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Mid-German Sepsis Cohort (MSC): a prospective observational study of sepsis survivorship

Carolin Fleischmann-Struzek, Miriam Kesselmeier, Dominique Ouart, Christiane S. Hartog, Michael Bauer, Sven Bercker, Michael Bucher, Andreas Meier-Hellmann, Sirak Petros, Torsten Schreiber, Philipp Simon, Lorenz Weidhase, Sebastian Born, Anke Braune, Hicham Chkirni, Cornelia Eichhorn, Sandra Fiedler, Christin Gampe, Christian König, Stephanie Platzer, Heike Romeike, Kristin Töpfer, Konrad Reinhart, André Scherag

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).

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. In 2017, an estimated 48.9 million sepsis cases were recorded worldwide, of which approximately 37.9 million patients survived the acute care hospitalisation. 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. 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, inflammation-associated encephalopathy, damage to muscles and nerves (critical illness polyneuropathy and polymyopathy) acquired on intensive care units (ICUs), as well as anxiety and depression. Many survivors suffer from a co-occurrence of symptoms.
Given this considerable health burden, the WHO emphasised the improvement of sepsis aftercare as a major priority in a recent resolution. 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. 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 morality and morbidity, health-related quality of life and healthcare utilisation. A study protocol has been previously published. 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 prospecitive 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, 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 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) 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, 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...
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 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 sample of 907 patients is one of the largest. Previously, long-term follow-up studies included considerably fewer patients, for example, Marra et al (259 patients with sepsis), Biason et al21 (242 patients with sepsis) or Battle et al22 (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.
| Characteristic                                     | ICU sepsis sample (n=3210) | Follow-up sepsis sample (n=907) |
|---------------------------------------------------|-----------------------------|---------------------------------|
| Age, in years                                     | 3210                        | 907                             |
| Male sex                                          | 2054 (64.0%)                | 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                           | 1–2                         |                                 |
| 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                        |                             |                                 |
|                                                    |                             |                                 |
| Admission type                                    |                             |                                 |
| 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                               |                             |                                 |
| Hospital-acquired                                 | 1754 (54.6%)                | 476 (52.5%)                     |
| Community-acquired                                | 1456 (45.4%)                | 431 (47.5%)                     |
| Focus of infection                                |                             |                                 |
| 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
### Characteristics

| 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 (79.9%) | 686 (96.2%) |
| Fungal pathogens   | 579 (18.4%) | 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

| 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%) |
Table 1  Continued

| Characteristic                                      | ICU sepsis sample (n=3210) | Follow-up sepsis sample (n=907) |
|-----------------------------------------------------|-----------------------------|----------------------------------|
|                                                     | N                           | Distribution                      | N                           | Distribution                      |
| Number of organ dysfunctions                        | 3 (2–4)                     |                                  | 3 (2–4)                     |
| Distribution                                        | 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%)                     |
|                                                     | 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 | 73 (2.3%)                      | 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%)                     | 907                         | 61 (6.7%)                      |
| In patients with septic shock††                     | 2509                         | 1056 (42.1%)                     | 683                         | 46 (6.7%)                      |
| In patients without septic shock††                  | 632                          | 166 (26.3%)                      | 198                         | 15 (7.6%)                      |
| 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                         | 1400 (92.2%)                     | 45                           | 73.8%                         |
| 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%)                    |
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. Pandharipande et al enrolled 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 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.

**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 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. 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).\textsuperscript{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)\textsuperscript{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.\textsuperscript{20} 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.\textsuperscript{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\textsuperscript{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)\textsuperscript{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 cardiovascular failure 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.\textsuperscript{20} 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.

**Author affiliations**

1Integrated Research and Treatment Center, Center for Sepsis Control and Care (CSCC), Jena University Hospital, Jena, Germany
2Research Group Clinical Epidemiology, CSCC, Jena University Hospital, Jena, Germany
3Institute of Medical Statistics, Computer and Data Sciences, Jena University Hospital, Jena, Germany
4Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany
5Department of Anesthesiology and Intensive Care Medicine, Charité - Universitätsmedizin Berlin, Berlin, Germany
6Klinik Bavaria Kreischa, Kreischa, Germany
7Department of Anaesthesiology and Intensive Care Medicine, University Hospital Leipzig, Leipzig, Germany
8Department of Anaesthesiology and Critical Care Medicine, Halle-Wittenberg University, Halle, Germany
9Helios-Kliniken, Berlin, Berlin, Germany
10Medical Intensive Care Unit, University Hospital Leipzig, Leipzig, Germany
11Zentrum für Anästhesie, Intensivmedizin und Notfallmedizin, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
12Center for Clinical Studies, Jena University Hospital, Jena, Germany

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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 and CF-S drafted the clinical research forms. MBA, SBe, MBu, AM-H, SP, TS, PS and LW coordinated the conduct 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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**Disclaimer**

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**Competing interests**

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**Patient consent for publication**

Not required.

**Ethics approval**

The study was approved by four local/federal responsible institutional ethics committees (lead: IBZ of the Jena University Hospital, no. 4669-01/16) and by the respective federal data protection commissioners.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**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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**ORCID iDs**
Carolin Fleischmann-Struzek http://orcid.org/0000-0002-1104-3191
Miriam Kesselmeier http://orcid.org/0000-0001-6462-2579
Christiane S. Hartog http://orcid.org/0000-0003-1098-9775
Sirak Petros http://orcid.org/0000-0002-2345-758X
Philip Simon http://orcid.org/0000-0003-2686-3254
Sebastian Born http://orcid.org/0000-0001-5803-7963
Christian König http://orcid.org/0000-0001-7671-231X
André Scherag http://orcid.org/0000-0002-9406-4704

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