Identification of cardiovascular and molecular prognostic factors for the medium-term and long-term outcomes of sepsis (ICROS): protocol for a prospective monocentric cohort study

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ABSTRACT

Introduction Sepsis is one of the most prevalent life-threatening conditions in the intensive care unit. Patients suffer from impaired organ function, reduced physical functional capacity and decreased quality of life even after surviving sepsis. The identification of prognostic factors for the medium-term and long-term outcomes of this condition is necessary to develop personalised theragnostic approaches. Sepsis can cause cardiac impairment. The impact of this septic cardiomyopathy on patient’s long-term outcome remains unclear. This study aims to evaluate cardiovascular risk factors, particularly the occurrence of septic cardiomyopathy, regarding their suitability as prognostic factors for the short-term and long-term outcomes of septic patients. Additionally, the study seeks to validate preclinical pathophysiological findings of septic cardiomyopathy in the clinical setting.

Methods and analysis In this prospective monocentric cohort study, patients will be clinically assessed during the acute and postacute phase of sepsis and two follow-ups after 6 and 12 months. To determine the effect of septic cardiomyopathy and concomitant cellular and molecular changes on patient mortality and morbidity, a comprehensive cardiovascular and molecular deep phenotyping of patients will be performed. This includes an echocardiographic and electrocardiographic assessment, and the evaluation of heart rate variability, body composition, mitochondrial oxygen metabolism, macrocirculation and microcirculation, and endothelial barrier function. These analyses are complemented by routine immunological, haematological and biochemical laboratory tests and analyses of the serum metabolome and lipidome, microbiome and epigenetic modifications of immune cells. The reversibility of patients’ organ dysfunction, their quality of life and physical functional capacity will be investigated in the follow-ups. Patients with cardiomyopathy without infection and healthy subjects will serve as control groups.

Ethics and dissemination Approval was obtained from the Ethics Committee of the Friedrich Schiller University Jena (5276-09/17). The results will be published in peer-reviewed journals and presented at appropriate conferences.

Strengths and limitations of this study

► Identification of cardiovascular and molecular prognostic factors for the medium-term and long-term outcomes of sepsis is a prospective study assessing the impact of septic cardiomyopathy on both the short-term and long-term morbidity and mortality of sepsis.

► The study combines an extensive clinical characterisation of patients—during the acute, postacute and late phase of sepsis—with an analysis of concomitant molecular changes in the metabolome, lipidome and microbiome.

► In a translational approach, the study seeks to validate preclinically identified pathophysiological findings of septic cardiomyopathy in the clinical setting.

► This study is exploratory, of moderate sample size and monocentric, and thus centre-specific or regional differences may limit generalisability.

Trial registration numbers DRKS00013347; NCT03620409.

INTRODUCTION

Background

In sepsis, an infection elicits a life-threatening host response resulting in organ failure.1 To this day, sepsis remains one of the leading causes of death worldwide.2 Even after surviving sepsis, patients’ morbidity and mortality are increased3 and quality of life reduced,4 a condition summarised as post-intensive care syndrome.5

Failure of the cardiovascular system is common in sepsis and a defining characteristic of septic shock. Aside from impairments of the macrovasculature and microvasculature, sepsis can also affect the heart directly. In the absence of a clear definition of septic
cardiomyopathy, a new left ventricular systolic dysfunction is oftentimes employed as a defining characteristic for this condition in clinical studies. Various studies have identified left ventricular systolic dysfunction or decreased heart rate variability as a predictor of decreased survival. However, other studies find no difference in long-term survival or even decreased mortality in septic patients with decreased systolic left ventricular function. These conflicting results are likely due to heterogeneity in study design, especially in varying definitions of septic cardiomyopathy. Furthermore, previous studies of septic cardiomyopathy assessed different parameters aside from left ventricular systolic function such as right ventricular systolic function, left ventricular diastolic function or longitudinal strain, impeding the comparison of results. Therefore, a generally accepted definition of this relevant condition is much needed.

Similarly to its influence on patient outcomes, the pathophysiology of septic cardiomyopathy is not entirely understood. Mitochondrial dysfunction has been postulated as an important pathophysiological mechanism in this condition. However, it is not clear whether this mitochondrial dysfunction is a protective (hibernation) or deleterious metabolic adaptation in sepsis. A mismatch of oxygen demand and delivery, a hallmark of (septic) shock, can be the result of an insufficient supply, an increased consumption or dysfunctional mitochondrial oxygen utilisation. Assessing and distinguishing between these three factors remain a clinical challenge. Mik et al devised a method to non-invasively measure mitochondrial oxygen tension and mitochondrial oxygen consumption using the protoporphyrin IX (PpIX) triplet state lifetime technique. This method could yield additional information for the management of oxygen therapy in critically ill patients as preclinical work by Harms et al suggests. In a pilot study in healthy adults, we found the method to be re-test reliable and free of side effects while also establishing the new parameter mitochondrial oxygen delivery for this method.

Aside from altered mitochondrial metabolism, there is evidence of a systemic metabolic dysfunction in sepsis. Thus far, genomics, transcriptomics and proteomics failed to identify prognostic biomarkers for sepsis relevant to clinical practice. Many metabolic products, especially bioactive lipids, cannot be identified by these high-throughput methods. Metabolomic and lipodomic approaches analyse endogenous metabolites and could, therefore, offer new pathophysiological insight and facilitate the identification of theragnostic targets. The entirety of bacterial colonisation of the body—the microbiome—has been the subject of recent research. First studies indicate that a disrupted microbiome is associated with adverse outcomes in patients with sepsis; however, the underlying mechanisms require further investigation.

Control of infection and supportive intensive care therapy are the existing treatment options for sepsis, of which an important element is fluid resuscitation. However, quantifying the patients' volume status remains challenging due to the absence of reliable surrogate parameters. Bioelectrical impedance analysis (BIA) measures body composition (ie, hydration status, adipose tissue and muscle mass) using an electric alternating current, also yielding resistance, reactance values (bioelectrical impedance vector analysis) and the corresponding phase angle. A study in critically ill patients showed an association between resistance and increased mortality. In patients with sepsis, a pilot study was able to demonstrate the influence of BIA variables on a patient's risk of requiring ventilation.

In conclusion, the clinical diagnosis and management of septic cardiomyopathy remains challenging. A clear and generally accepted definition is needed. Concepts for the diagnostic stratification of the very heterogeneous patient collective with the possibility of an individualised therapy do not exist in clinical practice. The identification of specific and sensitive clinical characteristics or theragnostic biomarkers or their combination is required to pursue novel therapeutic avenues in sepsis.

**Aim**

The overall objective of this prospective monocentric cohort study is the ‘identification of cardiovascular and molecular prognostic factors for the medium-term and long-term outcomes of sepsis’ (ICROS). The study combines an extensive clinical characterisation of patients—during the acute and late phase of sepsis—with an analysis of concomitant molecular changes to identify potential biomarkers or theragnostic target structures in sepsis. The primary endpoint is the assessment of the impact of septic cardiomyopathy on the 6-month mortality. Further study aims include assessing the suitability of cardiovascular risk factors to predict the short-term and long-term survival of patients with sepsis, the reversibility of organ dysfunctions, the quality of life and the degree of disability after surviving sepsis, and the validity of preclinically identified pathophysiological findings of septic cardiomyopathy in the clinical setting.

**METHODS AND ANALYSIS**

**Study design**

This study is a prospective monocentric cohort study of patients with sepsis. Patient recruitment commenced in April 2018 aiming to include 150 patients. The last follow-up is planned for June 2021.

**Study setting**

Patients will be recruited from the intensive care units (ICUs) of the Jena University Hospital, Jena, Germany. Follow-up and control group assessments will take place in outpatient facilities of the Department of Anaesthesiology and Intensive Care Medicine of Jena University Hospital.
Study population
The study population consists of 3 groups:
1. Patients with sepsis or septic shock according to sepsis-3 criteria.
2. Patients with cardiomyopathy without infection divided into two subgroups.
   a. Conservatively treated.
   b. Receiving a left-ventricular assist device (LVAD).
3. Healthy individuals.

The control groups (groups 2 and 3) are not relevant to the primary or secondary endpoints of this longitudinal cohort study. They rather serve to control for potential molecular changes found in patients with sepsis. We included a control group with cardiac dysfunction but no infection (group 2) to account for potential molecular changes unspecific to septic cardiomyopathy that might be related to changes in organ perfusion secondary to low cardiac output (subgroup 2a). In LVAD recipients, severely low cardiac output is ameliorated and the reduced organ perfusion might be reversible. We included LVAD recipients (subgroup 2b) to better differentiate between sepsis-related and non-sepsis-related metabolic changes. This exploratory approach shall help to develop new hypotheses for future prospective randomised clinical studies.

Sample size
The study aims to enrol 150 patients with sepsis. Up to 80 patients with cardiomyopathy without infection and 80 healthy individuals will serve as control groups.

Patient inclusion and exclusion criteria
Adult patients meeting the sepsis-3 criteria (box 1) are eligible to enter the study as long as no exclusion criterion is met (box 2). As for the control groups, patients with cardiomyopathy should, on inclusion into the study, not have recently suffered from sepsis (8 months) or sepsis-related organ failure (6 months) as well as other non-cardiac exclusion criteria already described for patients with sepsis. The exclusion criteria of the healthy individuals essentially consist of the exclusion criteria of all other groups.

Study outline
Table 1 shows an overview of the scheduled clinical and laboratory analyses for patients with sepsis. Baseline data (ie, demographic data) will be documented at study enrolment (T0). Clinical tests and blood sampling in the hospital setting will be performed during the acute phase of sepsis (T1: 3±1 days and T2: 7±1 days after sepsis onset), at discharge from ICU (T3: ±3 days) and after recovery from sepsis during two outpatient appointments (T4: 6±2 months and T5: 12±2 months after onset of sepsis).

In the control groups of healthy subjects and patients with cardiomyopathy without infection, comprehensive testing is performed once at study enrolment (T0) and T1; and T2; table 2). The follow-up status of controls with cardiomyopathy will be assessed preoperatively (T0), 7±1 days postoperatively (T1), at ICU discharge (T2) and 6±2 months postoperatively (T3). Heart, adipose and muscle tissue biopsies will be taken intraoperatively (T4).
| Domain                      | Subdomain                                                                 | T₀  | T₁  | T₂  | T₃  | T₄  | T₅  |
|-----------------------------|----------------------------------------------------------------------------|-----|-----|-----|-----|-----|-----|
| Pre-ICU data                | Patient history                                                            | X   | X   | X   |     |     |     |
|                             | General comorbidities: Charlson Comorbidity Index                          |     |     |     |     |     |     |
|                             | Cardiovascular comorbidities and risk factors                              | X   | X   | X   |     |     |     |
|                             | Previous cardiological findings and medication                             | X   | X   | X   |     |     |     |
|                             | Demographic information                                                    | X   |     |     |     |     |     |
| ICU and hospital data       | Sepsis criteria, including organ dysfunction (SOFA Score)                  |     | X   | X   | X   |     |     |
|                             | Severity of disease (APACHE II and SAPS)                                   | X   |     |     |     |     |     |
|                             | Microbiology                                                               | X   | X   | X   | X   |     |     |
|                             | Treatment and discharge data                                               |     |     |     | X   |     |     |
|                             | Cardiovascular events during hospital stay                                  |     |     |     | X   |     |     |
| Specific assessment         | Heart structure and function: echocardiography                             | X   | X   | X   | X   |     |     |
|                             | Mitochondrial oxygen metabolism: COMET monitor                             |     |     |     | X   |     |     |
|                             | Body composition: bioimpedance analysis                                     | X   | X   | X   | X   |     |     |
|                             | Autonomic function: 24-hour electrocardiography                            | X   | X   | X   | X   |     |     |
|                             | Extended haemodynamic monitoring (if available)                            | X   | X   |     |     |     |     |
|                             | Transient elastography                                                     |     |     | X   | X   |     |     |
| Laboratory analysis        | Routine blood tests                                                         | X   | X   | X   | X   | X   |     |
|                             | Cardiac and other organ functions                                          |     |     |     | X   | X   | X   |
|                             | Metabolome and lipidome                                                     | X   | X   | X   | X   |     |     |
|                             | Endothelial barrier function                                                |     | X   | X   | X   |     |     |
|                             | Immune status                                                              | X   | X   | X   | X   |     |     |
|                             | Microbiome                                                                 | X   |     |     |     |     |     |
| Patient’s status            | Survival status                                                             | X   | X   | X   | X   |     |     |
|                             | Infection                                                                  |     |     |     | X   | X   | X   |
| Physiological data          | Relevance medication                                                        | X   |     |     |     |     |     |
|                             | Patient history after hospital discharge                                    |     |     |     | X   |     |     |
|                             | Cardiovascular events after hospital discharge                             |     |     |     | X   |     |     |
|                             | Quality of life (present): EQ-5D-3L questionnaire                           |     |     |     | X   |     |     |
|                             | Quality of life (before sepsis): EQ-5D-3L questionnaire                     |     |     |     | X   |     |     |
|                             | Physical functional capacity: 6-minute walk test                            |     |     |     | X   | X   |     |

T₀: study enrolment.
T₁: 3±1 days after onset of sepsis.
T₂: 7±1 days after onset of sepsis.
T₃: ±3 days after discharge from ICU.
T₄: 6±2 months after onset of sepsis.
T₅: 12±2 months after onset of sepsis.

APACHE, acute physiology and chronic health evaluation; COMET, cellular oxygen metabolism; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment.

Patients discharged from hospital are monitored by the study team. The patient digital records are consulted for information regarding the patients’ current status during the follow-up period. The records may indicate either the patient’s death or the current readmission to the hospital. In the latter case, the patient is contacted directly. In all other cases, the patient is contacted by a medical doctor of the study team via telephone. Should contact not be possible and prior permission was granted, the patient’s legal proxy, next of kin or the patient’s family doctor are consulted. Should this not lead to the assessment of the patient’s status, the patient is contacted via letter. Should all these measures fail to establish contact by the end of the follow-up period or the patient revokes consent of participation in the study and data usage, the patient is classified as lost to follow-up. The following section will describe the various examinations and tests.
Table 2  Study outline for control groups

| Domain                      | Subdomain                                                                 | T_{HI} | T_{C1} | T_{C2} | T_{L0} | T_{L1} | T_{L2} | T_{L3} | T_{L4} |
|-----------------------------|---------------------------------------------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| General data                | Demographic information                                                   | X      | X      |        |        |        |        |        |        |
| General comorbidities:      | Charlson Comorbidity Index                                               | X      | X      |        |        |        |        |        |        |
| Cardiovascular comorbidities| and risk factors                                                           | X      | X      |        |        |        |        |        |        |
| Previous cardiac findings   | and medication                                                            | X      | X      |        |        |        |        |        |        |
| ICU and hospital data       | Sepsis criteria, including organ dysfunction (SOFA Score)                 | X      | X      |        |        |        |        |        |        |
|                             | Extended haemodynamic monitoring (if available)                           | X      |        |        |        |        |        |        |        |
| Study specific             | treatment and discharge data                                             | X      | X      | X      |        |        |        |        |        |
| assessment                  | Study specific assessment                                                 |        |        |        |        |        |        |        |        |
| General data                | Heart structure and function: echocardiography                           | X      | X      | X      |        |        |        |        |        |
| General comorbidities:      | Mitochondrial oxygen metabolism: COMET monitor                           | X      | X      | X      |        |        |        |        |        |
| Cardiovascular comorbidities| Body composition: bioimpedance analysis                                   |        |        |        |        |        |        |        |        |
| and risk factors            | Autonomic function: 24-hour electrocardiography                          | X      |        |        |        |        |        |        |        |
|                             | Transient elastography                                                   | X      |        |        |        |        |        |        |        |
| Laboratory analysis        | Routine blood tests                                                       | X      | X      | X      | X      | X      |        |        |        |
|                             | Cardiac and other organ functions                                        | X      | X      | X      | X      | X      |        |        |        |
|                             | Metabolome and lipidome                                                   | X      | X      | X      | X      | X      |        |        |        |
|                             | Microbiology                                                              | X      | X      | X      |        |        |        |        |        |
|                             | Endothelial barrier function                                              | X      | X      |        |        |        |        |        |        |
|                             | Immune status                                                             | X      | X      |        |        |        |        |        |        |
| Biopsies: heart, adipose and| Muscle tissues                                                            | X      |        |        |        |        |        |        |        |
| Percentage                  | Patient's status                                                          |        |        |        |        |        |        |        |        |
| Survival status             | Infection                                                                 |        |        |        |        |        |        |        |        |
| Relevant medication         |                                                                           | X      | X      | X      |        |        |        |        |        |
| Patient history after study inclusion |                                      |        |        |        |        |        |        |        |        |
| Cardiovascular events after | study inclusion                                                            | X      |        |        |        |        |        |        |        |
| inclusion                   | Quality of life: EQ-5D-3L questionnaire                                    | X      | X      |        |        |        |        |        |        |
| Physical functional capacity| 6-minute walk test                                                         | X      |        |        |        |        |        |        |        |

T_{HI}: healthy subjects: study enrolment.
T_{C1}: patients with cardiomyopathy: study enrolment.
T_{C2}: patients with cardiomyopathy: 12±2 months after study enrolment.
T_{L0}: patients with LVAD implantation: study enrolment (preoperative).
T_{L1}: patients with LVAD implantation: day of LVAD implantation.
T_{L2}: patients with LVAD implantation: 7±1 days postoperatively.
T_{L3}: patients with LVAD implantation: 6±2 months postoperatively.

*Telephone interview only for the control group cardiomyopathy without infection.

COMET, cellular oxygen metabolism; ICU, intensive care unit; LVAD, left-ventricular assist device; SOFA, Sequential Organ Failure Assessment.

Clinical and laboratory assessments

Patient history will be gathered from patient interviews, medical documents and hospital database checks. Clinical and physiological data will be obtained from the patients’ digital charts or by direct measurement and documentation.

In addition to routine blood tests, blood and urine tests analysing surrogate parameters of cardiac and other organ dysfunctions, endothelial barrier/glycocalyx dysfunction as well as analysis of metabolome, lipidome, immune status and epigenetic modifications of immune cells will be performed. Stool samples will be collected to analyse the microbiome.

Cardiac function will be monitored by transthoracic echocardiography using an Epiq 7 device (Philips Healthcare, Hamburg, Germany). Aside from standard two-dimensional techniques, three-dimensional echocardiography and speckle-tracking will quantify heart volumes and output. If the transthoracic route does not permit adequate assessment (eg, due to oedema), TOE will be performed. Data from advanced haemodynamic monitoring (if performed) will be documented.
Twenty-four-hour electrocardiography monitoring (AR4plus monitor, Schiller medilog, Baar, Switzerland) will be carried out to analyse heart rhythm, in particular heart rate variability.

Mitochondrial oxygen metabolism will be measured non-invasively using the cellular oxygen metabolism (COMET) measurement system (Photonics Healthcare BV, Utrecht, the Netherlands). For this measurement, a small patch of skin will be enriched with protoporphyrin IX using a 5-aminolevulinic acid (5-ALA) containing plaster (Alacare, Photonamic GmbH, Wedel, Germany) at least 5 hours before measurement. The measurement will not be carried out if there are contraindications to the 5-ALA plaster. Measurement will be performed on the thorax and will yield mitochondrial oxygen partial pressure, mitochondrial oxygen consumption and mitochondrial oxygen delivery.

To account for changes in fluid balance during sepsis potentially affecting the COMET measurement, BIA will be performed using a mBCA 525 (seca, Hamburg, Germany) to assess body composition, particularly total body water, body fat and fat-free mass. Transient elastography will be performed using a FibroScan 430 Mini+ (Echosens, Paris, France).

Quality of life will be assessed using the EQ-5D-3L descriptive system and physical functional capacity by means of the 6-minute walk test.

Outcome measures

The primary outcome measure of this study is the difference in 6-month mortality of septic patients with or without septic cardiomyopathy. In this study, septic cardiomyopathy is defined as a new systolic dysfunction (reduced left-ventricular EF: <52% in men and <54% in women or 10% reduction if previously reduced) during the acute phase of sepsis (T1 and/or T2).

The secondary outcome measures include differences in 12-month mortality between these patients and an estimation of the incidence of septic cardiomyopathy.

Further clinical research questions address the evaluation of the numerous clinical and laboratory assessments (see also table 1) as outcome variables and include:

- Characterisation of the acute (T1 and T2) and postacute (T3) courses of disease of patients with sepsis (stratified and unstratified for the occurrence of septic cardiomyopathy) to explore potential surrogate parameters for the occurrence of cardiac dysfunction.
- Characterisation of the patients with sepsis (stratified and unstratified for the occurrence of septic cardiomyopathy) during the acute (T and T3) and postacute (T3) phases in comparison with healthy subjects to identify parameters of diagnostic relevance to sepsis and septic cardiomyopathy.
- Observation of the medium-term and long-term disease progression (T1 and T3) of patients with sepsis (stratified and unstratified for the occurrence of septic cardiomyopathy) in comparison with healthy controls to determine the reversibility of organ dysfunction.
- Comparison of the cohorts during the medium-term and long-term (T1 and T2) phases of sepsis to determine biomarkers with therapeutic potential for further preclinical exploration.
- Characterisation of the medium-term and long-term (T1 and T2) morbidity of patients with sepsis compared with healthy controls as assessed by quality of life, physical functional capacity and incidence of cardiovascular events.
- Identification of predictors of the medium-term and long-term (T1 and T2) mortality, quality of life, cardiovascular events and physical functional capacities obtained by the analysis of data gathered during the acute (T1 and T2) and postacute (T3) courses of disease.
- Characterisation of the short-term and medium-term courses of disease of patients receiving an LVAD—focussing on cardiovascular and metabolic changes—to identify prognostic factors of the short-term and medium-term morbidity and mortality in these patients.

Sample size calculation and statistical analysis

The study is primarily exploratory. According to data from the Jena Sepsis Registry, 350–400 patients are treated in the ICUs of the Jena University Hospital every year. Initial considerations based on the exclusion criteria determined that the inclusion of 150 patients with sepsis during a 2-year period is feasible in the chosen setting. The number of septic patients with left-ventricular systolic dysfunction varies strongly between studies and time points. According to the literature, about one-third of patients with sepsis may show a reduced left-ventricular EF (<50%) as a criterion for septic cardiomyopathy. Based on the information from the Jena Sepsis Registry, table 3 summarises the expected case numbers of sepsis survivors at different time points for an identical mortality rate of patients with and without septic cardiomyopathy. For the control cohorts, we plan to include up to 80 healthy controls and up to 80 patients with cardiomyopathy.

The primary outcome measure will be analysed by Cox regression, focussing on the analysis of the influence of the occurrence of septic cardiomyopathy on the survival time of septic patients. First, univariate analyses and subsequently multivariable analyses including various other predictors (eg, demographics), will be performed. Power analyses were performed in a simplified setting (χ² test and two-sided α=0.05) for different sample sizes and mortality differences between patients with and without septic cardiomyopathy (see figure 1).

The secondary and further outcomes will be analysed with appropriate statistical standard procedures. Depending on distributional properties, means or medians will be reported as measures for central tendency in continuous variables, respectively. Accordingly, SD, 95% CI or IQR and first and third quartiles as a measure of dispersion will be shown. Results of dichotomous and categorical variables will be reported in absolute and
relative frequencies. Group comparison will be analysed by appropriate statistical tests depending on the distributional properties of the outcome measures (eg, t-test and Mann-Whitney U test). The identification of prognostic or predictive factors is primarily exploratory in nature.

No interim evaluation of the complete data set is planned for the primary and secondary endpoints. Hypothesis-generating further research questions that address the evaluation of epidemiological, clinical and laboratory assessments are planned to be evaluated in interim analyses, for example, in postgraduate research projects. To this end, specific limited data sets will be evaluated and may be published before completion of the study.

**Patient and public involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.
ETHICS

Informed consent

Written informed consent will be obtained by the patients. However, due to the disease studied, most patients will be incapable of giving informed consent. In this case, a legal representative or proxy will be sought. In the absence of both, a legal proxy will be appointed by court ruling. Until written informed consent is obtained, patients can be enrolled by consultation of an independent medical doctor assessing the patient’s incapacity and eligibility for the study.

Ethics approval, study registration and data management

The study in its current version (1.6, 20 March 2020) is in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Friedrich Schiller University Jena (5276-09/17, 10 October 2017, last approved amendment in consideration of SARS-CoV-2 pandemic-related circumstances 20 March 2020). It is registered at the German Clinical Trials Register (DRKS00013347) and at Clinical Trials.gov (NCT03620409). All protocol changes were noted in both registrations. The web-based data entry takes place via an encrypted data link (HTTPS) with pseudonymised patient identification numbers. The study management software (OpenClinica, Waltham, Massachusetts, USA) conforms to the Good Clinical Practice guidelines (21 CFR Part 11). The data is stored on servers of the Centre for Clinical Studies Jena at the Jena University Hospital.

Data sets for collaborating study groups will be transferred in anonymised form. Basic study monitoring will be performed by the Centre for Clinical Studies, Jena University Hospital.

DISCUSSION AND OUTLOOK

The ICROS study aims to address the lack of sufficient surrogate parameters for the outcome of patients with sepsis. It will explore prospectively the influence of septic cardiomyopathy on the medium-term and long-term outcomes combining extensive clinical patient characterisation with comprehensive laboratory analyses for the identification of new biomarkers. Its translational approach of validating existing preclinical data may improve the understanding of the pathophysiology of septic cardiomyopathy. A recent study stratified septic patients into four clinical phenotypes depending on biomarkers and clinical characteristics and showed patient outcome to be dependent on this stratification. The results of the ICROS study with a clear focus on septic cardiomyopathy may further contribute towards a stratification of patients with sepsis and in turn improve sepsis therapy by facilitating a more personalised approach.

Dissemination

The results will be published in peer-reviewed journals and presented to the scientific community at appropriate conferences. Results will be reported in accordance with the strengthening the reporting of observational studies in epidemiology (STROBE) criteria for the presentation of observational studies and transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) criteria for the reporting of prediction modelling studies in biomedical sciences.

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