Trial Description

Title

Identification of cardiovascular and molecular prognostic factors for the morbidity and mortality in COVID-19-sepsis

Trial Acronym

ICROVID

URL of the trial

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Brief Summary in Lay Language

Sepsis is a life-threatening condition which can affect people of any age. It can be caused by infections with bacteria, fungi or viruses. Severe cases of viral pneumonia, e.g. with the SARS-CoV-2 virus (COVID-19) or the flu virus (Influenza) can trigger a host response resulting in organ failure. The extent of the organ dysfunction varies between patients and during the course of the condition. Thus far, the only causal treatment option consists in treating the infection early e. g. by an operation or the use of antibiotics. Owing to advances in modern critical care, more patients survive sepsis. Nonetheless, sepsis survivors frequently show impaired organ function, physical disability and considerably decreased health-related quality of life. It is hypothesized that sepsis-induced cardiac dysfunction – septic cardiomyopathy – may influence mortality. The relationship between occurrence of cardiovascular dysfunction and metabolic changes in the course of sepsis remains unclear. Therefore, the aim of this study is the investigation of cardiovascular function and metabolic changes in septic patients. Apart from cardiological routine procedures (echo- and electrocardiography) blood and urine analysis, both routine parameters and parameters focusing on patient metabolism will be analysed. Septic patients will be assessed in the acute phase (3 and 7 days after sepsis diagnosis), the stable phase (14d after disease onset or hospital discharge) and after full or incomplete recovery (28d, 3 and 6 months after sepsis onset). The results will be compared between patients with COVID-19-sepsis and Influenza-associated sepsis. In addition, the results will be compared with data from another sepsis study ("Identification of Cardiovascular and Molecular Prognostic Factors for the Mid- and Long-term Outcome of Sepsis (ICROS)", DRKS: DRKS00013347). Another important aspect is the analysis of potential long-term consequences of a COVID-19-associated sepsis and Influenza-associated sepsis. The study aims to identify clinical parameters and signaling pathways involved in the development and course of sepsis. Furthermore, specific parameters associated with the medium- and long-term health status, physical performance and quality of life after sepsis are to be identified. The overall aim of the study is the development of novel diagnostic and therapeutic approaches in sepsis.

Brief Summary in Scientific Language

The overall aim of this project is to identify cardiovascular and molecular prognostic factors for medium-term morbidity and mortality after COVID-19-associated sepsis as a basis for the development of targeted personalized

strategies in a prospective multicenter cohort study in German intensive care units. A comprehensive clinical and molecular characterization of patients with COVID-19-sepsis is planned to identify cardiovascular and molecular prognostic markers for the occurence of cardiovascular events, short- and medium-term disease progression, and mortality. In order to detect potential specific changes, the results will be compared with a group of patients with influenza-associated sepsis. In addition, results will be compared with a cohort of septic patients and healthy volunteers from the study "Identification of cardiovascular and molecular prognostic factors for mid- and long-term morbidity and mortality in sepsis" [DRKS: DRKS00013347]. The primary end point of the study is the difference in mortality-rates between patients with COVID-19-associated sepsis with or without the presence of septic cardiomyopathy in 3 months after diagnosis of sepsis. Further questions relate to differences between patients with COVID-19 patients with or without the presence of septic cardiomyopathy with respect to clinical examinations and laboratory chemical analyses in the acute, intermediate, and long-term course. In addition, specific clinical and moleculare changes and long-term consequences, including post-traumatic stress disorder, symptoms of depression and anxiety, cognitive performance, chronic pain, fatigue, activitities of daily living and quality of life, in patients with COVID-19 will be assessed.

Do you plan to share individual participant data with other researchers?

No

Description IPD sharing plan

The study protocol will be published in a journal with peer-review. The raw data for publications regarding specific research questios will be made available by the prinicpal invesigator, without undue reservation.

Organizational Data

- DRKS-ID: **DRKS00024162**
- Date of Registration in DRKS: **2021/02/09**
- Date of Registration in Partner Registry or other Primary Registry: **[---]***
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **Approved**
- (leading) Ethics Committee Nr.: **2020-2052-BO , Ethikkommission der Friedrich-Schiller-Universität Jena an der Medizinischen Fakultät**

Secondary IDs

Health condition or Problem studied

- ICD10: **A41.9 - Sepsis, unspecified**
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ICD10: **J10 - influenza due to identified seasonal influenza virus**

- ICD10: **U07.1 - Emergency use of U07.1**

Interventions/Observational Groups

- Arm 1: **Patients with COVID-19-associated sepsis (with indication for critical care)**

  • T1 (3 d ± 24 h after sepsis diagnosis):
  o routine and study-specific blood tests
  o echocardiography
  o optional: transient elastography

  • T2 (7 d ± 24 h after sepsis diagnosis):
  o routine and study-specific blood tests
  o echocardiography
  o optional: transient elastography

  • T3 (14 d ± 24 h after sepsis diagnosis or hospital discharge):
  o routine and study-specific blood tests

  • T4 (28 d nach Sepsisbeginn):
  o telephone-interview: anamnestic information and patient status (survival)

  • T5 (3 M ± 14 d after sepsis diagnosis):
  o questionnaires and telephone-interview (disease course, cardiovascular events after discharge, long-term consequences)
  o Screening-questions
  o cognitive functioning: t-Montreal Cognitive Assessment (t-MoCa)
  o activities of daily living (ADL): Barthel Index
  o symptoms of anxiety and depression: Brief Symptom Inventory 18
  o fatigue: Fatigue Scale
  o instrumental activities of daily living (IADL)
  o health related quality of life: EQ-5D-3L
  o symptoms of post-traumatic stress disorder: Post Traumatic Symptom Scale – 10
  o pain: chronic pain and Korff Graded Chronic Pain Scale

  • T6 (6M ± 14 d after sepsis diagnosis):
  o the contents are identical with T5

- Arm 2: **patients with Influenza-associated sepsis (with indication for critical care)**

  The time points and methods are the same as in arm 1.

Characteristics

- Study Type: **Interventional**
- Study Type Non-Interventional: **[---]***
- Allocation: **Other**
- Blinding: **[---]***

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Study Type Non-Interventional: **[---]***

Allocation: **Other**

Blinding: **[---]***

- Who is blinded: **[---]***
- Control: **Other**
- Purpose: **Other**
- Assignment: **Other**
- Phase: **N/A**
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **N/A**

Primary Outcome

Differences in mortality rates between COVID-19-sepsis patients with vs. without septic cardiomyopathy 3 months after diagnosis of COVID-19-sepsis (T5)

Secondary Outcome

- Differences in mortality rates between COVID-19-sepsis patients with vs. without septic cardiomyopathy 6 months after diagnosis of COVID-19-sepsis (T6)

- Incidence of cardiovascular events in patients with COVID 19-sepsis during the acute (T1, T2), post-acute (T3-T4) and long-term course of disease (T5-T6)

- Differences in the incidence rates of septic cardiomyopathy during the acute course of disease (T1, T2) in patients with COVID-19-sepsis and patients with influenza-sepsis

- Differences in the incidence rates of cardiovascular events in patients with COVID 19-sepsis and patients with influenza-sepsis during the acute (T1, T2), post-acute (T3-T4) and long-term course of disease (T5-T6)

For further research questions patients with COVID-19-sepsis and patients with influenza-associated sepsis as well as pre-existing cohorts of patients with non-COVID-19-associated sepsis and healthy volunteers will be compared. For this purpose, further outcome measures including cardiovascular risk factors and function, liver/kidney stiffness, organ dysfunction, immune status, metabolome, lipidome and general functional level, will be analysed:

- differences in the occurence of septic cadiomyopathy between patients with COVID-19-sepsis and non-COVID-19-associated sepsis during the acute disease (cumulative T1 and T2)

- identification of COVID 19-specific clinical and molecular changes in the acute and post-acute course of disease

- analysis of potential group differences in the acute and post-acute course of

disease (complete sample and stratified by the occurence of septic cardiomyopathy) to identify varaibles with potential diagnostic relevance in COVID-19-sepsis

- characterisation of the acute and post-acute course of diseas in patients with COVID-19-sepsis (complete sample and stratified by the occurence of septic cardiomyopathy) to explore potential surrogate paramters for the occurence of cardial dysfunction

- comparison of the incidence of right heart failure during the acute course of disease (T1 and T2) in patients with COVID-19-Sepsis and influenza-sepsis

- influence of right heart failure on mortality and morbidity after COVID-19-sepsis and Influenza-sepsis. The focus lies on data from the acute (T1, T2) and post-acute phase (T3) treament phase.

- Analysis of potential group differences in the mid- (T5) and long-term (T6) course of disease in patients with COVID-19-sepsis (complete sample and stratified by the occurence of septic cardiomyopathy) und the other cohorts for the identification of potential biomarkers of the acute and post-acute course of disease and potential therapeutical target structures, which might further be analysed pre-clinically

- Analysis of the mid- and long-term morbidity in patients with COVID-19-sepsis regarding physical and cognitive performance and interference, health related quality of life and type and frequency of cardiovascular events after ICU admission (complete sample and stratified by the occurence of septic cardiomyopathy)

- Identification of potential predictors of mid- (T5) and long-term (T6) mortality and morbidity after COVID-19-sepsis. The focus lies on data from the acute (T1, T2) and post-acute phase (T3) treament phase.

Countries of recruitment

- DE **Germany**

Locations of Recruitment

- University Medical Center **Klinik für Anästhesiologie und Intensivmedizin, Jena**

Recruitment

- Planned/Actual: **Planned**
- (Anticipated or Actual) Date of First Enrollment: **2021/02/25**
- Target Sample Size: **320**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **National**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **18 Years**
- Maximum Age: **no maximum age**

Additional Inclusion Criteria

- written informed consent of the patient or his legal representative

- confirmed SARS-CoV-2 infection OR confirmed influenza virus infection.

- respiratory symptoms

- indication for ICU-therapy

- sepsis or septic shock according to Sepsis-3 criteria

- first infection-associated organ dysfunction (= sepsis diagnosis) no older than 4 days (first blood sample within 4 days after sepsis diagnosis)

Exclusion criteria

• cardiac surgery ≤ 12 months

• significant pre-existing heart condition
o endocarditis
o higher-grade valvular heart disease
o (grade 3 valve disease, symptomatic aortic stenosis, medium-degree mitral valve insufficiency with reduced ejection fraction or clinical symptoms)
o complex structural congenital heart condition (TGA, Tetralogy of Fallot, endocardial cushion defect etc.)
o hemodynamic relevant shunt deficit
o pre-existing significantly reduced cardiac performance
o (ejection fraction < 45 % or 10 % below norm value)
o pre-existing pulmonary hypertension
o myocardial infarction ≤ 1 year in patient history
o heart transplantation in patient history

• cardiopulmonary resuscitation<4 weeks before sepsis begin

• pneumonectomy in medical history

• liver cirrhosis Child C

• contraindication for transesophageal echocardiography (e.g. esophageal resection, higher-grade esophagus varices) and insufficient sonography conditions for transthoracic echocardiography

• terminal kidney disease with dialysis

• Sepsis/septic shock ≤ 8 months

- **pregnancy/breastfeeding**
- **therapy limitation, DNR / DNI order**
- **life expectancy ≤ 6 months due to comorbidities**
- **previous participation in this study**

Addresses

■ **Primary Sponsor**

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Sources of Monetary or Material Support

- **Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)**

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  Germany

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  E-mail: **[---]***
  URL: **[---]***

Status

- Recruitment Status: **Recruiting planned**
- Study Closing (LPLV): **[---]***

Trial Publications, Results and other documents

** This entry means the parameter is not applicable or has not been set.*

**** This entry means that data is not displayed due to insufficient data privacy clearing.*