**Clinical Research Protocol (S21-147)**

*This research protocol was previously approved as* ***S10-79*** *and* ***S20-025*** *by the Institutional Clinical Research Ethics Review Board of Saitama Medical Center, Jichi Medical University. It was subsequently submitted as an additional application and reapproved again as* ***S21-147*** *on February 10, 2022.*

**1. Title and Classification of the Research**

**(1) Title of the Research**

**Association Between Extreme Outliers in Clinical Laboratory Test Results and Prognosis**

**(2) Classification of the Research**

* ☑ Research conducted solely by Jichi Medical University
* ☐ Multi-center collaborative research led by Jichi Medical University
* ☐ Multi-center collaborative research led by another institution

**2. Research Implementation Framework**

**(1) Implementation Framework within the Institution**

* **Principal Investigator:**  
  Hitoshi Sugawara, MD, PhD, Division of General Medicine (Completed Ethical Training)
* **Co-investigators:**
  + Takahiko Fukuchi, MD, PhD, Division of General Medicine (Completed Ethical Training)
  + Tamami Watanabe, MD, PhD, Division of General Medicine (Completed Ethical Training)
  + Keishiro Sueda, MD, Division of General Medicine (Completed Ethical Training)

**3. Objective and Significance of the Research**

**(1) Objective**

To elucidate the relationship between extreme outliers in clinical laboratory tests and short-term prognosis within three days of testing.

**(2) Significance**

Patients occasionally exhibit extreme outliers in laboratory test results in routine clinical practice. However, the short-term prognosis and risk factors for such cases remain unclear. By identifying background factors, this research aims to facilitate short-term prognosis prediction, thereby improving the quality of medical care in primary care settings.

**4. Research Methods and Duration**

**(1) Research Methods**

**1. Study Design**

* **☑ Clinical Research**
* ☐ Epidemiological Research
* ☐ Other Medical Research
* **☐ Interventional Study**
  + ☐ Involves more than minimal invasiveness
  + ☐ No or minimal invasiveness
* **☑ Observational Study**
  + ☐ Involves more than minimal invasiveness
  + ☑ No or minimal invasiveness

**2. Specific Details**

Anonymous biochemical blood test data (complete blood count panel, biochemistry panel, and coagulation panel) collected over 14 years from January 1, 2004, to December 31, 2023, will be analyzed. The dataset will exclude duplicates and erroneous samples (e.g., blood drawn from an intravenous route, cardiopulmonary arrest [CPA], and cases with unknown short-term prognosis). Data from the top and bottom 0.1% of each test parameter will be extracted. Test items with at least 10% (≥50 cases) of deaths within three days among 500 cases will be analyzed.

**3. Estimated Sample Size and Rationale**

* **Estimated sample size per test item:** 500 patients
* **Rationale:** Previous clinical research indicates that approximately 0.1% of test cases correspond to 500 patients.

**4. Statistical Analysis Methods and Evaluation Criteria**

* **Statistical Analysis Methods:**
  + Retrospective analysis of risk factors such as age, sex, vital signs, Charlson Comorbidity Index (CCI), underlying disease, and biochemical test data.
  + Short-term prognosis is defined as death within three days of testing or survival beyond three days.
  + Univariate analysis will be performed, and significant factors will be analyzed using multiple logistic regression, receiver operating characteristic (ROC) analysis, and stepwise selection.
  + Machine learning analysis will be performed using gradient boosting methods (e.g., XGBoost, LightGBM, or CatBoost) to identify significant predictors and compare predictive performance with traditional statistical methods.
* **Evaluation Criteria:**
  + Identify risk factors predicting short-term prognosis for extreme outliers.
  + Develop a prognostic prediction formula using multiple logistic regression and machine learning models.
  + Compare regression coefficients, intercepts, adjusted odds ratios, 95% confidence intervals, C-statistics, sensitivity, specificity, and likelihood ratios between models.
  + Determine the simplest model that best predicts short-term prognosis based on the number of risk factors and C-statistics.

**(2) Research Duration**

* Until **March 31, 2025**, following approval.
* Results will be published in conferences and journals within **two years** after analysis completion.

**5. Selection of Research Subjects**

**(1) Number and Type of Subjects**

* **☑ Patients (Approx. 500 per test item)**
  + No specific disease name designated
  + ☑ Outpatients from Jichi Medical University Hospital and Saitama Medical Center
  + ☑ Inpatients from Jichi Medical University Hospital and Saitama Medical Center

**(2) Inclusion Criteria**

* Data extracted from the **top and bottom 0.1%** of each test parameter in the laboratory database.

**(3) Exclusion Criteria**

* Duplicate cases
* Erroneous samples (e.g., collected from an intravenous injection route)
* CPA on arrival cases
* Cases with unknown short-term prognosis

**(4) Age Limitations**

* **☑ Limited (18 years and older)**

**(5) Gender**

* **☑ Both male and female**

**(6) Recruitment Methods**

* **☑ No recruitment of subjects**

**6. Scientific Rationale**

Large volumes of blood test data are accumulated daily in medical institutions but are not fully utilized to improve healthcare quality. In clinical practice, extremely abnormal laboratory values are occasionally observed. These extreme values could indicate life-threatening conditions if not promptly addressed. Identifying predictive risk factors will enable rapid prognosis assessment and appropriate intervention. Machine learning techniques will enhance the predictive accuracy and provide novel insights into complex relationships among variables.

**7. Informed Consent Procedures**

**(1) Use of Samples and Information**

* **☑ Use of Existing Data**
  + **Data Source:** Blood test database from January 1, 2004, to December 31, 2023.
* **☑ Use of Information**
  + **☑ Opt-out method applied**
  + **Rationale:** As this is a retrospective study utilizing existing medical records, informed consent is waived per the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" (Chapter 5, Section 12.1(2)-i), ensuring subjects have an opportunity to opt out.

**8. Handling of Personal Information**

* **☑ Anonymization with Correspondence Table**
  + Hospital IDs will be replaced with alternative identifiers.
  + **Rationale:** Ensuring data accuracy, allowing corrections, and enabling withdrawal upon request.
* **☑ No exchange of samples or information with other institutions.**

**9. Burdens, Risks, and Benefits to Study Participants, Comprehensive Evaluation, and Measures to Minimize Burdens and Risks**

(1) **Burdens on Study Participants**

1. **Financial Burden**
   * □ Study participants will bear financial costs.
     + □ Within the scope of insurance-covered medical care
       - □ Does not include medical care for research purposes
       - □ Includes medical care for research purposes
     + □ Fully self-funded (Estimated amount: \_\_\_\_\_\_ yen)
     + □ Partially self-funded (Estimated amount: \_\_\_\_\_\_ yen)
     + □ Other (Specify: \_\_\_\_\_\_)
   * ☑ Study participants will not bear any financial costs.
2. **Other Burdens**
   * □ Study participants will experience other burdens.
     + Specific details: \_\_\_\_\_\_
   * ☑ Study participants will not experience other burdens.

(2) **Predicted Risks to Study Participants**

1. **Disadvantages**
   * □ Yes, details: \_\_\_\_\_\_
   * ☑ No
2. **Hazards**
   * □ Yes, details: \_\_\_\_\_\_
   * ☑ No
3. **Discomfort**
   * □ Yes, details: \_\_\_\_\_\_
   * ☑ No

(3) **Benefits to Study Participants**

1. **Compensation for Participants**
   * □ Yes (Specify: \_\_\_\_\_\_)
   * ☑ No
2. **Other Benefits**
   * □ Yes, details: \_\_\_\_\_\_
   * ☑ No

(4) **Comprehensive Evaluation of Burdens, Risks, and Benefits, and Measures to Minimize Burdens and Risks**

1. **Comprehensive Evaluation**
   * No burdens or predicted risks will arise for study participants.
2. **Measures to Minimize Burdens and Risks**
   * Strict management of personal information.
3. **Compensation for Losses**
   * □ Compensation for losses incurred due to this study will be provided.
     + Compensation details: \_\_\_\_\_\_
   * ☑ No compensation for losses incurred due to this study.

**10. Storage and Disposal of Samples and Information, and Record Keeping of Sample and Information Transfers**

(1) **Storage of Samples and Information During the Study**

1. **Types of Samples and Information**
   * ☑ Original samples and raw data (e.g., case report forms, questionnaires)
   * ☑ Processed data
   * □ Consent forms
   * ☑ Anonymization correspondence tables
   * □ Other (Specify: \_\_\_\_\_\_)
2. **Data Formats**
   * ☑ Paper records
   * ☑ Electronic records
   * □ Samples
   * □ Other (Specify: \_\_\_\_\_\_)
3. **Storage Locations**
   * ☑ Jichi Medical University (Specific location: Research Management Building, Room 516, cabinet)
     + ☑ Locked storage
     + □ Unlocked storage
   * □ Collaborative research facility (Specify: \_\_\_\_\_\_)
     + □ Locked storage
     + □ Unlocked storage
   * □ Other (Specify: \_\_\_\_\_\_)
     + □ Locked storage
     + □ Unlocked storage

(2) **Storage of Samples and Information After Study Completion**

* ☑ Samples and information will be retained for purposes beyond this study.
  + **Types of Data:** Blood test data, vital signs, primary diseases, and patient information.
  + **Reason for Retention:** Potential data review and future research use.
* ☑ Ethical committee approval will be required before reusing stored data for other purposes.
* □ Participant consent will be obtained before using stored data for other purposes.
* □ Participant consent will not be obtained before using stored data for other purposes.
  + **Reason:** \_\_\_\_\_\_
* **Storage Locations:**
  + ☑ Jichi Medical University (Research Management Building, Room 516, cabinet)
    - ☑ Locked storage
    - □ Unlocked storage
  + □ Collaborative research facility (Specify: \_\_\_\_\_\_)
    - □ Locked storage
    - □ Unlocked storage
  + □ Other (Specify: \_\_\_\_\_\_)
    - □ Locked storage
    - □ Unlocked storage
* ☑ Stored samples and data will be disposed of after 24 months.
  + **Types of Data:** Blood test data, vital signs, primary diseases, and patient information.

(3) **Methods of Data and Sample Disposal**

* □ Autoclaving and incineration
* ☑ Shredding paper records
* ☑ Secure deletion of electronic data using data erasure software

(4) **Record Keeping of Sample and Data Transfers**

* □ Sample and data transfers between institutions exist.
  + □ Records will be kept for three years after data transfer.
  + □ Records will be kept for five years after research completion.
* ☑ No sample or data transfers between institutions.

(5) **Reporting on Sample and Data Storage and Disposal**

* ☑ Within one year of study commencement, a report on data and sample storage will be submitted to the university president.
* ☑ Changes in data and sample storage procedures will be reported to the university president.
* ☑ Disposal of samples and data will be reported to the university president.

**11. Reporting to the University President**

* ☑ Annual progress reports on clinical research, adverse events, and complications will be submitted to the university president.
* ☑ If the clinical research is terminated, a termination report will be submitted to the university president.
* ☑ If the clinical research is completed, a completion report will be submitted to the university president.

**12. Funding, Conflicts of Interest, and Intellectual Property Rights**

(1) **Funding Source**

* □ Departmental research funds
* □ Contract research funds (Specify: \_\_\_\_\_\_)
* □ Scientific research grants (Specify: \_\_\_\_\_\_)
* ☑ Other: Donations

(2) **Affiliation with Related Organizations**

* None

(3) **Conflicts of Interest**

* None

(4) **Intellectual Property Rights**

* □ Potential for patent rights
  + Ownership: □ Jichi Medical University □ Individual researcher □ Other (Specify: \_\_\_\_\_\_)
* ☑ No potential for patent rights

**13. Information Disclosure on Research**

(1) **Study Registration and Results Disclosure**

* □ Study results will be registered.
  + □ National University Hospital Council (UMIN)
  + □ Japan Medical Information Center
  + □ Japan Medical Association
* ☑ Study results will not be registered.
  + **Reason:** Not an interventional study.

(2) **Disclosure of New Personal Data**

* ☑ No new personal data will be generated in this study.

(3) **Research Findings Disclosure**

* ☑ Research findings will be published.
  + ☑ Academic journal publications
  + ☑ Conference presentations
  + □ Online publication
  + □ Other (Specify: \_\_\_\_\_\_)

**14. Handling of Research in Emergencies**

* ☑ This research does not involve participants in life-threatening emergencies.

**15. Response to the Occurrence of Serious Adverse Events**

* □ Study involving interventions (excluding minimal interventions) [Subject to reporting]
  + **Response to the occurrence of serious adverse events:** \_\_\_\_\_\_
* ☑ Study not involving interventions (no or minimal interventions) [Not subject to reporting]

**16. Compensation for Health Damage and Its Content**

* □ Study involving interventions (excluding minimal interventions) [Eligible for compensation]
  + □ Compensation available
    - **Details:** \_\_\_\_\_\_
  + □ No compensation
    - **Reason:** \_\_\_\_\_\_
* ☑ Study not involving interventions (no or minimal interventions) [Not eligible for compensation]

**17. Provision of Medical Care After Study Completion**

* □ Study involving medical interventions beyond standard clinical care
  + **Specific methods for providing medical care after study completion:** \_\_\_\_\_\_
* ☑ Study not exceeding standard clinical care or not involving medical interventions

**18. Handling of Research Findings Related to Study Participants**

* □ The study may reveal significant findings related to the participant’s health or hereditary characteristics that could be inherited by descendants.
  + **Handling of research findings:** \_\_\_\_\_\_
* ☑ The study is not expected to reveal significant findings related to the participant’s health or hereditary characteristics that could be inherited by descendants.

**19. Delegation of Research-Related Tasks**

* □ Research-related tasks will be outsourced.
  + □ Contract in place (or planned) □ No contract
  + **Details of outsourced tasks:** \_\_\_\_\_\_
  + **Supervision method of the contractor:** \_\_\_\_\_\_
* ☑ Research-related tasks will not be outsourced.

**20. Monitoring and Audit System and Procedures**

* □ Monitoring and auditing will be conducted.
  + **Reason for audit implementation:** \_\_\_\_\_\_
* □ Monitoring will be conducted, but auditing will not be performed.
  + **Implementation system:** \_\_\_\_\_\_
  + **Implementation procedures:** \_\_\_\_\_\_
* ☑ Monitoring and auditing will not be conducted [Study not subject to these requirements].

**21. Inquiry and Complaint Handling Regarding the Research**

(1) **Inquiry Contact**

* **Affiliation:** Jichi Medical University Saitama Medical Center, Division of General Medicine
* **Title:** Professor
* **Name:** Hitoshi Sugawara
* **Phone Number:** 048-647-2111
* **Internal Extension Number:** 6516
* **PHS (if applicable):** 5565
* **Email:** hsmdfacp@jichi.ac.jp

(2) **Complaint Submission Contact**

* **Jichi Medical University Saitama Medical Center, General Affairs Division**
* **Phone Number:** 048-648-5225