

The Effect of Plasma TriglycERide Lowering Therapy on Organ FunctiOn in HypertRiglycerideMia-induced Acute Pancreatitis: a multicenter, registry-based, observational study (PERFORM)

Protocol and Statistical Analysis Plan Amendment History

1. Original protocol, final protocol, summary of changes

2. Statis	stical analysis plan	.36
1.3	Summary changes from V1-2	30
1.2	Protocol V2 June 2020 (updated before enrollment of patients)	15
1.1	Protocol V1 Dec 2019 (original protocol)	1

1	PERFORM
2	
3	The Effect of Plasma TriglycERide Lowering Therapy on Organ
4	FunctiOn in HypertRiglycerideMia-induced Acute Pancreatitis:
5	a multicenter, registry-based, observational study
6	(PERFORM)
7	
8	Protocol Ver:1.0 dated Dec.2019
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SUMMARY INFORMATION TYPE	SUMMARY DETAILS		
Acronym (Short Title)	PERFORM		
Long Title	The Effect of Plasma Triglyceride Lowering		
	Therapy on Organ Function in		
	Hypertriglyceridemia-induced Acute		
	Pancreatitis: a multicenter, registry-based,		
	observational study		
Version	1.0		
Date	10 th December 2019		
Trial registration	ChiCTR2000039541		
Study Design	A multi-centered, register-based, observational		
	study		
Type of Participants to be studied	Patients aged 18 to 70 years older who were		
	diagnosed with hypertriglyceridemia-induced		
	acute pancreatitis (See the study population in		
	detail)		
Setting	estimated 30-40 hospitals across China		
Study Aim	This study aims to evaluate the TG-lowering		
	effects of different therapies and their impact on		
	clinical outcomes in HTG-AP patients with		
	worrisome features.		
Primary Outcomes Measure(s)	organ failure-free days (OFFDs) to 14 days after		
	enrollment.		
Secondary Outcome Measure(s)	Part I: Secondary outcomes during the index admission		
	1. New-onset organ failure;		
	 New-onset organ failure, New-onset multiple-organ failure (MOF); 		
	 New-onset persistent organ failure (POF); New-onset persistent organ failure (POF); 		
	 New receipt of organ support; 		
	 Requirement of ICU admission; 		
	 ICU free days to day 14; 		
	7. Hospital free days to day 14;		
	Part II: Secondary outcomes within 60 days after		
	enrollment		
	1. Mortality censored at 60 days after enrollment;		
	2. AP severity grade (Based on the Revised		
	Atlanta Classification);		
	3. Incidence of infected pancreatic necrosis		
	(IPN);		
	4. Incidence of septic shock;		
	5. Incidence of abdominal bleeding;		
	6. Incidence of gastrointestinal fistula.		
Number of Participates to be studied	estimated 200 patients		
Duration	estimated 18 months		

	Sponsor	Jinling Hospital of Nanjing University
	Chief Investigators	Professor. Weiqin Li
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1 **1. Abrreviations**

2	HREC	Hospital Human Research Ethics Committee
3	CDMC	Coordinating and Data Management Center
4	AP	Acute pancreatitis
5	HTG-AP	Hypertriglyceridemia-induced AP
6	TG	Triglyceride
7	ASFA	American Society for Apheresis
8	TPE	Therapeutic plasma exchange
9	RCTs	randomize controlled trials
10	OF	organ failure
11		

12 2. Study Administrative information

13 **2.1 Steering and management committee**

- 14 The steering and management committee is responsible for the approval of the full protocol,
- 15 database, and related methods. The members of the committee will also oversee the implementation
- 16 of the study and play an advisory role.
- 17 Members of the steering committee are listed below
- 18 Prof. Weiqin Li
- 19 Prof. Zhihui Tong
- 20 Prof. Lu Ke
- 21 Prof. John Windsor
- 22 Dr. Jing Zhou
- 23 Dr. Longxiang Cao
- 24

25 **2.2 Coordinating and data management center**

26 Coordinating and data management centers (CDMC) will be organized before implementation of

- 27 the current study in the CAPCTG. They are responsible for the day to day management of the trial,
- 28 assistance for ethic application in each center, protocol and case report form design, online database

1	design and maintenance,	protocol training	g for the r	participating	g centers, data entr	v and qualit	v control.
-			r			J	J ,

- 2 severe adverse event monitor and notification and data analysis. The CDMC plans to meet before
- 3 enrollment, three months after initial enrollment and six months after initial enrollment to ensure
- 4 qualified data entry.
- 5 Members of CDMC are listed below
- 6 Prof. Zhihui Tong
- 7 Prof. Lu Ke
- 8 Dr.Jingzhou
- 9 Dr. Yuxiu Liu
- 10 Dr. Longxiang Cao and all the research nurses and coordinators from the participating centers.
- 11

12 **2.3 Writing and publication committee**

- 13 The writing and publication committee is responsible for drafting the manuscript and submission
- 14 of the manuscript to adequate journals. The Writing and publication committee will also decide on
- 15 the authorship of this study. After the conclusion of this study, every participating centers are
- 16 welcome to submit proposals for post-hoc analysis to the writing and publication committee, which
- 17 is responsible for reviewing and rating all the proposals for further analysis.
- 18 Members are listed below
- 19 Prof. Weiqin Li
- 20 Prof. Zhihui Tong
- 21 Prof. John Windsor
- 22 Dr. Lu Ke
- 23 Dr. Jing Zhou
- 24

25 **2.4 Registration**

26 The PERFORM study was_registered at the Chinese Clinical Trials Registry (ChiCTR2000039541)

- 27 before enrollment.
- 28

3. Background and rationale

Acute pancreatitis (AP) is a potentially life-threatening inflammatory disease with multiple etiologies, such as alcohol, gallstones and hypertriglyceridemia. HTG is the third most common cause of AP, accounting for 4-10% of cases globally, and the increasing prevalence of HTG-AP had been reported in recent studies[1-4]. In China, HTG had been the second leading cause of AP, and previous studies showed that HTG-AP patients had a higher risk of severe acute pancreatitis and multiple organ dysfunction syndrome (MODS) than other types of AP[2, 5-7].

8 Although the pathophysiology underlying HTG-AP remains controversial, it is widely accepted 9 that free fatty acid (FFA) is one of the driving factors[8]. FFA, produced by the hydrolysis of 10 triglyceride (TG), can initiate or worsen the disease by triggering inflammatory reactions, damaging 11 the pancreatic cell, and promoting microvascular thrombosis within the pancreatic tissue[9]. Nawaz 12 et al.[6] found that elevated serum TG levels in AP patients were independently and proportionally 13 correlated with persistent organ failure (POF) regardless of etiology. In an observational study 14 conducted by Lu et al. [10]timely reduction of serum TG during the early phase of HTG-AP was 15 found to be associated with decreased incidence of POF

16 Over the past years, several attempts had been made to lower serum TG more efficiently during 17 the acute phase of the disease, including medical treatment with insulin and/or heparin, blood 18 purification, and genetic therapy in cases[11]. Medical treatment is convenient and safe and is 19 considered the first-line choice for TG-lowering therapy[4]. Heparin stimulates the release of 20 endothelial lipoprotein lipase into circulation, while insulin activates lipoprotein lipase, thereby 21 increasing the clearance of chylomicrons from plasma[12]. However, the impact of medical therapy 22 on clinical outcomes is uncertain, and an observational study is ongoing to figure it out[13]. Blood 23 purification, especially plasmapheresis, is also widely used as a TG-lowering therapy. 24 Plasmapheresis rapidly removes triglycerides from plasma and is considered one of the most 25 efficient TG-lowering therapies [14]. Technically, it is a therapeutic procedure in which the blood 26 of the patient is passed through a medical device that separates plasma from other components of 27 blood. The plasma is removed and replaced by a replacement solution (e.g., albumin and/or plasma) 28 or a combination of crystalloid/colloid solution[15]. Double filtration plasmapheresis (DFPP) is a 29 semi-selective apheresis method based on a double filter system, which can remove macromolecules

selectively[16]. Both techniques are widely adopted, while plasmapheresis is thought to be more
effective in removing FFA [17]. Other blood purification modalities were also reported effective in
lowering plasma TG, including hemoperfusion and hemofiltration[18, 19]. A randomized control
trial (RCT) reported that high-volume hemofiltration (HVHF) decreased TG levels more efficiently
than medical therapy[18].

6 For the target of TG-lowering therapy, it is regarded that reducing the TG level to 5.65 mmol/L 7 might be clinically sufficient[20]. Lu et al.[10]found that patients with earlier TG levels of < 5.65 8 mmol/L were less likely to develop POF. However, the optimal TG lowering target and choice of 9 therapies in early HTG-AP are unclear due to the lack of high-quality studies. Given the paucity of 10 evidence in the literature and the variation in the management of HTG-AP, we conducted this multicenter, observational study and built "The effect of plasma triglyceride-lowering therapy on 11 12 the evolution of organ function in early hypertriglyceridemia-induced acute pancreatitis patients 13 with worrisome features" (PERFORM) registry to evaluate the TG-lowering effects of different 14 therapies and their impact on clinical outcomes in HTG-AP patients with worrisome features.

15 16

17 **4. Study Design**

18 4.1 Study aim

19 The PERFORM study aims to evaluate the association between different TG-lowering therapies and

20 clinical outcomes in HTG-AP patients with worrisome features.

21 *4.2 General study setting*

22 The present clinical study will be performed in 30-40 different hospitals across China. It is a 23 multi-centered, register-based, prospective, observational study.

24

25 **5. Study population**

26 *5.1 Patient recruitment*

27 We are going to collect approximately 200 patients presenting to the participating ICUs across

28 China during a two-year period. Based on the volume of all the participating centers, the aim should

- 1 be able to be achieved within the study period.
- 2 5.2 Eligibility Criteria
- 3 5.21 Inclusion Criteria
- 4 1. Informed consent form obtained from the patient or next of kin;
- 5 2. Age between 18 to 70 years old;
- 6 3. Within 72 hours of onset,
- 7 4. With a primary diagnosis of AP based on Abdominal Pain Suggestive of AP, Serum Amylase
- 8 at Least three Times the Upper Limit of Normal, and/or Characteristic Findings of AP on
- 9 Computed Tomography or Less Commonly Magnetic Resonance Imaging (MRI) or
- 10 Transabdominal Ultrasonography According to the Revised Atlanta Criteria[1].
- 5. When enrolled, TG>1000mg/dL (11.3mmol/L), accompanied by the clinical worrisome
 features of any one or more of the following[2]:
- 13 1) Signs of hypocalcaemia (calcium levels less than 2.1mmol/L)
- 14 2) Lactic acidosis (Lactate levels more than 2mmol/L and PH<7.35)
- 15 3) Signs of worsening systemic inflammation (two or more):
- 16 a) Temperature $>38.5^{\circ}$ C or $<35.0^{\circ}$ C
- b) Heart rate of >90 /min
- 18 c) Respiratory rate of >20 breaths/min or PaCO2 of <32 mmHg
- 19 d) WBC count of >12,000 cells/mL, <4000 cells/mL, or >10 percent immature (band) forms
- 20 4) Signs of worsening organ dysfunction or multi-organ failure as defined by Modified
- 21 Marshall scoring system for organ dysfunction ;
- 22
- 23 5.22 Exclusion Criteria
- 24 1. Failure to obtain informed consent;
- 25 2. Pregnant or lactating women; or have a pregnancy plan within a month after the
 study (including male subjects);
- 27 3. Researchers' family members who are directly involved in the study;
- 4. Patients are expected to die within 48 hours after enrollment, defined as patients
- 29 with norepinephrine usage at a dose of 25 mg/min or more under full-fluid
- 30 resuscitation, with a systolic blood pressure <90mm Hg and serum pH values <7.0.

- 1 The judgment will be made by the treating physician.
- 5.Additional exclusion criteria for this analysis: Patients undergo any invasive
 blood purification therapy other than plasmapheresis.
- 4

5 6. Patient management

6 We recommend all all patients receive standard treatment that follows the "Acute Pancreatitis 7 Treatment Guidelines" issued by the American College of Gastroenterology (ACG) in 2013 and the 8 standard treatment plan for acute pancreatitis provided in the "Evidence-Based Guidelines for the 9 Treatment of Acute Pancreatitis" issued by the International Association of Pancreatology (IAP) and 10 the American Pancreatic Association (APA)[23, 24]. Since the PERFORM study is an observational 11 one, all treatment decisions will be at the discretion of the treating physicians, including the use of 12 different TG-lowering therapies.

13

14 **7. Outcome measures**

- 15 7.1 Primary outcome
- 16 The primary outcome is organ failure_free days <u>(OFFDs)</u> to 14days after enrollment. Only the 17 final period of OF-free days is included, and patients who have OF at day 14 or died before day14 18 are assigned to zero OF-free days.
- 19 *7.2 Secondary outcome*
- 20 Secondary outcome measures
- 21 Part I: Secondary outcomes during the index admission
- 22 1. New-onset organ failure;
- 23 2. New-onset multiple-organ failure (MOF);
- 24 3. New-onset persistent organ failure (POF);
- 25 4. New receipt of organ support;
- 26 5. Requirement of ICU admission;
- 27 6. ICU free days to day 14;
- 28 7. Hospital free days to day 14;

- 2 1. Mortality censored at 60 days after enrollment;
- 3 2. AP severity grade (Based on the Revised

4 Atlanta Classification);

5 3. Incidence of infected pancreatic necrosis (IPN);

6 4. Incidence of septic shock;

7 5. Incidence of abdominal bleeding;

- 8 6. Incidence of gastrointestinal fistula.
- 9

10 Definition of seconday outcomes:1)An individual SOFA score of 2 or more for the respiration, 11 cardiovascular, or renal system is defined as the presence of organ failure. 2)New-onset organ failure 12 is defined as organ failure that is not present at any time in the 24 h after enrollment. Multiple organ 13 failure is defined as two or more organ failures present at the same time. 3)Persistent organ failure 14 is defined as organ failure that persists for more than 48 h. 4)ICU free days to day 14 after enrollment 15 is defined as the number of days alive and not admitted to an ICU after the patient' s latest discharge 16 from the ICU before day 14. If the patient is admitted to an ICU on day 14 or dies prior to day 14, ICU-free days will be 0. Hospital-free days to day 14 after enrollment is defined as the number of 17 18 days alive and not admitted to the hospital after the patient' s final discharge from the hospital 19 before day 14.

20

21 8. Ethics and dissemination

22 This study has been approved by the ethics committee of the Jinling Hospital (No. 2020NZKY-

- 23 016-01). Ethic approval of each participating center is required before initiation of enrollment.
- 24

25 8.1 Consent and confidentiality

26 Informed consent is required for each participant of this study, either signed by the patients himself

- 27 or next of kin. All the data stored in the electronical database are de-identified to guarantee patients'
- 28 privacy.

29 8.2 Dissemination policy

1 All the primary investigators and the sponsor will have full access to the data after conclusion of 2 the study. Anyone who want to do a post-hoc analysis need to submit a formal writing proposal to 3 the expert panel. Only approved author can have access to the database.

4 9. Data collection

A web-based electronic database (access through the website of the CAPCTG, 5 6 https://capctg.medbit.cn/) is used for data collection and storage. All data are de-identified and input 7 by the primary investigator or nominated investigators (less than two for each participating center) 8 approved by the primary nvestigator, and a double check will be done by the research coordinator. 9 Training for data entry is performed by the provider of the electrical database (Unimed Scientific, 10 Inc, Wuxi, China) and the coordinating and data management center of the CAPCTG. Data 11 including demographic characteristics, baseline characteristics, daily laboratory test, daily TG-12 lowering treatment, daily SOFA score, and follow-up characteristics. Demographic characteristics 13 include age and sex. Baseline characteristics include body mass index (BMI), SOFA score on 14 admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission, 15 the systemic inflammatory response syndrome (SIRS) on admission. Daily laboratory tests include 16 serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-17 density lipoprotein cholesterol (LDL-c), apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), 18 apolipoprotein E (Apo E), lipoprotein a [LP(a)], free fatty acids (FFA), C-reactive protein (CRP), 19 and procalcitonin (PCT). Daily TG-lowering treatment includes blood purification treatment (e.g., 20 plasma exchange, hemoperfusion, and hemofiltration) and medical treatment (e.g., insulin and 21 heparin). Follow-up characteristics include ICU days, hospital days, in-hospital cost, revision of the 22 Atlanta classification on admission, CT severity index (CTSI) score (Based on the last image before 23 discharge or death), mortality, and incidence of major complications on day 60. According to the 24 schedule shown in Table 1, the investigators are required to collect data during the index admission 25 and on day 60 after enrollment. And a follow-up on day 60 will be implemented through telephone.

			Study peri	od	
	Enrollmer	nt Obsei	rvational pe	riod	Discharge
Time point	<72h	Day0 ^a	Day1-Day1	4 ^b C	ay28 and Day60
Enrollment:					
Eligibility screen	Х				
Informed consent	Х				
Laboratory test	Х				
Imaging(CT scan etc.)	Х				
Assessment:					
Organ failure		Х	•	-	
Laboratory test		Х	•	-	
Major treatment		Х	•		
Adverse effects		Х	•		
Follow up:					
Vital status					Х
Major complication					Х
ICU days and hospital days	i				Х
Cost					Х

TABLE 1 | Schedule of enrollment, assessment and follow up.

^aDay0 is defined as the day from enrollment to 8 am the next day.

^bDayX is defined as the day from 8 am day X after enrollment to 8 am the next day.
 Assessments during this period need to be repeated on a daily basis.

1 2

3 10. Statistical analysis

4 10.1 Data collection methods:

5 A web-based electrical database will be used for data collection and storage. All data will be input

6 by the primary investigator or nominated investigator(less than two for each participating center)

7 approved by the primary investigator. Training for data entry will be performed by the supplier of

8 the electrical database and the sponsor of the PERFORM study, and the coordinating center of

9 CAPCTG.

10 10.2 Statistical methods

1 Continuous normally distributed data were reported as means with SDs. Skewed continuous data were reported as medians andby counts and percentages. The intergroup difference will be compared 2 3 by Student' s t-test or Wilcoxon rank-sum test for continuous variable depending on their normality 4 and chi-square test for categorical data. To evaluate the association between TG decline and OF free days, the study patients will be dichotomized depending on whether the TG level reaches 5.65 5 6 mmol/L on Day 3 (the day of enrollment is labeled Day 1, the next day labeled Day 2, and the 7 following day Day 3). For the primary outcome comparison, Wilcoxon rank-sum test will be 8 employed. However, since OF could be evaluated with a time-to-event analysis censored at 14 days 9 to account for the mortality as a competing event, Fine and Gray competing risk regression is used 10 to assess the group difference as a supportive analysis. For the association between different TG 11 lowering therapy and OF free days, we considered the possibility that baseline characteristics, which 12 were expected to be prognostic for OF, differ according to the choice of TG lowering therapies (i.e., 13 blood purification treatment and medical treatment). A propensity score matching will be further 14 used to compensate for the intergroup unbalance. For secondary outcomes, a multivariate analysis 15 generalized linear model (GLM) model will be performed to identify its association with TG decline 16 and TG-lowering therapy with proper link and distribution function. The variable included in the 17 model will be age, sex, TG level at enrollment, and other baseline variables that have significant 18 differences between groups.

19 **11. References**

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26		therapeutic plasma exchange in the treatment of acute hypertriglyceridemic pancreatitis.
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1	PERFORM
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4	FunctiOn in HypertRiglycerideMia-induced Acute Pancreatitis:
5	a multicenter, registry-based, observational study
6	(PERFORM)
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8	Protocol Ver:2.0 dated June.2020
9	Primary Investigator: Professor. Weiqin Li
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Acronym (Short Title)	PERFORM		
Long Title	The Effect of Plasma Triglyceride Lowering Therapy on Organ		
	Function in Hypertriglyceridemia-induced Acute Pancreatitis:		
	a multicenter, registry-based, observational study		
Version	2.0		
Date	10 th June 2020		
Trial registration	ChiCTR2000039541		
Study Design	Multicenter, registry-based, observational study		
Type of Participants to be Studied	Patients aged 18 to 70 years older who were diagnosed with		
	hypertriglyceridemia-induced acute pancreatitis (See the study		
	population in detail)		
Setting	Multicenter across China		
Study Aim	This study aimed to describe the practice variation in		
	triglyceride-lowering for HTG-AP patients with worrisome		
	clinical features. It also aimed to evaluate the triglyceride-		
	lowering effects of different therapies and their impact on		
	clinical outcomes in HTG-AP patients with worrisome		
	features.		
Primary Outcomes Measure(s)	Organ failure-free days (OFFDs) to 14 days after enrollment		
Key Secondary Outcome Measure(s)	Part I: Secondary outcomes during the index admission		
	8. a composite of death from any cause by day 28 and		
	the presence of at least one organ failure at day 7		
	9. ICU free days to day 14		
	10. hospital free days to day 14,		
	11. new onset organ failure		
	12. requirement of ICU admission and development of		
	infected pancreatic necrosis (IPN).		
	Part II: Secondary outcomes within 60 days after enrollment		

	 Mortality censored at 60 days after enrollment; hospital free days to day28 and day60 of enrollment
Number of Participates to be studied PERFORM is designed to be a long-running registry	
	phase-I goal is to recruit 300 patients.
Duration	Long-running
Sponsor	Jinling Hospital of Nanjing University
Chief Investigators	Professor. Weiqin Li

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1 2. Abrreviations

2	HREC	Hospital Human Research Ethics Committee
3	CDMC	Coordinating and Data Management Center
4	AP	Acute pancreatitis
5	HTG-AP	Hypertriglyceridemia-induced acute pancreatitis
6	TG	Triglyceride
7	ASFA	American Society for Apheresis
8	TPE	Therapeutic plasma exchange
9	RCTs	Randomize controlled trials
10	OF	Organ failure
11		

12 2. Study Administrative information

13 2.1 Study timelines

14	June 2019	Protocol manuscript
15		
16	December 2019	Protocol finalized
17		Initial expressions of interest sought from sites
18		Commence study organization
19		
20	June 2020	Hospital Human Research Ethics Committee (HREC) submissions
21		Study material V.1.0 finalized
22		HREC approvals obtained
23		
24	December 2020	Patient recruitment commences (in plan)
25		
26		
27		
28	2.2 Steering a	and management committee

- 1 The steering and management committee is responsible for the approval of the full protocol,
- 2 database, and related methods. The members of the committee will also oversee the implementation
- 3 of the study and play an advisory role.
- 4 Members of the steering committee are listed below
- 5 Prof. Weiqin Li
- 6 Prof. Zhihui Tong
- 7 Prof. Lu Ke
- 8 Prof. John Windsor
- 9 Dr. Jing Zhou
- 10 Dr. Longxiang Cao
- 11

12 **2.3 Coordinating and data management center**

- 13 Coordinating and data management centers (CDMC) will be organized before implementation of 14 the current study in the CAPCTG. They are responsible for the day to day management of the trial,
- 15 assistance for ethic application in each center, protocol and case report form design, online database
- 16 design and maintenance, protocol training for the participating centers, data entry and quality control,
- 17 severe adverse event monitor and notification and data analysis. The CDMC plans to meet before
- 18 enrollment, three months after initial enrollment and six months after initial enrollment to ensure
- 19 qualified data entry.
- 20 Members of CDMC are listed below
- 21 Prof. Zhihui Tong
- 22 Prof. Lu Ke
- 23 Dr.Jingzhou
- 24 Dr. Yuxiu Liu
- 25 Dr. Longxiang Cao and all the research nurses and coordinators from the participating centers.
- 26

27 **2.4 Writing and publication committee**

28 The writing and publication committee is responsible for drafting the manuscript and submission

29 of the manuscript to adequate journals. The Writing and publication committee will also decide on

- 1 the authorship of this study. After the conclusion of this study, every participating centers are
- 2 welcome to submit proposals for post-hoc analysis to the writing and publication committee, which
- 3 is responsible for reviewing and rating all the proposals for further analysis.
- 4 Members are listed below
- 5 Prof. Weiqin Li
- 6 Prof. Zhihui Tong
- 7 Prof. John Windsor
- 8 Dr. Lu Ke
- 9 Dr. Jing Zhou
- 10

11 **2.5 Registration**

The PERFORM study was registered at the Chinese Clinical Trials Registry (ChiCTR2000039541)
 before enrollment.

14 2.6 Funding

This study was funded by Key Research and Development Program Foundation of
Jiangsu Province of China (No. BE 2016749) and the National Science Foundation of
China (No. 81900592).

18

19 **3. Background and rationale**

Acute pancreatitis (AP) is a potentially life-threatening inflammatory disease with multiple etiologies, such as alcohol, gallstones and hypertriglyceridemia. HTG is the third most common cause of AP, accounting for 4-10% of cases globally, and the increasing prevalence of HTG-AP had been reported in recent studies[1-4]. In China, HTG had been the second leading cause of AP, and previous studies showed that HTG-AP patients had a higher risk of severe acute pancreatitis and multiple organ dysfunction syndrome (MODS) than other types of AP[2, 5-7]. Although the pathophysiology underlying HTG-AP remains controversial, it is widely accepted

27 that free fatty acid (FFA) is one of the driving factors[8]. FFA, produced by the hydrolysis of

28 triglyceride (TG), can initiate or worsen the disease by triggering inflammatory reactions, damaging

the pancreatic cell, and promoting microvascular thrombosis within the pancreatic tissue[9]. Nawaz et al.[6] found that elevated serum TG levels in AP patients were independently and proportionally correlated with persistent organ failure (POF) regardless of etiology. In an observational study conducted by Lu et al. [10]timely reduction of serum TG during the early phase of HTG-AP was found to be associated with decreased incidence of POF

6 Over the past years, several attempts had been made to lower serum TG more efficiently during 7 the acute phase of the disease, including medical treatment with insulin and/or heparin, blood 8 purification, and genetic therapy in cases[11]. Medical treatment is convenient and safe and is 9 considered the first-line choice for TG-lowering therapy[4]. Heparin stimulates the release of 10 endothelial lipoprotein lipase into circulation, while insulin activates lipoprotein lipase, thereby 11 increasing the clearance of chylomicrons from plasma[12]. However, the impact of medical therapy 12 on clinical outcomes is uncertain, and an observational study is ongoing to figure it out[13]. Blood 13 purification, especially plasmapheresis, is also widely used as a TG-lowering therapy. 14 Plasmapheresis rapidly removes triglycerides from plasma and is considered one of the most 15 efficient TG-lowering therapies [14]. Technically, it is a therapeutic procedure in which the blood 16 of the patient is passed through a medical device that separates plasma from other components of 17 blood. The plasma is removed and replaced by a replacement solution (e.g., albumin and/or plasma) 18 or a combination of crystalloid/colloid solution[15]. Double filtration plasmapheresis (DFPP) is a 19 semi-selective apheresis method based on a double filter system, which can remove macromolecules 20 selectively[16]. Both techniques are widely adopted, while plasmapheresis is thought to be more 21 effective in removing FFA [17]. Other blood purification modalities were also reported effective in 22 lowering plasma TG, including hemoperfusion and hemofiltration[18, 19]. A randomized control 23 trial (RCT) reported that high-volume hemofiltration (HVHF) decreased TG levels more efficiently 24 than medical therapy[18].

For the target of TG-lowering therapy, it is regarded that reducing the TG level to 5.65 mmol/L might be clinically sufficient[20]. Lu et al.[10]found that patients with earlier TG levels of < 5.65 mmol/L were less likely to develop POF. However, the optimal TG lowering target and choice of therapies in early HTG-AP are unclear due to the lack of high-quality studies. Given the paucity of evidence in the literature and the variation in the management of HTG-AP, we conducted this multicenter, observational study and built "The effect of plasma triglyceride-lowering therapy on the evolution of organ function in early hypertriglyceridemia-induced acute pancreatitis patients with worrisome features"(PERFORM) registry to evaluate the TG-lowering effects of different therapies and their impact on clinical outcomes in HTG-AP patients with worrisome features.

5 4. Study Design

6 *4.1 Study aim*

7 This study aimed to 1) describe the practice variation in triglyceride-lowering for HTG-AP patients

8 with worrisome clinical features; 2)evaluate the triglyceride-lowering effects of different therapies

9 and their impact on clinical outcomes in HTG-AP patients with worrisome features.

10 *4.2 General study setting*

11 The present clinical study will be performed in multiple sites across China . It is a multicenter, 12 registry-based, prospective, observational cohort study.

13

14 5. Study population

15 5.1 Patient recruitment and sample size considerations

16 Based on the feasibility and patient flow of the potential participating sites, a sample size of 300 17 patients was expected, with an average of 15 patients per month within 2 years. Considering an 18 estimate20% rate of incomplete data or losses of follow-up, our expected sample size (240 patients) 19 would provide 87% to detect a 2- days (SD: 5) or 82.5% for 1.5-days (SD: 4) improvement of organ 20 failure free days between patients achieve target TG and those not. The PERFORM study is aimed 21 to be a long-running registry, so the collection of patients will be continuous after achieving the 22 phase-I goal(300 patients). 23 5.2 Eligibility Criteria 24 5.21 Inclusion Criteria

25 6. Informed consent form obtained from the patient or next of kin;

26 7. Age between 18 to 70 years old;

27 8. Within 72 hours of onset,

28 9. With a primary diagnosis of AP based on Abdominal Pain Suggestive of AP, Serum Amylase

1	at Least three Times the Upper Limit of Normal, and/or Characteristic Findings of AP on
2	Computed Tomography or Less Commonly Magnetic Resonance Imaging (MRI) or
3	Transabdominal Ultrasonography According to the Revised Atlanta Criteria[21].
4	10. When enrolled, TG>1000mg/dL (11.3mmol/L), accompanied by the clinical worrisome
5	features of any one or more of the following[22]:
6	1) Signs of hypocalcaemia (calcium levels less than 2.1mmol/L)
7	2) Lactic acidosis (Lactate levels more than $2mmol/L$ and $PH \le 7.35$)
8	3) Signs of worsening systemic inflammation (two or more):
9	a) Temperature >38.5°C or <35.0°C
10	b) Heart rate of >90 /min
11	c) Respiratory rate of >20 breaths/min or PaCO2 of <32 mmHg
12	d) WBC count of >12,000 cells/mL, <4000 cells/mL, or >10 percent immature (band) forms
13	4) Signs of worsening organ dysfunction or multi-organ failure as defined by Modified
14	Marshall scoring system for organ dysfunction;
14 15	Marshall scoring system for organ dysfunction ; 5.22 Exclusion Criteria
15	5.22 Exclusion Criteria
15 16	5.22 Exclusion Criteria1. Failure to obtain informed consent;
15 16 17	5.22 Exclusion Criteria1. Failure to obtain informed consent;2. Pregnant or lactating women; or have a pregnancy plan within a month after the
15 16 17 18	 5.22 Exclusion Criteria 1. Failure to obtain informed consent; 2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects);
15 16 17 18 19	 5.22 Exclusion Criteria 1. Failure to obtain informed consent; 2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects); 3. Researchers' family members who are directly involved in the study;
15 16 17 18 19 20	 5.22 Exclusion Criteria 1. Failure to obtain informed consent; 2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects); 3. Researchers' family members who are directly involved in the study; 4. Patients are expected to die within 48 hours after enrollment, defined as patients
15 16 17 18 19 20 21	 5.22 Exclusion Criteria 1. Failure to obtain informed consent; 2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects); 3. Researchers' family members who are directly involved in the study; 4. Patients are expected to die within 48 hours after enrollment, defined as patients with norepinephrine usage at a dose of 25 mg/min or more under full-fluid
15 16 17 18 19 20 21 22	 5.22 Exclusion Criteria 1. Failure to obtain informed consent; 2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects); 3. Researchers' family members who are directly involved in the study; 4. Patients are expected to die within 48 hours after enrollment, defined as patients with norepinephrine usage at a dose of 25 mg/min or more under full-fluid resuscitation, with a systolic blood pressure <90mm Hg and serum pH values <7.0.
15 16 17 18 19 20 21 22 23	 5.22 Exclusion Criteria Failure to obtain informed consent; Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects); Researchers' family members who are directly involved in the study; Patients are expected to die within 48 hours after enrollment, defined as patients with norepinephrine usage at a dose of 25 mg/min or more under full-fluid resuscitation, with a systolic blood pressure <90mm Hg and serum pH values <7.0. The judgment will be made by the treating physician.

27 6. Patient management

We recommend all patients receive standard treatment that follows the "Acute Pancreatitis Treatment Guidelines" issued by the American College of Gastroenterology (ACG) in 2013 and the standard treatment plan for acute pancreatitis provided in the "Evidence-Based Guidelines for the Treatment of Acute Pancreatitis" issued by the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA)[23, 24]. Since the PERFORM study is an observational one, all treatment decisions will be at the discretion of the treating physicians, including the use of different TG-lowering therapies.

6

7 7. Outcome measures

8 7.1 Primary outcome

9 The primary outcome is organ failure-free days (OFFDs) to 14days after enrollment. Only the 10 final period of OFFDs is included, and patients who have OF at day 14 or died before day14 are 11 assigned to zero OFFDs.

- 12
- 13 *7.2 Secondary outcome*
- 14 Secondary outcome measures
- 15 Part I: Secondary outcomes during the index admission
- 16 1. a composite of death from any cause by day 28 and the presence of at least one organ failure at
- 17 day 7
- 18 2. ICU free days to day 14;
- 19 3. Hospital free days to day 14;
- 20 4. Requirement of ICU admission;
- 21 5. new onset organ failure to day 14;
- 22 6. SOFA_{RANK} to day 14;
- 23 7. Δ SOFA_{max} to day 14;
- 24 8. ΔSOFA14 to day14
- 25
- 26 Part II: Secondary outcomes within 60 days after enrollment
- 27 1. Mortality censored at 60 days after enrollment;
- 28 2. Hospital free days to day28 and day60 of enrollment;
- 29 3. Development of infected pancreatic necrosis (IPN);

1

2 Definition of seconday outcomes: New-onset organ failure is defined as organ failure that is not 3 present at any time in the first 24 h after enrollment. SOFA_{RANK} is a ranking parameter based on the 4 cumulative daily delta SOFA score from day 1 to day 14. For each patient, it is calculated as a sum 5 of the daily delta SOFA score (defined as the daily total SOFA score minus the baseline SOFA score) 6 over the first 14 study days. Discharge is counted (from the day of discharge forward) as a score of 7 0 minus baseline score, and death is counted (from the day of death forward) as a maximum score 8 of 24 minus baseline score. Δ SOFA_{max} is defined as the maximum SOFA score within 14 days minus 9 the baseline SOFA score, and \triangle SOFA₁₄ as the SOFA score at day14 minus the baseline. The 10 definition of other secondary outcomes can be found in the published protocol

11 8. Ethics and dissemination

12 This study has been approved by the ethics committee of the Jinling Hospital (No. 2020NZKY-

13 016-01). Ethic approval of each participating center is required before initiation of enrollment.

14

15 8.1 Consent and confidentiality

Informed consent is required for each participant of this study, either signed by the patients himself or next of kin. All the data stored in the electronical database are de-identified to guarantee patients' privacy.

19

20 8.2 Dissemination policy

All the primary investigators and the sponsor will have full access to the data after conclusion of the study. Anyone who want to do a post-hoc analysis need to submit a formal writing proposal to the expert panel. Only approved author can have access to the database.

24 9. Data collection

A web-based electronic database (access through the website of the CAPCTG, https://capctg.medbit.cn/) is used for data collection and storage. All data are de-identified and input by the primary investigator or nominated investigators (less than two for each participating center) approved by the primary nyestigator, and a double check will be done by the research coordinator.

1 Training for data entry is performed by the provider of the electrical database (Unimed Scientific, 2 Inc, Wuxi, China) and the coordinating and data management center of the CAPCTG. Data 3 including demographic characteristics, baseline characteristics, daily laboratory test, daily TGlowering treatment, daily SOFA score, and follow-up characteristics. Demographic characteristics 4 include age and sex. Baseline characteristics include body mass index (BMI), SOFA score on 5 6 admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission, 7 the systemic inflammatory response syndrome (SIRS) on admission. Daily laboratory tests include 8 serum total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c), low-9 density lipoprotein cholesterol (LDL-c), apolipoprotein A1 (Apo A1), apolipoprotein B (Apo B), 10 apolipoprotein E (Apo E), lipoprotein a [LP(a)], free fatty acids (FFA), C-reactive protein (CRP), and procalcitonin (PCT). Daily TG-lowering treatment includes blood purification treatment (e.g., 11 12 plasma exchange, hemoperfusion, and hemofiltration) and medical treatment (e.g., insulin and 13 heparin). Follow-up characteristics include ICU days, hospital days, in-hospital cost, revision of the 14 Atlanta classification on admission, CT severity index (CTSI) score (Based on the last image before 15 discharge or death), mortality, and incidence of major complications on day 60. According to the 16 schedule shown in Table 1, the investigators are required to collect data during the index admission and on day 60 after enrollment. And a follow-up on day 60 will be implemented through telephone. 17 18

			Study period		
	Enrollment	Observatio	nal period	Discharge	
Time point	<72h	Day1	Day2-Day14	Day60	
Enrollment:					
Eligibility screen	X				
Informed consent	X				
Laboratory test	Х				
Imaging (CT scan	X				
etc.)					
Assessment:					
Organ failure		Х	← →		
Laboratory test		Х	← →		
Major treatment		Х	← →		
Adverse effects		Х	← →		
Follow up:					
Vital status				X	
Major complication				X	
ICU days&				X	
hospital days					
Cost				X	

1 Table1 Schedule of enrollment, assessment and follow up.

2

3

4 10. Statistical analysis

5 10.1 Data collection methods:

A web-based electrical database will be used for data collection and storage. All data will be input
by the primary investigator or nominated investigator(less than two for each participating center)
approved by the primary investigator. Training for data entry will be performed by the supplier of
the electrical database and the sponsor of the PERFORM study, and the coordinating center of
CAPCTG.
10.2 Statistical methods

12 Continuous normally distributed data were reported as means with SDs. Skewed continuous data 13 were reported as medians and by counts and percentages. The intergroup difference will be 14 compared by Student's t-test or Wilcoxon rank-sum test for continuous variable depending on their 15 normality and chi-square test for categorical data. To evaluate the association between TG decline

1 and OFFDs, the study patients will be dichotomized depending on whether the TG level reaches 2 5.65 mmol/L on Day 3 (the day of enrollment is labeled Day 1, the next day labeled Day 2, and the 3 following day Day 3). For the primary outcome comparison, Wilcoxon rank-sum test will be 4 employed. However, since OF could be evaluated with a time-to-event analysis censored at 14 days to account for the mortality as a competing event, Fine and Gray competing risk regression is used 5 6 to assess the group difference as a supportive analysis. For the association between different TG lowering therapy and OFFDs, we considered the possibility that baseline characteristics, which were 7 8 expected to be prognostic for OF, differ according to the choice of TG lowering therapies (i.e., blood 9 purification treatment and medical treatment). A propensity score matching will be further used to 10 compensate for the intergroup unbalance. For secondary outcomes, a multivariate analysis 11 generalized linear model (GLM) model will be performed to identify its association with TG decline 12 and TG-lowering therapy with proper link and distribution function. The variable included in the 13 model will be age, sex, TG level at enrollment, and other baseline variables that have significant 14 differences between groups.

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- 38

Summary of protocol changes

List of Changes

Protocol Amendment (version 1 to version 2)

Page/ Line No.	Original Text	New Text	Reason
Page 2, Table, Setting	estimated 30-40 hospitals	Multicenter, registry-based, observational study	Expected sites to
	across China		be enrolled will
			not be limited.
Page 2, Table, Study	This study aims to evaluate the	This study aimed to describe the practice variation in triglyceride-	Add Study Aim
Aim	TG-lowering effects of different	lowering for HTG-AP patients with worrisome clinical features. It also	details.
	therapies and their impact on	aimed to evaluate the triglyceride-lowering effects of different therapies	
	clinical outcomes in HTG-AP	and their impact on clinical outcomes in HTG-AP patients with	
	patients with worrisome	worrisome features.	
	features.		
Page2,Table,	Part I: Secondary outcomes	Part I: Secondary outcomes during the index admission	Only key
Secondary Outcome	during the index admission	13. a composite of death from any cause by day 28 and the presence of at least	secondary
Measure(s)	1. New-onset organ failure;	one organ failure at day 7	outcome
	2. New-onset multiple-organ	14. ICU free days to day 14	measures are
	failure (MOF);	15. Hospital free days to day 14,	listed.
	3. New-onset persistent organ	16. new onset organ failure	
	failure (POF);	17. requirement of ICU admission and development of infected pancreatic	
	4. New receipt of organ	necrosis (IPN).	
	support;	Part II: Secondary outcomes within 60 days after enrollment	

	5. Requirement of ICU	1. Mortality censored at 60 days after enrollment;	
	admission;	2. hospital free days to day28 and day60 of enrollment	
	6. ICU free days to day 14;		
	7. Hospital free days to day 14;		
	Part II: Secondary outcomes		
	within 60 days after enrollment		
	1. Mortality censored at 60 days		
	after enrollment;		
	2. AP severity grade (Based on		
	the Revised		
	Atlanta Classification);		
	3. Incidence of infected		
	pancreatic necrosis (IPN);		
	4. Incidence of septic shock;		
	5. Incidence of abdominal		
	bleeding;		
	6. Incidence of gastrointestinal		
	fistula.		
Page 2, Table,	estimated 200 patients	PERFORM is designed to be a long-running registry. The phase-I goal is to recruit	The PERFORM
Number of		300 patients.	registry will be
Participates to be			long-running.
studied			
Page 2, Table,	estimated 18 months	Long-running	Same as above.
Duration			

Page 4, line 13	Study Administrative	Add 2.1 timeline	Describe in more
	information without timeline	June 2019 Protocol manuscript	detail about timeline.
		December 2019 Protocol finalized Initial expressions of interest sought from sites Commence study organization June 2020 Hospital Human Research Ethics Committee (HREC) submissions	umenne.
		Study material V.1.0 finalized HREC approvals obtained December 2020 Patient recruitment commences (in plan)	
Page 5,line 28	Study Administrative information without funding	Add 2.6 Funding This study was funded by Key Research and Development Program Foundation of Jiangsu Province of China (No. BE 2016749) and the National Science Foundation of China (No. 81900592).	Describe funding of the study.
Page7,line 19	The PERFORM study aims to evaluate the association between different TG-lowering therapies and clinical outcomes in HTG-AP patients with worrisome features.	This study aimed to 1) describe the practice variation in triglyceride-lowering for HTG-AP patients with worrisome clinical features; 2)evaluate the triglyceride- lowering effects of different therapies and their impact on clinical outcomes in HTG-AP patients with worrisome features.	Add Study Aim detals.

Page7,line 22	The present clinical study will	The present clinical study will be performed in multiple sites across China . It is a	The PERFORM
	be performed in 30-40 different	multicenter, registry-based, prospective, observational cohort study.	registry will be
	hospitals across China. It is a		long-running.
	multi-centered, register-based,		
	prospective, observational		
	study.		
Page 7,line 27	We are going to collect	Based on the feasibility and patient flow of the potential participating sites, a	Add sample size
	approximately 200 patients	sample size of 300 patients was expected, with an average of 15 patients per month	estimation.
	presenting to the participating	within 2 years. Considering an estimate20% rate of incomplete data or losses of	
	ICUs across China during a	follow-up, our expected sample size (240 patients) would provide 87% to detect a	
	two-year period. Based on the	2- days (SD: 5) or 82.5% for 1.5-days (SD: 4) improvement of organ failure free	
	volume of all the participating	days between patients achieve target TG and those not. The PERFORM study is	
	centers, the aim should be able	aimed to be a long-running registry, so the collection of patients will be continuous	
	to be achieved within the study	after achieving the phase-I goal(300 patients).	
	period.		
Page 9,line 22	Part I: Secondary outcomes	Part I: Secondary outcomes during the index admission	Changes in
	during the index admission	1. a composite of death from any cause by day 28 and the presence of at least one	secondary
	1. New-onset organ failure;	organ failure at day 7	outcomes
	2. New-onset multiple-organ	2. ICU free days to day 14;	including the
	failure (MOF);	3. Hospital free days to day 14;	addition of a
	3. New-onset persistent organ	4. Requirement of ICU admission;	composite
	failure (POF);	5. new onset organ failure to day 14;	outcome, and
	4. New receipt of organ	6. SOFARANK to day 14;	some other organ
	support;	7. Δ SOFAmax to day 14;	failure measures.
		8. Δ SOFA14 to day14	

	5. Requirement of ICU		
	-	Dent II. Communitation of the second state of the second line of	
	admission;	Part II: Secondary outcomes within 60 days after enrollment	
	6. ICU free days to day 14;	1. Mortality censored at 60 days after enrollment;	
	7. Hospital free days to day 14;	2. Hospital free days to day28 and day60 of enrollment;	
	Part II: Secondary outcomes	3. Development of infected pancreatic necrosis (IPN);	
	within 60 days after enrollment		
	1. Mortality censored at 60 days		
	after enrollment;		
	2. AP severity grade (Based on		
	the Revised		
	Atlanta Classification);		
	3. Incidence of infected		
	pancreatic necrosis (IPN);		
	4. Incidence of septic shock;		
	5. Incidence of abdominal		
	bleeding;		
	6. Incidence of gastrointestinal		
	fistula.		
Page 10, line 11	Definition of seconday	Definition of seconday outcomes: New-onset organ failure is defined as organ	Reword the
	outcomes:1)An individual	failure that is not present at any time in the first 24 h after enrollment.	definition and
	SOFA score of 2 or more for	SOFARANK is a ranking parameter based on the cumulative daily delta SOFA	description of the
	the respiration, cardiovascular,	score from day 1 to day 14. For each patient, it is calculated as a sum of the daily	secondary
	or renal system is defined as the	delta SOFA score (defined as the daily total SOFA score minus the baseline SOFA	outcoems.
	presence of organ failure.	score) over the first 14 study days. Discharge is counted (from the day of discharge	
	2)New-onset organ failure is	forward) as a score of 0 minus baseline score, and death is counted (from the day	

1		
		defined as organ failure that is
		not present at any time in the 24
	ent. Multiple score, and Δ SOFA14 as the SOFA score at day14 minus the baseline. The	h after enrollment. Multiple
	defined as two definition of other secondary outcomes can be found in the published protocol	organ failure is defined as two
	failures present	or more organ failures present
	e. 3)Persistent	at the same time. 3)Persistent
	defined as organ	organ failure is defined as organ
	sists for more	failure that persists for more
	U free days to	than 48 h. 4)ICU free days to
	rollment is	day 14 after enrollment is
	number of days	defined as the number of days
	dmitted to an	alive and not admitted to an
	atient's latest	ICU after the patient's latest
	the ICU before	discharge from the ICU before
	atient is	day 14. If the patient is
	ICU on day 14	admitted to an ICU on day 14
	day 14, ICU-	or dies prior to day 14, ICU-
	be 0. Hospital-	free days will be 0. Hospital-
	y 14 after	free days to day 14 after
	efined as the	enrollment is defined as the
	s alive and not	number of days alive and not
	hospital after	admitted to the hospital after
	nal discharge	the patient's final discharge
	al before day 14.	from the hospital before day 14.
	sists for more U free days to rollment is number of days dmitted to an atient's latest the ICU before atient is ICU on day 14 day 14, ICU- be 0. Hospital- y 14 after efined as the is alive and not hospital after hal discharge	failure that persists for more than 48 h. 4)ICU free days to day 14 after enrollment is defined as the number of days alive and not admitted to an ICU after the patient's latest discharge from the ICU before day 14. If the patient is admitted to an ICU on day 14 or dies prior to day 14, ICU- free days will be 0. Hospital- free days to day 14 after enrollment is defined as the number of days alive and not admitted to the hospital after the patient's final discharge



The Effect of Plasma TriglycERide Lowering Therapy on Organ FunctiOn in HypertRiglycerideMia-induced Acute Pancreatitis: a multicenter, registry-based, observational study (PERFORM)

Statistical Analysis Plan

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1. INTRODUCTION

Acute pancreatitis (AP) is a potentially life-threatening inflammatory disease with multiple etiologies, such as alcohol, gallstones and hypertriglyceridemia. HTG is the third most common cause of AP, accounting for 4-10% of cases globally, and the increasing prevalence of HTG-AP had been reported in recent studies[1-4]. In China, HTG had been the second leading cause of AP, and previous studies showed that HTG-AP patients had a higher risk of severe acute pancreatitis and multiple organ dysfunction syndrome (MODS) than other types of AP[2, 5-7].

Although the pathophysiology underlying HTG-AP remains controversial, it is widely accepted that free fatty acid (FFA) is one of the driving factors[8]. FFA, produced by the hydrolysis of triglyceride (TG), can initiate or worsen the disease by triggering inflammatory reactions, damaging the pancreatic cell, and promoting microvascular thrombosis within the pancreatic tissue[9]. Nawaz et al.[6] found that elevated serum TG levels in AP patients were independently and proportionally correlated with persistent organ failure (POF) regardless of etiology. In an observational study conducted by Lu et al. [10]timely reduction of serum TG during the early phase of HTG-AP was found to be associated with decreased incidence of POF

Over the past years, several attempts had been made to lower serum TG more efficiently during the acute phase of the disease, including medical treatment with insulin and/or heparin, blood purification, and genetic therapy in cases[11]. Medical treatment is convenient and safe and is considered the first-line choice for TG-lowering therapy[4]. Heparin stimulates the release of endothelial lipoprotein lipase into circulation, while insulin activates lipoprotein lipase, thereby increasing the clearance of chylomicrons from plasma[12]. However, the impact of medical therapy on clinical outcomes is uncertain, and an observational study is ongoing to figure it out[13]. Blood purification, especially plasmapheresis, is also widely used as a TG-lowering therapy. Plasmapheresis rapidly removes triglycerides from plasma and is considered one of the most efficient TG-lowering therapies [14]. Technically, it is a therapeutic procedure in which the blood of the patient is passed through a medical device that separates plasma from other components of blood. The plasma is removed and replaced by a replacement solution (e.g., albumin and/or plasma) or a combination of crystalloid/colloid solution[15]. Double filtration plasmapheresis (DFPP) is a semi-selective apheresis method based on a double filter system, which can remove macromolecules selectively[16]. Both techniques are widely adopted, while plasmapheresis is thought to be more effective in removing FFA [17]. Other blood purification modalities were also reported effective in lowering plasma TG, including hemoperfusion and hemofiltration[18, 19]. A randomized control trial (RCT) reported that high-volume hemofiltration (HVHF) decreased TG levels more efficiently than medical therapy[18].

For the target of TG-lowering therapy, it is regarded that reducing the TG level to 5.65 mmol/L might be clinically sufficient[20]. Lu et al.[10]found that patients with earlier TG levels of < 5.65 mmol/L were less likely to develop POF. However, the optimal TG lowering target and choice of therapies in early HTG-AP are unclear due to the lack of high-quality studies. Given the paucity of evidence in the literature and the variation in the management of HTG-AP, we conducted this multicenter, observational study and built "The effect of plasma triglyceride-lowering therapy on the evolution of organ function in early hypertriglyceridemia-induced acute pancreatitis patients with worrisome features"(PERFORM) registry to evaluate the TG-lowering effects of different therapies and their impact on clinical outcomes in HTG-AP patients with worrisome features.

2. STUDY DESIGN AND OBJECTIVE

This study is an analysis of data collected from the PERFORM study (ChiCTR2000039541, https://www.chictr.org.cn/index.aspx). This study aimed to 1) describe the practice variation in triglyceride-lowering for HTG-AP patients with worrisome clinical features; 2)evaluate the triglyceride-lowering effects of different therapies and their impact on clinical outcomes in HTG-AP patients with worrisome features.

3. ELIGIBILITY CRITERIA

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3.1 Patient recruitment

Based on the feasibility and patient flow of the potential participating sites, a sample size of 300 patients was expected, with an average of 15 patients per month within 2 years. Considering an estimate20% rate of incomplete data or losses of follow-up, our expected sample size (240 patients) would provide 87% to detect a 2-days (SD: 5) or 82.5% for 1.5-days (SD: 4) improvement of organ failure free days between patients achieve target TG and those not. The PERFORM study is aimed to be a long-running registry, so the collection of patients will be continuous after achieving the phase-I goal(300 patients).

3.2 Inclusion criteria for the PERFORM study

- 11. Informed consent form obtained from the patient or next of kin;
- 12. Age between 18 to 70 years old;
- 13. Within 72 hours of onset,
- 14. With a primary diagnosis of AP based on Abdominal Pain Suggestive of AP, Serum Amylase at Least three Times the Upper Limit of Normal, and/or Characteristic Findings of AP on Computed Tomography or Less Commonly Magnetic Resonance Imaging (MRI) or Transabdominal Ultrasonography According to the Revised Atlanta Criteria[21].
- 15. When enrolled, TG>1000mg/dL (11.3mmol/L), accompanied by the clinical worrisome features of any one or more of the following[22]:
 - 1) Signs of hypocalcaemia (calcium levels less than 2.1mmol/L)
 - 2) Lactic acidosis (Lactate levels more than 2mmol/L and PH<7.35)
 - 3) Signs of worsening systemic inflammation (two or more):
 - a) Temperature >38.5°C or <35.0°C
 - b) Heart rate of >90 /min
 - c) Respiratory rate of >20 breaths/min or PaCO2 of <32 mmHg
 - d) WBC count of >12,000 cells/mL, <4000 cells/mL, or >10 percent immature (band) forms

 Signs of worsening organ dysfunction or multi-organ failure as defined by Modified Marshall scoring system for organ dysfunction ; 3.3 Exclusion criteria for the PERFORM study

1. Failure to obtain informed consent;

2. Pregnant or lactating women; or have a pregnancy plan within a month after the study (including male subjects);

3. Researchers' family members who are directly involved in the study;

4. Patients are expected to die within 48 hours after enrollment, defined as patients with norepinephrine usage at a dose of 25 mg/min or more under full-fluid resuscitation, with a systolic blood pressure <90mm Hg and serum pH values <7.0. The judgment will be made by the treating physician.

3.4 Additional exclusion criteria for this analysis

1. Patients undergo any invasive blood purification therapy other than plasmapheresis.

4. PATIENT MANAGEMENT

We recommend all all patients receive standard treatment that follows the "Acute Pancreatitis Treatment Guidelines" issued by the American College of Gastroenterology (ACG) in 2013 and the standard treatment plan for acute pancreatitis provided in the "Evidence-Based Guidelines for the Treatment of Acute Pancreatitis" issued by the International Association of Pancreatology (IAP) and the American Pancreatic Association (APA)[23, 24]. Since the PERFORM study is an observational one, all treatment decisions will be at the discretion of the treating physicians, including the use of different TG-lowering therapies.

5. OUTCOME MEASURES

5.1 The primary outcome

The primary outcome was organ failure free days(OFFD) to study day14. The diagnosis of organ failure was made when an individual sequential organ failure assessment(SOFA) score of two or more for the respiration, cardiovascular, or renal system. In patients with transient organ failure resolution, only the final periods of OFFD were counted. Patients who had organ failure on day14 or died before day14

were assigned zero OFFD.

5.2 Secondary outcomes

Secondary outcomes included a composite endpoint of death from any cause by day28 and the presence of at least one organ failure at day7, SOFArank, Δ SOFAmax, and Δ SOFA14 to day14, ICU free days to day14, hospital free days to day14, day28, and day60, new onset organ failure (defined as organ failure that is no present at any time in the first 24h of enrolment) to day14, requirement of blood purification and ICU admission during the index admission, mortality and incidence of infected pancreatic necrosis(IPN) by day60. SOFArank was calculated as a sum of the daily delta SOFA score (defined as the daily total SOFA score minus the baseline SOFA score) over the first 14 days of enrolment. Discharge was counted (from the day of discharge forward) as a score of 0 and death as 24. Δ SOFAmax was defined as the maximum SOFA score within 14 days minus the baseline, and Δ SOFA14 as the SOFA score at day14 minus the baseline.

6. ETHICS AND DISSEMINATION

This PERFORM study has been approved by the ethics committee of the Jinling Hospital. Ethic approval of each participating center will also be obtained before the initiation of enrollment.

6.1 Consent and confidentiality

Informed consent will be required for each participant of this study, either signed by the patients or next of kin. All the data stored in the electronical database will be deidentified to guarantee the patients' privacy.

6.2 Dissemination policy

All the investigators will have full access to the data after the conclusion of the study. Anyone who wants to do a post-hoc analysis needs to submit a formal writing proposal to the expert panel. Only the approved authors can have access to the database.

7. DATA COLLECTION AND FOLLOW UP

In the original PERFORM study, a web-based electrical database (access through the website of the CAPCTG, https://capctg.medbit.cn/) will be used for data collection and storage. All data will be input by the primary investigator or nominated investigators (less than two for each participating center) approved by the primary investigator, and a double check will be done by the research coordinator from the coordinating and data management center of the CAPCTG. Training for data entry will be performed by the provider of the electrical database and the coordinating and data management center of the coordinating to the data collection schedule, the investigator will collect data during the index admission and on day 60 after enrollment.

8. STATISTICAL PLAN

8.1 General Considerations

8.1.1 Reporting guidelines

We will follow the STrengthening the Reporting of OBservational studies in Epidemiology guideline for explanation and elaboration of the study results.

8.1.2 Participant disposition and Flow chart

A flowchart will be drawn up showing the number of patients screened, enrolled, and followed up in each exposure group.

The number screened and not enrolled, and the reasons for non-enrollment will be reported, as well as the number and reasons of patients who are lost for follow up, or who are withdrawn from the study.

8.1.3 Data Summaries

Continuous normally distributed data will be reported as means with SDs. Skewed continuous data will be reported as medians and interquartile ranges (IQRs). Categorical data will be summarized by counts and percentages.

Mean values for some continuous outcomes (e.g., triglyceride, SOFA scores) by group will be plotted. Kaplan-Meier plots will be produced to display the time-to-event data.

8.1.4 Planned Covariates

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Covariate analysis will be performed, in particular, for the primary outcome. The prespecified covariates in this study will be:

- Age
- Sex
- Body Mass Index (BMI)
- baseline Acute Physiology and Chronic Health Evaluation II (APACHE II) score
- baseline triglyceride
- 8.1.5 Missing Data

For baseline covariates and efficacy outcomes, missing data less than 5% will be assumed to be missing at random (MAR) and thus will not be imputed in the primary analysis. However, if greater than 5% of data that should be available for analysis are missing, multiple imputation will be undertaken in the analysis.

8.2. Statistical Analysis

Continuous data were reported as means and SDs or medians and interquartile ranges (IQR) as appropriate, depending on their normality. The normality of data was determined by Shapiro-Wilk tests. Categorical data were summarised by counts and percentages. The intergroup differences were compared by Student's t-test or Wilcoxon rank-sum test for continuous variables depending on their normality and Fisher's exact test for categorical data.

Two statistical approaches were applied to assess the association between triglyceride-lowering effects(Triglyceride decline) and clinical outcomes. First, all the study individuals with triglyceride levels on study day3 were dichotomised depending on whether the Triglyceride level was \leq 5.65 (target-reaching). Comparisons were made between those who reached the target or not. For the primary outcome comparison, Wilcoxon rank-sum test was employed, and median difference (95% CI [confidence intervals]) was calculated by the Hodges–Lehmann estimation. For the sensitivity analysis of the primary outcome, the adjusted generalised linear model (GLM) was performed to assess its association with target-reaching. Furthermore, the Fine and Gray

competing risk model (competing factor=death) was adopted to assess the association between target-reaching and organ failure resolution.

Second, the decline rate of triglyceride for the first three days of enrolment (decline slope) was obtained from the linear regression with time as a dependent and TG as an independent variable, and the regression coefficient was the slope of the Triglyceride decline. The second approach involves patients with triglyceride levels measured on either day2 or day3. The adjusted GLMs were performed to assess the association between decline slope and OFFD. The confounders were the same as the primary analysis.

For the comparison of secondary outcomes, the adjusted generalised linear model (GLM) was performed to identify its association with target-reaching. The variables included in the model were the same as the adjusted analysis for the primary outcome.

We then assess the impact of blood purification on clinical outcomes. Propensity score matching (PSM) analysis was used to control potential confounders. Patients who received blood purification were matched 1:1 with patients who received conventional treatment using their propensity score. The propensity score was based on the same confounding variables for the adjusted GLM. Genetic Matching with a calliper width of 0.2 was used in the PSM. Comparisons of differences between groups in the PSM cohort were performed using Wilcoxon signed-rank test and McNemar's test for matched data. To evaluate the robustness of our findings, we also performed the inverse probability of treatment weighting (IPTW) analysis with the same variables as PSM. Comparisons of differences between performed using Wilcoxon rank-sum test and Fisher's exact test.

We performed data conversions (including log, reciprocal, and square root transformations) for the continuous outcomes with skewed distribution in the GLM models. Statistical tests were two-sided, and p values <0.05 were deemed significant unless otherwise stated. All statistical analyses were done in the SPSS 26.0 software and the R 4.2.1 software.

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