

Defining a Therapeutic Program for Recurrent Acute Pancreatitis Patients with Unknown Etiology

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ABSTRACT

AIM: To define a therapeutic program for mild-moderate acute pancreatitis (AP), often recurrent, which at the end of the diagnostic process remains of undefined etiology.

MATERIAL AND METHODS: In the period 2011–2012, we observed 64 cases of AP: 52 mild-moderate, 12 severe; biliary 39, biliary in alcoholic chronic pancreatitis 5, unexplained recurrent 20. The clinical and instrumental evaluation of the 20 cases of unexplained AP showed 6 patients with biliary sludge, 4 microlithiasis, 4 sphincter of Oddi dysfunction, and 6 cases that remained undefined.

RESULTS: Among 20 patients with recurrent, unexplained AP at initial etiological assessment, we performed 10 video laparo cholecystectomies (VLCs), 2 open cholecystectomies and 4 endoscopic retrograde cholangiopancreatography/endoscopic sphincterotomies (ERCP/ES) in patients who had undergone previous cholecystectomy; 4 patients refused surgery. Among these 20 patients, 6 had AP that remained unexplained after second-level imaging investigations. For these patients, 4 VLCs and 2 ERCP/ES were performed. Follow-up after six months was negative for further recurrence.

CONCLUSION: The recurrence of unexplained acute pancreatitis could be treated with empirical cholecystectomy and/or ERCP/ES in cases of previous cholecystectomy.

KEYWORDS: acute pancreatitis, recurrent pancreatitis, unexplained etiology, cholecystectomy, ERCP/ES

CITATION: Neri et al. Defining a Therapeutic Program for Recurrent Acute Pancreatitis Patients with Unknown Etiology. *Clinical Medicine Insights: Gastroenterology* 2014;7 1–7 doi:10.4137/CGast.S13531.

RECEIVED: October 30, 2013. **RESUBMITTED:** November 28, 2013. **ACCEPTED FOR PUBLICATION:** December 12, 2013.

ACADEMIC EDITOR: Melpakkam Srinivas, Editor in Chief

TYPE: Original Research

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

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Introduction

Acute pancreatitis (AP) is the most frequent pancreatic disease. AP is an inflammatory process of the pancreas, with a very wide range of manifestations and clinical variations. The disease is characterized by different degrees of severity, from a mild edematous-interstitial inflammation, which is a self-limiting disease, to a severe type with local necrotizing inflammation and systemic manifestations such as organ failure.^{1,2} Mild pancreatitis are self-limiting forms characterized by edema and normal enhancement of pancreatic parenchyma on contrast-enhanced CT. In moderate pancreatitis, there are early acute fluid collections located in or near the pancreas and minimal and transient organ dysfunction without wall of fibrous tissue, almost always with spontaneous regression.

Moderate/severe forms are characterized by great peri-pancreatic and pancreatic involvement with fluid/necrotic collections, but organ failure is transient or absent. Severe forms are characterized by diffuse or local areas of non-viable pancreatic parenchyma, peri-pancreatic fat necrosis, non-enhanced pancreatic parenchyma and/or fluid-necrotic peri-pancreatic collections with persistent or transient organ failure. Within the severe forms there are also critical or early severe forms, with persistent or transient organ failure and infected pancreatic and peri-pancreatic collections. In most cases, the causes of AP are: biliary lithiasis, excessive consumption of alcohol and hypertriglyceridemia. Dysfunction of the sphincter of Oddi, tumors obstructing the Wirsung and hypercalcaemia have a lower incidence. Pancreas divisum, annular pancreas

**Table 1.** Etiology of acute pancreatitis.

COMMON CAUSES	UNCOMMON CAUSES	RARE CAUSES
Gallstones	Autoimmune	Pancreas divisum
Alcoholism	Genetic	Annular pancreas
Hypertriglyceridemia	Abdominal trauma	Scorpion venom
Post-endoscopic retrograde cholangiopancreatography	Postoperative	Posterior penetrating ulcer
Drug induced	Sphincter of Oddi dysfunction	
	Ischemia	
	Infections	
	Hypercalcemia and hyperparathyroidism	

and abnormal bilio-pancreatic junction have an even smaller impact (see Table 1). The etiology of pancreatitis is variable among the various countries such as reported in literature.^{3,4} In most cases, laboratory tests and clinical instrumental examination make an etiological diagnosis possible and enable therapeutic decisions for cases of pancreatitis. However, in some patients, especially those where only first-line laboratory and imaging tests have been carried out, the cause of the acute attack often remains unclear and, without treatment, may well recur.¹ Quantifying recurrent cases of AP whose cause is unknown is far from easy, as it is characteristically variable because of the sequence of improvements followed by relapses. The matter warrants further investigation; hence, the goal of the current study is to identify a possible therapeutic program for recurrent AP whose etiology, despite diagnostic efforts, remains uncertain.

Patients and Methods

We examined 64 patients (25 males and 39 females, mean age 58 years, range 34–83 y) who were admitted to our Department of General Surgery with a diagnosis of AP in the 2011–2012 period. We included in the study all our observation and treatment of pancreatitis. During the study, the biliary etiology was prevalent. Patients were distributed according to severity as follows: 52 mild-moderate cases, including 13 moderate-severe cases; 12 severe cases, including 2 early severe acute pancreatitis (ESAP) (see Table 2). Initial etiological assessment

Table 2. 64 patients with acute pancreatitis: CT severity index: CT GRADE POINT + point for necrosis (Balthazar).

Grade B1	39 (60.9%)
Grade C2	13 (20.3%)
Grade D3	10 (15.7%)
Grade E4	2 (3.1%)

(Level 1) with liver function tests, fasting serum calcium, lipid profile and non-invasive imaging (abdominal ultrasound) provided the following breakdown: 39 acute biliary pancreatitis, 5 acute biliary pancreatitis in patients with chronic alcohol abuse, and 20 undefined pancreatitis (see Table 3). We evaluated the 20 patients with undefined pancreatitis, assessing the likelihood of a biliary origin. On the basis of our epidemiological data and under Bayes' theorem, a theorem of probability of causes, we calculated that there is an 80% chance that AP with initially undefined origin will be of biliary origin. At admission, all 20 patients had mild-moderate AP and all had a history of previous emergency hospitalizations (one or more) in other hospitals, attributed to mild-moderate AP, which, with medical support, regressed in a short period of time and was thus classified as idiopathic acute pancreatitis. The very low clinical impact and lack of any etiological definition justified therapeutic abstention on previous admissions. The previous medical history for liver-biliary-pancreatic disease in the 20 patients with recurrent mild acute unexplained pancreatitis may be summarized as follows: four patients had undergone cholecystectomy, two patients had chronic alcohol abuse and two had cirrhosis. Diagnostic procedures were initiated during hospitalization in our department with first-line laboratory investigations and imaging. In one patient there was laboratory evidence of cholestasis without jaundice. A modest dilation (8–10 mm) of the common bile duct (CBD) was demonstrated in five patients. The diagnostic findings were negative in this first diagnostic phase in all the other patients (14 of 20 patients with unexplained pancreatitis). However, further light was shed when second-level investigations were carried out in all 20 patients with previously unexplained pancreatitis using invasive imaging techniques, eg magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) after uncertain results of MRCP. These techniques revealed the presence of sludge in six patients, microlithiasis in four patients (Fig. 1), and slowed biliary outflow caused by dyskinesia or sclerosis of the sphincter of Oddi in four patients, presumable as a result of previous transit of stones but without of performance of sphincter of Oddi manometry. On the other hand, MRCP results were negative in six patients, with normal biliary-pancreatic morphology (Table 4).

Therapeutic and diagnostic procedures were standardized and approved in all 64 patients. Standard medical therapy includes fasting, intravenous infusions, pain medications and PPI therapy. In severe cases, the therapeutic approach is based on intensive care, fluid resuscitation, correction of hypoxemia and enteral nutrition. In cases of biliary pancreatitis, the therapeutic program includes assuring papillary patency and common bile duct cleaning,^{5–15} with ERCP/ES.^{16,17} In our department, ERCP is performed for severe, early severe and moderate-severe forms, and also in mild-moderate with laboratory or ultrasound (US) confirmation of CBD lithiasic obstacle. After ERCP, it is necessary to perform laparoscopic cholecystectomy to complete treatment for gallstones. The

Table 3. 64 patients with acute pancreatitis: demographic data, percentage incidence of biliary lithiasis and cholestasis indexes at initial etiological assessment.

MEAN AGE	SEX	DIR. BIL (0.02–0.30 mg/dL) <2 mg/dL	DIR. BIL (0.02–0.30 mg/dL) 2–5 mg/dL	AST/ALT × 3	G-GT (7–38 u/L) >200 u/L
58 (34–83)	F 39 M 25	60.4%	39.6%	26.8%	59.9%
CBD SIZE (US) (8 mm) >8 mm	SERUM CALCIUM (8,4–10.5 mg/dL) >10.5 mg/dL	TRYGLICERIDEMIA (40–170 mg/dL) >170 mg/dL	COLECYSTIC LITHIASIS	UNDEFINED ETIOLOGY	
40.7%	15%	39%	68.7%	31.3%	

timing of laparoscopic cholecystectomy is connected with acute pancreatitis evolution because it is preferable to wait for the stabilization of the patient's general condition. Treatment of the later phase of acute pancreatitis consists in control and treatment of local complications: infections, hemorrhage, and pancreatic and peri-pancreatic fluid necrotic collections. All patients that were examined and treated gave their written, informed consent. Finally, a clinical and instrumental follow-up six months after discharge, consisting of clinical control, laboratory tests and US, was carried out for the 20 patients with initial unexplained pancreatitis.

Results

Patients with a definite diagnosis of acute biliary pancreatitis (44) were subjected to a specific therapeutic program in our department, in addition to normal medical therapy. (See Table 5).

Diagnostic study of the 20 patients with undefined and recurrent AP clarified the cause in 14 cases, confirming the biliary origin as expected from the study of probabilities. Based

on this information, a therapeutic program was drawn up and implemented. However, the diagnostic dilemma was not resolved in six cases (6/64 = 9.3%). Following empirical criteria, four cholecystectomies and 2 ERCPs, in patients who had already undergone cholecystectomy, were carried out in the six patients whose etiology remained undefined. Our therapeutic decisions for the group of 20 patients are summarized in Table 6.

Four patients did not accept the surgical option. Medical therapy was initiated in these patients, two of whom had chronic alcohol abuse.

Clinical, laboratory and ultrasound checks six months after surgery in patients who underwent cholecystectomy (12) and ERCP/ES (4) were negative for further recurrences.

Of the four patients who refused surgery, two had shown no recurrence of pancreatitis at the time of follow-up; the other two patients, those with chronic alcohol abuse in their histories, were lost to follow-up.

Discussion

The etiology of AP in the majority of cases is from biliary lithiasis, excessive consumption of alcohol, or hypertriglyceridemia. Other causes are decidedly rarer. The literature reports the etiological significance of microlithiasis and biliary sludge in patients with isolated or recurrent attacks of pancreatitis defined as idiopathic or more exactly as undefined, in whom the prevalence of biliary etiology ranges between 70 and 80%.^{18–23} Correctly speaking, the term 'idiopathic' should be restricted to pancreatitis whose etiology remains undefined even after thorough diagnostic investigations which exclude all possible pathologies to which the acute attack can be ascribed.

Most patients with AP are diagnosed initially on the basis of routine diagnostic methods. It has been demonstrated that with the use of EUS and MRCP after the first level of investigation, the number of unexplained cases will be considerably reduced. Between 20 and 50% of patients with undefined AP are subject to repeated acute episodes. In these cases, thorough diagnostic investigations (eg, second-level imaging) may identify the cause of pancreatitis in many cases (up to 76%).^{19,24} Second-line imaging investigations (EUS, MRCP, CT) are required from the very first attack of AP in patients

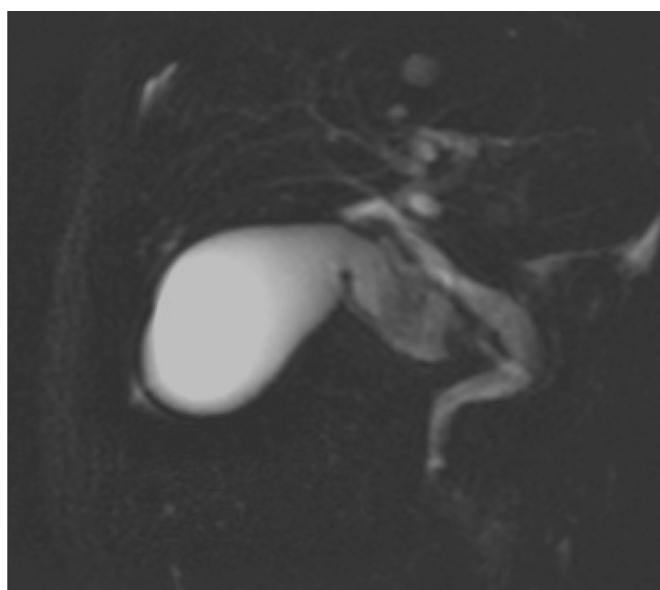


Figure 1. Microlithiasis at MRCP.



Table 4. 20 Patients with unexplained acute pancreatitis: clinical findings of first level and second line of image investigations.

Recurrent acute pancreatitis: 20	Previous history for hepatobiliary or pancreatic diseases	First level diagnostic investigations laboratory-US	Second line investigations EUS-MRCP
	Previous cholecystectomy: 4	Alkaline phosphates +++: 1	Biliary sludge: 6
	Chronic alcohol abuse: 2	gamma-gt +++ : 1	Microlithiasis: 4
	Liver cirrhosis: 2	CBD dilation size (>8–10 mm): 5	CBD dilation size (sclerosis of sphincter of Oddi): 4
			Normal biliary-pancreatic morphology: 6

whose condition is etiologically undefined after basic tests. The significant diagnostic role of spiral CT and EUS in excluding neoplastic causes has been demonstrated.²⁵ Moreover, where the gallbladder is *in situ*, the search for biliary sludge and microlithiasis is strongly suggested, since data reported in the literature confirm the role they play in the genesis of AP.^{26,27} Biliary sludge is made up of a suspension of cholesterol crystals mixed with mucins and cell detritus.²⁸ Abdominal ultrasound and EUS identify biliary sludge. The term microlithiasis refers to small gallstones whose size does not exceed 3 mm.²⁹ Biliary sludge and microlithiasis, together with stenotic changes caused by sclerosis of the sphincter of Oddi arising from the transit of cholesterol crystals and microlithiasis,^{30,31} are certainly the cause of AP in the pathogenetic condition of biliary reflux in the pancreatic ductal system.³² Indeed the association between microlithiasis/biliary sludge and the onset of AP has been demonstrated epidemiologically. After cholecystectomy and after ERCP/ES, the recurrence of pancreatitis becomes much less frequent.^{33,34} Microscopic examination of a sample of bile obtained by endoscopy has shown the presence of cholesterol crystals in 80% of patients whose AP was classified initially as undefined in the absence of a clear biliary origin.³⁵ The cause of AP may generally be ascribed after careful assessment of the patient’s case history, clinical and laboratory data, and imaging tests of both non-invasive and invasive nature, such as MRCP and EUS. In these patients, concrete support for diagnostic assessment can be obtained from clinical data and first-line investigations, independently of the recurrent attack of AP: mild colic pain in the right hypochondrium, modest dilation of CBD (US 8–10 mm), changes in indices for cholestasis without jaundice. Today, MRCP plays a primary role in biliary-pancreatic diagnosis. It may be considered as indispensable when defining the morphology and any biliary-pancreatic lesions. MRCP identifies the anatomy of biliary and pancreatic ducts, and any

Table 5. Specific therapeutic program of 44 patients with acute biliary pancreatitis with definite diagnosis.

Cholecystectomy (VLC) (within same hospital stay)	ERCP (within 72 hours)
44 (conversion rate 4.5%)	25 (12 SAP; 13 moderate/severe)

dilation, blockages or stenoses (whether neoplastic, inflammatory or lithiasic), stenosis of the main pancreatic duct, pancreas divisum, etc.³⁶ MRCP may be backed up by the secretin test, which can provide data on biliopancreatic altered flow from blockages along the ductal system or that are papillary in nature. The method has high sensitivity (80%–90%) in identifying lithiasis of CBD. MRCP is particularly effective when identifying small gallstones in those cases where the diameter of the biliary duct does not exceed 10 mm (sensitivity: 88.9%). Moreover, the concordance between MRCP and ERCP is in the order of 90%.³⁷ The diagnostic potential of EUS relates to pancreatic pathologies with a cephalic or corpo-caudal location (Intraductal papillary mucinous neoplasm (IPMN), pancreas divisum, ductal gallstones as in chronic pancreatitis, neuroendocrine tumors, small adenocarcinoma) and biliary pathologies (small gallstones, biliary sludge). The method is extremely sensitive (70%) as regards identifying microlithiasis or biliary sludge in patients with unexplained recurrent pancreatitis.²⁶ Today, EUS occupies an important position in the assessment of unexplained acute recurrent pancreatitis because its use contributes in many cases to clarifying the etiopathogenesis, often by excluding other pathologies.³⁸ In our experience of the diagnostic evaluation of acute biliary pancreatitis, the most frequently performed second-line imaging technique was MRCP; EUS was performed in a few cases after uncertain results of MRCP because its invasiveness. We followed the therapeutic program shown Figure 2, based on imaging and clinical results with definite etiology. We underline the usefulness of MRCP in patients with mild pancreatitis but present predictive factors of choledocholithiasis (ALP,

Table 6. Specific therapeutic program of 20 patients with acute unexplained pancreatitis at admission.

Cholecystectomy (VLC) (within same hospital stay)	ERCP (within 72 hours)
8 (definite diagnosis of biliary etiology with second level investigations)	2 (definite diagnosis of biliary etiology with second level investigations)
4 (unexplained etiology. Empirical criteria)	2 (unexplained etiology. Empirical criteria)
4 patients did not accept surgical option	



gamma-gt, CBD size > 10 mm) before cholecystectomy.³⁹ In patients for whom no etiology can be given and in whom therapy is delayed or suspended, AP frequently recurs. Indeed, in cases of recurrent AP, no etiological definition is given for a percentage of patients that varies between 10 and 30%.⁴⁰ In our experience, all patients (20/64 = 31.25%) who on hospitalization in our department did not receive an initial clear etiological definition of pancreatitis, reported previous hospitalizations for AP. The possibility that, with pancreatitis of undefined etiology, some diagnostic findings may be 'missed' with current laboratory and instrument tests needs to be considered. This possibility relates to microlithiasis and biliary sludge, dysfunction of the sphincter of Oddi, IPMN, occult pancreatic tumors and underlying chronic pancreatitis, mostly alcoholic in origin, with ductal stenosis and intraductal gallstones blocking the flow of pancreatic secretions.^{20,41-43} Moreover, the blockage of the flow of pancreatic secretions with consequent pancreatitis, may be caused by anatomical abnormalities such as pancreas divisum, annular pancreas and choledocolithiasis.^{44,47} Autoimmune pancreatitis, with histological features of sclerotic lymphoplasmacellular pancreatitis, may present as AP; the abnormally high level of IgG4 (a quantitative immunoglobulin test) and findings from echo-endoscopy (EUS) can guide diagnosis. In conclusion, at the end of a complete diagnostic program (first-line imaging and second-level investigations), from the data reported in the literature and our experience, it is clear that the number of patients with acute recurrent pancreatitis that cannot be attributed to any particular cause, and may be defined as unexplained, is limited and may be quantified at around 15%.^{48,49} The issue of the

therapeutic approach to be adopted in a patient with undefined AP, especially where it is recurrent, is controversial. In 80% of cases,⁴⁸⁻⁴⁹ the acute episode of pancreatitis of undefined etiology of mild-moderate degree. It clears up rapidly with basic medical support. The clinical evidence for these events cannot be considered as manifest. Hence, when mild-moderate AP attacks clear up rapidly with basic medical therapy, and in the absence of any certain etiological definition, no further therapeutic procedures are usually prescribed.⁵⁰ Inevitably, this exposes the patient to further recurrent episodes, the severity of which cannot be predicted; this suggests the need to adopt therapy that provides a definitive solution. A considerable body of data in the literature shows that lithiasis, in forms that are hard or even impossible to recognize diagnostically, is the most frequent cause (over 80%)^{37,49} of acute pancreatitis *in toto* and unexplained recurrent pancreatitis.^{51,52} Hence, once other causes of pancreatitis have been excluded in cases of a recurring acute episode probable but not certain biliary origin, it is advisable, even when second-level imaging investigations are uncertain or negative, to carry out cholecystectomy in patients with an intact gallbladder, and ERCP/ES where the patient has already had the gallbladder removed.^{28,48,53,54} Both therapeutic options are based on empirical criteria. ERCP/ES by itself is also an appropriate option in patients with high surgical risks for cholecystectomy who have recurrent AP arising from suspected microlithiasis.⁵⁵ Both these therapeutic procedures have been proposed on the basis of the assumption, which can be supported by epidemiologic and laboratory data, that the cause is biliary in nature, by a blockage in the biliary-pancreatic flow. Our

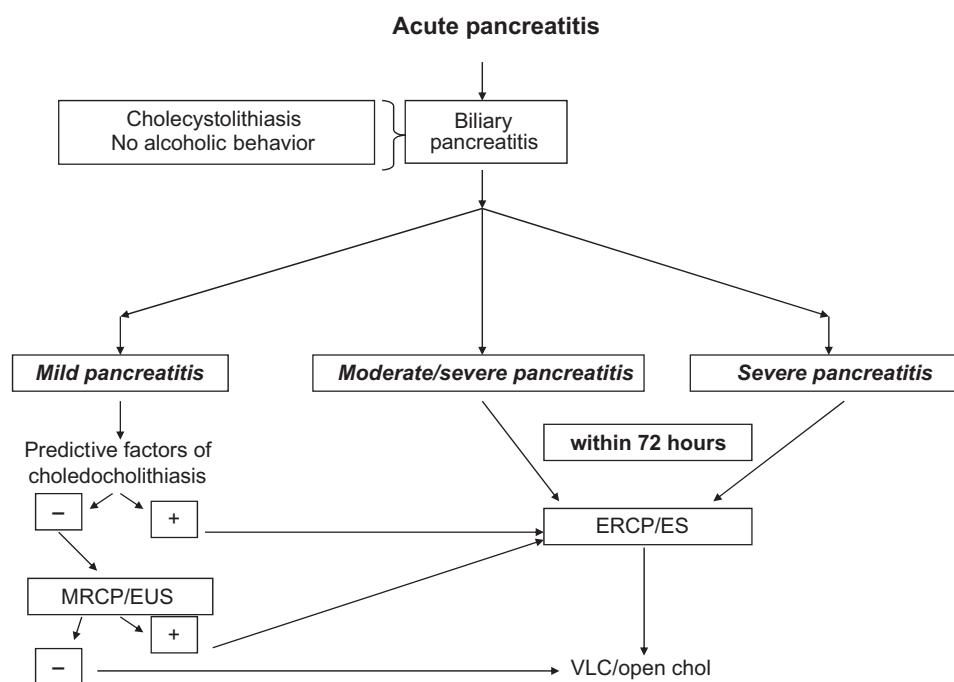


Figure 2. Decisional algorithm based on results.



experience, albeit restricted to a limited number of patients, confirms the absence of any recurrence at the time of the six-month follow up in the six patients with unexplained pancreatitis who underwent VLC, or ERCP/ES if they had previously had a cholecystectomy.

Conclusions

In conclusion, diagnostic procedures of second-level laboratory and MRCP investigation can be proposed for patients with recurrent and unexplained episodes of mild-moderate acute pancreatitis. In a high percentage of cases, these procedures make it possible to obtain a precise diagnostic overview, allowing therapy to be undertaken to provide a definitive solution. In a limited number of patients (9.3% in our cohort) with recurrent but completely negative diagnostic findings (laboratory tests and MRCP), therapy can be based on the empirical criterion of the likelihood, but not certainty, of a biliary etiology treatable with a cholecystectomy or, alternatively, ERCP/ES.

Author Contributions

All authors contributed to the development of this manuscript. All authors conceived and designed the experiments. All authors analyzed the data. All authors wrote the first draft of the manuscript. All authors agree with the results and conclusions. All authors jointly developed the structure and arguments for the paper. All authors made critical revisions and approved final version. All authors reviewed and approved of the final manuscript.

DISCLOSURES AND ETHICS

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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