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Early Achievable Severity (EASY) Index for Simple and Accurate Expedite Risk Stratification in Acute Pancreatitis

István Hritz[1,2], **Péter Hegyi**[1,3]

1)1st Department of Medicine, University of Szeged, Szeged;
2) Bács-Kiskun County University Teaching Hospital, Kecskemét;
3) MTA-SZTE Lendület Translational Gastroenterology Research Group, Szeged, Hungary

Address for correspondence:
Péter Hegyi, MD, PhD, DSc
1st Department of Medicine, University of Szeged
Korányi fasor 8
6720 Szeged, Hungary
hegyi.peter@med.u-szeged.hu

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ABSTRACT

Background: Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract associated with significant morbidity and mortality. The assessment of severity is crucial in the management of the disease. Current methods of risk stratification in AP have a limited value, as they provide little additional information thus delaying appropriate patient care. Early recognition of severe disease may prevent serious adverse events and improve patient management as well as overall clinical outcome.
Methods/Design: The EASY trial is an observational, multicenter, prospective cohort study for establishing a simple, easy and accurate clinical scoring system for early prognostication of AP. Evaluation of simple attainable potential prognostic parameters obtained at admission (or not later than 6-12 hours afterwards) from patients diagnosed with AP will be performed to assess their potential correlation with the disease severity. The selected parameters that show the strongest correlation with severe disease course will be further utilized as potential early severity prognostic markers for prospective new patient stratification. Comparison of patients' clinical course with the obtained results of early risk stratification may validate the utilized parameters as prognostic markers. The trial has been (i) discussed and (ii) accepted in a distinguished international scientific meeting, (ii) receiving the relevant ethical approval (TÜKEB: 30595-1/2014/EKU), (ii) registered at the ISRCTN registry which is a primary clinical trial registry recognized by WHO (Trial registration number: ISRCTN10525246).
Conclusion: The EASY trial is designed to develop a simple and accurate clinical scoring system that can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course.

Key words: acute pancreatitis – disease severity – risk stratification – prognostication – EASY clinical scoring system.

Abbrevations: AP: acute pancreatitis; APA: American Pancreatic Association; APACHE: Acute Physiology and Chronic Health Examination; BISAP: Bedside Index of Severity in Acute Pancreatitis; EASY Index: Early Achievable Severity Index; HAPS: Harmless Acute Pancreatitis Score; IAP: International Association of Pancreatology.

INTRODUCTION

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract that requires acute hospitalization and despite the special care is still associated with significant morbidity and mortality worldwide [1]. The assessment of severity is a crucial issue in the management of AP. It is critical to identify patients who are at high risk for a severe disease course, since they require close monitoring and immediate aggressive treatment.

A number of predictive scoring systems have been developed with the aim of assisting the clinicians in predicting prognosis during the early phase. However, the current methods of risk stratification in AP have important limitations. The Ranson [2] and the modified Glasgow score [3] contain data not routinely collected at the time of hospitalization. In addition, both require 48 hours to be completed, missing a potentially valuable early therapeutic window [4]. The most commonly utilized predictive scoring system for clinical research studies in AP is the Acute Physiology and Chronic Health Examination (APACHE) II [5]. However, the APACHE II was originally developed as an intensive care tool and requires the collection of a large number of parameters, some of which may not be relevant to prognosis in AP [6]. The recently developed new scoring systems such as the Bedside Index of Severity in Acute Pancreatitis (BISAP) and the Harmless Acute Pancreatitis Score (HAPS) involve a simplified approach that

can be performed during the first 24 hours of hospitalization. The BISAP score was developed as a simple system to assess the risk of in-hospital mortality in AP and is a facile tool available for early prediction of persistent organ failure and mortality [6]. The HAPS can predict a non-severe disease course with 96-97% specificity with a positive predictive value of 98% [7]. However, both scoring systems have important disadvantages and therefore, they have not been found to be more accurate than other scoring systems [8].

In general, AP-specific scoring systems have a limited value, as they provide little additional information to the clinician in the evaluation of patients and thus may delay appropriate management [9]. There is still a need for simple, more chiseled and clinically oriented novel models to further improve predictive accuracy of severity in acute pancreatitis within 12 hours of presentation [10].

Our aim is to develop a simple, EASY and accurate clinical scoring system that can be performed also in small hospitals with limited access to diagnostic tools, which can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course. The ability to perform risk stratification of patients earlier and simpler in their disease course would take a major step to improving future management strategies in AP.

We propose an observational, multicenter, prospective cohort trial for establishing a simple, EASY and accurate clinical scoring system for early prognostication of AP.

METHODS / DESIGN

Preliminary settings

The Hungarian National Pancreas Registry (Registry) has been established by the Hungarian Pancreatic Study Group (HPSG) for data collection of patients with different pancreatic disorders. This unique collective platform in Hungary provides a database for all pancreatic diseases and offers an interdisciplinary consultation opportunity for physicians nationwide. In terms of AP the aim of the Registry has been to record and provide information on the etiology, diagnosis, clinical features and management of patients with AP [11, 12]. To date, data of more than 700 patients with AP from more than 25 different centers – including the four Medical Universities/ Faculties – have been uploaded into this database.

The web-based Registry provides the background for data management of this trial (www.pancreas.hu).

Assessment of potential prognostic parameters

A comprehensive literature search in terms of patient stratification and prognostication in AP resulted in the identification of different potential prognostic markers. The parameters that were selected had been already used and shown effective in different AP severity scoring systems, or were demonstrated to be risk factors for severe AP, or reported to have a potential effect on the disease course.

The Ranson, modified Glasgow, APACHE II, BISAP and HAPS scoring systems were assessed and the simple obtainable parameters from each system were selected: age, white blood cell (WBC) count, serum glucose, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), hematocrit, serum calcium and blood urea nitrogen (BUN) from Ranson; age, WBC count, serum calcium, BUN, LDH, AST, albumin, glucose from the modified Glasgow; age, body temperature, blood pressure, heart- and respiratory rate, serum sodium, potassium, creatinine, hematocrit, WBC count, Glasgow coma scale (GCS) from APACHE II; age, BUN, GCS, body temperature, heart- and respiratory rate, WBC, pleural effusion from BISAP; hematocrit, serum creatinine, rebound tenderness and guarding from HAPS.

The aim was to choose parameters that can be obtained simply and early at patient admission.

Patients and centers involved into the trial

The EASY trial is a large population based observational, multicenter, prospective cohort study of patients hospitalized due to AP irrespectively of the etiology.

Approximately 1200 (900+300) patients from multiple centers will be enrolled into this trial using the Registry. Patients with AP diagnosed based on the fulfillment of "2 out of 3" of the criteria [13, 14] will be selected.

Until now, 6 centers from Hungary, 4 centers from Romania and 13 other centers from 8 countries (Belarus, Czech Republic, Finland, Italy. Lithuania, Republic of Moldova, Russian Federation, Ukraine) have been assigned to the study (Table I).

However, other centers throughout the world are welcome to participate in the EASY trial. Online Call for Centers is available at http://www.pancreas.hu/en/studies. Completion of the LETTER OF INTENT form will be mandatory for registering the participation of each institution. HPSG will acknowledge receipt of the LETTER OF INTENT form and will contact centers providing them with additional study information.

The trial was discussed during the 3rd meeting of the Hungarian Pancreatic Study Group (Szeged. Hungary, November 21, 2014) and accepted by the participants.

Preliminary data collection and evaluation

In the first part of the trial, collection of potential prognostic parameters of prospectively enrolled 900 patients within 6-12 hours after admission will be performed. Simple obtainable data (e.g. medical history, physical examination, laboratory tests and diagnostic imaging) (Table II) from patients with AP will be collected and recorded. The available questionnaires will help in the proper data collection (see http://www.pancreas.hu/en/studies/easy).

The obtained data will be individually statistically analyzed to assess their potential correlation with the disease severity.

Validation and utilization of potential prognostic markers

Those parameters that show the strongest correlation with severe disease course of AP will be in the second part of the trial selected and collectively utilized as potential early severity prognostic markers for stratification of the prospectively enrolled new patients' (~300 patients). The comparison of patients' clinical course with the obtained results of early risk stratification in case of correlation may validate the utilized parameters as prognostic markers. By assessing the ability of these markers for prognostication of AP the goal is to establish

Table I. List of centers already assigned to the study

Country	City	Institute
Belarus	Gomel	Gomel Regional Clinical Hospital
Czech Republic	Ostrava	Vitkovicka Nemocnice A. S.
Finland	Helsinki	Hospital of Helsinki, University Central Hospital
Hungary	Szeged	University of Szeged
Hungary	Pécs	University of Pécs
Hungary	Székesfehérvár	Szent György University Teaching Hospital of County Fejér
Hungary	Budapest	Bajcsy-Zsilinszky Hospital
Hungary	Békéscsaba	Dr. Réthy Pál Hospital
Hungary	Debrecen	University of Debrecen
Italy	Rome	S. Andrea Hospital University La Sapienza
Italy	Pavia	University Hospital of Pavia, IRCCS Foundation San Matteo University Hospital
Lithuania	Vilnius	Vilnius University Hospital Santariskiu Klinikos
Republic of Moldova	Chisinau	The State University of Medicine and Pharmacy
Romania	Bucharest	University of Medicine and Pharmacy Carol Davila, Fundeni Clinical Institute
Romania	Targu Mures	Mures County Emergency Hospital
Romania	Cluj Napoca	Regional Institute of Gastroenterology and Hepatology
Romania	Craiova	University of Medicine and Pharmacy
Russian Federation	Saint-Petersburg	Saint-Luke Clinical Hospital
Russian Federation	Simferopol	Hospital of Medical Academy named after SI Georgievsky
Russian Federation	Moscow	Moscow Clinical Scientific Center
Ukraine	Kiev	Bohomolets National Medical University
Ukraine	Kiev	Shalimovs National Institute of Surgery and Transplantology
Ukraine	Ivano-Frankivsk	Ivano-Frankivsk National Medical University, Regional Clinical Hospital

a new simple scoring system, the Early Achievable SeveritY (EASY) index. The chart of the experimental design is shown on Figure 1.

Patient enrollment and data collection will be performed at all centers and data analysis will take place at the 1st Department of Medicine, University of Szeged. All of the patients' data will be handled anonymously.

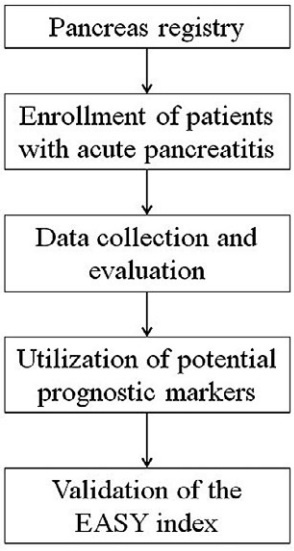

Fig. 1. Chart of the experimental design

Statistical analysis

Acute pancreatitis severity will be the variable to be explained; with the help of 29 potential prognostic parameters this variable will be predicted. Statistical analysis will be carried out by data mining methods: classification models will be used to create the scoring system. The applied method will be determined based on the main characteristics of the collected data, and the most suitable method – or method combination – will be chosen. The following data mining methods are being contemplated: logistic regression, discriminant analysis, random forest analysis, decision tree, and cluster analysis.

The above classification or prediction models allow detecting the most important parameters in the prognostication of AP severity and help to prepare a classification algorithm, which may facilitate the fast decision. ROC analysis and/or confusion matrix will be performed to evaluate the predictive power of the classification algorithm.

In order to carry out data mining with reliable results the sample size must be sufficiently large. A commonly used rule of thumb is to collect a minimum of 10 cases per predictor, therefore the planned sample size of 1200 (900+300) should be adequate.

Expected results

The expectation is to develop a simple, EASY and accurate clinical scoring system that can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course.

Table II. Potential prognostic parameters of severity in AP

Medical history
previous acute pancreatitis
alcohol intake
disorder of lipid metabolism
smoking
comorbidities (e.g. diabetes, hypertension, ischemic heart disease)
Physical examination
age
weight/height – body mass index (BMI)
abdominal tenderness and/or guarding
heart rate
body temperature
respiratory rate
blood pressure
mental state (Glasgow coma scale)
Laboratory tests
white blood cell (WBC) count
hematocrit
serum glucose
blood urea nitrogen (BUN)
creatinine
sodium
potassium
estimated glomerular filtration rate (eGFR)
C-reactive protein (CRP)
amylase
aspartate aminotransferase (AST)
calcium
albumin
lactate dehydrogenase (LDH)
Diagnostic imaging (ultrasonography/X-ray/CT)
pleural fluid or effusion, pulmonary infiltration
abdominal fluid

The applicable EASY scoring system may serve as a useful clinical tool at the early phase of the disease course to identify those patients who are at risk of severe morbidity or mortality, since early recognition of severe AP enables clinicians to facilitate proper management thus improve clinical outcome and survival of the patients.

Ethical issues

This is an observational prospective cohort study (in which the care or services that patients receive will not be altered); therefore it has a relatively low-risk. The study has an ethical approval (No. 30595-1/2014/EKU) by the National Hungarian Ethical Authority (ETT TUKEB). Study management will strictly follow the Ethical Guidelines for Observational Studies.

Trial registration

The study has been registered in the International Standard Randomised Controlled Trial Number (ISRCTN) Register (trial ID: ISRCTN10525246).

DISCUSSION

Acute pancreatitis is one of the most common diseases of the gastrointestinal tract associated with significant morbidity and mortality. The assessment of severity is crucial in the management of the disease. Although the majority of cases of AP are categorized as mild or moderately severe, it is critical to promptly identify those patients who are at risk for severe disease course, since they require close monitoring and immediate aggressive treatment.

The revised Atlanta Classification recognizes three degrees of severity [13, 15, 16]. The majority of patients develop mild AP that is characterized by the absence of organ failure and local or systemic complications and is associated with a low mortality rate (1-3%) [17]. Moderately severe AP is characterized by the presence of transient organ failure (<48 hours) or local or systemic complications and is associated with lower mortality rates than in severe disease course. Fifteen to 20% of the patients develop severe AP that is characterized by persistent organ failure (>48 hours) and is often associated with one or more local complications. The mortality in severe AP ranges high, between 36 and 50% [18]. Early mortality (first 1-2 weeks) is the result of the systemic pro-inflammatory response with multiple organ failure. Late mortality (after 3 weeks) is observed during the anti-inflammatory response which is usually the result of infection of pancreatic necrosis and peripancreatic fluid collections that leads to sepsis and late multiple organ failure [19].

Although the majority of cases of AP are categorized as mild or moderately severe, it is critical to promptly identify those patients who are at risk of severe morbidity or mortality to facilitate management and start proper treatment. It is a challenge to determine the severity of AP during its early stages. Multiple individual risk factors for severe AP have been previously demonstrated including age (>60 years of age) [20], comorbid illnesses (heart failure, chronic renal and liver diseases, cancer) [21], history of chronic alcohol consumption [22] and obesity (BMI >30 kg/m^2) [23]. The initial 24 hours of hospitalization are critical in patient management, because the highest incidence of organ dysfunction occurs during this period [24].

According to the recently published IAP/APA (International Association of Pancreatology / American Pancreatic Association) evidence-based guidelines for the management of AP, systemic inflammatory response syndrome (SIRS) is advised to predict severe AP at admission and persistent SIRS at 48 hours [14]. Early recognition of severe disease would enable clinicians to consider more aggressive interventions within a time frame that could potentially prevent adverse outcomes and improve patient care and survival.

The BISAP and the HAPS can be evaluated during the first 24 hours of hospitalization. However, they have several limitations: a) they do not contain all of the easily achievable parameters (such as BMI or CRP); b) BISAP has the disadvantage that it cannot easily distinguish between transient and persistent organ failure [25, 26], whereas HAPS between the moderate and severe disease course; c) none of them include the time difference between the start of symptoms (pain) and admission, a time window which is crucially

important for drafting the management plan. Importantly, these limitations may delay an appropriate disease management and can influence patient survival. Neither BISAP nor HAPS have become widely utilized in general practice; moreover, both can be rarely visible in scientific publications (while 4,552 publications about AP, 23 papers about BISAP and 6 papers about HAPS have been published during the last 5 years) (data obtained from PubMed). It is obvious that there is still a need for simple and clinically oriented novel models to further improve the predictive accuracy of severity in AP.

The EASY trial is designed to develop a simple and accurate clinical scoring system that can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course. The uniformity of data collection and timing as well as patient management is crucial in this study. The provided questionnaires help in proper data collection, whereas the IAP/APA evidence-based guidelines help in the uniform patient management. We hypothesize that the newly developed EASY scoring system will assist the clinicians to consider more interventions that could potentially prevent serious adverse events and improve patient care as well as overall clinical outcome in the early phase of AP.

Conflicts of interest: No conflict to declare.

Authors' contribution: P.H. initiated the trial. I.H. and P.H. designed the trial. I.H. drafted, whereas P.H. finalized the manuscript.

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