HHS Public Access

Author manuscript

Pancreas. Author manuscript; available in PMC 2021 May 17.

Published in final edited form as:

Pancreas. 2020 ; 49(10): 1276–1282. doi:10.1097/MPA.0000000000001686.

Introduction and Validation of a Novel Acute Pancreatitis Digital Tool:

Interrogating Large Pooled Data From 2 Prospectively Ascertained Cohorts

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D.M.S., C.R.B., and D.C.W designed and built the ADAPT tool. (D.M.S. and D.C.W. are co-inventors in ADAPT, patent pending). P.P. organized APPRENTICE data from database and oversaw cleaning and management of data. P.P. provided expert annotations of APPRENTICE data, and performed statistical analysis comparing ADAPT outputs with patient data and expert annotations. D.M.S. evaluated APPRENTICE data on the ADAPT tool from both phases with initial blinding to outcomes. P.P., D.M.S., A.G., M.H., and G.I.P. interpreted results of study. P.P., D.M.S., and D.C.W wrote article, with M.H., G.I.P., A.G., and C.R.B. editing. J.A.G., R.T., R.K., M.K.G., V.K.S., M.F., T.S., S.T.B., H.N., S.C.G., N.O.Z., L.A., J. J.E., K.T., M.P.-L., S.T., C.O., E.d.-M., G.A.C., and B.U.W. participated in the final revision of the article.

D.M.S. is an employee of Ariel Precision Medicine. C.R.B. is a consultant for Ariel Precision Medicine. D.C.W is a co-founder of Ariel, an unpaid consultant and may have equity. G.I.P. may also have financial interests in Ariel Precision Medicine. The remaining authors had no conflict of interest pertaining to this article. ADAPT was invented by D.M.S. and D.C.W with intellectual property and rights to commercial use are owned by Ariel Precision Medicine, Pittsburgh, Pa (US patent 146945.00101 US Publication No. 20200176119A1 dated 6.4.20).

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.pancreasjournal.com).

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Abstract

Objectives: Acute pancreatitis (AP) is a sudden onset, rapidly evolving inflammatory response with systemic inflammation and multiorgan failure (MOF) in a subset of patients. New highly accurate clinical decision support tools are needed to allow local doctors to provide expert care.

Methods: Ariel Dynamic Acute Pancreatitis Tracker (ADAPT) is a digital tool to guide physicians in ordering standard tests, evaluate test results and model progression using available data, propose emergent therapies. The accuracy of the severity score calculators was tested using 2 prospectively ascertained Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience cohorts (pilot University of Pittsburgh Medical Center, n = 163; international, n = 1544).

Results: The ADAPT and post hoc expert-calculated AP severity scores were 100% concordant in both pilot and international cohorts. High-risk criteria of all 4 severity scores at admission were associated with moderately-severe or severe AP and MOF (both $P < 0.0001$) and prediction of no MOF was 97.8% to 98.9%. The positive predictive value for MOF was 7.5% to 14.9%.

Conclusions: The ADAPT tool showed 100% accuracy with AP predictive metrics. Prospective evaluation of ADAPT features is needed to determine if additional data can accurately predict and mitigate severe AP and MOF.

Keywords

acute pancreatitis; organ failure; outcomes; pancreas; precision medicine

Acute pancreatitis (AP) is a potentially life-threatening inflammatory disease, and one of the most prevalent gastrointestinal disorders requiring hospitalization.[1] The natural course of disease varies from mild and self-limited to a fulminant life-threatening condition.[2] Acute pancreatitis is a complex, progressive syndrome with multiple etiologies and risk factors, with the severity of the inflammatory response correlating poorly with the degree of injury.[3] Unpredictable progression from injury to systemic inflammation (eg, systemic inflammatory response syndrome [SIRS]) and variable progression from systemic inflammation to multiorgan failure (MOF) result in a highly variable clinical course and difficulty managing patients with effective triage and interventions.[4,5]

The progression from AP to MOF occurring over hours to days provide a window of opportunity to make an accurate assessment of the patient to predict severity of disease and provide interventions that may mitigate some of the pathogenic processes. The sequential category of steps in the diagnosis, management and prevention, or recurrence is given in List 1 in Supplemental Digital Content 1 (http://links.lww.com/MPA/A831). Among the most important steps in the acute management of AP are the clinical measures that may determine severity.

The 1974 publication of Ranson criteria drew attention to the fact that a variety of risk factors contribute to and may predict worse outcomes in patients with AP.[6] Since then, dozens of alternative clinical prediction scores have been published, including modifications to Ranson criteria,[7,8] the Glasgow-Imrie criteria,[9] the computed tomography severity index or Balthazar score,[10] the Acute Physiology and Chronic Health Examination II scores,[11] the Bedside Index for Severity in AP (BISAP),[12] the Harmless Acute Pancreatitis Score (HAPS),[13] the Determinant-Based Classification of Acute Pancreatitis Severity,[14] the revised Atlanta classification,[15] the Pancreatitis Outcome Prediction,[16] the Japanese Severity Score,[17] a predictive combinations of multiple scores using Mounzer rules,[18] and others. However, these scores were largely validated in post hoc analyses, are often too complex for widespread adoption and clinical application. Although they provide acceptable negative predictive value (NPV) their positive predictive value (PPV) is generally poor, meaning that the currently recommended early biomarkers of severity do not accurately predict MOF. Some of the limitations of using simple severity scores to predict severe outcomes include the wide variety of etiologies with different severity implications, the effects of unmeasured risk factors including genetic variants, the age, size, morphology and fragility of the patient, and the mitigating effects of early interventions aimed specifically at altering outcome.[19,20] Furthermore, clinically available physiologic, radiographic, and biochemical biomarkers largely measure the magnitude of the ongoing inflammatory response and organ dysfunction rather than identifying the pathogenic mechanisms that lead to organ disfunction and recommending problem-specific interventions to prevent or minimize MOF.[20]

Most scores focus on the patient’s status at 24, 48, and/or 72 hours over real-time monitoring of a rapidly progressing inflammatory process potentially bypassing early pathologic trajectories.[17,18] Thus, the limitations in achieving an acceptable PPV also reflects—in part—the dynamic nature of AP over time, delayed tracking of optimal severity biomarkers without guidance on how to intervene, missing variables in the severity equation of individual patients, and variable responses to treatment linked to essential differences

among patients.[21,22] Furthermore, the existing models are generally population based where they are more accurate in predicting the outcome of the average patient, but inaccurate in predicting outliners, such as MOF. Better prediction models must return to the fundamental biological principles that govern cellular injury, inflammatory responses, organ and systems dynamics and susceptibilities, and the mechanisms that normally protect the body from injury and inflammation.

We believe that patients with new-onset AP will have better outcomes, on average, if they are immediately cared for by expert physician-scientists.[23] However, most patients present to their local health care facility and are cared for by physicians or physician extenders who have excellent skill sets but lack training and guidance in managing complex AP patients. We also believe that this problem may be largely resolved using optimized digital AP management tools (List 2 in Supplemental Digital Content 1, http://links.lww.com/MPA/A831) serving as a clinical decision support system (CDS). To address this perceived need, we developed a new AP CDS tool (Ariel Dynamic Acute Pancreatitis Tracker [ADAPT]; Ariel Precision Medicine, Pittsburgh, Pa) that can be made available at the point of care, processes patient data as they become available, computes patient status and prognostic measures based on the individual patient's unique features, provides evidence- and guideline-based recommendations to assist clinicians in real-time management, and is designed with ease-of-use in mind. The aim of the current study is to conduct a clinical validation on 4 of the severity score calculators in 2 prospective cohorts.

MATERIALS AND METHODS

ADAPT Tool

Ariel Dynamic Acute Pancreatitis Tracker (Patent 146945.00101 US Publication No. 20200176119A1 dated 6.4.20) is a CDS that uses a series of mathematical and rule-based models to emulate features of individual subjects based on, (a) the size of various compartments in an individual case adjusted for age, sex, body composition [eg, fat]; (b) functions of various cells, tissues, organs, and systems; (c) connections between systems (variable permeabilities between compartments to simulate models of vascular leak syndrome [VLS] and gut transepithelial permeability); (d) clinically relevant biomarkers to represent the state of various systems at any time point [including traditional severity scores]; (e) trajectory models to track changes in the biomarkers, compartments, and biological systems using data from pre-AP and throughout the dynamic stages of the disease (eg, to day 7); and (f) predictive models to link trajectories to outcomes, with or without interventions [eg, fluid replacement and/or resuscitation, medical interventions]. Thus, ADAPT is designed to assist clinicians managing individual patients with AP. Ariel Dynamic Acute Pancreatitis Tracker provides a unique opportunity for clinical trials to investigate the effect of treatment regimens in clinical trials.

The novel ADAPT tool utilizes limited available data in a real-world setting and provides evidence-based information through a variety of devices. It was also designed to interface with electronic health records so that useful information from a variety of time points could be integrated into the system directly, or through supervised approaches. This tool's logic computes the maximal subset of severity scores, etiology approximates, and guidance

statements based on the available data, using surrogate measures if necessary (eg, translation of pulse oximetry date into PaO_2 if results of an arterial blood gas is not available). It also assists the clinician with expert-recommended order sets and management plans for consideration. Figure 1 illustrates the logic and process map of ADAPT tool. All patient data can be tracked and analyzed for clinical or translational research, with options to link multiple team members into the care of 1 or more patient. A demonstration of many ADAPT features is available as a freeware research tool at http://adapt-demo.arielmedicine.com/.

In this study, we seek to validate 4 severity measures, from the CDS "severity measure" module, that can be computed in a previously ascertained AP cohort. Additional prospective studies are needed to fully demonstrate ADAPT's potential impact in the field.

Study Design

We examined ADAPT capability to incorporate data and compute 4 predictive metric. The calculated scores were compared with actual scores calculated by a blinded University of Pittsburgh Medical Center (UPMC) investigator. The study hypotheses were tested using previously collected data from Acute Pancreatitis Patient Registry to Examine Novel Therapies in Clinical Experience (APPRENTICE) dataset that was blinded to the outcomes after 24 hours. Two prospective cohorts from the APPRENTICE consortium[24] were used. For the initial phase, investigators analyzed data from UPMC cohort.[25] The second phase included the complete APPRENTICE data set.

Patient Cohort

As an international, multicenter consortium, APPRENTICE applies consistent inclusion/exclusion criteria and shared online data registry.[24] This collaborative platform was launched in 2015 and included 22 sites: 8 sites in the United States, 6 European, 5 Latin American, and 3 Indian sites. Over 1500 patients with AP were prospectively ascertained, with clinical information captured on case report forms and outcomes recorded.

The study protocols were approved by each institution's institutional review board with University of Pittsburgh serving as the coordinating data center and umbrella institutional review board for all subsites (PRO15040389). The study was registered in clinicaltrials.gov (NCT03075618). The detailed description of the approach and methodology of APPRENTICE has been previously published[24] (Supplemental Digital Content 2, http://links.lww.com/MPA/A831).

Phase 1: Accuracy Testing in a UPMC Pilot Cohort

The ADAPT tool is currently capable of calculation of over a dozen different published independent and mixed severity scores. For each patient, ADAPT downloads all available patient information related to pancreatitis. It then partitions the data based on type, and bins dynamic physiological, laboratory, and other time-dependent variables based on time stamps. Within each bin, the tool sequentially evaluates whether it is possible to calculate the next severity score based on availability of required variables or surrogate variables. The data available in the APPRENTICE cohorts allowed the following severity scores to be calculated: SIRS, HAPS, BISAP, and Panc 3.

Severity scores computed by ADAPT were tested for accuracy in a homogenous population of 163 patients from Pittsburgh, Pa who were consecutively enrolled in the APPRENTICE study.[25] The calculated metrics—which include SIRS, HAPS, BISAP, and Panc 3—and predictive Mounzer rules[18] that were computed by ADAPT were compared with the values from a UPMC independent investigator's calculations and annotations.

Phase 2: Accuracy Testing in an International APPRENTICE Cohort

Following phase 1, a larger APPRENTICE dataset consisting of 1544 patients was utilized, following data use agreements and data quality review. Deidentified data limited to the first 24 hours of inpatient care were provided to Ariel through a secure platform. The ADAPT outputs—including SIRS, HAPS, Panc 3, BISAP, and suggested maintenance fluid volumes —, as well as the predictive Mounzer rules for organ failure in each patient (OF likely, OF not likely, or outcome uncertain) were returned to the APPRENTICE investigators. The APPRENTICE-recorded outcomes were considered as ground truth for true positive and true negative, and the concordance between ADAPT calculations and the clinical scores calculated by APPRENTICE investigators who were not potentially conflicted with Ariel was assessed.

For each baseline metric, sensitivity, specificity, NPV, and PPV were calculated by software and by UPMC investigators. The association of each metric with outcome of interest was separately investigated.

Data Analysis

Each of the 4 clinical scores on admission were analyzed for association with clinical outcomes. The outcomes were persistent organ failure, MOF, and prolonged hospital stay. A χ^2 test was applied to analyze these data. SPSS software version 25 (IBM Corp., Armonk, NY) was applied to conduct the statistical analysis. A P value less than 0.05 was considered statistically significant.

RESULTS

Phase 1: UPMC Pilot Cohort

Data related to 163 subjects from UPMC were examined. This cohort consisted of 83% white, with male/female ratio of 1:1. At the time of enrollment, median age of the pilot cohort was 53 years and mean body mass index (BMI) of 31 kg/m^2. In the pilot cohort, 50% had active alcohol consumption and 29% were active smokers at the time of enrollment. In terms of etiology, there were 36% biliary, 22% alcoholic, and 19% idiopathic AP.

Data from the first 24 hours were used to calculate BISAP, HAPS, Panc 3, and SIRS in 163 subjects. The investigators noted 100% concordance between ADAPT output and calculations by an independent UPMC investigator in 4 tested clinical scores, as well as the predictive Mounzer rules. Among the 4 metrics, admission SIRS (P = 0.003) and BISAP (P = 0.001) showed significant association with development of organ failure. Admission SIRS was the only metric which showed significant association with the Revised Atlanta Criteria

(RAC) severity (moderately severe and severe vs mild AP, $P < 0.001$) and intensive care unit admission ($P < 0.001$).

Phase 2: International APPRENTICE Cohort

A total number of 1544 of subjects from 22 sites were analyzed. This cohort was comprised of 49.8% White, 23.7% Asian Indian, and 5.2% Black/African Americans, and 20.3% were Hispanic or Latino. Median age of the study population was 49 years, with a male/female ratio of 1.1 and mean BMI of 27.6 (standard deviation, 6.4 kg/m^2). In terms of etiology, gallstone (45.1%), alcoholic (21.4%), and idiopathic AP (16.1%) were the most common etiologies. The studied cohort was comprised of 1024 (66%) mild, 354 (23%) moderately severe, and 166 (11%) severe AP subjects. Baseline characteristics of APPRENTICE cohort are shown in Table 1.

Data collected within patients' first 24 hours were used to calculate BISAP in 1365 (88.4%), HAPS in 1427 (92.4%), Panc 3 in 1414 (91.6%), and SIRS in 1481 (96.0%) subjects from the total study population. After adjudication, there was 100% concordance between ADAPT output and the independent calculation of scores.

Among subjects with calculated admission SIRS, 805 were SIRS-positive (score ≥2), and 676 were SIRS-negative. In the SIRS-positive subset, 152 (19%) developed severe AP, 235 (29%) developed moderately severe AP, and 418 (52%) were mild AP. In the SIRS-negative subset, 557 (82%) patients were mild, and 103 (15%) were moderately-severe AP. Only 16 (2%) SIRS-negative cases eventually developed severe AP.

All 4 clinical scores on admission showed significant association with eventual development of MOF and severity defined based on RAC (Table 2). The scores had low positive predictive value ranging from 7.5% to 14.9% but a high negative predictive value (range, 97.8%–98.9%). Systemic inflammatory response syndrome demonstrated the highest NPV in prediction of MOF (98.9%) and moderate/severe AP (82.3%). Positive predictive value and NPV of scores for development of MOF and severe AP are summarized in Table 3.

DISCUSSION

The management of patients with AP remains challenging,[26,27] especially for nonexperts because of the complexity and variability between patients,[28] the dynamic nature of the evolving inflammatory response,[29,30] the need for etiology-specific interventions, the ongoing emergence of complications, and the reactive nature of supportive care.[23] We believe that development of new CDS tools that utilize available health information and advanced, patient-specific modeling will help overcome these challenges resulting in better outcomes and lower costs. Herein, we report the clinical validation of one module of ADAPT tool using clinical data collected in the APPRENTICE studies with 100% accuracy in calculating 4 widely used severity scores. Furthermore, the severity scores generated within the first 24 hours were highly accurate in identifying a subset of patients that would not progress to MOF (ie, NPV for MOF). This has immediate clinical utility in downgrading the intensity of care for this large subset of patients.

The APPRENTICE data set did not include all the data necessary to calculate all of the previous published severity scores, limiting the analysis to BISAP, SIRS, HAPS, and Panc 3. As expected, these scores were calculated with 100% accuracy. All 4 clinical scores exhibited correlation with MOF as well as moderately severe or severe AP based on RAC classification.[15]

The 4 historical severity scores showed low PPV when applied according to the conventional cutoffs (Table 3) as seen in previous studies.[18] Mounzer et al[18] published a study of 9 scoring systems and 2 biomarkers for MOF in a training (n = 256) and a validation (n = 397) cohort. Most of the scores performed well in *excluding* MOF (eg, at 24 or 48 hours when the outcome was evident), but these scores failed to accurately predict MOF using admission data with PPV ranging from 0.34 to 0.70 in the training set and were much worse in the validation set with PPVs of 0.11 to 0.23. At 48 hours after admission, the scores were only slightly better, with PPV ranging from 0.35 to 0.72 in the training set and 0.17 to 0.45 in the validation set. Machine learning was used to develop 12 rules to determine likely or unlikely to develop MOF with 95% confidence. The area under the curves reached 0.92 in the training set, and 0.84 in the validation set.[18] However, this approach required multiple biomarkers that are not generally ordered, the calculations are complex and only half of the patients could be classified at admission, and therefore, the golden time for intervention is not well managed.[26] These data demonstrate that population-based, case-control, *post hoc* analysis of a highly variable disorder is severely limited, but that admission data can be used to identify a subset of patients with a high probability of either MOF or non-MOF.

The ADAPT tool is predicted to outperform the traditional population-based statistical approaches by rapidly generating a patient-specific, mixed, mechanistic model that considers most etiologies and system-based responses to disease trajectories and interventions. Each of the components of the model (eg, each organ and system) has different risk and thresholds of failure,[31] so outcomes must be calibrated with risks and stressors within each component. Etiologies are also important, because MOF from hypertriglyceridemic AP, for example, may be driven by lipotoxicity with a relatively mild acute inflammatory response versus biliary or alcoholic AP[32–34] Although mechanistic models are much more difficult to build, [35,36] we have the advantage of having components reflecting the underlying biological functions and thresholds for dysfunction, of linking different organs together with sequential and contingent specifications, and tracking each component with mechanism-specific biomarkers. Thus, rather than classifying a patient as likely MOF, this type of model should be able to predict why MOF will likely occur, how MOF will occur, when MOF will occur, by how much, and what various intentions are likely to do to avert MOF. These additional features will also require clinical validation.

A major need in AP clinical research is the ability to rapidly identify patients with AP, to assess disease severity and to review inclusion/exclusion criteria for enrollment in randomized clinical trials.[37] Linking a digital tool with the EHR to assist in patient identification and classification of potential research patients and alerting care providers and research team could markedly accelerate the ascertainment process so that early interventions are possible. This may result in higher patient enrollment rates for these trials,

reduced cost associated with patient identification, screening and ascertainment and overcome the major limit of delayed enrollment as seen in previous clinical trials.[27]

This study had several limitations. First, the APPRENTICE study was not designed to cross-examine full capacity of the ADAPT tool. Therefore, there were many measures and analytes that ADAPT utilizes that were not available such that the Acute Physiology and Chronic Health Examination II, Glasgow-Imrie, Japanese Severity Score, Pancreatitis Outcome Prediction, and Ranson's risk scores could not be calculated. Furthermore, important features of ADAPT could not be tested, such as the type of fluid deficit, the presence of shock, and the approach to management of the patients (eg, maintenance fluids vs maintenance plus fluid resuscitation). These features, which are currently built into ADAPT, should be tested in future studies.

This is the first report on a novel digital tool designed to capture and process large-volume clinical and laboratory data. The strengths of this study include the large number of consecutively ascertained patients from several centers, including international centers, and a distribution of study sites from both academic centers and community-based centers, representing a realistic cross section of the AP population and management approaches. We could examine ADAPT functionality in processing large data and calculating of 4 well-established metrics in a timely fashion.

In summary, we report on the testing of a new digital tool designed to support physicians caring for patients with AP using the APPRENTICE cohort. Calculations of 4 of the currently used scores were 100% accurate. Furthermore, the tool proved to be useful in assessing the predictive value of existing severity scores. Considering the paucity of clinical trial in AP, the ADAPT tool shows promise of being instrumental in future randomized clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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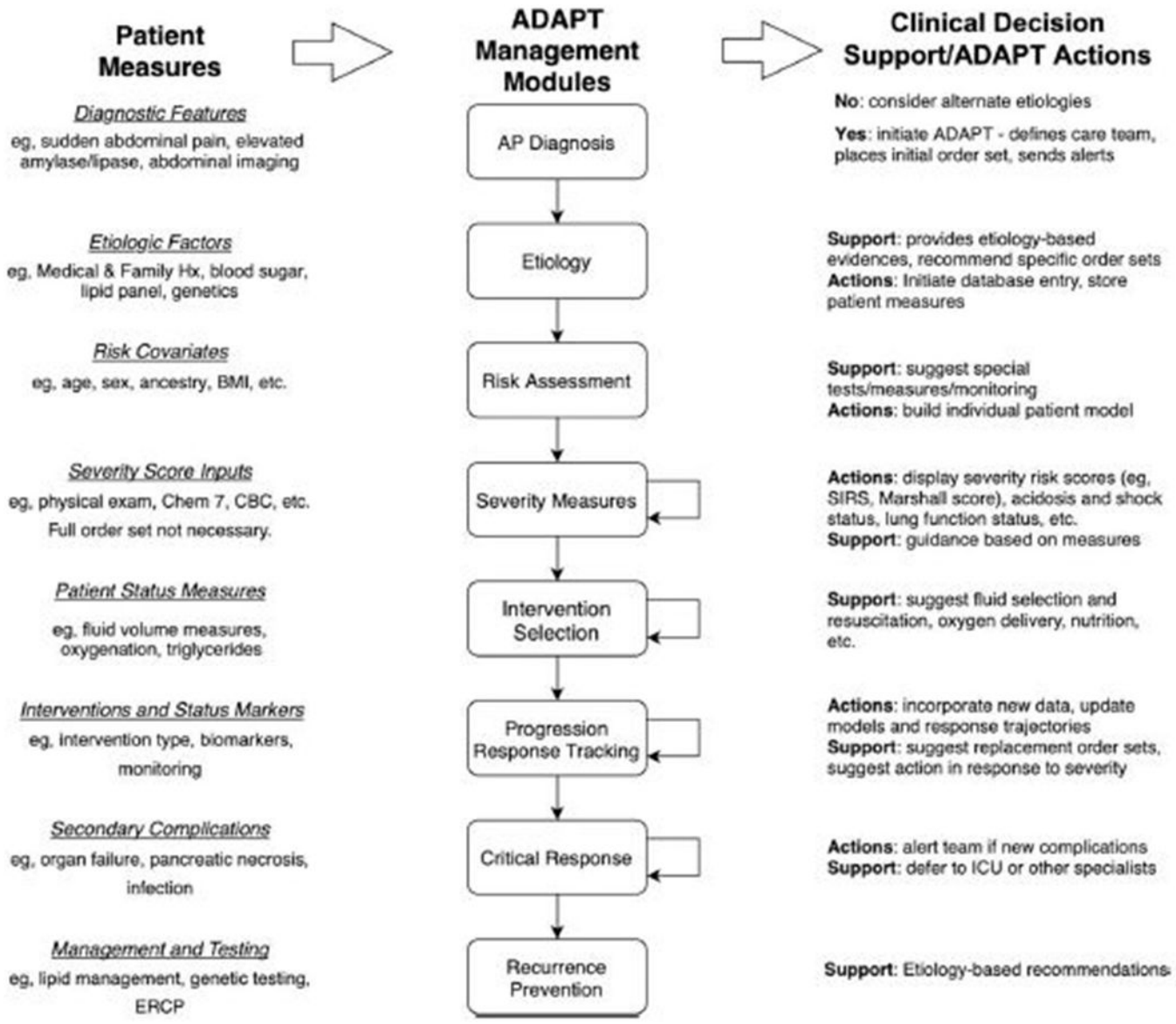

FIGURE 1.

Flow diagram of the functions of ADAPT at sequential stages of management. Center column; the management steps of AP are outlined from top to bottom (see List 1 in Supplemental Digital Content 1, http://links.lww.com/MPA/A831). Left column, the types of information used by ADAPT (Input Parameters). Right column, the functions of ADAPT and the resulting Alerts, Clinical Decision Support guidance, and ordering templates. Circle arrows, continuously updated modules during the AP event. ABG, arterial blood gas; BMP-Chem7, basic metabolic panel including serum sodium, chloride, potassium, bicarbonate, BUN, and Cr. BUN, blood urea nitrogen; Cr, creatinine; CBC, complete blood count [including hematocrit]; CRF, case report form; CRP, c-reactive peptide; DIC, disseminated intravascular coagulation; DM, diabetes mellitus; EHR, electronic health record; ERCP, endoscopic retrograde cholangiopancreatography, Hx, history, ICU, intensive care unit;

LDH, lactate dehydrogenase; LFT, liver function [injury] test. The diagram is for illustrative purposes and does not provide a complete description of ADAPT or its uses.

TABLE 1.

Baseline Characteristics and Clinical Outcomes of the APPRENTICE Acute Pancreatitis Cohort

Variables	Value
Age, median (IQR), y	49 (34–64)
Sex, male, n (%)	808 (52.3)
Race/ethnicity, n (%)	
White	769 (49.8)
Asian Indian	366 (23.7)
Black or African American	80 (5.2)
Hispanic or Latino	314 (20.3)
BMI, mean (SD), kg/m^2	27.6 (6.4)
Active smoking, n (%)	352 (22.8)
Active alcohol consumption, n (%)	587 (38.0)
Etiology, n (%)	
Biliary	697 (45.1)
Alcoholic	331 (21.4)
HTG	70 (4.5)
Idiopathic	249 (16.1)
Post-ERCP	131 (8.5)
Length of hospital stay, median (IQR), d	8 (5–13)
Revised Atlanta Classification, n (%)	
Mild	1023 (66.2)
Moderately-severe	351 (22.7)
Severe	170 (11.1)
Pancreatic necrosis, n	310 *
ICU admission, n (%)	257 (16.6)
Death, n (%)	39 (2.5)

* Of 903 subjects with contrast-enhanced CT scan.

ERCP indicates endoscopic retrograde cholangiopancreatography; HTG, hypertriglyceridemia; IQR, interquartile range.

TABLE 2.

Association Between Admission Metrics Values and Development of Single Organ Failure or MOF

	Severity Based on RAC, n				Organ Failure Status, n		
Metrics on Admission	**Mild**	**Moderately Severe**	**Severe**	***P***	**SOF/NOF**	**MOF**	***P***
SIRS				<0.001			<0.001
Negative	557	103	16		669	7	
Positive	418	235	152		727	78	
Panc 3				<0.001			<0.001
Negative	420	93	25		526	12	
Positive	508	231	137		806	70	
BISAP				<0.001			<0.001
Negative	701	180	43		908	16	
Positive	195	129	117		375	66	
HAPS				0.017			<0.001
Negative	307	101	31		433	6	
Positive	636	222	130		913	75	

NOF indicates no organ failure; SOF, single-organ failure.

Pancreas. Author manuscript; available in PMC 2021 May 17.

TABLE 3.

Negative and Positive Predictive Values of The 4 Metrics Investigated

	PPV, %	NPV, %	Outcome of Interest
SIRS	9.6	98.9	MOF
	39.3	82.3	Moderate/severe
Panc 3	8.0	97.8	MOF
	42.0	82.0	Moderate/severe
HAPS	7.5	98.6	MOF
	35.3	70.0	Moderate/severe
BISAP	14.9	98.3	MOF
	55.6	75.9	Moderate/severe