


SHORT COMMUNICATIONS

Open Access



The challenge of prognostic markers in acute pancreatitis: internist's point of view

Ombretta Para¹, Lorenzo Caruso¹, Maria Teresa Savo^{1,2*} , Elisa Antonielli¹, Eleonora Blasi¹, Fabio Capello³, Tiziana Ciarambino⁴, Lorenzo Corbo¹, Armando Curto⁵, Margherita Giampieri¹, Lucia Maddaluni¹, Giacomo Zaccagnini¹ and Carlo Nozzoli¹

Abstract

Acute pancreatitis, the most frequent hospitalization reason in internal medicine ward among gastrointestinal diseases, is burdened by high mortality rate. The disease manifests mainly in a mild form, but about 20-30% patients have a severe progress that requires intensive care. Patients presenting with acute pancreatitis should be clinically evaluated for organ failure signs and symptoms. Stratifying patients in the first days from symptoms onset is essential to determine therapy and care setting. The aim of our study is to evaluate prognostic factors for acute pancreatitis patients, hospitalized in internal medicine wards, and moreover, understanding the role of various prognostic scores validated in intensive care setting in predicting in-hospital mortality and/or admission to intensive care unit. We conducted a retrospective study enrolling all patients with diagnosis of acute pancreatitis admitted to an internal medicine ward between January 2013 and May 2019. Adverse outcome was considered in-hospital mortality and/or admission to intensive care unit. In total, 146 patients (137 with positive outcome and 9 with adverse outcome) were enrolled. The median age was (67.89 ± 16.44), with a slight prevalence of male (55.1%) compared to female (44.9%). C protein reactive ($p = 0.02$), creatinine ($p = 0.01$), sodium ($p = 0.05$), and troponin I ($p = 0.013$) after 48 h were significantly increased in patients with adverse outcome. In our study, progression in SOFA score independently increases the probability of adverse outcome in patients hospitalized with acute pancreatitis. SOFA score > 5 is highly predictive of in-hospital mortality (O.R. 32.00; C.I. 6.73-152.5; $p = 0.001$) compared to other scores. The use of an easy tool, validated in intensive care setting such as SOFA score, might help to better stratify the risk of in-hospital mortality and/or clinical worsening in patients hospitalized with acute pancreatitis in internal medicine ward.

Keywords: Acute pancreatitis, Prognostic factors, Score, Internal wards, Outcome

Introduction

The number of hospitalizations for acute pancreatitis (AP) has doubled over the two last decades [1, 2]. AP is the leading cause of hospitalization in the USA in internal medicine wards among gastrointestinal diseases and is burdened by a high mortality rate [3, 4]. In most cases, the disease manifests in a mild form, but about 20-30% of patients have a severe evolution associated with a single or multi-organ failure that requires

intensive care. An early assessment of severity in AP is crucial, the initial 12 to 48 h of hospitalization are critical for patient management, as this period is considered a window of opportunity for defining interventions to prevent pancreatic necrosis and organ failure [5, 6]. The challenge is indeed to assess AP severity during its early stages in order to prevent complications. Extensive researches have already focused on risk and prognostic factors. Nevertheless, none of the current clinical scoring systems or biochemical markers plays a definitive role, has widespread applicable value or is consistently accurate [7, 8]. The aim of our study is to assess the prognostic factors of patients hospitalized for AP in a specific ward, internal medicine. We also evaluate the efficacy of

* Correspondence: mariatita.savo@hotmail.it

¹Medicina per la complessità assistenziale 1 AOU Careggi, Largo Piero Palagi, 1, 50139 Florence, Italy

²Società Italiana di Salute Digitale Telemedicina, via Teodoro Valfrè, 00165 Rome, Italy

Full list of author information is available at the end of the article



© The Author(s). 2021 **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

different prognostic scores, validated in setting different from internal medicine in predicting mortality among patients with AP diagnosis.

Materials and methods

Design of study

We conducted a retrospective study on patients admitted between January 2013 and May 2019 to an internal medicine ward in AOU Careggi, in Florence, Italy. The patients were enrolled through a computerized electronic medical record (Archimed® medical software version 6.20 by B. Dannaoui, Florence, Italy).

Inclusion criteria

We enrolled patients, transferred from emergency department to internal ward, whose clinic and radiological findings did not suggest the need of high intensity care at first assessment. The patients enrolled were both males and females, aged above 18 years old. We enrolled all the patients with diagnosis of AP during the recovery or at the entrance in ward. According to the revised Atlanta classification, the diagnosis of AP requires at least 2 of the following features [9]:

- (a) Characteristic abdominal pain
- (b) Biochemical evidence of pancreatitis (amylase or lipase elevated > 3 times the upper limit of normal)
- (c) Radiographic evidence of pancreatitis on cross-sectional imaging

Exclusion criteria

Patients who did not satisfy Atlanta classification or needed high intensity care at first assessment were excluded.

All the procedures performed in this study were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a retrospective study that include anonymized patients extracted from hospital database; data are presented aggregated and anonymously. No informed consent was taken.

We also categorized AP presentation as mild, moderately severe, or severe, based on Atlanta classification [9].

Patients were divided in two groups: those with positive outcome (discharged) and those with adverse outcomes (died or transferred to an intensive care unit).

For each enrolled patient were collected: personal data, admission data; comorbidity (gallstones disease, hypertension, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, previous pathology cerebrovascular disease, dementia, presence of solid or hematological neoplasia, alcoholism and smoking habit, body mass index), laboratory analysis (creatinine, sodium, potassium, calcium, brain natriuretic peptide (BNP), troponin I, protein C reactive, procalcitonin, hematocrit, albumin) on the first admission day and after 48 h, arterial blood gas (ABG) parameters at admission and after 48 h, antibiotic and fluid therapy during hospitalization, home therapy. We also computed for each patient the following score, validated for AP in different setting from internal ward: RANSON, APACHE II, MEWS, SOFA score, Q-SOFA, BISAP, CCI, HAPS, ECOG/PS score, BALTHAZAR.

Statistical analysis

Continuous variables were expressed through means and standard deviation, while dichotomous variables were expressed like number and percentage of patients. The Student’s t test was used to compare continuous variables, whereas the chi-squared test was used for the comparison of non-continuous variables. We used Shapiro-Wilk test to verify continuous variables normality. We performed univariate analysis to examine the contribution of the variables in predicting the chosen outcome. The results were considered statistically significant for values of p < 0.05 and 95% of the confidence interval (C.I.). The receiver operating characteristic (ROC) analysis was used to obtain the most accurate cut-off of some single continuous variables. We performed logistic regression multivariate analysis (using a stepwise forward regression model, with an entry probability for each variable set at 0.05) to assess the independent contribution of the variables in predicting the chosen outcome. Statistical analysis was conducted with SPSS statistical software version 20.0 (SPSS Chicago, IL).

Table 1 Demographic characteristic in the two groups

Demographic characteristic	Positive outcome	Adverse outcome	P
Age	67.49 ± 16.28	71.67 ± 18.75	0.46
Male	77 (52.7%)	4 (2.7%)	/
Female	60 (41.1%)	5 (3.4%)	/
B.M.I. ¹	26.95 ± 5.58	26.78 ± 4.82	0.939

¹B.M.I body mass index

Table 2 Comorbidities in the two groups

Comorbidity	Positive outcome	Adverse outcome	Total
Chronic renal failure	13 (9.4%)	3 (33.33%)	16 (10.88%)
Dementia	15 (10.95%)	3 (33.33%)	18 (12.92%)
Gallstone disease	81 (59.6%)	5 (55.6%)	86 (59.18%)
Hematological neoplasia	5 (3.7%)	1 (11.1%)	6 (4.08%)
Solid neoplasia	31 (22.8%)	2 (22.2%)	33 (22.45%)
Previous TIA ¹ or stroke	13 (9.6%)	13 (9.6%)	16 (10.88%)
COPD ²	7 (5.1%)	1 (12.5%)	8 (5.5%)
Heart failure	17 (12.5%)	2 (22.5%)	19 (13.60%)
Hypertension	80 (58.8%)	5 (55.6%)	85 (58.50%)
Diabetes	27 (19.9%)	2 (22.2%)	29 (19.73%)

¹TIA transient ischemic attack,

²COPD chronic obstructive pulmonary disease

Results

Between 1 January 2013 and 20 May 2019, 12,499 patients were admitted to Internal Medicine AOU Careggi department. Of these, 146 patients with AP (137 with positive outcome and 9 with adverse outcome) were enrolled. The median age was 67.89 ± 16.44 , with a slight prevalence of male (55.14%) compared to female (44.9%). Stratifying the patients according to classification of Atlanta, we find 122 mild pancreatitis, 8 moderately severe, 16 severe. The main cause of AP resulted the gallstones disease (59.18%), followed by alcoholism (7.48%), and post ERCP-pancreatitis (7.56%). Patients with severe AP were significantly older than patients with mild-moderate pancreatitis ($p = 0.025$) (Table 1).

For each group, we examined the main comorbidities associated to AP. Patients with chronic kidney disease had acute kidney injury in 56% of cases. Characteristically, the average creatinine serum was higher in patients with severe AP ($p = 0.014$) (Table 2).

Regarding the laboratory analysis, there were no significant differences between two groups at the admission in the hospital. As it is seen in Table 3 C-reactive protein (CPR) ($p = 0.02$), creatinine ($p = 0.01$), sodium ($p = 0.05$), and troponin I ($p = 0.013$) after 48 h from the admission were significantly increased in patients with adverse outcome.

Regarding ABG, after 48 h from admission, more acid pH was associated with a negative outcome ($p = 0.027$) (Table 4).

The receiver operating characteristic (ROC) analysis was used to obtain the most accurate cut-off for the score significantly different between two groups: values above the cut-off were associated to a poor prognosis (Figs. 1, 2, 3, 4, 5, 6, and 7) (Table 5).

SOFA score > 5 was the most accurate to predict adverse outcome (O.R. 32.000, $p = 0.001$); q-SOFA score > 1 also showed a good correlation with adverse outcome (O.R. 16.625, $p = 0.001$).

Table 3 Blood samples after 48 h

Blood samples after 48 h	Positive outcome	Adverse outcome	P
C reactive protein (mg/dL)	87.03 ± 83.4	240 ± 61.24	0.02
Procalcitonin (ng/mL)	10.37 ± 46.92	4.53 ± 7.61	0.747
Heart troponin I (ng/mL)	0.053 ± 0.965	0.32 ± 0.64	0.013
Hematocrit (%)	36.47 ± 4.66	34.26 ± 9.74	0.232
Creatinine (mg/dL)	1.08 ± 0.897	1.96 ± 1.755	0.01
NT-pro BNP ¹ (pg/ml)	$3826.39 \pm 10,497.48$	$11,174 \pm 17,452$	0.471
Potassium (mEq/L)	3.734 ± 0.45	4.022 ± 0.58	0.184
Sodium (mEq/L)	139.41 ± 3.658	143.56 ± 8.22	0.05
Calcium (mg/dL)	8.35 ± 0.73	8.08 ± 0.64	0.386
Albumin (g/L)	33.33 ± 8.13	25.4 ± 9.96	0.301

¹N-terminal prohormone of brain natriuretic peptide

Table 4 pH and lactate at admission and after 48 h

	Positive outcome	Adverse outcome	P
A.B.G. at admission			
pH	7.44 ± 0.08	7.36 ± 0.075	0.05
Lactate	7.61 ± 19.37	7.98 ± 8.94	0.939
A.B.G. after 48 h			
pH	7.43 ± 0.047	7.37 ± 0.104	0.027
Lactate	5.64 ± 4.20	11.7 ± 11.17	0.05

In patients with adverse outcome, more aggressive fluid therapy (2777.8 ml ± 1545.545) was administered compared to patients with a positive outcome (1772.96 ± 763 ml) (**p = 0.001**).

We also conducted a multi-variate analysis whose results are not reported because they were not statistically significant.

Discussion

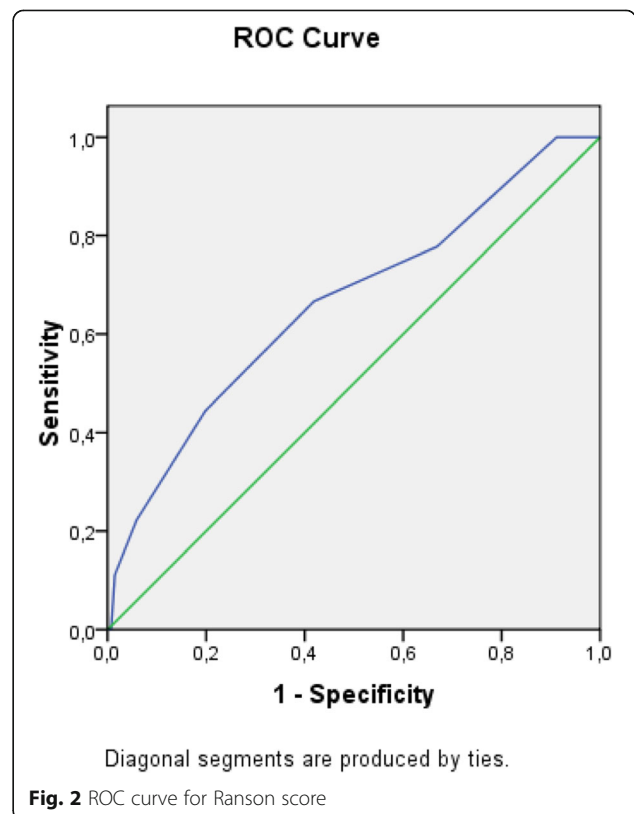
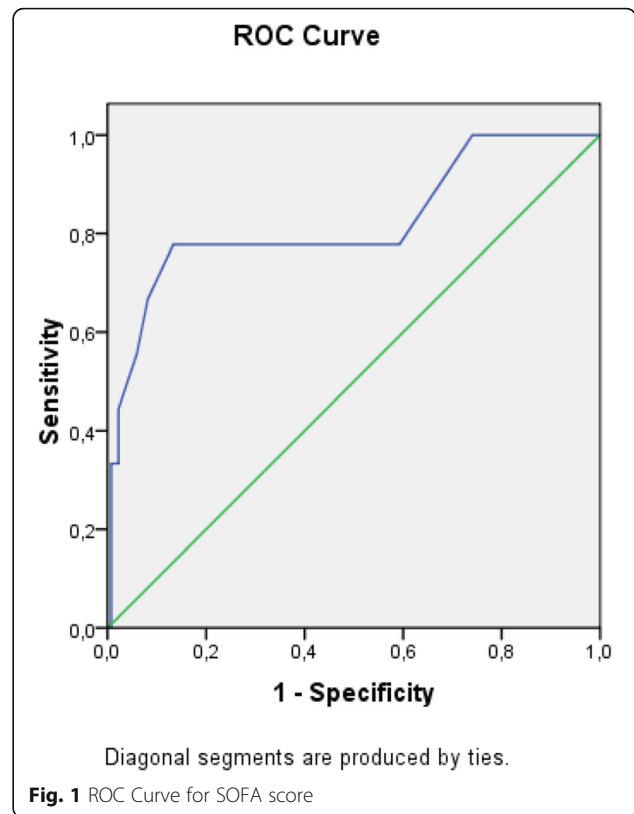
In our case study, the mortality rate resulted 2.77%, similar to data reported in literature (the mortality rate changes from 2.5% for mild AP to 30% for moderate-severe form 30%) [1, 10, 11].

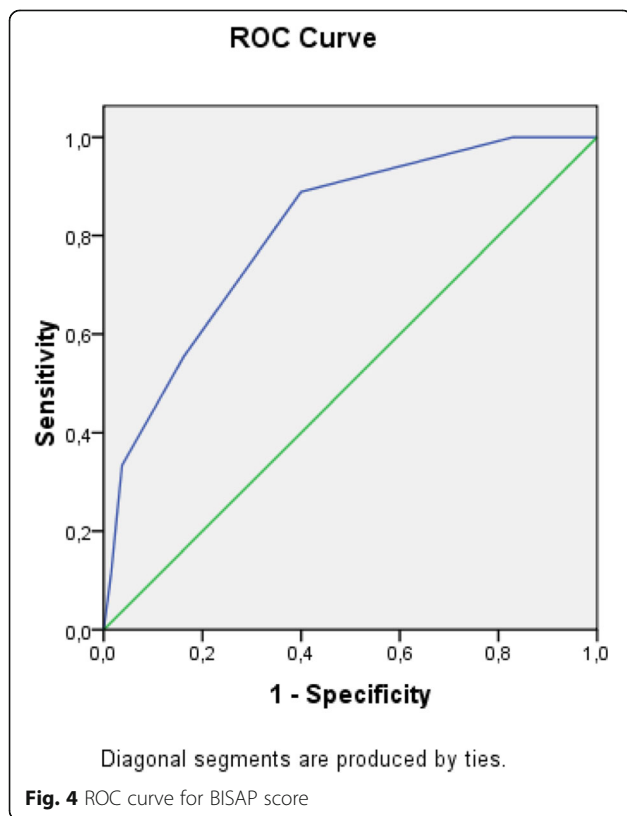
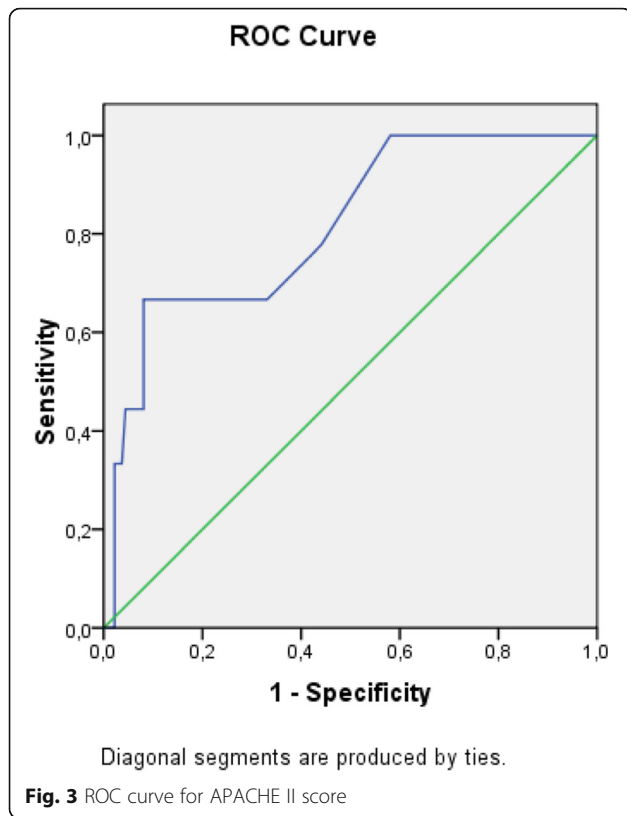
According to classification of Atlanta, we stratify 122 mild pancreatitis, 8 moderately severe, and 16 severe. Severe AP was observed in older patients as elderly age is an important prognostic factor [12, 13]. Indeed, older patients have more frequently organ failure during AP, probably due to intestinal bacterial translocation [14]. The increase of intestinal bacterial translocation is correlated to a pro-inflammatory status [15–17] called *inflammaging*, which is the reason of a lack immune system response to antigens [18]. Cellular aging in older patients is also an important cause of poor immune response [15, 19].

The first aim of our study was to evaluate blood samples analytes to find prognostic factors: increase of C-reactive protein, creatinine, sodium and troponin I, and reduction of pH after 48 h from the onset of symptoms result as prognostic factors in patients with adverse outcome.

Table 5 Cut off determined for each score

Score	Cut-off	O.R.	C.I. > 95%	P
APACHE II	> 13	9.531	2.32-39.21	0.001
MEWS	> 2	4.808	1.07-21.52	0.026
SOFA score	> 5	32.000	6.73-152.5	0.001
Q-SOFA	> 1	16.625	3.02-91.54	0.001
BISAP	> 3	4.218	1.05-16.96	0.03
HARMS	> 1	4.429	0.996-19.69	0.035
BALTHAZAR	> 3	6.225	1.25-31.34	0.012





Troponin I is an important heart damage marker but its diagnostic capacity is more quantitative than qualitative: according to recent European Society of Cardiology guidelines, increment of troponin should be at least three times higher than 99 percentile of reference to be diagnostic of heart injury [16]. The increase of troponin levels, in patients with normal electrocardiogram and in absence of chronic renal failure, is compatible with acute pancreatitis in the first 72 h from the onset of symptoms [17]. We speculate that the higher value of troponin should be due to asymptomatic rhabdomyolysis which is one of the least known and recognized complications of AP [20].

Patients with poor outcome had an elevated value of C-reactive protein. During the first phase of acute pancreatitis, cytokine pro-inflammation, as TNF (tumor necrosis factor) α , interleukins (IL-1, IL-2, IL-18, IL-6) [21] and chemokine, oxygen radical oxidant are released [22]. In mild acute pancreatitis, immune system of patients limits inflammation in the pancreatic area. In severe form of AP, massive damage and inflammation determine systemic inflammatory response syndrome (SIRS) [23]. The systemic inflammation causes a release of cytokine in blood circulation [24, 25]. In the liver, IL-6 is a very powerful indicator of C-reactive proteins and procalcitonin [26].

The increase of creatinine serum in patient with AP has been largely studied [27]. Acute kidney injury (AKI) can be a systemic complication of AP; pancreatic amylase can damage renal microcirculation, causing both hypoxic and toxic damage due to pancreatic phospholipase A2 action on proximal tubule. All these factors contribute to reduce renal perfusion, to damage tubules, and to increase creatinine serum concentration [28]. The AKI incidence in patients with AP is between 1 and 15% and it is an important cause of death with percentage between 0 and 30% [29].

In patients with adverse outcome, ABG after 48 h from admission reported an average pH more acidic than patients with positive outcome. We speculate that extracellular acidosis determines release of cytokines as interleukin 1β from the immune cells [30, 31] causing necrosis and further inflammation in patients with AP [32].

Secondary aim of our study was the assessment of different prognostic scores (in Table 6, we reported a brief introduction to the main scores) in predicting mortality and need of high intensity care among patients with AP admitted in internal ward. For each patient, we calculated the main score validated in setting different from internal medicine, as emergency department, or high intensity unit care. Although SOFA score, quick-SOFA, and APACHE II were validated in different setting, their application in internal ward demonstrated the most accurate relationship with patients' outcome. Also, Tee

Table 6 A brief introduction to scores

Score	Setting	Specific*	Usual cut-off#	Cut-off for AP in our study
APACHE II	Intensive unit care	Designed for AP, then used in intensive setting for different disease	> 8	> 13
MEWS	Clinic score, at patient's bed, in emergency	Used everywhere for its ease.	> 3	> 2
SOFA score	Intensive unit care	Sepsis and the multi-organ failure	Each result correlates to a higher risk of mortality	> 5
Q-SOFA	Intensive unit care	As SOFA score but simple to assess	> 2	> 1
BISAP	At patient's bed	Designed for AP, in the first hours from hospitalization	As SOFA, not a really cut-off but a higher risk of mortality	> 3
BALTHAZAR	Radiological score obtained with computed tomography	Specific for AP, correlates to complication, local, and systemic	> 2	> 3

*Designed or not for AP

#A superior value is associated to a poor prognosis

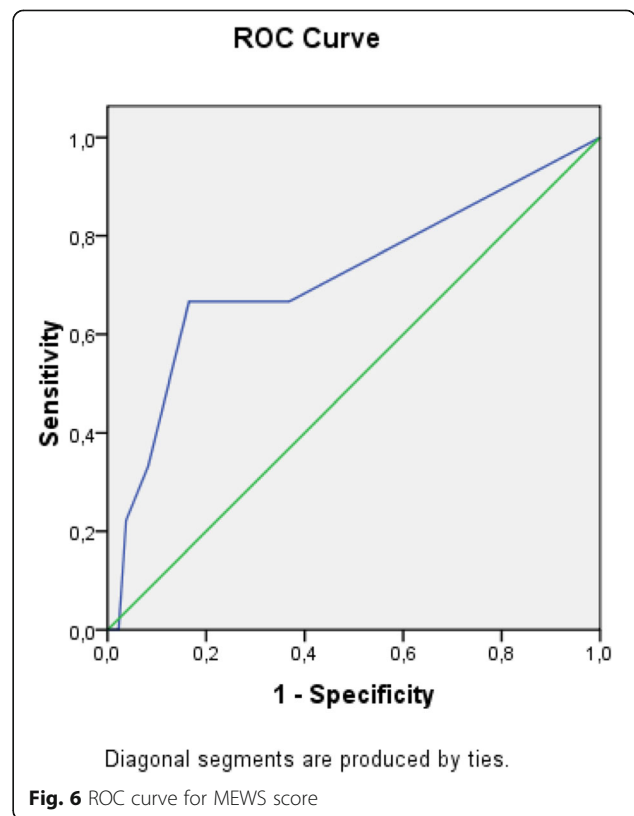
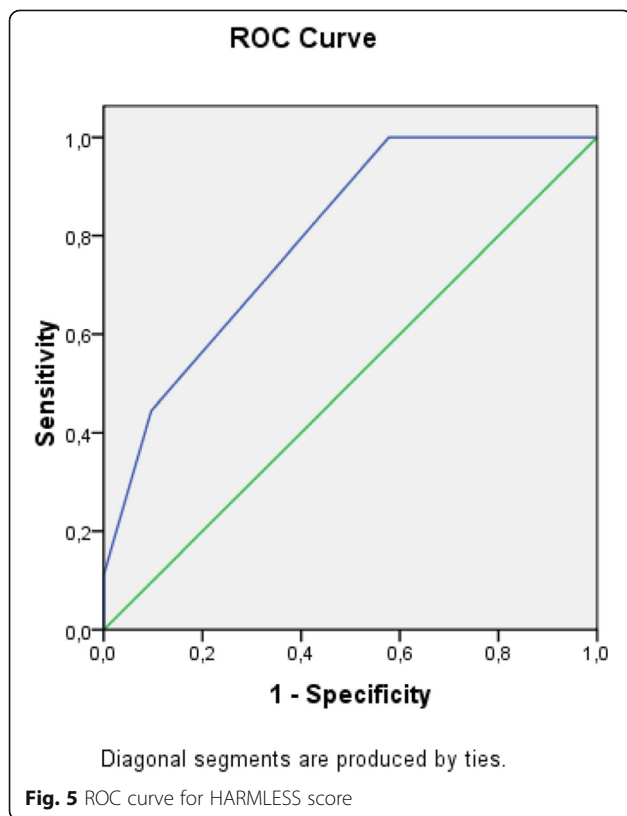
and Fang [33] compared RANSON, APACHE II, and SOFA score demonstrating similar sensibility and specificity in predicting mortality in severe acute pancreatitis after 48 h from the admission.

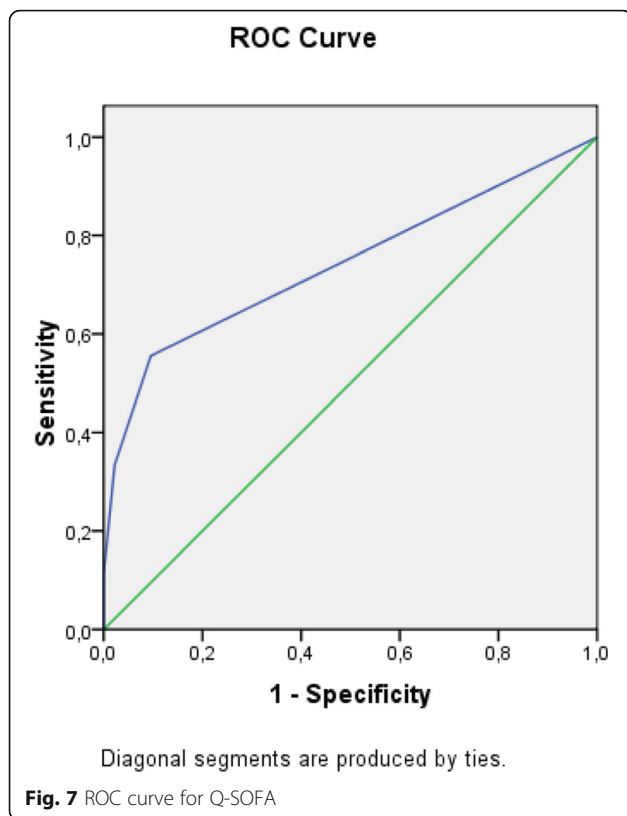
SOFA score > 5 shows the best correlation to a poor outcome. SOFA score is a useful tool to evaluate patients admitted in high intensity unit care; however, its use is reduced in low-care setting such as internal wards; for this reason, SEPSIS-3 [34] guidelines suggest to use rather q-SOFA, more easily and quickly applicable to assess septic patient prognosis. The application of q-SOFA

demonstrated more elevated value in patients with poor outcome recovered in internal wards. The main limit of q-Sofa is underestimating the gravity of illness which can determine undertreatment [35].

In our study, RANSON score was not associated with adverse outcome. Also, recent literature support a better prognostic capacity for APACHE II e BISAP [36, 37].

Patients with negative outcome received more aggressive fluids therapy compared to patients with a positive outcome. Although fluid therapy is one of the hinges in the AP management to prevent hypovolemia and





hypoperfusion of tissues, data on the amount of fluid needed to prevent necrosis or to improve outcome is contradictory. The amount of liquid must be adjusted to the patient's age, weight, and pre-existing renal and/or cardiac conditions. More fluid were administered to patients with severe AP because of their hemodynamic impairment.

American Gastroenterological Association (AGA) guidelines suggest the use of goal direct therapy in patients with AP [38]. Goal-directed therapy is successful in septic patients but in patients with AP there are no reported reduction of mortality rate or risk of multi-organ failure [39]. In addition, respiratory distress and abdominal compartmental syndrome are reported as side effects of a too much aggressive fluid therapy [39, 40]. In two prospective randomized trials, therapy with Ringer lactate had more effectiveness than fluid resuscitation with saline solution in reducing value of C-reactive protein and incidence of SIRS in patients with AP [41, 42]. For the lack of evidence, AGA guidelines do not make recommendation regarding the choice between Ringer's lactate versus normal saline as the optimal fluid solution for resuscitation. Normal saline solution can increase hyperchloremic acidosis, worsening the inflammation and pancreatic necrosis [43]; in the other side, Ringer lactate can reduce inflammation inhibiting macrophages [44] and has a less acid pH (6.5 vs 5.5).

Different studies confirmed the role of acid pH into worsening necrosis and pancreatic inflammation [32]. We speculate that Ringer lactate can improve the outcome of patients but the study in support of Ringer lactate has the important limit of poor primary end-point, as organ failure, pancreatic necrosis, and mortality.

It is difficult from data in the literature understanding the relationship between the severity of illness, the quantity of fluids administered and outcome [45, 46]. The difficulties derived from the retrospective nature of our study which, as the main in literature, show bias about causality relationship [47].

Our study has some limitations because it is carried out in a single department of a single hospital center and the population examined consists of a limited number of patients. Moreover, patients with severe acute AP from the onset of symptoms were admitted directly to high intensity care unit from emergency department; this implicated reduced sample for patients with negative outcome as only mild and moderate AP at the onset of symptoms were recovered in internal ward. For an internal ward, expanding the poor sample might lead the study for at least 10 years. Further studies in multicenter system should be conducted to assess prognostic factors in patients recovered in internal wards, because of the rapidly evolving AP which makes stratification of patients at the onset of symptoms a real challenge.

Conclusions

In the setting of internal medicine, acute pancreatitis causes significant mortality rate. Stratifying patients according to prognosis at the onset of symptoms is essential to optimize therapy and establish correct care setting. Our study showed that an increase of C-reactive protein, creatinine, sodium, and troponin I after 48 h from the onset of symptoms are prognostic factors for patients with adverse outcome. Moreover, the main score, validated in different settings from internal medicine demonstrated a good correlation with our patients' outcome.

Abbreviations

A.B.G.: Arterial blood gas; A.P.: Acute pancreatitis; APACHE II: Acute Physiology And Chronic Health Evaluation II; BNP: Brain natriuretic peptide; BISAP: Bedside Index of Severity in Acute Pancreatitis; CCI: Charlson Comorbidity Index; CPR: C-reactive protein; ECOG/PS: Eastern Cooperative Oncology Group/Performance Status; HAPS: Harmless Acute Pancreatitis Score; IL: Interleukin; MEWS: Modified Early Warning Score; Q-SOFA: Quick - Sequential Organ Failure Assessment; SIRS: Systemic Inflammatory Response Syndrome; SOFA: Sequential Organ Failure Assessment

Acknowledgements

Not applicable

Authors' contributions

O.P.: conceptualization and methodology. C.N.: conceptualization and methodology. M.T.S.: writing original draft. L. Caruso and L. Corbo:

supervision and funding. All the other authors: Resources. The authors read and approved the final manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All the procedures performed in this study were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This is a retrospective study that include anonymized patients extracted from hospital database; data are presented aggregated and anonymously. No informed consent was taken.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Author details

¹Medicina per la complessità assistenziale 1 AOU Careggi, Largo Piero Palagi, 1, 50139 Florence, Italy. ²Società Italiana di Salute Digitale Telemedicina, via Teodoro Valfrè, 00165 Rome, Italy. ³International Study Center of Society of Telemedicine and Digital Health, 40100 Bologna, Italy. ⁴Presidio Ospedaliero Marciariane UOC Medicina Interna, Viale Sossietta Scialla, 81025 Marciariane, ASL, Caserta, Italy. ⁵Clinic Gastroenterology, AOU Careggi, Largo Piero Palagi, 1, 50139 Florence, Italy.

Received: 12 September 2020 Accepted: 10 May 2021

Published online: 25 May 2021

References

- Schiemer M, Treiber M, Heeg S. Akute pankreatitis [Acute Pancreatitis]. *Dtsch Med Wochenschr.* 2021 Feb;146(4):229-236. German. doi: <https://doi.org/10.1055/a-1221-7186>. Epub 2021 Feb 16. PMID: 33592658, Akute Pankreatitis
- Carnovale A, Rabitti PG, Manes G, Esposito P, Pacelli L, Uomo G (2005) Mortality in acute pancreatitis: is it an early or a late event? *J Pancreas*
- Wu BU, Banks PA (2013) Clinical management of patients with acute pancreatitis. *Gastroenterology* 144(6):1272–1281. <https://doi.org/10.1053/j.gastro.2013.01.075>
- Peery AF, Crockett SD, Murphy CC, Lund JL, Dellon ES, Williams JL, Jensen ET, Shaheen NJ, Barritt AS, Lieber SR, Kochar B, Barnes EL, Fan YC, Pate V, Galanko J, Baron TH, Sandler RS (2019) Burden and cost of gastrointestinal, liver, and pancreatic diseases in the United States: update 2018. *Gastroenterology* 156(1):254–272.e11. <https://doi.org/10.1053/j.gastro.2018.08.063>
- Harrison DA, D'Amico G, Singer M (2007) Case mix, outcome, and activity for admissions to UK critical care units with severe acute pancreatitis: a secondary analysis of the ICNARC Case Mix Programme Database. *Crit Care* 11(Suppl 1):S1. <https://doi.org/10.1186/cc5682>
- Wu BU, Conwell DL (2010) Update in acute pancreatitis. *Curr Gastroenterol Rep* 12(2):83–90. <https://doi.org/10.1007/s11894-010-0091-6>
- Zhang XX, Deng LH, Chen WW, Shi N, Jin T, Lin ZQ, Ma Y, Jiang K, Yang XN, Xia Q (2017) Circulating microRNA 216 as a marker for the early identification of severe acute pancreatitis. *Am J Med Sci* 353(2):178–186. <https://doi.org/10.1016/j.amjms.2016.12.007>
- Silva-Vaz P, Abrantes AM, Castelo-Branco M, Gouveia A, Botelho MF, Tralhão JG (2020) Multifactorial scores and biomarkers of prognosis of acute pancreatitis: applications to research and practice. *Int J Mol Sci* 21(1). <https://doi.org/10.3390/ijms21010338>
- Kinns H (2013) Classification of acute pancreatitis - 2012: revision of the Atlanta classification and definitions by international consensus. *Ann Clin Biochem* 50(2):182. <https://doi.org/10.1177/0004563213480712>
- Toh SKC, Phillips S, Johnson CD (2000) A prospective audit against national standards of the presentation and management of acute pancreatitis in the south of England. *Gut* 46(2):239–243. <https://doi.org/10.1136/gut.46.2.239>
- Chen L, Huang Y, Yu H, Pan K, Zhang Z, Man Y, Hu D (2021) The association of parameters of body composition and laboratory markers with the severity of hypertriglyceridemia-induced pancreatitis. *Lipids Health Dis* 20(1): 9. <https://doi.org/10.1186/s12944-021-01443-7>
- Pendharkar SA, Mathew J, Zhao J, Windsor JA, Exeter DJ, Petrov MS (2017) Ethnic and geographic variations in the incidence of pancreatitis and postpancreatitis diabetes mellitus in New Zealand: a nationwide population-based study *N Z Med J.* 130(1450):55–68
- Fan ST, Choi TK, Lai CS, Wong J (1988) Influence of age on the mortality from acute pancreatitis. *Br J Surg* 75(5):463–466. <https://doi.org/10.1002/bjs.1800750520>
- Machado MCC, Coelho AMM, Carneiro D'Albuquerque LA, Jancar S (2012) Effect of ageing on systemic inflammatory response in acute pancreatitis. *Int J Inflam* 2012:1–4. <https://doi.org/10.1155/2012/270319>
- Freund A, Orjalo AV, Desprez PY, Campisi J (2010) Inflammatory networks during cellular senescence: causes and consequences. *Trends Mol Med* 16(5):238–246. <https://doi.org/10.1016/j.molmed.2010.03.003>
- Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA et al (2019) Fourth universal definition of myocardial infarction (2018). *Russ J Cardiol.* <https://doi.org/10.15829/1560-4071-2019-3-107-138>
- Pezzilli R, Barassi A, Iammarino MT, d'Eril GM (2013) Is troponin T a useful marker of myocardial damage in acute pancreatitis? A prospective time course study. *Dig Liver Dis* 45(4):347–348. <https://doi.org/10.1016/j.dld.2012.09.019>
- Candore G, Caruso C, Jirillo E, Magrone T, Vasto S (2010) Low grade inflammation as a common pathogenetic denominator in age-related diseases: novel drug targets for anti-ageing strategies and successful ageing achievement. *Curr Pharm Des* 16(6):584–596. <https://doi.org/10.2174/138161210790883868>
- Jeyapalan JC, Sedivy JM (2008) Cellular senescence and organismal aging. *Mech Ageing Dev* 129(7-8):467–474. <https://doi.org/10.1016/j.mad.2008.04.001>
- Pezzilli R, Billi P, Cappelletti O, Barakat B, Miglio F (1999) Rhabdomyolysis and acute pancreatitis. *J Gastroenterol Hepatol* 14(2):168–171. <https://doi.org/10.1046/j.1440-1746.1999.01835.x>
- Simovic MO, Bonham MJD, Abu-Zidan FM, Windsor JA (1999) Anti-inflammatory cytokine response and clinical outcome in acute pancreatitis. *Crit Care Med* 27(12):2662–2665. <https://doi.org/10.1097/00003246-199912000-00009>
- Booth DM, Mukherjee R, Sutton R, Criddle DN (2011) Calcium and reactive oxygen species in acute pancreatitis: Friend or Foe? *Antioxid Redox Signal* 15(10):2683–2698. <https://doi.org/10.1089/ars.2011.3983>
- Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, Rubenfeld G, Kahn JM, Shankar-Hari M, Singer M, Deutschman CS, Escobar GJ, Angus DC (2016) Assessment of clinical criteria for sepsis. *JAMA* 315(8): 762–774. <https://doi.org/10.1001/jama.2016.0288>
- Montravers P, Chollet-Martin S, Marmuse JP, Gougerot-Pocidallo MA, Desmots JM (1995) Lymphatic release of cytokines during acute lung injury complicating severe pancreatitis. *Am J Respir Crit Care Med* 152(5): 1527–1533. <https://doi.org/10.1164/ajrccm.152.5.7582288>
- Malmström ML, Hansen MB, Andersen AM, Ersbøll AK, Nielsen OH, Jørgensen LN, Novovic S (2012) Cytokines and organ failure in acute pancreatitis: inflammatory response in acute pancreatitis. *Pancreas* 41(2): 271–277. <https://doi.org/10.1097/MPA.0b013e3182240552>
- Castell JV, Gómez-Lechón MJ, David M, Andus T, Geiger T, Trullenque R, Fabra R, Heinrich PC (1989) Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett* 242(2):237–239. [https://doi.org/10.1016/0014-5793\(89\)80476-4](https://doi.org/10.1016/0014-5793(89)80476-4)
- Lipinski M, Rydzewski A, Rydzewska G (2013) Early changes in serum creatinine level and estimated glomerular filtration rate predict pancreatic necrosis and mortality in acute pancreatitis creatinine and eGFR in acute pancreatitis. *Pancreatology* 13(3):207–211. <https://doi.org/10.1016/j.pan.2013.02.002>
- Petejova N, Martinek A (2013) Acute kidney injury following acute pancreatitis: a review. *Biomed Pap* 157(2):105–113. <https://doi.org/10.5507/bp.2013.048>

29. Zhou J, Li Y, Tang Y, Liu F, Yu S, Zhang L, Zeng X, Zhao Y, Fu P (2015) Effect of acute kidney injury on mortality and hospital stay in patient with severe acute pancreatitis. *Nephrology* 20(7):485–491. <https://doi.org/10.1111/nep.12439>
30. Sharma V, Devi TS, Sharma R, Chhabra P, Gupta R, Rana SS et al (2014) Arterial pH, bicarbonate levels and base deficit at presentation as markers of predicting mortality in acute pancreatitis: a single-centre prospective study. *Gastroenterol Rep* 2(3):226–231. <https://doi.org/10.1093/gastro/gou037>
31. Rajamäki K, Nordström T, Nurmi K, Åkerman KE, Kovanen PT, Öörni K, Eklund KK (2013) Extracellular acidosis is a novel danger signal alerting innate immunity via the NLRP3 inflammasome. *J Biol Chem* 288(19):13410–13419. <https://doi.org/10.1074/jbc.M112.426254>
32. Noble MD, Romac J, Vigna SR, Liddle RA (2008) A pH-sensitive, neurogenic pathway mediates disease severity in a model of post-ERCP pancreatitis. *Gut* 57(11):1566–1571. <https://doi.org/10.1136/gut.2008.148551>
33. Tee YS, Fang HY, Kuo IM, Lin YS (2018) Serial evaluation of the SOFA score is reliable for predicting mortality in acute severe pancreatitis. In: Huang SF, Yu MC. Serial evaluation of the SOFA score is reliable for predicting mortality in acute severe pancreatitis, *Med (United States)*. <https://doi.org/10.1097/MD.00000000000009654>
34. Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M et al (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - J Am Med Assoc* 315(8):801–810. <https://doi.org/10.1001/jama.2016.0287>
35. Hallac A, Puri N, Applebury D, Myers K, Dhumal P, Thatte A, Srikureja W (2019) The value of quick sepsis-related organ failure assessment scores in patients with acute pancreatitis who present to emergency departments: a three-year cohort study. *Gastroenterol Res* 12(2):67–71. <https://doi.org/10.14740/gr1132>
36. Basit H, Ruan GJ, Mukherjee S (2020) Ranson criteria. [Updated 2020 Sep 27]. In: StatPearls [Internet]. StatPearls Publishing, Treasure Island (FL)
37. Yang L, Liu J, Xing Y, Du L, Chen J, Liu X et al (2016) Comparison of BISAP, Ranson, MCTSI, and APACHE II in predicting severity and prognoses of hyperlipidemic acute pancreatitis in Chinese patients. *Gastroenterol Res Pract* 2016:1–7. <https://doi.org/10.1155/2016/1834256>
38. Crockett SD, Wani S, Gardner TB, Falck-Ytter Y, Barkun AN, Crockett S, Falck-Ytter Y, Feuerstein J, Flamm S, Gellad Z, Gerson L, Gupta S, Hirano I, Inadomi J, Nguyen GC, Rubenstein JH, Singh S, Smalley WE, Stollman N, Street S, Sultan S, Vege SS, Wani SB, Weinberg D (2018) American Gastroenterological Association Institute Guideline on initial management of acute pancreatitis. *Gastroenterology* 154(4):1096–1101. <https://doi.org/10.1053/j.gastro.2018.01.032>
39. De-Madaria E, Soler-Sala G, Sánchez-Payá J, Lopez-Font I, Martínez J, Gómez-Escobar L et al (2011) Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. *Am J Gastroenterol* 106(10):1843–1850. <https://doi.org/10.1038/ajg.2011.236>
40. Mifkovic A, Skultety J, Sykora P, Prochotsky A, Okolicany R (2013) Intra-abdominal hypertension and acute pancreatitis. *Bratislava Med J* 114(03):166–171. https://doi.org/10.4149/BLL_2013_036
41. Wu BU, Hwang JQ, Gardner TH, Repas K, Delee R, Yu S, Smith B, Banks PA, Conwell DL (2011) Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 9(8):710–717.e1. <https://doi.org/10.1016/j.cgh.2011.04.026>
42. de-Madaria E, Herrera-Marante I, González-Camacho V, Bonjoch L, Quesada-Vázquez N, Almenta-Saavedra I, et al. Fluid resuscitation with lactated Ringer's solution vs normal saline in acute pancreatitis: a triple-blind, randomized, controlled trial. *United Eur Gastroenterol J* 2018. <https://doi.org/10.1177/2050640617707864>.
43. Bhoomagoud M, Jung T, Atladottir J, Kolodecik TR, Shugrue C, Chaudhuri A, Thrower EC, Gorelick FS (2009) Reducing extracellular pH sensitizes the acinar cell to secretagogue-induced pancreatitis responses in rats. *Gastroenterology* 137(3):1083–1092. <https://doi.org/10.1053/j.gastro.2009.05.041>
44. Iraporda C, Errea A, Romanin DE, Cayet D, Pereyra E, Pignataro O, Sirard JC, Garrote GL, Abraham AG, Rumbo M (2015) Lactate and short chain fatty acids produced by microbial fermentation downregulate proinflammatory responses in intestinal epithelial cells and myeloid cells. *Immunobiology* 220(10):1161–1169. <https://doi.org/10.1016/j.imbio.2015.06.004>
45. De-Madaria E, Martínez J, Pérez-Mateo M (2012) The dynamic nature of fluid resuscitation in acute pancreatitis. *Clin Gastroenterol Hepatol* 10(1):95–96. <https://doi.org/10.1016/j.cgh.2011.08.020>
46. De-Madaria E, Banks PA, Moya-Hoyo N, Wu BU, Rey-Riveiro M, Acevedo-Piedra NG et al (2014) Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 12(6):997–1002. <https://doi.org/10.1016/j.cgh.2013.10.017>
47. Faghieh M, Fan C, Singh VK (2019) New Advances in the treatment of acute pancreatitis. *Curr Treat Options Gastroenterol* 17(1):146–160. <https://doi.org/10.1007/s11938-019-00223-8>

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Submit your manuscript to a SpringerOpen® journal and benefit from:

- Convenient online submission
- Rigorous peer review
- Open access: articles freely available online
- High visibility within the field
- Retaining the copyright to your article

Submit your next manuscript at ► [springeropen.com](https://www.springeropen.com)