

Genetic and Clinical Research of Chronic Pancreatitis in China

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Chronic Pancreatitis

Definition:

- A continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function.



Steven Freedman
Harvard Medical School



The NEW ENGLAND
JOURNAL of MEDICINE

REVIEW ARTICLE

A Correction

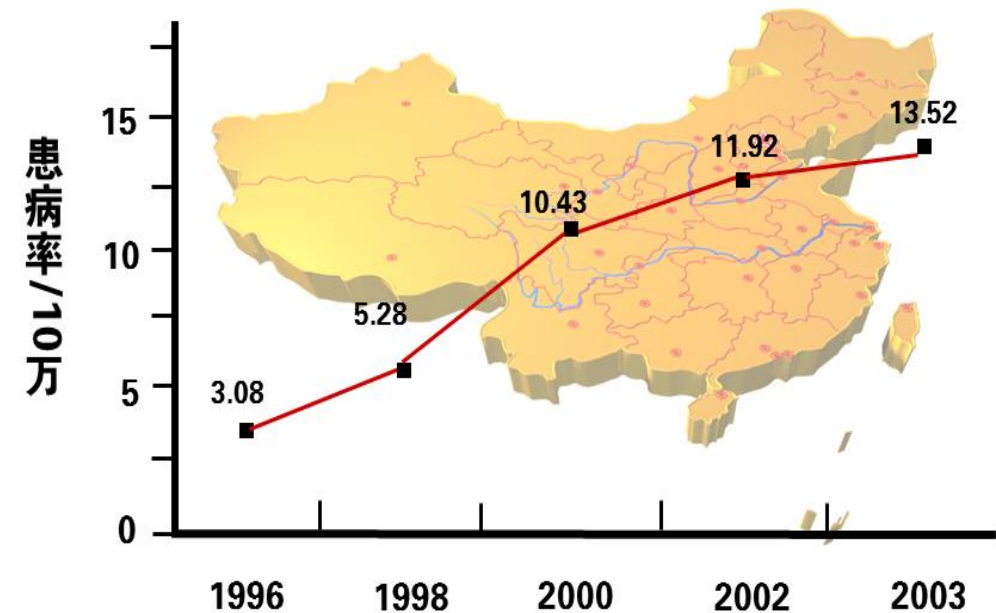
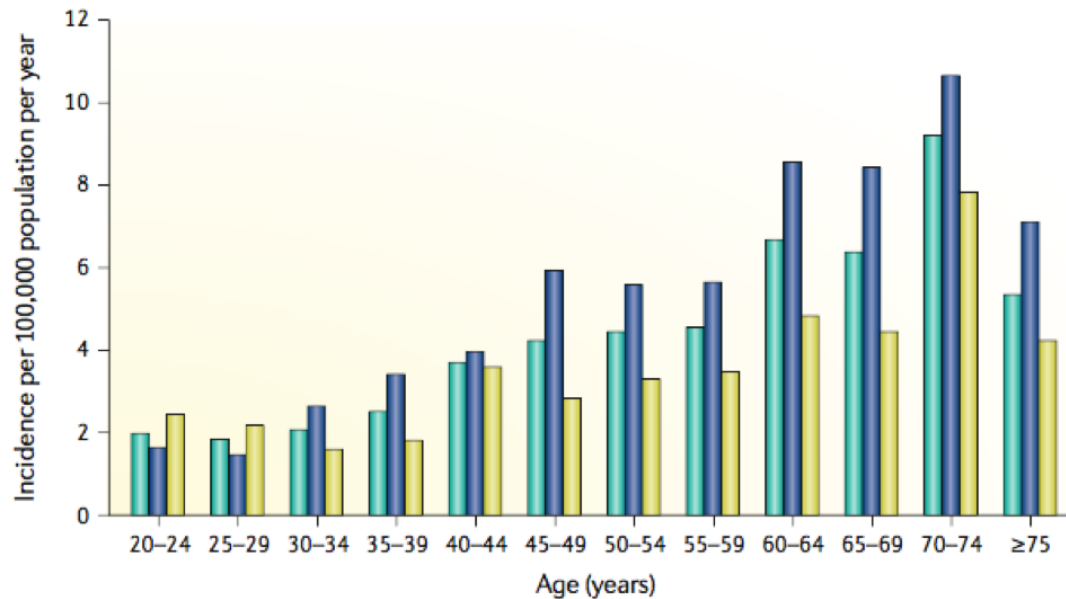
Chronic Pancreatitis

Michael L. Steer, M.D., Irving Waxman, M.D., and Steven Freedman, M.D.
N Engl J Med 1995; 332:1482-1490 | June 1, 1995 | DOI: 10.1056/NEJM199506013322206

Chronic pancreatitis remains an **enigmatic** process of **uncertain** pathogenesis, **unpredictable** clinical course, and **unclear** treatment.....

Chronic Pancreatitis

- Global pooled incidence of CP is 10/100,000 population per year
- In China, prevalence of CP is 13.5/100,000



Etiology

Risk factors:

➤ Endogenous(**Genetic**), Environmental(**Alcohol**、**Smoking...**), Others...

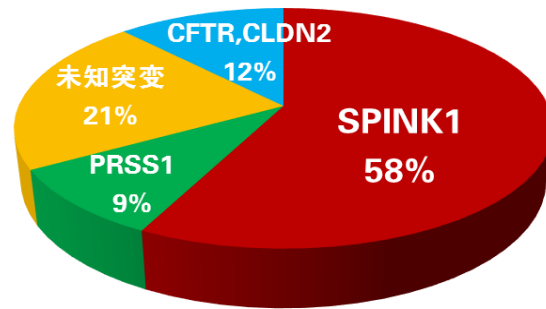
Country	Primary cause	Second cause	Third cause
Western countries	Alcoholic (70%)	Idiopathic (20%)	Others (10%)
Japan	Alcoholic (68%)	Idiopathic (20%)	Others (12%)
Korea	Alcoholic (64%)	Idiopathic (21%)	Others (15%)
Europe	Alcoholic (54%)	Idiopathic (31%)	Others (15%)
India	Idiopathic (60%)	Alcoholic (39%)	Others (1%)
China	Idiopathic (76%)	Alcoholic (19%)	Others (5%)

- Spanier BW. *Best Pract Res ClinGastroenterol* 2008;22:45-63
- Balakrishnan V. *JOP* 2008; 9: 593-600
- Ryu JK. *Digestion* 2005; 72(4):207-11
- Hao L, *J Gastroenterol Hepatol* 2017; 32(7):1403-1411
- Cahen DL. *NEJM* 2007; 356(7):676-84
- Hirota M. *Pancreatology* 2005; 14(6):490-6

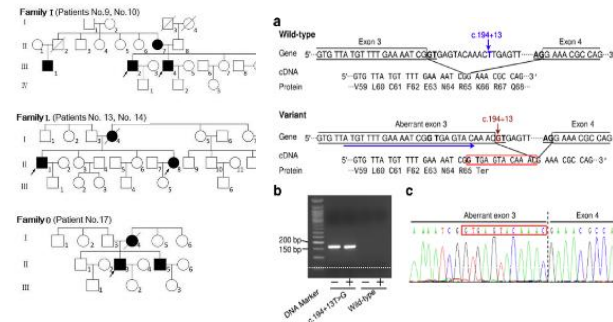
Genetic Research

Genetic characteristics and pathogenesis of CP in China

- Study the most common CP pathogenic gene mutation(*SPINK1* c.194+2T > C) in China
- Report several CP related genes (*CPA1*, *CTRB1*, *CEL*, *STIM1* et, al)
- Uncover different genetic backgrounds between East and West



Mutation spectrum



Genotype and phenotype

CEL 变异	腺泡细胞	功能
欧洲 HYB1		Impaired protein secretion Chronic pancreatitis
亚洲 HYB2		Reduced protein expression?

Subjects	Case	Control	P		
Chinese	19/799	2.4	20/1028	1.9	0.64
Japanese	4/248	1.6	7/403	1.7	0.85
Indian	0/280	0	1/225	0.4	0.91
Asian	23/1327	1.7	28/1656	1.7	0.96
European	42/1122	3.7	30/4152	0.7	<0.01

Novel mutation of CEL

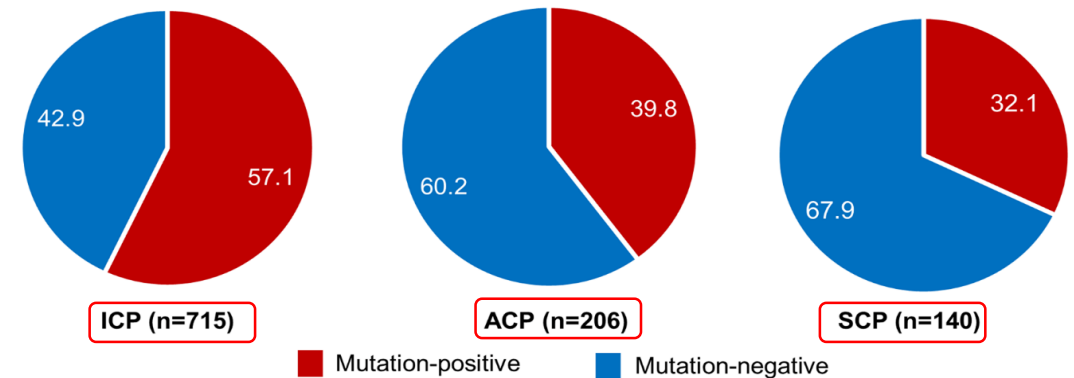


Cover paper IF=18.4

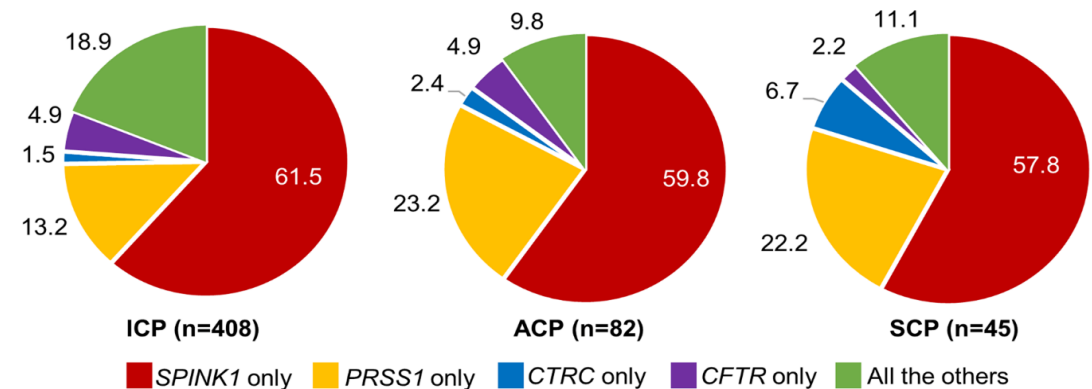
Genetic Research

- 1061 Han Chinese CP patients and 1196 controls
- Pathogenic genotypes involving *SPINK1*, *PRSS1*, *CTRC*, *CFTR*
- 50.42% in CP vs. 5.94% in controls (OR=16.12; P<0.001).
- ICP vs. ACP vs. SCP

A Overall Mutation Detection Rates in Patients (%)

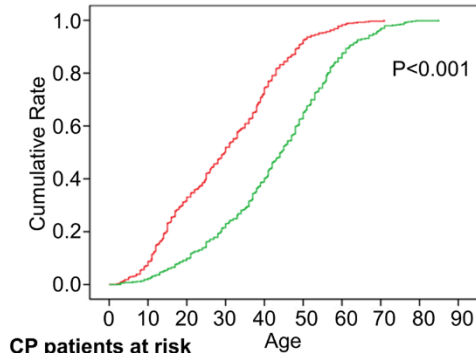


B Relative Frequencies of Pathogenic Genotypes in Mutation-Positive Patients (%)



Genetic Research

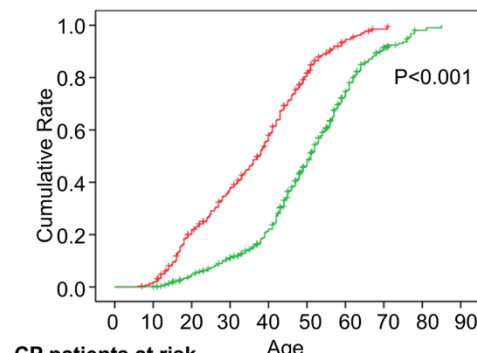
A Time to Disease Onset



CP patients at risk

Age	0	10	20	30	40	50	60	70	80	90
(n=535)	497	366	267	149	46	12	2	0		
(n=526)	516	477	413	322	196	75	20	1	0	

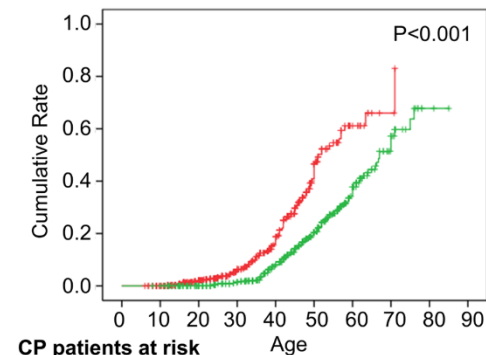
B Time to Diagnosis of Pancreatic Stones



CP patients at risk

Age	0	10	20	30	40	50	60	70	80	90
(n=535)	526	417	325	222	91	21	3	0		
(n=526)	525	491	451	383	240	98	26	2	0	

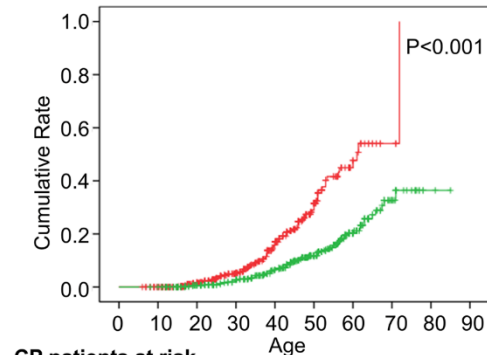
C Time to Diagnosis of Diabetes Mellitus



CP patients at risk

Age	0	10	20	30	40	50	60	70	80	90
(n=535)	415	315	211	73	15	3	0			
(n=526)	452	374	232	92	25	2	0			

D Time to Diagnosis of Steatorrhea



CP patients at risk

Age	0	10	20	30	40	50	60	70	80	90
(n=535)	417	323	208	85	20	3	0			
(n=526)	490	449	375	237	96	25	2	0		

Kaplan-meier model

Positive VS Negative

(median ages)

- disease onset (-14.4Y)
- pancreatic stones (-13.6Y)
- diabetes mellitus (-15.9Y)
- steatorrhea (57.7%VS31%)

***SPINK1* c.194 + 2T> C**

Liver, Pancreas and Biliary Tract

The contribution of the *SPINK1* c.194 + 2T> C mutation to the clinical course of idiopathic chronic pancreatitis in Chinese patients

Chang Sun^{a,1}, Zhuan Liao^{a,1}, Lili Jiang^{a,1}, Fu Yang^b, Geng Xue^b, Qi Zhou^b, Ruiwen Chen^b, Shuhan Sun^{b,*}, Zhaoshen Li^{a,**}

^a Department of Gastroenterology, Changhai Hospital, Second Military Medical University, Shanghai, China

^b Department of Medical Genetics, the Second Military Medical University, Shanghai, China

BMJ
open

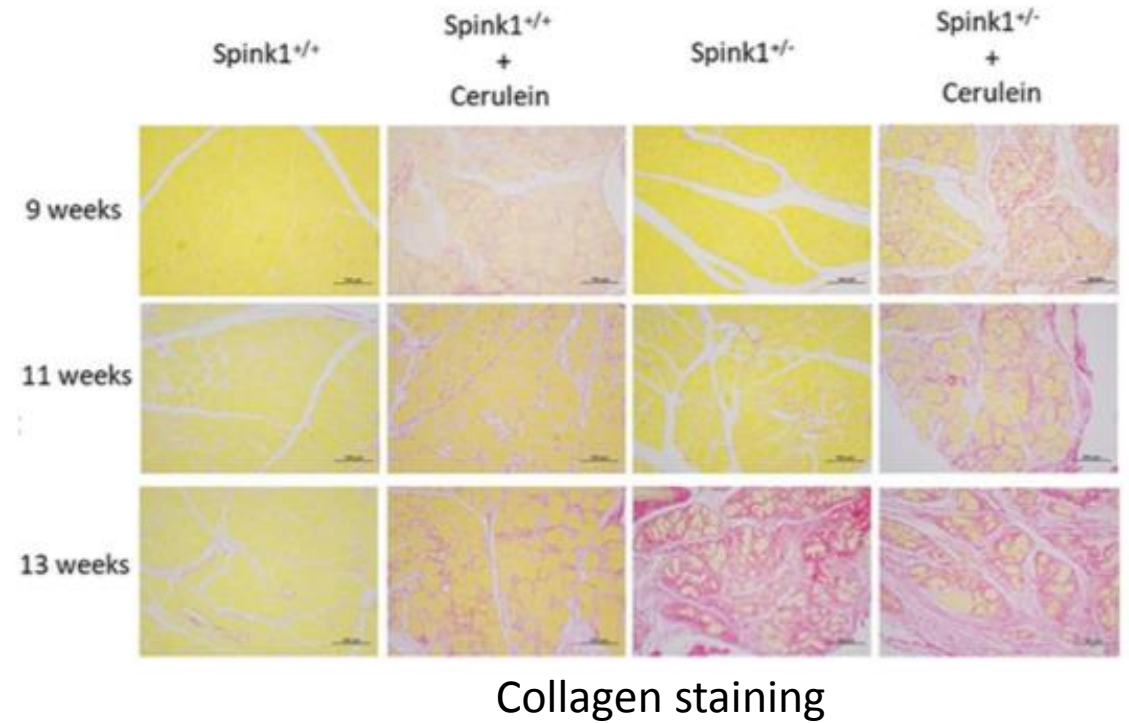
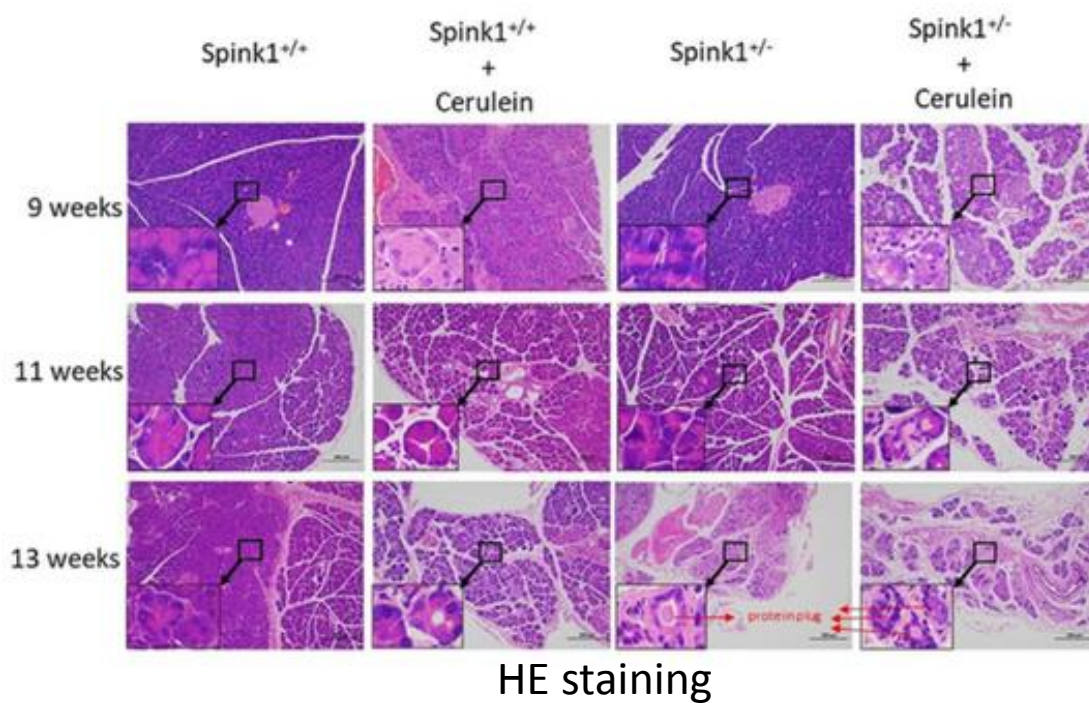
Comprehensive screening for PRSS1,
SPINK1, CFTR, CTRC and CLDN2
gene mutations in Chinese paediatric
patients with idiopathic chronic
pancreatitis: a cohort study



- ***SPINK1* c.194+2T > C** mutation may play an important role in the pathogenesis of Chinese pediatric ICP
- ***SPINK1* c.194 + 2T> C** could predispose individuals to pancreatic diabetes onset at an earlier age

SPINK1 c.194 + 2T>C

Animal model



➤ Heterozygous *Spink1* c.194+2T>C mutant mice spontaneously develop CP

CEL & CPA1 & CTRB

A recombined allele of the lipase gene **CEL** and its pseudogene *CELP* confers susceptibility to chronic pancreatitis

nature
genetics

Variants in **CPA1** are strongly associated with early onset chronic pancreatitis



ORIGINAL ARTICLE

Genome-wide association study identifies inversion in the **CTRB1-CTRB2** locus to modify risk for alcoholic and non-alcoholic chronic pancreatitis

- Fjeld K et al. Nat Genet 2015;47(5):518-522
- Witt H et al. Nat Genet 2013; 45(10):1216-20
- Rosendahl J et al. Gut 2018;67(10):1855-1863

CEL & CPA1 & CTRB

No Association Between **CEL-HYB Hybrid Allele and Chronic Pancreatitis in Asian Populations**

No significant enrichment of rare functionally defective **CPA1 variants in a large Chinese idiopathic chronic pancreatitis cohort**

The **CTRB1-CTRB2** risk allele for chronic pancreatitis discovered in European populations does not contribute to disease risk variation in the Chinese population due to near allele fixation

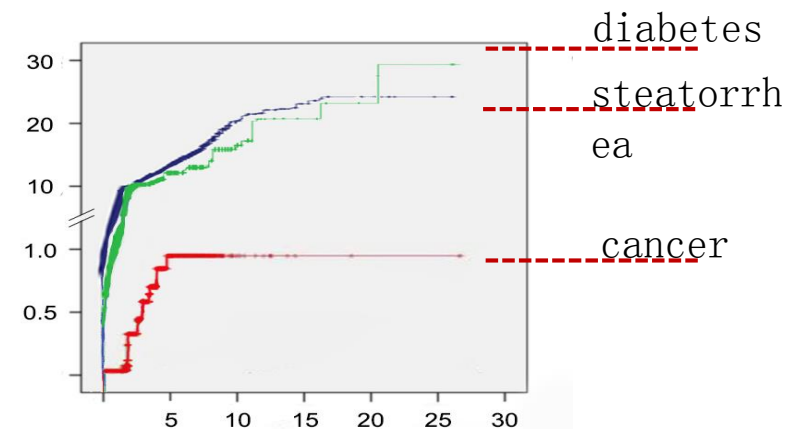
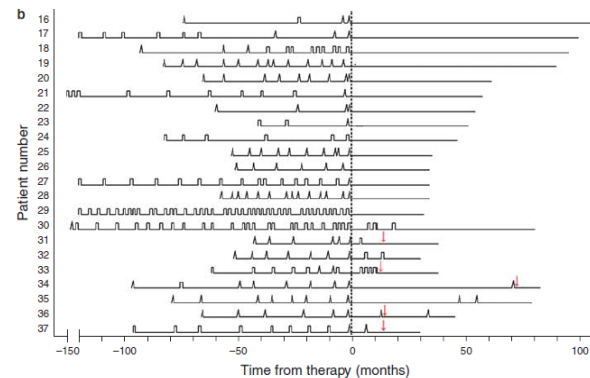


- Zou WB et al. *Gastroenterology* 2016; 150(7):1558-1560
- Wu H et al. *Hum Mut* 2017; 38(8): 959-963
- Liao Z et al. *Gut* 2017; 67(7): 1368-1369

Clinical Features and Natural Course of CP in China

★Leading the establishment of **Chinese largest CP clinical research cohort**
(more than 3000)

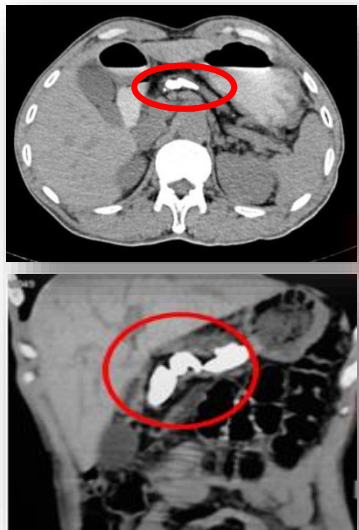
- Etiology: 19% alcoholism, 76% idiopathic (different from the west)
- Natural course (10-year cumulative incidence): 28% diabetes, 20% steatorrhea, 1% cancer



Establish ESWL/ERCP Series Treatment System

★ Treat more than **6,000** cases, the **earliest** in China, the **largest** in the world

- Efficacy : success rate 99%, stone removal rate 87%, pain relief rate 95%
- Proposed the classification definitions of major complications of ESWL



治疗前

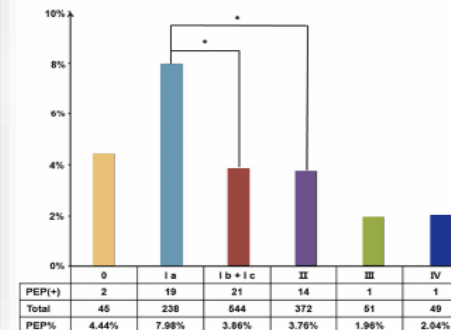


ESWL+内镜治疗



治疗后

	胰腺炎	感染	石街	出血	穿孔
轻度	52	19	5	4	4
中度	10	0	1	1	0
重度	2	1	0	0	0
发生率	4.4%	1.4%	0.4%	0.3%	0.3%



Peter D. Siersema, Mário Dinis, René Laugier
Editor-in-Chief, Co-Editor-in-Chief & Co-Editor, Endoscopy
We consider that your paper addresses an important point i.e. adverse events after (or induced) by ESWL while usually only positive effects of this treatment have been reported. Nevertheless referring to statistical analysis and its presentation.....



MEEES Treatment Strategy

Medicine

- enzymes
- insulin
- analgesics
- vitamins
- antioxidants
- steroids (AIP)

ESWL

- stones
> 5mm
positive

Endotherapy

- strictures
- pseudocysts
- EUS-guided celiac plexus block

Surgery

- endotherapy failed
- complicated CP
- suspected canceration

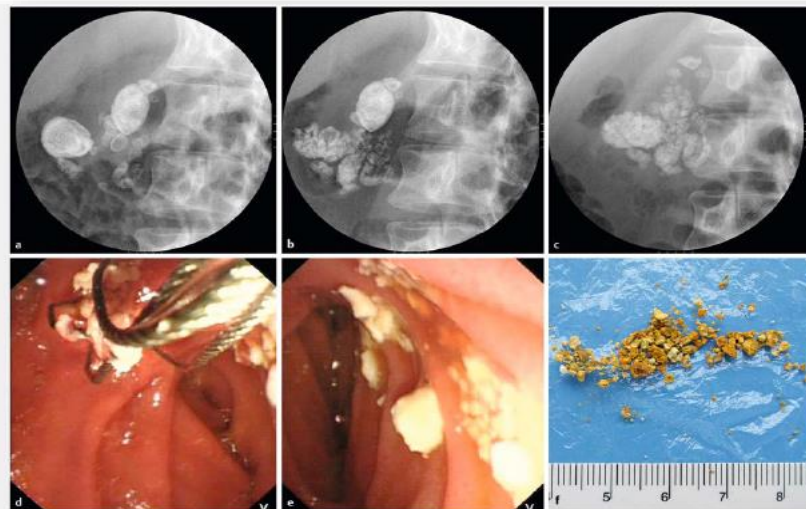


ESWL & ERCP

ESWL & ERCP treatment of CP is effective

214 cases, 18-month follow-up (ESWL+ERCP)

- Stone removal **87%**, Turn to surgery **2%**
- Pain relief **95%**, Quality-of-life scores (**8 vs. 5**)

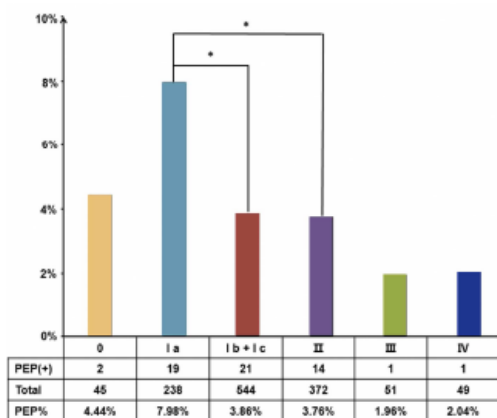


	Pre-ESWL	Post-ESWL	P
Pain relief			
Complete	N/A	139 (71.3)	
Partial	N/A	47 (24.0)	
No	N/A	9 (4.7)	
Quality-of-life scores (mean ± SD)	5.77 ± 1.68	8.06 ± 1.23	<0.001
SF-36 quality-of-life scores*			
Physical health component (mean ± SD)	56.87 ± 18.67	59.20 ± 14.77	0.277
Mental health component (mean ± SD)	52.24 ± 21.49	58.53 ± 16.44	0.009
Weight (mean ± SD), kg	58.98 ± 9.93	60.89 ± 10.50	<0.001
Diabetes, n (%)	52 (24.3)	57 (26.6)	0.657
Steatorrhea, n (%)	24 (11.2)	34 (15.9)	0.203

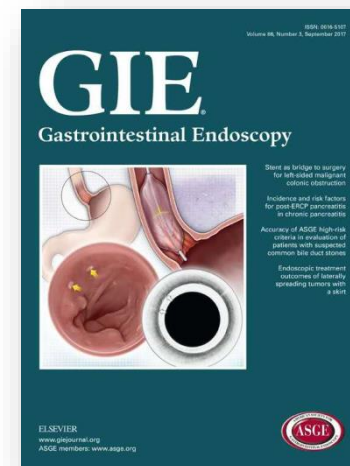
ESWL & ERCP

Post-ERCP Pancreatitis in CP

- Incidence of PEP (Biliary disease vs. CP): 4.5% (92/2028) vs. 4.8%(96/2000)
- The incidence of PEP in CP patients **decreased** with disease progression



varians	P	OR(95% CI)
Female	<0.001	2.34 (1.52-3.61)
Pancreatitis history	<0.001	2.49 (1.71-3.63)
PEP history	0.006	2.81 (1.34-5.88)
ESWL	0.004	0.51 (0.33-0.81)



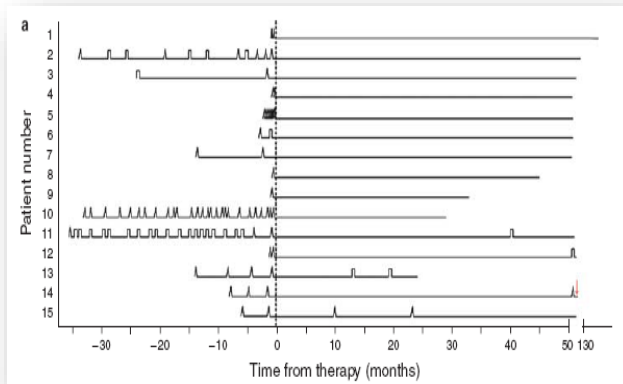
★ **ESWL+ERCP is a safe treatment**

ESWL & ERCP

ESWL for pediatric and geriatric patients

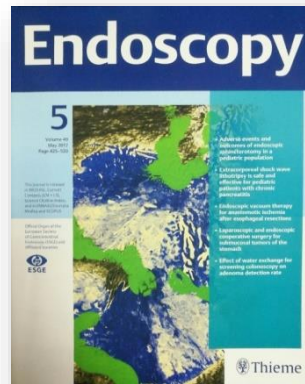
Pediatric patients (<18 years old)

- stone removal rate: 86%
- Pain relief rate: 89%
- Height growth : 4.2cm



Geriatric patients(>65 years old)

- No significant difference in post-ESWL complication (P=0.364)
- Pain relief rate: 73.6%



Complications	Geriatric group (n = 72)	Control group (n = 1332)	P value
Type			
PEP	4 (5.6%)	124 (9.3%)	0.196
Infection	2 (2.8%)	14 (1.1%)	0.196
Bleeding	0	2 (0.2%)	0.900
Perforation	0	4 (0.3%)	0.810
Steinstrasse	0	11 (0.8%)	0.599
Others	0	0	—
Severity			0.058
Mild	5 (6.9%)	114 (8.6%)	
Moderate	0	42 (3.2%)	
Severe	1 (1.4%)	2 (0.2%)	
Total	6 (8.3%)	158 (11.9%)	0.364
complications			

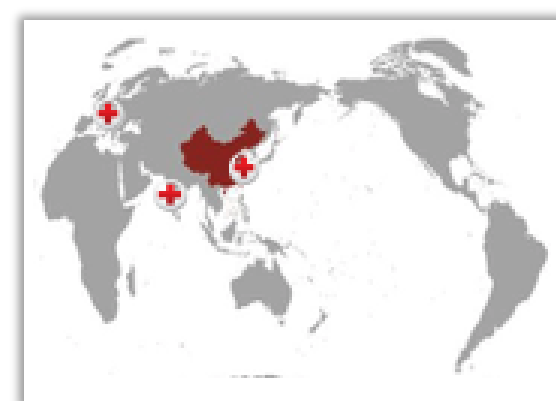
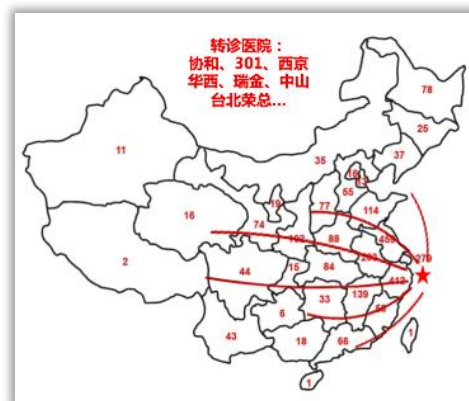
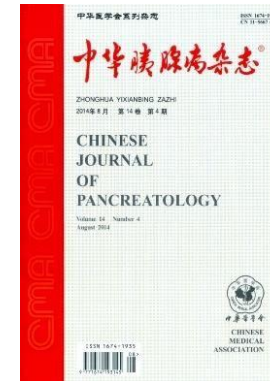
★ ESWL is safe and effective for pediatric & geriatric patients

Next steps...

1. *Collect clinical information and samples of CP patients, build clinical database and sample library*
2. *Analyze the CNV-seq data and identify new CP-related genes*
3. *Construct genetic models of CP: mechanism research and drug screening*
4. *Multi-center RCT study to optimize the standardized endoscopic treatment system for CP patients*

Department of Gastroenterology Changhai Hospital

- National Clinical Medical Research Center (Digestive disease)
- Established the first chronic pancreatitis group in China (2017)
- *Guidelines of chronic pancreatitis 2018 ; PEI consensus 2018*



Thank you!



Zhuan Liao, MD

- *Chairman of the CP group in China*
- *Vice-director of Shanghai Institute of Pancreatic Diseases*
- *Vice-president of Changhai Hospital*
- *Deputy Director of Dept. of Gastroenterology*
- *Email: zhuanleo@126.com*