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08.03.2021/Vb

Projekt Nr: **21-0126** (bitte bei Schriftwechsel angeben)

Beratung nach Fakultätsrecht

Studientitel: Machine learning aided stratification of microlithiasis induced pancreatitis
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Sehr geehrter Herr Dr. Sirtl,

der Antrag zur o.g. Studie wurde auf der Basis der vorgelegten Unterlagen und Informationen entsprechend § 15 der Berufsordnung und des Fakultätsrechts beraten.

Die Ethikkommission (EK) erhebt keine Einwände gegen die Durchführung der Studie.

Allgemeine Hinweise:

- Änderungen im Verlauf der Studie sind der EK zur erneuten Prüfung vorzulegen.
- Schwerwiegende unerwartete studienabhängige Ereignisse sind der EK mitzuteilen (trifft nur für interventionelle Projekte zu).
- Das Ende der Studie ist anzuzeigen und das Ergebnis vorzulegen.
- Die ärztliche und juristische Verantwortung bei der Durchführung der Studie verbleibt uneingeschränkt bei Ihnen und Ihren Mitarbeitern.
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Die Ethikkommission wünscht Ihnen für Ihr Vorhaben viel Erfolg.

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Betreff: Ethikantrag

Inhaltsangabe des Ethikantrags zur Studie:

*Machine learning aided stratification of microlithiasis induced pancreatitis
from other pancreatitis based on clinical laboratory pattern*

1. SUMMARY
2. INTRODUCTION
3. STUDY DESIGN
4. STUDY POPULATION
 - 4.1 Population (base)
 - 4.2 Inclusion criteria
 - 4.3 Exclusion criteria
5. METHODS
 - 5.1 Study endpoints
 - 5.1.1 Primary study endpoints
 - 5.1.2 Secondary study endpoints
6. STATISTICAL ANALYSIS
7. DATA MANAGEMENT
 - 7.1. Regulation statement
 - 7.2 Recruitment and consent
8. REFERENCES

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***Machine learning aided stratification of microlithiasis induced pancreatitis
from other pancreatitis based on clinical laboratory pattern (01 / 2021)***

1 SUMMARY

Rationale: After a basic clinical workup, acute pancreatitis etiology can be established in the majority of patients, but in up to 10-30% of cases, the cause is not found despite a clinical history, laboratory tests (triglyceride and calcium concentrations) and conventional cross-sectional imaging, such as transabdominal ultrasound and computed tomography (CT). The percentage of patients with acute idiopathic pancreatitis and microlithiasis detection is reported to be up to 75% depending on the study.

Objective: Analysis of the clinical and laboratory data of the patients with confirmed acute pancreatitis and hospitalization within the period from 01.01.2015 – 01.10.2020 at the Department of Medicine II, LMU Klinikum

Study design: Retrospective single-center study (Department of Medicine II, LMU Klinikum)

Study population: Patients diagnosed with acute pancreatitis (2015-2020)

Main study parameters/endpoints:

Due to the lack of a clear diagnostic algorithm to perform an EUS-examination in order to determine the cause of acute idiopathic pancreatitis, the aim of the study is to develop a laboratory pattern by using a Machine (Deep) Learning Algorithm

2 INTRODUCTION

AP is the leading cause of hospital admissions among benign gastrointestinal conditions, with more than 275,000 annual hospitalizations in the United States. The incidence varies from 5 to 30 cases per 100,000 individuals (1). Although it can be caused by many different conditions, it is well known that alcohol and gallstone disease are the primary causes, accounting for more than two thirds of the cases of AP worldwide (2,3). After a basic clinical workup, an etiology can be established after an acute episode in the majority of patients, but in up to 10-30% of cases, the cause is not found despite a clinical history, laboratory tests (triglyceride and calcium concentrations) and conventional cross-sectional imaging, such as transabdominal ultrasound and computed tomography (CT). Biliary microliths are defined as concrements smaller than three millimeters, which usually cannot be detected by conventional imaging

techniques, but which can be identified as characteristic crystals or granules under the polarizing microscope. Thanks to high sensitivity and specificity, endosonographic ultrasonography is considered the "gold standard" for the diagnosis of sludge or microlithiasis (4,5). A study published in 2015 had retrospectively shown that the cumulative rate of biliary complications, such as acute cholecystitis, acute cholangitis, and acute pancreatitis, was significantly higher in patients with biliary sludge than in those without biliary sludge (33,9% vs 15.8%, $p = 0,021$) (6). A small randomized trial in 85 patients with acute pancreatitis of unclear etiology, but not studied by endosonography, had also reported that the recurrence rate after cholecystectomy was significantly reduced at 10% compared with 41% in the control group; 60% of the operated patients had detectable sludge (7).

Considering IAP/APA guidelines, the etiology of acute pancreatitis should be determined on admission, using:

- detailed personal history (i.e., previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as ERCP)
- detailed family history of pancreatic disease
- physical examination
- laboratory serum tests (i.e., liver enzymes, calcium, triglycerides)
- imaging (i.e., right upper quadrant ultrasonography). (GRADE 1B, strong agreement)

If the patient does not meet the above criteria, idiopathic pancreatitis is considered. Endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, which is considered as one of the most frequent etiologies. The percentage of patients with acute idiopathic pancreatitis and microlithiasis detection is reported to be up to 75% depending on the study [6 - 8]. Due to the lack of a clear diagnostic algorithm to perform an EUS-examination in order to determine the cause of acute idiopathic pancreatitis, the aim of the study is to develop a laboratory pattern by using a Deep Machine Learning Algorithm, which will help in the diagnostic work-up to determine whether further (invasive) diagnostics (for the detection of suspected microlithiasis) is necessary.

3 STUDY DESIGN

Retrospective single-center analysis (Department of Medicine II, LMU Klinikum).

4 STUDY POPULATION

4.1 Population (base)

Patients with confirmed acute pancreatitis and hospitalization within the period from 01.01.2015 – 01.10.2020 at the Department of Medicine II, LMU Klinikum

4.2 Inclusion criteria

Patients who were hospitalized for acute pancreatitis in 2015 - 2020 and received an endoscopic ultrasound examination as part of the diagnostic workflow. A distinction will be made between the group that has no possible cause of acute pancreatitis other than microlithiasis (and the corresponding endosonographic evidence of microlithiasis) and the group of patients whose pancreatitis episode can be adequately explained by another cause. The aim is to determine retrospectively in this group of patients whether one of the here named known pancreatitis risk factors can be linked to the episode:

Detailed personal and family history:

Alcohol use, recent ERCP, recent start or changes in use of drugs associated with acute pancreatitis , recent major abdominal trauma, recent abdominal surgery, familial and hereditary pancreatitis, cystic fibrosis-related pancreatitis

Laboratory tests, including:

Elevated blood serum triglyceride level,

Elevated blood serum calcium level (corrected for the blood serum albumin level)

4.3 Exclusion criteria

Patients Patients in whom the diagnosis of acute pancreatitis has not been confirmed

5 METHODS

5.1 Study endpoints

Evidence of a laboratory pattern that can serve as a predictor of microlithiasis-related acute pancreatitis

6. STATISTICAL ANALYSIS

We will train linear and non-linear machine learning classifiers using the H2O.ai selecting automatically the best suitable machine learning method on the training set, to distinguish patients. We want to categorize patient variables among the parameters assessed at the first contact to identify and compute the predictor model with a mean area under the curve using AUC and PPV in the test and control cohort. Access to personal information will be restricted to the study doctor / collaborators to check the study's data and procedures, but always maintaining their confidentiality according to current legislation. The Investigator, when processing and treating the data, will take the appropriate measures to protect them and prevent access to them by unauthorized third parties. A anonymisation of the data ensures that the user data / user profiles cannot be linked to personnel data and will take place before matching the dataset within an excel file. Password protected clinical (personnel) data (collected from endoscopy and ward obtained results and matched within an excel database) cannot be read, copied, altered or removed by unauthorized persons.

7. DATA MANAGEMENT

7.1. Regulation statement

The Investigator, when processing and treating the data, will take the appropriate measures to protect them and prevent access to them by unauthorized third parties. A anonymisation of the data ensures that the user data / user profiles cannot be linked to personnel data and will take place before matching the dataset within an excel file. Password protected clinical (personnel) data (collected from endoscopy and ward obtained results and matched within an excel database) cannot be read, copied, altered or removed by unauthorized persons. Patients will be enrolled to this retrospective cohort study according to this study protocol and all applicable laws, regulations, and guidance regarding patient protection.

7.2 Recruitment and consent

Patient data will be collected retrospectively from the already existing electronic patient records. We do not ask the patients for informed consent as they will not be subjected to any procedures, there are no risks associated with this study, and all their data will be handled in a coded (anonymized) manner. As all data will be anonymized no information to any patient included can be traced back.

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Sirtl et al. A machine-learning based decision tool selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary etiology

Dear Professor Tarnawski,
Dear Editorial Board,

June 26, 2023

we are pleased to submit our manuscript "*A machine-learning based decision tool selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary etiology*" to your renowned journal. The last author of our manuscript, Mr Ujjwal M. Mahajan, PhD and Assistant Professor at the LMU University Hospital Munich, is a native English speaker, so we do not require a *Non-Native Speakers of English Editing Certificate*.

We look forward to your feedback on the manuscript and
send you our best regards from Munich!

Dr. Simon Sirtl
LMU University Hospital Munich

Vorstand

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Sirtl et al. A machine-learning based decision tool selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary etiology

Dear Professor Tarnawski,
Dear Editorial Board,

June 26, 2023

We herewith confirm that the statistics of our manuscript "*A machine-learning based decision tool selecting patients with idiopathic acute pancreatitis for endosonography to exclude a biliary etiology*" was led by our experienced bioinformatician/statistician Ujjwal M. Mahajan (PhD, Assistant Professor). All data R scripts or functions are available online at the following link: <https://github.com/mayerlelab/microlithiasisPredict>.

To underline Mr. Mahajan's outstanding statistical skills, here are some selected references from very renowned journals:

1. **Mahajan UM** et al.. Independent Validation and Assay Standardization of Improved Metabolic Biomarker Signature to Differentiate Pancreatic Ductal Adenocarcinoma From Chronic Pancreatitis. **Gastroenterology**. 2022 Nov;163(5):1407-1422. (IF = 33.8)
2. **Mahajan UM** et al. Tumor-Specific Delivery of 5-Fluorouracil-Incorporated Epidermal Growth Factor Receptor-Targeted Aptamers as an Efficient Treatment in Pancreatic Ductal Adenocarcinoma Models. **Gastroenterology**. 2021 Sep;161(3):996-1010.e1. (IF = 33.8)
3. **Mahajan UM** et al. Tumour-specific delivery of siRNA-coupled superparamagnetic iron oxide nanoparticles, targeted against PLK1, stops progression of pancreatic cancer. **Gut**. 2016 Nov;65(11):1838-1849. (IF = 16.6)

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We are always available for questions and look forward to your feedback on our manuscript.
your feedback on our manuscript!

Kind regards,

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