to-severe dysphagia in CSA were investigated by FEES. As additional outcome parameters of FEES, the pharyngeal residue severity scale and the penetration-aspiration scale were reported[30,31]. Data on infections during hospitalization are based on clinical diagnoses documented in the medical records. The National Institutes of Health Stroke Scale (NIHSS) scores had been evaluated by a trained clinician and were collected from the case report forms of the stroke quality monitoring registry.

Statistical analyses were performed using the Statistical Package for Social Sciences version 25.0 (IBM SPSS Statistics, Armonk, N.Y., USA). Differences in metric data between groups were assessed using Mann–Whitney U tests. Differences in frequencies between groups were assessed using Pearson chi-square test. Correlation of ordinal data was assessed using Spearman's rank correlation. Absolute risk reduction and the number needed to treat/harm were calculated using standard formula. Multivariable analyses were performed using binominal regression analyses with a backward stepwise selection of variables based on a likelihood-ratio statistic. A collinearity analysis was conducted for the independent variables in the regression models. If the variance inflation factor was below 5, no multicollinearity was assumed. All tests were 2-tailed. Statistical significance was determined at an α level of 0.05. In case of multiple comparisons, a Holm adjustment was used to determine corrected p-values.

Results

A total of 923 patients admitted for acute ischemic or hemorrhagic stroke in the study period were identified according to the inclusion criteria. A flow chart of the included patients and of the swallowing assessments available for analysis is shown in figure 1. 127 (13.8%) patients developed fever within five days after admission. The daily incidence rates are shown in table

1. Most patients developed fever on day 2 after admission. An infectious cause of fever was diagnosed in 78 (61.4%) patients.

The data on demographics, medical history and clinical course of patients with fever compared to patients without fever are given in table 2. Both cohorts significantly differed for a number of variables as follows.

Patients with fever more often suffered from intracerebral hemorrhage (15.7% versus 6.8%, $p<0.001$), had more severe stroke, represented by higher NIHSS scores on admission (median: 8 versus 2, $p<0.001$), and more often had impaired consciousness (17.7% versus 6.3%, $p<0.001$). Patients with fever were older (median: 80 versus 76 years, $p<0.001$), less often male (37.8% versus 54.5%, $p<0.001$), and more often had a history of atrial fibrillation (44.4% versus 30.8%, $p=0.003$).

Regarding laboratory parameters within 24 hours after admission, patients with fever had higher leukocyte counts (median: 8.9 versus 8.1 10^9/l, $p=0.003$) and higher values of C-reactive protein (median: 7.2 versus 4.6 mg/l, $p<0.001$).

Regarding the clinical course during hospitalization, NIHSS scores at discharge were higher in patients with fever (4 versus 1, $p<0.001$). Patients with fever more often had a nasogastric tube (49.6% versus 19.5%, $p<0.001$) and a urinary catheter (59.1% versus 23.6%, $p<0.001$), were more often diagnosed with infections (stroke-associated pneumonia: 40.7% versus 9.9%, $p<0.001$; urinary tract infection: 28.2% versus 13.7%, $p<0.001$), and were more often treated with antibiotics within five days after admission (56.7% versus 18.5%, $p<0.001$).

The results of CSA and FEES of patients with and without fever are given in table 3. Two out of six Daniels predictors (indicating moderate-to-severe dysphagia) were present in patients with fever more often (78.8% versus 42.2%, $p<0.001$). The following single CSA items were more frequent in patients with fever: dysarthria (59.8% versus 43.6%, $p=0.001$), dysphonia

(77.4% versus 55.3%, p<0.001), abnormal volitional cough (54.0% versus 22.3%, p<0.001), and cough after swallow (38.6% versus 18.1%, p<0.001). Patients with fever scored worse on dysphagia rating scales (median FOIS score: 1 [1-4] versus 7 [1-7], p<0.001; median Swallowing Impairment Scale score: 6 [4-6] versus 0 [0-6], p<0.001). Accordingly, swallowing of fluids was deemed safe in patients with fever less often (24.0% versus 61.1%, p<0.001).

Multivariable logistic regression analyses – adjusted for age, sex, atrial fibrillation, intracerebral hemorrhage, admission NIHSS, impaired consciousness, nasogastric tube, urinary catheter, and severity of dysphagia – were conducted in order to identify independent predictors of fever. Since there was considerable multicollinearity between clinical dysphagia parameters, positive Daniels predictors were chosen to adjust the model for dysphagia because they are a valid and easy-to-use assessment. Positive Daniels predictors were the strongest predictors of fever (odds ratio, OR [95% confidence interval] 3.05 [1.65-5.66]). NIHSS score on admission (OR: 1.06 per point [1.01-1.11]) and urinary catheter (OR: 2.03 [1.13-3.65]) were other significant predictors. If the FOIS score (according to CSA) was entered into the model instead of positive Daniels predictors, the results were comparable: FOIS score (OR: 1.22 per point decrease [1.09-1.35]), admission NIHSS score (OR: 1.06 per point [1.01-1.11]), urinary catheter (OR: 1.93 [1.11-3.37]) and intracerebral hemorrhage (OR: 2.18 [1.01-4.71]) were significant predictors of fever (see supplemental table I and II for more details).

A correlation analysis between the number of positive Daniels predictors and the FOIS score (according to FEES) revealed a significant negative correlation $\rho = -0.28$ ($p<0.001$). If the single dysphagia items dysarthria, dysphonia, abnormal volitional cough and cough after water swallow were entered into a multivariable regression model as independent variables, fever was significantly predicted by abnormal volitional cough (OR: 3.56 [2.15-5.89]) and

cough after water swallow (OR: 1.91 [1.12-3.26]). Substituting Daniels predictors for abnormal volitional cough or cough after water swallow in the model adjusted for all relevant variables did not improve the model (data not shown).

A subset of 264 patients was investigated by FEES (see table 2). The frequency of FEES was numerically higher in patients with fever (35.4% versus 27.5%, p=0.067). In the subset of patients investigated by FEES, patients with fever more often had evident aspiration (22.2% versus 10.0%, p=0.023) and significantly lower FOIS scores (median 4 versus 5, p=0.025), indicating more severe dysphagia.

For a combined analysis of CSA and FEES findings, patients with proven risk of aspiration – demonstrated by FEES, clinical evidence of aspiration in CSA or by impaired consciousness with impaired airway protective reflexes – were analysed. Dysphagia with proven risk of aspiration was more frequent in patients with fever (38.6% versus 11.8%, p<0.001). In a multivariable logistic regression model – adjusted for age, sex, atrial fibrillation, intracerebral hemorrhage, admission NIHSS, impaired consciousness, nasogastric tube and urinary catheter – dysphagia with proven risk of aspiration was a significant predictor of fever (OR: 1.79 [1.07-3.00]). Other significant predictors of fever in this analysis were admission NIHSS (OR: 1.06 per point [1.02-1.10]), urinary catheter (OR: 2.12 [1.30-3.44]) and intracerebral hemorrhage (OR: 2.19 [1.16-4.13]) (see supplemental table III for more details).

Absolute risk reduction for fever and numbers needed to treat and harm, respectively, were calculated to estimate the possible impact of interventions. The absolute risk reduction for fever of CSA was 4.8% and the number needed to prevent fever by CSA was 21. The absolute risk increase for fever of a nasogastric tube was 20.1% and the number needed to harm was 5. The absolute risk increase for fever of a urinary catheter was 21.0% and the number needed to harm was 5.

Discussion

In this cohort of patients with ischemic or hemorrhagic stroke, fever in the acute phase of stroke was independently predicted by severe dysphagia according to CSA complemented by FEES, stroke severity according to the NIHSS on admission, the use of urinary catheters and intracerebral hemorrhage.

Post-stroke fever was observed in 13.8% of patients in our cohort within 5 days after using a cut-off temperature of 38.0°C and tympanic measurements. Previously reported rates of post-stroke fever differ largely from 4 up to 60%. This is mainly due to the use of different cut-off temperatures (ranging from 37.4 to 38.3°C), different methods of temperature measuring, and different study cohorts (ischemic and/or hemorrhagic stroke)[1–7]. The daily incidence of fever in our cohort was highest on day 2 after admission, which is in line with previous studies[1,3,8,9]. An infectious cause of fever was established in the majority of cases (61.4%) with stroke-associated pneumonia and urinary tract infection being the most frequent causes of infection, confirming the results of previous studies [1,3–5,16–18]. As a consequence, patients with fever were more often treated with antibiotics. Leukocytes and C-reactive protein had already been elevated at admission in most patients who developed fever later on. This could suggest a subclinical onset of infection shortly after stroke due to dysphagia and aspiration, while overt febrile infection will develop with a delay of 1-2 days.

Previous studies observed a number of predictors of post-stroke fever including poor neurological status, intracerebral hemorrhage, infections, dysphagia, placement of nasogastric tubes and urinary catheters, mechanical ventilation, higher age, atrial fibrillation, diabetes, smoking, and chronic obstructive pulmonary disease[13–15]. While most of these variables were also observed to be associated with fever in our study cohort in univariate analysis, multivariable analyses only identified severe dysphagia, NIHSS on admission and urinary catheters as independent predictors of fever. Additionally, intracerebral hemorrhage was a

predictor in some analyses, suggesting that other mechanisms such as central fever may be of importance in intracerebral hemorrhage compared to ischemic stroke.

A detailed CSA was used to evaluate the severity of dysphagia. Out of the assessed dysphagia parameters, particularly strong predictors were the Daniels predictors, which identify patients with moderate-to-severe dysphagia, and the FOIS, which represents the severity of dysphagia on an ordinal scale. The number of Daniels predictors was negatively correlated with the FOIS score according to FEES, confirming the predictive value of Daniels predictors for moderate-to-severe dysphagia in this patient cohort. Regarding single CSA items, abnormal volitional cough and to a lesser degree cough after water swallow were best at predicting fever, but could not substitute for the whole assessment. Both of these parameters evaluate a patient's ability to protect the airways from aspiration. Consistently, dysphagia with clinically or instrumentally proven risk of aspiration was an independent predictor of fever in a multivariable analysis.

It is interesting to note that placement of nasogastric tubes was not an independent predictor of fever when adjusted for dysphagia parameters. This is in contrast to the results of Brogan et al. who proposed nasogastric tube insertion within 7 days after stroke as an independent predictor of pneumonia, the most common source of post-stroke fever[32]. In that study dysphagia was evaluated as a binary condition without assessment of severity of dysphagia, which may have led to an underestimation of the impact of dysphagia on post-stroke fever. Prospective trials would be needed to assess whether nasogastric tubes are an independent risk factor of post-stroke fever, e.g. a trial of stroke patients with severe dysphagia randomized to nutrition via nasogastric tube or parenteral nutrition.

In the subset of patients who were investigated by FEES, dysphagia was significantly more severe in patients with fever. However, this difference was less pronounced than in the whole cohort as patients with clinically proven risk of aspiration were not investigated by FEES.

FOIS scores were consistent with moderate dysphagia in the subset of FEES patients (4 versus 5 in FEES patients with and without fever, respectively). Thus, there may be other factors causing fever in patients with moderate dysphagia. Indeed, the placement of an urinary catheter was observed to be an independent predictor of fever in FEES patients. Additionally, it can be hypothesized that moderate dysphagia causes post-stroke fever in patients who are immunodepressed due to the stroke. It has been shown that stroke-induced immunodepression and dysphagia interact to increase the risk of stroke-associated pneumonia, however, the severity of dysphagia was not assessed in that study [33]. Due to the retrospective design, immunocompetence could not be assessed in our study.

Three independent predictors of post-stroke fever, which can potentially be modified by interventions, were consistently identified in this study: severe dysphagia, the severity of stroke indicated by NIHSS and the use of urinary catheters. Revascularisation by intravenous thrombolysis or endovascular therapy can improve neurological deficits and has been extensively studied in the last few years. Avoiding respectively removing urinary catheters, if possible, is already common practice to avoid post-stroke fever. The impact of dysphagia and CSA on post-stroke fever has not been studied in detail before. The Quality in Acute Stroke Care study demonstrated a better outcome of stroke patients using a protocol combining interventions by nurses to manage fever, hyperglycaemia and dysphagia[34]. The study design did not allow to delineate the effects of particular items of the protocol such as dysphagia screening. Implementing a detailed CSA (potentially supported by FEES or other instrumental testing) might be helpful in preventing fever and its deleterious effects on stroke patients.

Dysphagia severity assessed by FEES was previously shown to predict stroke-associated pneumonia, the need for mechanical ventilation and the overall functional outcome 3 months after stroke[35]. Moreover, implementation of a FEES service may help to reduce pneumonia rates in stroke patients[36]. A recent registry-based study demonstrated in a sizeable cohort that

FEES can be integrated into clinical practice safely and effectively, even with limited clinical experience of the examiner[37]. FEES did not seem to have major additional value over CSA for preventing post-stroke fever in our study cohort. However, as not all patients with suspected dysphagia were investigated by FEES, no definitive conclusions on the impact of FEES on preventing fever can be drawn from this study. Prospective randomized studies would be needed to evaluate the role of CSA and FEES in preventing post-stroke fever. The observations of this study are also of importance for future trials on interventions to prevent and treat post-stroke fever: Including a swallowing assessment to identify patients at high risk of post-stroke fever may improve the power of such trials.

Other interventions to be considered with regard to post-stroke fever are free water protocols and oral care interventions. While these interventions have been shown to reduce the risk of pneumonia in patients with dysphagia[38–40], their effect on post-stroke fever has not been studied. Free water protocols were not used in this patient cohort and oral care interventions were not routinely recorded, so the impact of these interventions on post-stroke fever could not be assessed.

In our cohort, the number needed to prevent fever by CSA was 21 and the number needed to harm was 5 for nasogastric tubes and 5 for urinary catheters, respectively. Of course, these numbers can only serve as estimates as they are based on a retrospective non-randomized sample.

The strengths of this study are its comparatively large cohort, the “real-life setting” and the detailed swallowing assessments. The main limitation is the potential selection bias due to the retrospective design as patients might have not received a CSA or FEES even though it had been indicated by the in-house standards.

Summary

In this study of 923 patients, fever within 5 days after ischemic or hemorrhagic stroke was predicted by severe dysphagia, poor neurological status and the placement of urinary catheters. The results suggest that early identification of patients with moderate-to-severe dysphagia after stroke by CSA complemented by instrumental testing and followed by consequent monitoring and treatment might be effective in reducing post-stroke fever and in selecting patients for randomized trials on prevention of post-stroke fever.

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The authors have no conflicts to declare.

Supplemental Materials

Supplemental Table I-III

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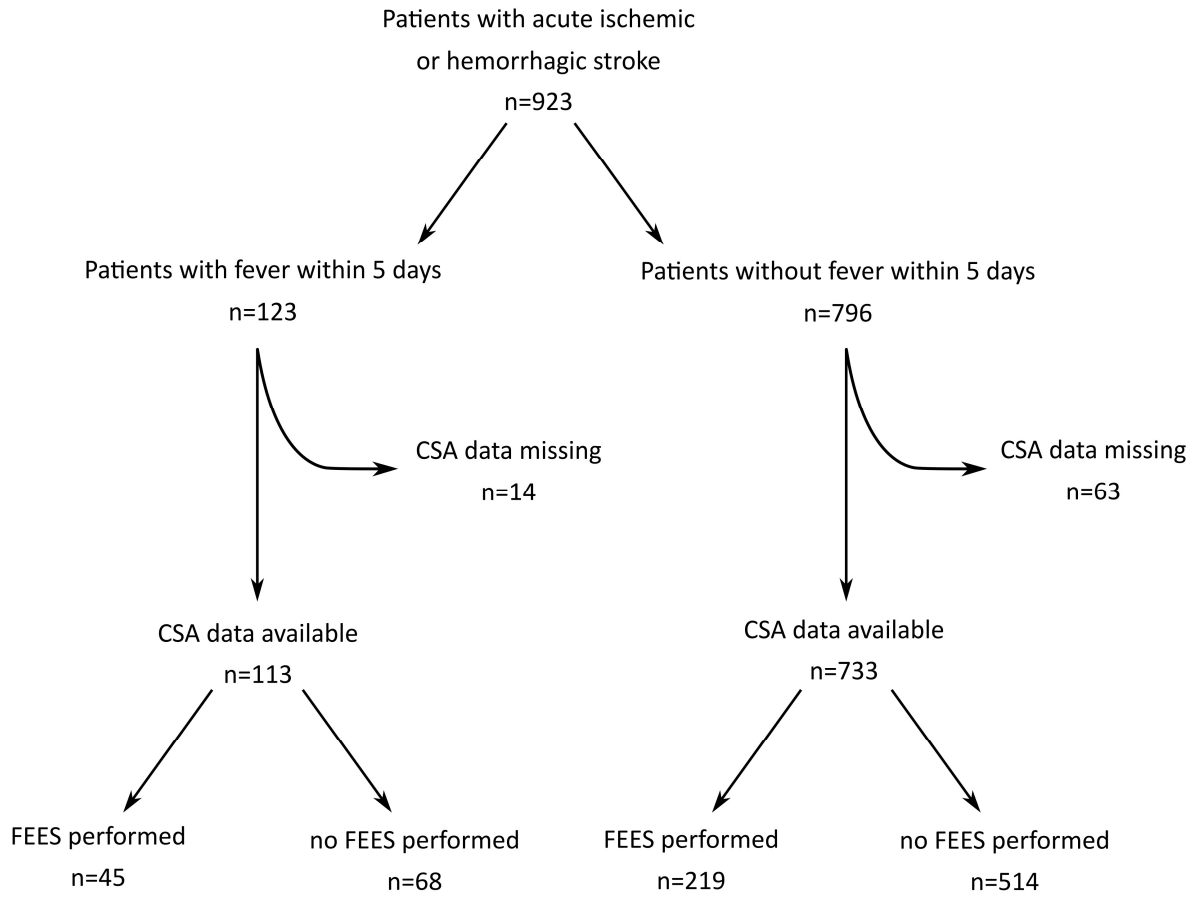
Figure legend

Figure 1. Flow chart of the included patients and the swallowing assessments available for analysis. CSA = clinical swallowing assessment, FEES = fiberoptic endoscopic swallowing assessment.



Tables

Table 1. Incidence rates of fever within five days of admission

Day after admission	Incidence of fever, n (%)	Day by day comparisons, p-values			
		Day 2	Day 3	Day 4	Day 5
1	22 (2.4%)	0.001	n.s.	n.s.	n.s.
2	55 (6.0%)	–	0.001	<0.001	<0.001
3	21 (2.3%)	0.001	–	n.s.	n.s.
4	20 (2.3%)	<0.001	n.s.	–	n.s.
5	9 (1.0%)	<0.001	n.s.	n.s.	–

Caption: Significant p-values ($p<0.05$) corrected for multiple comparisons are reported for day by day comparisons. ‘n.s.’ indicates a non-significant test result ($p>0.05$).

Table 2. Demographics, medical history and clinical course of patients with fever compared to patients without fever

Variables	No Fever % (n/N)	Fever % (n/N)
Demography and medical history		
Age, years, median (Q1-Q3)	76 (66-82)	80 (72-85) *
Male sex	54.5% (434/796)	37.8% (45/127) *
Previous pneumonia	10.0% (66/661)	12.7% (10/79)
Chronic obstructive pulmonary disease	5.5% (43/781)	4.8% (6/125)
Diabetes mellitus	25.1% (190/758)	28.2% (35/124)
Arterial hypertension	88.3% (669/758)	92.7% (115/124)
Atrial fibrillation	30.8% (233/757)	44.4% (55/124) *
Clinical characteristics of stroke		
Intracerebral hemorrhage	6.8% (54/796)	15.7% (20/127) *
NIHSS at admission, median (Q1-Q3)	2 (1-5)	8 (3-15) *
Supratentorial stroke	83.3% (659/791)	88.1% (111/126)
Infratentorial stroke	22.6% (180/795)	18.1% (23/127)
Left hemispheric/sided stroke	48.0% (380/792)	52.0% (66/127)

Impaired consciousness	6.3% (48/756)	17.7% (22/124) *
Acute lesion on neuroimaging	97.9% (741/757)	99.2% (123/124)
Intravenous thrombolysis administered	20.6% (155/752)	19.5% (23/118)
Intracerebral hemorrhage after intravenous thrombolysis	8.2% (4/49)	5.1% (10/196)
Laboratory parameters		
Leukocytes (10^9/l), median (Q1-Q3)	8.1 (6.5-10.1)	8.9 (6.8-12.2) *
C-reactive protein (mg/l), median (Q1-Q3)	4.6 (1.9-12.9)	7.2 (3.1-27.4) *
Stroke treatment		
NIHSS at discharge, median (Q1-Q3)	1 (0–3)	4 (1-9) *
Nasogastric tube	19.5% (151/775)	49.6% (63/127) *
Stroke-associated pneumonia	9.9% (76/768)	40.7% (46/113) *
Urinary catheter	23.6% (183/775)	59.1% (75/127) *
Urinary tract infection	13.7% (107/781)	28.2% (35/124) *
Other infections	4.6% (36/782)	7.2% (9/125)
Antibiotic treatment within 5 days after admission	18.5% (147/796)	56.7% (72/127) *
Mechanical ventilation	2.0% (15/757)	4.0% (5/124)

Caption: n = absolute frequency, N = number of patients with available data, NIHSS = National Institutes of Health Stroke Scale, Q = quartile. '*' indicates a significant test result ($p<0.05$).

Table 3. Swallowing assessments of patients with fever compared to patients without fever

Variables	No Fever % (n/N)	Fever % (n/N)
CSA		
Data on CSA available	92.1% (733/796)	89.0% (113/127)
Daniels predictors “2 out of 6“ positive	42.2% (281/666)	78.8% (63/80) *
Dysarthria	43.6% (327/750)	59.8% (67/112) *
Dysphonia	55.3% (375/678)	77.4% (65/84) *
Abnormal volitional cough	22.3% (152/681)	54.0% (47/87) *
Cough after water swallow (Daniels)	18.1% (121/670)	38.6% (32/83) *
Swallowing Impairment Scale (according to CSA), median (Q1-Q3)	0 (0-6)	6 (4-6) *
Swallowing fluids safe (according to CSA)	61.1% (429/702)	24.0% (23/96) *
FOIS score (according to CSA), median (Q1-Q3)	7 (1-7)	1 (1-4) *
FEES		
FEES completed	27.5% (219/796)	35.4% (45/127)
Pharyngeal residue severity scale, median (Q1-Q3)	0 (0-0)	0 (0-1)
Penetration–aspiration scale, maximum value, median (Q1-Q3)	2 (2-6)	2 (2-3)

Evidence of aspiration (in FEES)	10.0% (22/219)	22.2% (10/45) *
Swallowing Impairment Scale (according to FEES), median (Q1-Q3)	3 (1-4)	3 (2-5)
Swallowing fluids safe (according to FEES)	44.7% (98/219)	33.3% (15/45)
FOIS score (according to FEES), median (Q1-Q3)	5 (4-7)	4 (4-5) *
Dysphagia with proven risk of aspiration (according to FEES and CSA)	11.8% (94/796)	38.6% (49/127) *

Caption: CSA = clinical swallowing assessment, FEES = fiberoptic endoscopic evaluation of swallowing, FOIS = Functional Oral Intake Scale, n = absolute frequency, N = number of patients with available data. '*' indicates a significant test result ($p<0.05$).

3.4 Stösser et al., Frontiers in neurology 13: 902809

In der Arbeit „Sepsis in Patients With Large Vessel Occlusion Stroke – Clinical Characteristics and Outcome" wurde eine Kohorte von 406 Schlaganfallpatienten mit Verschluss eines großen hirnversorgenden Gefäßes, die am Universitätsklinikum Bonn zwischen 2016 und 2020 mittels ET behandelt und in das GSR-ET-Register eingeschlossen worden waren, analysiert. Die Registerdaten wurden durch eine retrospektive Datenerfassung zu schlaganfallassoziierten Infektionen ergänzt. Die Kriterien einer Sepsis waren bei 54 (13,3%) der Patienten erfüllt. Eine Infektion ohne septischen Verlauf war bei 138 (38,9%) der Patienten festzustellen. Diagnosezeitpunkt der Sepsis war im Median zwei Tage nach Aufnahme. Der häufigste Infektfokus für eine Sepsis war die Pneumonie (85,2%). Die Organsysteme, die infolge einer Sepsis am häufigsten betroffen waren, waren die Atmung (53,8%), das zentrale Nervensystem (37,7%), das Herz-Kreislauf-System (35,8%) und die Nierenfunktion (7,4%).

Der qSOFA-Score wies eine Sensitivität von 86,8% und eine Spezifität von 52,2% für die Diagnose einer Sepsis auf. Eine Analyse der Einzelkategorien des qSOFA-Scores erbrachte folgende Ergebnisse: eine Sensitivität von 94,3% und eine Spezifität von 37,5% für verändertes Bewusstsein, eine Sensitivität von 71,7% und eine Spezifität von 30,0% für Tachypnoe, sowie eine Sensitivität von 49,1% und eine Spezifität von 75,6% für arterielle Hypotonie.

Sepsispatienten wiesen zu 72,5% nach drei Monaten ein schlechtes klinisches Outcome auf (Wert von 5 oder 6 auf der modifizierten Rankin-Scala, entsprechend einer ständigen Pflegebedürftigkeit mit Bettlägerigkeit bzw. dem Tod), verglichen mit 25,7% der Kontrollen ohne Infekt und 42,7% der Patienten mit Infekt ohne septischen Verlauf. Die für Störfaktoren adjustierten Odds Ratios für ein schlechtes Outcome waren 11,4 (4,4-29,2) für Sepsis gegenüber Kontrollen und 3,5 (1,6-7,5) für Sepsispatienten gegenüber Patienten mit Infektion ohne septischen Verlauf.

Zusammenfassend ist die Sepsis eine häufige Komplikation bei Schlaganfallpatienten mit Verschluss eines großen hirnversorgenden Gefäßes und ist ein eigenständiger Prädiktor für ein schlechtes klinisches Outcome.

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Sepsis in Patients With Large Vessel Occlusion Stroke–Clinical Characteristics and Outcome

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Background: Infections are an important complication after stroke and negatively affect clinical outcome. While pneumonia and urinary tract infections are well recognized after stroke, the incidence and consequences of sepsis remain unclear. The aim of this study was to evaluate the frequency and characteristics of sepsis in patients undergoing endovascular therapy for large vessel occlusion stroke, and its association with clinical outcome.

Methods: We analyzed a cohort of patients who underwent endovascular therapy at a single center between 2016 and 2020. The diagnosis and timing of infections and Sequential Organ Failure Assessment scores were evaluated retrospectively to identify patients with sepsis. Patients with sepsis were compared to controls regarding clinical characteristics and outcome.

Results: Fifty-four of 406 patients (13.3%) were found to have sepsis. The median onset of sepsis was 2 days after admission. The majority of cases (85.2%) was caused by pneumonia. At 3 months, 72.5% of patients with sepsis were bedridden or dead compared to 25.7 and 42.7% of controls and patients with an infection without sepsis, respectively. The adjusted odds ratio (95% confidence interval) for a poor outcome was 5.4 (1.6–17.6) for patients with sepsis vs. controls, and 2.0 (0.8–5.2) for patients with sepsis vs. patients with an infection without sepsis.

Conclusions: Sepsis is a frequent complication after large vessel occlusion stroke, and may be associated with a poor clinical outcome. More studies are needed to determine specific risk factors and measures to early recognize and reduce the possibly negative impact of sepsis on outcome after stroke.

Keywords: sepsis, ischemic stroke, thrombectomy, patient outcome assessment, infections, organ dysfunction scores

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INTRODUCTION

Infections are an important complication after stroke and have a strong association with an unfavorable clinical outcome (1, 2). The most common stroke-associated infections are pneumonia and urinary tract infections, occurring in 12 and 8–19%, respectively (3, 4). While these infections are well recognized after stroke, less is known about sepsis after stroke. Berger et al. reported sepsis in 12.6% of patients admitted to a neurological intensive care unit for ischemic or hemorrhagic stroke and an association of sepsis with poor outcome in 2014 (5).

In 2016, new diagnostic criteria for sepsis were established. The Sepsis-3 definition relies on the detection of life-threatening organ dysfunction consequent to an infection assessed by the Sequential Organ Failure Assessment (SOFA) score (acute increase of ≥2 points) (6). Further, the quick Sequential Organ Failure Assessment (qSOFA) score was introduced to facilitate the diagnosis of sepsis in a non-intensive care unit setting (7). However, studies employing the Sepsis-3 definition to investigate sepsis after ischemic stroke are missing.

The aim of this study was to evaluate the frequency and characteristics of sepsis in patients undergoing endovascular therapy (ET) for LVOS using the Sepsis-3 definition, to evaluate the impact of sepsis on clinical outcome in these patients, and to assess the predictive value of the qSOFA score.

METHODS

All data analyzed in this study were derived from patients included in the German Stroke Registry–Endovascular Therapy (GSR-ET) Study at University Hospital Bonn between June 2016 and January 2020. The GSR-ET is an ongoing, open-label, prospective, multicenter registry of patients with LVOS treated with ET (https://www.clinicaltrials.gov; unique identifier: NCT0335639). A detailed description of the GSR-ET study design has been published (8, 9). Data collection was centrally approved by the ethics committee of the Ludwig-Maximilian University Munich (689-15) and the local ethics committee of the University of Bonn (054/16) and was thus in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The data supporting the findings of this study are available from the corresponding author upon reasonable request.

In addition to data prospectively collected in GSR-ET, clinical and laboratory data were retrospectively collected from individual electronic medical records. Patients with infections were identified by screening medical records for, firstly, a diagnosis of infection documented by the treating clinician and, secondly, subsequent antibiotic therapy. Diagnosis and treatment of infections was in accordance with current national guidelines (10–12). A summary of the standard operating procedures for diagnosis and treatment of infections at our institution is provided in the supplement. Pneumonia was also evaluated according to the modified Centers for Disease Control and Prevention (CDC) criteria for probable stroke-associated pneumonia and according to the CDC criteria for health care-associated pneumonia in ventilated patients (13, 14). The source of infections was classified as "other" if there was a clear source of infection other than pneumonia or urinary tract infection and as "undetermined" if the source of infection was unclear after diagnostic workup. Patients who were diagnosed with an infection, but not treated by antibiotics because of a comfort measures only agreement, were defined as having an infection too. The onset of infection was defined as the first day of either antibiotic therapy or microbiological culture sampling (if sampling was done within 48 h prior to antibiotic therapy) (7). SOFA and qSOFA scores were determined at admission and daily within the period from 2 days before the onset of infection to 1 day after the onset of infection (7, 15). The SOFA score assesses the function of six vital organ systems based on physiological parameters (15). The qSOFA score is a simplified version of the SOFA score developed to screen patients with an infection for sepsis outside the intensive care unit (7). Patients who did not have an infection served as controls. In this group, SOFA and qSOFA scores were determined at admission and for the following 4 days. If P_aO_2 was not available, the P_aO_2/FiO_2 ratio was substituted by the SpO_2/FiO_2 ratio as described previously (16). Sepsis was defined as an increase in total SOFA score of two points or more over the baseline score at admission within the period from 2 days before the onset of infection to 1 day after the onset of infection according to the Sepsis-3 definition (6).

Primary outcome measure was the frequency of patients with a score of five to six on the modified Rankin Scale (mRS) after 90 days. Secondary outcome measures included National Institutes of Health Stroke Scale (NIHSS) scores, the length of hospitalization, the frequency of patients with a mRS score of zero to two, median mRS scores and mortality. Symptomatic intracranial hemorrhage was evaluated retrospectively according to the European Cooperative Acute Stroke Study (ECASS) II definition (17).

Statistical analyses were performed using the Statistical Package for Social Sciences version 27.0.0.0 (IBM SPSS Statistics, Armonk, N.Y., USA). Propensity score matching was performed using R (R version 4.1.3, R core team 2021, package "MatchIt", R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/). Propensity score matching was performed using a 1:1 nearest neighbor matching without replacement. Propensity scores were estimated using logistic regression with the following relevant covariates: age, sex, NIHSS at admission, premorbid mRS and Charlson Comorbidity Index. Cases with missing data on those covariates were excluded from the analysis of matched cohorts. Differences in metric data were assessed using Kruskal-Wallis tests and Mann-Whitney U tests where appropriate. Differences in frequencies were assessed using Pearson chi-square tests. Regression analyses were conducted using multivariable linear, logistic and ordinal models based on the dependent variable. Multivariable analyses of outcome measures were adjusted for a predefined set of variables (age, sex, NIHSS at admission, premorbid mRS, Charlson Comorbidity Index, and either intracranial hemorrhage for the 24 h and discharge follow ups, or the combined frequency of intracranial hemorrhage, recurrent stroke and malignant infarction within 90 days for the 90 days follow up). Missing SOFA score variables from the day of admission were imputed by the value from the following day ("carried backwards"), all other missing data including follow up SOFA score variables were not imputed. Sensitivity and specificity were calculated using standard formula. All tests were two-tailed. Statistical significance was determined at an α level of 0.05. A Bonferroni-Holm correction was applied to *p*-values for pairwise comparisons.

RESULTS

The data of 406 patients who underwent ET for LVOS between June 2016 and December 2019 were available and included in the analysis. Fifty-four (13.3%) patients had sepsis. One hundred fifty-eight (38.9%) patients had an infection without fulfilling

the Sepsis-3 definition. The remaining 194 (47.8%) patients had no evidence of infection (see **Supplementary Figure S1** for the study flowchart).

The demographics, medical history as well as clinical, imaging and treatment characteristics of patients with sepsis, patients with an infection without sepsis, and control patients are shown in **Table 1**. The three cohorts were evenly balanced regarding these baseline variables with the following significant exceptions. Patients with an infection without sepsis were older than controls (median 79 vs. 74 years). Patients with sepsis and patients with an infection without sepsis had a higher frequency of arterial hypertension compared to controls (90.7 and 87.3, respectively, vs. 76.4%). Patients with an infection without sepsis had a higher frequency of atrial fibrillation compared to controls (54.5 vs. 41.1%).

Details regarding the timing and site of infection and the SOFA scores are given in **Table 2**. The median onset of sepsis was 2 days after admission, compared to 3 days for the median onset of infection without sepsis. Pneumonia was the most common source of sepsis (85.2%) and infection without sepsis (56.3%) and was more common in patients with sepsis than in patients without sepsis. If pneumonia was evaluated to the

TABLE 1 | Baseline characteristics of control patients, patients with an infection without sepsis and patients with sepsis.

	Controls % (*n*/*N*)	**Infection without sepsis % (*n*/*N*)**	**Sepsis % (*n*/*N*)**
Age, year, median (Q1–Q3) *n*, cases available	74 (63–82) *n* = 194	79 (69–84)* *n* = 158	76 (64–83) *n* = 54
Sex, female	57.7% (112/194)	55.7% (88/158)	42.6% (23/54)
Arterial hypertension	76.4% (146/191)	87.3% (137/157)*	90.7% (49/54)†
Dyslipidemia	67.2% (129/192)	65.6% (103/157)	50.9% (27/53)
Atrial fibrillation	41.1% (78/190)	54.5% (85/156)*	46.2% (24/52)
Smoking	19.4% (36/186)	12.2% (18/147)	20.8% (10/48)
Diabetes mellitus	21.1% (44/190)	23.1% (36/156)	18.9% (10/53)
Charlson comorbidity index score, median (Q1–Q3)	1 (0–2) *n* = 194	1 (0–2) *n* = 158	1 (0–3) *n* = 54
Premorbid modified rankin scale score, median (Q1–Q3)	0 (0–1) *n* = 188	0 (0–2) *n* = 152	0 (0–1) *n* = 51
Onset of symptoms known	57.7% (112/194)	48.7% (77/158)	63.0% (34/54)
Time from onset to admission, min, median (Q1–Q3)	105 (55–198) *n* = 194	95 (57–194) *n* = 158	89 (60–220) *n* = 54
ASPECTS at admission	8 (8–10) *n* = 154	8 (7–9) *n* = 77	8 (7–10) *n* = 35
NIHSS score at admission	13 (9–17) *n* = 191	14 (10–17) *n* = 156	14 (11–17) *n* = 52
Occluded vessel			
Middle cerebral artery, M1 segment	60.5% (115/190)	53.5% (84/157)	48.1% (26/54)
Middle cerebral artery, M2 segment	20.5% (39/190)	20.4% (32/157)	25.9% (14/54)
Intracranial internal carotid artery	18.4% (35/190)	22.9% (36/157)	18.5% (10/54)
Basilar artery	10.0% (19/190)	8.9% (14/157)	14.8% (8/54)
Other	1.6% (3/190)	1.9% (3/157)	7.4% (4/54)
Side of occluded vessel, left	52.9% (91/172)	49.3% (73/148)	52.1% (25/48)
Stroke etiology			
Cardioembolism	49.2% (94/191)	60.8% (96/158)	52.8% (28/53)
Large artery arteriosclerosis	22.0% (42/191)	18.4% (29/158)	17.0% (9/53)
Other determined etiology	3.7% (7/191)	4.4% (7/158)	7.5% (4/53)
Undetermined etiology	25.1% (48/191)	16.5% (26/158)	22.6% (12/53)
Intravenous thrombolysis	53.6% (104/194)	41.8% (66/158)	46.3% (25/54)
Successful recanalization (mTICI 2b-3)	96.3% (154/160)	93.3% (111/119)	92.9% (39/42)
General anesthesia	100% (192/192)	100% (157/157)	100% (53/53)
Time from onset to flow restoration, min, median (Q1–Q3)	228 (188–314) *n* = 88	231 (192–315) *n* = 58	252 (190–352) *n* = 27

ASPECTS, Alberta stroke programme early CT score; NIHSS, National Institutes of Health Stroke Scale; mTICI, modified Thrombolysis In Cerebral Infarction Scale.
**Indicates a significant difference between patients with an infection without sepsis and controls ($p < 0.05$ after Bonferroni-Holm adjustment for multiple comparisons).*
† Indicates a significant difference between sepsis patients and controls ($p < 0.05$ after Bonferroni-Holm adjustment for multiple comparisons).

TABLE 2 | Timing, source of infection and Sequential Organ Failure Assessment (SOFA) scores of controls, patients with an infection without sepsis and patients with sepsis.

	Controls % (*n*/*N*)	Infection without sepsis % (*n*/*N*)	Sepsis % (*n*/*N*)
Time from admission to diagnosis of infection, days, median (Q1–Q3) *n*, available cases	–	3 (1–5) *n* = 155	2 (1–5) *n* = 53
Source of infection			
Pneumonia (clinical diagnosis)	–	56.3% (89/158)	85.2% (46/54)‡
Pneumonia (diagnosis according to modified CDC criteria)	–	41.7% (65/156)	75.5% (40/53)‡
Urinary tract infection	–	22.8% (36/158)	13.0% (7/54)
Other	–	7.0% (11/158)	1.9% (1/54)
Undetermined	–	15.2% (24/158)	3.7% (2/54)‡
Dysphagia with risk of aspiration	17.9% (34/190)	39.2% (62/158)*	74.1% (40/54)†‡
Mechanical ventilation on assessment of follow up SOFA scores	12.9% (24/186)	15.4% (23/149)	49.1% (26/53)†‡
Duration of mechanical ventilation, h, median (Q1–Q3)	0 (0–0) *n* = 24	0 (0–0) *n* = 23	0 (0–53.5)†‡ *n* = 26
Positive microbiological cultures	–	54.9% (50/91)	57.1% (24/42)
Positive blood cultures	–	27.6% (16/58)	33.3% (9/27)
SOFA score at admission, median (Q1–Q3)	2 (0–3) n=192	3 (1–4)* *n* = 157	2 (1–5) *n* = 53
Maximum SOFA score, median (Q1–Q3)	2 (1–4) n=194	3 (2–4)* *n* = 157	8 (4–11)†‡ *n* = 54
SOFA subcategories–increase of score ≥2 compared to admission			
Central nervous system	6.6% (11/166)	0.7% (1/150)*	37.7% (20/53)†‡
Respiration	7.6% (13/172)	5.3% (7/133)	53.8% (28/52)†‡
Coagulation	0.5% (1/194)	0% (0/156)	1.9% (1/54)
Liver	2.1% (1/48)	1.9% (1/52)	3.0% (1/33)
Cardiovascular	2.4% (4/168)	0% (0/153)	35.8% (19/53)†‡
Renal	0% (0/194)	0.6% (1/156)	7.4% (4/54)†‡
Increase of maximal SOFA score ≥2 without CNS subcategory	12.4% (24/194)	3.8% (6/157)	83.3% (45/54)

CDC, Centers for Disease Control and Prevention; SOFA, Sequential Organ Failure Assessment; CNS, Central nervous system.

**Indicates a significant difference between patients with an infection without sepsis and controls ($p < 0.05$ after Bonferroni adjustment for multiple comparisons).*

†Indicates a significant difference between sepsis patients and controls ($p < 0.05$ after Bonferroni adjustment for multiple comparisons).

‡Indicates a significant difference between sepsis patients and patients with an infection without sepsis ($p < 0.05$ after Bonferroni adjustment for multiple comparisons).

stricter modified CDC criteria for probable stroke-associated pneumonia, the results were similar (75.5% in patients with sepsis vs. 41.7% in patients with an infection without sepsis). The overall frequency of pneumonia in all three groups combined was 33.2% (135/406) and 25.9% (105/406) according to the modified CDC criteria. Dysphagia with risk of aspiration was more common in patients with sepsis compared to patients with an infection without sepsis and controls (74.1 vs. 39.2 and 17.9%, respectively). The same held true for mechanical ventilation (49.1 vs. 15.4 and 12.9%, respectively). The overall frequency of urinary tract infections in all three groups combined was 10.6% (43/406). Moreover, the cause of infection was undetermined in more patients with infection without sepsis (15.2%) than in patients with sepsis (3.7%).

The median of the maximal SOFA score within the period of 2 days before until 1 day after the onset of infection of patients with sepsis was eight (from a baseline of two), while the SOFA scores did not increase in controls and patients with an infection without sepsis as per definition. The time courses of total SOFA scores and scores of SOFA subcategories are shown in **Supplementary Figure S2**. The most frequently affected organ systems in patients with sepsis were respiration (53.8%), the central nervous system (37.7%), the cardiovascular system (35.8%) and renal function (7.4%). If SOFA scores were calculated without the central nervous system (CNS) subcategory, 9 (16.7%) patients with sepsis failed to meet the Sepsis-3 definition. On the other hand, 6 (3.8%) patients with an infection without sepsis did meet the Sepsis-3 definition if the CNS subcategory was left out. Additional laboratory and clinical parameters are shown in **Supplementary Table S1**.

The qSOFA score was significantly more often positive in patients with sepsis at the onset of infection (86.8%) compared to patients with an infection without sepsis (58.5%) and to controls (37.2%). This resulted in a sensitivity of 86.8% and a specificity of 52.2% of the qSOFA score for the diagnosis of sepsis. When analyzing the qSOFA subcategories, the mental status showed a sensitivity and specificity of 94.3 and 37.5%, respectively, the respiratory rate a sensitivity and specificity of 71.7 and 30.0%, respectively, and the systolic blood pressure a sensitivity and specificity of 49.1 and

75.6%, respectively. The data on qSOFA scores are shown in **Supplementary Table S2**.

Clinical outcome parameters are shown in **Table 3** and are illustrated in **Figure 1**. A poor outcome at 90 days, indicated by an mRS of five or six, was more common in patients with sepsis compared to controls and to patients with an infection without sepsis (72.5 vs. 25.7 and 42.7%, respectively). The adjusted odds ratio (95% confidence interval) for a poor outcome was 11.4 (4.4–29.2) for patients with sepsis vs. controls, 3.5 (1.6–7.5) for patients with sepsis vs. patients with an infection without sepsis, and 5.9 (2.7–12.9) for patients with sepsis vs. all patients without sepsis. If adjusted for the NIHSS at 24 hours instead of NIHSS at admission, the odds ratio (95% confidence interval) for a poor outcome was 5.4 (1.6–17.6) for patients with sepsis vs. controls, 2.0 (0.8–5.2) for patients with sepsis vs. patients with an infection without sepsis, and 2.7 (1.0–6.8) for patients with sepsis vs. all patients without sepsis.

The secondary outcome measures also demonstrated a significantly worse outcome in patients with sepsis compared to controls (median NIHSS at 24 h: 16 vs. 5; median NIHSS at discharge: 11 vs. 2; median length of stay 13 vs. 7 days; median mRS at 90 days: 5 vs. 2; frequency of mRS 0-2: 7.8 vs. 54.1%). Compared to patients with an infection without sepsis, the following secondary outcome measures showed a significantly worse outcome of patients with sepsis (median NIHSS at 24 h: 16 vs. 11; median NIHSS at discharge: 11 vs. 6; median mRS at 90 days: 5 vs. 4).

Clinical outcome was also analyzed in modified cohorts that included patients with sepsis and infection without sepsis, respectively, based on the SOFA score calculated without the CNS subcategory. This modified cohort of patients with sepsis included 51 patients, and the modified cohort of patients with an infection without sepsis 161 patients. The results were comparable to the analysis of the original cohort and are shown in **Supplementary Table S3**. Notably, poor outcome at 90 days was even more frequent in the modified sepsis cohort compared to controls and to the modified infection cohort than in the original cohort (80.9% vs. 25.7 and 40.8%, respectively). Further, in contrast to the original cohorts, mortality at 90 days in patients with sepsis was not only significantly higher than in controls, but also compared to patients with an infection without sepsis (53.2 vs. 22.4 and 25.2%, respectively). A sensitivity analysis of clinical outcome parameters after exclusion of 4 patients with comfort measures only agreements did not yield relevant differences compared to the analysis of the complete cohort. The results are shown in **Supplementary Table S4**.

Clinical outcome was further analyzed in patients with sepsis compared to propensity score matched cohorts of controls and patients with infection without sepsis. Five patients with sepsis had to be excluded for that analysis because of partially missing data for covariates of the propensity score and 3 further patients for partially missing outcome data, leaving 46 patients with sepsis for this analysis. A poor outcome at 90 days was more common in patients with sepsis compared to matched controls and to matched patients with an infection without sepsis (69.6 vs. 26.1 and 47.8%,

TABLE 3 | Clinical outcome of controls, patients with an infection without sepsis and patients with sepsis.

	Controls % (*n*/*N*)	Infection without sepsis % (*n*/*N*)	Sepsis % (*n*/*N*)
24 h follow-up			
NIHSS, median (Q1–Q3)	5 (3–10)	11 (7–16)*	16 (12–19)†‡
n, available cases	*n* = 162	*n* = 148	*n* = 43
Any intracranial hemorrhage	4.7% (9/192)	8.3% (13/156)	11.1% (6/54)
Symptomatic intracranial hemorrhage	1.1% (2/190)	2.6% (4/156)	1.9% (1/52)
Discharge follow up			
NIHSS, median (Q1–Q3)	2 (0–5)	6 (2–12)*	11 (6–17)†‡
	n = 141	*n* = 111	*n* = 27
Length of stay, d, median (Q1–Q3)	7 (4–12)	13 (8–19)*	13 (7–18)†
	n = 194	*n* = 157	*n* = 54
Treatment on the intensive care unit	21.1% (41/194)	29.7% (47/158)	61.1% (33/54)†‡
Death	11.6% (22/189)	11.0% (17/154)	24.1% (13/54)†
90 days follow up			
Modified Rankin Scale score, median (Q1–Q3)	2 (1–5)	4 (3–6)*	5 (4–6)†‡
	n = 183	*n* = 143	*n* = 51
Good outcome (mRS 0–2)	54.1% (99/183)	20.3% (29/143)*	7.8% (4/51)†
Poor outcome (mRS 5–6)	25.7% (47/183)	42.7% (61/143)*	72.5% (37/51)†‡
Death	22.4% (41/183)	28.7% (41/143)	41.2% (21/51)†

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.

**Indicates a significant difference between patients with an infection without sepsis and controls ($p < 0.05$ after Bonferroni-Holm adjustment for multiple comparisons).*

† Indicates a significant difference between sepsis patients and controls ($p < 0.05$ after Bonferroni-Holm adjustment for multiple comparisons).

‡indicates a significant difference between sepsis patients and patients with an infection without sepsis ($p < 0.05$ after Bonferroni-Holm adjustment for multiple comparisons).

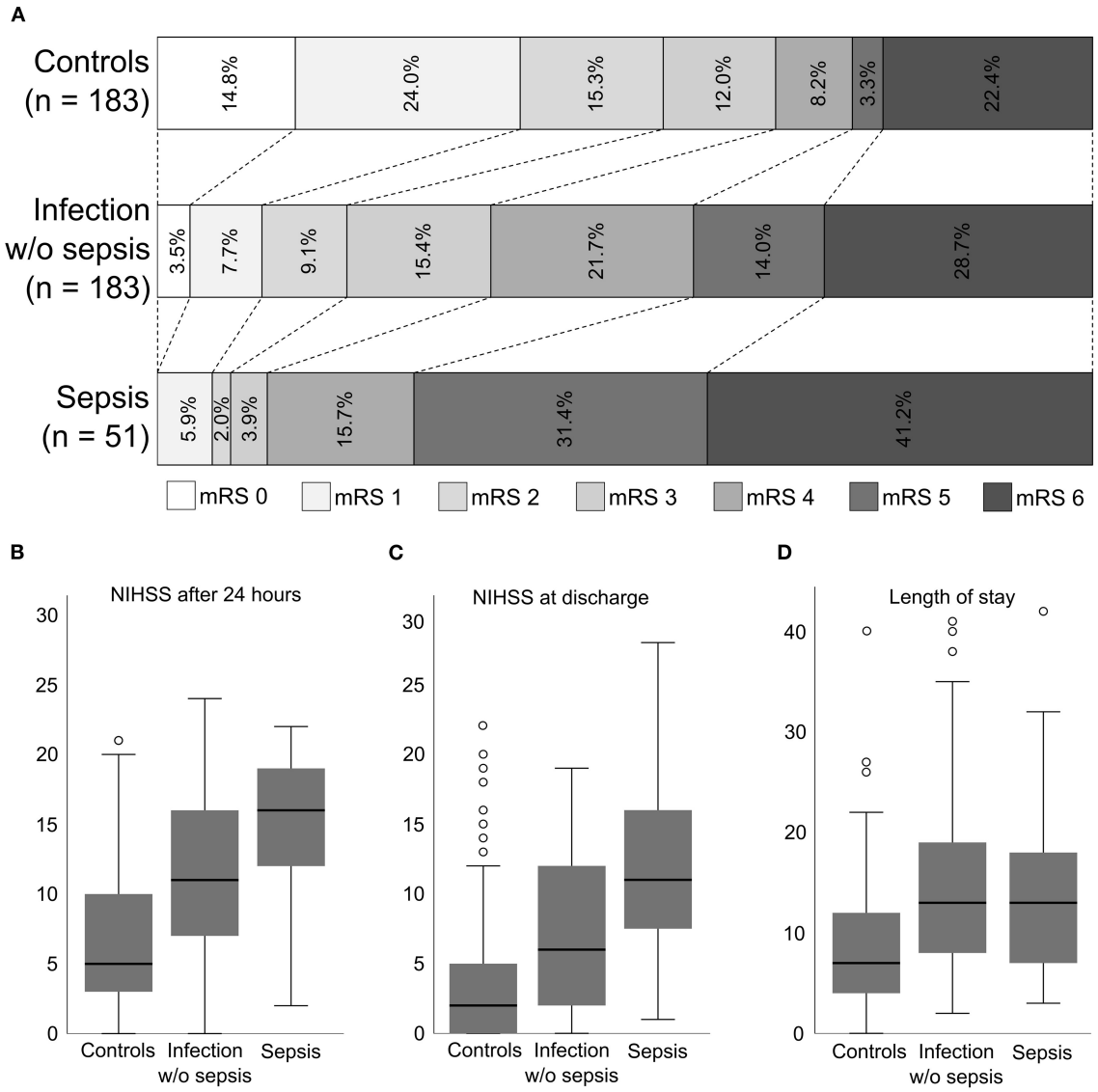

FIGURE 1 | Primary and secondary outcome parameters of patients with sepsis, patients with infection without sepsis and control patients. **(A)** modified Rankin scale (mRS) scores at 3 months. **(B)** National Institutes of Health Stroke Scale (NIHSS) scores at 24 h. **(C)** NIHSS scores at hospital discharge. **(D)** Length of hospitalization in days. The data in **(B–D)** are displayed as boxplots; the box represents the median and interquartile range; the whiskers represent 1.5 times the interquartile range; the circles represent outliers.

respectively). The adjusted odds ratio (95% confidence interval) for a poor outcome was 9.0 (2.9–28.0) for patients with sepsis vs. controls, and 2.8 (1.1–6.9) for patients with sepsis versus patients with an infection without sepsis. Further results of the propensity score matched cohorts are reported in detail in **Supplementary Table S5**.

DISCUSSION

In this analysis of 406 patients who underwent endovascular therapy for LVOS, sepsis was detected in 13.3% with a median onset of 2 days after admission. The outcome at 90 days was poor (bedridden or dead) in 72.5% of patients with sepsis compared to 25.7% in control patients and to 42.7% in patients with an infection without sepsis.

A previous study observed sepsis in 12.6% of patients admitted to a neurological intensive care unit for ischemic or hemorrhagic stroke (5). While this frequency is numerically similar to our dataset, the results cannot be compared directly as the previous study analyzed a different category of patients and used a now outdated sepsis definition. The same holds true for the clinical outcome: An unfavorable outcome with high mortality was observed in sepsis patients in that study, but the control group also had a comparably poor outcome.

In our cohort, there were no relevant differences between controls and patients with sepsis regarding demographics, medical history as well as clinical, imaging and treatment characteristics at baseline, which could point to specific risk factors for sepsis in this cohort. While arterial hypertension was more prevalent in sepsis patients, the Charlson comorbidity index as a general measure of comorbidity was not significantly different between groups.

Pneumonia was the source of sepsis in the majority of patients (85.2 and 75.5% according to modified CDC criteria, respectively). Accordingly, the main risk factors for stroke-associated pneumonia, dysphagia with risk of aspiration and mechanical ventilation, were significantly more common in patients with sepsis. The overall frequency of pneumonia in our cohort (33.2 and 25.9% according to modified CDC criteria, respectively) was high compared to the frequency described for a general stroke population (12%) (3). This may be explained by the fact that all patients in our cohort had EVT in general anesthesia, which is associated with a higher risk of pneumonia. Indeed, a *post-hoc* analysis of the SWIFT PRIME thrombectomy trial demonstrated a similar frequency of pneumonia after EVT in general anesthesia as in our cohort (34.4%) (18). The overall infection rate including patients with and without sepsis was rather high (52.2%) in our cohort compared to the rates reported for general stroke populations (24–36%) and intensive care stroke patients (38–52%) (1). Possible reasons are that LVOS patients share more characteristics with intensive care patients than with general stroke patients, and that the diagnostic criteria for infections were liberal in our study. Application of strict operational criteria of infections leads to lower rate of infections, as reported above for pneumonia. Accordingly, the frequency of sepsis in a general stroke population including non-LVOS would be expected to be lower than in our cohort.

Pathophysiologically, there are several mechanisms making stroke patients prone to infections and consecutively sepsis. On the one hand, stroke patients often have an increased exposure to microbiological pathogens: Dysphagia and disorders of consciousness with impaired airway protection reflexes, and mechanical ventilation are risk factors for pneumonia (18, 19). Urinary catheters that are frequently used in severely affected stroke patients predispose to urinary tract infections. On the other hand, stroke affects the immune system as a host-intrinsic risk factor for infections (2, 19–21). Within hafter stroke, there is a systemic immunodepression, in particular a depression of $CD4^+$ T-lymphocytes as well as reduced proinflammatory and increased anti-inflammatory cytokines, mainly driven by an excessive activation of the autonomic nervous system, increasing the susceptibility for infections (19, 20, 22, 23). In response to an infection, a host inflammatory response is initiated – in the case of sepsis, this response becomes dysregulated on the basis of both proinflammatory and anti-inflammatory mechanisms and compromises organ function (24, 25). Moreover, stroke-associated infections are suspected to trigger an autoimmune response against brain antigens, which may explain the poor outcome in these patients (2, 26). In stroke patients with sepsis, this phenomenon might be particularly important for clinical outcome given the central role of the dysregulated immune response in sepsis.

The most frequently affected organ systems in patients with sepsis were respiration, the cardiovascular system and renal function, consistent with pneumogenic sepsis. In a subset of patients without sepsis, the analysis of SOFA subcategories revealed relevant organ dysfunction, for example respiratory failure in 5.3% of patients with infection without sepsis. In these patients, the total SOFA score did not show an increase of $\geq$2 compared to admission, explaining why they were not classified as sepsis cases. A worsening of CNS function was often observed in sepsis patients, which might have been either caused by septic encephalopathy, by the stroke itself, mechanical ventilation with consecutive sedation, or other stroke-related complications. This might hamper the applicability of the SOFA score to diagnose sepsis in stroke patients. Indeed, we observed that 16.7% of patients with sepsis no longer fulfilled the Sepsis-3 definition if the SOFA score was calculated without the CNS subcategory. This indicates that the diagnosis of sepsis was based on a worsening of the neurological status in these patients. Thus, clinical reasoning is needed in practice to determine if worsening of the neurological status is due to septic encephalopathy, the stroke itself or other stroke-related complications.

The qSOFA score, a resource-efficient screening tool for sepsis, demonstrated very good sensitivity, but only mediocre specificity for the diagnosis of sepsis in our cohort. An analysis of the qSOFA subcategories revealed that the rather low overall specificity was due to low specificities of the mental status and respiratory rate categories. The drawbacks of using the neurological status for diagnosis of sepsis in stroke patients are the same as discussed above for the SOFA score. The respiratory rate subcriterion was often met in all 3 groups (60.2 to 81.2%), indicating that tachypnea occurred not only due to infection, but also due to the stroke itself, as disturbances of respiratory patterns with tachypnea are frequently observed in stroke patients (27, 28). Accordingly, tachycardia was frequently observed in all patients, which may rather reflect stroke-associated cardiovascular autonomic dysfunction than a clinical sign of infection or sepsis in these patients (29). Thus, our data confirm that the qSOFA score may be a helpful screening tool that should not be used without confirmatory tests, such as the regular SOFA score (6).

Patients with sepsis had a significantly worse clinical outcome than control patients without infection and patients with an infection but without sepsis. The most drastic difference was observed for a poor outcome (mRS five or six), but secondary outcome measures also showed a worse outcome in sepsis patients after adjustment for possible confounders. Notably, patients with sepsis had a significantly higher NIHSS at 24 h than controls and patients with an infection without sepsis. This difference cannot be attributed to septic encephalopathy in most patients, as the median onset of sepsis was 2 days after admission. If the NIHSS at 24 h was taken into account in multivariable analyses instead of the NIHSS at admission, sepsis was still an independent predictor of a poor outcome, but with a smaller effect size. Thus, stroke severity partly mediated the poor outcome observed in sepsis patients. An analysis restricted

to sepsis patients in whom the diagnosis of sepsis was based on the dysfunction of organs other than the CNS also indicated that the association of sepsis with poor outcome was independent of factors affecting CNS function, such as stroke severity or mechanical ventilation with sedation.

The prevention, early diagnosis and effective treatment of sepsis might improve outcome after ET for LVOS. As the majority of cases were caused by pneumonia, preventative measures for pneumonia, such as swallowing assessments and therapy, oral hygiene measures and possibly the usage of conscious sedation for ET, may reduce the frequency of sepsis as well (18, 30–32). Previous trials showed that prophylactic antibiotic therapy does not improve outcome in stroke patients (33, 34). Thus, diagnostic criteria for infections, such as the SOFA score, should be applied thoroughly before antibiotic therapy is initiated. Collecting SOFA scores daily on a routine basis in patients with severe stroke would help with a timely diagnosis and might be a measure worthwhile exploring in future prospective studies.

This study has several limitations: the single center design, retrospective data collection and thus partly missing data, and that a special subgroup of stroke patients (LVOS undergoing ET) was studied, which limits the applicability of the results to a general population of stroke patients. A major limitation is that the SOFA score and thus the diagnosis of sepsis in stroke patients depended on stroke severity and other factors, such as mechanical ventilation. This might have affected the analysis of clinical outcome due to selection bias. Further, even though the same treatment guidelines were in use for all patients, the treatment might have deviated from the guidelines in some cases causing heterogeneity of treatment. Since we could not properly control for this, this is a potential source of omitted variable bias.

CONCLUSIONS

Sepsis frequently occurs in patients with LVOS undergoing ET and may be associated with poor clinical outcome. More studies are needed to determine specific risk factors and measures for early recognition to reduce the possibly negative impact of sepsis on the outcome after LVOS.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Ludwig-Maximilian University Munich, Germany, and the Ethics Committee of the University of Bonn, Germany. The patients/participants provided their written informed consent to participate in this study.

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AUTHOR CONTRIBUTIONS

SS and GP conceptualized and designed the study and drafted the manuscript. All authors acquired and analyzed the data and approved the final version. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.902809/full#supplementary-material

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4 Diskussion

In den vier dieser kumulativen Habilitationsschrift zugrundeliegenden Arbeiten wurden verschiedene Aspekte der Akutdiagnostik und –therapie von Hirninfarkten sowie der Vermeidung früher schlaganfallassoziierter Komplikationen analysiert. Der Wissenszugewinn im Kontext der aktuellen Studienlage sowie die Relevanz der Ergebnisse für die klinische Praxis werden im Folgenden Punkt für Punkt dargestellt.

Das zentrale Ergebnis der Arbeit "Workflow Times and Outcome of Endovascular Therapy in Stroke Patients with Initial MRI or CT" war, dass eine initiale Untersuchung mit MRT statt CT die Zeit von Aufnahme bis zum Beginn der Bildgebung im Arbeitsablauf der endovaskulären Schlaganfalltherapie verzögerte, jedoch ohne dass dies nachfolgende Arbeitsschritte verzögerte und ohne nachteiligen Effekt auf das klinische Outcome.

Der Vergleich dieser Ergebnisse zu den meisten vorherigen Studien, die unter 2.2.1 dargestellt wurden, ist nur eingeschränkt möglich, weil in den Vorarbeiten nicht jeder Einzelschritt des Prozessablaufes erhoben wurde. Zu einem ähnlichen Ergebnis wie die vorliegende Arbeit kam die registerbasierte Analyse von Kim et al. Hier wurde die Verzögerung der Gesamtprozesszeit bei Untersuchung mit MRT ebenfalls mit einer Verzögerung der Zeit von Aufnahme bis zur Bildgebung erklärt (Kim et al., 2019). Allerdings wurde nicht berichtet, ob der Zeitpunkt der Bildgebung sich auf den Beginn oder das Ende der bildgebenden Untersuchung bezieht, was die Interpretation und Vergleichbarkeit mit der vorliegenden Arbeit deutlich einschränkt. Des Weiteren erhielten in dieser Studie etwa ein Drittel der Patienten in der MRT-Gruppe eine zusätzliche CT-Angiographie, was die Ergebnisse in der MRT-Gruppe verfälscht, während in der vorliegenden Arbeit Patienten mit MRT und zusätzlicher CT-Diagnostik aus diesem Grund ausgeschlossen wurden. In der Studie von Provost et al. wurden längere Untersuchungszeiten bei MRT gegenüber CT, jedoch keine Verzögerung der nachfolgenden Arbeitsschritte festgestellt (Provost et al., 2019). Der in der vorliegenden Arbeit wichtigste Parameter, die Zeit von Aufnahme bis zur Bildgebung, wurde in dieser Studie jedoch nicht untersucht. Die Ergebnisse der vorliegenden Arbeit stützen also die Ergebnisse der beiden, bisher am besten

konzipierten Studien zu dieser Fragestellung, ergänzen jedoch das bisherige Wissen durch eine detailliertere Analyse sowohl zum zeitlichen Arbeitsablauf als auch zu Störfaktoren, die in bisherigen Studien nicht adäquat analysiert wurden. Folgende Schlüsse für die klinische Praxis ergeben sich aus dieser Arbeit: Da sich das klinische Outcome in der MRT- nicht von der CT-Gruppe unterschied, können beide Verfahren gleichwertig in der Diagnostik von Schlaganfallpatienten vor der ET zum Einsatz kommen. Eine MRT-Untersuchung geht jedoch mit einer Verzögerung im Arbeitsablauf einher, die vor Beginn der MRT-Untersuchung stattfindet und nicht durch die längere Untersuchungszeit des MRT bedingt ist. Mit diesem Wissen können die praktischen Arbeitsabläufe bei einer initialen MRT-Untersuchung optimiert werden, damit die Vorteile des MRT gegenüber dem CT nicht durch eine Verzögerung des Arbeitsablaufes aufgewogen werden.

In der Arbeit „Recent silent infarcts do not increase the risk of haemorrhage after intravenous thrombolysis" wurde gezeigt, dass der MR-tomographische Nachweis von RSIs bei Patienten, die aufgrund eines akuten Hirninfarkt mittels IVT behandelt wurden, nicht mit einem erhöhten Risiko einer hämorrhagischen Transformation oder einem schlechteren klinischen Outcome assoziiert ist.

Die beobachtete Häufigkeit von RSIs lag bei 11,8% und somit in einer ähnlichen Größenordnung wie in den Vorarbeiten von Gaillard et al. (11,6%) und Tisserand et al. (18,3%) (Tisserand et al., 2011; Gaillard et al., 2012). Dies illustriert, dass es sich bei RSIs um einen häufigen Nebenbefund in der MRT-Diagnostik von Patienten mit akutem Hirninfarkt handelt. Die Häufigkeit von symptomatischen intrazerebralen Blutungen nach IVT bei Patienten mit RSIs war mit 1,8% vergleichbar zu der großen SITS-MOST-Registerkohorte (Wahlgren et al., 2007). Die Häufigkeit aller hämorrhagischen Transformationen lag mit 26,7% ebenfalls im zu erwartenden Bereich (29,7% bei Caparros et al.) (Caparros et al., 2020). Insgesamt sind die Daten der untersuchten Kohorte somit als repräsentativ und valide anzusehen. Die Ergebnisse der vorliegenden Arbeit deuten darauf hin, dass das Vorliegen von RSIs nicht mit einem erhöhten Risiko einer hämorrhagischen Transformation oder einem schlechten klinischen Outcome einhergeht. Daraus folgt, dass die Kontraindikation „Schlaganfall in den letzten drei

Monaten“ für die IVT zu hinterfragen und zu präzisieren ist. Gemäß den Ergebnissen der vorliegenden Arbeit sollte das Vorliegen von RSIs nicht als Kontraindikation für eine IVT betrachtet werden. Über rezente symptomatische Hirninfarkte lässt die vorliegende Arbeit jedoch keine Rückschlüsse zu, so dass diese weiterhin als Kontraindikation für eine IVT gelten sollten.

In der Arbeit “Severe Dysphagie Predicts Poststroke Fever“ wurde nachgewiesen, dass eine schwergradige Dysphagie ein unabhängiger Risikofaktor für schlaganfallassoziiertes Fieber ist. Dieser Zusammenhang wurde bereits von Ruborg et al. beschrieben, wie unter 2.3.3 erwähnt, jedoch erfolgte in dieser Studie lediglich ein nicht näher spezifiziertes Schluckscreening und keine vollständige klinische Schluckuntersuchung oder eine apparative Diagnostik, so dass der Schweregrad der Dysphagie in dieser Studie nicht bestimmt werden konnte (Ruborg et al., 2017). In der vorliegenden Arbeit erfolgte dagegen eine ausführliche klinische Schluckuntersuchung, die bei Patienten mit unklarem Befund um eine apparative Diagnostik mittels FEES ergänzt wurde. So konnte gezeigt werden, dass eine schwergradige Dysphagie mit klinisch oder apparativ nachgewiesenem Aspirationsrisiko einen unabhängigen Risikofaktor für Fieber darstellt. In zwei weiteren Studien wurde das Vorliegen einer nasogastralen Sonde als Prädiktor für Fieber und auch als unabhängiger Prädiktor für eine Pneumonie, die häufigste Ursache für Fieber, beschrieben (Brogan et al., 2014; Muscari et al., 2015; Wästfelt et al., 2018). In der vorliegenden Arbeit wurde mit Hilfe der detaillierten Daten zur Schluckfunktion gezeigt, dass das Vorliegen einer nasogastralen Sonde keinen unabhängigen Prädiktor für Fieber darstellt, sondern der entscheidende Faktor das Vorliegen einer schweren Dysphagie ist. Aus den Ergebnissen dieser Arbeit kann geschlussfolgert werden, dass eine detaillierte Dysphagiediagnostik Patienten mit schwerer Dysphagie und somit einem Risiko für die Entwicklung von schlaganfallassoziiertem Fieber identifizieren könnte. Dieses Wissen könnte genutzt werden, um Fieber als Komplikation nach Schlaganfall vorzubeugen und so ein besseres klinisches Outcome zu erzielen. Um diese Hypothese zu überprüfen, sind prospektive randomisierte Studien vonnöten.

Das Auftreten von schlaganfallassoziiertem Fieber ist eng verknüpft mit dem Auftreten von schlaganfallassoziierten Infektionen. In der dieser Habilitation zugrundeliegenden Arbeit „Sepsis in Patients With Large Vessel Occlusion Stroke – Clinical Characteristics and Outcome" wurde die Sepsis als Komplikation schlaganfallassoziierter Infektionen untersucht.

Die Inzidenz einer schlaganfallassoziierten Sepsis betrug in der untersuchten Kohorte von Schlaganfallpatienten mit Verschlüssen von großen Gefäßen 13,3%. Diese Ergebnisse sind ähnlich wie in der einzigen anderen Arbeit zur schlaganfallassoziierten Sepsis (12,6%) (Berger et al., 2014). Eine Assoziation von Sepsis mit einem schlechten Outcome nach Schlaganfall wurde ebenfalls in beiden Arbeiten festgestellt. Die Studien sind allerdings nicht direkt vergleichbar, da in der Arbeit von Berger et al. nicht die aktuell gültige Sepsis-3-Definition zur Anwendung kam und eine andere Kohorte, nämlich intensivpflichtige Patienten inklusive hämorrhagischer Schlaganfälle, untersucht wurde, so dass die vorliegende Arbeit erstmalig valide aktuelle Daten für Schlaganfallpatienten mit Verschlüssen von großen Gefäßen bietet.

Der zum Screening auf eine Sepsis entwickelte qSOFA-Score wies bei Schlaganfallpatienten in der untersuchten Kohorte zwar eine gute Sensitivität, jedoch eine unzureichende Spezifität auf. Zurückgeführt werden konnte dies auf die qSOFA-Parameter verändertes Bewusstsein und Tachypnoe, die eine sehr niedrige Spezifität aufwiesen. Ein verändertes Bewusstsein wird bei Schlaganfallpatienten häufig als direkte Folge des Schlaganfalls beobachtet und ist seltener Folge einer septischen Enzephalopathie, was die niedrige Spezifität dieses Parameters erklärt. Ebenso kann eine Tachypnoe bei Schlaganfallpatienten nicht nur infolge einer Sepsis auftreten, sondern ist häufig durch eine zentrale Atemstörung infolge des Schlaganfall bedingt (Lee et al., 1974; Kim et al., 2018). Somit sind weitere Studien nötig, um spezifischere Diagnostikinstrumente zur Erkennung der schlaganfallassoziierten Sepsis zu entwickeln und den negativen Einfluss der Sepsis auf das Outcome nach Schlaganfall zu vermindern.

5 Zusammenfassung

Der Schlaganfall ist weltweit eine der führenden Ursachen für Mortalität und erworbene Behinderungen. Das klinische Outcome nach einem Schlaganfall kann mittels Behandlung auf der Stroke Unit einschließlich der Akuttherapie mit intravenöser Thrombolyse und endovaskulärer Therapie positiv beeinflusst werden. In den vier Arbeiten, die dieser kumulativen Habilitationsschrift zugrunde liegen, wurden verschiedene Aspekte der Akuttherapie und der Behandlung früher Komplikationen von Schlaganfällen mittels klinischer Kohorten- und Registerstudien analysiert.

Eine Analyse des Arbeitsablaufes bei der endovaskulären Schlaganfalltherapie ergab, dass eine initiale Bildgebung mittels MRT im Vergleich zu einer CT-Bildgebung zu einer Verzögerung des Zeitintervalls von der Aufnahme bis zum Beginn der Bildgebung führt. Die Wahl der Bildgebungsmodalität beeinflusste jedoch weder die darauffolgenden Arbeitsschritte noch das klinische Outcome nach drei Monaten. Dies spricht dafür, dass sowohl eine MRT- als auch eine CT-Diagnostik eine effektive endovaskuläre Schlaganfalltherapie ermöglichen können. Bei Einsatz des MRTs ist jedoch eine Optimierung des Arbeitsablaufes, insbesondere von der Aufnahme bis zum Beginn der Bildgebung, nötig, um Verzögerungen bei der Behandlung zu vermeiden.

Das Vorliegen von rezenten Hirninfarkten gilt als Kontraindikation für die intravenöse Thrombolysetherapie bei akutem Hirninfarkt. Eine Analyse von Blutungskomplikationen und klinischem Outcome nach intravenöser Thrombolyse von Patienten, die neben dem akuten Hirninfarkt zusätzlich im MRT rezente klinische stumme Hirninfarkte aufwiesen, ergab jedoch, dass diese rezenten klinische stummen Infarkte weder mit einem erhöhten Blutungsrisiko noch einem schlechteren klinische Outcome einhergehen. Diese Ergebnisse sind hilfreich, um die Indikation zu intravenösen Thrombolysetherapie präziser zu stellen und diese Therapie einer breiteren Patientengruppe anzubieten.

Als eine wesentliche Ursache für die schlaganfallassoziierte Komplikation Fieber wurde eine schwergradige Dysphagie identifiziert. Dieser Zusammenhang wurde erstmalig anhand einer

Stufendiagnostik der Dysphagie mit klinischer Schluckuntersuchung ergänzt durch apparative Verfahren belegt. Eine detaillierte Dysphagiediagnostik erscheint daher hilfreich, um Fieber als Komplikation nach Schlaganfall vorzubeugen und so ein besseres klinisches Outcome zu erreichen.

Infolge schlaganfallassoziierter Infektionen kann es zu einer Sepsis kommen. In der Analyse einer Kohorte von Schlaganfallpatienten mit Verschluss eines großen hirnversorgenden Gefäßes war festzustellen, dass die Sepsis eine häufige Komplikation ist und einen unabhängigen Prädiktor für ein schlechtes klinisches Outcome darstellt.

Zusammenfassend bieten die Ergebnisse der vier Arbeiten, die dieser kumulativen Habilitationsschrift zugrunde liegen, mehrere Ansatzpunkte, mit denen die Akuttherapie von Schlaganfällen verbessert und frühe schlaganfallassoziierte Komplikationen vermieden und behandelt werden können.

6 Mögliche Überlappung zu anderen kumulativen Habilitationsschriften

Die vier dieser kumulativen Habilitationsschrift zugrundeliegenden Originalarbeiten habe ich als alleiniger hauptverantwortlicher Erstautor veröffentlicht. Eine Überlappung zu anderen kumulativen Habilitationsschriften ist somit nicht gegeben.

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