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ABSTRACT

Purpose The Mid-German Sepsis Cohort (MSC) aims to investigate mid-term and long-term functional disabilities in sepsis survivors from intensive care unit (ICU) discharge until 1 year after. Secondary, post-acute mortality and morbidity, health-related quality of life and healthcare utilisation will be investigated.

Participants The MSC comprises adult (aged ≥18 years) patients who were treated for (severe) sepsis or septic shock on ICU. The participants were recruited between 15 April 2016 and 30 November 2018 from five German centres. Three thousand two hundred and ten patients with sepsis were identified, of which 1968 survived their ICU stay and were eligible for enrolment in the follow-up cohort. Informed consent for follow-up assessment was provided by 907 patients (46.1% of eligible patients).

Findings to date The recruitment of the participants for follow-up assessments and the baseline data collection is completed. Incidence of sepsis was 116.7 patients per 1000 ICU patients. In this cohort profile, we provide an overview of the demographics and the clinical characteristics of both the overall sepsis cohort and the ICU survivors who provided informed consent for follow-up assessment (907 out of 1968 ICU survivors (46.1%)).

Future plans The follow-ups are conducted 3, 6 and 12 months after ICU discharge. Another yearly follow-up up to 5 years after ICU discharge is pursued. Several cooperation and satellite projects were initiated. This prospective cohort offers a unique resource for research on long-term sequelae of sepsis survivors.

Trial registration number German Clinical Trials Registry (DRKS00010050).

Strengths and limitations of this study

- The Mid-German Sepsis Cohort (MSC) is one of the largest prospective sepsis cohorts to date and is special due to the wide spectrum of morbidities and functional outcomes assessed.
- Consecutive enrolment of all adult patients with sepsis was realised by daily screening of all intensive care unit (ICU) patients by trained study nurses or physicians over the study period in five study centres.
- Comprehensive follow-up assessments are conducted 3, 6 and 12 months after ICU discharge.
- A potential selection bias towards younger and healthier participants consenting in the follow-up cannot be ruled out.
- Three of five participating sites were academic centres, which may account for the inclusion of patients with a higher severity of the disease.

INTRODUCTION

Sepsis, defined as a dysregulated host response to infection leading to life-threatening organ dysfunction, is a medical emergency which requires rapid and adequate treatment.[1] In 2017, an estimated 48.9 million sepsis cases were recorded worldwide, of which approximately 37.9 million patients survived the acute care hospitalisation.[2] However, sepsis is not overcome when patients are discharged from the hospital. In addition to increased late mortality, a majority of sepsis survivors suffer from life-changing long-term consequences.[3] The acute disease can affect every organ system and pathway by mechanisms which are insufficiently understood, including inflammation, ischaemia and ischaemia reperfusion. Moreover, long-term consequences are exacerbated by use of invasive measures, drugs and prolonged immobilisation. Survivorship is associated with immunosuppression,[4] inflammation-associated encephalopathy,[5] damage to muscles and nerves (critical illness polyneuropathy and polymyopathy) acquired on intensive care units (ICUs),[6] as well as anxiety and depression.[7] Many survivors suffer from a co-occurrence of symptoms.[8]

Given this considerable health burden, the WHO emphasised the improvement of sepsis aftercare as a major priority in a recent resolution.[9] However, existing research on sepsis survivorship is limited due to variable inclusion/exclusion criteria, outcome measures and timing of outcome assessments as well as analyses of small or highly selected patient populations with a focus on single domains.[3] Thus, it is difficult to integrate and generalise the existing evidence. We need to know more about the incidence, extent, progression and co-occurrence of long-term consequences after sepsis in order to identify vulnerable patient groups and draw implications for appropriate aftercare and rehabilitation.

The Mid-German Sepsis Cohort (MSC) was set up to assess long-term morbidity after sepsis by a comprehensive follow-up of 3000 consecutive patients with sepsis recruited from ICUs in five participating hospitals in Germany. The primary outcome is functional disability as assessed by (instrumental) activities of daily living from ICU discharge to 1 year after. Secondary outcomes comprise long-term mortality and morbidity, health-related quality of life and healthcare utilisation. A study protocol has been previously published.[10] This cohort profile reports on the baseline characteristics of the recruited patients during their (index) ICU/hospital stay.

COHORT DESCRIPTION

Recruitment

The MSC is a prospective observational study, for which patient recruitment took place between 15 April 2016 and 30 November 2018 in the ICUs of five German hospitals. Per protocol, an additional ICU in the acute care hospital and rehabilitation centre Kreischa was planned for recruitment, but withdrew their participation prior to study beginning. Basic description of the participating centres is provided in online supplemental table 1. All ICU patients treated in the participating centres were screened daily for eligibility. Patients were eligible if they were aged ≥18 years (at ICU discharge), were diagnosed with (severe) sepsis or septic shock and had no prior enrolment in the MSC. (Severe) sepsis is defined as clinically suspected or microbiologically proven infection and presence of at least one organ dysfunction due to infection. Septic shock is defined as persistent infection-related hypotension (systolic arterial blood pressure ≤90 mm Hg or mean arterial blood pressure ≤65 mm Hg for >1 hour, or need of vasopressor support to raise the blood pressure above these limits; online supplemental table 2). We applied the organ dysfunction and shock definitions of the German Sepsis Society valid between 2016 and 2018,[11] which are in accordance with the sepsis-1 criteria. Documentation of the study also included lactate levels and the Sequential (sepsis-related) Organ Failure Assessment (SOFA) score, so that the sepsis-3 criteria[1] could also be applied retrospectively. According to the institutional review boards (IRBs, including data protection/privacy aspects), informed consent was not necessary to obtain routinely documented patient data according to the federal hospital laws of Thuringia, Saxony and Saxony-Anhalt for our research purpose, but was required for follow-up investigations with patients and proxies. In order to obtain written informed consent for follow-up, patients or legal representatives were approached in the hospital. If neither patient nor legal representative was available, a family member or close relative was asked for permission to contact the patient after hospital discharge in order to obtain consent. In this case, consent was asked in the first follow-up assessment. Accordingly, all consecutive patients with sepsis who were treated in the ICU constitute the 'ICU sepsis sample', while all ICU survivors who gave written informed consent and have sufficient German language skills were included in the follow-up assessments and constitute the 'follow-up sepsis sample'. For the arrangement of the follow-up appointments, patients were contacted by phone (twice) or mail (once), that is, in sum up to three times for each appointment. If patients missed two subsequent follow-up assessments (no contact or denial), they were deemed 'lost to follow-up'.

Measurements and data collection

Before the start of patient screening, all centre representatives met in person and a consensus was reached on the data to be collected. After 12 months, a protocol amendment was submitted to and endorsed by IRBs to allow for a more detailed documentation regarding delirium. The documentation of hospital baseline data and follow-up interviews is performed via web-based electronic case report forms in the validated management software 'OpenClinica' by trained study nurses, physicians or experienced and trained medical students.

Hospital (baseline) data were documented in the centres at sepsis onset in the ICU, at ICU discharge and at hospital discharge. Sepsis onset was defined as time of ICU admission for patients admitted with sepsis or as the respective time point during the ICU stay. We assessed underlying infection focus, onset (hospital-acquired vs community-acquired)[12] and sepsis-related organ dysfunctions (online supplemental table 2). Furthermore, laboratory values (eg, lactate, creatinine, white cell count), diagnostic measures (eg, blood culture sampling), therapies (eg, mechanical ventilation, vasopressor therapy), documented pre-existing comorbidities according to the Charlson Comorbidity Index,[13] the maximum SOFA score, end-of-life decisions (do not resuscitate, withhold, withdraw therapy order), length of ICU/hospital stay and time/cause of death were taken from the electronic medical records. We also collected data on presence and length of delirium as identified by specific scores at use in the participating centres (positive Confusion Assessment Method for the ICU, Intensive Care Delirium Screening Checklist ≥4, Nursing Delirium Screening Scale ≥2) or clinical judgement of the treating physicians. If information on single comorbidities, organ dysfunctions, systemic inflammatory response syndrome criteria or infection

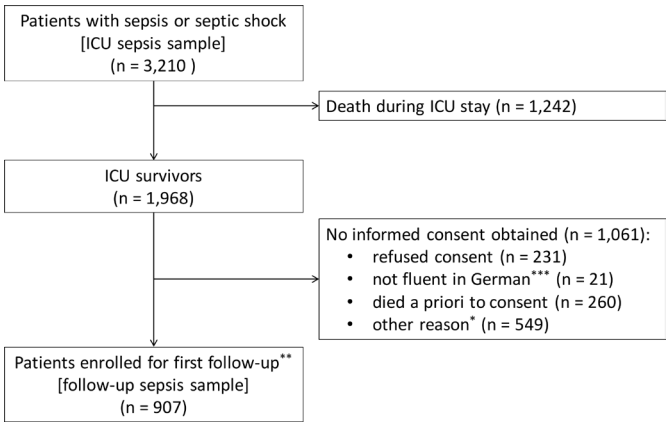

Figure 1 Patient flow of the follow-up sepsis sample of the Mid-German Sepsis Cohort. *Includes primarily patients who were discharged to hospice and thus were not further contacted; or patients who did not reply within 3 months after ICU discharge (for details on the standardised contact procedure, see text). **Includes the permission provided by a close relative or spouse to contact the patient for later consent (after hospital discharge). ***Given that follow-up interviews were performed in German. ICU, intensive care unit; n, number.

foci was not documented, they were considered as not pre-existing or present.

The follow-up interviews are scheduled 3, 6 and 12 months after ICU discharge and yearly thereafter. They are performed centrally by the Jena University Hospital study team. Follow-up assessment includes physical, functional, cognitive and mental health outcomes. Furthermore, sociodemographic information, dependence for chronic care, hospital readmissions, recurrence of sepsis or severe infections, use of rehabilitation or ambulant therapies, and a list of potential sepsis sequelae in patient-reported terms were assessed from the patients, patients' relatives or caregivers. Interviews are performed by telephone or face-to-face. Face-to-face interviews were offered to patients irrespective from which centre they were recruited. For further details, we refer to the study protocol.[10]

Characteristics of study participants

Patient flow from sepsis onset to follow-up enrolment is provided in figure 1. Three thousand two hundred and ten patients were identified with sepsis and constitute the ICU sepsis sample. Among the 1968 ICU survivors, 907 patients (46.1%) provided consent and constitute the follow-up sepsis sample. Baseline characteristics of the patients are provided in table 1. The consent rate was lower in patients with pre-existing dementia (21.5%), but did not differ in scale in patients with pre-existing severe liver disease (48.9%), congestive heart failure (46.1%) or patients discharged with mechanical ventilation from the hospital (44.1%).

A comparison of all ICU survivors who provided informed consent (follow-up sepsis sample) and those who did not is provided in online supplemental table 3. Patients in the follow-up sample were younger and less comorbid, including a lower proportion of patients who suffered from dementia. They less often received mechanical ventilation or therapeutic limitations (indicating a palliative care indication) and had a lower maximal SOFA score and a shorter hospital length of stay. Furthermore, there were differences in the distributions of the kind of organ dysfunctions and the infection foci between ICU survivors with and without informed consent. However, we did not observe differences in the frequency of septic shock.

FINDINGS TO DATE

Among 3210 ICU-treated patients with sepsis, ICU mortality was 38.7% and hospital mortality was 47.4%. In-hospital survival rates are provided in figure 2. Three out of five participating hospitals ensured a continuous daily patient screening over the study period. Based on these three study centres, which were academic centres, the overall incidence of sepsis was 116.7 patients per 1000 ICU patients. This is in the range of the incidence and mortality estimates from two previous prospective studies which assessed ICU-treated patients with sepsis using comparable sepsis criteria in Germany. In 2007, Engel *et al*[14] identified 415 patients (10.7%) with sepsis among 3877 ICU patients with a hospital mortality of 55.2%. In the nationwide point prevalence study INSEP,[15] 1503 patients (12.6%) with sepsis were identified out of 11 883 ICU patients with a hospital mortality of 40.4% in 2016. In a population-based analysis of ICU-treated and non-ICU-treated patients with sepsis based on hospital discharge data in Germany, the estimated hospital mortality was 41.7%.[16]

Of note, the ICU sepsis sample is one of the largest prospective sepsis cohorts to date. Most of the other prospective sepsis studies with clinical documentation were no cohort studies or did not realise a sequential patient screening/inclusion. Examples are a Brazilian point-prevalence study (794 patients with sepsis among 2632 ICU patients in 2014, hospital mortality of 55.7%),[17] the worldwide point-prevalence audit ICON (2973 patients with sepsis of 10 069 ICU patients, hospital mortality of 35.3%),[18] a Japanese prospective sepsis registry (624 sepsis cases among 14 417 ICU patients, hospital mortality 29.5%)[19] or the PROGRESS registry (14 543 patients with sepsis, hospital mortality of 49.7%).[20]

The follow-up sepsis sample of 907 patients is one of the largest. Previously, long-term follow-up studies included considerably fewer patients, for example, Marra *et al*[8] (259 patients with sepsis), Biason *et al*[21] (242 patients with sepsis) or Battle *et al*[22] (106 patients with sepsis).

Given the difficulty of obtaining written informed consent from severely ill patients, stressed relatives or from discharged survivors (see also online supplemental table 3), we believe that the proportion of included patients (46.1%) is still satisfying and compares favourably with those from other follow-up cohort studies of ICU patients.

Table 1 Demographic and clinical characteristics of patients with sepsis with respect to their enrolment in the intensive care unit (ICU) and follow-up sepsis sample

	ICU sepsis sample (n=3210)		Follow-up sepsis sample (n=907)	
Characteristic	**N**	**Distribution**	**N**	**Distribution**
Age, in years	3210	67 (58–77)	907	65 (56–74)
Male sex	3210	2054 (64.0%)	907	584 (64.4%)
Comorbidities* as documented in the patient file	3206		906	
Diabetes		957 (29.9%)		265 (29.2%)
Chronic pulmonary disease		535 (16.7%)		153 (16.9%)
Renal disease		458 (14.3%)		110 (12.1%)
Congestive heart failure and myocardial infarction		753 (23.5%)		191 (21.1%)
Cancer		837 (26.1%)		216 (23.8%)
Dementia		144 (4.5%)		20 (2.2%)
Cerebrovascular disease		256 (8.0%)		65 (7.2%)
Liver disease		362 (11.3%)		75 (8.3%)
HIV/AIDS		7 (0.2%)		5 (0.6%)
Other		534 (16.7%)		121 (13.4%)
Number of comorbidities		1 (1–2)		1 (1–2)
Distribution				
0		631 (19.7%)		212 (23.4%)
1		1114 (34.7%)		339 (37.4%)
2–4		1373 (42.8%)		333 (36.8%)
>4		88 (2.7%)		22 (2.4%)
Charlson Comorbidity Index		4 (3–6)		4 (2–6)
Admission type	3210		907	
Non-surgical emergency		2367 (73.7%)		647 (71.3%)
Surgical emergency		597 (18.6%)		185 (20.4%)
Elective surgery		246 (7.7%)		75 (8.3%)
Incidence of sepsis/septic shock, in patients per 1000 ICU patients†		116.7		
Origin of infection	3210		907	
Hospital-acquired		1754 (54.6%)		476 (52.5%)
Community-acquired		1456 (45.4%)		431 (47.5%)
Focus of infection	3209		906	
Known		2966 (92.4%)		843 (93.0%)
Among them:				
Pneumonia		1473 (49.7%)		379 (45.0%)
Other upper or lower respiratory tract		216 (7.3%)		59 (7.0%)
Intra-abdominal		577 (19.5%)		195 (23.1%)
Primary bacteraemia		533 (18.0%)		122 (14.5%)
Urogenital		439 (14.8%)		117 (13.9%)
Bones/soft tissue		280 (9.4%)		82 (9.7%)
Postoperative wound infection		135 (4.6%)		27 (3.2%)
Gastrointestinal		133 (4.5%)		28 (3.3%)
Thoracic (empyema/mediastinitis)		89 (3.0%)		36 (4.3%)
Cardiovascular		86 (2.9%)		26 (3.1%)
Device-related infection		79 (2.7%)		23 (2.7%)

Continued

Table 1 Continued

Characteristic	ICU sepsis sample (n=3210)		Follow-up sepsis sample (n=907)	
	N	Distribution	N	Distribution
Central nervous system		54 (1.8%)		13 (1.5%)
Other		5 (0.2%)		3 (0.4%)
Microbiological aetiology				
Blood culture sampling	3206		907	
Positive blood cultures		1603 (50.0%)		432 (47.6%)
Negative blood cultures		1470 (45.9%)		438 (48.3%)
No blood cultures performed		133 (4.1%)		37 (4.1%)
Cultures from other sterile compartments	3180		898	
Positive cultures		2246 (70.6%)		615 (68.5%)
Negative cultures		934 (29.4%)		283 (31.5%)
Type of microbiologically proven infection				
Pathogens detected	3184	2583 (81.1%)	899	713 (79.3%)
Among them:				
Bacterial pathogens		2477 (95.9%)		686 (96.2%)
Fungal pathogens		579 (22.4%)		125 (17.5%)
Viral pathogens		69 (2.7%)		14 (2.0%)
Presence of multiresistant pathogens	3178	624 (19.6%)	896	147 (16.4%)
Among them:				
Gram-positive bacteria		272 (43.6%)		63 (42.9%)
Gram-negative bacteria		379 (60.7%)		87 (59.2%)
Unknown		14 (2.2%)		5 (3.4%)
SIRS criteria met at sepsis onset*	3208		906	
Tachypnoea/hypocapnia/ventilation‡		2849 (88.8%)		788 (87.0%)
Tachycardia§		2540 (79.2%)		714 (78.8%)
Leucocytosis/leucopenia/>10% immature forms¶		2377 (74.1%)		681 (75.2%)
Hypothermia or hyperthermia**		2054 (64.0%)		553 (61.0%)
Number of SIRS criteria met		3 (3–4)		3 (2–4)
Distribution				
0		24 (0.7%)		13 (1.4%)
1		138 (4.3%)		34 (3.8%)
2		600 (18.7%)		182 (20.1%)
3		1302 (40.6%)		370 (40.8%)
4		1144 (35.7%)		307 (33.9%)
Organ dysfunction*‡‡	3210		907	
Arterial hypoxaemia		2395 (74.6%)		646 (71.2%)
Renal dysfunction		1923 (59.9%)		452 (49.8%)
Metabolic acidosis		1730 (53.9%)		424 (46.7%)
Acute encephalopathy		902 (28.1%)		209 (23.0%)
Thrombocytopenia		817 (25.5%)		198 (21.8%)
Septic shock		2509 (78.2%)		683 (75.3%)
Among them:				
Patients with septic shock with >2.0 mmol/L serum lactate at sepsis onset		1670 (66.6%)		420 (61.5%)

Continued

Table 1 Continued

Characteristic	ICU sepsis sample (n=3210) N	ICU sepsis sample (n=3210) Distribution	Follow-up sepsis sample (n=907) N	Follow-up sepsis sample (n=907) Distribution
Number of organ dysfunctions		3 (2–4)		3 (2–4)
Distribution				
0		0 (0.0%)		0 (0.0%)
1		292 (9.1%)		116 (12.8%)
2		702 (21.9%)		246 (27.1%)
>2		2216 (69.0%)		545 (60.1%)
Presence of delirium during ICU stay	3201	1062 (33.2%)	906	288 (31.8%)
Duration in respective patients, in days		4 (2–8)		4 (2–9)
Vasopressor therapy during ICU stay	3208	2738 (85.3%)	907	721 (79.5%)
Organ replacement or support therapy during ICU stay				
Mechanical ventilation	3205	2587 (80.7%)	905	627 (69.3%)
Among them:				
Controlled ventilation		1378 (53.3%)		340 (54.2%)
Duration in respective patients, in days		4 (2–11)		6 (2–16)
Assisted ventilation		1597 (61.7%)		327 (52.2%)
Duration in respective patients, in days		6 (3–15)		8 (2–21)
ECMO or other lung replacement therapy	3204	73 (2.3%)	906	17 (1.9%)
Duration in respective patients, in days		7 (5–9)		9 (6–14)
Renal replacement therapy	3200	1466 (45.8%)	901	273 (30.3%)
Other replacement therapy	3202	22 (0.7%)	905	5 (0.6%)
Maximal SOFA score during ICU stay	2911	15 (12–18)	815	13 (10–15)
Length of ICU stay, in days	3210	9 (4–21)	907	10 (4–26)
Length of hospital stay, in days	3210	25 (13–43)	907	34 (21–52)
ICU mortality				
Overall	3210	1242 (38.7%)		
In patients with septic shock††	2509	1056 (42.1%)		
In patients without septic shock††	632	166 (26.3%)		
Cause of death among ICU decedents	1242			
Sepsis as direct or indirect cause		1180 (95.0%)		
Other causes of death		62 (5.0%)		
Hospital mortality				
Overall	3210	1520 (47.4%)	907	61 (6.7%)
In patients with septic shock††	2509	1265 (50.4%)	683	46 (6.7%)
In patients without septic shock††	632	234 (37.0%)	198	15 (7.6%)
Cause of death among hospital decedents	1519		61	
Sepsis as direct or indirect cause		1400 (92.2%)		45 (73.8%)
Other causes of death		119 (7.8%)		16 (26.2%)
Limitation of life-sustaining therapy	3188	1170 (36.7%)	900	49 (5.4%)
Among them:				
DNR		838 (71.6%)		44 (89.8%)
Withhold		560 (47.9%)		13 (26.5%)
Withdraw		572 (48.9%)		2 (4.1%)
Tracheostomy at hospital discharge	1689	287 (17.0%)	845	129 (15.3%)

Continued

Table 1 Continued

Characteristic	ICU sepsis sample (n=3210)		Follow-up sepsis sample (n=907)	
	N	Distribution	N	Distribution
Ventilation at hospital discharge	1687	136 (8.1%)	845	60 (7.1%)
Dialysis at hospital discharge	1689	138 (8.2%)	845	74 (8.8%)
Discharge to	1681		839	
Home		831 (49.4%)		437 (52.1%)
Rehabilitation facility		398 (23.7%)		216 (25.7%)
Transfer to acute care hospital		309 (18.4%)		144 (17.2%)
Nursing home		108 (6.4%)		25 (3.0%)
Other		35 (2.1%)		17 (2.0%)

Absolute and relative frequencies or median with first and third quartile are provided (distribution). The number of patients in the respective sample (n) is indicated. For several characteristics, multiple answers per patient were possible. Note that numbers do not necessarily add up to the total number of patients due to missing/unknown values; number of patients with information in the respective item (N) is provided in a separate column. Relative frequencies are related to these numbers if not otherwise indicated.
*If individual items were not documented, they were considered as not existent. Patients with no documentation were excluded.
†Approximation based on information in terms of ICU patients per year provided by the three (academic) study centres that ensured a continuous screening of ICU patients over the study period.
‡Tachypnoea (≥20 breaths/min) and/or arterial partial pressure of carbon dioxide ≤4.3 kPa (32 mm Hg) and/or mechanical ventilation.
§≥90 beats/min.
¶Leucocytosis (leucocyte count ≥12 x 10^9 / L) or leucopenia (leucocyte count ≤4 x 10^9 / L) and/or >10% immature forms.
**Hypothermia (body temperature ≤36°C) or hyperthermia (body temperature ≥38°C).
††Missing information on the presence of a septic shock: in 69 patients of the ICU and in 26 patients of the follow-up sepsis sample.
‡‡Definitions of these organ dysfunctions are provided in online supplemental table 2.
DNR, do not resuscitate; ECMO, extracorporeal membrane oxygenation; ICU, Intensive Care Unit; SIRS, systemic inflammatory response syndrome; SOFA, Sequential Organ Failure Assessment.

The multicentre cohort study in Germany of ICU patients with acute respiratory distress syndrome (DACAPO trial) included 876 patients of 1900 eligible patients (46.1%) in the follow-up assessment.[23] Pandharipande *et al*[24] enrolled in the BRAIN-ICU Study 826 patients (medical or surgical ICU patients with respiratory failure, cardiogenic shock or septic shock) of 5210 eligible patients (15.9%) in the USA. Mitchell *et al*[25] enrolled 148 patients of 421 eligible general ICU patients (35.2%) in Australia to assess long-term cognitive impairment and delirium among survivors from critical illness.

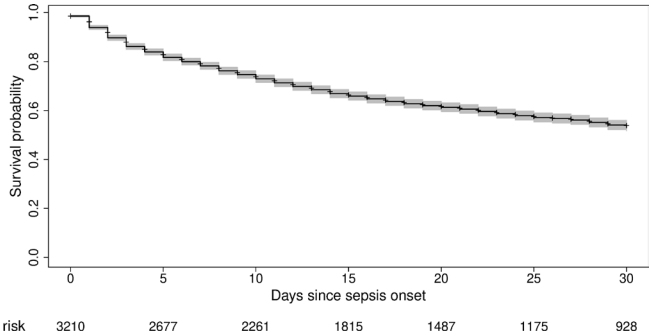

Figure 2 In-hospital survival since sepsis onset (in days) of patients in the ICU sepsis sample. The survival curve is censored at day 30. The number of participants at risk is given below the plot area. Right censoring is indicated by + and 95% confidence intervals are provided in grey. ICU, intensive care unit.

STRENGTHS AND LIMITATIONS

The MSC has several strengths, including the prospective study design with its focus on post-ICU assessment and measures to ensure consistent data quality. The latter comprises, for example, onsite training and monitoring in all participating centres, use of a good clinical practice conform internet-based database comprising an integrated audit trail and electronic plausibility checks, daily screening of all ICU patients by trained study nurses or physicians over the study period and the consecutive enrolment of all patients aged 18 years or older. Sepsis surveillance and follow-up in prospective cohorts is therefore considered advantageous compared with administrative data.[26] The MSC is also special due to the wide spectrum of morbidities assessed including cognitive dysfunction, post-traumatic stress symptoms, depression,

fatigue or pain (for details see the previously published protocol).[10] By this, we aim to gain important and valid insights into the (long-term) burden and dynamics of post-sepsis morbidity of ICU-treated patients with sepsis. However, the study also has several limitations. Three of five participating sites were academic centres, which may account for the inclusion of patients with a higher severity of the disease. These centres implemented a continuous screening over the 2.5-year study period and contributed data to the analysis of sepsis incidence among ICU-treated patients. The remaining two centres also realised a complete screening of ICU-treated patients but only for a shorter or a discontinuous period of time. Their patients were also eligible for follow-up, but their data were not included in the incidence estimation. Furthermore, our cohort is restricted to ICU patients from selected hospitals, and thereby does not capture information on the considerable proportion of patients with sepsis treated outside the ICU (46.2% in 2015 according to nationwide hospital discharge data)[16] or patients with sepsis in the emergency department. Changing ICU admission policies and capacities over time and in different regions/countries also limits the comparability and conclusion about the general population of ICU populations.[26] Moreover, there was a certain proportion of ICU survivors who we could not reach to obtain informed consent, which may have introduced a certain selection bias towards younger and healthier patients included in the follow-up sepsis sample. This may lead to an underestimation of long-term sequelae, which affect older and pre-morbid patients more frequently.[27] In addition, about 10% of eligible ICU survivors or their proxies refused consent. Obtaining consent for observational studies in critically ill patients and their proxies remains challenging. Nevertheless, a participation rate of about 46.1% is higher than in other cohorts.

COLLABORATIONS

The MSC is linked to the ICROS Study[28] which has a focus on deep phenotyping including clinical and laboratory tests, cardiovascular function, metabolome, lipidome, microbiome, mitochondrial oxygen metabolism, heart rate variability, body composition and immune status assessments. Both studies (MSC and ICROS)[10 28] use the same core documentation. However, the ICROS Study is a monocentric study that aims at including three cohorts: 130 patients with sepsis, 80 patients with cardiomyopathy without infection and 80 healthy individuals. The overlap of the studies enables analyses that include both studies. Furthermore, the MSC has already served to support several add-on projects such as a comparative validation of three screening instruments to assess symptoms of post-traumatic stress disorder after intensive care for sepsis.[29] Patients enrolled in the MSC were also invited to participate in another interview study on satisfaction with follow-up care and rehabilitation after sepsis, which forms part of the SEPFROK Study (Sepsis long-term impairments, risk factors, healthcare use and costs study; German Clinical Trials Registry number DRKS00016340). For details regarding the availability of data for potential new collaborators, see the data sharing section.

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Contributors CF-S, MK and DO contributed equally to this work. AS and KR designed the study and applied for funding. AS, KR, CSH, CF-S and DO drafted the clinical research forms. MBa, SBe, MBu, AM-H, SP, TS, PS and LW coordinated the conduction of the study and data acquisition at the participating study centres. HC, SF and SP were responsible for the project management of the study. CE was responsible for the data management in OpenClinica. AB and CG performed the monitoring of the study sites. HR, KT, CK, DO and CF-S performed follow-up interviews. MK performed the statistical analyses under the supervision of AS. AS, CSH, MK, DO, CF-S, SBo and KR interpreted the data. AS, CSH, MK, DO and CF-S drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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Data availability statement Data are available upon reasonable request. Data access to the final cleaned data set is provided to all project applicants (primarily within the MSC investigator group) along with written use and access rules of the CSCC which include a brief proposal including a sketch indicating the envisaged analysis project and an additional ethical or data protection vote depending on the type of project. To ensure confidentiality, data distributed to project applicants will be double pseudonymised and any directly identifying patient information will not be provided. Due to data economy and subsequently

data protection, only the variables required for the analysis project will be provided.

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