Medical University of Karaganda

Study protocol

Analysis of laboratory markers for severe COVID-19
SC19MI-ARICU-1T
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I. Purpose of the study and introduction.

1. **Purpose of the study :** to determine the level of significance of biochemical markers in severe patients with coronavirus infection COVID-19 hospitalized in the intensive care unit, to search for possible predictor markers of the course and outcome of this disease .

2. **Research objective:**

2.1 To evaluate the indicators of biomarkers of the systemic inflammatory response in the systemic bloodstream in patients in serious condition with confirmed coronavirus infection. Based on the obtained critical levels of early markers studied at different times, it will be possible to predict the risks of developing an unfavorable outcome.

2.2 Assess the structure of complications in the selected category of patients.

2.3 Identify the presence of correlations between clinical and laboratory parameters (laboratory parameters and the degree of pulmonary infiltration , outcome and length of stay, age group, gender, presence of concomitant pathology).

2.4 Determine critical levels of biomarkers to predict mortality. The resulting critical levels will be significant indicators in the dynamic assessment of the condition of patients in the ICU.

Introduction. The manifest course of COVID-19 often involves a fairly high risk of death due to the frequent development of serious complications in the form of Acute respiratory distress syndrome (ARDS), acute respiratory failure (ARF), pulmonary embolism (PE), sepsis, shock, multiple organ failure (MOF), and due to the absence at the current stage of highly proven safe methods of etiotropic therapy.

Of particular relevance in this regard was the search for reliable data that would make it possible to predict the severity and outcome, more effectively plan the management of different groups of patients, and provide the opportunity for timely response of medical personnel, and rational distribution of limited health care system resources during a pandemic.

Thus, in a study by Moon SS et al., which included 352 patients with identified new coronavirus infection, it has been shown that patients aged ≥ 70 years, patients with fever on admission and patients with malignancy or diabetes are more likely die from COVID-19 [1].

In the study by Zhou F, patients' old age and some concomitant diseases, such as hypertension and diabetes, were identified as factors contributing to severe progression [2]. A number of studies confirm that a comorbid background reliably suggests a more severe course of this pathology, however, of greater interest, in our opinion, is the search for more dynamic indicators. Jang JG, in addition to diabetes mellitus, hyperthermia ≥ 37.8°C, peripheral oxygen saturation <92% and creatine kinase-MB (CK-MB) level > 6.3 were proposed as independent predictors of severe course in hospitalized patients with COVID-19. [3]. In the study by Suh H.J.[4] dyspnea (60.0%) and elevated CRP levels (median 7.35 mg/dL; IQR 3.17–12.02) indicated severe clinical course and were suggested to evaluate patients with COVID-19 for initiation of oxygen therapy. In a prospective study by Rong-Hui Du, in addition to comorbidities and age (age ≥65 years, pre-existing concomitant cardiovascular or cerebrovascular diseases) as factors associated with death in patients with COVID-19-associated pneumonia cardiac troponin I ≥0.05 ng mL -1 and CD3 + CD8 + T cells ≤75 cells·μl -1 were identified. The last two factors, in particular, were predictors of mortality in patients with COVID-19 pneumonia[5].

One of the hallmarks of SARS-CoV-2 infection is induced immune dysregulation, which often leads to a cytokine storm and the development of multiorgan dysfunction syndrome [6]. Available research allows us to judge what multiorgan failure syndrome appears the leading cause of high mortality among intensive care patients infected withCOVID-19 [7]. This condition is based on an increased risk of developing disseminated intravascular coagulation (DIC) in patients with SARS-CoV-2, as indicated by clinical reports indicating frequent thrombocytopenia and increased D-dimer in infected individuals with manifest disease [8].

Abnormal coagulation in patients with COVID-19 is characterized by increased levels of fibrinogen and D-dimer in parallel with an increase in inflammatory markers. At the same time, an increase in prothrombin time and time of partial activation of thrombin, in combination with thrombocytopenia, suggests activation of the coagulation pathway with the development of consumptive coagulopathy due to an excessive inflammatory response. These processes cause microcirculatory dysfunction and the development of systemic microangiitis and extensive microthrombosis, which ultimately leads to multi-organ dysfunction syndrome (MODS) [7,8,9]. It is worth noting the difficulty of drawing up an optimal management plan for patients with such complications, the treatment of which should be carried out in an intensive care unit. It is even more difficult to timely assess the risk of developing these complications for timely transfer the patients to the department of anesthesiology, resuscitation and intensive care (ICU).
Therefore, in addition to the data already accumulated to date, the authors of this work conducted a retrospective analysis to determine the clinical profile of patients with COVID-19 requiring intensive care, as well as to search for available and reliable predictors of the course and outcome of the disease for this cohort of patients.

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II. Criteria for selecting study participants.

1. Number of participants . Retrospective analysis of medical records (case histories) of 193 patients who received treatment in the intensive care unit of the Regional Clinical Hospital of Karaganda .

2. Gender distribution . The expected gender distribution is uneven, due to the lack of information about significant differences in laboratory markers among representatives of different sexes.

3. Age. From 18 years old without age restrictions

4. Nationality (ethnicity). Those with different national and ethnic backgrounds undergoing treatment at the center.

5. Criteria for inclusion . Case histories of treated patients with severe cases confirmed by PCR of a nasopharyngeal smear of coronavirus infection COVID -19.

6. Criteria for exclusion . Pregnancy.

7. Vulnerable groups . No

III. Methods and procedures

1. Methods and procedures . The study plans to retrospectively analyze the medical records of patients who received treatment in the intensive care unit of the Regional Clinical Hospital for severe COVID19 infection. The retrospective analysis will evaluate the results of diagnostic procedures performed, including computed tomography of the chest and analysis of biochemical parameters, including procalcitonin, C-reactive protein, D- dimer and ferritin, identified as markers of the systemic inflammatory response.

2. Data analysis and monitoring . Statistical processing of the obtained data was carried out using statistical software jamovi (Computer Software , Version 2.3.26), MedCalc (MedCalc Software Ltd , Ostend, Belgium), Microsoft programs Office Excel , 2016. Statistical research methods include: calculation of median and mode, standard deviation. In order to determine correlations between quantitative and qualitative data at different stages of treatment, a correlation analysis was carried out (Spearman's test was used). To evaluate selected laboratory markers as predictors of outcome, the ROC analysis method was selected, followed by an assessment of the odds ratio (OR) taking into account the obtained J Youden index and the associated criterion (Associated criterion) for each of the selected markers in relation to patient outcome. It is preliminary planned to compile a contingency table in relation to laboratory parameters and outcomes (2x2).

Data storage and privacy. Confidentiality is ensured by encrypting the personal data of the subject with a digital code. Storage of information about patients is carried out in written form in the registration journal of the research topic, in electronic form on a computer in Microsoft program databases Excel and jamovi. Access to the data is available to the supervisor of the research and the main researcher, with the consent of the administration of the Regional Clinical Hospital of the city of Karaganda.

IV. Risk/benefit assessment

1. Degree of risk . There are no risks.

2. Potential risk . There are no risks.

3. Risk protection . Each patient is assigned a code to anonymize the data.

4. Potential benefit to the participant . none

5. Alternatives for the participant are missing.

V. Identification of study participants, recruitment and consent

At the time of hospitalization and during treatment, informed consent was obtained from each patient for medical procedures and processing of personal data.

1. Methods for identifying participants and recruiting them . Materials (medical histories of treated patients) are selected using a continuous method in accordance with the ICU-CVI patient register for the period 08/01/2021-02/14/2022.

2. Consent process . Access to medical documentation was obtained with the consent of the administration of the Regional Clinical Hospital of Karaganda. Consent to the processing of patients' personal data was obtained during treatment in the intensive care unit of the Regional Clinical Hospital in the form of oral and written consent.

3. Participant's condition . obtaining informed consent in person from the patient/official representative.

4. Understanding . At the time of hospitalization and during treatment, informed consent was obtained from each patient for medical procedures and processing of personal data.

5. Consent forms . The informed consent form was compiled according to the recommendations of the EC.

6. Documentation of consent . Access to medical documentation was obtained with the consent of the administration of the Regional Clinical Hospital of Karaganda. Consent to the processing of patients' personal data was obtained during treatment in the intensive care unit of the Regional Clinical Hospital in the form of written consent, which is stored in the archives of the Clinic and in a scanned version in the database of an integrated medical information system.

7. Participation price . There is no cost of participation for patients.

8. Participation fee . There is no payment to the participant.