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Diagnostik und Prävention des Post-Intensive Care Syndroms bei Überlebenden kritischer Erkrankung

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Abkürzungsverzeichnis

6-MWT	Sechs-Minuten-Gehtest
ARDS	Acute Respiratory Distress Syndrome
COS	Core Outcome Set
EQ-5D-5L	EuroQol-5 Dimensions-5 Level
HADS-A	Hospital Anxiety and Depression Scale–Anxiety Subscale
HADS-D	Hospital Anxiety and Depression Scale–Depression Subscale
HrQoL	Health-related Quality of Life
ICU-AW	Intensive Care Unit-acquired Weakness
IES-R	Impact of Event Scale–Revised
ITS	Intensivstation
KI	Konfidenzintervall
OR	Odds Ratio
PICS	Post-Intensive Care Syndrom
PTBS	Posttraumatische Belastungsstörung
QI	Qualitätsindikator
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomisierte kontrollierte Studie
SF-36	Short Form-36

1. Einleitung

1.1. Überlebende kritischer Erkrankung: Eine wachsende Herausforderung

In den letzten Jahrzehnten sind in Deutschland und den Vereinigten Staaten die Zahl der intensivstationären Betten, die Zahl der intensivstationären Behandlungstage und die intensivstationären Belegungsraten angestiegen [1-5]. Auch global wird ein steigender Bedarf intensivstationärer Versorgung vorhergesagt [6-8]. In den USA versterben derzeit bereits zwei von fünf Personen im Krankenhaus und einer von fünf Personen auf der Intensivstation (ITS) [9]. Parallel zum steigenden Bedarf zeigt sich bei intensivstationär behandelten Patient*innen ein steigendes Alter, ein steigender Body Mass Index, eine steigende Krankheitsschwere (gemessen am Acute Physiology And Chronic Health Evaluation Score) und eine steigende Rate an Patient*innen, die mit Vasoaktiva behandelt werden [10]. Diesem Anstieg der Krankheitsschwere stehen in den letzten Jahrzehnten sinkende Mortalitätsraten von ITS-Patient*innen gegenüber [10-12], bedingt durch technologische Fortschritte und neue, evidenzbasierte Behandlungen. Aufgrund steigender Patientenzahlen, gepaart mit sinkenden Mortalitätsraten, entsteht eine wachsende Gruppe von Überlebenden kritischer Erkrankung und intensivstationärer Behandlung [13].

1.2. Mortalität und funktionelle Beeinträchtigungen als Outcome-Parameter kritischer Erkrankung

In der Vergangenheit fokussierte sich die intensivmedizinische Forschung auf die Untersuchung der Mortalität als Outcome-Parameter. Neue Interventionen ließen sich daran messen, ob sie mit einer Verringerung der Sterblichkeit einhergingen [14, 15]. Obgleich die Sterblichkeit zweifelsohne noch immer ein sehr wichtiger Parameter ist, zeigte sich, dass bloßes Überleben für viele Intensivpatient*innen nicht das wichtigste Outcome ist [16]. In einer im New England Journal of Medicine publizierten Studie wurden 226 Patient*innen über 60 Jahre mit fortgeschrittener internistischer Erkrankung und begrenzter Lebenserwartung nach ihren Behandlungspräferenzen befragt [17]. Im ersten Szenario war die Behandlung mit geringer Belastung (z.B. Blutentnahmen oder Infusionen) und einer vollen Regeneration verbunden, im zweiten Szenario mit einer hohen Belastung (z.B. Operationen oder ITS-Behandlung) und

einer vollen Regeneration und im dritten sowie vierten Szenario mit einer niedrigen Belastung und schweren physischen Einschränkungen (Bettlägerigkeit, Pflegebedürftigkeit) bzw. schweren kognitiven Beeinträchtigungen. Die Alternative zur Behandlung war stets das sichere Versterben. Ein Anteil von 88.8% wünschten eine Behandlung mit großer Belastung, wenn diese mit vollständiger Regeneration verbunden war, jedoch wünschten sich lediglich 25.6% bzw. 11.2% eine Behandlung, wenn diese mit schweren physischen bzw. schweren kognitiven Beeinträchtigungen verbunden war [17]. Das Überleben ohne funktionelle Beeinträchtigungen hatte somit für teilnehmende Patient*innen einen hohen Stellenwert. In einer anderen Studie bewertete die Mehrzahl der Patient*innen Situationen funktioneller Beeinträchtigungen, wie z.B. die langfristige Abhängigkeit von einem Beatmungsgerät, als genauso schlimm oder sogar schlimmer als das Versterben [18]. Eine weitere Umfrage unter 121 Patient*innen, Familienmitgliedern und Forscher*innen zur Relevanz von 19 Domänen als Outcomes zukünftiger Studien zum akuten Lungenversagen (englisch Acute Respiratory Distress Syndrome, ARDS) zeigte, dass >90% der Patient*innen und Familienmitglieder kognitive Funktionen, mentale Gesundheit und physische Funktionen als wichtig oder sehr wichtig erachteten. Überleben wurde lediglich von 72% bzw. 83% der Patient*innen und Familienmitglieder als ein wichtiger oder sehr wichtiger Outcome-Parameter bewertet [19].

1.3. Post-Intensive Care Syndrom bei Überlebenden kritischer Erkrankung

Ihrer hohen Bedeutung für Patient*innen folgend, hat sich die intensivmedizinische Forschung in den letzten Jahrzehnten zunehmend auf funktionelle Beeinträchtigungen nach intensivstationärer Behandlung fokussiert [20]. Diese Beeinträchtigungen betreffen verschiedene kognitive Funktionen, die mentale Gesundheit, physische Funktionen, soziale Funktionen wie Teilhabe am gesellschaftlichen Leben und die gesundheitsbezogene Lebensqualität (englisch Health-related Quality of Life, HrQoL). In einer Konsensus-Konferenz der amerikanischen Society of Critical Care Medicine im Jahr 2010 wurden die funktionellen Beeinträchtigungen nach intensivstationärer Behandlung konzeptionell unter dem Terminus Post-Intensive Care Syndrom (PICS) zusammengefasst [21]. PICS beschreibt neue Beeinträchtigungen der Kognition, der mentalen Gesundheit (vornehmlich Depressionen, Posttraumatische

Belastungsstörungen (PTBS) und Angststörungen) und der physischen Funktionen (z.B. der Muskelkraft, der pulmonalen Funktionen und Einschränkungen in der Durchführung täglicher Aktivitäten), welche negative Auswirkungen auf die HrQoL haben [21]. Die Beeinträchtigungen der mentalen Gesundheit von Familienmitgliedern von Überlebenden kritischer Erkrankung wurden zudem als PICS-Family zusammengefasst [21]. Mit einer häufigen Überlappung von Beeinträchtigungen in den verschiedenen Domänen besitzt PICS einen syndromalen Charakter [22].

1.3.1. Beeinträchtigungen der Kognition

Überlebende intensivmedizinischer Behandlung leiden häufig an Beeinträchtigungen verschiedener kognitiver Funktionen. Eine große Studie (BRAIN-ICU), in die 821 intensivstationäre Patient*innen mit Lungenversagen oder Schock eingeschlossen wurden, untersuchte die Patient*innen nach drei und 12 Monaten mittels der Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), einem Test für die globale Kognition (inklusive der Domänen Kurzzeitgedächtnis, Aufmerksamkeit, Sprache und räumlich-visuelle Vorstellung), und dem Trail Making Test, einem Test für die ausführende Funktion (kognitive Flexibilität und Umschaltvermögen) [23]. Der mediane RBANS-Score der Teilnehmer*innen nach drei und 12 Monaten entsprach einer milden kognitiven Dysfunktion. Nach drei und 12 Monaten zeigten 40% bzw. 34% der überlebenden Patient*innen Ergebnisse, die mit einem moderaten Schädel-Hirn-Trauma vereinbar wären. Etwa ein Viertel der überlebenden Patient*innen zeigten gar kognitive Funktionen vergleichbar mit Alzheimer-Erkrankten [23]. Einschränkungen traten auch beim Trail Making Test auf [23]. Eine weitere Studie unter 74 ARDS-Überlebenden verwendete eine neurokognitive Testbatterie zur Erfassung der globalen kognitiven Funktion, der Konzentration, des Gedächtnisses, der Prozessierungsgeschwindigkeit, der räumlich-visuellen Vorstellung und der ausführenden Funktion. Zum Zeitpunkt der Krankenhausentlassung zeigten 73% der Patient*innen relevante kognitive Einschränkungen. Auf eine gewisse Erholung im ersten Jahr nach Entlassung hinweisend, verringerte sich diese Zahl auf 46% nach einem und auf 47% nach zwei Jahren [24]. In einer anderen prospektiven Populationsstudie aus Seattle wurden 2929 Personen, die mindestens 65 Jahre alt waren, über einen mittleren Zeitraum von sechs Jahren alle zwei Jahre kognitiv getestet. Patient*innen, welche im Krankenhaus oder gar auf der ITS behandelt wurden, zeigten einen signifikant größere Abnahme

kognitiver Leistungen als Patient*innen, die nicht im Krankenhaus behandelt wurden [25]. Auch andere Studien mit verschiedenen Designs und Patientenkohorten (z.B. Sepsis-Patient*innen, ARDS-Patient*innen oder allgemeinen ITS-Patient*innen) zeigten relevante Einschränkungen verschiedener kognitiver Funktionen bei Überlebenden kritischer Erkrankung [26-33]. Eine systematische Übersichtsarbeit mit 19 Studien fand kognitive Beeinträchtigungen bei 4% bis 62% der Patient*innen, die Follow-Up-Zeiten der eingeschlossenen Studien variierten jedoch von vier Monaten bis 156 Monate [34]. Eine weitere große Schwierigkeit beim Vergleich der Prävalenz-Zahlen zwischen den Arbeiten ist die große Variabilität der verwendeten Instrumente und der getesteten kognitiven Funktionen. Manche Studien verwendeten Screening-Instrumente, andere Studien verwendeten neuropsychologische Testbatterien. Zudem variierten die Patientenkohorten. Auch wenn die grundsätzliche Aussage kognitiver Beeinträchtigungen nach ITS-Behandlung Konsens zu sein scheint, erklärt diese Heterogenität der Studien die im Detail stark divergierenden Prävalenzen [34].

1.3.2. Beeinträchtigungen der mentalen Gesundheit

Neben kognitiven Störungen sind Beeinträchtigungen der mentalen Gesundheit bei Überlebenden kritischer Erkrankung häufig. Dies betrifft unter anderem die Prävalenz von Symptomen einer Depression. Beispielsweise hatten in einer Analyse der BRAIN-ICU-Studie, einer prospektiven multizentrischen Kohortenstudie mit 821 Überlebenden eines Lungenversagens oder Schocks, etwa ein Drittel der Patient*innen drei und 12 Monate nach Entlassung Symptome einer Depression [35]. Eine systematische Übersichtsarbeit von 2016 fand 38 Studien, welche die Symptome einer Depression nach kritischer Erkrankung untersucht haben. Die Autor*innen fanden eine Prävalenz von 29% sowohl zwei bis drei Monate als auch 12 bis 14 Monate nach Entlassung [36]. In einer früheren systematischen Übersichtsarbeit von 2009, welche 14 Artikel mit 1621 Patient*innen einschloss, betrug die Prävalenz einer “klinisch signifikanten“ Depression im Median 28% [37]. Die Follow-Ups in den eingeschlossenen Studien wurden zwei Wochen bis 14 Monate nach Entlassung durchgeführt. In einer Übersichtsarbeit von 2008, welche sich speziell mit Patient*innen nach akutem Lungenschaden und ARDS beschäftigte, zeigten 17% bis 43% der Patient*innen in vier eingeschlossenen Observationsstudien nach Entlassung Symptome einer „klinisch signifikanten“ Depression [38].

Neben Depressionen sind Überlebende intensivstationärer Behandlung häufig von PTBS betroffen. In einer prospektiven multizentrischen Kohortenstudie in 41 Krankenhäusern mit 698 ARDS-Überlebenden betrug die PTBS-Prävalenz, gemessen mit der Impact of Event Scale–Revised (IES-R), 24% nach sechs Monaten und 23% nach 12 Monaten [39]. Eine 2015 veröffentlichte systematische Übersichtsarbeit fand 40 Studien, welche die Prävalenz von PTBS nach kritischer Erkrankung untersuchten, am häufigsten mit der IES [40]. In sechs Studien mit 456 Patient*innen betrug die mittlere PTBS-Prävalenz 25% (95%-Konfidenzintervall [KI] 18–34%) bzw. 44% (95%-KI 36–52%) in den ersten sechs Monaten, je nach verwendetem IES-Grenzwert. Fünf Studien mit 698 Patient*innen, die die PTBS-Prävalenz zwischen sieben Monaten und einem Jahr nach Entlassung untersuchten, zeigten mit 17% (95%-KI 10–26%) bzw. 34% (95%-KI 22–50%), je nach zugrundeliegendem IES-Grenzwert, etwas niedrigere mittlere Prävalenzen [40].

Neben Depressionen und PTBS treten bei ITS-Überlebenden häufig Angststörungen auf. In einer prospektiven longitudinalen Kohortenstudie mit 74 ARDS-Überlebenden zeigten 24% und 23% der Überlebenden nach einem bzw. zwei Jahren Zeichen einer Angststörung [24]. Eine systematische Übersichtsarbeit von 2016 fand 27 Studien mit insgesamt 2880 Patient*innen, welche die Prävalenz von Angststörungen nach ITS-Aufenthalt untersuchten. Zwei bis drei Monate nach Entlassung betrug die Prävalenz von Symptomen einer Angststörung in 12 Studien und 1080 Patient*innen 32% (95%-KI 27-38%), nach sechs Monaten in sieben Studien und 760 Patient*innen 40% (95%-KI 33-46%) und nach 12-14 Monaten in sechs Studien und 1041 Patient*innen 34% (95%-KI 25-42%) [41]. Das am häufigsten eingesetzte Instrument zur Detektion einer Angststörung war die Hospital Anxiety and Depression Scale–Anxiety Subscale (HADS-A) [41].

Patient*innen zeigten sogar bis zu fünf Jahre nach Entlassung von der ITS noch Symptome einer PTBS, Angststörung und Depression. Beeinträchtigungen traten selten isoliert auf, sondern in der Mehrzahl der Fälle in Kombination; 13% der Patient*innen zeigten sogar alle drei Krankheitsbilder [42, 43]. Überlappungen von Depression, PTBS und Angststörungen wurden auch in anderen Studien beschrieben [39].

1.3.3. Beeinträchtigungen der physischen Gesundheit

Zusätzlich zu kognitiven und mentalen Beeinträchtigungen leiden Überlebende kritischer Erkrankung häufig an Einschränkungen der physischen Gesundheit und Mobilität, was wiederum ihre Alltagsfunktionalität verringert. Beispielsweise wurden in einer prospektiven, longitudinalen Kohortenstudie, die 2011 im New England Journal of Medicine publiziert wurde, 109 ARDS-Patient*innen von vier kanadischen Zentren eingeschlossen [44]. In den ersten Monaten nach Entlassung zeigten die Patient*innen deutliche Einschränkungen ihrer Ausdauer im Sechs-Minuten-Gehtest (englisch Six-Minute Walk Test, 6-MWT). Die Ausdauer erholte sich in den ersten eineinhalb Jahren, blieb jedoch auch fünf Jahre nach Entlassung mit 76% der vorhergesagten Distanz im 6-MWT unter der Referenzpopulation der nicht kritisch Erkrankten [44]. In einer anderen prospektiven Observationsstudie mit 56 australischen ITS-Überlebenden, welche zuvor bereits an einer randomisierten kontrollierten Studie (englisch randomized controlled trial, RCT) teilgenommen hatten [45], wurden vier bis fünf Jahre nach ITS-Entlassung die körperlichen Funktionen mittels 6-MWT, Timed Up-and-Go und Handkraftmessung untersucht [46]. Obwohl bei mehr als einem Drittel der Patient*innen die Gehstrecke des 6-MWT im Vergleich zum Ein-Jahres-Follow-Up zugenommen hatte, betrug die Gehstrecke nach vier bis fünf Jahren nur 70% der erwarteten Distanz der alters- und geschlechtsspezifischen Referenzpopulation [46]. In einer weiteren Studie, einer sekundären Analyse einer RCT zu einem Rehabilitationsprogramm nach ITS-Entlassung, wurden Überlebende kritischer Erkrankung eine und 26 Wochen nach Entlassung untersucht [47]. Hier zeigten etwa zwei Drittel der Patient*innen zwischen beiden Evaluationszeitpunkten eine Verbesserung im 6-MWT von 75 Metern oder mehr, was für eine gewisse Erholung der körperlichen Funktionen nach der kritischen Erkrankung spricht [47]. Auch andere Studien fanden relevante Einschränkungen der physischen Gesundheit, der Mobilität und der Muskelfunktion nach Entlassung von der ITS, die sich teilweise jedoch in den Monaten nach Entlassung wieder unvollständig erholte [48-51]. Größere Beeinträchtigungen der körperlichen Funktionen bei Krankenhaus-Entlassung waren zudem mit einer höheren Mortalität in den Monaten nach Entlassung assoziiert [52].

Das Auftreten einer auf der ITS erworbenen Muskelschwäche während der kritischen Erkrankung (englisch Intensive Care Unit-acquired Weakness, ICU-AW) erhöht das Risiko von langfristigen Beeinträchtigungen der körperlichen Funktionen [53, 54]. ICU-

AW entsteht durch eine Polyneuropathie (englisch Critical Illness Polyneuropathy) und durch eine primäre Myopathie (englisch Critical Illness Myopathy). Es gibt Überlappungen zwischen Critical Illness Polyneuropathy und Myopathy [55, 56]. Das Vorliegen einer ICU-AW wird mithilfe der Medical Research Council-Skala diagnostiziert, welche die Muskelkraft verschiedener Muskelgruppen des Körpers untersucht [57]. Eine Punktzahl unter 48 diagnostiziert eine ICU-AW [55, 58]. Das Auftreten einer ICU-AW ist assoziiert mit einer erhöhten Sechs-Monats-Mortalität [59], Ein-Jahres-Mortalität [60] und Fünf-Jahres-Mortalität [61].

Muskelschwäche und Beeinträchtigungen der physischen Funktionen nach ITS-Entlassung tragen zu funktionellen Problemen der Betroffenen bei. Eine Analyse der Patient*innen der BRAIN-ICU-Studie, Überlebende eines Lungenversagens oder Schocks, zeigte, dass 32% der Patient*innen nach drei Monaten und 27% der Patient*innen nach 12 Monaten Einschränkungen in Basis-Aktivitäten des täglichen Lebens (englisch Activities of Daily Living) hatten, gemessen mit der Katz Activities of Daily Living-Skala [35]. Diese Aktivitäten beinhalteten z.B. die Nahrungsaufnahme oder das Waschen. Zudem zeigten 26% der Patient*innen nach drei Monaten und 23% der Patient*innen nach 12 Monaten Beeinträchtigungen in instrumentalen Aktivitäten des täglichen Lebens (englisch Instrumental Activities of Daily Living) [35]. Diese Aktivitäten beinhalteten z.B. das Kümmern um die eigenen Finanzen. Auch andere Studien fanden bei Überlebenden kritischer Erkrankung Probleme bei der Bewältigung alltäglicher Aktivitäten [62]. Es konnte zudem gezeigt werden, dass Überlebende kritischer Erkrankung zwei Monate nach ITS-Entlassung im Mittel nur 57 Minuten pro Tag körperlich aktiv waren; 90% ihrer wachen Zeit waren die Studienteilnehmer körperlich inaktiv [63].

1.3.4. Beeinträchtigungen der gesundheitsbezogenen Lebensqualität

Funktionelle Beeinträchtigungen von physischer Gesundheit, Kognition und mentaler Gesundheit vermindern die HrQoL bei Überlebenden kritischer Erkrankung. Dies wurde in zahlreichen Studien (z.B. [64-67]) und mehreren systematischen Übersichtsarbeiten bereits gezeigt. Ein systematisches Review von 2019 identifizierte 48 Studien, welche die HrQoL nach Entlassung von der ITS erhoben [68]. Die HrQoL nach Entlassung war in den meisten Domänen unterhalb der HrQoL einer Referenzpopulation ohne ITS-Aufenthalt. Auch bereits vor ITS-Aufnahme war die HrQoL stets schlechter als in einer Referenzpopulation [68]. Unter allgemeinen ITS-

Patient*innen, besonders schwer kranken ITS-Patient*innen und Sepsis-Patient*innen kam es zu einer Verbesserung der physischen Funktion, der Vitalität und der sozialen Funktion in den ersten Monaten nach Entlassung [68]. Andere systematische Übersichten kamen zu ähnlichen Ergebnissen: Ein systematisches Review von 2005 analysierte 21 Studien mit 7320 Patient*innen [69], ein anderes Review von 2010 15 Studien [70]. Auch hier schlussfolgerten die Autor*innen, dass die HrQoL bereits vor ITS-Aufnahme schlechter als in den Referenzpopulationen war und sich nach ITS-Entlassung teilweise und auch nur inkomplett erholte [69, 70]. Die am häufigsten verwendeten Instrumente zur Erhebung der HrQoL sind der Short Form-36 (SF-36) und der EuroQol-5 Dimensions (EQ-5D) [68]. Der SF-36 und der EQ-5D sind generische Instrumente zur Erfassung der HrQoL, die nicht speziell für ITS-Patient*innen entwickelt wurde [71-73].

Der Gesundheitsstatus vor Aufnahme auf die ITS scheint eine wichtige Rolle bei funktionellen Langzeit-Outcomes und der HrQoL nach Entlassung zu spielen [74]. Eine niedrige HrQoL vor dem ITS-Aufenthalt [75-79] und vorher bestehende Komorbiditäten [78, 80] sind mit einer schlechteren HrQoL nach Entlassung assoziiert. Da jedoch eine ITS-Aufnahme in der Regel nicht vorhersehbar ist, gibt es wenige Studien, die den HrQoL-Status prospektiv vor Aufnahme auf die ITS erhoben haben. Die meisten Studien erhoben die HrQoL vor dem ITS-Aufenthalt retrospektiv, indem Patient*innen zum Follow-Up oder während der ITS-Behandlung rückwirkend zu ihrem Prä-ITS-Status befragt wurden. In dem oben zitierten systematischen Review wurden fünfzehn Studien identifiziert [68], die einen Prä-ITS-Status retrospektiv zum Zeitpunkt des Follow-Ups erhoben hatten (z.B. [65, 76, 81-85]). Eine kürzlich erschienene Studie mit 2345 Patient*innen untersuchte neu aufgetretene physische, mentale und kognitive Beeinträchtigungen ein Jahr nach ITS-Behandlung, indem Patient*innen, die sich einer elektiven Operation mit geplanter ITS-Aufnahme unterzogen, vor Krankenhausaufnahme ein Assessment durchführten. Bei Patient*innen mit nicht vorhersehbarer ITS-Aufnahme wurde das Assessment zu Beginn des Aufenthalts retrospektiv durchgeführt [86]. Alle Patient*innen wurden nach einem Jahr nachuntersucht. Patient*innen, die aufgrund von Notfalloperationen auf die ITS aufgenommen wurden, zeigten im Gegensatz zu Patient*innen mit elektiven Operationen oder medizinischen Aufnahmegründen einen deutlichen Abfall ihrer

HrQoL nach Entlassung und eine höhere Inzidenz von Angststörungen, Müdigkeit, Störungen der Kognition und Depressionen nach einem Jahr [86].

1.3.5. Beeinträchtigungen durch langfristige Abhängigkeit vom Respirator

Ein weiterer Aspekt funktioneller Beeinträchtigungen bei Überlebenden kritischer Erkrankung betrifft die maschinelle Beatmung. Eine Analyse von 991.571 ITS-Aufenthalten auf 160 ITS in den USA zwischen 2009 und 2013 zeigte, dass mehr als ein Viertel der Patient*innen eine invasive Beatmung benötigte [10]. Zudem zeigte eine Populationsstudie aller erwachsenen Patient*innen, die zwischen 2002 und 2013 in Ontario, Kanada, auf einer ITS behandelt und maschinell beatmet wurden, dass 5.4% der 213.680 Patient*innen eine Beatmung für >21 Tage benötigten [87]. Dies wird als prolongierte maschinelle Beatmung bezeichnet. Nur etwa die Hälfte dieser Patient*innen kann laut einem systematischen Lancet-Review während des Krankenhausaufenthalts erfolgreich von der maschinellen Beatmung entwöhnt werden [88]. Gelingt keine Entwöhnung von der Beatmung (auch Weaning genannt), kann unter Berücksichtigung des Patientenwillens die Entlassung in spezialisierte Weaning-Einrichtungen, in Rehabilitations-Einrichtungen, Pflegeeinrichtungen oder nach Hause erfolgen [89, 90]. Routinedaten aus Deutschland zeigen, dass die Zahl der Patient*innen mit einer Langzeitabhängigkeit vom Beatmungsgerät zwischen 2006 und 2016 [91] bzw. zwischen 2008 und 2019 deutlich zugenommen hat [92].

Ehemalige ITS-Patient*innen mit langfristiger Abhängigkeit vom Respirator sind aus der PICS-Perspektive relevant, da sie zum einen ein wenig untersuchtes Patientenkollektiv bilden und zum anderen sehr häufig funktionelle Langzeitbeeinträchtigungen zeigen [93, 94]. Eine deutsche Mixed-Methods-Studie mit 25 Patient*innen mit invasiver Heimbeatmung zeigte die stark eingeschränkte Lebensqualität der Teilnehmer*innen [93]. Die Mehrzahl der Patient*innen benötigte Unterstützung bei alltäglichen Aufgaben wie dem Anziehen oder dem Toilettengang. Die Patient*innen waren unzufrieden mit ihrer Mobilität, der Fähigkeit der Kommunikation, dem Leben im Allgemeinen, der Abhängigkeit von anderen und mit ihren sozialen Kontakten [93]. Circa ein Drittel der Patient*innen gab an, dass sie sich, sollten sie noch einmal vor der Entscheidung stehen, gegen eine Tracheotomie und den Beginn einer Heimbeatmung entscheiden würden, auch wenn dies das Versterben bedeutet [93]. Eine andere Studie mit 85 Patient*innen, bei denen eine nicht-invasive Heimbeatmung begonnen wurde, zeigte jedoch eine Zunahme der

Lebensqualität in den Monaten nach dem Beginn der Heimbeatmung [95]. Auch wenn in den letzten Jahren vermehrt Studien zu Patient*innen mit langfristiger Abhängigkeit vom Respirator in Deutschland publiziert wurden, gibt es noch immer Wissenslücken zur Lebensqualität, zu funktionellen Einschränkungen und zur sozialen Teilhabe dieser Patient*innen [96]. Genauso existieren Optimierungspotentiale im Überleitmanagement von der stationären Akutversorgung in die ambulante Langzeitbeatmungssituation [97].

1.4. Wissenslücken und Fragestellung der vorliegenden Arbeit

Obgleich es mittlerweile zahlreiche Studien zur Prävalenz funktioneller Langzeitbeeinträchtigungen bei verschiedenen Populationen ehemaliger Intensivpatient*innen gibt, existieren in den Bereichen der PICS-Diagnostik und der PICS-Prävention große Wissenslücken. Die vorliegende Arbeit beschäftigt sich im ersten Teil mit der Frage, welche Instrumente zur Diagnostik eines PICS geeignet sind und wie man PICS-Patient*innen auf der Basis von Routinedaten identifizieren und charakterisieren kann. In zwei Studien werden zunächst diagnostische Instrumente zur schnellen Einschätzung der mentalen und körperlichen Gesundheit von ITS-Überlebenden hinsichtlich ihrer Validität und Korrelation mit der HrQoL untersucht. In der darauffolgenden Studie werden Patient*innen mit langfristiger Abhängigkeit vom Respirator in Deutschland anhand von Routinedaten identifiziert und charakterisiert.

Im zweiten Teil widmet sich diese Habilitationsschrift der Frage, welche Strategien geeignet sind, um die Entstehung eines PICS bereits während der ITS-Behandlung zu verhindern. In einer systematischen Arbeit wird zunächst untersucht, inwieweit sich Maßnahmenpakete zur Qualitätsverbesserung der intensivmedizinischen Behandlung (sog. Care-Bundles) eignen, um PICS-bezogene Langzeit-Outcomes zu verbessern. Danach wird in zwei Studien untersucht, inwieweit sich der Einsatz eines multimodalen Schulungsprogramms und der Einsatz einer telemedizinischen Visite eignet, um die Qualität der intensivmedizinischen Versorgung zu erhöhen und Beeinträchtigungen im Sinne eines PICS zu vermeiden. In der letzten Studie wird das PICS-Forschungsfeld bibliometrisch und anhand einer Netzwerk-Analyse untersucht, um existierende PICS-Forschung bezüglich ihres geographischen Fokus und behandelter Themenfelder zu untersuchen und aktuelle Lücken in der Forschung aufzuzeigen.

2. Eigene Arbeiten

2.1. Originalarbeit 1: Validierung kurzer Instrumente zur Messung der subjektiven mentalen und körperlichen Gesundheit anhand des EQ-5D-5L bei Überlebenden kritischer Erkrankung

Zum gegenwärtigen Zeitpunkt gibt es keinen Konsens über die in der PICS-Diagnostik verwendeten Messinstrumente. In Studien zu Langzeitbeeinträchtigungen der Kognition, der mentalen Gesundheit, der körperlichen Gesundheit und der HrQoL bei Überlebenden kritischer Erkrankung werden häufig Instrumente verwendet, die für andere Patientenkollektive entwickelt wurden. Nur für wenige der verwendeten Instrumente existieren Validierungsstudien bei Überlebenden kritischer Erkrankung [98]. Wenn solche Studien existieren, zeigen sie zudem häufig Qualitätsmängel [98]. In *Originalarbeit 1* wird die Konstruktvalidität zweier für die Nachsorge von ITS-Patient*innen entwickelter Items zur Einschätzung der subjektiven mentalen und körperlichen Gesundheit untersucht. Diese kurzen Items können schnell und auch in der hausärztlichen Umgebung eingesetzt werden, um Post-ITS-Patient*innen hinsichtlich funktioneller Beeinträchtigungen zu untersuchen.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Paul N*, Cittadino J*, Weiss B, Krampe H, Denke C, Spies CD: Subjective ratings of mental and physical health correlate with EQ-5D-5L index values in survivors of critical illness: a construct validity study. Crit Care Med 2023; 51(3):365-375. doi:10.1097/CCM.0000000000005742.

„Zielsetzung: Überlebende kritischer Erkrankung zeigen häufig Einschränkungen ihrer gesundheitsbezogenen Lebensqualität (HrQoL). Wir untersuchten, ob die HrQoL durch zwei kurze, einfach anwendbare Items, die in der hausärztlichen Versorgung eingesetzt werden können, eingeschätzt werden kann. Design: Sekundäranalyse von Daten der multizentrischen, cluster-randomisierten kontrollierten Studie Enhanced Recovery after Intensive Care (ClinicalTrials.gov: NCT03671447) und Studie zur Untersuchung der Konstruktvalidität. Ort: Zehn Cluster von Intensivstationen in der Metropolregion Berlin, Deutschland. Patienten: Achthundertfünfzig ITS-Überlebende wurden auf gemischten, internistischen oder chirurgischen Intensivstationen

*eingeschlossen, wenn sie eine erwartete Intensivstations-Liegedauer von mindestens 24 Stunden hatten, mindestens 18 Jahre alt waren und bei einer gesetzlichen Krankenversicherung versichert waren. Interventionen: Keine. Messungen und Hauptergebnisse: Patient*innen erhielten Follow-Ups, die drei und sechs Monate nach Entlassung von der Intensivstation geplant wurden. Die HrQoL wurde mittels des EuroQol-5 Dimensions-5 Level (EQ-5D-5L) untersucht und Patient*innen wurden gebeten, ihre aktuelle mentale und körperliche Gesundheit auf einer Skala von 0 (am schlimmsten) bis 10 (am besten) zu bewerten. Wir errechneten mittels dieser zwei Items und weiterer Kovariablen unter Verwendung der Methoden Stepwise Regression und Adaptive LASSO Prädiktionsmodelle für den EQ-5D-5L Index-Wert. Die subjektive mentale Gesundheit (Spearman: 0,59) und die subjektive körperliche Gesundheit (Spearman: 0,68) korrelierten mit dem EQ-5D-5L Index-Wert und waren bessere Prädiktoren des EQ-5D-5L Index-Werts in einer Zwei-Item-Regression (normalized root mean squared error [nRMSE] 0,164; normalized mean absolute error [nMAE] 0,118; R^2_{adj} 0,43) als die Visuelle Analogskala des EQ-5D (nRMSE 0,175; nMAE 0,124; R^2_{adj} 0,35). Die Verwendung von Stepwise Regression mit weiteren Kovariablen erhöhte die Prädiktions-Performance zusätzlich (nRMSE 0,133; nMAE 0,1; R^2_{adj} 0,51). Schlussfolgerungen: Patient*innen nach einer Einschätzung ihrer mentalen und körperlichen Gesundheit zu fragen, kann ein einfaches Werkzeug für eine erste Abschätzung der HrQoL im hausärztlichen Setting sein.“* (Übersetzung durch den Autor.)

OPEN

Subjective Ratings of Mental and Physical Health Correlate With EQ-5D-5L Index Values in Survivors of Critical Illness: A Construct Validity Study*

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OBJECTIVES: Survivors of critical illness commonly show impaired health-related quality of life (HrQoL). We investigated if HrQoL can be approximated by brief, easily applicable items to be used in primary care.

DESIGN: Secondary analysis of data from the multicenter, cluster-randomized controlled Enhanced Recovery after Intensive Care trial (ClinicalTrials.gov: NCT03671447) and construct validity study.

SETTING: Ten participating clusters of ICUs in the metropolitan area of Berlin, Germany.

PATIENTS: Eight hundred fifty ICU survivors enrolled in a mixed, medical or surgical ICU when they had an expected ICU length of stay of at least 24 hours, were at least 18 years old, and had statutory health insurance coverage.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Patients received follow-ups scheduled 3 and 6 months after ICU discharge. HrQoL was assessed with the EuroQol 5-Dimension 5-Level (EQ-5D-5L), and patients were asked to rate their current mental and physical health state from 0 (worst) to 10 (best). We fitted prediction models for the EQ-5D-5L index value using these two items and additional covariates, applying stepwise regression and adaptive lasso. Subjective mental health (Spearman: 0.59) and subjective physical health (Spearman: 0.68) correlated with EQ-5D-5L index values and were better predictors of EQ-5D-5L index values in the two-item regression (normalized root mean squared error [nRMSE] 0.164; normalized mean absolute error [nMAE] 0.118; R^2_{adj} 0.43) than the EQ-5D Visual Analog Scale (nRMSE 0.175; nMAE 0.124; R^2_{adj} 0.35). Stepwise regression with additional covariates further increased prediction performance (nRMSE 0.133; nMAE 0.1; R^2_{adj} 0.51).

CONCLUSIONS: Asking patients to rate their subjective mental and physical health can be an easily applicable tool for a first impression of the HrQoL in primary care settings.

KEY WORDS: critical care; postintensive care unit care; postintensive care syndrome; primary care; quality of life

The demand for intensive care medicine has been increasing (1, 2) and is forecasted to further grow in the future (3). At the same time, ICU mortality rates are steadily declining (4). Various studies have shown that the growing cohort of survivors of critical illness commonly faces long-term impairments of their health-related quality of life (HrQoL) (5–10). This might be attributable to long-term sequelae of their mental health, cognition,

***See also p. 418.**

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KEY POINTS

Question: Do two brief items asking patients to rate their mental and physical health reflect the health-related quality of life (HrQoL) in critical illness survivors?

Findings: In this secondary analysis of 850 post-ICU patients of the Enhanced Recovery after Intensive Care (ERIC) trial, we fitted prediction models of the EQ-5D-5L index value using two items asking patients to rate their current mental and physical health. These two items are better predictors of the EQ-5D-5L index value than the EQ-5D-5L Visual Analog Scale.

Meaning: Asking patients to rate their mental and physical health depict two easily applicable, free-to-use tools to approximate post-ICU patients' HrQoL in primary care.

or physical functions (11), summarized as postintensive care syndrome (PICS) (12). Although HrQoL of critically ill patients appears already worse than in a matched reference population prior to ICU admission, ICU treatment further diminishes HrQoL (8, 13).

The most commonly used instruments to assess post-ICU HrQoL are the Short Form 36 (SF-36) (14) and the EuroQol-5Dimension (EQ-5D) (10, 15). The EQ-5D includes an assessment of the five dimensions mobility, self-care, usual activities, pain/discomfort, and anxiety/depression that are either rated on a three-level (EQ-5D-3L) or five-Level (EQ-5D-5L) scale (16) and converted to an index value (17). In the second part of the EQ-5D, patients rate their current overall health on a vertical Visual Analog Scale (VAS) from 0 to 100. International (18–21) and national (22) consensus statements on care for ICU survivors uniformly recommended application of the EQ-5D to assess HrQoL.

Worse HrQoL may lead to worse patient satisfaction and increased utilization of healthcare resources (6). Despite the importance of HrQoL and recommendations to assess it (23), HrQoL appears to be measured primarily in study settings, if measured at all. Specialized ICU recovery centers or routine post-ICU follow-up exist (24) but are not common practice (25–29). In absence of follow-up structures, post-ICU patients often consult their general practitioners with little experience in the sequelae of critical illness and their impact on HrQoL (30, 31).

In their proposed measurement instrument set for PICS, Spies et al (22) introduced two short, easily applicable items to approximate HrQoL for primary care settings. Patients were asked to rate their current mental health state and current physical health state on a scale from 0 (worst) to 10 (best). In conjunction, patients specified current mental (e.g., difficulties reading) or physical (e.g., difficulties climbing stairs) health concerns. The separation of ratings of mental and physical health and the connection with specific health concerns might be an advantage over the EQ-5D, but feasibility of this assessment was piloted on 17 patients only (22).

It is unknown, first, if the two items on subjective mental and physical health ratings adequately reflect a patient's HrQoL and second, which current health concerns are frequently reported by patients that score low ratings on these items. Aim of this study was to assess how well the subjective mental and physical health ratings predict the EQ-5D-5L index value compared with the EQ-5D VAS and which current health concerns are frequently reported by post-ICU patients.

MATERIALS AND METHODS

Study Design, Study Population, and Setting

We conducted a secondary analysis of the multicenter, stepped-wedge cluster-randomized controlled Enhanced Recovery after Intensive Care (ERIC) trial (ClinicalTrials.gov: NCT03671447) (32, 33). ERIC was approved by the Institutional Review Board of Charité—Universitätsmedizin Berlin (EA1/006/18) on January 26, 2018. The presented analysis is original, has not been published before, adhered to the ethical standards of the Declaration of Helsinki from 1964 and its later amendments, and adhered to the Transparent Reporting of multivariable predication model for Individual Prognosis Or Diagnosis (TRIPOD) statement (**Supplement A**, http://links.lww.com/CCM/H251) (33).

Patients were enrolled in one of 10 participating clusters of ICUs in the metropolitan area of Berlin, Germany, if they had an expected ICU length of stay of greater than or equal to 24 hours in a mixed, medical, or surgical ICU, were at least 18 years old, and had

statutory health insurance coverage. Patients or legal representatives gave written informed consent. For this analysis, we analyzed ERIC trial participants who were discharged alive from the ICU and completed one or two follow-ups.

Follow-Ups

Patients received two follow-ups scheduled 3 and 6 months after ICU discharge. Follow-ups were conducted by trained study personnel either in the study center or as home visits. In the rare event that a personal visit was not possible, follow-ups were conducted via phone or mail. Follow-ups were conducted using a recently proposed instrument set for PICS assessment (22). For this analysis, we included data from each patient's first follow-up.

EQ-5D-5L, Subjective Mental and Physical Health, and Current Health Concerns

HrQoL was assessed using the EQ-5D-5L. Participants rate mobility, self-care, usual activities, pain/discomfort, and anxiety/depression from 1 (no problems) to 5 (unable/extreme problems). Results are converted to country-specific index values (1: best possible HrQoL; 0: death; below 0: health state worse than death) (15, 35). We applied two novel, brief items of self-reported, subjective mental and physical health (22). Patients were asked to rank their mental and physical health status in the last week on a VAS from 0 (worst) to 10 (best) (**Supplement B**, http://links.lww.com/CCM/H251). Before filling in the subjective health items, patients indicated (yes/no) if they experienced one or more of the following: nightmares, mood changes, anxiety attacks, outbursts, depressive symptoms, difficulties sleeping, difficulties remembering phone numbers, difficulties remembering familiar names, difficulties concentrating, difficulties reading, less contact to friends, and trying not to think of the ICU (mental health), as well as difficulties walking, difficulties climbing chairs, difficulties swallowing, digestive problems, incontinence, fatigue, lack of strength, and pain (physical health).

Covariates

Our models included covariates that were previously considered predictors of reduced HrQoL (7–10, 36–39). Demographic data, Simplified Acute Physiology Score (SAPS) II at ICU admission, ICU admission date, and reason of admission were collected at study enrollment. Results of routine delirium screening instruments were documented during ICU treatment, and duration of mechanical ventilation and discharge date were documented after ICU discharge. During follow-ups, patients were asked if they live in a partnership or marriage and about their highest education. Patients or their general practitioner were asked which of the following organ systems were impaired prior to ICU admission: 1) pulmonary system, 2) metabolic system, 3) kidneys and urogenital system, 4) cardiovascular system, 5) bones, joints, and muscles, and 6) CNS.

Statistical Analysis

Descriptive statistics are presented as median and interquartile range (IQR) or as mean and SD for continuous variables and as frequencies (*n*, %) for categorical variables. EQ-5D-5L conditions were converted to index values using the German value set (17). Correlations between EQ-5D-5L index values, EQ-5D VAS, and subjective mental and physical health state were quantified using Spearman rank correlation coefficients and violin plots.

We estimated different regression models to predict the EQ-5D-5L index value. First, using linear regression, we used the VAS (independent variable) to predict the EQ-5D-5L index value (dependent variable).

Second, we estimated regression models with the subjective mental and physical health states as independent variables (two-item models), after calculating the variance inflation factor to check for multicollinearity. A variance inflation factor of greater than or equal to 3 was considered relevant multicollinearity (40). We randomly split the sample in 10 equally sized parts; the models were fitted with nine of 10 parts and validated with the remaining part (41).

Third, we estimated additional regression models after adding the following predefined covariates: number of organ systems affected prior to ICU admission, age, sex, body mass index (BMI), length of mechanical ventilation, time between ICU discharge and follow-up, ICU length of stay, SAPS II at ICU admission, admission due to trauma (yes/no), delirium (yes/no), university degree (yes/no), and partnership/

marriage (yes/no). Regression models were fitted using stepwise regression with backward elimination. With this method, a model that includes all independent variables is compared with a model where the least significant variable is omitted (42, 43). Iteration with the next least significant variable yields a model where all nonsignificant variables have been removed. In another approach, we estimated regression models with the adaptive least absolute shrinkage and selection operator (LASSO), which performs estimation and selection of a subset of regression covariates from a set of many covariates (44, 45).

For all models, we fitted polynomials up to the third degree. To prevent overfitting, we used 10-fold cross-validation for stepwise regression and lasso. Cross-validation split the sample randomly into 10 equal subsamples (41). The model is fitted with nine of 10 subsamples (training sample), and the tenth subsample is used for validation. This process was repeated 10 times.

Goodness of fit was determined using the normalized root mean squared error (nRMSE) between the observed and predicted values, the normalized mean absolute error (nMAE), the adjusted R^2, and the width of empirical and theoretical 95% limits of agreement (LoA). Normalization was performed with the range of EQ-5D-5L index values in our dataset. Theoretical LoA were computed with ± 1.96 SD (residuals) (46). Bland-Altman plots were prepared for the best-fitting two-item model and the best-fitting stepwise regression or adaptive LASSO model. We excluded cases for which at least one covariate was missing. Significance was defined at less than 0.05. Statistical analysis was performed using Stata17 SE (StataCorp LLC, College Station, TX).

RESULTS

Characteristics of the Study Population and Follow-Ups

Of 1,463 patients enrolled in the study, 1,304 patients were discharged alive from the ICU. Eight hundred fifty patients received at least one follow-up (**Fig. S1**, http://links.lww.com/CCM/H251), with a median of 3.2 months (IQR, 2.8–4.5) after discharge. Patients showed a variety of admission diagnoses, two of three patients received mechanical ventilation, and about one in five patients had delirium during ICU treatment (**Table 1**).

TABLE 1.
Patient Characteristics of the Study Population Upon ICU Admission

Characteristics[a]	Study Population ($N = 850$)
Age, yr, median (IQR)	67 (56–77)
Female, *n* (%)	383 (45.1)
Length of ICU stay, d ($N = 849$), median (IQR)	5 (2–10)
Mechanical ventilation ($N = 846$), *n* (%)	569 (66.9)
Mechanical ventilation, hr ($N = 846$), median (IQR)	10.5 (0–111)
Delirium,[b], *n* (%)	190 (22.4)
Simplified Acute Physiology Score II at admission, median (25–75th percentile)	29 (17–41)
Organ systems affected prior to ICU admission,[c] median (IQR)	3 (2–5)
Body mass index, kg/m^2, median (IQR)	26.1 (23.4–29.7)
Admission type ($N = 840$), *n* (%)	
Medical	358 (42.6)
Emergency surgery	238 (28.3)
Elective surgery	244 (29.1)
Admission diagnosis, *n* (%)	
Respiratory	88 (10.4)
Sepsis/infection	124 (14.6)
Gastrointestinal	91 (10.7)
Cardiovascular	238 (28)
Trauma	74 (8.7)
Neurologic	62 (7.3)
Metabolic/endocrine	37 (4.4)
Oncologic	124 (14.6)
Other[d]	12 (1.4)
University degree ($N = 835$), *n* (%)	125 (15)
In partnership/marriage ($N = 843$), *n* (%)	463 (54.9)

IQR = interquartile range.
[a]*n* other than 850 in brackets.
[b]At least one positive delirium screening during ICU stay.
[c]As assessed by the general practitioner or study personnel. Organ systems were defined as follows: 1) pulmonary system, 2) metabolic system, 3) kidneys and urogenital system, 4) cardiovascular system, 5) bones, joints, and muscles, and 6) CNS.
[d]Other includes multiple organ failure, trimalleolar fracture, urolithiasis, acute kidney injury (3 patients), placement of catheter for hemodialysis, reduced vigilance of unknown cause, bilateral ureter stenosis with recurrent urinary tract infections, spinal deformity, medication-induced osteonecrosis of the jawbone, and inguinal seroma.

EQ-5D-5L Domain Items, EQ-5D-5L Index Scores, and Subjective Health State

EQ-5D-5L assessments indicate a high level of morbidity in our cohort (**Table 2**). The median EQ-5D-5L index value was 0.78 (IQR 0.45–0.91), and the mean EQ-5D-5L index value was 0.66 (SD 0.33). On average, patients reported an EQ-5D VAS of 60 (median, IQR 45–80). Median subjective mental and physical health were 7 (IQR 5–9; *n* = 840) and 6 (IQR 4–8, *n* = 848), respectively. Violin plots, which visualize summary statistics and the data's density functions, display the relationship between subjective mental and physical health states and EQ-5D-5L index values (**Fig. 1**). Spearman rank correlation coefficients between the subjective mental and physical health states and the EQ-5D-5L index value were 0.59 and 0.68, respectively (**Table S1**, http://links.lww.com/CCM/H251). This correlation shows that higher subjective mental and physical health state scores are associated with higher EQ-5D-5L index values. With 0.65, the Spearman rank correlation coefficient for the EQ-5D VAS and the EQ-5D index value was in a similar range.

Best-Fitting Models: Two-Item Linear Regression and Linear Stepwise Regression

With a variance inflation factor between the subjective mental and physical health states of 1.66, we did not detect relevant multicollinearity. Among the two-item models, which use the subjective mental and physical health status to predict EQ-5D-5L index values, linear regression showed the best fit (**Table 3**) (**Table S2**, http://links.lww.com/CCM/H251). Subjective mental and physical health status explains 43% of the variance in the EQ-5D-5L index value. The low nMAE (0.118) and nRMSE (0.164) indicate good prediction performance.

Including previously defined covariates and fitting regression models with stepwise regression or adaptive Lasso increased the goodness of fit (Table S2, http://links.lww.com/CCM/H251). Models estimated with stepwise regression showed higher goodness of fit than models estimated with adaptive LASSO. The subjective mental health state, subjective physical health state, the number of affected organ systems prior to ICU admission, and the BMI were significant in all tested models, but delirium, SAPS II, time since ICU discharge, and ICU length of stay were excluded in all models (**Table S3**, http://links.lww.com/CCM/H251). The best-fitting model was estimated using stepwise regression with

TABLE 2.
Results of the EuroQol-5D-Five-Level Domain Items and Index Score

EuroQol-5D-Five-Level Items	Study Population (*N* = 850)
Mobility, *n* (%)	
No problems	269 (31.7)
Slight problems	138 (16.2)
Moderate problems	181 (21.3)
Severe problems	179 (21.1)
Extreme problems/unable to do	83 (9.8)
Self-care, *n* (%)	
No problems	462 (54.4)
Slight problems	117 (13.8)
Moderate problems	122 (14.4)
Severe problems	83 (9.8)
Extreme problems/unable to do	66 (7.8)
Usual activities, *n* (%)	
No problems	244 (28.7)
Slight problems	179 (21.1)
Moderate problems	166 (19.5)
Severe problems	153 (18)
Extreme problems/unable to do	108 (12.7)
Pain/discomfort, *n* (%)	
No problems	227 (26.7)
Slight problems	254 (29.9)
Moderate problems	238 (28)
Severe problems	120 (14.1)
Extreme problems/unable to do	11 (1.3)
Anxiety/depression, *n* (%)	
No problems	418 (49.2)
Slight problems	188 (22.1)
Moderate problems	160 (18.8)
Severe problems	70 (8.2)
Extreme problems/unable to do	14 (1.7)
Index score[a]	
Median (IQR)	0.78 (0.45–0.91)
Mean (SD)	0.66 (0.33)
Minimum; maximum	–0.549; 1
Visual Analog Scale (*N* = 728)	
Median (IQR)	60 (45–80)
Mean (SD)	59.3 (23.3)
Minimum; maximum	0; 100

IQR = interquartile range.
[a]Calculated from the single items as follows: (1—[mobility + self-care + usual activities + pain/discomfort + anxiety/depression]).

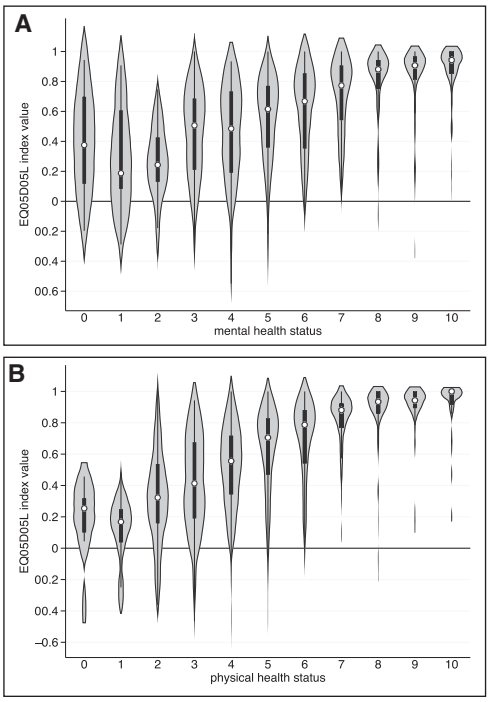

Figure 1. *Violin plots* showing ratings of subjective mental (**A**) and physical (**B**) health state and corresponding EuroQol 5-Dimension 5-Level (EQ-5D-5L) index scores.

linear coefficients (nRMSE 0.133; nMAE 0.1), explaining 51% of the variation in the EQ-5D-5L index values. Interestingly, explaining the EQ-5D-5L index value with the VAS only showed the worst fit of all tested models (nRMSE 0.175, nMAE 0.124, and R^2_{adj} 0.35).

The Bland-Altman plots for the best-fitting two-item model and the best-fitting stepwise regression model indicate that prediction performance becomes better with higher EQ-5D-5L index values. For EQ-5D-5L index values below 0.7, predicted EQ-5D-5L index values are, on average, above observed values, and for EQ-5D-5L index values above 0.7, predicted EQ-5D-5L index values tend to be below observed values (**Fig. 2**).

Current Health Concerns and Subjective Health Status

Patients with high ratings of subjective mental health state reported the absence of any current mental health concerns more frequently than patients with low ratings of their subjective mental health state. For example, 60% (73/121) with a subjective mental health state of 10 indicated the absence of any current mental health concerns. Patients with low ratings of their subjective mental health state frequently described current mental health concerns, particularly mood changes, depressive symptoms, and difficulties sleeping (**Fig. 3*A***).

Patients with high ratings of their subjective physical health state frequently reported the absence of any current physical health concern: On the one hand, 59% (19/32) with a subjective physical health state of 10 reported that they did not have any current physical health concern. On the other hand, patients with low subjective physical health state frequently reported various physical health concerns, in particular difficulties walking, difficulties climbing stairs, lack of strength, fatigue, and pain (**Fig. 3*B***).

DISCUSSION

This secondary analysis of a large multicenter trial shows that asking ICU survivors to rate their current mental and physical health state on a scale from 0 (worst) to 10 (best) serves as an excellent predictor of the magnitude of their EQ-5D-5L index value. These two items are brief and can easily be applied in primary care settings to approximate patients' HrQoL.

Several previous studies have reported reductions in HrQoL in survivors of critical illness for up to 5 years after ICU discharge (5–10). With a median of 0.78 (IQR 0.45–0.91), the EQ-5D-5L index value in our analysis was comparable with previous studies (10). For example, a large multicenter study on ICU survivors found median EQ-5D-5L index values of 0.73 1–3 years after ICU discharge (47). In only 10.7% of our follow-ups, patients reported the absence of problems in all EQ-5D-5L dimensions, which was much lower compared with 36.4% in the general population (17).

Two items rating subjective mental and physical health to approximate HrQoL of critical illness survivors have recently been introduced by Spies et al (22). The authors proposed that patients should be assessed for PICS in primary care settings 3 months after ICU discharge, and in case of PICS-related impairments, patients should be transferred to specialized ICU rehabilitation centers. Although the two items of mental and physical health were piloted on 17 patients and considered feasible, the

TABLE 3.

Coefficients and Goodness of Fit of the Best-Fitting Two-Item Regression Model, the Overall Best-Fitting Model, and the EuroQol 5-Dimension Visual Analog Scale Model

	Two-Item Regression (Linear)			Stepwise Regression (Linear)			EQ-5D VAS Regression (Linear)		
Covariate	**Coefficient**	**SE**	***p***	**Coefficient**	**SE**	***p***	**Coefficient**	**SE**	***p***
Physical health state[a]	0.067	0.005	< 0.001	0.057	0.005	< 0.001			
Mental health state[a]	0.029	0.005	< 0.001	0.035	0.005	< 0.001			
Organ systems affected prior to ICU admission, *n*[b]				−0.018	0.005	<0.001			
Mechanical ventilation, hr				< −0.001	< 0.001	0.005			
Body mass index, kg/m^2				−0.004	0.001	0.009			
EQ-5D VAS[c]							0.008	< 0.001	< 0.001
Constant	0.083	0.027	0.002	0.270	0.049	< 0.001	0.189	0.028	< 0.001
Goodness of fit									
Normalized root mean squared error	0.164			0.133[d] (0.155[e])			0.175		
Normalized mean absolute error	0.118			0.1[d] (0.112[e])			0.124		
R^2_{adj}	0.43			0.51			0.35		
95% limits of agreement									
Empiricial	−0.508; 0.499			−0.47; 0.486			-0.588; 0.529		
Theoretical	± 0.483			± 0.461			± 0.513		

EQ-5D = EuroQol 5-Dimension, VAS = Visual Analog Scale.

[a]From 0 (worst) to 10 (best).

[b]As assessed by the general practitioner or study personnel. Organ systems were defined as follows: 1) pulmonary system, 2) metabolic system, 3) kidneys and urogenital system, 4) cardiovascular system, 5) bones, joints, and muscles, and 6) CNS.

[c]From 0 (worst) to 100 (best).

[d]Best-fitting model after tenfold cross-validation.

[e]Mean of the tenfold cross-validations.

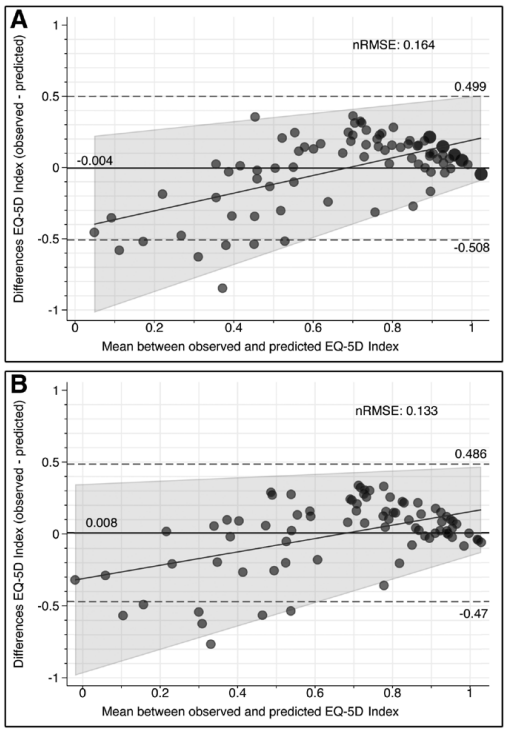

Figure 2. Bland-Altman plot for the best-fitting two-item model (linear) (**A**) and the best-fitting stepwise regression model (linear) (**B**). EQ-5D = EuroQol 5-Dimension, nRMSE = normalized root mean square error.

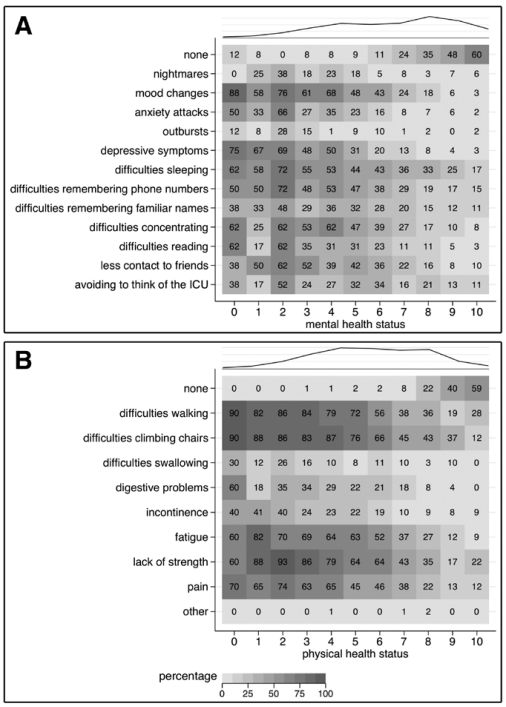

Figure 3. A, Subjective mental health state and current mental health concerns ($n = 840$; density function displayed above heatmap). **B**, Subjective physical health state and current physical health concerns ($n = 848$; density function displayed above heatmap). Other includes shortness of breath, leg edema, loss of vision, and vertigo.

authors acknowledged that measurement properties of the assessments are indispensable (22).

The two items of current mental and physical health showed high correlation coefficients with the EQ-5D-5L index value. Linear regression analysis revealed that a combination of these two items explained 43% of the variation in the EQ-5D-5L index values. Still, goodness of fit parameters of our prediction model (nRMSE, nMAE, LoA, and Bland-Altman plot) indicated differences between predicted and observed EQ-5D-5L index values. We are not aware of studies that explored the minimum clinically important difference in EQ-5D-5L index values for survivors of critical illness, but the minimum clinically important difference for other interventions has been found to vary substantially from 0.03 to 0.52 (48). Although the clinical importance of the differences in predicted and observed EQ-5D-5L index values in our analysis is unknown, we can conclude that the two items on subjective mental and physical health provide good estimates of the EQ-5D-5L index value.

The prediction performance of the subjective mental and physical health status can be increased when the number of affected organ systems prior to ICU admission, length of mechanical ventilation, and BMI are taken into consideration. These variables are usually easily available, and taking this information into consideration can refine a general practitioner's impression of the HrQoL. Interestingly, the time after ICU discharge was not significantly associated with the EQ-5D-5L index value in our analysis, even though previous studies found fluctuations of HrQoL within 1 year after ICU discharge (10).

When patients stated a low subjective mental health status, they frequently reported mood changes, depressive symptoms, and difficulties sleeping; when patients

stated a low subjective physical health status, they frequently reported difficulties walking, difficulties climbing stairs, lack of strength, fatigue, and pain. For patients with low subjective mental or physical health, general practitioners could therefore target their diagnostics toward these health concerns. This is particularly true for depression, which has several treatment options and was shown to be a strong predictor of HrQoL (36).

There are great variations in the organization of post-ICU care between hospitals and healthcare systems (26, 27). For many patients, post-ICU care is organized by primary care physicians (31) and outpatient specialists (49), who might lack experience in sequelae of critical illness (30). The two items on subjective mental and physical health, which do not have a copyright and are free to use, can be applied as a brief tool that adequately reflects HrQoL in these outpatient settings. If a patient scores low on these items, the primary care physician can either conduct a more elaborate assessment of HrQoL (e.g., the SF-36), conduct further diagnostics in relevant PICS domains, or refer the patient to post-ICU specialists.

This analysis is subject to strengths and limitations. We analyzed a large cohort of ICU survivors who were treated in 10 clusters and showed a wide range of admission diagnoses. We were able to include many variables in our prediction models that were shown to have an association with HrQoL, including pre-ICU morbidity. Furthermore, follow-ups were conducted on more than three quarters of study participants who were discharged alive and survived up to 8 months after ICU care. As a limitation, our data might have been subject to survivor bias (50), as we only analyzed patients who did not pass away before their follow-up. Also, patients with particularly impaired HrQoL might have been more likely to be lost to follow-up or to withdraw from the study. Finally, by its nature, this secondary analysis is hypothesis-generating only.

CONCLUSIONS

We showed that asking survivors of critical illness to rank their current subjective mental and physical health from 0 (worst) to 10 (best) is a good reflection of their HrQoL as determined using the EQ-5D-5L index value. The two items on subjective mental and physical health can easily be applied in primary care settings to rapidly assess the HrQoL of survivors of critical illness.

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Data will be made available from the corresponding author upon a reasonable request.

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2.2. Originalarbeit 2: Analyse von Determinanten einer Verbesserung oder Verschlechterung der subjektiven mentalen und körperlichen Gesundheit bei Überlebenden kritischer Erkrankung

Die Prävalenz PICS-bezogener Beeinträchtigungen nach Entlassung von der ITS wurde in zahlreichen vorherigen Studien untersucht, jedoch gibt es nur wenige Arbeiten, die den funktionellen Status vor Aufnahme auf die ITS berücksichtigen. Somit gibt nur wenige Studien, welche die Inzidenz neu aufgetretener PICS-bezogener Beeinträchtigungen untersuchen. Die wenigen Arbeiten, welche den Prä-ITS-Status berücksichtigen, weisen darauf hin, dass ITS-Patient*innen bereits vor ihrer Aufnahme häufig an Beeinträchtigungen ihrer mentalen Gesundheit, körperlichen Gesundheit und Kognition leiden, und dass der Status vor ITS-Aufnahme das Behandlungsergebnis nach Entlassung maßgeblich beeinflusst [99, 100]. In *Originalarbeit 2* wird die subjektive mentale und körperliche Gesundheit teilnehmender Patient*innen vor und nach dem ITS-Aufenthalt verglichen. Es wird untersucht, welche Faktoren zu einer Verschlechterung der subjektiven Gesundheit führen. Damit baut *Originalarbeit 2* auf der in *Originalarbeit 1* durchgeführten Validierungsstudie zweier Items zur Einschätzung der subjektiven mentalen und körperlichen Gesundheit auf.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Paul N, Cittadino J, Krampe H, Denke C, Spies CD, Weiss B: Determinants of subjective mental and functional health of critical illness survivors: comparing pre-ICU and post-ICU status. Crit Care Med 2024. doi:10.1097/CCM.0000000000006158.

*„Zielsetzung: Der Vergleich der subjektiven mentalen und körperlichen Gesundheit vor Aufnahme und nach Entlassung von der Intensivstation und die Untersuchung von Determinanten einer Verbesserung oder Verschlechterung der subjektiven Gesundheit. Design: Sekundäranalyse der multizentrischen, cluster-randomisierten Studie Enhanced Recovery after Intensive Care (ClinicalTrials.gov: NCT03671447). Ort: Zehn Cluster von Intensivstationen in Deutschland. Patienten: Achthundertfünfundfünfzig Patient*innen mit 1478 Follow-Up-Untersuchungen. Interventionen: Keine. Messungen und Hauptergebnisse: Patient*innen bewerteten ihre subjektive mentale und körperliche Gesundheit bei zwei Follow-Up-Untersuchungen, die drei und sechs Monate nach Entlassung von der Intensivstation*

*geplant wurden, auf zwei separaten visuellen Analogskalen von 0 (am schlimmsten) bis 10 (am besten) in der Woche vor dem Follow-Up und vor der Intensivstations-Aufnahme. Wir verglichen die subjektive Gesundheit vor und nach der Intensivstation und verwendeten gemischte Regressionsmodelle, um Determinanten von Verbesserungen oder Verschlechterungen der subjektiven Gesundheit zu identifizieren. Beim ersten Follow-Up gaben 20% (n = 165/841) und 30% (n = 256/849) der Patient*innen eine Verschlechterung ihrer subjektiven mentalen bzw. körperlichen Gesundheit von mindestens 3 Punkten an; 16% (n = 133/841 und n = 137/849) gaben Verbesserungen ihrer mentalen bzw. körperlichen Gesundheit an. Für 65% (n = 543/841) und 54% (n = 456/849) veränderte sich die mentale und körperliche Gesundheit beim ersten Follow-Up um weniger als 3 Punkte. Die multivariablen gemischten Regressionsmodelle zeigten, dass eine längere Intensivstations-Liegedauer mit einer höheren Wahrscheinlichkeit einer Verschlechterung der mentalen (adjustiertes Odds Ratio [OR] pro Intensivstations-Tag, 1,04; 95%-Konfidenzintervall [KI], 1,00–1,09; p = 0,038) und körperlichen Gesundheit einherging (adjustiertes OR pro Intensivstations-Tag, 1,06; 95%-KI, 1,01– 1,12; p = 0,026). Die Wahrscheinlichkeit einer Verschlechterung der mentalen Gesundheit nahm mit zunehmendem Alter ab (adjustiertes OR pro Lebensjahr, 0,98; 95%-KI, 0,96–0,99; p = 0,003) und die Wahrscheinlichkeit einer Verschlechterung der körperlichen Gesundheit nahm mit zunehmender Zeit nach Entlassung ab (adjustiertes OR pro Monat, 0,86; 95%-KI, 0,79–0,94; p = 0,001). Schlussfolgerungen: Die Mehrzahl der Intensivstations-Überlebenden gab keine substanzielle Änderung ihres subjektiven Gesundheitsstatus an, aber Patient*innen mit langer Intensivstations-Liegedauer neigten zu Verschlechterungen ihrer subjektiven mentalen und körperlichen Gesundheit. Folglich könnten sich Post-Intensivstations-Ambulanzen besonders auf diese Patient*innen fokussieren."* (Übersetzung durch den Autor.)

OPEN

Determinants of Subjective Mental and Functional Health of Critical Illness Survivors: Comparing Pre-ICU and Post-ICU Status

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OBJECTIVES: To compare ICU survivors' subjective mental and functional health before ICU admission and after discharge and to assess determinants of subjective health decline or improvement.

DESIGN: Secondary analysis of the multicenter cluster-randomized Enhanced Recovery after Intensive Care trial (ClinicalTrials.gov: NCT03671447).

SETTING: Ten ICU clusters in Germany.

PATIENTS: Eight hundred fifty-five patients with 1478 follow-up assessments.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: At two patient follow-ups scheduled 3 and 6 months after ICU discharge, patients rated their subjective mental and functional/physical health on two separate visual analog scales from 0 (worst) to 10 (best) in the previous week and before ICU admission. We compared pre-ICU and post-ICU subjective health and used mixed-effects regression to assess determinants of a health decline or improvement. At the first follow-up, 20% (n = 165/841) and 30% (n = 256/849) of patients reported a decline in subjective mental and functional health of at least three points, respectively; 16% (n = 133/841 and n = 137/849) outlined improvements of mental and functional health. For 65% (n = 543/841) and 54% (n = 456/849), mental and functional health did not change three points or more at the first follow-up. Multivariable mixed-effects logistic regressions revealed that the ICU length of stay was a predictor of mental (adjusted odds ratio [OR] per ICU day, 1.04; 95% CI, 1.00–1.09; p = 0.038) and functional health (adjusted OR per ICU day, 1.06; 95% CI, 1.01–1.12; p = 0.026) decline. The odds of a mental health decline decreased with age (adjusted OR per year, 0.98; 95% CI, 0.96–0.99; p = 0.003) and the odds of a functional health decline decreased with time after discharge (adjusted OR per month, 0.86; 95% CI, 0.79–0.94; p = 0.001).

CONCLUSIONS: The majority of ICU survivors did not experience substantial changes in their subjective health status, but patients with long ICU stays were prone to subjective mental and functional health decline. Hence, post-ICU care in post-ICU clinics could focus on these patients.

KEYWORDS: intensive care; post-intensive care syndrome; post-ICU care; pre-ICU status; quality of life

ICU survivors frequently suffer from impairments of cognition (1), physical function (2), and mental health (3–6). This nexus is commonly referred to as post-intensive care syndrome (PICS) (7). The prevalence of impairments related to the PICS domains is well described (1, 5, 6, 8). The occurrence of new PICS impairments after ICU discharge, however, has been studied far less. In particular, patients' pre-ICU health status has been frequently overlooked. Yet, evidence is accumulating that ICU patients commonly show impairments

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KEY POINTS

Question: What are the determinants of a subjective mental and functional health decline in survivors of critical illness?

Findings: In this secondary analysis of 855 patients from the multicenter cluster-randomized Enhanced Recovery after Intensive Care trial, we found that the majority of patients did not report substantial changes of their subjective mental and functional health. A longer ICU length of stay, however, was associated with higher odds of subjective mental and functional health decline.

Meaning: Limited resources in ICU follow-up services and primary care should be dedicated to patients with long ICU stays who are prone to a subjective health decline.

already before admission (9–11) and that critical illness acts as an external stressor contributing to further health decline (9, 10, 12). A poor pre-ICU status has also been linked to poor functional outcomes (13, 14).

PICS-related impairments correspond to a low health-related quality of life (HrQoL) among ICU survivors (15, 16). Due to the unpredictable nature of an ICU admission, the prospective collection of pre-ICU HrQoL data is challenging. Previous studies have examined pre-ICU HrQoL retrospectively by asking patients at ICU admission or thereafter to recall previous HrQoL. These studies show pre-ICU HrQoL was already lower than in comparable populations (15–18) and that poor pre-ICU HrQoL (19–22) and preexisting comorbidities (22, 23) were predictive of poor HrQoL after ICU discharge.

HrQoL after critical illness has most commonly been assessed using the generic Short-Form Health Survey-36 (SF-36) or the EuroQol-5D (EQ-5D) (15, 16). As part of a PICS measurement instrument set, we introduced two short items to assess HrQoL in critical illness survivors (24). Patients rated their mental and functional health status on a scale from 0 (worst) to 10 (best). Advantages over other HrQoL instruments include their brevity, the separation of mental and functional health, which may show diverging trajectories after critical illness (16), and the conjunction with the assessment of specific mental and functional health concerns (25). In a validation study, we demonstrated that these items correlate well with the EQ-5D-5L (25).

The two items on subjective mental and functional health have not been used to assess ICU survivors' pre-ICU health status. It is also unknown which factors determine a decline or an improvement in subjective mental or functional health after ICU discharge. The aims of this study were, first, to compare patients' pre-ICU health status with their post-ICU health status. Second, we aimed at identifying demographic and illness-related patient characteristics associated with either a decline or an improvement of subjective mental or functional health.

MATERIALS AND METHODS

Study Characteristics, Inclusion Criteria, and Ethics

We present a hypothesis-driven analysis of data from the multicenter, stepped-wedge cluster-randomized controlled Enhanced Recovery after Intensive Care (ERIC) trial (ClinicalTrials.gov: NCT03671447) (26, 27). ERIC was approved by the institutional review board of Charité-Universitätsmedizin Berlin (EA1/006/18; January 26, 2018) and was conducted in accordance with the Helsinki Declaration of 1964 in its most recent amendment from 2013 (28). Ten clusters of ICUs in Berlin and the neighboring federal state of Brandenburg, Germany, enrolled patients with an expected ICU length of stay (LOS) of greater than or equal to 24 hours in a medical, surgical, or mixed ICU, who were 18 years old or older, and had German statutory health insurance coverage. Patients or legal representatives consented to study participation. In this analysis, we included patients who were discharged alive and completed at least one of two post-ICU follow-ups.

Post-ICU Follow-Ups

Follow-up examinations were targeted at 3 and 6 months after ICU discharge and focused on PICS-related impairments. Following a validated instrument set (24), patients completed tests pertaining to their cognition, mental health, physical function, disability, HrQoL, and subjective health (**Table S1**, http://links.lww.com/CCM/H471). Follow-up examinations were conducted by trained study personnel (i.e., research assistants, medical doctors, study nurses, and

psychologists in training). Patients either visited the study center or received home visits. Few patients received phone-based follow-ups.

Subjective Mental and Functional/Physical Health Status

Patients were asked to rank their mental and functional/physical health status in the previous week on two separate visual analog scales from 0 (worst) to 10 (best) (24). We also asked patients to retrospectively rank their mental and functional health status before ICU admission on two separate visual analog scales from 0 (worst) to 10 (best). The accuracy of a retrospective assessment of pre-ICU HrQoL was validated in a previous study on patients with preplanned ICU admissions (29). Pre-ICU data from the first available follow-up went into analysis, as a retrospective assessment after 3 months was shown to be more accurate than a retrospective assessment after 6 months (29).

Covariates

We employed covariates of demographics, biometrics, and severity of illness that were previously shown to affect HrQoL in ICU survivors (16, 18, 30–33). We collected demographic and biometric data, Simplified Acute Physiology Score (SAPS) II, ICU admission date, and admission reason at study enrollment; results from routine delirium screening during ICU treatment; and the duration of mechanical ventilation and the ICU LOS at ICU discharge. During follow-ups, we collected the following: living in a partnership/marriage, highest education, and the number of organ systems with comorbidities before ICU admission (defined as the pulmonary system, the metabolic system, the kidneys and urogenital system, the cardiovascular system, the CNS, and/or the bones, joints, and muscles).

Statistical Analysis

Data from follow-up assessments with at least one pair of pre-ICU and post-ICU subjective health status (mental and/or functional health) were analyzed. Patients contributed data from either one or two follow-ups. Continuous variables are presented as mean (SD) and median (interquartile range [IQR]). Categorical variables are shown as absolute (*n*) and relative (%) frequencies. Characteristics of patients with one follow-up and patients with two follow-ups are compared using Mann-Whitney *U* tests and Pearson's χ^2 tests. Timing of follow-ups was visualized using histograms. Subjective mental and functional health before ICU admission and at the follow-ups were compared using descriptive statistics, violin plots, Spearman rank correlation coefficients, and Wilcoxon signed-rank tests.

As we did not have a suitable external anchor available, we determined the relevant difference of the subjective health items using a distribution-based approach (34, 35). We defined a subjective health change of at least ± 1 SD as a relevant decline/improvement. Given a SD of 2.9 points for mental health and 3.2 points for functional health among the first follow-ups, we considered a change of at least three points as a relevant decline/improvement. In sensitivity analyses, we also considered a change of at least two points as relevant decline/improvement.

We used mixed-effects logistic regression models to identify factors associated with a decline or improvement in mental and/or functional health. Most patients received two assessments (mean: 1.7 assessments). To account for the clustered nature of our observations as additional source of variance, our models included a random effect for the unique patient identification number (patient ID). Independent fixed-effects variables included: age, gender, body mass index, time between ICU discharge and follow-up, SAPS II at admission, delirium (yes/no), ICU LOS, duration of mechanical ventilation, living in a partnership or marriage (yes/no), university degree (yes/no), and number of organ systems with comorbidities before admission. The dependent variable was either a relevant decline or improvement in mental or functional health. We report rho (ρ) of each model, which depicts the proportion of the total variance contributed by the patient-level variance component, and employed likelihood-ratio tests to compare the mixed-effects models with models without random effect. Independent variables, which were significantly associated with a decline of subjective health in univariable regression models were included in multivariable mixed-effects logistic regression models. In postestimations, we visualized the probability of a decline of subjective health dependent on the ICU LOS. In sensitivity analyses, we employed mixed-effects ordered logistic regression models to determine factors associated with an absolute mental

or functional health change, independent of defining a relevant health change. Statistical significance was set at 0.05. Analyses were carried out using Stata17 SE (StataCorp LLC, College Station, TX).

RESULTS

Characteristics of the Study Population

Of 1463 patients enrolled in the ERIC trial (27), 1304 patients were discharged from the ICU alive; 226 patients died before the first follow-up. Of 855 patients who received at least one follow-up, 623 patients were followed up twice and 232 were followed up once (**Fig. S1**, http://links.lww.com/CCM/H471). We collected 1478 follow-ups in total, which took place after a median of 161 days (IQR, 93–200 d). First follow-ups took place after a median of 97 days (IQR, 83–131.5 d), and second follow-ups after a median of 196 days (IQR, 179–232 d) (**Fig. S2**, http://links.lww.com/CCM/H471). Patients had a median ICU LOS of 5 days (IQR, 2–10 d) and a median admission SAPS II of 29 (IQR, 17–42). Almost two-thirds of the patients were mechanically ventilated, and about one third had at least one episode of delirium (**Table 1**).

Subjective Mental and Functional Health Before ICU Admission and at Follow-Ups

On a scale from 0 (worst) to 10 (best), patients rated their mental health before ICU admission with 8 (median, IQR, 5–9; mean, 6.8; SD, 2.8). At their first follow-up, the median rating was 7 (IQR, 5–9; mean, 6.6; SD, 2.5; $p < 0.001$ compared with pre-ICU). While 65% (n = 543/841) reported no relevant change in mental health, 16% (n = 133/841) reported an improvement, and 20% (n = 165/841) outlined a mental health decline. At their second follow-up, the share of patients reporting a decline (19%; n = 114/616) or improvement (18%, n = 113/616) remained relatively stable (**Fig. 1** and **Table 2**; and **Table S2**, **Fig. S3**, and **Fig. S4** [http://links.lww.com/CCM/H471]).

Patients rated their functional health before ICU admission with 7 (median, IQR, 4–9; mean, 6.4; SD, 2.9). Functional health ratings decreased to a median of 6 (IQR, 4–8; mean, 5.7; SD, 2.3; $p < 0.001$ compared with pre-ICU) at their first follow-up. More than half of patients (54%, n = 456/849) reported no relevant change, whereas about one third (30%, n = 256/849) reported a functional health decline, and 16% (n = 137/849) reported an improvement. At the second follow-up, the share of patients describing a functional health decline decreased to 24% (n = 151/623) and the percentage reporting an improvement increased to 19% (n = 121/623).

Determinants of a Decline or Improvement in Subjective Mental and/or Functional Health

The ICU LOS, the duration of mechanical ventilation, and an episode of delirium were significantly associated with a decline in mental (odds ratio [OR] per ICU day, 1.04; 95% CI, 1.02–1.05; $p < 0.001$; OR per ventilation hour, 1.001; 95% CI, 1.001–1.002; $p < 0.001$; and OR for delirium, 1.64; 95% CI, 1.06–2.55; $p = 0.027$) and functional health (OR per ICU day, 1.05; 95% CI, 1.03–1.07; $p < 0.001$; OR per ventilation hour, 1.002; 95% CI, 1.001–1.003; $p < 0.001$; and OR for delirium, 2.05; 95% CI, 1.20–3.48; $p = 0.008$). Conversely, age decreased the odds of a mental health decline (OR per year, 0.98; 95% CI, 0.97–0.99; $p = 0.004$), and the odds of a functional health decline decreased over time after discharge (OR per month, 0.86; 95% CI, 0.79–0.94; $p = 0.001$) (**Table 3**; and **Table S3**, http://links.lww.com/CCM/H471).

In multivariable mixed-effects logistic regression, the ICU LOS remained significantly associated with a decline in mental (OR per ICU day, 1.04; 95% CI, 1.00–1.09; $p = 0.038$) and functional health (OR per ICU day, 1.06; 95% CI, 1.01–1.12; $p = 0.026$) after adjusting for other covariates. Postestimation showed that the probability of a mental health decline increased from 15% at an ICU LOS of 1 day to 29% at an ICU LOS of 30 days. The probability of a functional health decline increased from 22% at an ICU LOS of 1 day to 41% at an ICU LOS of 30 days. The probability of mental and functional health decline exceed 50% at a LOS of 62 and 42 days, respectively. Age was associated with lower odds of a mental health decline (OR per year, 0.98; 95% CI, 0.96–0.99; $p = 0.003$), and the odds of a functional health decline decreased over time after discharge (OR per month, 0.86; 95% CI, 0.79–0.94; $p = 0.001$) (**Table 4** and **Fig. 2**).

Our sensitivity analyses also showed that ICU LOS and the time of the follow-up after ICU discharge were significantly associated with a change in subjective health. We also found an association between the number of affected organ systems before ICU admission with functional health (**Tables S4–S8** and **Fig. S5**, http://links.lww.com/CCM/H471).

TABLE 1.
Baseline Characteristics of the Study Population, All Patients and by the Number of Follow-Ups Received

Characteristic	All Patients ($n = 855$)	Patients With One or Two Follow-Ups		p
		One ($n = 232$)	Two ($n = 623$)	
Age, yr	67 (56–77)	68 (56–77)	67 (57–77)	0.919[a]
Female	384 (45%)	102 (44%)	282 (45%)	0.734[b]
ICU length of stay, d	5 (2–10) ($n = 854$)	5 (2–11)	4 (2–9) ($n = 622$)	0.150[a]
Mechanical ventilation	570 (67%)	143 (62%)	427 (69%)	0.057[b]
Mechanical ventilation, hr (all patients)	11 (0–111) ($n = 851$)	8 (0–123) ($n = 231$)	12 (0–104) ($n = 620$)	0.478[a]
Mechanical ventilation, hr (among those ventilated)	57.5 (11–208) ($n = 566$)	75 (16–233) ($n = 142$)	51 (10–191) ($n = 424$)	0.106[a]
Body mass index, kg/m^2	26 (23–30)	26 (23–30)	26 (24–30)	0.790[a]
Delirium	304 (36%)	98 (42%)	206 (33%)	**0.013**[b]
Simplified Acute Physiology Score II at admission	29 (17–42)	30 (18–45)	29 (17–41)	0.492[a]
Organ systems affected before ICU admission	3 (2–5) ($n = 832$)	3 (1–4) ($n = 213$)	3 (2–5) ($n = 619$)	**0.019**[a]
Admission mode	($n = 845$)	($n = 229$)	($n = 616$)	
Emergency surgery	240 (28%)	79 (34%)	161 (26%)	**0.034**[b]
Elective surgery	244 (29%)	55 (24%)	189 (31%)	
Medical	361 (43%)	95 (41%)	266 (43%)	
Admission diagnosis				
Respiratory	88 (10%)	22 (9%)	66 (11%)	0.824[b]
Sepsis/infection	125 (15%)	36 (16%)	89 (14%)	
Gastrointestinal	90 (11%)	24 (10%)	66 (11%)	
Cardiovascular	240 (28%)	62 (27%)	178 (29%)	
Trauma	74 (9%)	22 (9%)	52 (8%)	
Neurologic	63 (7%)	21 (9%)	42 (7%)	
Metabolic/endocrine	37 (4%)	13 (6%)	24 (4%)	
Oncologic	125 (15%)	29 (12%)	96 (15%)	
Other[c]	13 (2%)	3 (1%)	10 (2%)	
University degree	126 (15%) ($n = 839$)	30 (14%) ($n = 217$)	96 (15%) ($n = 622$)	0.568[b]
Married or in stable partnership	468 (55%) ($n = 851$)	111 (49%) ($n = 228$)	357 (57%)	**0.025**[b]

[a]Mann-Whitney *U* test.
[b]Pearson's χ^2 test.
[c]Includes trauma in the context of recurrent syncopes, acute kidney injury ($n = 3$), chronic kidney failure, urethra stenoses and recurrent urinary tract infections, multiple organ failure (including liver failure), postoperative after spinal surgery, inguinal seroma after surgery, urolithiasis, opioid-induced pain exacerbation, reduced vigilance of unknown cause, and medication-related necrosis of the jaw.
n (%) or median (25th–75th percentiles). In case of missing data, *n* is listed in parentheses. Significant *p* values ($p < 0.05$) are in boldface font.

DISCUSSION

Main Findings

In this secondary analysis of a large multicenter trial in Germany, we compared subjective mental and functional health of 855 patients before ICU admission and after discharge. While more than half of patients did not report substantial changes in their subjective functional or mental health, we found that one in five patients reported a mental health

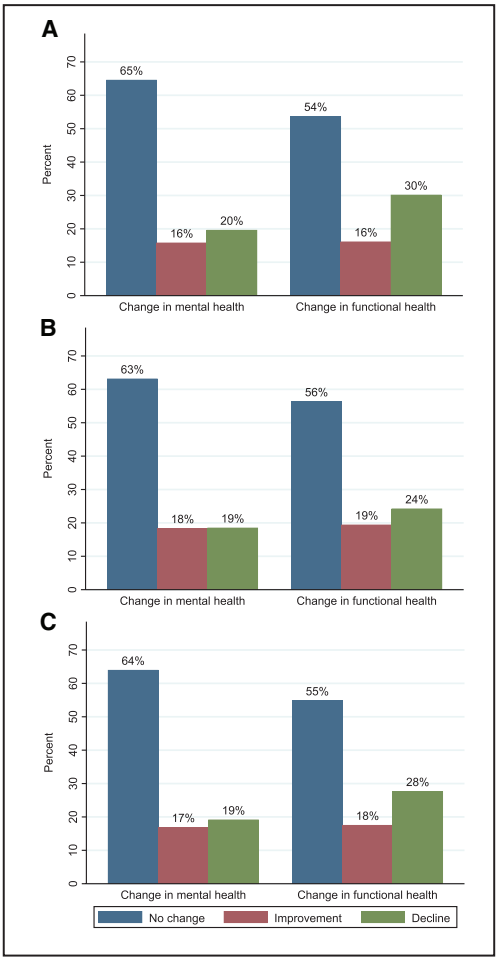

Figure 1. Relevant changes of subjective mental or functional health. **A**, First follow-up. **B**, Second follow-up. **C**, All-follow-ups. A subjective health change of at least three points (on a scale from 0 to 10) was considered a relevant decline/improvement.

decline and at least one in four patients reported a functional health decline. The ICU LOS was strongly associated with a health decline: Compared with patients with an ICU LOS of 1 day, patients with an ICU LOS of 30 days had a 97% higher probability of a mental health decline (15% vs. 29%) and an 88% higher probability of a functional health decline (22% vs. 41%).

What Is Already Known

Past studies have highlighted reductions in HrQoL following critical illness (15, 16, 18, 36), commonly assessed using SF-36 and EQ-5D (15, 16, 18, 36). EQ-5D index values were shown to correspond well to the subjective mental and functional health ratings used in this study (25). Previous studies either anchored their HrQoL estimates with a reference non-ICU population or asked participants to retrospectively report their HrQoL before ICU admission (15). These studies showed that pre-ICU HrQoL was lower than in the matched general population (15). For example, it has been previously shown in a Dutch prospective cohort study that pre-ICU HrQoL (using SF-36) in ICU survivors was lower than in an age-matched Dutch general population (37, 38). This suggests that many ICU patients already have preexisting health impairments before admission. In addition, previous studies showed that HrQoL partially recovered after discharge from the ICU, particularly in physical health domains (15, 16, 18). Consistent with this finding, our analysis indicated that with increasing time after discharge, patients were the less likely to report a functional health decline.

We identified distinct patient cohorts with unchanged, improved, or declined mental and/or functional health. This reflects a Dutch study where mental and physical SF-36 summary scores remained unchanged after 1 year for medical ICU patients, decreased for urgent surgical patients, but improved for elective surgical patients (12). In another Portuguese study, only 17% of 275 ICU survivors reported an unchanged health state compared with before, but 54% reported an improvement (39). The difference to our findings may be explained by our definition of a minimum relevant difference of three points.

Our analysis revealed that ICU LOS was significantly related to a mental and functional health decline, aligning with studies from Portugal (39) and Belgium (40), but contrasting other findings (41). A review from 2005 (18) concluded that only one (42) of eight studies analyzing the impact of ICU LOS on HrQoL found a significant association. Higher age appeared to be protective against a mental but not functional health decline. Previous studies on the impact of age on HrQoL after critical illness found diverging results (16, 18, 22, 23). Conflicting results may be explained by the finding

TABLE 2.
Subjective Mental Health and Subjective Functional Health Before ICU Admission and After ICU Discharge

Subjective Health	Mental Health	Functional Health
First follow-ups	(*n* = 841)	(*n* = 849)
Before ICU admission, median (IQR), mean (SD)	8 (5–9)[b], 6.8 (2.8)	7 (4–9)[d], 6.4 (2.9)
At follow-up, median (IQR), mean (SD)	7 (5–9)[b], 6.6 (2.5)	6 (4–8)[d], 5.7 (2.3)
Absolute change, median (IQR), mean (SD)[a]	0 (−2 to 1), −0.2 (2.9)	−1 (−3 to 1), −0.7 (3.2)
Spearman rank correlation coefficient of health status before ICU and at follow-up	0.45	0.30
Decline, *n* (%)	165 (20)	256 (30)
No change, *n* (%)	543 (65)	456 (54)
Improvement, *n* (%)	133 (16)	137 (16)
Second follow-ups	(*n* = 616)	(*n* = 623)
Before ICU admission, median (IQR), mean (SD)	8 (5–9)[c], 6.8 (2.9)	7 (4–9)[e], 6.4 (2.9)
At follow-up, median (IQR), mean (SD)	7 (5–9)[c], 6.9 (2.4)	6 (5–8)[e], 6.1 (2.2)
Absolute change, median (IQR), mean (SD)[a]	0 (−2 to 2), 0.1 (3.1)	−1 (−2 to 2), −0.3 (3.3)
Spearman rank correlation coefficient of health status before ICU and at follow-up	0.37	0.22
Decline, *n* (%)	114 (19)	151 (24)
No change, *n* (%)	389 (63)	351 (56)
Improvement, *n* (%)	113 (18)	121 (19)
All follow-ups	(*n* = 1457)	(*n* = 1472)
Before ICU admission, median (IQR), mean (SD)	8 (5–9)[f], 6.8 (2.8)	7 (4–9)[f], 6.4 (2.9)
At follow-up, median (IQR), mean (SD)	7 (5–9)[f], 6.7 (2.5)	6 (4–8)[f], 5.8 (2.3)
Absolute change, median (IQR), mean (SD)[a]	0 (−2 to 1), −0.1 (3.0)	−1 (−3 to 1), −0.6 (3.2)
Spearman rank correlation coefficient of health status before ICU and at follow-up	0.42	0.27
Decline, *n* (%)	279 (19)	407 (28)
No change, *n* (%)	932 (64)	807 (55)
Improvement, *n* (%)	246 (17)	258 (18)

IQR = interquartile range.
[a](Post-ICU status−pre-ICU status); i.e., a positive value indicates a health improvement and a negative value indicates a health decline.
[b]$p < 0.001$ (Wilcoxon signed-rank test).
[c]$p = 0.560$ (Wilcoxon signed-rank test).
[d]$p < 0.001$ (Wilcoxon signed-rank test).
[e]$p < 0.001$ (Wilcoxon signed-rank test).
[f]No comparison was performed due to the clustered nature of the data.
A subjective health change of at least three points (on a scale from 0 to 10) was considered a decline/improvement.

that physical rather than mental health items drive a negative effect of age on HrQoL (43), and by a possible U-shaped association of age and mental health (44): That is, the rate of depressive symptoms in the general population decreases until the early 60s/70s, and increases again for older individuals (44). Given our median age of 67 (IQR, 56–77), we may detect the protective effect of age on mental health described in the general population (44, 45). In an aging ICU population, where age is associated with increased mortality (46, 47), research on the influence of age on health outcomes is of utmost importance. Severity of illness and

TABLE 3.

Univariable Mixed-Effects Logistic Regression Models of Factors Associated With a Decline of Subjective Mental Health or of Subjective Functional Health After ICU Discharge, With a Random Effect for the Patient Identification Number

	Decline of Subjective Mental Health		Decline of Subjective Functional Health	
Covariate	OR (95% CI)	*p*	OR (95% CI)	*p*
University degree, yes	0.77 (0.42–1.43)	0.411	1.02 (0.50–2.09)	0.957
ICU length of stay, d	1.04 (1.02–1.05)	**< 0.001**	1.05 (1.03–1.07)	**< 0.001**
Gender, female	1.08 (0.70–1.65)	0.733	0.93 (0.56–1.56)	0.792
Partner or marriage	1.24 (0.81–1.92)	0.325	0.96 (0.57–1.60)	0.878
Duration of mechanical ventilation, hr	1.001 (1.001–1.002)	**< 0.001**	1.002 (1.001–1.003)	**< 0.001**
Time of follow-up after ICU discharge, mo	0.96 (0.90–1.04)	0.336	0.86 (0.79–0.94)	**0.001**
Delirium during ICU stay, yes	1.64 (1.06–2.55)	**0.027**	2.05 (1.20–3.48)	**0.008**
Body mass index, kg/m^2	0.99 (0.96–1.02)	0.590	0.98 (0.94–1.02)	0.283
Age, yr	0.98 (0.97–0.99)	**0.004**	1.00 (0.98–1.01)	0.655
Organ systems affected before ICU admission, *n*	0.91 (0.81–1.02)	0.118	0.89 (0.77–1.02)	0.102
Simplified Acute Physiology Score II at admission	1.02 (1.00–1.03)	**0.012**	1.01 (1.00–1.03)	0.129

OR = odds ratio.

A subjective health change of at least three points (on a scale from 0 to 10) was considered a decline/improvement. Decline of mental health: $n = 1431–1457$ observations from 824 to 846 patients. Decline of functional health: $n = 1445–1472$ observations from 827 to 850 patients. Rho (ρ; proportion of the total variance contributed by the patient-level variance component): 0.489–0.702. Likelihood-ratio tests comparing models to logistic regression without random effect: $p < 0.001$ for all models. Significant *p* values ($p < 0.05$) are in boldface font.

TABLE 4.

Multivariable Mixed-Effects Logistic Regression Models of Factors Associated With Decline in Subjective Mental Health or Subjective Functional Health After ICU Discharge, With a Random Effect for the Patient Identification Number

	Decline in Subjective Mental Health		Decline in Subjective Functional Health	
Covariate	OR (95% CI)	*p*	OR (95% CI)	*p*
ICU length of stay, d	1.04 (1.00–1.09)	**0.038**	1.06 (1.01–1.12)	**0.026**
Duration of mechanical ventilation, hr	1.00 (1.00–1.00)	0.562	1.00 (1.00–1.00)	0.438
Delirium during ICU stay, yes	1.03 (0.63–1.68)	0.905	1.32 (0.73–2.38)	0.364
Age, yr	0.98 (0.96–0.99)	**0.003**		
Simplified Acute Physiology Score II at admission	1.01 (1.00–1.02)	0.128		
Time of follow-up after ICU discharge, mo			0.86 (0.79–0.94)	**0.001**
Intercept	0.24 (0.09–0.64)	**0.004**	0.18 (0.10–0.32)	**< 0.001**

OR = odds ratio.

A subjective health change of at least three points (on a scale from 0 to 10) was considered a decline/improvement. Decline in subjective mental health: $n = 1450$ observations from 842 patients; Rho (ρ; proportion of the total variance contributed by the patient-level variance component): 0.484. Decline in subjective functional health: $n = 1447$ observations from 843 patients; Rho (ρ): 0.691. Likelihood-ratio tests comparing models to logistic regression without random effect: $p < 0.001$ for both models. Significant *p* values ($p < 0.05$) are in boldface font.

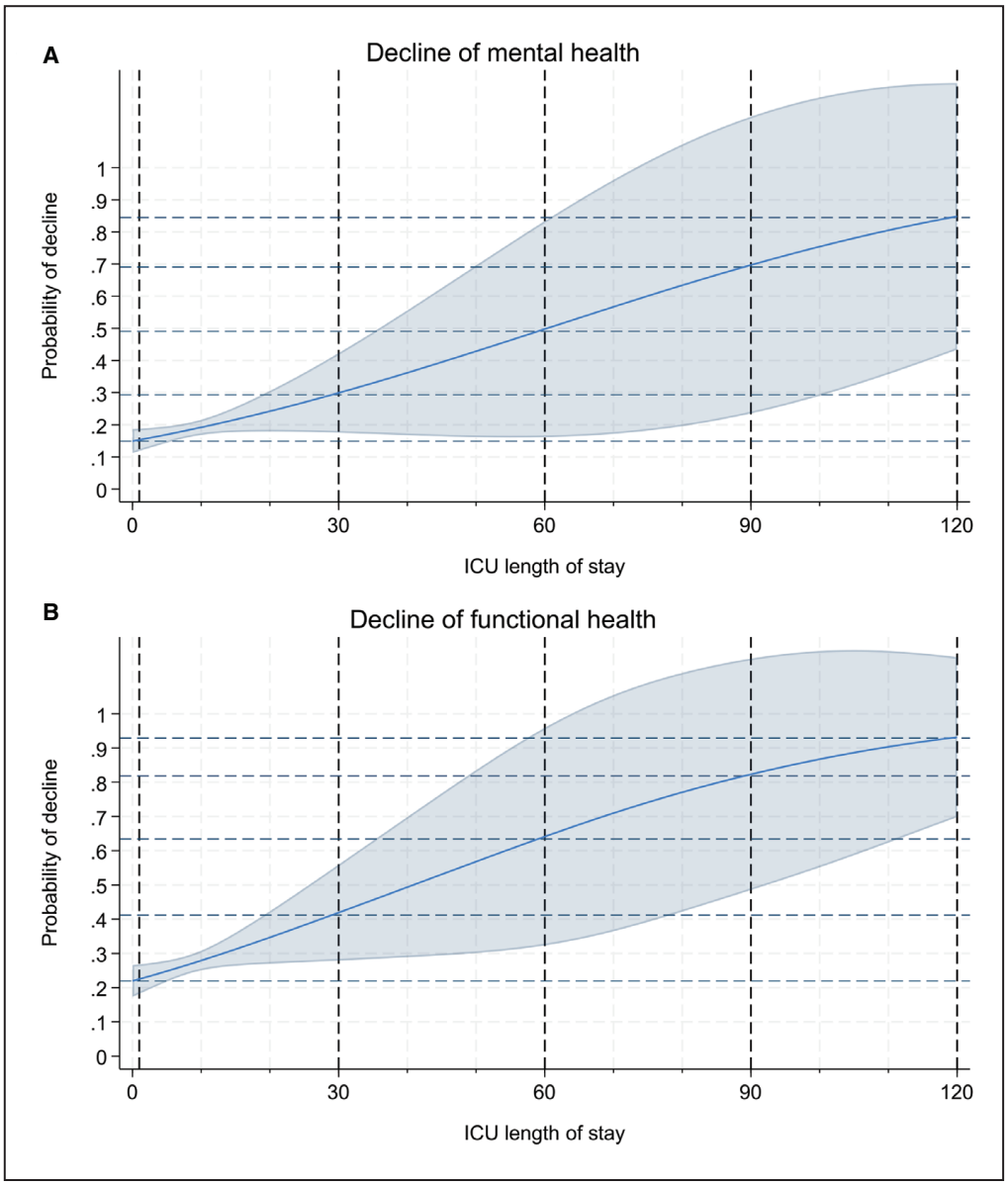

Figure 2. Probability of subjective health a decline in relation to the ICU length of stay. **A**, Probability of a mental health decline. **B**, Probability of a functional health decline. Independent variables included in the underlying multivariable random-effects logistic regression models were ICU length of stay, duration of mechanical ventilation, and delirium during ICU stay in both models; age and Simplified Acute Physiology Score II at admission in the mental health decline model; and time of follow-up after ICU discharge in the functional health decline model.

duration of mechanical ventilation were not associated with subjective health in multivariable analyses, mirroring previous results (23).

What This Study Adds

Although follow-up of ICU survivors and HrQoL measurement is recommended (48, 49), only few patients receive follow-ups (50–54). Study protocols often state the planned time of follow-ups, but actual assessment times frequently remain unknown. We showed that the time of follow-ups has an impact on the functional health status. Hence, the timing of follow-ups has to be considered in post-ICU clinics and should be transparently reported in studies. Patients with a long ICU LOS are at particular risk of impaired HrQoL. Thus, tailored follow-up assessments in ICU follow-up clinics and primary care should focus on these groups. As patients may trivialize or overemphasize symptoms, the administration of a proxy evaluation by a caregiver could provide a complimentary perspective and give additional, supplementary information (55).

Strengths and Limitations

We present a secondary analysis from a large German multicenter trial with a representative cohort of surgical and medical ICU patients. We collected pre-ICU and post-ICU HrQoL of almost 80% of patients who survived until 8 months after discharge. Our study also comes with limitations. First, our data could have been skewed by a survivor bias. That is, we could not include patients who passed away before their assessments and patients who withdrew from the study, who may have had worse health than follow-up participants. Second, we assessed pre-ICU health by retrospectively asking patients, so our assessments may have been subject to recall bias. However, retrospective assessments of pre-ICU HrQoL have been commonly used in previous studies (15). Further, another study compared EQ-5D scores that were assessed before a planned ICU admission with EQ-5D scores that were recalled after 3 and 6 months. The authors found high levels of agreement between actual and recalled assessments (29), although this approach has only been validated for elective but not for unplanned ICU admissions. Third, patients were recruited in Berlin and the neighboring federal state of Brandenburg. Recruitment in a limited geographical region with high quality of healthcare and healthcare access poses limitations to external generalizability to more rural regions, areas with fewer resources, and areas with more difficult healthcare access. Nevertheless, considering the broad inclusion criteria, the study cohort comprised medical and surgical ICU patients, which had a variety of admission diagnoses and were enrolled in small, medium-sized, and large hospitals. Fourth, we used the SD as a distribution-based method to justify our minimal important subjective health difference. Anchor-based methods are generally recommended over distribution-based methods, so future studies should use external anchors. Nevertheless, sensitivity analyses with a minimal important subjective health difference of two points and ordered logistic regression, which does not require defining a relevant health change, showed results similar to our main analysis. Finally, we did not systematically assess if patients suffered from preexisting mental health conditions. These patients may have already had lower pre-ICU mental health ratings and may have also faced greater mental health declines after ICU discharge than healthy individuals.

CONCLUSIONS

More than half of 855 critical illness survivors did not show substantial mental or functional health changes, but about one in five patients experienced a mental health decline, and at least one in four patients experienced a functional health decline. Multivariable mixed-effects logistic regressions showed that longer ICU LOS increased the likelihood of a subjective health decline. With increasing age, the likelihood of a mental health decline decreased, and with increasing time after discharge, the likelihood of a functional health decline decreased. Post-ICU care in post-ICU clinics and primary care should focus on patients with extended ICU LOS, as this group is particularly susceptible for subjective health decline.

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Dr. Paul was involved in conceptualization and methodology. Drs. Paul and Cittadino were involved in validation, formal analysis, data curation, writing–original draft preparation, and visualization. Drs. Paul, Cittadino, and Weiss were involved in investigation. Dr. Spies was involved in resources and supervision. Drs. Krampe, Denke, Spies, and Weiss were involved in writing–review and editing. Drs. Spies and Weiss were involved in project administration and funding acquisition. All authors have read and agreed to the published version of the article.

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Data will be made available from the corresponding author upon a reasonable request.

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2.3. Originalarbeit 3: Verwendung von Routinedaten zur Identifikation und Charakterisierung von Patient*innen mit Heimbeatmung

Eine besondere Population von Überlebenden kritischer Erkrankung sind Patient*innen, bei denen eine Entwöhnung von einer maschinellen Beatmung erfolglos bleibt und die mit maschineller Beatmung aus der stationären Behandlung entlassen werden. Ziel von *Originalarbeit 3* ist die Detektion und Charakterisierung von Patient*innen mit langfristiger Abhängigkeit vom Respirator anhand von Routinedaten. Hierfür wurden Daten zu stationären Krankenhausfällen herangezogen, welche das Institut für das Entgeltsystem im Krankenhaus regelmäßig an das Statistische Bundesamt übermittelt. Auf Basis verschiedener Operationen- und Prozedurenschlüssel konnten Patient*innen, bei denen eine Heimbeatmung initiiert, kontrolliert oder beendet wurde, erfasst werden. *Originalarbeit 3* bezieht sich somit, genau wie *Originalarbeit 1* und *Originalarbeit 2*, auf die Detektion von Patient*innen mit funktionellen Beeinträchtigungen nach kritischer Erkrankung. Anders als die vorherigen Arbeiten wurde hier jedoch ein epidemiologischer Ansatz gewählt, bei dem nicht der/die einzelne Patient*in untersucht wird, sondern das Patientenkollektiv anhand von Routinedaten erkannt wird. Beide Ansätze sind komplementär zueinander zu betrachten.

Der nachfolgende Text entspricht dem Abstrakt der Arbeit:

Paul N, Spies CD, Adam MF, Berger E, Busse R, Weiss B: Entwicklung der außerklinischen Beatmung im ersten Jahr der COVID-19-Pandemie in Deutschland: Eine Routinedaten-Analyse. Anasthesiol Intensivmed 2022; 63:174-186. doi:10.19224/ai2022.174.

„Hintergrund: Bisherige Routinedaten-Analysen haben gezeigt, dass die Einleitungen außerklinischer Beatmung in Deutschland rasant zunehmen. Es ist bislang nicht untersucht, wie sich die außerklinischen Beatmungen während des ersten Jahres der COVID-19-Pandemie entwickelt haben. Methodik: Fallzahlen der Ersteinstellung, Kontrolle und Beendigung invasiver und nicht-invasiver Beatmung von 2017 bis 2020 wurden für Deutschland und nach Bundesländern untersucht. Patienten mit Ersteinstellung einer invasiven außerklinischen Beatmung von 2017 bis 2020 wurden hinsichtlich ICD-Diagnosen analysiert (Daten vom Statistischen Bundesamt). Ausgaben der gesetzlichen Krankenversicherungen für ambulante Intensivpflege von

2017 bis 2020 wurden analysiert (Daten des Bundesministeriums für Gesundheit). Ergebnisse: Entgegen dem Trend vorheriger Jahre nahmen die Ersteinstellungen außerklinischer Beatmungen 2020 im Vergleich zum Vorjahr um 14,9 % ab, von N = 17.958 (2019) auf N = 15.279 (2020). Diese Entwicklung war zurückzuführen auf eine deutschlandweite Abnahme der Ersteinstellungen nicht-invasiver außerklinischer Beatmungen um 15,9 %. Die Ersteinstellungen invasiver außerklinischer Beatmungen blieben 2020 hingegen auf ähnlichem Niveau, wobei sich regionale Unterschiede zeigten. Sowohl Kontrollen (-24 % bzw. -28 %) als auch Beendigungen (-15,1 % bzw. -45,3 %) nicht-invasiver und invasiver außerklinischer Beatmungen nahmen im Jahr 2020 ab. Patienten, für die eine invasive Beatmung etabliert wurde, zeigten eine Vielzahl an Komorbiditäten und einen hohen Pflegebedarf. Die Ausgaben der gesetzlichen Krankenversicherungen für ambulante Intensivpflege stiegen von 1,52 Milliarden Euro (2017) auf 2,16 Milliarden Euro (2020; +42,3 %). Schlussfolgerungen: Nach Zunahme der Kontrollen und Beendigungen invasiver und nicht-invasiver außerklinischer Beatmungen in Deutschland in den letzten Jahren zeigt sich 2020 eine Trendumkehr. Auch die Initiierungen nicht-invasiver außerklinischer Beatmungen nahmen 2020 ab. Inwieweit diese Entwicklungen mit der COVID-19-Pandemie zusammenhängen, sollte weitergehend untersucht werden.“

Paul N, Spies CD, Adam MF, Berger E, Busse R, Weiss B: Entwicklung der außerklinischen Beatmung im ersten Jahr der COVID-19-Pandemie in Deutschland: Eine Routinedaten-Analyse. Anasthesiol Intensivmed 2022; 63:174-186. https://doi.org/10.19224/ai2022.174

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2.4. Originalarbeit 4: Verbesserung patientenrelevanter Langzeit-Outcomes durch die Implementierung von Care-Bundles auf der Intensivstation: Ein Scoping Review

Neben dem Forschungsbedarf bei der PICS-Diagnostik gibt es große Wissenslücken in der PICS-Prävention und der Therapie eines bestehenden PICS. Welche Maßnahmen können während der intensivmedizinischen Behandlung ergriffen werden, um die Entstehung eines PICS zu verhindern? *Originalarbeit 4* beschäftigt sich mit sogenannten Care-Bundles, also Paketen von drei bis fünf evidenzbasierten Maßnahmen, zur Verbesserung der Qualität der akuten intensivmedizinischen Behandlung. Diese Care-Bundles betreffen beispielsweise die frühe Diagnose und Behandlung von Sepsis (das sogenannte Sepsis-Bundle), Aspekte der Beatmung oder auch Aspekte des Delir- und Sedierungsmanagements. Im Rahmen eines Scoping Reviews wurde in *Originalarbeit 4* untersucht, ob die Implementierung von Care-Bundles auf der ITS die Entstehung funktioneller Beeinträchtigungen nach Entlassung verhindern kann.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Paul N, Ribet Buse E, Knauthe A-C, Nothacker M, Weiss B, Spies CD: Effect of ICU care bundles on long-term patient-relevant outcomes: a scoping review. BMJ Open 2023; 13(2):e070962. doi:10.1136/bmjopen-2022-070962.

*„Zielsetzung: Care-Bundles sind ein essenzielles Werkzeug zur Verbesserung der Qualität der intensivmedizinischen Versorgung. Wir untersuchten den Effekt von Care-Bundles auf patientenrelevante Langzeit-Outcomes. Design: Systematische Literatursuche und Scoping Review. Datenbanken: Wir suchten in PubMed, Embase, CINAHL, APA PsycInfo, Web of Science, CDSR und CENTRAL für Schlüsselwörter, die mit Intensivmedizin, Care-Bundles, patientenrelevanten Outcomes und Follow-Up-Studien zusammenhingen. Einschlusskriterien: Originalarbeiten, welche die Implementierung von Care-Bundles und ihren Effekt auf patientenrelevante (d.h. Mortalität, gesundheitsbezogene Lebensqualität (HrQoL), Post-Intensive Care Syndrom (PICS), versorgungsbezogene Outcomes, unerwünschte Ereignisse und soziale Gesundheit) Langzeit-Outcomes (d.h. Entlassung von der Intensivstation oder später) bei Patient*innen, die auf einer Erwachsenen-Intensivstation behandelt*

*wurden, untersucht haben. Datenextraktion und Datensynthese: Zwei Personen führten eine unabhängige, zweistufige Selektion und Charting durch. Eingeschlossene Artikel wurden kritisch bewertet und bezüglich ihres Bundle-Typs, der Implementierungsstrategien und ihres Effekts auf patientenrelevante Langzeit-Outcomes untersucht. Ergebnisse: Von 2012 Artikeln erfüllten 38 die Einschlusskriterien; 55% (n=21) waren Vorher-Nachher-Studien, 21% (n=8) Beobachtungskohortenstudien, 13% (n=5) randomisierte kontrollierte Studien, und 11% (n=4) hatten andere Designs. Die Care-Bundles bezogen sich auf Sepsis (n=11), Neurokognition (n=6), Kommunikation (n=4), frühe Rehabilitation (n=3), Beendigung nicht indizierter Medikamententherapien (n=3), Beatmung (n=2) und kombinierte Care-Bundles mehrerer Versorgungsbereiche (n=9). Beinahe zwei Drittel der Studien untersuchten das Überleben (n=24), 45% (n=17) untersuchten versorgungsbezogene Outcomes (z.B. den Ort der Entlassung) und 13% (n=5) der Studien untersuchten die HrQoL. Mit Bezug auf PICS untersuchten 24% (n=9) die Kognition, 13% (n=5) die körperliche Gesundheit und 11% (n=4) die mentale Gesundheit nach bis zu einem Jahr nach Entlassung. Der Effekt der Care-Bundles auf patientenrelevante Langzeit-Outcomes war bis auf einen positiven Effekt der Sepsis-Bundles auf das Überleben nicht eindeutig. Der fehlende klare Effekt könnte auf ein hohes Risiko eines Bias in den eingeschlossenen Studien und einer großen Variabilität der Implementierungsstrategien, der verwendeten Instrumente und der Follow-Up-Zeitpunkte zurückzuführen sein. Schlussfolgerungen: Der Effekt von Care-Bundles auf die HrQoL und PICS-Outcomes muss in Zukunft verstärkt untersucht werden. Das Schließen dieser Wissenslücke ist unverzichtbar, um den Wert von Care-Bundles für Patient*innen einschätzen zu können.“* (Übersetzung durch den Autor.)

BMJ Open

Effect of ICU care bundles on long-term patient-relevant outcomes: a scoping review

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ABSTRACT

Objective Care bundles are considered a key tool to improve bedside quality of care in the intensive care unit (ICU). We explored their effect on long-term patient-relevant outcomes.

Design Systematic literature search and scoping review.

Data sources We searched PubMed, Embase, CINAHL, APA PsycInfo, Web of Science, CDSR and CENTRAL for keywords of intensive care, care bundles, patient-relevant outcomes, and follow-up studies.

Eligibility criteria Original articles with patients admitted to adult ICUs assessing bundle implementations and measuring long-term (ie, ICU discharge or later) patient-relevant outcomes (ie, mortality, health-related quality of life (HrQoL), post-intensive care syndrome (PICS), care-related outcomes, adverse events, and social health).

Data extraction and synthesis After dual, independent, two-stage selection and charting, eligible records were critically appraised and assessed for bundle type, implementation strategies, and effects on long-term patient-relevant outcomes.

Results Of 2012 records, 38 met inclusion criteria; 55% (n=21) were before–after studies, 21% (n=8) observational cohort studies, 13% (n=5) randomised controlled trials, and 11% (n=4) had other designs. Bundles pertained to sepsis (n=11), neurocognition (n=6), communication (n=4), early rehabilitation (n=3), pharmacological discontinuation (n=3), ventilation (n=2) or combined bundles (n=9). Almost two-thirds of the studies reported on survival (n=24), 45% (n=17) on care-related outcomes (eg, discharge disposition), and 13% (n=5) of studies on HrQoL. Regarding PICS, 24% (n=9) assessed cognition, 13% (n=5) physical health, and 11% (n=4) mental health, up to 1 year after discharge. The effects of bundles on long-term patient-relevant outcomes was inconclusive, except for a positive effect of sepsis bundles on survival. The inconclusive effects may have been due to the high risk of bias in included studies and the variability in implementation strategies, instruments, and follow-up times.

Conclusions There is a need to explore the long-term effects of ICU bundles on HrQoL and PICS. Closing this knowledge gap appears vital to determine if there is long-term patient value of ICU bundles.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The protocol of this scoping review has been published in a peer-reviewed journal, and we followed the high standards of the Arksey and O'Malley framework and the Joanna Briggs Institute.
⇒ Our search strategy was independently peer-reviewed as recommended in the Peer Review of Electronic Search Strategies guidelines, and we conducted a comprehensive hand search of reference lists of all included studies and relevant reviews identified in the screening.
⇒ We grouped bundle implementation strategies using the *Expert Recommendations for Implementing Change* taxonomy of 73 implementation strategies.
⇒ Although not mandatory for scoping reviews, we conducted a quality appraisal of included studies using recommended tools from the Joanna Briggs Institute.
⇒ By using 'bundle' as an obligatory term in our search strategy, we may have missed articles that implemented bundle-like interventions without explicitly referring to them as 'bundles'.

INTRODUCTION

The complex environment of an intensive care unit (ICU) is characterised by severely ill patients[1] and a high density of treatment decisions.[2] On average, intensivists face more than 100 treatment decisions per day, where they put evidence-based measures into practice.[2] While intensive care research has focused on finding new therapies, little attention has been paid to knowledge transfer.[3] This led to a stark discrepancy between research-based best practice and bedside care.[3–7] For example, a study on the implementation of 11 evidence-based practices in the ICU found that best-practice care was prescribed in only 56.5% of the instances.[8] Existing ICU culture, low prioritisation on introducing novel care strategies, an ICU's organisational complexity, and lack of staff training have been identified as potential barriers to the implementation of evidence-based practices.[7]

Care bundles have been heralded as a potential remedy to leap the gap between evidence and practice.[9] Care bundles group three to five evidence-based practices.[10] Each bundle

element stands independently, is non-controversial, has a strong evidence base,[10] and the conjunctive application multiplies the effect on patient outcomes.[9] Each bundle element is clearly defined, and bundle implementation is monitored continuously.[10] Over the last decades, several ICU-specific bundles have emerged, such as the sepsis bundle of the Surviving Sepsis Campaign,[11] the ventilator bundle,[12] and the ABCDEF bundle.[13]

Bundle implementation studies in the ICU have commonly assessed bundle adherence,[14–17] ICU[14 17 18] or hospital mortality,[15 18] ICU length of stay,[17 18] costs,[17] and incidence of adverse events such as ventilator-associated pneumonia.[14 16] Undoubtedly, these short-term outcomes, which commonly focus on improvements in quality of care and clinical parameters, remain relevant. Yet, critical care research has acknowledged the importance of long-term patient-relevant sequelae of critical illness.[19–21] In addition to long-term mortality, these include a decreased health-related quality of life (HrQoL),[22] and specific morbidities like impairments of physical function,[23] cognition[24] and mental health,[25] summarised as post-intensive care syndrome (PICS).[26]

Previous reviews have explored the effect of non-pharmacological ICU interventions to improve long-term outcomes,[27] but we are unaware of previous research on ICU bundles. The effect of the implementation of ICU bundles on long-term patient-relevant outcomes appears unknown. First, we assessed if original ICU bundle research articles have reported effects on long-term patient-relevant outcomes. We included any study that assessed patient outcomes beyond ICU discharge. Second, we determined bundle types, implementation strategies, time points of outcome assessment of included studies. Given the heterogeneous nature of bundles, implementation strategies and outcomes, we considered a scoping review most suitable to answer the research question. With this work, we aim to identify knowledge gaps that may guide future studies on the long-term patient value of ICU bundles.

METHODS

Study design and definitions

We conducted a systematic literature search and scoping review to identify the effect of ICU bundles on long-term patient-relevant outcomes. We adhered to the Arksey and O'Malley framework[28] and additions,[29] and the Preferred Reporting Items for Systematic Review and Meta-Analysis Extension for Scoping-Reviews checklist (online supplemental file 1).[30] The scoping review was pre-registered on Open Science Framework,[31] and the protocol has been published.[32]

Patient-relevant outcomes were defined as outcomes of mortality, symptoms, adverse events/complications, and social health (eg, return to work).[33] Additionally, we included HrQoL and the PICS domains cognition, mental health and physical health. Long-term was defined as assessment at ICU discharge or later, except that we excluded mere assessment of hospital mortality.

Study identification

We searched PubMed, Embase (via Ovid), CINAHL and APA PsycInfo (via EBSCOhost), Web of Science, CDSR and CENTRAL on 12 December 2021 using a combination of English keywords and medical subject headings for four concepts: (1) intensive care, (2) care bundles, (3) patient-relevant outcomes, and (4) follow-up studies, without restrictions to the publication date (online supplemental table S1). On 21 August 2021, a preliminary search and independent pilot screening of 100 records by two authors (ERB and A-CK) was conducted to test and refine the search strategy, which adhered to the guidelines of Peer Review of Electronic Search Strategies (PRESS).[34]

Study selection

Search results were assessed in a two-stage process. Records were imported to EndNote (V.20.1, Clarivate Analytics, Philadelphia, USA) and, after duplicate removal, imported to Rayyan.[35] Two authors (NP and ERB) independently screened titles and abstracts using Rayyan's blinding option. Additionally, we conducted a hand search of reference lists of all included studies and relevant reviews identified in the screening to find additional literature. Two authors (NP and ERB) independently assessed the full texts of the remaining records. Disagreements between authors were solved through discussions. Reasons for exclusion were documented (online supplemental table S2).

Inclusion criteria were as follows: (1) participants were ≥18 years; (2) more than 50% of the patients received ICU treatment; (3) an ICU care bundle (≥3 bundled measures) was compared with standard care; (4) patient-relevant outcomes were measured at ICU discharge or later; (5) original research article; (6) published in English, German or Spanish. Exclusion criteria were as follows: (1) paediatric patients; (2) no measurement of patient-relevant outcomes at ICU discharge or later; (3) records were based on expert opinion or secondary research only.

Data charting and critical appraisal

Eligible records were charted individually by two authors (ERB and A-CK) using the Joanna Briggs Institute extraction form,[36] which was piloted with 10 publications and refined. Disagreements were resolved through discussions. Study designs were classified following the definitions of the Joanna Briggs Institute.[37] Experimental designs without randomised study arm allocation (eg, before–after designs) were classified as quasi-experimental studies. Studies that related the number of performed bundle items or bundle compliance to patient outcomes without implementing an intervention were classified as observational cohort studies. Bundles were categorised: (1) communication, (2) early

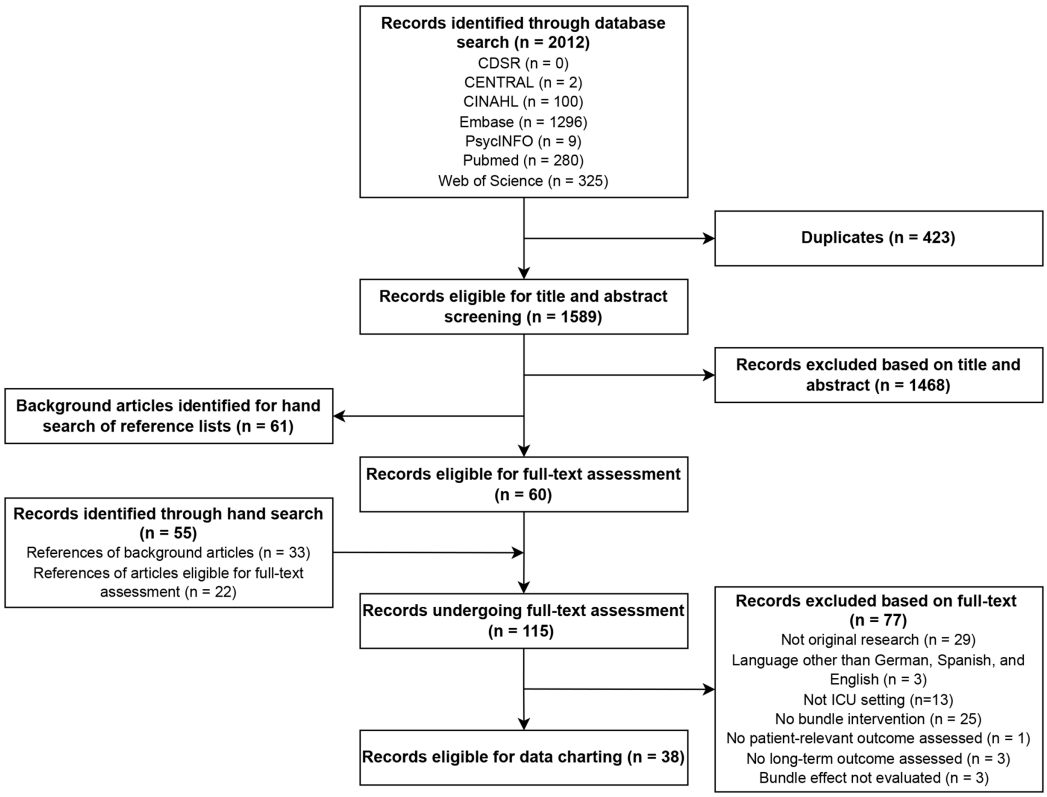

Figure 1 Study inclusion flowchart. ICU, intensive care unit.

rehabilitation, (3) neurocognition, (4) pharmacological discontinuation, (5) sepsis, (6) ventilation, and (7) combined bundles (eg, ABCDEF bundle). Outcomes were categorised: (1) survival, (2) HrQoL, (3) care-related outcomes (outcomes pertaining to care after discharge, ie, readmissions or discharge disposition), the PICS domains (4) cognition, (5) mental health, and (6) physical health/mobility, (7) social health (ie, return to work) and (8) adverse events. To enhance the comparability of implementation strategies, we adhered to the taxonomy of implementation strategies proposed in the *Expert Recommendations for Implementing Change (ERIC)* project.[38] Bundle effects of included studies on long-term patient-relevant outcomes were categorised as positive, possibly positive and no effect. Two authors (ERB and A-CK) individually performed a critical appraisal of included records using the Joanna Briggs Institute Critical Appraisal Tools.[37] Disagreements were resolved through discussions. Studies were not excluded based on inferior quality. Study data were managed using MS Excel (Microsoft Corporation, Redmond, Washington, USA).

Patient and public involvement

We did not involve patients in designing or conducting the review. For public involvement, we plan to disseminate our results through the authors' department website.

RESULTS

Characteristics of included studies

Of identified 2012 records, 60 remained for full-text assessment after dual title and abstract screening. We identified another 55 records through hand search of reference lists of background articles (n=33) and of articles included after screening (n=22). Of 115 records undergoing dual full-text assessment, 77 were excluded, leaving 38 records for dual charting (figure 1, online supplemental table S2).

Articles were published between 2000 and 2022, with half of the studies (n=19) published in 2016 or later. They were conducted in the US (n=15),[39–53] France (n=4),[54–57] Australia (n=5),[58–62] China (n=3),[63–65] Spain (n=2),[66 67] Norway (n=2),[68 69] Scotland,[70]

Portugal,[71] Northern Ireland,[72] Italy,[73] Germany,[74] Canada[75] and Uganda (each n=1).[76] Two studies depict separate outcome analyses of data collected within one clinical trial (ClinicalTrials.gov identifier: NCT01656317).[68 69] We identified 19 single-centre studies,[39–41 44 45 47 49 50 52 56 62–64 68 69 72–75] three two-centre studies,[43 57 76] and 16 multicentre studies.[42 46 48 51–53 55–58 61–65 67 70 71] Thirty studies were prospective,[39–45 48 51–59 61 62 64–69 71–73 75 76] and eight studies were retrospective.[46 47 49 50 60 63 70 74] Eight studies were observational cohort studies,[50 53 59 63 65 66 70 71] 21 studies were quasi-experimental before–after studies,[39–41 43–47 49 54–58 67–69 73–76] 1 study was a quasi-experimental single-arm study (which compared patients from the early and late implementation phases of a bundle intervention),[51] 1 study was a quasi-experimental controlled non-randomised comparative time-series study,[72] 1 study was a cost-effectiveness analysis,[42] 5 studies were randomised controlled trials (RCTs) (one cluster RCT and 4 individually RCTs)[48 52 61 62 64] and 1 study was a quasi-experimental trial following an RCT.[60] Settings varied from 42 hospitals[59] and 68 ICUs[53] to 1 ICU.[50 75] Sample sizes varied from 36 055[70] to 30[62] (online supplemental table S3).

Bundle type and implementation strategies

Eleven studies investigated the implementation of a sepsis bundle based on recommendations from the Surviving Sepsis Campaign or similar.[44 45 54 63–67 71 74 76] Nine studies explored combined bundles, including five studies on the ABCDE(F) bundle,[41–43 53 62] one study on geriatric-focused practices,[50] two studies on a fever, sugar and swallowing bundle[60 61] and one study comprising delirium and sedation management, mobilisation and rounding strategies.[46] Six studies explored the implementation of neurocognitive bundles, with one sleep quality intervention,[40] one psychological intervention,[73] two stroke bundles,[59 70] one cognitive and physical therapy bundle,[52] and one bundle on protocolised sedation, analgesia and delirium management.[75] Four studies investigated the implementation of a communication bundle, which comprised interaction with patient and family.[39 47 51 72] Three bundles pertained to early rehabilitation.[56 68 69] Three studies investigated pharmacological discontinuation bundles on stress ulcer prophylaxis discontinuation,[58] antipsychotic medication discontinuation[49] and pharmacological delirium management.[49] Two studies were about ventilation bundles with lung-protective ventilation and early extubation[55 57] (table 1, online supplemental table S3).

We identified 44 *ERIC* implementation strategies to implement bundles. Most commonly, studies conducted educational meetings (n=23) such as seminars or supervised training, or developed and implemented tools for quality monitoring (n=19), for example, change cycles and algorithms. Often studies developed (n=13) and distributed (n=12) educational materials by, for example, uploading information to the institute's website or providing posters. Studies identified and prepared

Table 1 Categories of long-term patient-relevant outcomes, by bundle category

Outcome and bundle category	All (n=38)	Combined bundle (n=9)*	Communication (n=4)	Early rehabilitation (n=3)	Neurocognition (n=6)	Pharmacological discontinuation (n=3)	Sepsis (n=11)	Ventilation (n=2)
Survival	24 (63)	4 (44)	1 (25)	3 (100)	3 (50)	1 (33)	11 (100)	1 (50)
Care-related outcome†	17 (45)	6 (67)	3 (75)		3 (50)	2 (67)	1 (9)	2 (100)
Health-related quality of life	5 (13)	2 (22)			3 (50)			
PICS—physical health	5 (13)	2 (22)		2 (67)	1 (17)			
PICS—cognition	9 (24)	2 (22)		3 (100)	3 (50)			1 (50)
PICS—mental health	4 (11)	1 (11)	1 (25)		1 (17)	1 (33)		
Social health	1 (3)				1 (17)			
Adverse events	1 (3)			1 (33)				

n (%).
*Includes the ABCDEF bundle.
†Care-related outcomes comprise outcomes pertaining to care after intensive care unit discharge, eg, readmissions or discharge disposition.
PICS, post-intensive care syndrome.

champions (n=11) to implement the intervention in their ICU and built a coalition to strengthen partner relationships (n=10). Studies rarely involved executive boards or used advisory boards and workgroups. Notably, reporting of implementation strategies was not standardised, and four studies did not report any implementation strategy (table 2).

Long-term patient-relevant outcomes used

Almost two-thirds (n=24) of the studies reported survival after hospital discharge, most commonly 28-day,[44–46 54 63–67 71 76] 30-day,[48 70 74 75] 60-day,[63] 90-day,[57 61 63 69] 180-day,[59 70] 1 year,[42 56 68] or 3–5 year mortality,[60] or survival to discharge from acute and rehabilitative care to home and mortality in the rehabilitation facility[39] (tables 1 and 3).

Long-term HrQoL was assessed in five studies.[42 52 59 62 73] Concerning the PICS domains, nine studies assessed cognition,[40 52 55 56 61 62 68 69 73] five studies assessed physical health,[52 56 61 62 69] and four studies assessed mental health.[49 61 72 73] Care-related outcomes, that is, outcomes associated with patient care after discharge, were assessed in 17 studies. These include discharge destination,[42 47 48 50 51 53 59] change in residence,[41 70] return to independent living,[75] hospital or ICU readmission rates,[43 53] inappropriate continuation of stress ulcer prophylaxis at discharge,[58] ICU-free days and ventilator-free days,[55 57 74] risk of remaining in the ICU[39] or discharge diagnosis of aspiration pneumonia.[61] One study assessed adverse events within 90 days after stroke,[69] and one study assessed return to work within 12 months[73] (tables 1 and 3). Notably, even within similar outcome categories (eg, mental health), studies varied with respect to test instruments used. Further, the time points of outcome measurement varied from ICU discharge to 3–5 years after stroke onset[60] (table 3).

Effects on long-term patient-relevant outcomes

We grouped studies based on the effect on patient-relevant outcomes, but due to the variability in instruments and time points, we did not perform a meta-analysis. Thirteen studies found a positive effect of the bundle intervention on survival,[44 45 54 55 59 64–67 70 71 74 76] whereas nine studies did not find a survival benefit.[39 46 48 56 57 63 68 69 75] Interestingly, 10 of 11 studies on sepsis bundles showed superior survival. For care-related outcomes, HrQoL, and the PICS domains cognition, mental health and physical health, we found mixed evidence: Some studies detected a positive effect, others possibly a positive effect, and other studies could not find any effect at all (table 4, online supplemental table S4).

As an example of a positive effect on PICS outcomes, a before–after study in an Italian mixed ICU evaluated an in-ICU psychological intervention including emotional support to patients and family members, counselling, stress management, coping strategies and family-centred decision-making. One year after ICU discharge, fewer patients from the intervention group showed a high risk for post-traumatic stress disorder (21.1% vs 57%) or needed psychiatric medication after discharge (1.7% vs 8.1%), and their HrQoL was higher (EQ-5D visual analogue scale 77.4 vs 72.4). No significant differences were found concerning anxiety, depression, and return to previous employment.[73]

Critical appraisal

In almost half of the RCTs and the quasi-experimental studies (n=12/30), baseline characteristics of control and intervention group significantly differed, posing a high risk of confounding bias.[40–42 45 52 54 57 58 62 74–76] The proportion of studies lacking comparability of study groups could be even higher as articles frequently lacked information to assess the comparability of the study groups. Another issue with included RCTs was the lack of blinding: All RCTs (n=5) blinded the outcome assessor for treatment assignment, but only one study reported patient blinding,[61] and no study reported study team blinding. The reliability of outcome measures in quasi-experimental studies was often compromised or not reported. In three studies, participants selectively received different care other than the exposure, making these studies prone to confounding bias.[46 57 69] In two of eight cohort studies, the study groups did not originate from the same population, posing a risk of selection bias[59 66] (online supplemental tables S5–S7).

DISCUSSION

Main findings

We conducted a scoping review on the long-term effects of ICU bundles on patient-relevant outcomes. Our five main findings were as follows: First, most included studies reported long-term survival or care-related outcomes, but few studies assessed HrQoL or PICS-related outcomes of cognition, mental health and physical health. Second, even if studies assessed HrQoL or PICS, we found little standardisation in methodology, instruments and follow-up time. Third, most studies on sepsis bundles found a positive effect on survival, but there was no conclusive positive effect of other bundles on different patient-relevant outcome categories. Fourth, interventions commonly relied on simple implementation strategies such as conducting educational meetings. Fifth, while studies were conducted in a variety of settings, more than half were before–after studies and half were single-centre studies. In the critical appraisal, we identified a high risk of bias.

What is already known

Outside of ICU bundle implementation research, the epidemiology of long-term sequelae after critical illness is well described: Up to 34% of the patients show anxiety symptoms 12–14 months after ICU discharge,[77] up to 29–30% have depressive symptoms 12–14 months after discharge,[78] and up to 34% have symptoms of post-traumatic stress disorder.[79] Cognitive impairments occur in 4–62% of the patients,[80] 5–70% show dependencies in

Table 2 Implementation strategies* used in included studies (n=38), in descending order

Implementation strategy	n (%)	References
Conduct educational meetings	23 (61)	40–47 49 51 54–58 60–62 67 71–73 75
Develop and implement tools for quality monitoring	19 (50)	40 43–47 49 51 52 54–57 62 67 68 71 75 76
Develop educational materials	13 (34)	41 47 49 51 54–56 58 60 61 67 71 72
Distribute educational materials	12 (32)	41 47 49 51 54–56 58 60 61 71 72
Identify and prepare champions	11 (29)	40–43 48 51 60 61 71 75 76
Build a coalition	10 (26)	40 41 43 47 49 51 52 68 71 75
Audit and provide feedback	9 (24)	39 41–43 46 51 60 61 67
Conduct ongoing training	8 (21)	41 43 45 47 49 51 56 75
Develop and organise quality monitoring systems	8 (21)	41 42 46–48 51 65 71
Develop a formal implementation blueprint	7 (18)	41 43 47 51 54 65 71
Provide ongoing consultation	6 (16)	43 48 60–62 71
Change record systems	5 (13)	41–43 46 71
Stage implementation scale up	5 (13)	40 46 47 62 72
Create new clinical teams	5 (13)	41 43 47 60 61
Involve patients/consumers and family members	4 (11)	39 47 72 76
Centralise technical assistance	4 (11)	46 48 62 71
Assess for readiness and identify barriers and facilitators	4 (11)	43 49 60 61
Remind clinicians	4 (11)	40 48 60 61
No strategy reported	4 (11)	51 61 63 70
Conduct educational outreach visits	3 (8)	51 60 61
Tailor strategies	3 (8)	47 49 75
Provide clinical supervision	3 (8)	43 48 73
Purposely re-examine the implementation	3 (8)	41 54 57
Conduct local consensus discussions	2 (5)	41 75
Organise clinician implementation team meetings	2 (5)	41 55
Facilitation	2 (5)	43 72
Provide local technical assistance	2 (5)	48 71
Change physical structure and equipment	2 (5)	40 75
Conduct cyclical small tests of change	2 (5)	46 47
Mandate change	2 (5)	43 47
Develop academic partnerships	2 (5)	43 71
Make training dynamic	2 (5)	55 62
Create a learning collaborative	1 (3)	41
Recruit, designate, and train for leadership	1 (3)	41
Intervene with patients/consumers to enhance uptake and adherence	1 (3)	72
Obtain and use patients/consumers and family feedback	1 (3)	72
Prepare patients/consumers to be active participants	1 (3)	72
Facilitate relay of clinical data to providers	1 (3)	68
Conduct local needs assessment	1 (3)	65
Inform local opinion leaders	1 (3)	46
Use an implementation advisor	1 (3)	46
Involve executive boards	1 (3)	43
Work with educational institutions	1 (3)	43

Continued

Table 2 Continued

Implementation strategy	n (%)	References
Promote adaptability	1 (3)	75
Use advisory boards and workgroups	1 (3)	75

Studies[68 69] are separate outcome analyses of unique data collected within one clinical trial (ClinicalTrials.gov identifier: NCT01656317).
*According to the *Expert Recommendations for Implementing Change (ERIC)* taxonomy.[38]

instrumental activities of daily living,[81] and the HrQoL is below population norms.[22]

Although the high frequency of long-term impairments constitutes an imperative to include these outcomes in ICU bundle research, no other review of ICU bundles has focused on long-term patient-relevant outcomes. Previous reviews have assessed ICU bundle implementation strategies,[82] barriers and facilitators of ICU bundle implementation[83] and the effect on outcomes.[84] Our results support previous reviews, which concluded that studies implementing ICU bundles often lack structure regarding use, reporting and justification of implementation strategies.[83 84] In line with previous reviews,[82–84] we showed that some implementation strategies (eg, educational activities and audit and feedback) were more frequently used than others. We translated implementation strategies to the respective *ERIC* strategies to enhance comparability; however, just like previous reviews on ICU bundles found out,[83] none of our included studies used the *ERIC* taxonomy. Another scoping review for evidence-based practices in critical care in general also found considerable variability in the nomenclature that was used to describe implementation strategies.[85] Standardised and transparent reporting is recommended to compare the effectiveness of certain strategies.[83 86] Corresponding to our critical appraisal, previous reviews also found that most evidence on ICU bundle effects has weak methodological quality.[85] In our work, half of the studies were conducted in a single centre, making them prone to centre-specific effects such as local ICU culture. Unknown centre-specific effects may limit the generalisability of results to other hospitals and contexts.

Practical implications and directions of future research

Our work yields practical implications and directions for future research. Studies on ICU bundles that used long-term patient-relevant outcomes mostly assessed mortality or care-related outcomes, but HrQoL and PICS appear rarely assessed. Hence, this scoping review identified a research gap for high-quality research on the effect of ICU bundles on HrQoL and PICS, but not so much on mortality and care-related outcomes. Closing the research gap is difficult as post-ICU follow-up studies take time and are challenging for research teams.[87] Reasons include high post-ICU mortality, loss to follow-up, missing data, instrument selection and high demands on constraint time and personnel.[87] However, the relevance for patients provides a strong impetus for conducting these studies, with observation periods ideally years after discharge. To ease the comparison and facilitate results synthesis in meta-analyses, there is a need to adhere to a common and standardised instrument set (eg,[88 89]). The definition of a core outcome set for long-term effects of ICU bundle interventions, which could be included in the Core Outcome Measures in Effectiveness Trials initiative database,[90] may facilitate the harmonisation.

We identified several studies that implemented a sepsis bundle and found a positive effect on long-term survival. Hence, as a practical implication, clinicians may consider using multicomponent implementation strategies to implement a sepsis bundle, ideally using a theory-guided approach.[91] For a stronger recommendation, studies identified in this review could be included in a meta-analysis. For other bundles, for example, neurocognitive bundles or combined bundles (including the ABCDEF bundle), we found little and inconclusive evidence of improved outcomes. Hence, at this point we are unable to recommend that intensivists implement these bundles to improve long-term patient-relevant outcomes. The variation in instruments and time points, the risk of bias and the varying complexity level of implementation strategies may have contributed to the unequivocal conclusions on the bundle effects. ICU bundles may improve short-term patient outcomes, but the low-quality evidence has already prevented a clear recommendation for ICU bundle implementation in a previous review.[84]

Strengths and limitations

Strengths of this scoping review include the rigorous methodology: First, the review was preregistered on Open Science Framework[31] and its protocol was published.[32] Second, the search strategy was developed according to PRESS recommendations.[34] Third, we performed an extensive hand search to collect records missed by our search strategy. Fourth, selection, charting and critical appraisal were performed independently by two researchers. Fifth, though not mandatory for scoping reviews, we performed a quality appraisal. Finally, we used the *ERIC* framework to group implementation strategies,[38] which enhances the comparability to other studies.

Limitations of this work also warrant consideration. First, there is no consensus on a definition of patient-relevant outcomes. We intended to use a broad definition that included general and ICU-specific outcomes but might have missed relevant studies. Second, there is no consensus on the definition of long-term. We used a broad definition of ICU discharge or later to include any study that assessed outcomes beyond a patient's ICU

Table 3 Instruments and evaluation periods for the assessment of long-term patient-relevant outcomes

Outcome category	Instruments	At discharge*	After discharge*						Other time	References
			28–30 d/1 m	60 d/2m	90 d/3m	180 d/6m	1y	3–5 y		
Survival (n=24)	Mortality		x†							44–46 48 54 64–67 71 74–76
			x	x	x					63
					x					57 61 69
					x‡					61 69
			x‡			x‡				70
						x‡				59
							x§			42
							x¶			42 56 68
								x‡		60
									At discharge to rehabilitation, to home and in rehabilitation	39
HrQoL (n=5)	SF-36				x					62
	EQ5D VAS				x					52
	EQ5D VAS				x**	x**				59
	EQ5D domain scores, EQ5D VAS						x			73
	QALYs						x§			42
PICS—cognition (n=9)	Modified Rankin Scale; Glasgow Outcome Scale Extended						x¶			68
	Glasgow Outcome Scale				x¶					55
	Modified Rankin Scale				x§					61
	Functional Independence Measure	x								62
	CAM-ICU; Digit Span Forward and Backward test; TMT A and B	x††								40
	Tower Test; dysexecutive questionnaire, MMSE	x			x					52
	Glasgow Coma Scale	x								69 73
	ASIA motor and sensitive score	x					x¶			56
PICS—physical health (n=5)	Physical Function ICU Test-scored, Functional Independence Measure	x								62
	Timed Up-and-Go; Katz Activities of Daily Living; Functional Activities Questionnaire	x			x					52
	Mobilisation level	x								69
	ASIA motor and sensitive score	x					x¶			56
	Mean physical component summary score, Barthel index				x§					61

Continued

Table 3 Continued

Outcome category	Instruments	At discharge*	After discharge*					Other time	References
			28–30 d/1 m	60 d/2 m	90 d/3 m	180 d/6 m	1 y	3–5 y	
PICS—mental health (n=4)	Sickness Impact Profile		x§	x§	x§				72
	IES-R; HADS; need for psychotherapy, anxiolytic and/or antidepressant medication						x		73
	Antipsychotic medication use	x							49
	Mean SF-36 mental component summary score				x§				61
Care-related outcomes (n=17)	Discharge destination	x							42 47 48 50 51 53 59
	Change in residence	x							41
	Discharge to usual residence		x§			x§			70
	Return to independent living	x							75
	ICU readmission rate, ICU discharge destination other than home	x							53
	Inappropriate continuation of stress ulcer prophylaxis	x							58
	ICU-free days and ventilator-free days				x¶				55 57
	Ventilator-free days		x‡‡						57 74
	Readmission rate		x						43
	Risk of remaining in the ICU							Until day 20	39
	Discharge diagnosis of aspiration pneumonia	x							61
Adverse events (n=1)	Adverse events				x‡				69
Social health (n=1)	Return to work						x		73

Studies[68 69] are separate outcome analyses of unique data collected within one clinical trial (ClinicalTrials.gov identifier: NCT01656317).
*ICU and/or hospital discharge.
†After discharge, except for one study that considered those discharged before 28 days to be alive[44] and one study that assessed 30-day mortality after hospital admission.[76]
‡After stroke.
§After ICU/hospital admission.
¶After trauma/haemorrhage.
**EQ5D VAS measured at 90-180 days after the index event.
††Right after ICU discharge.
‡‡After trauma[37] or hospital admission.[74]
ASIA, American Spinal Injury Association; CAM-ICU, Confusion Assessment Method for the ICU; d, days; EQ5D, EuroQol 5 dimensions; HADS, Hospital Anxiety and Depression Scale; HrQoL, health-related quality of life; ICU, intensive care unit; IES-R, Impact of Event Scale-Revised; m, months; MMSE, Mini-Mental State Examination; QALY, quality-adjusted life year; SF-36, Short Form (36); TMT, Trail Making Test; VAS, visual analogue scale; y, years.

Table 4 Effects of bundles on long-term patient-relevant outcomes

Bundle category	Outcome	Effect		
		Positive	Possibly positive	None
All (n=38)	Survival	13[44 45 54 55 59 64–67 70 71 74 76]	2[60 61]	9[39 46 48 56 57 63 68 69 75]
	Care-related outcomes *	12[39 42 49–51 53 55 57–59 70 75]	4[43 47 61 62]	5[41 48 69 73 74]
	Health-related quality of life	2[59 73]	2[42 62]	1[52]
	PICS—physical health	3[56 61 69]		2[52 68]
	PICS—cognition	1[56]		3[40 52 68]
	PICS—mental health	2[72 73]		1[61]
	Adverse events			1[69]
	Social health			1[73]
Communication (n=4)	Survival			1[39]
	Care-related outcomes*	2[39 51]	1[47]	
	PICS—mental health	1[72]		
Early rehabilitation (n=3)	Survival			3[56 68 69]
	Care-related outcomes*			1[69]
	PICS—physical health	2[56 69]		1[68]
	PICS—cognition	1[56]		1[68]
	Adverse events			1[69]
Neurocognitive (n=6)	Survival	2[59 70]		1[75]
	Care-related outcomes*	3[59 70 75]		1[73]
	Health-related quality of life	2[59 73]		1[52]
	PICS—physical health			1[52]
	PICS—cognition			2[40 52]
	PICS—mental health	1[73]		
	Social health			1[73]
Pharmacological discontinuation (n=3)	Survival			1[48]
	Care-related outcomes*	2[49 58]		1[48]
Sepsis (n=11)	Survival	10[44 45 54 64–67 71 74 76]		1[63]
	Care-related outcomes*			1[74]
Ventilation (n=2)	Survival	1[55]		1[57]
	Care-related outcomes*	2[55 57]		
Combined (n=9)†	Survival	1[42]	2[60 61]	1[46]
	Care-related outcomes*	3[42 50 53]	3[43 61 62]	1[41]
	Health-related quality of life		2[42 62]	
	PICS—physical health	1[61]		
	PICS—mental health			1[61]

Studies[68 69] are separate outcome analyses of unique data collected within one clinical trial (ClinicalTrials.gov identifier: NCT01656317).
*Care-related outcomes comprise outcomes pertaining to care after ICU discharge, eg, readmissions or discharge disposition.
†Includes the ABCDEF bundle.
ICU, intensive care unit; PICS, post-intensive care syndrome.

stay, but our pragmatic definition resulted in the inclusion of studies that only measured outcomes shortly after or at ICU discharge. A more restrictive definition would have drastically reduced the number of included studies. Third, by including 'bundle' as a necessary term in our search strategy, we may have missed articles that described multicomponent interventions without referring to them as bundles. For example, a recently published cluster RCT evaluated the effects of an individually tailored, multicomponent nursing intervention on delirium prevention, which may be considered a bundle. Despite implementation efforts, the time spent on intervention components, ICU readmission rate, 28-day and 90-day mortality did not improve significantly.[92] The term 'bundle' has been well-established for many years, and we mitigated the risk of missing relevant articles by conducting a comprehensive hand search. Fourth, the research question and search strategy were developed by a research team with expertise in critical care, quality improvement, care bundles, PICS and post-ICU follow-ups. While this expertise relates

to many areas of the review, the clinical focus may have biased our results. Finally, as this was not intended in our study protocol,[32] we did not synthesise the effects of the included studies. A synthesis could be performed in future meta-analyses, despite the challenges due to the heterogeneity of implemented bundles, outcomes, instruments and time points.

CONCLUSIONS

Our systematic literature search and scoping review identified 38 studies on the effect of ICU bundles on long-term patient-relevant outcomes. The studies pertained to a variety of bundles, most commonly the sepsis bundle. The majority were quasi-experimental before–after studies and single-centre or two-centre studies with bias risks identified in the critical appraisal. Despite their undisputed relevance for patients, we only identified a few studies that reported long-term HrQoL and PICS outcomes of cognition, mental health and physical health. While most studies on sepsis bundles indicated a survival benefit, the effect of other bundles on different long-term patient-relevant outcomes was inconclusive. This may have been due to the large variability in instruments and time points. Hence, future research should focus on: (1) Assessing long-term HrQoL and PICS-related outcomes; (2) using standardised instruments and common time points; (3) employing high-quality research designs and clearly describing bundle interventions and implementation strategies.

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2.5. Originalarbeit 5: Verbesserung der Adhärenz zu leitliniengerechtem Delir-, Sedierungs- und Analgesie-Management auf der Intensivstation

Vorarbeiten haben einen engen Zusammenhang zwischen dem Auftreten eines Delirs während der intensivmedizinischen Versorgung und langfristigen kognitiven Defiziten gezeigt [23, 101]. Die Umsetzung eines leitliniengerechten Managements von Delir, Sedierung und Analgesie, was zur Prävention, zur frühen Detektion und zur adäquaten Behandlung eines manifesten Delirs führt, könnte somit zu einer Verringerung kognitiver Langzeitbeeinträchtigungen beitragen. In *Originalarbeit 5* wird untersucht, ob ein mehrwöchiges Schulungsprogramm zum Management von Delir, Sedierung und Analgesie die Rate der Patient*innen, die systematisch auf das Vorliegen eines Delirs, bezüglich ihrer Sedierungstiefe und bezüglich ihres Schmerzlevels untersucht werden, erhöhen kann. Zudem wird untersucht, ob durch das Schulungsprogramm nicht-medikamentöse Maßnahmen zur Delir-Prävention verstärkt zum Einsatz kommen.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Paul N*, Grunow JJ*, Rosenthal M, Spies CD, Page VJ, Hanison J, Patel B, Rosenberg A, von Haken R, Pietsch U, Schrag C, Waydhas C, Schellongowski P, Lobmeyr E, Sander M, Piper SK, Conway D, Totzeck A, Weiss B: Enhancing European Management of Analgesia, Sedation, and Delirium: a multinational, prospective, interventional before-after trial. Neurocrit Care 2023. doi:10.1007/s12028-023-01837-8.

“Hintergrund: Das Ziel dieser Studie war die Analyse des Einflusses eines strukturierten Schulungsprogramms auf die Implementierung von leitliniengerechtem Assessment von Schmerz, Agitation und Delir (PAD). Methoden: Diese Studie war eine prospektive, multinationale Interventionsstudie im Vorher-Nachher-Design, die auf 12 Intensivstationen in zehn Zentren in Deutschland, Österreich, der Schweiz und dem Vereinigten Königreich durchgeführt wurde. Teilnehmende Intensivstationen durchliefen ein sechswöchiges strukturiertes Schulungsprogramm, bestehend aus Online-Vorlesungen, Schulungsvideos, Handouts und Ausbildung am Patientenbett. Patientendaten zu PAD-Assessments wurden an drei Ein-Tages-Prävalenzerhebungen vor (T1), sechs Wochen nach (T2) und ein Jahr nach (T3) dem

*Schulungsprogramm erhoben. Ergebnisse: Insgesamt wurden 430 Patient*innen eingeschlossen. Die Rate der Patient*innen, die alle drei PAD-Assessments erhielten, betrug 55% (107/195) zu T1 und 53% (68/129) zu T2, stieg aber auf 73% (77/106) zu T3 (p = 0,003). Die Delir-Screening-Rate stieg von 64% (124/195) zu T1 auf 65% (84/129) zu T2 und 77% (82/106) zu T3 (p = 0,041). Die Schmerz-Assessment-Rate stieg von 87% (170/195) zu T1 auf 92% (119/129) zu T2 und 98% (104/106) zu T3 (p = 0,005). Die Rate der Assessments der Sedierungstiefe veränderte sich nicht signifikant. Der Anteil der Patient*innen, die nicht-pharmakologische Maßnahmen zur Delir-Prävention erhielten, stieg von 58% (114/195) zu T1 auf 80% (103/129) zu T2 und 91% (96/106) zu T3 (p < 0,001). Multivariable Regressionsanalysen zeigten, dass Patient*innen zum Zeitpunkt T3 mit höher Wahrscheinlichkeit ein Delir-Assessment (Odds Ratio [OR] 2,138, 95%-Konfidenzintervall [KI] 1,206–3,790; p = 0,009), Sedierungstiefe-Assessment (OR 4,131, 95%-KI 1,372–12,438; p = 0,012) und alle drei PAD-Assessments (OR 2,295, 95%-KI 1,349–3,903; p = 0,002) im Vergleich zu T1 erhielten. Schlussfolgerungen: In der Routineversorgung erhielten viele Patient*innen kein PAD-Assessment. Die Rate der Patient*innen, die ein PAD-Assessment erhielten, nahm ein Jahr nach einem strukturierten Schulungsprogramm signifikant zu. Registrierung: ClinicalTrials.gov: NCT03553719."* (Übersetzung durch den Autor.)

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ORIGINAL WORK

Enhancing European Management of Analgesia, Sedation, and Delirium: A Multinational, Prospective, Interventional Before-After Trial

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Abstract

Background: The objective of this study was to analyze the impact of a structured educational intervention on the implementation of guideline-recommended pain, agitation, and delirium (PAD) assessment.

Methods: This was a prospective, multinational, interventional before-after trial conducted at 12 intensive care units from 10 centers in Germany, Austria, Switzerland, and the UK. Intensive care units underwent a 6-week structured educational program, comprising online lectures, instructional videos, educational handouts, and bedside teaching. Patient-level PAD assessment data were collected in three 1-day point-prevalence assessments before (T1), 6 weeks after (T2), and 1 year after (T3) the educational program.

Results: A total of 430 patients were included. The rate of patients who received all three PAD assessments changed from 55% (107/195) at T1 to 53% (68/129) at T2, but increased to 73% (77/106) at T3 ($p = 0.003$). The delirium screening rate increased from 64% (124/195) at T1 to 65% (84/129) at T2 and 77% (82/106) at T3 ($p = 0.041$). The pain assessment rate increased from 87% (170/195) at T1 to 92% (119/129) at T2 and 98% (104/106) at T3 ($p = 0.005$). The rate of sedation assessment showed no signficiant change. The proportion of patients who received nonpharmacological delirium prevention measures increased from 58% (114/195) at T1 to 80% (103/129) at T2 and 91% (96/106) at T3 ($p < 0.001$). Multivariable regression revealed that at T3, patients were more likely to receive a delirium assessment (odds ratio [OR] 2.138, 95% confidence interval [CI] 1.206–3.790; $p = 0.009$), sedation assessment (OR 4.131, 95% CI 1.372–12.438; $p = 0.012$), or all three PAD assessments (OR 2.295, 95% CI 1.349–3.903; $p = 0.002$) compared with T1.

Conclusions: In routine care, many patients were not assessed for PAD. Assessment rates increased significantly 1 year after the intervention.

Clinical trial registration ClinicalTrials.gov: NCT03553719.

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Keywords: Critical care, Delirium, Delivery of health care, Europe, Intensive care units

Background

Pain, agitation/sedation, and delirium (PAD) are common among critically ill patients. Previous studies have shown that pain is experienced by about half of medical and surgical intensive care unit (ICU) patients at rest [1, 2], severe or dangerous agitation is present in about half of ICU patients [3], 27% of ICU patients have been found to be deeply sedated [4], and up to 82% of ICU patients undergoing mechanical ventilation are affected by delirium [5, 6]. PAD are detrimental to patient outcomes. High-quality pain management reduces the duration of mechanical ventilation and the nosocomial infection rate [7], and early deep sedation is an independent predictor for delayed extubation and 6-month mortality [8]. Delirium is associated with a longer duration of mechanical ventilation [6], longer hospitalization [5, 6], increased mortality [9, 10], and higher rates of long-term cognitive impairment [11]. Hence, PAD management is an integral part of intensive care [12–14].

Guidelines recommend that PAD should be assessed every 8 h using validated screening tools [12–14]. Self-assessment is useful among patients able to report pain (e.g., the Numeric Rating Scale [NRS]) [15], alternatively observational tools such as the Behavioral Pain Scale (BPS) [16, 17] or the Critical-Care Pain Observation Tool for those unable to [12–14, 18]. Guidelines consider the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [19] and the Intensive Care Delirium Screening Checklist (ICDSC) [20] as the most suitable delirium screening instruments and recommend the Richmond Agitation Sedation Scale (RASS) [21] or the Sedation Agitation Scale [22] for sedation assessment [12–14].

Despite the relevance of evidence-based PAD assessment, previous studies from routine care have indicated poor implementation rates in various settings. In a multinational survey in 2019/20 among a convenience sample of 1474 intensivists, 95.4% of respondents reported assessing delirium daily, but two thirds only assessed patients they considered to be at risk [23]. Although 85.4% of participants responded to assess sedation levels and 86.7% responded to assess pain in patients able to communicate, only two thirds assessed pain in those unable to communicate [23]. In a 2014 survey among 101 European ICUs, 49%, 30%, and 79% of centers reported the 8-hourly assessments of pain, agitation or delirium, respectively, but under half of patients in this study actually received PAD monitoring [24]. These results mirror surveys from Poland in 2016 [25], Belgium in 2011 [26], Australia/New Zealand in 2006/7 [27], Canada in 2002 [28], and Germany in 2002 [29].

Structured face-to-face training and e-learning have been employed as effective strategies to increase staff knowledge and improve the frequency and quality of routine PAD assessment in previous studies [30–37]. A prospective cohort study on three German ICUs of one university hospital showed an improvement in PAD screening rates more than 1 year following the implementation of formal and bedside teaching as well as the provision of educational resources and delirium support teams [38].

We are not aware of recent data on the real-world, guideline-adherent PAD assessment rates in European ICUs. In this prospective before-after trial among patients of 12 European ICUs, we first investigated whether PAD assessment rates change 6 weeks and 1 year following a structured educational program. Second, we explored which patient-specific characteristics might determine whether a patient was assessed for pain, sedation, or delirium.

Methods

Study Design

In this prospective, multinational, interventional before-after trial, data on the assessment of delirium, analgesia, and sedation for inpatients in participating adult ICUs were collected at three 1-day (i.e., 24-h) point-prevalence assessments. Immediately after the first 1-day assessment from December 2018 to January 2019, study sites underwent a structured 6-week educational program, aimed at improving the frequency and quality of PAD assessments. The educational program was based on a previously published extensive training algorithm [38]. Data for two additional 1-day point prevalences were collected 6 weeks (May–June 2019) and 1 year (March–May 2020) after the conclusion of the educational program (Fig. 1). The study adhered to the ethical standards of the Declaration of Helsinki and its later amendments and its protocol was registered at ClinicalTrials.gov on June 12, 2018 (Identifier: NCT03553719). Ethical approval at the coordinating study site was granted by the Institutional Review Board (IRB) of Charité–Universitätsmedizin Berlin (EA2/022/18) on March 23, 2018. Participating centers obtained their IRB approval before study commencement as required by local regulations. Written

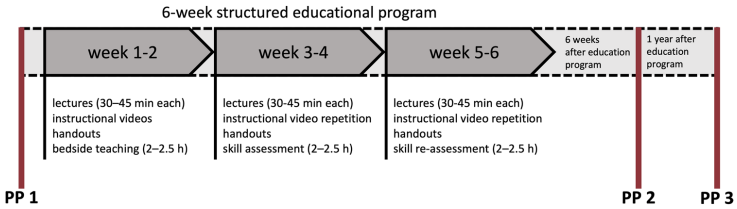

Fig. 1 Concept of the structured educational program and data collection at assessment points (red lines). *PP* point prevalence

consent or a waiver was subject to the decision of the local IRBs.

Trial ICUs and Participants

The trial was hosted by Charité–Universitätsmedizin Berlin and conducted at 12 European adult ICUs from 10 centers, located in Germany, the UK, Austria, and Switzerland (Table S1). Centers were recruited from members of the Working Group Postoperative Delirium and Cognitive Dysfunction of the European Society of Intensive Care Medicine and its NEXT Committee.

Patients qualified for inclusion if they were treated in a participating ICU on a day of a point-prevalence assessment and were $\geq$ 18 years of age. Patients were excluded for blindness, deafness, or an insurmountable language barrier.

Structured Educational Program

We applied a structured educational algorithm pertaining to PAD based on a previously described training algorithm [38]. In short, the educational program consisted of three 2-week cycles and was based on the train-the-trainer concept. It combined theoretical lectures, handouts with key points, instructional videos, and bedside teaching. On the first 4 days of each cycle, trained PAD experts from Charité (MR and BW) provided participants of all study centers with 30–45-min webinars on the assessment of sedation and pain, the minimization of sedation, the pathophysiology, symptomatology, prevention, and detection of delirium, and provided a demonstration of the CAM-ICU. These webinars were recorded and provided to participants for later review and dissemination. All informational content was distributed to local study coordinators to adapt into their units' practice, providing the core messages and structure remained unchanged. On the fifth day of each cycle, theoretical teaching was followed by 2–2.5-h face-to-face bedside teaching from PAD experts at each participating center, with immediate feedback and debriefing for participants. PAD experts were consultants with expertise in pain, sedation and delirium, and they were part of the study team. Bedside teaching also addressed a potential lack of documentation of assessments. At three centers where the local PAD expert was not available, bedside teaching was provided by a PAD expert from Charité (MR or BW). In the second week of each cycle, ICU staff were expected to apply the learning content in routine care. Our overarching goal was to train local "PAD leaders." Local project leaders were tasked with recruting interested staff members. Participation was voluntary and open to all ICU staff members (doctors, nurses, and other health care professionals), but most participants were ICU nurses. Every center received its individual training to keep group sizes small and lower the barriers for questions during the training. Training of centers was performed sequentially and in close temporal proximity (Fig. 1).

Outcomes

The primary outcome was the percentage of patients screened for delirium at least once on the day of the point-prevalence assessment (delirium screening rate). Secondary outcomes comprised percentage of patients who received at least one pain or sedation assessment on the day of the point-prevalence assessment (pain and sedation assessment rates), delirium, pain, and sedation screening tools used, respective pain and sedation scores, delirium prevalence in routine delirium screening, and nonpharmacological measures to prevent or treat delirium (i.e., reorientation method, early mobilization, and sensory shielding) [39–41].

Data Collection

Patient characteristics, treatment data, and PAD management were recorded for each patient in an electronic case report form (LimeSurvey, Hamburg, Germany). Data on PAD assessment were taken from the patients' health care records to obtain information on the current ICU practice. The assessors were therefore ICU physicians and nurses as per local standard. Data were stored on a

secure server on the premises of the coordinating study site and handled according to European Union General Data Protection Regulations. Except for local study coordinators, ICU staff was unaware of the assessment days. Local study coordinators were also prompted to pick days that were not particularly busy or had usual staffing.

Data Analysis

In previously published work [24], 27% of patients received routine delirium screening prior to an educational program, and in a study implementing an educational program similar to our proposed intervention, the routine delirium screening rate increased by about 15% after a month of training [42]. According to our a priori sample size calculation, we could detect an increase in screening rate from 27% before the educational program to 42% following the educational program if each participating ICU enrolled 14 patients on average (170 patients total) per assessment point, with a power of at least 0.8 and a two-tailed significance level of 0.05 (Fisher's exact test; nQuery Advisor 7.0, Statsols, Cork, Ireland). Although sample size planning was done conservatively on the basis of a simple two-group test, we planned to account for the clustered data structure in the analysis.

Descriptive statistics of the study population are either presented as medians with limits of the interquartile range (IQR) or absolute (n) with relative frequencies (%). Patient characteristics and PAD assessment points were compared using Pearson's χ^2 tests for categorical variables and Kruskal–Wallis test for continuous variables. Adjustments were not made for multiple testing. Multivariable mixed-effect logistic regression analyses were used to assess the association between the assessment points and the likelihood for a patient to receive a delirium, sedation, or pain assessment, all PAD assessments, or nonpharmacological measures to prevent or treat delirium, respectively. The regression models included sex, age, extracorporeal membrane oxygenation provision (yes/no), and mechanical ventilation (yes/no) as fixed effects. To account for the clustered nature of the data, a random effect for the treating country was added (Germany, Austria, Switzerland, or the UK). Statistical analyses were performed using Stata 17SE (StataCorp LP, College Station, TX).

Results

Study Population

A total of 430 patients from 12 ICUs from 10 centers were included, with 195 patients at the first (December 2018–January 2019), 129 patients from 8 centers at the second (May–June 2019), and 106 patients from 6 centers at the third (March–May 2020) 24-h assessment point. Recruitment by center and assessment point is shown in Table S1.

At the first, second, and third assessment points 76%, 66%, and 72% of patients, respectively, were mechanically ventilated. The median Simplified Acute Physiology Score II scores at admission were 37 (IQR 27–53), 41.5 (IQR 31.5–49), and 40 (IQR 28–51). There were no significant differences between patients of the three assessment points with respect to age, sex, height, weight, admitting diagnosis, current length of ICU stay, organ support received, mechanical ventilation, extracorporeal membrane oxygenation provision, and severity of illness (Table 1).

Delirium, Sedation, and Pain Assessments

Delirium screening was performed in 64% (124/195) of patients at least once daily at baseline. The CAM-ICU was used in 56% (109/195) of patients, the nursing delirium screening scale in 4% (7/195), and the ICDSC in 5% (10/195) of patients. Two patients received both CAM-ICU and ICDSC assessments. After completion of the educational program, the delirium screening rate increased to 65% (84/129) at 6 weeks, and 77% (82/106) at 1 year ($p = 0.041$). Among those screened, 26% (32/124), 23% (19/84), and 13% (11/82) screened positive for delirium at assessment points 1, 2, and 3, respectively. Screening for delirium at assessment points 2 and 3 was conducted solely using the CAM-ICU, as the two centers using the ICDSC and nursing delirium screening scale at assessment point 1 did not recruit patients at later assessment points (Table 2, Fig. 2a, Fig. S1a).

At baseline, 58% (114/195) of patients received nonpharmacological measures to prevent or treat delirium. After the educational program, 80% (103/129) received nonpharmacological measures at assessment point 2, and 91% (96/106) at assessment point 3 ($p < 0.001$). The most common measure was reorientation (e.g., clock or whiteboard), which was used in 45% (87/195), 53% (68/129), and 67% (71/106) of patients at assessment points 1, 2, and 3, respectively ($p = 0.001$). The second most common nonpharmacological measure was early mobilization, which was provided to 43% (83/195), 46% (59/129), and 58% (61/106) of patients at assessment points 1, 2, and 3, respectively ($p = 0.042$).

Sedation depth was assessed in 88% (171/195) of patients at least once per day at baseline. After the educational program, 86% (111/129) received sedation depth assessment at assessment point 2, and 93% (99/106) at assessment point 3 ($p = 0.182$). RASS was used in 87% (169/195), 86% (111/129), and 74% (78/106) of patients ($p = 0.009$). The Sedation Agitation Scale was not used in any ICUs. Other sedation scales included the alert, verbal, pain, unresponsive scale, which was used in 20%

Table 1 Characteristics of the study population

Variable	Assessment point			*p* value
	1 (*n* = 195)	2 (*n* = 129)	3 (*n* = 106)	
Age (years)	63 (52–73)	59 (52–73)	64 (52–74)	0.552[a]
Female sex	75 (38%)	41 (32%)	47 (44%)	0.173[b]
BMI (kg/m^2)	26.4 (23.2–30.7)	26.2 (23.9–29.7)	25.7 (23.1–29.4)	0.513[a]
Primary ICU admission diagnosis				
Respiratory	43 (22%)	26 (20%)	21 (20%)	0.107[b]
Septic/infectious	20 (10%)	12 (9%)	12 (11%)	
Gastrointestinal	28 (14%)	9 (7%)	15 (14%)	
Cardiovascular	45 (23%)	45 (35%)	23 (22%)	
Traumatic	24 (12%)	6 (5%)	8 (8%)	
Neurologic	17 (9%)	18 (14%)	17 (16%)	
Metabolic or endocrine	2 (1%)	4 (3%)	4 (4%)	
Oncologic	9 (5%)	3 (2%)	3 (3%)	
Others[c]	7 (4%)	6 (5%)	3 (3%)	
ICU length of stay at day of assessment (d)	7 (3–17)	7 (2–15)	7 (3–15)	0.819[a]
Received any organ support	156 (80%)	98 (76%)	83 (78%)	0.65[b]
Mechanical ventilation	147 (76%)	89 (66%)	78 (72%)	0.321[b]
ECMO	19 (10%)	20 (16%)	7 (7%)	0.083[b]
RASS on assessment day	0 (− 2–0)	− 1 (− 3.5–0)	− 1 (− 3–0)	0.087[a]
SAPS II at admission	37 (27–53)	41.5 (31.5–49)	40 (28–51)	0.709[a]
SOFA at admission	7 (4–10)	8 (5–12)	7 (4–10)	0.247[a]

n (% of patients at respective assessment point) or median (25th percentile to 75th percentile). Ten centers participated at assessment point 1, eight centers participated at assessment point 2, and six centers participated at assessment point 3

BMI body mass index, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit, *RASS* Richmond Agitation Sedation Scale, *SAPS II* Simplified Acute Physiology Score II, *SOFA* Sequential Organ Failure Assessment Score

[a] Kruskal-Wallis test

[b] Pearson's χ^2 test

[c] Others include e.g. acutekidney injury, laryngectomy, Cesarean section, autosomal dominant polycystic kidney disease, renal transplant, neck dissection, or sickle cell crisis

(21/106) of patients, all of which were treated in one UK center at assessment point 3 (Table 2, Fig. 2b, Fig. S1c).

Pain was evaluated in 87% (170/195) of patients at least once per day at baseline. After completion of the educational program, the rate increased to 92% (119/129) and 98% (104/106) at assessment points 2 and 3, respectively ($p = 0.005$). The NRS was applied most frequently (46%, 39%, and 51% of patients at assessment points 1, 2, and 3, respectively), followed by the BPS (24%, 24%, and 40% of patients). The critical-care pain observation tool was only used by one UK center, which recruited patients at assessment points 1 and 2, but not 3 (Table 2, Fig. 2c, Fig. S1b).

At assessment point 1, 55% (107/195) of patients received all PAD assessments (pain, sedation, and delirium) at least once per day. Six weeks after completion of the educational program, 53% (68/129) of patients received all PAD assessments, which increased to 73% (77/106) at 1 year ($p = 0.003$; Table 2, Fig. 2d, Fig. S1d, Fig. S2). As shown in Fig. S1, centers started at different assessment rates for all PAD assessments, and while some centers improved, others stayed the same or worsened.

Determinants of Delirium, Pain, and Sedation Assessment

Multivariable mixed-effects logistic regression revealed that patients were more than twice as likely to receive delirium screening 1 year after the educational program (odds ratio [OR] 2.138, 95% confidence interval [CI] 1.206–3.790; $p = 0.009$) compared with before. Mechanical ventilation (OR 0.266, 95% CI 0.147–0.481; $p < 0.001$) or male sex (OR 0.635, 95% CI 0.404–0.997; $p = 0.049$) lowered the likelihood to receive delirium screening in our adjusted model. Compared with before, patients were more than twice as likely to receive nonpharmacological measures for delirium treatment or prevention 6 weeks after the educational program (OR 2.751, 95% CI 1.592–4.753; $p < 0.001$), and almost 10 times as likely 1 year after the educational program (OR 9.943, 95% CI 4.436–22.282; $p < 0.001$). The odds for sedation assessment were four times higher 1 year after the educational program

Table 2 Characteristics of delirium, pain, and sedation assessments

Variable	Assessment point			*p* value[a]
	1 (*n* = 195)	2 (*n* = 129)	3 (*n* = 106)	
Delirium screening with validated tool on assessment day	124 (64%)	84 (65%)	82 (77%)	**0.041**
CAM-ICU used	109 (56%)[b]	84 (65%)	82 (77%)	**0.001**
Nu-DESC used	7 (4%)[c]	0 (0%)	0 (0%)	–
ICDSC used	10 (5%)[b,d]	0 (0%)	0 (0%)	–
Positive delirium screening, *n* (% of those screened)	32 (26%)	19 (23%)	11 (13%)	0.099
Sedation depth assessed with validated tool on assessment day	171 (88%)	111 (86%)	99 (93%)	0.182
RASS used	169 (87%)	111 (86%)	78 (74%)	**0.009**
SAS used	0 (0%)	0 (0%)	0 (0%)	–
Other sedation scale used	2 (1%)	0 (0%)	21 (20%)[e]	**< 0.001**
Pain assessed with validated tool on assessment day	170 (87%)	119 (92%)	104 (98%)	**0.005**
VAS used	12 (6%)	5 (4%)	4 (4%)	0.538
NRS used	89 (46%)	50 (39%)	54 (51%)	0.167
BPS used	47 (24%)	31 (24%)	42 (40%)	**0.008**
BPS-NI used	5 (3%)	5 (4%)	1 (1%)	0.367
CPOT used	16 (8%)[f]	18 (14%)[f]	0 (0%)	–
Delirium, sedation, and pain assessed on assessment day	107 (55%)	68 (53%)	77 (73%)	**0.003**
Nonpharmacological measures to prevent or treat delirium	114 (58%)	103 (80%)	96 (91%)	**< 0.001**
Sensory shielding	47 (24%)	41 (32%)	33 (31%)	0.236
Reorientation (e.g., clock or whiteboard)	87 (45%)	68 (53%)	71 (67%)	**0.001**
Early mobilization	83 (43%)	59 (46%)	61 (58%)	**0.042**

Bold values represent significant *p* values with $p < 0.05$

n (% of patients at assessment point) if not indicated otherwise. Ten centers participated at assessment point 1, eight centers participated at assessment point 2, and six centers participated at assessment point 3

CAM-ICU Confusion Assessment Method for the Intensive Care Unit, *BPS* Behavioral Pain Scale, *BPS-NI* Behavioral Pain Scale–Nonintubated, *CPOT* Critical Care Pain Observation Tool, *ICDSC* Intensive Care Delirium Screening Checklist, *NRS* Numeric Rating Scale, *Nu-DESC* Nursing Delirium Screening Scale, *SAS* Sedation Agitation Scale, *RASS* Richmond Agitation Sedation Scale, *VAS* Visual Analogue Scale

[a] Pearson's χ^2 test if not indicated otherwise

[b] *n* = 2 patients received both, a CAM-ICU assessment and an ICDSC assessment. In both patients, assessments were negative

[c] The Nu-DESC was applied by one German center that did not recruit patients at assessment points 2 and 3

[d] The ICDSC was applied by one German center that did not recruit patients at assessment points 2 and 3

[e] The Alert, Verbal, Pain, Unresponsive (AVPU) scale was applied in 21 patients in one UK center at assessment point 3

[f] The CPOT was applied by one UK center that did not recruit patients at assessment point 3

(OR 4.131, 95% CI 1.372–12.438; $p = 0.012$) compared with before. Mechanical ventilation further increased the odds for sedation assessment (OR 5.684, 95% CI 2.765–11.683; $p < 0.001$). Almost all patients (98%) received pain assessment 1 year after the educational program. Finally, patients were more than two times more likely to receive all PAD assessments after 1 year (OR 2.295, 95% CI 1.349–3.903; $p = 0.002$) compared with before (Table 3).

In sensitivity analyses, we first excluded two centers that only recruited patients at assessment point 1 from the analysis. This reduced the screening rate of delirium, pain, sedation, and all PAD assessments for assessment period 1, and resulted in increased effects observed in the multivariable regression (Tables S2 and S3). Second, we excluded four centers that did not recruit at all assessment points from the analysis. This resulted in increased odds of a sedation and complete PAD assessment at assessment point 3, but the significant association of assessment point 3 with the odds of a delirium screening disappeared. Yet, assessment point 2 was newly associated with higher odds of a pain and complete PAD assessment (Tables S4 and S5).

Discussion

In this prospective before-after trial, we examined PAD assessment rates among patients of 12 European ICUs before and after the implementation of a structured educational intervention. About two thirds of patients were screened for delirium at baseline (64%) and 6 weeks after the educational program (65%), which increased

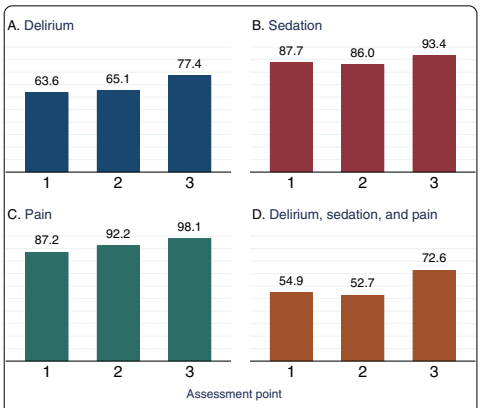

Fig. 2 Percentage of patients who received a **a** delirium screening, **b** sedation assessment, **c** pain assessment, or **d** complete PAD assessment (delirium, sedation, and pain), by assessment point. In percentages. Assessment point 1 comprised $n = 195$ patients. Assessment point 2 comprised $n = 129$ patients. Assessment point 3 comprised $n = 106$ patients. Pearson's χ^2 test for differences between assessment points for delirium screening ($p = 0.041$), sedation assessment ($p = 0.182$), pain assessment ($p = 0.005$), and complete PAD assessment ($p = 0.003$). *PAD* pain, agitation, and delirium

to 77% after 1 year. Further, before the intervention, 55% of patients received a complete PAD assessment, which increased to almost three quarters (73%) 1 year after the intervention. Multivariable regression revealed that patients were more than twice as likely to receive a complete PAD assessment 1 year after the educational program.

PAD assessment rates in routine ICU care have been analyzed in previous studies. A study on ABCDEF (Awakening and Breathing Coordination, Delirium monitoring/management, Early exercise/mobility, Family engagement) bundle implementation among critically ill patients with Covid-19 found pain, sedation, and delirium assessment rates of 45%, 52%, and 35%, respectively [43]. These rates are much lower compared to the third assessment point in our study, which fell in the Covid-19 pandemic. However, contrary to our study, participating ICUs did not undergo a structured training, and they only included patients with Covid-19. Because of isolation and preventive measures, PAD assessment and mobilization may have been more difficult for patients with Covid-19 than for patients without Covid-19. In a recent international survey, 85.4% of the 1474 intensivists reported using sedation scales [23]. Just like in our study, the RASS was the commonest. Almost all intensivists (95.4%) reported assessing patients for delirium at least

Table 3 Multivariable mixed-effects logistic regression on the assessment of delirium, sedation, and/or pain, and the use of nonpharmacological measures to prevent or treat delirium

Variable	Delirium assessed with validated screening tool		Sedation assessed with validated tool		Pain assessed with validated tool		Delirium, sedation, and pain assessed		Nonpharmacological measures to prevent or treat delirium used[a]	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Male sex	0.635 (0.404; 0.997)	**0.049**	1.183 (0.576; 2.429)	0.647	0.560 (0.246; 1.275)	0.167	0.780 (0.514; 1.184)	0.244	0.809 (0.494; 1.326)	0.401
Age (years)	0.998 (0.984; 1.011)	0.723	1.001 (0.979; 1.024)	0.902	0.985 (0.959; 1.011)	0.258	1.001 (0.988; 1.013)	0.935	0.994 (0.979; 1.009)	0.447
ECMO, yes	0.660 (0.337; 1.290)	0.224	6.008 (0.753; 47.955)	0.091	0.574 (0.149; 2.210)	0.42	0.750 (0.384; 1.465)	0.4	1.158 (0.523; 2.567)	0.717
Mechanical ventilation, yes	0.266 (0.147; 0.481)	**< 0.001**	5.684 (2.765; 11.683)	**< 0.001**	1.069 (0.391; 2.923)	0.896	0.828 (0.503; 1.361)	0.456	0.869 (0.478; 1.582)	0.647
Assessment point 1 (reference)	1		1		1		1		1	
Assessment point 2	0.990 (0.603; 1.626)	0.969	0.886 (0.413; 1.903)	0.757	1.393 (0.593; 3.273)	0.447	0.901 (0.565; 1.437)	0.662	2.751 (1.592; 4.753)	**< 0.001**
Assessment point 3	2.138 (1.206; 3.790)	**0.009**	4.131 (1.372; 12.438)	**0.012**	NA	NA[b]	2.295 (1.349; 3.903)	**0.002**	9.943 (4.436; 22.282)	**< 0.001**
Constant	12.464 (3.571; 43.501)	**< 0.001**	4.656 (0.366; 59.312)	0.236	128.239 (7.040; 2,336.128)	**0.001**	2.127 (0.662; 6.834)	0.205	2.814 (0.596; 13.284)	0.191

To account for the clustered data, a random effect for the treating country was included in the regression models

Bold values represent significant *p* values with $p < 0.05$

CI confidence interval, *ECMO* extracorporeal membrane oxygenation, *NA* not available

[a] Nonpharmacological measures to prevent or treat delirium comprised reorientation, early mobilization, and/or sensory shielding

[b] At assessment point 3, 104/106 (98%) of patients received a pain assessment. Hence, no odds ratio could be estimated

once per day [23], which is contrary to our measured findings and may be indicative of a discrepancy between surveys among ICU staff and real-world point-prevalence studies. In another point-prevalence estimation among a convenience sample of European ICU patients in 2011, more than half (57%) of the 868 patients were not assessed for pain or sedation depth on the study day [24], and almost three quarters (73.1%) were not screened for delirium with a validated instrument. Those rates are below the baseline assessment rates found in our study, where almost nine of ten patients received a pain and/or sedation assessment and 64% were screened for delirium. Another survey among 165 Polish ICUs from 2016 showed that only 10.9% of ICUs monitored delirium and 46.1% reported using sedation scales [25]. The sedation scale most used was the Ramsey scale, and delirium was most commonly identified using the International Classification of Diseases, 10th revision, whereas in our study, the RASS and CAM-ICU were most used [25]. In another survey among 214 ICUs in the UK in 2013/14, 57% of ICUs reported having a sedation protocol, 69.7% reported daily delirium screening, and 93.4% reported routine application of sedation scales [44], which appears consistent with our findings.

We found at 1 year after the educational program, PAD assessment rates significantly improved compared with baseline, with no effect seen at 6 weeks. These findings are consistent with a study conducted among three ICUs of one German hospital, which were subject to similar PAD training consisting of lectures, educational material, and tailored bedside teaching [38]. Similar to our study, their reported frequency of daily PAD monitoring significantly increased more than a year after the training [38]. In contrast to our study, they observed already improvements about 4 weeks after the training. However, their training was twice as long, they had a permanent on-site support team, and they trained all ICU staff instead of using a train-the-trainer concept. The observed delay in improvement in our study could possibly be explained by the train-the-trainer concept and the organizational nature of an ICU, as more than 6 weeks are likely required for the trainer to have sufficient face-to-face time with other staff members to disseminate and implement the content. This explanation is supported by reports on the challenges of changing routine actions and putting new evidence into practice [45]. Our results appear even more noteworthy considering that the third assessment point coincided with the Covid-19 pandemic, which put pressure on already constrained ICU resources. In the absence of the Covid-19 pandemic, we might have observed a stronger increase in PAD assessment rates. Alternatively, the Covid-19 pandemic may have prompted hospitals to focus more on intensive care practice.

PAD assessment is the important first step of adequate pain control, sedation management and delirium prevention, which is known to improve patient outcomes. Systematic pain and sedation assessments three times per day and after painful procedures have been shown to decrease the incidence of severe pain, the duration of mechanical ventilation, and nosocomial infections on a surgical ICU [7]. In a single-center study, an educational intervention using lectures and posters was used to implement an updated protocol mandating documented sedation assessment every 4 h, documented delirium assessment twice daily, and protocolized sedative dose reductions for patients with RASS −2 or −3 [46]. After implementation, patients had increased PAD assessment rates, reduced excess sedation, shorter mechanical ventilation, reduced ICU and hospital lengths of stay, and a lower risk of developing delirium [46]. High-quality PAD assessment and management should be part of a broader bundled quality improvement approach such as the ABCDE bundle. Rigorous application of the ABCDE bundle was shown to be associated with lower odds of delirium, more time breathing without mechanical assistance, and a greater likelihood of mobilization [47]. Interestingly, with increasing delirium screening rates, we observed a decline in positive delirium screenings from 26% at assessment point 1 to 13% at assessment point 3. This may indicate that 1 year after the training, a broad cohort of patients received a validated screening, and not only those patients appearing conspicuous of having delirium. Additionally, the higher rate of patients who received nonpharmacological measures to prevent or treat delirium 1 year after the intervention may have reduced the delirium incidence.

The strengths of this study include the international multicenter study design in a distinct geographical region. This enabled us to capture a range of PAD management practices in Europe. Patients were recruited prospectively, and patients treated on a particular day and ICU were enrolled. This should reduce the selection bias inherent to previous studies of routine PAD assessment that used cross-sectional surveys and convenience sampling [24, 27–29]. However, our findings come with limitations. Our before-after trial design does not allow for causal inferences on the effects of the educational program as external effects between time points one and three cannot be excluded. That is, we may have detected a general trend of improved PAD assessments or improved documentation over time, independent from our educational program. Further, we considered PAD assessments documented in the medical records. However, patients may have been assessed without documentation,

although documentation is part of a complete formal assessment. Also, we did not collect longitudinal data on PAD management in patients throughout their ICU stay, but rather captured three cross-sectional time points. The train-the-trainer concept may have impeded penetration of the educational program, especially because we did not track how many training participants worked in the respective ICU at the 1-year follow-up. In addition, we observed a discrepancy between ICU bed capacity and patient enrollment in many centers, but it is uncertain if these ICUs were running below capacity on the assessment days or if some patients were not enrolled. Furthermore, we determined the rate of patients receiving PAD assessment, but an analysis of the quality or accuracy of these assessments and changes in PAD therapy, outcomes, or adverse events was beyond our study's scope. Two centers ceased recruiting for the second assessment point and another two centers ceased recruiting at the third assessment point due to the onset of the Covid-19 pandemic in March 2020. In response, we conducted sensitivity analyses where we excluded the center dropouts to exclude the attrition bias. Finally, baseline delirium assessment rates were higher than we had anticipated based on previous literature. This may be due to improvements in delirium screening over time or may suggest that included centers already had above-average delirium screening rates.

Conclusions

In routine care, only about half of included ICU patients received a complete PAD assessment. Six weeks after a PAD educational program, we observed no significant improvement of PAD assessment rates, but a significant improvement 1 year after the educational program. The instruments most frequently used were the CAM-ICU for delirium, the RASS for sedation, and either the NRS or BPS for pain. Notably, at 6 weeks and at 1 year after the educational program, significantly more patients received nonpharmacological measures to prevent or treat delirium. Future randomized cohort studies should analyze the time lag of educational programs to cause behavioral changes and confirm that educational programs effectively improve PAD assessment rates.

Supplementary Information
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Conflict of interest
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Ethical Approval/Informed Consent

The study adhered to the ethical standards of the Declaration of Helsinki and its later amendments. Ethical approval at the coordinating study site was granted by the Institutional Review Board (IRB) of Charité–Universitätsmedizin Berlin (EA2/022/18) on March 23, 2018. Participating centers obtained IRB approval before study commencement as required by local regulations. Written consent or a waiver was subject to the decision of the local IRBs.

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2.6. Originalarbeit 6: Effekt eines Telemedizin-Programms auf der Intensivstation zur Verbesserung der Qualität der intensivmedizinischen Versorgung

Die Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin veröffentlicht periodisch sogenannte Qualitätsindikatoren (QIs) der akuten intensivmedizinischen Versorgung. In ihrer dritten Edition von 2017 beinhalten diese QIs unter anderem Maßnahmen zum „Management von Sedierung, Analgesie und Delir“ (QI 2), die „frühzeitige Entwöhnung von einer invasiven Beatmung (Weaning)“ (QI 4) und „Frühmobilisation“ (QI 9) [102]. Die verstärkte Umsetzung dieser QIs in der intensivmedizinischen Versorgung könnte zur Prävention eines PICS beitragen. So könnten beispielweise durch die konsequente Frühmobilisation körperliche Beeinträchtigungen reduziert werden und durch das konsequente Ausschöpfen von Weaning-Potentialen eine langfristige Abhängigkeit vom Respirator vermieden werden. Ein mögliches Werkzeug zur Verbesserung der QI-Umsetzung ist die Telemedizin. In *Originalarbeit 6* wird über die Studie Enhanced Recovery after Intensive Care (ERIC) berichtet, in der die Adhärenz zu den QIs in einem Netzwerk von ITS mithilfe einer komplexen telemedizinischen Intervention gesteigert wurde.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Spies CD, **Paul N***, Adrion C*, Berger E, Busse R, Kraufmann B, Marschall U, Rosseau S, Denke C, Krampe H, Dähnert E, Mansmann U, Weiss B: Effectiveness of an intensive care telehealth programme to improve process quality (ERIC): a multicentre stepped wedge cluster randomized controlled trial. Intensive Care Med 2023; 49(2):191-204. doi:10.1007/s00134-022-06949-x.

*“Ziel: Die Unterstützung intensivmedizinischer Versorgung durch Telemedizin könnte die Prozessqualität verbessern. Dies könnte wiederum zu einer Verbesserung der Genesung und der Langzeit-Outcomes der Patient*innen führen. Wir untersuchten den Einfluss einer komplexen telemedizinischen Intervention auf die Adhärenz zu deutschen Qualitätsindikatoren (QIs) in einem regionalen Netzwerk von Intensivstationen in Deutschland. Methoden: Wir führten eine große, offene, cluster-randomisierte Studie im Stepped-Wedge-Design durch, in die erwachsene Patient*innen mit einer erwarteten Intensivstations-Liegedauer von ≥24h*

*eingeschlossen wurden. Zwölf Cluster von Intensivstationen in Berlin und Brandenburg wurden zufällig drei Sequenzgruppen zugeordnet, welche von der Kontrollphase (Regelversorgung) in die Interventionsphase (Telemedizin) wechselten. Die Intervention zur Qualitätsverbesserung beinhaltete tägliche telemedizinische Visiten, welche sich auf die Einhaltung von acht deutschen QIs der akuten intensivmedizinischen Behandlung fokussierten. Ko-primäre Wirksamkeits-Endpunkte waren die patientenspezifischen, täglich erhobenen QI-Adhärenzen (erfüllt ja/nein), welche durch ein zentrales Gremium bewertet wurden. Die Daten wurden mittels gemischter logistischer Modelle unter Berücksichtigung der Zeit ausgewertet. Diese Studie ist registriert unter ClinicalTrials.gov (NCT03671447). Ergebnisse: Zwischen dem 04. September 2018 und dem 31. März 2020 wurden 1463 Patient*innen (414 unter Kontrollbedingungen, 1049 unter Interventionsbedingungen) in zehn Clustern eingeschlossen, was insgesamt 14.783 bewertete QI-Tage ergab. Zwei randomisierte Cluster rekrutierten keine Patient*innen (ein Cluster zog die Zustimmung zur Teilnahme zurück und ein Cluster stieg vorzeitig aus der Studie aus). Die Intervention führte zu einer signifikanten Verbesserung der QI-Adhärenz für "Management von Sedierung, Analgesie und Delir" (adjustiertes Odds Ratio (99,375%-Konfidenzintervall) 5,328, 3,395-8,358), "patientenadaptierte Beatmung" (OR 2,248, 1,198-4,217), "Weaning von einer invasiven Beatmung" (OR 9,049, 2,707-30,247), "Infektionsmanagement" (OR 4,397, 1,482-13,037), "frühe enterale Ernährung" (OR 1,579, 1,032-2,416), "strukturierte Patienten- und Angehörigenkommunikation" (OR 6,787, 3,976-11,589) und "Frühmobilisation" (OR 3,161, 2,160-4,624). Für den QI „tägliche multiprofessionelle und interdisziplinäre klinische Visite“ wurde keine signifikante Veränderung der QI-Adhärenz zwischen Kontroll- und Interventionsbedingungen gefunden (OR 1,606, 0,780-3,309). Es wurden von der Intervention abhängige und unabhängige zeitliche Trends gefunden. 149 Patient*innen verstarben während ihres Index-Aufenthalts (45 unter Kontrollbedingungen, 104 unter Interventionsbedingungen). Schlussfolgerung: Ein telemedizinisches Qualitätsverbesserungs-Programm erhöhte die Adhärenz zu sieben evidenzbasierten deutschen QIs der intensivmedizinischen Versorgung. Diese Ergebnisse sollten in einem breiteren Spektrum regionaler, nicht-akademischer Krankenhäuser und in anderen Gesundheitssystemen bestätigt werden.“*
(Übersetzung durch den Autor.)

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ORIGINAL

Effectiveness of an intensive care telehealth programme to improve process quality (ERIC): a multicentre stepped wedge cluster randomised controlled trial

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Abstract

Purpose: Supporting the provision of intensive care medicine through telehealth potentially improves process quality. This may improve patient recovery and long-term outcomes. We investigated the effectiveness of a multifaceted telemedical programme on the adherence to German quality indicators (QIs) in a regional network of intensive care units (ICUs) in Germany.

Methods: We conducted an investigator-initiated, large-scale, open-label, stepped-wedge cluster randomised controlled trial enrolling adult ICU patients with an expected ICU stay of ≥ 24 h. Twelve ICU clusters in Berlin and Brandenburg were randomly assigned to three sequence groups to transition from control (standard care) to the intervention condition (telemedicine). The quality improvement intervention consisted of daily telemedical rounds guided by eight German acute ICU care QIs and expert consultations. Co-primary effectiveness outcomes were patient-specific daily adherence (fulfilled yes/no) to QIs, assessed by a central end point adjudication committee. Analyses used mixed-effects logistic modelling adjusted for time. This study is completed and registered with ClinicalTrials.gov (NCT03671447).

Results: Between September 4, 2018, and March 31, 2020, 1463 patients (414 treated on control, 1049 on intervention condition) were enrolled at ten clusters, resulting in 14,783 evaluated days. Two randomised clusters recruited no patients (one withdrew informed consent; one dropped out). The intervention, as implemented, significantly increased QI performance for "sedation, analgesia and delirium" (adjusted odds ratio (99.375% confidence interval [CI]) 5.328, 3.395–8.358), "ventilation" (OR 2.248, 1.198–4.217), "weaning from ventilation" (OR 9.049, 2.707–30.247), "infection

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The members of the ERIC Study Group are listed in the Acknowledgement section of the manuscript.

management" (OR 4.397, 1.482–13.037), "enteral nutrition" (OR 1.579, 1.032–2.416), "patient and family communication" (OR 6.787, 3.976–11.589), and "early mobilisation" (OR 3.161, 2.160–4.624). No evidence for a difference in adherence to "daily multi-professional and interdisciplinary clinical visits" between both conditions was found (OR 1.606, 0.780–3.309). Temporal trends related and unrelated to the intervention were detected. 149 patients died during their index ICU stay (45 treated on control, 104 on intervention condition).

Conclusion: A telemedical quality improvement program increased adherence to seven evidence-based German performance indicators in acute ICU care. These results need further confirmation in a broader setting of regional, non-academic community hospitals and other healthcare systems.

Keywords: Telemedicine, Critical care, Critical illness, Quality of care, Quality improvement, Guideline adherence, Healthcare quality indicators, Implementation, Stepped wedged cluster randomised controlled trial, Comparative effectiveness

Introduction

In Germany, the number of patients admitted to intensive care units (ICU) increased from 2.15 million in 2015 to 2.52 million in 2019 [1]. Roughly one-third of these patients were treated in hospitals with fewer than 400 beds [1]. Having access to large academic hospitals with full-time intensivist staffing is associated with increased adherence to evidence-based intensive care and improved outcomes [2–4]. It is currently unclear, however, if telemedicine can improve adherence to comprehensive evidence-based practice.

Though several studies from the United States (US) have shown that telemedical treatment support might reduce ICU and hospital mortality and length of stay (LOS) [5–7], two studies (one single-centre and one multicentre trial) revealed that telemedicine improved adherence to best-practice measures like deep vein thrombosis prevention and infectious disease management [8, 9].

In 2010, the German Interdisciplinary Society of Intensive Care Medicine (DIVI) established quality indicators (QIs) to promote adherence to evidence-based principles [10–12]. The third edition, published in 2017, identified ten indicators that include key elements of intensive care medicine: (1) daily multi-professional and interdisciplinary clinical ward rounds with documentation of daily goals, (2) management of sedation, analgesia and delirium, (3) patient-adapted ventilation, (4) early weaning from invasive ventilation, (5) monitoring of infection prevention measures, (6) infection management measures, (7) early enteral nutrition, (8) documentation of structured patient and family communications, (9) early mobilisation, and (10) ICU leadership. All except QIs 5 and 10 refer to process quality elements and can be implemented at the individual patient level [10].

Studies report poor implementation of QI-based key performance parameters [13, 14]. To the best of our knowledge, no randomised controlled trials have specifically investigated the effectiveness of telemedicine on a comprehensive evidence-based medicine bundle like QI-implementation. To address these knowledge gaps, the Enhanced Recovery after Intensive Care (ERIC) study was initiated to establish and evaluate whether telemedicine support can be used as a vehicle to increase adherence to evidence-based medicine compared to standard of care, and thus improve intensive care medicine quality.

Take-home message

A telemedical quality improvement programme increased adherence to seven evidence-based German performance indicators in the acute ICU care. These results need further confirmation in a broader setting of regional, non-academic community hospitals and other healthcare systems.

Methods

Study design, setting and participants

ERIC was an investigator-initiated, multicentre, superiority stepped-wedge cluster randomised controlled trial (SW-CRT) with three sequence groups (waves) and a continuous-recruitment short-exposure design investigating the effectiveness of a structured, telemedical quality improvement intervention at ICU on the adherence to evidence-based QIs.

This pragmatic trial was conducted at adult ICUs of academic, non-academic and community hospitals in the metropolitan area of Berlin, Germany, with approximately six million inhabitants and 150,000 ICU admissions annually [1]. Due to the unidirectional crossover in a stepped-wedge design, all trial sites commenced treating patients on control condition (standard of care). Sites were randomly selected to transition to the experimental intervention sequentially at three different protocol-defined time points scheduled for 3, 6 and 9 months after trial commencement, until all clusters have received the intervention.

The decision to use a stepped-wedge design was supported by the following aspects: the intervention was considered potentially beneficial for all sites; practical interest to implement the technical infrastructure of the intervention and related training tools, mimicking a natural (non-experimental) implementation process; statistical interest regarding a potentially more effective control for intra-cluster correlation which might enable a statistical power greater than that of a conventional cluster trial with the same number of patients; exploration of underlying temporal trends; and utility of obtaining balance in characteristics of sequence groups after randomisation, especially in the case of a small number of sequences (steps).

Eligible hospitals were located in the metropolitan area of Berlin and the surrounding federal state of Brandenburg, provided adult intensive care medicine, adhered to the legal obligations, and complied with cluster randomisation and the staggered schedule. Participating hospitals were selected according to their letter-of-intent written during the project application and based on their anticipated recruitment and technical prerequisites (e.g. wireless network) to implement the secure, privacy-compliant infrastructure for the telemedical intervention.

Patients were eligible if they were admitted to a participating ICU, were aged ≥ 18, had an expected ICU LOS ≥ 24 h, and were covered by a German statutory health insurance policy. Written informed consent was obtained by the patient or a legal representative. In case of readmission to a participating ICU, eligible patients could be enrolled multiple times. Screening and enrolment of eligible patients were continuously performed by local ICU staff. The study took place within the framework of statutory health insurance in Germany.

The study was approved by the ethics committee of Charité (EA1/006/18) and Brandenburg Medical School (Z-01-20180828). This article adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement extended for stepped-wedge cluster randomised trials [15] and related guidelines [16]. Details of the study protocol with intervention details have been published elsewhere [17]. The study was prospectively registered with ClinicalTrials.gov (NCT03671447).

Randomisation and masking

A total of 16 ICUs were organised to geographical clusters on an institutional level. One cluster (randomisation unit) consisted of one to three ICUs. There was no structural exchange of ICU staff between clusters, minimising the risk of intervention contamination. A cluster design rather than individual randomisation was chosen to facilitate a change in management at a hospital level rather than at an individual patient level, thus allowing the comparative effectiveness of the intervention to be evaluated pragmatically. Before trial commencement, all 12 clusters were randomly allocated to one of three sequence groups of four units to switch from the control to the intervention according to a staggered timetable. The randomisation list defining the order of the treatment switch was generated by the independent trial statistician using a computer-generated algorithm (nQuery Advisor V.7., block size = 3, without stratification by prespecified characteristics).

Due to a 3-month training period before the sequential switch to the intervention period, ICU staff were not masked to the allocated sequence group and were notified prior to the study start about their crossover date. Since study personnel and patients knew when they were and were not engaged in the telemedical intervention, blinding was not possible. General practitioners and investigators collecting data during post-ICU follow-up visits may have been aware of the treatment condition on the patient-level.

Procedures

Patients treated on intervention condition received a tailored telemedical intervention in addition to standard of care. In brief, the complex intervention, i.e., the ERIC programme, targeting healthcare providers as well as patients, encompassed two key components. (1) Daily, QI-guided, structured ward rounds for study patients were conducted using a telemedical cart (Appendix, Fig. S1). These telemedical ward rounds were carried out by a specialist and an ICU nurse from the hub (i.e. tele-ICU) at Charité, together with the treating physician (consultant and/or physician in training) and bedside nurse of the respective unit (i.e. local-ICU). Specialists in the tele-ICU were senior, board-certified consultants in intensive care at the site of the tele-ICU (Appendix, p. 2). A secure, bedside connection for audio-visual, face-to-face communication between the tele-ICU and the local-ICU was established. The tele-ICU specialists were able to inspect the patient and monitoring devices (e.g., ventilator settings, monitors and infusion pumps), and microphone and speakers allowed for direct dialogue between both parties. Each ward round being scheduled for 20 min was guided by the predefined QIs, which were then discussed between staff at the tele-ICU and local-ICU. The tele-ICU consultant also gave non-QI-related medical advice if required. Treatment decisions were ultimately taken by the local-ICU staff. In case of disagreement, the tele-ICU consultants did not have autonomy to make treatment decisions themselves. After rounding, tele-ICU consultants assessed

the criteria for QI adherence based on patient-specific parameters obtained from documentation of routine data at the local-ICU. (2) Expert teleconsultations: the tele-ICU offered a 24/7 service staffed with ICU consultants to respond to urgent medical issues. On request, the tele-ICU consultant established an audio-visual connection to the respective local-ICU. To address intervention fidelity, connection success rates were continuously monitored by the provider of the telemedical carts, and tele-ICU staff ensured that study patients received daily telemedical ward rounds.

The implementation of telemedicine at the cluster level started 3 months before the planned switch to the intervention with setup of the required hardware infrastructure at the respective ICUs. During this 3-month transition period at the end of the control period of the respective site, clinical experts received a blended-learning training programme (ten e-learning modules, followed by four simulator-based workshops on the QIs and on-the-job training) to ensure that teams at the local-ICUs were familiar with the telemedical cart and the QIs. One physician (any qualification level) and one ICU nurse (any qualification level) per local-ICU were invited to participate in the training. It was at the discretion of the local-ICU to send the same person or different people to each simulator-based workshop.

The control condition was standard of care according to local standards of the hospital site without telemedical support, and was also delivered throughout the 3-month training period. In both phases (control, intervention), local study personnel routinely documented QI-related key performance parameters on the patient's medical record.

Patients received two follow-up examinations scheduled 3 and 6 months after their index (i.e., first study-related) ICU discharge to assess post-ICU impairment including quality of life and functional outcomes [17]. These outcome data based on self-administered patient questionnaires and tests were recorded by the patient's general practitioner and/or trained study personnel at Charité, during home visits, via mail, or via telephone, depending on in-person visiting restrictions due to the coronavirus disease 2019 (COVID-19) pandemic.

Outcomes

The eight co-primary outcomes were binary composite measures defined based on patient-individual raw parameter measurements related to eight performance indicators with predetermined definitions (Appendix, p. 8) [10]. For each of these QIs, the adherence (fulfilled yes/no) was assessed daily (within a 24-h time frame) on a patient level starting from the date of enrolment (ICU admission; or the following day) until ICU discharge (or the previous day). Seven tele-ICU consultants affiliated to the coordinating investigator at Charité participated in a central endpoint adjudication and retrospectively rated the adherence to a single QI for patient i on day t (denoted as QI day) using the local-ICU's documentation of routinely collected clinical data. Although the independent raters were aware of the respective treatment condition, assessing QI adherence to derive primary outcomes can be considered objective and reliably reproducible. This process was applied irrespective of whether the patient was treated on control or on intervention condition (Appendix, p. 2).

Secondary outcomes were assessed during the patient's ICU stay and at two post-ICU follow-up visits. Key secondary outcomes included all-cause mortality up to 180 days after index ICU discharge (validated with data from the municipal personal records database) and study-related ICU LOS (per ICU stay, in days). Remaining secondary endpoints including health–economic outcomes will be analysed separately and made available in subsequent papers.

Statistical analysis

A fixed sample size calculation was performed, considering eight co-primary outcomes. Applying a Bonferroni correction for multiple testing yields a one-sided type 1 error of alpha/8 = 0.625% for confirmatory testing of a single QI. Assuming a minimum clinically relevant absolute difference in QI adherence of 10% (for all QIs), a two-group χ^2 test has a power of 82% to detect the difference between a proportion of 60% on control and 70% on intervention (odds ratio, OR 1.556) with a sample size of 530 independent patients on each treatment condition (nQuery Advisor V.7.0). To deal with the correlation between individuals from the same cluster, we further prespecified at the design stage a variance inflation factor of 1.35, and a patient-level intra-cluster correlation coefficient (ICC) of 0.117 (estimated from preliminary data on QI 2 for a small number of patients from site Charité only; independency of time assumed) which measures the correlation between observations within the same cluster [17]. This yields a total target sample size of 1431 patients required for the CRT design (neglecting stepped-wedge design-specific methodological issues). This pragmatic sample size calculation which was performed during the planning phase in 2015 neither accounted for a transition period between standard of care and intervention, nor for variable cluster sizes. Several changes in prespecified design features throughout the course of the trial may have rendered the initial sample size estimates invalid.

The eight co-primary effectiveness outcomes were analysed by logistic mixed-effects models with random intercepts for cluster and patient, and fixed effects for intervention (assuming level change), cluster-specific linear 'exposure time' (in months; ≥ 0 at(after) start of intervention, < 0 otherwise), and the interaction between both (assuming time-dependent slope change). To account for deviations from the staggered randomisation schedule, an 'as-implemented' analysis was conducted defining intervention periods according to the actual start of the first local telemedical-based QI visit. The cluster-specific 3-month training period was analysed as part of the control period, and data contributed to the primary endpoint analysis. All patients with at least one QI assessment were included in the full analysis set (FAS). Few patients who were enrolled under control condition shortly before the crossover date and received the intervention after the crossover were analysed as control patients. Missing values were handled under the assumption of missing at random, and no imputation methods were applied (number of QI visits negligibly small) [18–20].

Sensitivity analyses for each QI were performed based on five additional mixed-model specifications by changing the variance structure and/or adjusting for two different time effects to address robustness of results. Thus, a covariate for sequence group (together with group-by-treatment effect interactions) was incorporated as fixed effect to account for underlying secular trends (i.e., clusters classified according to their allocated step, defining 'early' [first; coded as − 1], 'middle' [second; chosen as reference group 0], or 'late' [third group; coded as 1] adopter sites to adjust for (categorical) 'time period of implementation'), or patient- or centre-specific random intercepts omitted (Appendix, p. 13).

For each QI, adjusted ORs for the QI adherence on intervention compared to standard of care are reported expressing relative effects of primary interest. Besides, the endpoint-specific cluster-level ICCs were calculated [21]. The results of the co-primary endpoints were considered statistically significant if the two-sided $p < 0.00625$ (eight relative effects for level change at the crossover time defined as primary estimates of interest; remaining time-related estimates tested hierarchically).

The secondary endpoint all-cause mortality within 180 days post-enrolment was analysed using a Cox regression model with frailty term for cluster, adjusting for baseline Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) Score (SAPS II and SOFA measurements at the first QI day were defined as pseudo-baseline values in the case of missing documentation at the day of ICU admission, assuming first observation carried backward). Results were reported as hazard ratios (HRs). The ICU LOS in days was compared between the two conditions by using a negative binomial mixed model with cluster-specific random intercepts. Because of the potential for type I error due to multiple comparisons, the findings of analyses of secondary endpoints should be interpreted as exploratory. 99.375% CI were reported for primary outcomes, 95% CIs otherwise.

The study database was stored on REDCap (Research Electronic Data Capture; version 10.6.16 Vanderbilt University, Nashville, Tennessee, USA) hosted at Charité. Statistical analyses were carried out using R (version 4.0.4), mixed-effects regression analyses were performed using the lme4 (version 1.1-25) package.

Results

Participating units and patients

Of the 12 clusters randomised, one (allocated to third sequence group) withdrew consent before the global trial start, and one (allocated to the first sequence group) dropped out after the training period without recruiting any patients, from which no data were collected (Fig. 1). All 14 ICUs at 12 hospitals enrolling patients received the intervention, but not all opened simultaneously with recruitment. Further basic characteristics of the randomisation units together with crossover times and sequence groups are provided in the Appendix (Table S2, Fig. S2). There was considerable variation in the hospitals' involvement and adherence to the randomisation schedule.

Given underrecruitment, the planned recruitment period was extended from 12 to 19 months, while postponing the prespecified third crossover date by 3 months (extension of the rollout period) to further enhance the number of patients treated on control condition, and lengthening the post-rollout period.

During the 19-month recruitment period between September 4, 2018, and March 31, 2020, 1463 patients comprising 1554 ICU stays (433 control, 1120 intervention) were enrolled into the trial. Of these, one patient discharged from ICU at the next day was excluded from the FAS population since no QI evaluation was performed, and no post-enrolment data documented. The final numbers for analysis thus included 414 participants randomised to control and 1048 to intervention according to their first ICU admission. A single ICU stay was documented for 1386 (94.8%) patients, and up to six ICU readmissions were documented for 76 patients during the trial (66 patients had 2, 7 had 3, 2 had 4, and 1 patient had 6 ICU stays over time [one single cluster, each time on the control condition]). Overall, a total number of 14,783 QI days were evaluated (Appendix, Figs. S3–4). The median number of ICU stays across clusters was 100

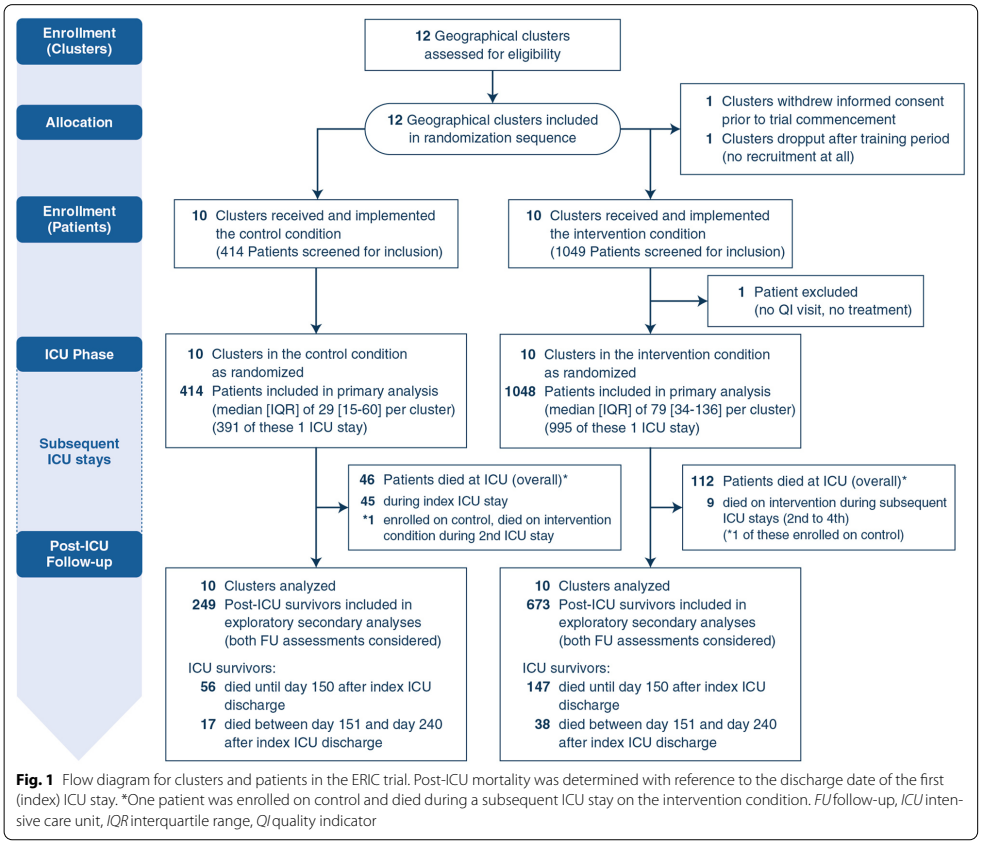

Fig. 1 Flow diagram for clusters and patients in the ERIC trial. Post-ICU mortality was determined with reference to the discharge date of the first (index) ICU stay. *One patient was enrolled on control and died during a subsequent ICU stay on the intervention condition. *FU* follow-up, *ICU* intensive care unit, *IQR* interquartile range, *QI* quality indicator

(IQR 73–230). The median number of QI days per patient was 5 (IQR 2–11) (Table S3).

Patient-level characteristics at the time of first ICU admission are displayed in Table 1. There were no major differences between both cohorts with respect to demographic characteristics and primary admission diagnosis. However, the severity of illness at baseline was lower for patients treated on standard of care vs on intervention [median SOFA at the first QI day: 4 (IQR 1–7) vs. 6 (3–9); median SAPS II at the first QI day: 28 (IQR 16–42.25) vs. 35 (22–48)]. On control condition, patients were more frequently admitted due to medical reasons (50.2% vs.42.8%) and admitted from emergency medical services (32% vs. 24.8%) and wards (19.8% vs. 15.5%), but fewer postoperative admissions (38% vs. 44.8%) were observed compared to during the intervention period.

Primary outcomes

For 97.4% (1512/1553) of ICU stays, QI adherence data were assessed daily throughout the patient's ICU stay, indicating a high level of completeness regarding primary outcome data. In the confirmatory model-based principal analysis, the intervention, as implemented, significantly increased the odds for adherence on seven of eight QIs (Table 2). For QI 1 (daily multi-professional and interdisciplinary clinical visits), no evidence of a difference in adherence between both treatment conditions was found in the principal model (adjusted relative difference of OR 1.606, 99.375% CI 0.780–3.309; $p = 0.073$). However, we observed a positive effect of the exposure time on QI adherence (i.e., the cluster-specific time since the beginning of the intervention) for QI 1 (OR 1.394, 1.228–1.582), which declines after

Table 1 Population characteristics of the intention-to-treat (ITT) population according to date of first ICU admission

Variable	Control ($n = 414$)	Intervention ($n = 1048$)
Age (years), mean (SD)	68.74 (14.41)	67.25 (14.88)
Gender, *n* (%)		
Female	186 (44.9%)	477 (45.5%)
Male	228 (55.1%)	571 (54.5%)
Admission status, *n* (%)		
Medical	208 (50.2%)	449 (42.8%)
Emergency surgery	105 (25.4%)	319 (30.4%)
Elective surgery	93 (22.5%)	259 (24.7%)
Missing	8 (1.9%)	21 (2%)
Admission source, *n* (%)		
Emergency medical services	141 (32%)	276 (24.8%)
Surgical	167 (38%)	499 (44.8%)
Normal ward	87 (19.8%)	173 (15.5%)
Other ICU	20 (4.5%)	86 (7.7%)
External	25 (5.7%)	79 (7.1%)
ICU primary admission diagnosis, *n* (%)		
Respiratory	49 (11.7%)	102 (9.8%)
Sepsis/infection	65 (15.5%)	167 (16%)
Gastrointestinal	47 (11.2%)	104 (10%)
Cardiovascular	101 (24%)	281 (27%)
Trauma	42 (10%)	92 (8.8%)
Neurologic	33 (7.9%)	107 (10.3%)
Metabolic or endocrine	20 (4.8%)	36 (3.5%)
Oncologic	55 (13.1%)	140 (13.4%)
Other†	8 (1.9%)	13 (1.2%)
SOFA score (at first QI day)		
Mean (SD)	4.32 (3.9)	6.14 (3.88)
Median (IQR)	4 (1–7)	6.00 (3–9)
SAPS II score (at first QI day)		
Mean (SD)	30.58 (18.61)	36.17 (18.9)
Median (IQR)	28 (16.00–42.25)	35 (22–48)
Missing, *n* (%)	2 (< 0.01%)	10 (0.01%)

In the case of multiple enrolment, the first (index) ICU stay is displayed. 11 patients were enrolled on control condition during their index ICU stay, and on intervention at one or more subsequent ICU stays

ICU intensive care unit, *IQR* interquartile range, *SAPS II* Simplified Acute Physiology Score II, *SD* standard deviation, *SOFA* Sequential Organ Failure Assessment Score

† Other includes removal of osteosynthesis plate, urolithiasis, medication-induced osteonecrosis of the jaw bone, pregabalin intoxication, acute kidney injury, catatonic schizophrenia, autoimmune haemolytic anaemia, and ureteral stenosis

the start of the telemedical care by 20.9% per month (OR 0.791, 0.69–0.908). Results were not robust across all supportive analyses taking into account the time adopting the intervention (assuming categorical temporal effects) and differing variance components. However, sensitivity analysis with both sequence group and exposure time (Appendix, sensitivity analysis model SM.4) supported the findings of the principal model, i.e., the lack of an intervention effect and a significant temporal effect which was considerably diminished after switch to the intervention.

A beneficial intervention effect on the guideline adherence was revealed for ICU performance indicators QI 2 (OR 5.328, 3.395–8.358), QI 3 (OR 2.248, 1.198–4.217), QI 4 (OR 9.049, 2.707–30.247), QI 6 (OR 4.397, 1.482–13.037), QI 7 (OR 1.579, 1.032–2.416), QI 8 (OR 6.787, 3.976–11.589), and QI 9 (OR 3.161, 2.160–4.624).

Table 2 Primary efficacy end points in the principal analysis

Guideline adherence on quality indicator	Adjusted analyses *									
	Marginal means at time 0			OR						
	Control	Intervention	Absolute difference	Treatment	*p* value	Time	*p* value	Treatment × time	*p* value (for interaction)	ICC
QI 1 (daily multi-professional and interdisciplinary clinical visits with documentation of daily goals)	0.977 (0.915; 0.994)	0.985 (0.945; 0.996)	0.009 (− 0.009; 0.026)	1.606 (0.78; 3.309)	0.073	1.394 (1.228; 1.582)	< 0.001	0.791 (0.69; 0.908)	< 0.001	0.255
QI 2 (management of sedation, analgesia and delirium)	0.084 (0.026; 0.243)	0.329 (0.125; 0.627)	0.245 (0.06; 0.43)	5.328 (3.395; 8.358)	< 0.001	0.991 (0.904; 1.087)	0.793	0.982 (0.892; 1.081)	0.607	0.284
QI 3 (patient-adapted ventilation)	0.952 (0.911; 0.975)	0.978 (0.959; 0.989)	0.026 (0.001; 0.051)	2.248 (1.198; 4.217)	< 0.001	1.05 (0.931; 1.185)	0.264	0.937 (0.825; 1.063)	0.158	0.044
QI 4 (early weaning from invasive ventilation)	0.994 (0.983; 0.998)	0.999 (0.998; 1)	0.005 (− 0.001; 0.011)	9.049 (2.707; 30.247)	< 0.001	0.833 (0.681; 1.017)	0.012	1.094 (0.878; 1.365)	0.264	0.124†
QI 6 (measures for infection management)	0.994 (0.982; 0.998)	0.999 (0.995; 1)	0.005 (− 0.001; 0.011)	4.397 (1.482; 13.037)	< 0.001	1.123 (0.942; 1.339)	0.07	0.857 (0.703; 1.045)	0.033	0.091†
QI 7 (early enteral nutrition)	0.893 (0.846; 0.927)	0.93 (0.896; 0.953)	0.036 (0; 0.072)	1.579 (1.032; 2.416)	0.003	0.995 (0.919; 1.077)	0.863	0.979 (0.898; 1.068)	0.512	0.022
QI 8 (documentation of structured patient and family communication)	0.851 (0.676; 0.94)	0.975 (0.933; 0.991)	0.124 (0.017; 0.231)	6.787 (3.976; 11.589)	< 0.001	0.815 (0.737; 0.901)	< 0.001	0.931 (0.837; 1.035)	0.065	0.163
QI 9 (early mobilization)	0.917 (0.759; 0.975)	0.972 (0.908; 0.992)	0.055 (− 0.008; 0.119)	3.161 (2.16; 4.624)	< 0.001	0.834 (0.769; 0.904)	< 0.001	1.106 (1.015; 1.205)	0.001	0.331

Marginal means (with 99.375% CIs) at the start of the intervention (time = 0), i.e., overall immediate effect at implementation (step change). Effects (with 99.375% CIs) reported as absolute differences in marginal probabilities and Odds ratios for QI adherence on intervention vs. standard of care

CI confidence interval, *OR* odds ratio, *QI* quality indicator, *ICC* cluster-level intra-class correlation coefficient

*Mixed-effects logistic regression models adjusted for time, with random intercepts for patient and centre levels. Treatment: intervention vs. control condition (reference level). Time is defined as cluster-specific exposure time (in months). Treatment × time depicts the interaction effect. The difference is expressed as intervention minus control, and the ratio as odds of the outcome for the intervention compared with the control period. *p* values unadjusted for multiple testing (type 1 error of alpha/8 = 0.625%, see "Methods" section)

† ICC for the model "SM.5" (sensitivity analyses) instead of the principal model due to low between-clusters variance and related variance components could not be fitted (see Appendix for details)

Furthermore, we found a negative temporal trend attenuating the adherence to QI 4 (OR 0.833, 0.681–1.017), to QI 8 (OR 0.815, 0.737–0.901), and to QI 9 (OR 0.834, 0.769–0.904) in the course of time after start of the intervention. For QI 9, however, the negative effect of exposure time was partially compensated, as indicated by the positive interaction between exposure time and treatment (OR 1.106, 1.015–1.205). Quantitative results of the confirmatory analyses for each QI and cluster are displayed in Fig. 2 illustrating statistically significant level changes in adherence for all QIs except QI 1 with start of the intervention, and positive (QI 1) or negative (QI 4, 8, and 9) confounding temporal effects suggesting the intervention effect was not consistent over time. Additionally, the figure reveals an already high QI adherence during the control phase for all indicators except QI 2, and a substantial heterogeneity between clusters. The ICC for most of the QIs (except QI 4 and QI 6) was far higher than expected in the planning stage showing a high degree of similarity among patients from the same cluster which reduces overall power and resulting precision (Appendix, p. 21–24).

Secondary outcomes

Table 3 provides details of mechanical ventilation during patients' index ICU stay. Patients treated on intervention condition were more frequently mechanically ventilated than patients treated on control condition [74.3% (779 patients) vs. 60.6% (251 patients)]. The median duration of mechanical ventilation was, however, similar among patients on intervention and control (79 (IQR 20–251) hours vs 71 (IQR 16–204) hours).

With respect to the patients' discharge position after their index ICU stay, more patients were referred to another ICU after being treated on intervention compared to standard of care [20.2% (212 patients) vs. 11.3% (47 patients)]. 1313 patients were discharged alive from the index ICU stay, and 258 patients died within 240 days after index ICU discharge (73 patients treated on control, 185 on intervention). 922 survivors received at least one follow-up. 814 patients received the first follow-up (median 93 (IQR 81–117) days after discharge), and 786 patients received a second follow-up visit (median 199 (IQR 181–238) days after discharge). Last post-ICU follow-up assessment took place on November 17, 2020.

Altogether, 385 deaths were reported up to day 180 post-enrolment, 107/414 patients (25.85%) treated on control, and 278/1048 patients (26.53%) on intervention condition. A Cox proportional hazards model with frailty term for cluster and adjusting for baseline SAPS II and SOFA score revealed no significant beneficial effect of the telemedical intervention on overall 180-day mortality compared with standard of care (HR 0.847, 95% CI 0.668–1.073; $p=0.170$), see Appendix (Fig. S5) for estimated cumulative incidence of death. There was no statistically significant difference in the intervention vs control condition regarding median (IQR) ICU LOS (6 [4–13] days vs 5 [3–11] days; unadjusted ratio 1.079, 95% CI 0.967–1.204; $p=0.173$).

Discussion

The ERIC trial demonstrated the comparative effectiveness of a telemedical programme in a network of 12 clusters of ICUs in the area of Berlin and Brandenburg. The odds for adherence to seven of eight QIs was significantly increased for patients receiving the intervention vs. standard of care (although below the predefined minimum clinically important absolute difference of 10% [intervention minus control]). The daily intervention as implemented was most effective on the domains for sedation, analgesia and delirium (QI 2), early weaning from invasive ventilation (QI 4), and documentation of patient and family communication (QI 8). Only for QI 1 (daily multi-professional and interdisciplinary clinical visits), no significant difference in adherence between telemedicine-based care and standard of care was found.

Previous studies have primarily explored short-term mortality and hospitalisation time as primary outcome. In two systematic reviews with meta-analyses, tele-ICU programmes were associated with a reduction in mortality (ICU and hospital) and ICU LOS [5, 6], but only one meta-analysis revealed a statistically significant and clinically relevant lower hospital LOS [5]. Another systematic review, however, revealed a reduction in ICU mortality and LOS, but no beneficial effect regarding in-hospital mortality and LOS [22]. These contradictory findings may be explained by the observational design of these studies and differing confounders in the before-after designs [5]. There were notable differences regarding various characteristics in the studies with respect to used technology and hospitals. Most importantly, tele-ICU intensivist autonomy and ICU practice prior to tele-ICU implementation is a study-specific feature that should be considered [6]. Only one study that was included in the abovementioned reviews on tele-ICU programmes investigated the effectiveness of telemedical care on adherence to evidence-based practice [8]. Using a before-versus-after design, they found that patients undergoing telemedicine were more likely to receive best-practice therapy for the prevention of deep vein thrombosis, stress ulcers, ventilator-associated pneumonia, and cardiovascular protection. In another study, pharmacological, telemedical consultations during night hours revealed significantly more guideline-conformed daily sedation interruptions [23]. A German multicentre

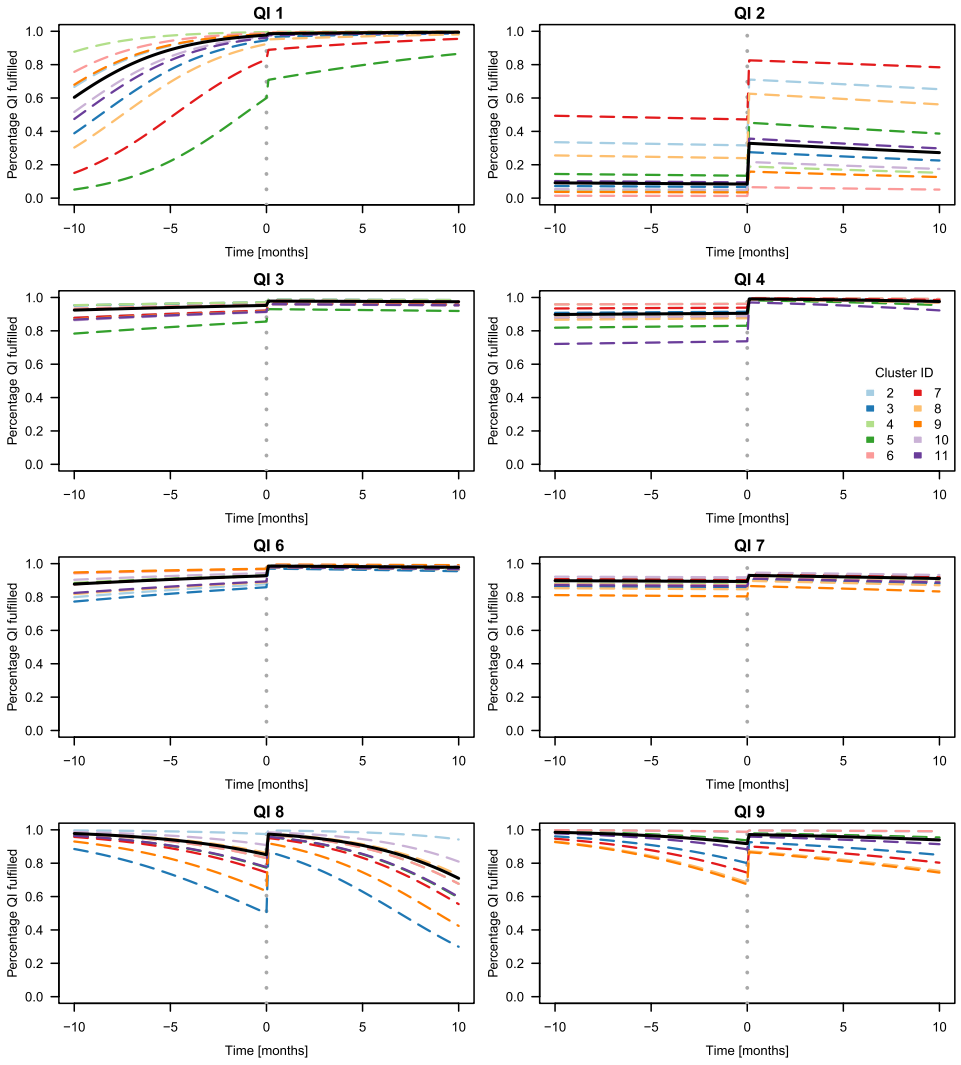

Fig. 2 Mean QI adherence [percentages] over time before and after implementation of the intervention (model-based principal analysis for each patient QI). Black continuous lines display the global (marginal) effect (fixed effects without random effects) for each QI. Coloured dashed lines display the fixed effects and cluster-specific intercepts (without patient-specific intercepts). Vertical dashed grey line: actual switch from control to the intervention period. For QI 4 and QI 6, the principal model could not estimate the variance component for the cluster-specific intercepts (due to lack of variability). Therefore, estimates of the sensitivity analysis model SM.5 are displayed (see Appendix for further details)

Table 3 Mechanical ventilation and ICU discharge position of patient's index (first) ICU stay in the ITT population, stratified by treatment condition (control vs. intervention)

Variable	Control ($n=414$)	Intervention ($n=1048$)	Total ($n=1462$)
Received mechanical ventilation, *n* (%)	251 (60.63)	779 (74.33)	1030 (70.45)
Duration of mechanical ventilation of mechanically ventilated patients (hours)			
Median (IQR)	71 (16–204)	79 (20–251)	77 (19–236)
Mean (SD)	196.17 (343.75)	212.02 (320.18)	208.16 (325.98)
ICU discharge disposition, *n* (%)			
Hospital ward	295 (71.26)	654 (62.4)	949 (64.91)
Home	4 (0.97)	8 (0.76)	12 (0.82)
Other ICU*	47 (11.35)	212 (20.23)	259 (17.72)
Rehabilitation facility	19 (4.59)	55 (5.25)	74 (5.06)
Nursing facility	2 (0.48)	3 (0.29)	5 (0.34)
Missing†	2 (0.48)	12 (1.15)	14 (0.96)
Death at ICU	45 (10.87)	104 (9.92)	149 (10.19)

Study-related ICU readmissions not considered in this table (i.e., only the first study-related ICU stay counted)

*76 patients with study-related subsequent ICU stays at participating sites

† Item related to discharge position not documented

SW-CRT recently revealed that tele-ICU support significantly improved sepsis management guideline compliance, but sepsis-related mortality (subgroup of 276 sepsis patients) was not significantly reduced [9]. It remains to be seen if increased QI adherence translates into better patient outcomes—the current evidence appears insufficient and conflicting. For example, one study showed that increasing guideline adherence to more than 70% is necessary for quantitative outcome effects to be observed in infectious disease management [24], but data also suggest that improvements from a very high baseline adherence (> 90%) result in better patient outcomes. We also observed an attenuation of adherence to three QIs over time that is comparable to educational programmes and might indicate a demand to repeat the blended learning or the on-the-job training [25].

The strengths of this study include its innovative stepped-wedge design which allows for rigorous evaluation of a large-scale intervention implemented in different types of hospitals, ranging from large academic centres to small community hospitals. The heterogeneous study population consisted of adults with, e.g., cardiovascular, sepsis/infectious, oncological, or trauma primary admission diagnoses, supporting the real-world pragmatic trial character. Hence, our study patients reflect the multidisciplinary nature of intensive care medicine and can be generalised, as the sample is representative for the German ICU population.

We investigated the feasibility of this telemedical implementation in a defined local network of ICUs. Upon the end of recruitment (last patient first visit on March 31, 2020), the network was scaled up for the management of the COVID-19 pandemic, and international programmes adopted the telemedical approach, which is indicative for a high acceptance within the critical care community.

This pragmatic superiority trial has several limitations. First, there may have been selection bias as cluster-level participation was on a voluntary basis. We might have recruited a population of clusters already showing a high motivation before the study to improve their quality of care. Clinical sites already showed a high level of performance during the control period prior to the implementation of the intervention (Fig. 2), which was above the average baseline level of adherence documented in the literature and expected during the planning phase [13, 14, 26–30]. Second, 44.6% (652/1462) of patients were enrolled at two highly recruiting academic clusters affiliated to the sponsor of the trial providing the tele-ICU. Thus, trial findings may not be fully applicable to Germany's hospital landscape. Third, clusters' trial participation and the consequent focus on the QIs may have already resulted in better QI adherence, irrespective of the treatment condition. This so-called Hawthorne effect observed in previous quality improvement studies may have been aggravated by the training of QI experts for each cluster already during the control phase [31]. These experts may have put more attention on the QIs in the study centres, even before transitioning to the intervention phase. Hence, we may have overestimated QI adherence on standard of care. Forth, the sample size calculation performed in 2015 was rather pragmatic due to difficulties obtaining reliable values for the correlation structure at the design stage. However, the resulting 99.375% confidence intervals for estimators for intervention effects regarding all 8 QIs indicate a high level of precision based on the actual design features. Therefore, we believe to have made rather conservative assumptions. Fifth, the trial was not powered with respect to secondary endpoints (e.g. survival) which limits the interpretation of these endpoints. We evaluated the immediate effect of the telemedical intervention on the QI adherence and the sustained effect on the 6-month all-cause mortality. The trial did not analyse if the effect regarding QIs translates into a survival benefit. This so-called surrogacy between QI adherence and survival was not the focus of our trial [32, 33]. Even if higher QI adherence were associated with better survival, its surrogacy in the context of the telemedical intervention is still not evident. If QI adherence only has a short-term effect on survival but no effect on the 6-month or 12-month survival rates, a general survival benefit may not be seen by a standard survival

analysis. Sixth, patients enrolled on intervention showed a significantly higher severity of illness (according to baseline SAPS II and SOFA scores). Participating centres may have selected patients in the intervention phase who they considered to benefit most from the telemedical intervention. This identification and recruitment bias may have diluted a beneficial effect in survival between patients treated on intervention vs. control condition.

In conclusion, a structured, bundled telemedical intervention implemented in a diverse local network of hospitals in Germany improved the quality of care compared to standard of care. Although the primary efficacy endpoints were met, further research is needed to evaluate the generalizability outside the German healthcare sector and in a broader setting of regional, non-academic community hospitals. It is also important to explore long-term intervention sustainability. Therefore, future controlled trials in Germany should be designed to investigate the effectiveness of virtual care networks on long-term survival and early and late post-ICU functional impairments in a well-defined ICU population.

Supplementary Information
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Author contributions
CDS, BW, and SR conceptualised the trial. As coordinating investigator, CDS initiated the collaborative project, was the sponsor-delegated person of this trial, and is the guarantor. CA and UMan designed the trial, contributed to the preceding research proposal leading to the funding of the trial and study protocol, and conducted the independent evaluation regarding clinical effectiveness. EB and RB were responsible for all legal aspects of the implementation of the intervention and conducted supporting health-economic analyses. BW was in charge of the trial conduction and management. NP coordinated post-ICU follow-up visits and contributed to trial management. UMar had oversight from the statutory health insurance and the legal trial aspects affecting German health insurances. BK set up the IT infrastructure of the intervention, implemented the REDCap eCRF, and prepared the EU tender, together with CDS and BW. CDS, NP, CD, HK, ED, BW, and all investigators of the recruiting study sites acquired the data. CDS, NP, CA, and BW wrote the first draft. NP and CA contributed equally to the work and are joint second authors. CA and UMan performed the statistical analyses, created tables and figures, and the appendix. All authors have critically read, contributed with input and revisions, and approved the final manuscript.

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Data sharing
Data cannot be shared publicly because participants did not explicitly consent to the sharing of their data as per European Union's General Data Protection Regulation (EU GDPR) and the corresponding German privacy laws. Upon request, researchers who meet the criteria for access to confidential data can be given access to the selected raw data for further scientific projects provided the positive evaluation of a scientific application by the Data Use and Access Committee of the Charité and the coordinating investigator. Data will be made available for a minimum of 3 years after publication.

Declarations

Conflicts of interest
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2.7. Originalarbeit 7: Bibliometrische Analyse und Netzwerk-Analyse von Studien über das Post-Intensive Care Syndrom

Die bisherigen Arbeiten dieser Habilitation beschäftigten sich mit der Detektion und der Prävention von PICS. Bei der Durchführung dieser Arbeiten fiel der starke Fokus des PICS-Forschungsfeldes auf die USA, aus der die Mehrzahl der wegweisenden Studien stammt, auf (nicht zuletzt das Konsensus-Statement zur Definition von PICS aus dem Jahr 2012 [21]). Zudem entstand der Eindruck, dass es viele Studien zur Prävalenz PICS-bezogener Beeinträchtigungen gibt, jedoch nur wenige Arbeiten zur Prävention und Behandlung eines PICS. Diesem Eindruck nachgehend, wurde in *Originalarbeit 7* das PICS-Forschungsfeld systematisch mithilfe von Netzwerkanalysen und bibliometrischen Kennzahlen analysiert, um Schwerpunkte und Tendenzen in dem Forschungsfeld auszumachen sowie Wissenslücken zu erfassen.

Der nachfolgende Text entspricht einer wörtlichen Übersetzung des Abstrakts der Arbeit:

Paul N, Albrecht V, Denke C, Spies CD, Krampe H, Weiss B: A decade of post-intensive care syndrome: a bibliometric network analysis. Medicina 2022; 58(2):170. doi:10.3390/medicina58020170.

*“Hintergrund und Zielsetzung: Der Begriff Post-Intensive Care Syndrom (PICS) wurde 2012 eingeführt, um die funktionellen und langfristigen Beeinträchtigungen von Überlebenden kritischer Erkrankung zusammenzufassen. Wir zeigen Ergebnisse einer bibliometrischen Netzwerk-Analyse des PICS-Forschungsfeldes. Material und Methoden: Die Web of Science Core-Datenbank wurde mit dem Suchbegriff ‘post-intensive care syndrome’ oder verwandten Schreibweisen auf Artikel, die 2012 oder später publiziert wurden, durchsucht. Wir verwendeten die Software VOSviewer, um Netzwerke von Ländern, Institutionen, Koautor*innen und gemeinsamen Schlüsselwörtern zu erstellen. Wir berechneten die relative Forschungsleistung jedes Landes und den Category Normalized Citation Index über die Zeit. Wir analysierten die 100 meistzitierten Artikel bezüglich des Artikel-Typs, des Ursprungslandes und des publizierenden Journals. Ergebnisse: Unsere Suche ergab 379 Artikel, von denen 373 in die Analyse einflossen. Die Zahl der jährlich publizierten Forschungsartikel zu PICS stieg von 11 (2012) auf 95 Artikel (2020). Die meiste PICS-Forschung stammte*

*aus den USA, gefolgt von England, Australien, den Niederlanden und Deutschland. Wir fanden zahlreiche Kollaborationen zwischen Ländern, Institutionen und Autor*innen, mit kürzlich entstandenen Kollaborations-Netzwerken von englischen und australischen Institutionen. Schlüsselwörter der eingeschlossenen Artikel bezogen sich auf Aspekte der Kognition, der mentalen Gesundheit, der körperlichen Gesundheit und seit kurzem auch Covid-19. Nur wenige Schlüsselwörter bezogen sich auf die Prävention und Behandlung von PICS. Schlussfolgerung: Unsere Analyse von im Web of Science gelisteten Arbeiten zeigt die starke Zunahme an PICS-Artikeln in den letzten Jahren. Die Artikel stammen primär von Autor*innen und Institutionen aus den USA und Europa. Ungeachtet des Wachstums des Forschungsbereichs gibt es große Wissenslücken in Bezug auf die Prävention und die Behandlung von PICS.“* (Übersetzung durch den Autor.)

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Article

A Decade of Post-Intensive Care Syndrome: A Bibliometric Network Analysis

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Abstract: *Background and Objectives:* In 2012, the umbrella term post-intensive care syndrome (PICS) was introduced to capture functional long-term impairments of survivors of critical illness. We present a bibliometric network analysis of the PICS research field. *Materials and Methods:* The Web of Science core database was searched for articles published in 2012 or later using 'post-intensive care syndrome' and variant spellings. Using VOSviewer, we computed co-authorship networks of countries, institutions, and authors, as well as keyword co-occurrence networks. We determined each country's relative research effort and Category Normalized Citation Index over time and analyzed the 100 most-cited articles with respect to article type, country of origin, and publishing journal. *Results:* Our search yielded 379 articles, of which 373 were analyzed. Annual PICS research output increased from 11 (2012) to 95 articles (2020). Most PICS research originates from the US, followed by England, Australia, the Netherlands, and Germany. We found various collaborations between countries, institutions, and authors, with recent collaborative networks of English and Australian institutions. Article keywords cover aspects of cognitive, mental health, and physical impairments, and more recently, COVID-19. Only a few keywords and articles pertained to PICS prevention and treatment. *Conclusions:* Our analysis of Web of Science-indexed PICS articles highlights the stark increase in PICS research output in recent years, primarily originating from US- and Europe-based authors and institutions. Despite the research field's growth, knowledge gaps with respect to PICS prevention and treatment remain.

Keywords: bibliometric analysis; critical illness; intensive care unit; PICS; post-intensive care syndrome; research collaboration; research output; survivorship

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1. Introduction

Over the last decades, the number of patients admitted to an intensive care unit (ICU) and the capacities in intensive care medicine have been growing continuously [1]. Although the average age and severity of illness have been increasing [2], mortality rates are steadily declining, which has been attributed to advances in technology and a growing evidence base [3]. As a result, we observe a growing cohort of patients surviving their critical illness.

Initially, research in intensive care focused on interventions to improve ICU-centered and short-term outcome measures, such as ICU or hospital mortality [4]. In the 1980s and 1990s, only a few studies explored mortality, quality of life, and functional outcomes beyond ICU discharge [5–9]. In this millennium, however, the intensive care research community acknowledged that mere survival of critical illness comes short of capturing the poor functional outcome of many ICU patients after leaving the hospital, which constitutes a heavy burden to both patients and caregivers [10]. The 2002 Brussels Roundtable identified the need for research on the determinants of long-term wellbeing and on interventions that improve long-term, patient-centered outcomes [4]. Eight years later, at a Society of Critical

Care Medicine conference, a nomenclature was developed to conceptualize and organize functional impairments after ICU discharge [11]. Due to the often-overlapping nature of functional post-ICU impairments, the use of the single term post-intensive care syndrome (PICS) was recommended [11]. PICS comprises new or worsening ICU treatment-associated impairments of cognitive functions, mental health (anxiety, depression, and post-traumatic stress disorder (PTSD)), and physical functions [11]. Moreover, it was recognized that not only patients are commonly affected by PICS but also their caregivers, which was described as PICS-F [11]. Similar to the term post-cardiac arrest syndrome [12], agreement on a common PICS terminology should raise awareness for the prevalence of functional impairments after ICU care [11]. The demand for research and awareness for PICS was reiterated at a Society of Critical Care Medicine stakeholder conference in 2012 [13]. Since its introduction, the PICS framework has become well-established and is now the most commonly used terminology to describe post-ICU impairments.

Marking a decade of PICS research, we observe a surging number of publications which pertain to different aspects of the concept, published by various research groups. Network analysis of bibliometric data of publications on PICS can help understand the current and past PICS research agenda and community. As the most apparent form of collaboration [14], co-authorship networks may facilitate understanding of ongoing and past research collaborations on an individual, institutional, and country level [15,16]. Bibliometric analysis may also reveal the most influential articles, journals, and authors, and identify knowledge gaps in the field.

To our knowledge, a science mapping of publications on PICS has not been performed yet. The aim of this study was to conduct a bibliometric network analysis of PICS research. We quantified the annual research output and visualized co-authorship networks on an individual, institutional, and country level, as well as keyword co-occurrence networks over time. We determined the relative quantity and impact of each country's research output and analyzed the 100 most-cited articles with respect to article type, country of origin, and publishing journal. Results from our analysis may help identify current and past research trends, common collaborations, and knowledge gaps in the PICS research field.

2. Materials and Methods

2.1. Web of Science Export and Data Cleaning

On 7 September 2021, we searched the Web of Science core database using the search terms 'post-intensive care syndrome', 'post intensive care syndrome' and 'postintensive' care syndrome' for all fields. We included articles published in 2012 or later without restrictions with respect to article type and language. Full records of article metrics were extracted and imported to Microsoft Excel. We also extracted a citation report that included each article's annual citations. Based on titles, articles were screened for suitability by one author (VA). In the case of ambiguity, abstracts and full texts were assessed. After discussion with another author (NP), articles were excluded if they did not pertain to ICU patients and/or PICS.

Titles, abstracts, and, in case of ambiguity, full texts were screened by one author (NP) to assign publications to article types. Reports from consensus and stakeholder conferences were considered original work. Based on authors' addresses, we identified articles' countries of origin (one article could be assigned to several countries). For all articles published prior to 2018, the annual number of citations for the publication year and the two following years were calculated. To merge various notations of the same author, institution, or keyword, data were cleaned using OpenRefine (version 3.4.1; Google LLC, Mountain View, CA, USA). Bar graphs were created using Prism 9 (version 9.3.1; GraphPad Software LLC, San Diego, CA, USA).

2.2. Distance-Based Networks

Co-authorship networks for countries, institutions, and authors as well as keyword co-occurrence networks were computed using VOSviewer (version 1.6.17 for Mac; Leiden University, Leiden, The Netherlands) [17]. VOSviewer networks consist of items (i.e., countries, institutions, authors, or keywords). The closer items are related to each other, the closer they appear in the network. An item's size is determined by its importance relative to the other items (i.e., the number of publications or keyword occurrences). Direct links between items indicate immediate connections (i.e., a co-authorship or a co-occurrence of keywords). A link's thickness indicates its strength (i.e., the number of co-authorships or the number of publications where two keywords co-occur). VOSviewer assigns each item to a cluster of related items [16]. Color overlays indicate the average publication year of articles of the respective item [18]. Balancing readability and information in the visualizations, the minimum number of articles was set to three for the country network, to four for the institution and author networks, and to five for the keyword co-occurrence network.

2.3. Category Normalized Citation Index and Relative Research Activity

We calculated each country's median Category Normalized Citation Impact (CNCI) [19] and relative research activity [20] for three time periods: 2012–2014, 2015–2017, and 2018–2021. The CNCI indicates the ratio of an article's citations and the average citations of articles within the same research field, document type, and year [19]. Hence, a CNCI >1 or <1 indicates above-average or below-average citations per article, respectively. For the CNCI calculation, we defined our sample of PICS research as the research field of reference, and documents were grouped in original research (including protocol papers), reviews, and other articles (editorials, letters, case reports, meeting abstracts, and book reviews).

The relative research activity indicates the ratio between a country's PICS research output and the average research output across countries that contribute to PICS research in a given time period. Thus, a relative research activity >1 or <1 indicates above-average or below-average research output, respectively.

2.4. Analysis of the 100 Most-Cited Articles

We identified the 100 most-cited articles on PICS and analyzed them with respect to article type, country of origin, and publishing journal. Based on the corresponding author's affiliation, each of the 100 most-cited articles was assigned to a single country of origin. Journal impact factors were drawn from Clarivate Analytics Journal Citation Reports 2020 [21].

3. Results

3.1. Study Sample

The Web of Science search yielded 379 articles, from which six articles were excluded as they did not pertain to ICU patients and/or PICS (Figure 1). Of the remaining 373 articles, 145 were original research articles, 103 reviews, 58 editorial articles or letters, 33 meeting abstracts, 19 protocol papers, nine case reports, five research letters, and one was a book review (Table 1).

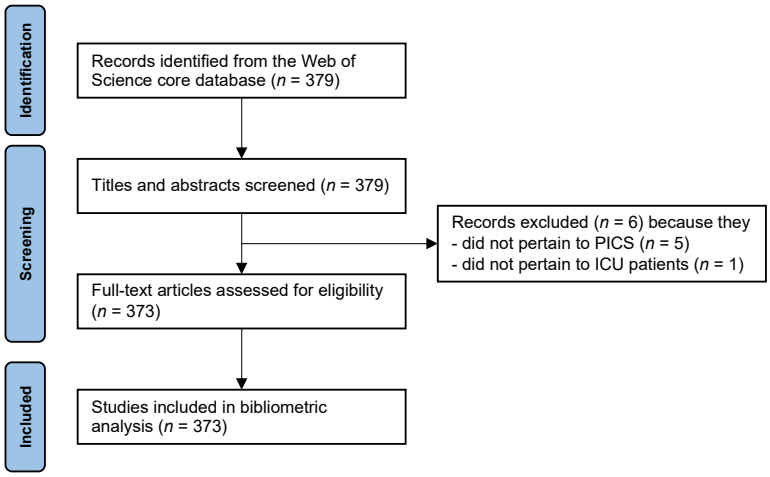

Figure 1. Study inclusion flowchart. ICU, intensive care unit; PICS, post-intensive care syndrome.

Table 1. Articles on post-intensive care syndrome, by article type.

Article Type	Articles, *n*
Original research	145
Review	103
Editorial or letter	58
Meeting abstract	33
Protocol paper	19
Case report	9
Research letter	5
Book review	1

3.2. Characteristics of Articles

Articles were written by 1621 different authors from 793 institutions and 39 countries, with a mean number of 6.4 (SD 6.3) and a median number of 5 (IQR 3; 8) authors per article. The mean number of countries of origin was 1.4 (SD 1.0) per article, and the median number of countries of origin was 1 (IQR 1; 1) per article. On average, each article had 5.6 (SD 2.5) keywords, with a median of 5 (IQR 4; 6) keywords per article. The annual research output steadily increased from 11 articles in 2012 to 95 articles in 2020 (Figure 2A). Articles were cited 5415 times, with a mean of 14.5 (SD 57.3) citations per article and a median of 3 (IQR 0; 11) citations per article. Eight articles (2%) were cited >100 times, while 116 articles (31%) were uncited, and 67 articles (18%) were cited once or twice (Figure 2B).

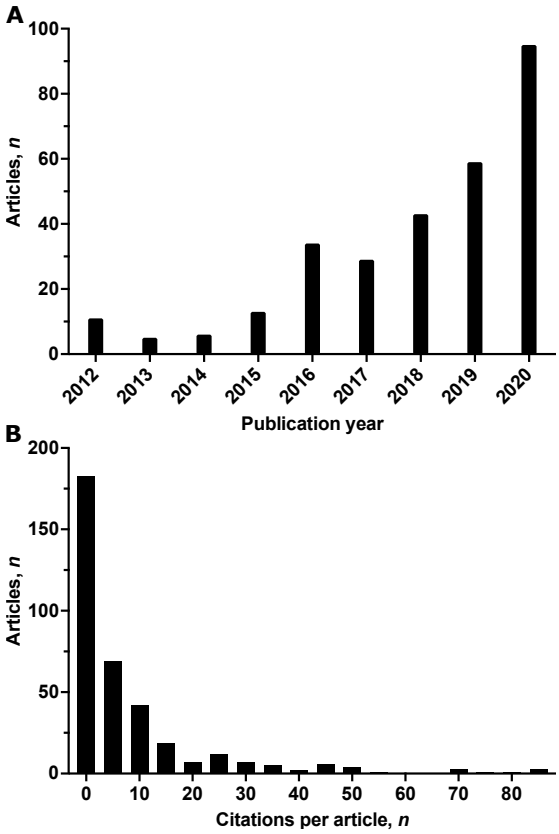

Figure 2. (**A**) Number of articles on post-intensive care syndrome, by year. Up to the Web of Science search on 7 September 2021, 78 articles were published in 2021. (**B**) Histogram of the number of citations per article (bin width of five citations). Eight articles with >100 citations (range: 125–939 citations) are not displayed.

3.3. Bibliometric Analysis by Country

We identified 26 countries with at least three publications (Figure 3). As Greece, Portugal, and South Korea did not bear connections to the network, they were not displayed. The US lies in the network's center and has collaborations with 21 countries, followed by the Netherlands (14 links), Australia (12 links), England (17 links), Canada (10 links), and Germany (nine links). With an average publication year of 2018, articles from the US and the Netherlands were published earlier than articles from other countries.

Each of the 20 countries with the highest number of PICS articles has increased its research output since 2012 (Table 2). With 203 publications, most articles on PICS were published by authors affiliated with US institutions, which is also reflected by the relative US research activity during the three time periods of 3.9, 10.7, and 13.4, respectively. At the same time, the median CNCI of US-affiliated articles decreased from 0.8 (IQR 0.3; 2.6) in 2012–2014 to 0.4 (IQR 0.0; 1.0) in 2018–2021. Similar to the US, the relative research activity of England, Australia, the Netherlands, and Germany increased in 2018–2021 compared to previous years. Authors affiliated with institutions from various other countries entered the research field after 2015, for example, authors affiliated with institutions from Spain, Japan, and Italy.

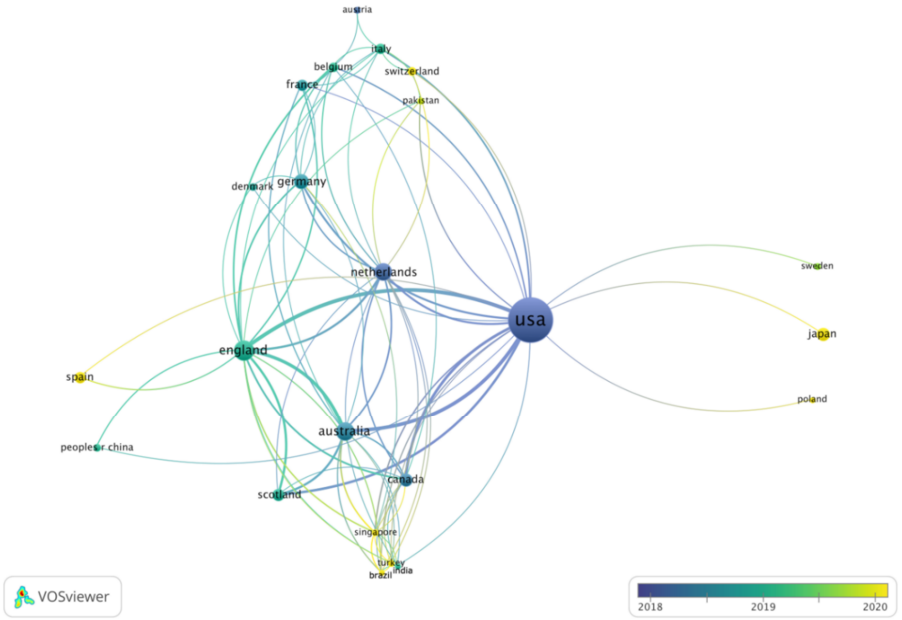

Figure 3. Collaborations between countries among articles on post-intensive care syndrome. Co-authorship-based network. Lines between countries indicate direct links (i.e., co-authorships). Thicker lines are indicative of stronger links (i.e., more co-authorships). The further two countries are apart, the weaker is their relation. Colors indicate the average publication year of a country's articles. A number of 26 countries with at least three publications were identified. Greece, Portugal, and South Korea were excluded as they did not have any connection to the network. Created using VOSviewer.

Table 2. Research output, Category Normalized Citation Index, and relative research activity, by country and time period.

Country	2012–2014			2015–2017			2018–2021			All Years
	N	CNCI §	RRA	N	CNCI §	RRA	N	CNCI §	RRA	N
USA	14	0.8 (0.3; 2.6)	3.9	56	0.5 (0.1; 1.4)	10.7	133	0.4 (0.0; 1.0)	13.4	203
England	2	2.4 (1.0; 3.9)	0.6	5	0.7 (0.7; 2.1)	1.0	35	0.5 (0.2; 2.3)	3.5	42
Australia	3	1.0 (0.3; 1.0)	0.8	7	1.1 (0.3; 2.3)	1.3	24	0.9 (0.0; 2.2)	2.4	34
Netherlands	4	0.4 (0.0; 0.9)	1.1	5	1.3 (0.7; 1.4)	1.0	23	0.7 (0.1; 1.6)	2.3	32
Germany	3	0.4 (0.0; 1.0)	0.8	2	0.8 (0.1; 1.4)	0.4	18	0.3 (0.0; 0.8)	1.8	23
Japan	0			1	0.3 (0.3; 0.3)	0.2	17	0.2 (0.0; 0.8)	1.7	18
Canada	0			4	2.1 (1.7; 2.3)	0.8	12	1.2 (0.3; 2.1)	1.2	16
Scotland	0			2	1.9 (0.4; 3.4)	0.4	12	2.2 (0.7; 3.6)	1.2	14
France	1	0.9 (0.9; 0.9)	0.3	2	1.2 (1.1; 1.3)	0.4	10	0.3 (0.0; 2.4)	1.0	13
Spain	0			0			12	0.0 (0.0; 0.1)	1.2	12
Italy	1	0.1 (0.1; 0.1)	0.3	0			9	0.0 (0.0; 2.9)	0.9	10
Belgium	0			2	1.7 (1.3; 2.1)	0.4	7	0.7 (0.0; 2.4)	0.7	9
South Korea	0			1	1.1 (1.1; 1.1)	0.2	7	0.4 (0.0; 0.8)	0.7	8
Switzerland	0			0			7	0.5 (0.0; 2.9)	0.7	7
China	0			1	0.4 (0.4; 0.4)	0.2	5	0.2 (0.2; 0.4)	0.5	6
Denmark	0			1	0.9 (0.9; 0.9)	0.2	5	0.3 (0.0; 0.3)	0.5	6
Pakistan	0			0			5	0.3 (0.2; 0.5)	0.5	5
Singapore	0			0			5	0.3 (0.0; 0.5)	0.5	5

Table 2. *Cont.*

Country	2012–2014			2015–2017			2018–2021			All Years
	N	CNCI §	RRA	N	CNCI §	RRA	N	CNCI §	RRA	N
Turkey	0			0			5	0.2 (0.0; 0.9)	0.5	5
Sweden	0			1	0.3 (0.3; 0.3)	0.2	4	0.2 (0.0; 2.0)	0.4	5

Countries with at least five publications shown. § Median (IQR). Depending on authors' affiliations, one article may be assigned to multiple countries. CNCI, Category Normalized Citation Index; RRA, relative research activity.

3.4. Bibliometric Analysis by Institution

As indicated in the highly linked network, we found a large number of research collaborations between institutions (Figure 4). At the center of the network, Johns Hopkins University and the University of Pennsylvania have the most institutional links (44 each), followed by Brigham Young University (43 links). VOSviewer identified nine clusters, most of which are formed around US-based institutions. The exceptions are clusters around the University of Nottingham (England) and the University of Queensland (Australia), as well as other institutions, for example, Charité—Universitätsmedizin Berlin (Germany), the University of Amsterdam (the Netherlands), the University of Melbourne (Australia), McMaster University (Canada), or the University of Glasgow (Scotland).

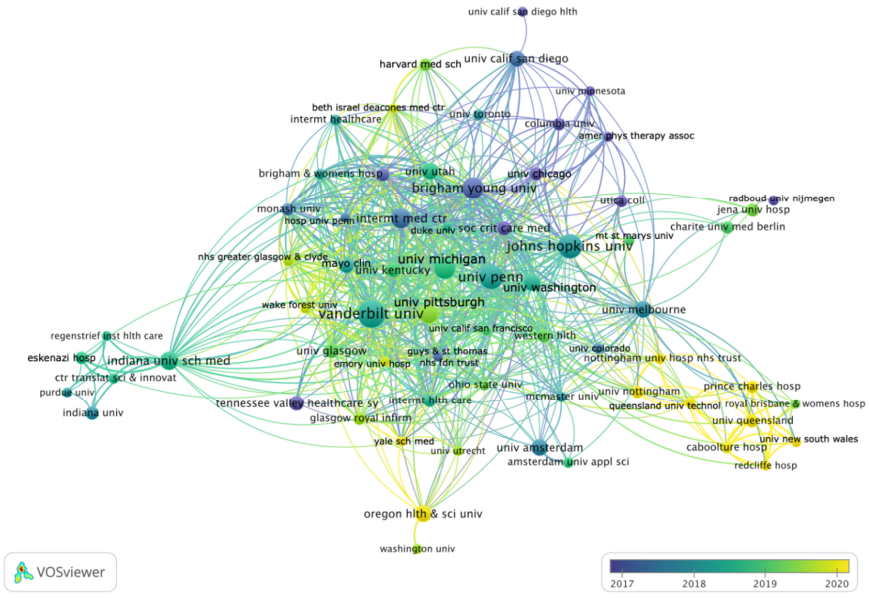

Figure 4. Collaborations between institutions among articles on post-intensive care syndrome. Co-authorship-based network. Lines between institutions indicate direct links (i.e., co-authorships). Thicker lines are indicative of stronger links (i.e., more co-authorships). The further two institutions are apart, the weaker is their relation. Colors indicate the average publication year of an institution's articles. Institutions with at least four publications are shown. Five institutions were excluded as they did not show any connection with the network. Created using VOSviewer.

Apart from the main cluster, institutions from the US state of Indiana have formed a separate collaborative network, primarily linked to the main cluster via collaborations

of the Indiana University School of Medicine. When we analyzed collaborations between individual authors, we also observed a separate, Indiana-based cluster (Figure S1).

Recent collaborations (yellow circles in the periphery of the network in Figure 4) have formed around the Oregon Health and Science University and Yale School of Medicine in the US, as well as the University of Nottingham, Nottingham University Hospitals NHS Trust, the University of Queensland, Caboolture Hospital, Prince Charles Hospital, the University of New South Wales, Queensland University of Technology, and Redcliffe Hospital in Australia and the United Kingdom. A separate, recently formed collaborative network of authors from Oregon (TA Hall and K Bradbury, among others) also appeared in the collaborative author network (Figure S1).

3.5. Keyword Co-Occurrence Network

The keyword 'post-intensive care syndrome' lies in the center of the keyword co-occurrence network (Figure 5). Keywords with most co-occurrences apart from PICS are 'critical care', 'intensive care unit', 'intensive care', and 'critical illness'. The visual overlay of the average publication year of keywords allows for the identification of trends over time. Early keywords with an average publication year of 2018 include 'family', 'pain', 'cognitive impairment', and 'activities of daily living'. Keywords on mental health impairments such as 'anxiety', 'depression', and 'posttraumatic stress disorder', as well as 'ICU-acquired weakness' and 'health-related quality of life' center around 2019. Starting with the emergence of the COVID-19 pandemic in 2020, COVID-19-related keywords have entered the PICS research field. More recently, the keywords 'frailty', 'sleep', and 'chronic pain' have been used in the context of PICS, indicating new aspects of research in the field.

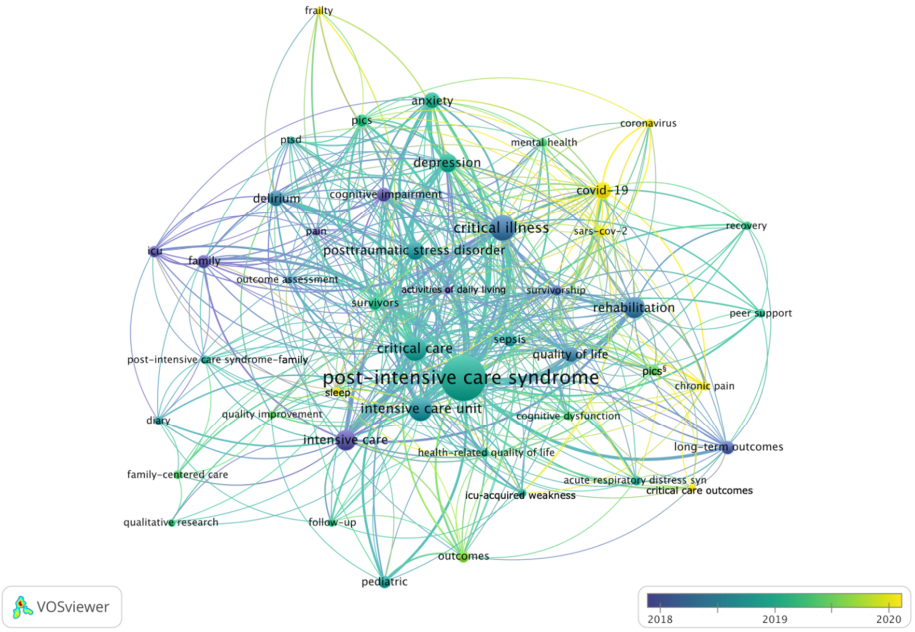

Figure 5. Keyword co-occurrence among articles on post-intensive care syndrome. Lines indicate direct keyword co-occurrences. Thicker lines are indicative for more direct keyword co-occurrences. The further two keywords are apart, the weaker is their relation. Colors indicate the average publication year of articles with the respective keyword. Keywords with at least five publications are shown. § Abbreviation for the keyword 'post-intensive care syndrome (pics)'. Created using VOSviewer.

3.6. Characteristics of the 100 Most-Cited Articles on Post-Intensive Care Syndrome

Half of the 100 most-cited articles on PICS were original research articles (50 articles), 42 articles were reviews, seven articles were editorials/letters, and one article was a study protocol (see Table S1 for full list). More than half of the articles originate from the US, followed by the Netherlands (eight articles), Australia (seven articles), and England (six articles) (Table 3). With 21 articles, *Critical Care Medicine* was the most popular journal, followed by *AACN Advanced Critical Care* (eight articles), *Critical Care*, and *Current Opinion in Critical Care* (both five articles) (Table 4).

Table 3. Countries of origin of the 100 most-cited articles on post-intensive care syndrome.

Country	Articles, *n*
USA	52
Netherlands	8
Australia	7
England	6
Scotland	5
France	4
Germany	4
Japan	3
Canada	2
South Korea	2
Denmark	2

Countries with at least two top-100 publications shown. The corresponding author's institutional affiliation defined the country of origin.

Table 4. Publishing journals of the 100 most-cited articles on post-intensive care syndrome.

Rank	Journal	Impact Factor 2020 *	Articles, *n*
1	Critical Care Medicine	7.598	21
2	AACN Advanced Critical Care	- §	8
3	Critical Care	9.097	5
	Current Opinion in Critical Care	3.687	5
4	Journal of Critical Care	3.425	4
	Annals of the American Thoracic Society	6.831	4
5	Intensive Care Medicine	17.440	3
	Physical Therapy	3.140 †	3
	Seminars in Respiratory and Critical Care Medicine	3.119	3
6	Annals of Intensive Care	6.925	2
	BMJ Open	2.692	2
	British Journal of Anaesthesia	9.166	2
	Journal of Rehabilitation Medicine	2.912	2
	Rehabilitation Psychology	2.564	2
	Pediatric Critical Care Medicine	3.624	2

Journals with at least two top-100 publications shown. * Based on Clarivate Analytics Journal Citation Reports 2020 [21]. § *AACN Advanced Critical Care* has not received an impact factor yet. † The latest impact factor of *Physical Therapy* is from 2019.

The most-cited article on PICS is the report from the Society of Critical Care Medicine conference that initially introduced the PICS terminology [11] (Table 5). The report from the second stakeholder meeting of the Society of Critical Care Medicine on this topic received the second most citations among original research articles [13]. The other top ten original research articles were published in 2016 or later [22–29], with two recent articles pertaining to COVID-19 [22,25] and one article pertaining to the establishment of an ICU recovery center [27]. The most frequently cited review on PICS discusses the ramifications of critical illness for family members (Table 6) [30]. Another top ten review also discusses repercussions for the families of ICU patients [31]. Two reviews are dedicated to measures for PICS prevention and treatment (ICU bundles and rehabilitation) [32,33], four reviews

cover PICS in general [34–37], one review discusses PICS in pediatric ICU patients [38], and one recent review is on COVID-19 [39].

Table 5. Most-cited original research articles on post-intensive care syndrome, ordered by citations.

Rank	Year	Title of Original Research Article	First Author	Citations	Citations (First Three Years)
1	2012	Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference	DM Needham	939	91
2	2014	Exploring the scope of post-intensive care syndrome therapy and care: Engagement of non-critical care providers and survivors in a second stakeholders meeting	D Elliott	206	42
3	2021	Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation	SJ Halpin	162	-
4	2018	Co-occurrence of post-intensive care syndrome problems among 406 survivors of critical illness	A Marra	86	50
5	2018	Anxiety, depression and post traumatic stress disorder after critical illness: A UK-wide prospective cohort study	R Hatch	83	35
6	2020	Rehabilitation and respiratory management in the acute and early post-acute phase: Instant paper from the field on rehabilitation answers to the COVID-19 emergency	C Kiekens	50	-
7	2018	Determinants of long-term outcome in ICU survivors: Results from the FROG-ICU study	E Gayat	49	33
8	2018	Comprehensive care of ICU survivors: Development and implementation of an ICU recovery center	CM Sevin	47	35
9	2016	Resilience in survivors of critical illness in the context of the survivors' experience and recovery	JH Maley	46	13
10	2016	Surviving critical illness: What is next? An expert consensus statement on physical rehabilitation after hospital discharge	ME Major	44	14

Table 6. Most-cited reviews on post-intensive care syndrome, ordered by citations.

Rank	Year	Title of Review	First Author	Citations	Citations (First Three Years)
1	2012	Family response to critical illness: Postintensive care syndrome-family	JE Davidson	396	40
2	2020	COVID-19: ICU delirium management during SARS-CoV-2 pandemic	K Kotfis	163	-
3	2017	The ABCDEF bundle: Science and philosophy of how ICU liberation serves patients and families	W Ely	152	69
4	2017	Post-intensive care syndrome: An overview	G Rawal	135	34
5	2014	Rehabilitation interventions for postintensive care syndrome: A systematic review	J Mehlhorn	125	35
6	2012	Having a loved one in the ICU: The forgotten family	M Schmidt	87	10
7	2018	Conceptualizing post intensive care syndrome in children—The PICS-p framework	JC Manning	74	48
8	2019	Post-intensive care syndrome: Its pathophysiology, prevention, and future directions	S Inoue	72	-
9	2016	Postintensive care syndrome: Right care, right now . . . and later	MA Harvey	71	19
10	2012	The burdens of survivorship: An approach to thinking about long-term outcomes after critical illness	TJ Iwashyna	69	12

4. Discussion

Since the introduction of the PICS terminology, research output in the field has increased exponentially from 11 articles in 2012 to 95 articles in 2020. While the umbrella term

PICS was introduced in 2012 [11], researchers in critical care had already demanded for research on the frequent functional impairments after critical illness in the early 2000s [10]. The stark increase in PICS research output in recent years, particularly after 2017, reveals that the research community has indeed acted upon these demands, albeit with a delay of more than ten years.

Most publications originate from the US—203 of 373 articles in our sample were written by authors affiliated with US institutions—followed by England, Australia, the Netherlands, and Germany (Table 7). The relative research output of these countries has increased from 2012–2014 to 2018–2021, as indicated by above-average relative research activities. These five countries are also in the center of the co-authorship-based collaboration network. On an institutional level, we identified a separate cluster around Indiana-based institutions, and a recently formed cluster of collaboration among institutions from Australia and England. The predominant role of a few high-income countries implies that the knowledge on PICS and the trajectories of post-ICU care stem primarily from highly developed health care systems in the US and Europe. As there are large global discrepancies in the organization of critical care, available resources, quality of acute as well as post-ICU care, and patient characteristics [40], our analysis uncovers the need for more diverse PICS research outside of Europe and the US. Studies in Asia, Africa, and South America could help validate existing findings on the epidemiology of PICS, risk factors, and effective treatment options. In this context, it is a positive development that authors affiliated with institutions from a more diverse set of countries, such as China, Pakistan, and Turkey have entered the PICS research stage in recent years. The newcomers usually collaborate with established institutions and authors from the US and Europe.

Table 7. Aspects of the current PICS research field.

Strengths	Limitations
- We observe a stark increase in PICS research output in recent years. - Since 2015, publications from a broader array of countries have been entering the research field, e.g., from Spain, Italy, China, or Japan. - Network analysis shows a high level of collaboration among institutions and individual authors. - Research has focused on all three PICS domains, namely impairments of cognitive functions, mental health, and physical functions. - Responding to the COVID-19 pandemic, studies at the intersection of COVID-19 and PICS have been emerging.	Few of the highly-cited publications pertain to measures of PICS treatment or prevention. Most publications originate from few high-developed countries, namely the US, England, Australia, the Netherlands, and Germany.

PICS, post-intensive care syndrome.

Our analysis of keyword co-occurrence unveils past and recent trends in PICS research. Not surprisingly, we reveal that common keywords pertain to cognition, mental health, physical health, and quality of life. As an interesting finding, articles with keywords on cognitive impairment center on 2018, whereas the keywords on mental health impairment (e.g., depression or anxiety) and physical impairment center on 2019. Notably, family was already a common keyword in early PICS publications, and the second most-cited PICS publication from 2012 pertains to PICS-F [30]. Very recently, COVID-19-related keywords have entered the PICS research field. Two of the ten most-cited original research articles [22,25] and one of the ten most-cited reviews [39] is about COVID-19, which underlines the highly dynamic and rapidly evolving research at the intersection of COVID-19 and PICS.

The most-cited article in the field is the stakeholder conference report by Needham et al. [11], which initially introduced the PICS terminology. It was published in *Critical Care Medicine*, which is the most common outlet for highly-cited PICS research, with 21 of the 100 most-cited articles published in this journal.

While many keywords and most-cited publications explored epidemiological aspects of PICS, we found very few keywords and articles on effective ways to prevent or counteract PICS. The only keywords in our network on PICS prevention and treatment were 'diary', 'family-centered care', and 'peer support'. One top-cited review focused on ICU bundle implementation to prevent PICS [33], one top-cited review focused on early rehabilitation [32], and one top-cited original research article illustrated the establishment of an ICU recovery center [27]. Our analysis demonstrates the pressing need for sound evidence on effective measures for PICS prevention, PICS treatment, and organization of post-ICU care—a demand that is mirrored by recent reviews [41,42].

Several limitations of this study warrant consideration. Most importantly, only the Web of Science, which allowed for the extensive export of bibliometric data, was searched for articles on PICS. Not all research articles are indexed in the Web of Science. Thus, articles and citations that were indexed in other databases were not included in this study. The Web of Science, however, was searched using multiple spelling variants of PICS. Second, research on long-term impairments in ICU survivors had already been conducted before the introduction of the PICS terminology [10], for example, in a Dutch ICU study from 1988 with a two-year follow-up [9]. Hence, some articles on post-ICU impairments that were published after 2012 might not have used the PICS terminology and could have been missed by our search strategy. By the same token, the observed increase in PICS research output might possibly be due to an incremental establishment of the term PICS in an already existent research field. However, various consensus conferences have reiterated the lack of research on long-term functional impairments in ICU patients [4,11,13]. Third, we used the CNCI to determine the normalized citations of individual publications. The CNCI puts an article's citations in relation to the average number of citations of articles of the same document type, year, and research field [19]. As the CNCI is, by definition, influenced by outliers (e.g., few highly-cited articles), it should be interpreted with caution in the case of small sample sizes (such as the period 2012–2015). Finally, articles that have been published longer have had more time to accumulate citations [43]. To account for this bias, we calculated the CNCI, which is independent of an article's age, and report articles' citations in the year of publication and the two following years. Furthermore, two of the ten most-cited original articles and two of the ten most-cited reviews were published in 2019 or later, which might indicate that time bias could be less relevant in the relatively young PICS research field.

5. Conclusions

Our bibliometric network analysis of Web of Science-indexed PICS publications shows a sharp increase in publication output since 2017. Most articles originate from US-based institutions and authors, followed by England, Australia, the Netherlands, and Germany. We found strong collaborations between different countries, institutions, and individuals, with a recent formation of a collaborative network of English and Australian institutions. Article keywords pertain to various aspects of PICS domains, and more recently, COVID-19. Only a few keywords and highly-cited articles, however, explore interventions to prevent or treat PICS. Our analysis maps out a highly dynamic and growing research field, predominantly with contributors from the US and Europe.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/medicina58020170/s1, Figure S1: Collaboration between authors of articles on post-intensive care syndrome, Table S1: One hundred most-cited articles on post-intensive care syndrome, ordered by number of total citations.

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3. Diskussion

3.1. Zusammenfassung der Ergebnisse der Originalarbeiten

Funktionelle Beeinträchtigungen der Kognition, der mentalen Gesundheit und der körperlichen Gesundheit bei Überlebenden kritischer Erkrankung werden unter dem Terminus PICS zusammengefasst. In der vorliegenden Arbeit werden zwei wichtige Aspekte des PICS untersucht. Im ersten Teil werden Möglichkeiten erforscht, wie man ein PICS bei Patient*innen diagnostizieren kann. In *Originalarbeit 1* werden zwei Items zur schnellen Einschätzung der subjektiven mentalen und körperlichen Gesundheit validiert [103]. Es zeigt sich, dass diese beiden Items die HrQoL, gemessen anhand des EuroQol-5 Dimensions-5 Level (EQ-5D-5L) Index-Wertes, besser vorhersagen als die Visuelle Analogskala des EQ-5D. *Originalarbeit 2* baut auf den Ergebnissen von *Originalarbeit 1* auf, indem die beiden kurzen Items der subjektiven Gesundheit verwendet werden, um den Gesundheitsstatus vor der Aufnahme auf die ITS retrospektiv zu erfassen und mit dem Gesundheitsstatus nach ITS-Entlassung zu vergleichen [104]. Es zeigt sich, dass die Mehrzahl der Patient*innen zwar keine Verschlechterung ihrer subjektiven Gesundheit berichtet, jedoch ist die ITS-Liegedauer eine wesentliche Determinante für eine Verschlechterung der subjektiven mentalen und körperlichen Gesundheit. In *Originalarbeit 3* wird ein anderer Ansatz zur Erkennung von Patient*innen mit einem PICS verfolgt [105]. Anders als die individuelle Untersuchung von Patient*innen mit geeigneten Messinstrumenten werden hier Routinedaten verwendet, um Patient*innen mit langfristiger Abhängigkeit vom Respirator zu identifizieren und zu charakterisieren. Es zeigte sich im untersuchten Jahr 2020 eine deutschlandweite Abnahme der Ersteinstellungen einer außerklinischen Beatmung. Begleitende ICD-10-Codierungen dieser Patient*innen zeugen zudem von vielen Komorbiditäten und einem großen Pflegebedarf in dieser Patientenkohorte [105].

Im zweiten Teil dieser Habilitation werden Maßnahmen untersucht, welche die Qualität der akuten intensivmedizinischen Versorgung verbessern und damit die Entstehung eines PICS verhindern könnten. In *Originalarbeit 4* werden systematisch Studien zur Implementierung von Care-Bundles auf der ITS untersucht [106]. Es zeigt sich, dass bisher nur wenige Studien den Effekt von Care-Bundles auf Langzeit-Outcomes untersucht haben. Ob intensivstationäre Care-Bundles PICS-bezogene Langzeit-

Outcomes verbessern, ist aufgrund der wenigen heterogenen Studien und ihrer methodischen Schwächen zum gegenwärtigen Zeitpunkt nicht abschließend zu bewerten. In *Originalarbeit 5* [107] und *Originalarbeit 6* [108] werden Programme evaluiert, welche die akute intensivmedizinische Versorgung auf der ITS verbessern und das Risiko für ein PICS verringern könnten. In *Originalarbeit 5* wurde gezeigt, dass ein strukturiertes Schulungsprogramm das leitliniengerechte Management von Delir, Sedierung und Analgesie nachhaltig und langfristig verbessern kann [107]. *Originalarbeit 6* zeigt, dass eine komplexe telemedizinische Intervention geeignet ist, um die Adhärenz zu QIs der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin zu verbessern [108]. Diese QIs beinhalten Aspekte wie die Frühmobilisation, das Management von Delir, Sedierung und Analgesie und das Weaning von invasiver Beatmung. In *Originalarbeit 7* konnte anhand einer Analyse bislang veröffentlichter Forschungsartikel zu PICS gezeigt werden, dass es zwar eine steigende Zahl an Publikationen zu PICS gibt, diese jedoch vornehmlich aus den USA und Europa stammen und selten die Prävention oder die Behandlung eines PICS untersuchen [20].

3.2. Diagnostik eines Post-Intensive Care Syndroms

In *Originalarbeit 1* und *Originalarbeit 2* werden zwei Items zur Erfassung der subjektiven mentalen und körperlichen Gesundheit bei Post-ITS-Patient*innen evaluiert und angewandt [103, 104]. Es zeigt sich, dass diese Items mit dem EQ-5D-5L Index-Wert korrelieren und sich damit eignen, die HrQoL bei Überlebenden kritischer Erkrankung abzubilden. Zudem lassen sich die Items verwenden, um den subjektiven Gesundheitsstatus vor der ITS-Aufnahme und nach der ITS-Entlassung zu vergleichen.

Die Evaluation geeigneter Instrumente und Algorithmen zur PICS-Diagnostik ist Gegenstand aktueller Forschung. Eine systematische Übersicht aus dem Jahr 2016 identifizierte 425 Artikel, die zwischen 1970 und 2013 veröffentlicht wurden und Daten zu Kognition, mentaler Gesundheit, körperlicher Gesundheit und HrQoL bei Überlebenden kritischer Erkrankung erhoben. Viele dieser Artikel erfassten die HrQoL (65%) und die gesellschaftliche Teilhabe bzw. das Bewältigen von Alltagsaktivitäten (46%). Deutlich weniger Artikel erfassten die Kognition (9%), die mentale Gesundheit

(27%) und die körperliche Gesundheit (6%). Die Autor*innen fanden 250 verschiedene Messinstrumente über alle PICS-Domänen und somit einen Mangel an Standardisierung in der PICS-Diagnostik [109]. Ein kürzlich veröffentlichtes Scoping Review, welches engere Selektionskriterien verwendete und nur Artikel mit explizitem Hinweis auf PICS einschloss, fand 18 Artikel, in denen insgesamt 45 verschiedene Messinstrumente verwendet wurden [110]. Diese fehlende Standardisierung in der PICS-Diagnostik führt zu einer fehlenden Vergleichbarkeit zwischen Studien und könnte ein Grund für die stark divergierenden Prävalenzen von Beeinträchtigungen in den PICS-Domänen zwischen verschiedenen Studien sein.

Welche Testinstrumente sollten nun also Anwendung finden? In diesem Zusammenhang gibt es Bestrebungen, ein sogenanntes Core Outcome Set (COS) für PICS zu entwickeln, also ein standardisiertes Bündel an Instrumenten zur PICS-Diagnostik [109]. Im Laufe der letzten Jahre erschienen mehrere Publikationen von Konsensus-Konferenzen, in denen ein solches COS definiert werden sollte. Für Überlebende eines ARDS wurde 2017 der Vorschlag eines COS publiziert, welches u.a. den EQ-5D, die IES-R, die HADS–Depression Subscale (HADS-D), die HADS-A und, optional, den SF-36 beinhaltete [111]. Für die Messung körperlicher und kognitiver Beeinträchtigungen erreichte kein Instrument die erforderliche Zustimmung im Delphi-Verfahren. Die Autor*innen betonten zudem die Notwendigkeit weiterer Validierungs- und Evaluationsstudien [111]. Ein anderes PICS-COS der amerikanischen Society of Critical Care Medicine, welches 2020 publiziert wurde, beinhaltet mit starker Empfehlung das Montreal Cognitive Assessment, die HADS-A und die HADS-D sowie mit schwacher Empfehlung die IES-R, die IES-6, den 6-MWT und den EQ-5D-5L [112]. Die Autor*innen betonten zudem die Notwendigkeit eines seriellen Assessments, welches eine Einschätzung des Zustands vor Krankenhausaufnahme, ein Assessment bei ITS-Entlassung und ein Assessment zwei bis vier Wochen nach ITS-Entlassung beinhalten solle [112]. Kürzlich veröffentlichte auch die Japanese Society of Critical Care Medicine die Ergebnisse eines Delphi-Prozesses für ein PICS-COS [113]. Das vorgeschlagene COS beinhaltet 20 Instrumente in den verschiedenen Domänen und schließt auch Angehörige der Patient*innen mit ein [113]. Die vorgeschlagenen Messinstrumente überschneiden sich teilweise mit den Messinstrumenten vorheriger COS-Vorschläge (z.B. die HADS-A, die HADS-D, die IES-R oder der EQ-5D-5L). Ergebnisse eines deutschen COS-

Konsensus beinhalten hingegen ein zweistufiges Verfahren zur PICS-Diagnostik, welches in der ersten Stufe die Verwendung kurzer Screening-Instrumente und in der zweiten Stufe ausführlichere Messinstrumente empfiehlt [114]. Teil beider Stufen sind auch in die in *Originalarbeit 1* und *Originalarbeit 2* validierten Items subjektiver mentaler und körperlicher Gesundheit [103, 104]. Wichtige Kriterien zum Einschluss in das COS waren u.a. die kurze und einfache Anwendbarkeit der Screening-Instrumente in der ersten Stufe, damit das Screening auch in der Routineversorgung der Hausarztpraxis durchgeführt werden kann und Überlebende kritischer Erkrankung zeitlich nicht überfordert werden, sowie fehlende Gebühren der Instrumente für eine breite Anwendung [114]. Diese Voraussetzungen erfüllen die in *Originalarbeit 1* und *Originalarbeit 2* verwendeten Items, welche auch durch Mediziner*innen verschiedener Fachrichtungen angewandt werden können. Die Kürze der Items ermöglicht zudem die einfache Übertragbarkeit von einer Studienumgebung in die Routineversorgung [103].

Die zahlreichen COS-Vorschläge und die Variabilität der vorgeschlagenen Instrumente offenbaren ein Problem der PICS-Forschung: Es fehlen Validierungsstudien für viele Instrumente in der Population der Überlebenden kritischer Erkrankung. Ein systematisches Review von 2017 analysierte Studien, welche die Messeigenschaften von PICS-Instrumenten bei Post-ITS-Patient*innen untersuchten [98]. Die Autor*innen fanden 20 Studien, welche die Messeigenschaften von 21 Instrumenten analysierten. Sie kamen zu dem Schluss, dass die vorliegenden Daten und die Qualität der Studien nicht ausreichen, um die Messeigenschaften von PICS-Instrumenten bei Überlebenden kritischer Erkrankung zu bewerten [98]. Dies ist eine mögliche Erklärung für die Variabilität der COS-Vorschläge und unterstreicht die Notwendigkeit von Studien wie *Originalarbeit 1* und *Originalarbeit 2* [103, 104].

3.3. Prävention und Therapie des Post-Intensive Care Syndroms

Originalarbeit 4 [106], *Originalarbeit 5* [107] und *Originalarbeit 6* [108] beschäftigten sich mit möglichen Strategien zur Prävention eines PICS durch Verbesserung der akuten intensivmedizinischen Versorgung. Diese Überlegungen basieren auf Studien, die Risikofaktoren während der intensivmedizinischen Behandlung identifizieren

konnten, welche mit Beeinträchtigungen in einzelnen PICS-Domänen assoziiert waren.

Das Auftreten eines Delirs während des ITS-Aufenthalts zeigt eine starke Assoziation mit kognitiven Defiziten nach Entlassung. So konnte in der BRAIN-ICU-Studie gezeigt werden, dass das Delir ein Risikofaktor für schlechtere kognitive Funktionen drei und 12 Monate nach Entlassung war [23]. Eine systematische Übersichtsarbeit, welche 24 Studien mit 3562 Patient*innen mit Delir und 6987 Patient*innen ohne Delir einschloss, zeigte, dass in allen eingeschlossenen Studien Patient*innen mit Delir schlechtere kognitive Funktionen nach Entlassung als Patient*innen ohne Delir hatten [101]. Patient*innen mit Delir hatten mit einem Odds Ratio (OR) von 2,3 (95%-KI 1,85-2,86) eine höhere Wahrscheinlichkeit einer kognitiven Beeinträchtigung [101]. Zur Prävention kognitiver Beeinträchtigungen sollte somit ein Delir auf der ITS verhindert, erkannt und adäquat therapiert werden. Dazu gehört das leitliniengerechte regelmäßige Testen auf ein Delir, beispielsweise mithilfe der Confusion Assessment Method for the Intensive Care Unit oder der Intensive Care Delirium Screening Checklist [115, 116]. Auch könnte die Vermeidung von Benzodiazepinen zur Sedierung das Auftreten eines Delirs verhindern [115, 117-121]. Zusätzlich können Veränderungen der Patientenumgebung, wie beispielsweise die Geräuschreduktion mittels Gehörstöpseln, das Delir-Risiko reduzieren [122, 123].

Qualitätsprogramme zur Vermeidung von Benzodiazepinen, zur Förderung des regelmäßigen Messens der Sedierungstiefe und zur Förderung der regelmäßigen Durchführung eines Delir-Screenings konnten die Wahrscheinlichkeit eines Delirs auf der ITS senken [124-126]. In *Originalarbeit 5* wurde untersucht, ob ein strukturiertes Schulungsprogramm das leitliniengerechte Management von Delir, Sedierung und Analgesie nachhaltig verbessern kann [107]. Diese Studie zeigte, dass ein strukturiertes Schulungsprogramm mittels wiederholter Vorlesungen, Seminare, Handouts und Hands-On-Training die Rate an Patient*innen, die ein Assessment für Delir, Sedierungstiefe und Schmerzlevel erhielten, langfristig erhöhen konnte [107]. Ein Einfluss auf Langzeit-Outcomes wie Kognition oder HrQoL wurde in dieser Studie jedoch nicht untersucht, was sicherlich eine wichtige Limitation darstellt.

In *Originalarbeit 6* wurde die Telemedizin als eine mögliche Strategie zur Verbesserung der Behandlungsqualität untersucht [108]. Es konnte gezeigt werden,

dass eine regelmäßige, interdisziplinäre telemedizinische Visite durch erfahrene Intensivmediziner*innen in einem Netzwerk von ITS die Adhärenz zu evidenzbasierten QIs der Deutschen Interdisziplinären Vereinigung für Intensiv- und Notfallmedizin signifikant steigert. Ein besonders großer Effekt wurde für die Adhärenz zum QI 2 „Management von Sedierung, Analgesie und Delir“ mit einem adjustierten OR von 5,328 (99,375%-KI 3,395–8,358) gefunden. Dieser QI beinhaltet die Frage, ob Standard Operating Procedures zum Management von Sedierung, Analgesie und Delir vorhanden sind, wie oft die richtigen Scores angewandt und dokumentiert werden, und, optional, wie die Qualität der Assessments ist. Eine durch Telemedizin verbesserte Adhärenz zu diesem QI verbessert somit die Qualität des Delir-Managements und könnte damit zu einer Verringerung von kognitiven Langzeitbeeinträchtigungen beitragen. Ein solcher Langzeiteffekt wurde in der ERIC-Studie jedoch nicht gezeigt; zukünftige Arbeiten sollten sich darauf konzentrieren.

Auch die Implementierung von Care-Bundles, also von definierten Maßnahmenpaketen zur Verbesserung der Behandlungsqualität, kann zur Prävention eines Delirs beitragen. Beispielsweise konnte in einer monozentrischen Vorher-Nachher-Studie die Implementierung des ABCDE-Bundles (“*Awakening and Breathing Coordination of daily sedation and ventilator removal trials, Choice of sedative or analgesic exposure, Delirium monitoring and management; Early mobility and Exercise”* [127, 128]) die Delir-Inzidenz deutlich senken (OR 0,55, 95%-KI 0,33-0,93) [129]. In einer anderen Studie war die Care-Bundle-Adhärenz mit mehr Tagen am Leben, ohne Delir und ohne Koma assoziiert [130]. In *Originalarbeit 4* wurde der Frage nachgegangen, ob die Umsetzung von Care-Bundles auf der ITS patientenrelevante Langzeit-Outcomes verbessern und ein PICS verhindern kann [106]. Es zeigte sich, dass es zwar zahlreiche Studien gibt, welche die Umsetzung von Care-Bundles untersuchten, jedoch nur wenige Studien den Einfluss von Care-Bundles auf patientenrelevante Langzeit-Outcomes betrachteten. Diese Studien zeigen uneindeutige Ergebnisse, was durch die Variabilität der Care-Bundles, durch unterschiedliche Implementierungsstrategien und durch heterogene Follow-Up-Zeitpunkte, Studienpopulationen und Messinstrumente zu erklären ist.

Das Delir ist auch ein möglicher Risikofaktor für Beeinträchtigungen der mentalen Gesundheit nach ITS-Entlassung, vor allem für das Auftreten einer Angststörung [41]. In zwei systematischen Reviews fanden sich nur uneindeutige Ergebnisse für die

Assoziation zwischen einem Delir auf der ITS und Depression nach Entlassung [36] und keine Assoziation zwischen einem Delir auf der ITS und PTBS-Symptomen nach Entlassung [40]. Die Verwendung von Benzodiazepinen, die ein Delir wiederum fördern können [117-121], war jedoch ein Risikofaktor für PTBS-Symptome [40], nicht jedoch für die Symptome einer Depression [36]. Tiefe Sedierung konnte interessanterweise weder als Risikofaktor für PTBS noch für Depression identifiziert werden [36, 40]. Zeichen psychischer Belastung auf der ITS (z.B. Nervosität, starker Stress, Angst oder Albträume) und wahnhafte Erfahrungen während der Behandlung waren mit dem Auftreten von Angststörungen [41], Depressionen [36] und PTBS assoziiert [40]. Vorbestehende Beeinträchtigungen der mentalen Gesundheit waren starke Risikofaktoren für eine Depression [36] und PTBS nach der ITS-Entlassung [40]. Das Auftreten von Angststörungen, Depressionen oder PTBS nach ITS-Entlassung korrelierte mit anderen Beeinträchtigungen der mentalen Gesundheit [36, 40, 41], was den syndromalen Charakter von PICS unterstreicht. Die Vermeidung der soeben genannten Faktoren (z. B. die Vermeidung traumatischer Erfahrungen oder die Vermeidung von Benzodiazepinen während der Behandlung) könnte somit die Inzidenz von Angststörungen, PTBS und Depressionen nach ITS-Entlassung reduzieren. In *Originalarbeit 6* konnten wir zeigen, dass eine strukturierte telemedizinische Visite die Adhärenz zum QI 8 „Dokumentation einer strukturierten Patienten- und Angehörigenkommunikation“ mit einem adjustierten OR von 6,787 (99,375%-KI 3,976–11,589) erhöhen konnte [108]. Dieser QI beinhaltet das frühe Einbinden der Familie und der Angehörigen in den Behandlungsprozess. Neben besserem Sedierungs- und Analgesie-Management könnte dies den Stress der Patient*innen reduzieren und möglicherweise die mentale Gesundheit positiv beeinflussen. Diese Assoziation muss jedoch in zukünftigen Studien weitergehend untersucht werden.

Eine wichtige Strategie zur Vermeidung von Beeinträchtigungen der physischen Gesundheit nach ITS-Entlassung ist die Frühmobilisation. In einer RCT in zwei amerikanischen Universitätskliniken mit 104 Patient*innen wurde gezeigt, dass durch die frühe und intensive Physio- und Ergotherapie während täglicher Sedierungspausen die Rate an Patient*innen mit funktioneller Unabhängigkeit zum Zeitpunkt der Krankenhausentlassung gesteigert werden konnte [131]. Die Mobilität und die körperlichen Funktionen über die Krankenhausentlassung hinaus wurden

jedoch nicht untersucht. In einer anderen internationalen RCT mit 200 Patient*innen konnte durch die zielorientierte Frühmobilisation die funktionelle Mobilität bei der Krankenhausentlassung gesteigert werden [132]. Es zeigte sich allerdings kein Unterschied der HrQoL (gemessen mit dem SF-36) zwischen der Interventions- und Kontrollgruppe nach drei Monaten. Dies ist jedoch mit Vorsicht zu interpretieren, da mehr als ein Drittel der Studienteilnehmer*innen nicht nachverfolgt werden konnten [132]. Ein systematisches Review mit sechs RCTs kam zu dem Schluss, dass durch die Frühmobilisation die ICU-AW reduziert und die Muskelkraft im Krankenhaus verbessert werden kann [133]. Es gab jedoch nur zwei RCTs, die den Einfluss auf Langzeit-Outcomes (EQ-5D und SF-36) untersucht haben, sodass eine Schlussfolgerung gegenwärtig schwierig scheint [133]. Die in *Originalarbeit 6* untersuchte komplexe telemedizinische Intervention konnte auch in Bezug auf die Frühmobilisation zu einer Outcome-Verbesserung führen [108]. Die Intervention konnte die Wahrscheinlichkeit, dass Patient*innen eine Frühmobilisation erhielten, mit einem OR von 3,161 (99,375%-KI 2,160–4,624) deutlich steigern. Somit könnte die in dieser Studie untersuchte telemedizinische Intervention die Beeinträchtigungen der Mobilität reduzieren, wobei der Zusammenhang zwischen Frühmobilisation und besseren körperlichen Langzeit-Outcomes noch gezeigt werden muss.

Die Wichtigkeit der Prävention eines PICS durch Optimierung der intensivstationären Behandlung ergibt sich aus einem Mangel an Studien, welche effektive Behandlungsstrategien eines bereits manifesten PICS untersuchen. Die Notwendigkeit von Forschung in dem Bereich der PICS-Behandlung wurde in *Originalarbeit 7* hervorgehoben [20]. Zur Behandlung bereits vorhandener kognitiver Störungen nach ITS-Aufenthalt gibt es nur wenige Daten. Eine kleine Pilotstudie eines 12-wöchigen Rehabilitationsprogramms, welches Kognitionstraining, körperliche Rehabilitation und funktionelle Rehabilitation beinhaltete, zeigte Hinweise auf Verbesserungen der Kognition [134]. Eine weitere Studie konnte zeigen, dass Kognitionstraining am Computer die kognitiven Leistungen verbessern kann [135], während eine andere Studie keinen Effekt von Kognitionstraining in Kombination mit körperlicher Rehabilitation fand [136].

Auch zur effektiven Behandlung von Beeinträchtigungen der mentalen Gesundheit nach ITS-Aufenthalten gibt es nur wenige und nicht eindeutige Daten. In einer RCT aus Großbritannien war ein intensives, sechswöchiges Physiotherapie-Programm

während und nach dem Krankenhausaufenthalt mit einer niedrigeren Prävalenz von Angststörungen drei Monate nach ITS-Entlassung assoziiert [137]. In einer anderen kleinen prospektiven Kohortenstudie aus Großbritannien zeigten Patient*innen, die nach Entlassung ein sechswöchiges Rehabilitationsprogramm mit Übungen und Fortbildungen durchliefen, eine signifikante Reduktion von Symptomen einer Depression und Angststörung [138]. Entgegen dieser beiden Studien fand eine RCT in zwei schottischen Krankenhäusern mit 240 Patient*innen keinen Vorteil einer intensivierten Rehabilitations-Intervention nach Entlassung von der ITS im Vergleich zur konventionellen Rehabilitation in Bezug auf die HrQoL, die Mobilität, die Handkraft und die Symptome einer Depression, einer Angststörung und einer PTBS bis zu 12 Monate nach Entlassung [139]. Die intensivierte Rehabilitation beinhaltete unter anderem individualisierte Rehabilitations-Ziele, Physiotherapie, Ergotherapie, Logopädie, Ernährungsberatung, psychologische Unterstützung, ein strukturiertes Entlassungsmanagement und das Angebot, die ITS später zu besuchen und mit einem/einer Intensivmediziner*in zu sprechen [139]. Ein anderer Ansatz ist die Verwendung von durch ITS-Personal und ggf. durch Verwandte geführten ITS-Tagebüchern. In einer pragmatischen RCT konnten ITS-Tagebücher, welche nach der Behandlung gemeinsam mit dem/der Patient*in durchgegangen wurden, die Symptome einer Angststörung und einer Depression reduzieren [140]. In einer anderen Vorher-Nachher-Studie aus Frankreich war die Verwendung von ITS-Tagebüchern mit keiner Reduktion der Symptome einer Depression, Angststörung oder PTBS drei Monate nach ITS-Entlassung, jedoch mit einer Reduktion von PTBS-Symptomen bei Patient*innen und Verwandten 12 Monate nach ITS-Entlassung assoziiert [141]. Die jüngste und bislang größte RCT zu ITS-Tagebüchern unter 657 Patient*innen in 35 französischen ITS zeigte keine Veränderung der Symptome einer PTBS, Depression und Angststörung nach drei Monaten [142]. Obwohl bisherige Studien keinen eindeutigen Vorteil von ITS-Tagebüchern belegen konnten, wird ihr Einsatz von Patient*innen als positiv wahrgenommen, wie in einem systematischen Review mit qualitativer Datensynthese gezeigt wurde [143]. In einer anderen RCT mit 126 Patient*innen wurde die Verwendung eines sechswöchigen Selbsthilfe-Manuals untersucht [144]. Während die Autor*innen keinen Effekt des Selbsthilfe-Manuals auf die Symptome von Depressionen und Angststörungen nach acht Wochen und sechs Monaten fanden, zeigte sich eine Reduktion von PTBS-Symptomen nach acht Wochen und eine Verbesserung physischer Funktionen [144].

Eine kürzlich erschienene S2e-Leitlinie zur multimodalen Rehabilitation von PICS-Patient*innen artikuliert vier starke Empfehlungen: Erstens, die individualisierte Frühmobilisation; zweitens, die nicht-pharmakologische Delir-Prophylaxe, welche unter anderem die Mobilisation, re-orientierende Maßnahmen und die Interaktion mit Familienmitgliedern beinhaltet; drittens, die Verwendung von ITS-Tagebüchern; und viertens, die Bearbeitung der ITS-Tagebücher nach Entlassung [145]. Die übrigen 12 Empfehlungen bzw. Therapieoptionen erreichten lediglich niedrigere Empfehlungsgrade, was die Notwendigkeit der PICS-Prävention und den Bedarf an Studien zu effektiven Behandlungsstrategien von PICS unterstreicht.

3.4. Stärken und Limitationen

Die in dieser Habilitationsschrift zusammengefassten Originalarbeiten unterliegen zahlreichen Limitationen, von denen einige hier Erwähnung finden sollten. Bei *Originalarbeit 1* und *Originalarbeit 2* handelt es sich um sekundäre Analysen der ERIC-Studie, welche in *Originalarbeit 6* publiziert wurde. Die ERIC-Studie ist eine prospektive, cluster-randomisierte kontrollierte Studie mit hochwertigem Studiendesign und einer großen, repräsentativen Kohorte von chirurgischen und internistischen ITS-Patient*innen. Von mehr als drei Vierteln der Studienteilnehmer*innen, die acht Monate nach Entlassung überlebten, konnten Follow-Up-Daten erhoben werden. Diese Rate ist im Vergleich zu anderen Studien bei Post-ITS-Überlebenden hoch [146]. Dennoch nahmen die Studienzentren freiwillig an der ERIC-Studie teil, sodass möglicherweise nur besonders motivierte Zentren, die bereits vor der Studie viel Wert auf ihre Behandlungsqualität gelegt hatten, eingeschlossen wurden. Zudem waren alle Zentren in der Metropolregion Berlin und Brandenburg und ein großer Anteil der Studienteilnehmer*innen wurde in den universitären Zentren rekrutiert. Eine Übertragbarkeit der Ergebnisse auf andere Krankenhäuser, insbesondere in ländlichen Regionen in Deutschland, ist somit unsicher. Zudem könnte in *Originalarbeit 1* und *Originalarbeit 2* eine Überlebenden-Verzerrung vorliegen, da Patient*innen, die nach ITS-Entlassung verstarben, nicht mehr am Follow-Up teilnehmen konnten. Auch könnte eine Selektions-Verzerrung vorliegen, da die Patient*innen, die ein Follow-Up ablehnten, möglicherweise eine schlechtere HrQoL aufwiesen als die Patient*innen, die am Follow-Up teilnahmen. Die ERIC-Studie wurde nicht konzipiert, um die Fragestellungen von *Originalarbeit 1* und

Originalarbeit 2 zu beantworten. Diese Sekundäranalysen sind somit lediglich explorativ.

Zu den Stärken von *Originalarbeit 5* zählt der internationale und multizentrische Charakter der Studie. Jedoch wurde die Studie nicht als prospektive RCT, sondern als Vorher-Nachher-Studie mit drei Prävalenzerhebungen konzipiert. Dieses Studiendesign ist nicht in der Lage, Kausalitäten nachzuweisen. Der Zunahme der Rate an dokumentierten Delir-, Sedierungstiefe- und Schmerzlevel-Assessments könnte ein zeitlicher Trend zugrunde liegen, der unabhängig von dem Schulungsprogramm ist. Eine wichtige Limitation beider *Originalarbeiten 5* und *6* ist eine mögliche Verzerrung der Ergebnisse durch den Hawthorne-Effekt. Dieser Effekt beschreibt eine Verhaltensänderung von Studienteilnehmenden durch die Tatsache, dass sie im Rahmen der Studie unter verstärkter Beobachtung stehen [147]. Übertragen auf die vorliegenden Arbeiten bedeutet dies, dass allein durch die verstärkte Aufmerksamkeit und die Erfassung des Delir-, Sedierungs- und Analgesie-Managements in *Originalarbeit 5* und die stärkere Aufmerksamkeit und die Erfassung der QI-Adhärenz in *Originalarbeit 6* eine Verbesserung der Versorgung eingetreten sein könnte. Der Hawthorne-Effekt kann sowohl die Kontrollgruppe als auch die Interventionsgruppe betreffen [147] und tritt häufig bei Studien zur Qualitätsverbesserung auf [148].

Bei *Originalarbeit 3* handelt es sich, anders als bei den anderen Arbeiten, um eine retrospektive Analyse von Routinedaten des Instituts für das Entgeltsystem im Krankenhaus. Diese Routinedaten besitzen von Natur aus eine gewisse Unschärfe und lassen keine Rückschlüsse auf individuelle Patientenfälle zu. Zudem lässt die durchgeführte Analyse der vorliegenden ICD-10-Codierungen nur eingeschränkt Rückschlüsse auf die Häufigkeit bestimmter Erkrankungen zu, da für eine Erkrankung häufig mehrere, sich teilweise überschneidende ICD-10-Codierungen existieren. Bei der *Originalarbeit 4* handelt es sich um eine systematische Literaturübersicht. Zu erwähnen ist der hohe methodische Standard der Studie mit einer Registrierung des Scoping Reviews [149], mit der Publikation des Protokolls im Peer-Review-Verfahren in *BMJ Open* [150], mit dem Peer-Review der Suchstrategie nach den *PRESS*-Leitlinien [151], mit der für Scoping-Reviews nicht erforderlichen kritischen Bewertung der eingeschlossenen Artikel und mit dem für Scoping Reviews hohen Maß der Evidenzsynthese, u.a. geleitet durch die *ERIC*-Taxonomie für

Implementierungsstrategien [152]. Limitiert werden die Ergebnisse der Studie durch einen fehlenden Konsensus bei der Definition von patientenrelevanten Outcomes und bei der Definition von Langzeit-Outcomes in der Literatur. In der Studie wurden deshalb eher breite, inklusive Definitionen gewählt. Bei *Originalarbeit 7* handelt es sich um eine Netzwerkanalyse bibliometrischer Daten bereits publizierter PICS-Artikel. Zu wichtigen Limitationen dieser Arbeit zählen, dass lediglich die Datenbank Web of Science durchsucht wurde und nur explizit nach Artikeln, welche die Terminologie PICS verwendeten, gesucht wurde.

3.5. Ausblick

Die in dieser Habilitationsschrift vorgestellten Arbeiten betreffen drei Schwerpunkte zukünftiger PICS-Forschung:

1. In der PICS-Diagnostik besteht der große Bedarf an weiteren Arbeiten, die geeignete Messinstrumente bei Überlebenden kritischer Erkrankung validieren. Solche Studien sollten zu Instrumenten in jeder PICS-Domäne durchgeführt werden. Bei diesen Validierungsstudien ist es wichtig, dass verschiedene Messeigenschaften eines Instruments untersucht werden; diese sind (englisch) *„internal consistency“*, *„reliability“*, *„measurement error“*, *„content validity“*, *„structural validity“*, *“hypothesis testing”*, *“cross-cultural validity”*, *“criterion validity”*, und *“responsiveness”* [153]. Diese Studien sollten sich auch an konsentierten Reporting-Leitlinien und Checklisten der COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)-Initiative orientieren [153-156]. Durch Studien in diesem Bereich ließe sich beispielsweise herausfinden, welche Messinstrumente bei Überlebenden kritischer Erkrankung geringe Boden- und Deckeneffekte aufweisen und die Veränderungen des Gesundheitsstatus adäquat abbilden. Ungeklärt sind auch die optimalen Zeitpunkte, an denen Patient*innen auf PICS-bezogene Beeinträchtigungen untersucht werden sollten. In dem Konsens-Artikel der amerikanischen Society of Critical Care Medicine werden Erhebungen bei ITS-Aufnahme und Krankenhaus-Entlassung empfohlen, gefolgt von einem PICS-Assessment bei Risikopatient*innen zwei bis vier Wochen nach Entlassung [112]. Ein Konsensus-Statement unserer Arbeitsgruppe schlägt hingegen ein Screening nach drei Monaten vor, welches auch beim Hausarzt durchgeführt werden kann, gefolgt von einer ausführlichen

Untersuchung auffälliger Patient*innen in spezialisierten PICS-Ambulanzen nach sechs Monaten [114]. Diese Empfehlungen stützen sich jedoch auf Expertenmeinungen und müssen mit Studien unterlegt werden.

2. Vorherige Studien konnten Risikofaktoren für PICS-bezogene Beeinträchtigungen identifizieren, wie beispielsweise die Beziehung zwischen einem Delir während der ITS-Behandlung und langfristigen kognitiven Defiziten [157]. Es fehlen bislang jedoch Studien, die zeigen konnten, dass Interventionen, die PICS-Risikofaktoren auf der ITS verringern, auch zu einer Reduktion von PICS-bezogenen Beeinträchtigungen führen. Auch die Studien in *Originalarbeit 5* und *Originalarbeit 6* dieser Habilitation konnten zwar Verbesserungen der akuten intensivmedizinischen Versorgung zeigen; ob dies jedoch tatsächlich Auswirkungen auf die Prävalenz von PICS-bezogenen Beeinträchtigungen hat, muss noch gezeigt werden. So konnte beispielweise die Umsetzung des ABCDE-Bundles die Wahrscheinlichkeit eines Delirs verringern und die Wahrscheinlichkeit für eine Mobilisation aus dem Bett steigern [129], allerdings konnte eine Arbeit aus Japan keine Beziehung zwischen der Umsetzung des ABCDEF-Bundles und funktionellen Outcomes nach sechs Monaten feststellen [158]. Es sind größere Studien mit hochwertigem Studiendesign notwendig, die einen Bezug zwischen der Reduktion von PICS-Risikofaktoren und der Reduktion von PICS-bezogenen Beeinträchtigungen herstellen.

3. Zukünftige Arbeiten sollten effektive Strategien zur Behandlung eines bereits manifesten PICS entwickeln und evaluieren. Diese Forschung kann durch Post-ITS-Ambulanzen an Universitätskliniken erleichtert werden, in die Patient*innen nach ihrer ITS-Behandlung als Teil der Routineversorgung einbestellt werden. Ein Cochrane-Review von 2018 fand lediglich fünf Studien, die den Effekt einer solchen Post-ITS-Ambulanz auf PICS-bezogene Beeinträchtigungen untersuchten [159]. Die Autor*innen fanden damit zu wenig Evidenz für ein abschließendes Urteil über den Effekt von Post-ITS-Ambulanzen [159]. Ein großer Vorteil solcher universitärer Post-ITS-Ambulanzen ist jedoch die enge Anbindung an die Intensivmedizin und eine Routine in der Durchführung von klinischen Studien. Ein Beispiel ist das das ICU Recovery Center an der Vanderbilt University in den USA [160]. Im Zuge der in *Originalarbeit 6* durchgeführten ERIC-Studie entstand auch in unserer Klinik eine PICS-Ambulanz, in der Post-ITS-Patient*innen drei Monate nach Entlassung eingeladen werden. In dieser Ambulanz sind weitere Interventionsstudien zur PICS-Diagnostik und Behandlung geplant.

4. Zusammenfassung

Überlebende kritischer Erkrankung zeigen häufig auch Jahre nach Entlassung von der Intensivstation (ITS) funktionelle Beeinträchtigungen. Diese Beeinträchtigungen betreffen die kognitiven Funktionen, die mentale Gesundheit und die körperlichen Funktionen. Sie werden als Post-Intensive Care Syndrom (PICS) zusammengefasst und beeinträchtigen die gesundheitsbezogene Lebensqualität.

Der erste Teil dieser Habilitationsschrift beschäftigt sich mit der Detektion von Patient*innen mit PICS. Es wurde zunächst gezeigt, dass sich zwei kurze Items zur Einschätzung der subjektiven mentalen und körperlichen Gesundheit eignen, um die gesundheitsbezogene Lebensqualität von ITS-Überlebenden einzuschätzen. Durch die Kürze der Items können diese auch sehr gut im ambulanten und hausärztlichen Bereich eingesetzt werden. Diese Items können auch genutzt werden, um eine Veränderung der subjektiven Gesundheit im Vergleich zum Status vor der ITS-Aufnahme festzustellen. Patient*innen mit PICS lassen sich nicht nur durch individuelle Untersuchungen, sondern auch anhand von Routinedaten identifizieren. Aus Routinedaten der Krankenhäuser können beispielsweise Patient*innen mit einer langfristigen Abhängigkeit vom Respirator identifiziert und charakterisiert werden.

Der zweite Teil dieser Habilitation beschäftigt sich mit Maßnahmen, um die Qualität der ITS-Behandlung zu steigern und damit Risikofaktoren für die Entstehung eines PICS zu reduzieren. Care-Bundles auf der ITS können die Behandlungsqualität steigern, jedoch gibt es noch keine ausreichende Evidenz eines Effekts auf funktionelle Langzeit-Outcomes. Darüber hinaus wurde gezeigt, dass ein strukturiertes Schulungsprogramm das Management von Delir, Sedierung und Analgesie auf der ITS verbessern kann. Neben strukturierten Schulungen kann auch eine komplexe telemedizinische Intervention in einem Netzwerk von ITS die Behandlungsqualität verbessern, gemessen an der Adhärenz zu evidenzbasierten Qualitätsindikatoren, die z.B. Weaning und Frühmobilisation betreffen. Zuletzt offenbarte eine systematische Netzwerkanalyse der PICS-Literatur, dass es zwar eine zunehmende Zahl an Studien zu PICS gibt, diese jedoch selten die Themen PICS-Prävention und PICS-Behandlung betreffen. Hier ergibt sich ein großer zukünftiger Forschungsbedarf, um PICS nicht nur zu erkennen, sondern auch effektiv zu verhindern und zu behandeln.

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7. Erklärung

§ 4 Abs. 3 (l) der HabOMed der Charité

Hiermit erkläre ich, dass

- weder früher noch gleichzeitig ein Habilitationsverfahren durchgeführt oder angemeldet wurde,
- die vorgelegte Habilitationsschrift ohne fremde Hilfe verfasst, die beschriebenen Ergebnisse selbst gewonnen sowie die verwendeten Hilfsmittel, die Zusammenarbeit mit anderen Wissenschaftlern/Wissenschaftlerinnen und mit technischen Hilfskräften sowie die verwendete Literatur vollständig in der Habilitationsschrift angegeben wurden,
- mir die geltende Habilitationsordnung bekannt ist.

Ich erkläre ferner, dass mir die Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis bekannt ist und ich mich zur Einhaltung dieser Satzung verpflichte.

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