Supplementary Materials

A multicenter, double-blind, randomized, comparison study of the efficacy and safety of tigecycline to imipenem/cilastatin to treat complicated intra-abdominal infections in hospitalized subjects in China

Yijian Chen*, Demei Zhu*, Yingyuan Zhang, Yongjie Zhao, Gang Chen, Ping Li, Lihong Xu, Ping Yan, M. Anne Hickman, Xiajun Xu, Margaret Tawadrous, Michele Wible

* These authors contributed equally to this study.

Contents

Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria

Eligible subjects were expected to meet the following criteria:

- Hospitalized male or female patients, at least 18 years of age.
- Patients of childbearing potential had to agree to use a highly effective contraception method throughout the study and for at least 28 days after the last dose of assigned treatment. A subject was of childbearing potential if, in the opinion of the investigator, he/she was biologically capable of having children and was sexually active. Female subjects who were not of childbearing potential (must have met at least 1 of the following criteria): had undergone hysterectomy or bilateral oophorectomy, had medically confirmed ovarian failure or were medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause)
- Subjects were required to be candidates for or have had a laparotomy, laparoscopy or percutaneous drainage of an intra-abdominal abscess within 24 hours of enrolment. Subjects could have been enrolled preoperatively, however, investigational products should not have been given unless there was a strong suspicion (elevated white blood cell [WBC], elevated bands counts, or fever, or highly suggestive radiographic findings etc.) or a confirmed diagnosis of an intra-abdominal infection (presence of pus within the abdominal cavity) and the baseline intra-abdominal culture was obtained or planned to be obtained from the infected site.
- cIAI of less than 2 weeks duration, such as:
    - An intra-abdominal abscess.
    - Appendicitis complicated by perforation (grossly visible) and abscess or periappendicular abscess.
    - Perforated diverticulitis complicated by abscess formation or fecal contamination.

- Complicated cholecystitis with evidence of perforation or empyema.
- Perforation of the large or small intestine with abscess or fecal contamination.
- Purulent peritonitis.
- Gastric or duodenal ulcer perforation with symptoms lasting at least 24 hours before operation.
- Traumatic bowel perforation with symptoms lasting at least 12 hours before operation.

- Minimal clinical criteria at the time of intra-abdominal infection diagnosis or highly suspected intra-abdominal infection that included the presence of either:
  - Fever defined as an oral temperature ≥38.0°C, axillary temperature ≥37.5°C, or a rectal temperature ≥38.5°C, or hypothermia defined as an oral temperature <35.5°C, axillary temperature <35.0°C, or a rectal temperature <36.0°C.
  - Leukocytosis defined as WBC count >10,000/mm^3, or leucopenia defined as WBC <5000/mm^3, or >10% immature (band) forms.
- Plus at least 1 of the following:
  - Localized or diffuse abdominal wall rigidity and /or involuntary guarding, abdominal tenderness or abdominal pain.
  - Nausea or vomiting or ileus.
  - Radiographic, scintigraphic, sonographic, computed tomography (CT) or magnetic resonance imaging (MRI) studies suggesting a perforated viscus, an intra-abdominal abscess, or other focus of intra-abdominal infection.
- Evidence of a personally signed and dated informed consent document (ICD) indicating that the subject (or a legal representative) had been informed of all pertinent aspects of the study. If any subject was unable to give consent, it may have been obtained from the subject's legal representative if in accordance with local laws and regulations. Subject would then sign an ICD as soon as possible.

- Subjects who were willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

Exclusion Criteria

Subjects were ineligible to participate in this study if any of the following criteria were met:

- Any concomitant condition that, in the opinion of the investigator, precluded an evaluation of a response or made it unlikely that the contemplated course of therapy or follow-up visits could have been completed.
- Active or treated leukemia or systemic malignancy that required treatment with chemotherapy, immunotherapy, radiation therapy, or other antineoplastic therapy within the 3 months before entry into the study, or any metastatic malignancy to the abdomen with life expectancy less than 6 months.
- Anticipated length of antibiotic therapy less than 5 days or the likelihood that the subject would not complete the course of treatment.
- Presence of any uncontrolled central nervous system disease, including epilepsy or unexplained seizures.
- Concomitant treatment with ganciclovir.
- Known or suspected hypersensitivity to tigecycline, tetracycline agents, imipenem, cilastatin, or other compounds related to these classes of antibacterial agents.
- Organ function failure.
    - Hepatic function:
        - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT), or alkaline phosphatase (ALP) >10 × the upper limit of normal (ULN) of the local laboratory reference range.
        - Bilirubin >3 × ULN, unless isolated hyperbilirubinemia was directly related to the acute process.
        - Acute hepatic failure or acute decompensation of chronic hepatic failure.
    - Renal Function: Calculated creatinine clearance (Cl_{CR}) less than

41 mL/min/1.73 m^2 after adequate hydration. Cl_{CR} may have been calculated from the serum creatinine (S_{CR}) concentration by the following equation:

- Male: Cl_{CR} mL/min = (140-age) × weight (kg) / [72 × S_{CR} (mg/dL)]
- Female: Cl_{CR} mL/min = 0.85 × Cl_{CR} derived by above formula.
- Body surface area (BSA) (m2) = $(\text{weight[kg]})^{0.425} \times (\text{height [cm]})^{0.725} \times 0.007184$
- Cl_{CR} / BSA × 1.73 = mL/min/1.73 m^2

– Bone Marrow function:

- Neutropenia defined as absolute neutrophil count (ANC) <1000/mm^3
- Thrombocytopenia defined as platelet count <35,000/mm^3

- Intra-abdominal infection known to be caused by 1 or more organism(s) which were not susceptible to either of the test articles (eg, methicillin-resistant staphylococci [methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*], or *Pseudomonas aeruginosa*) and which, in the investigator's opinion, required treatment with an additional antibacterial agent.
- Receipt of more than 24 hours of non-study systemic antibiotics within 72 hours before enrolment should have been excluded except for subjects declared prior failures. A subject may have been declared a prior failure if he/she received more than 72 hours of systemic non-study antibacterial therapy prior to study entry and declared a clinical or microbiological failure. An intra-abdominal culture had to be obtained from the infected site.
- Previous participation in this study.
- Participation in other studies within 4 weeks before the current study began and/or during study participation.
- Anticipation of leaving the fascia or deep muscular layers open or expectation of planned abdominal re-exploration either in or out of the operating room.
- Subjects suspected preoperatively to have had a diagnosis of spontaneous bacterial

peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess, or infected necrotizing pancreatitis.

- Weight less than 40 kg.
- Life expectation less than 30 days.
- Immunosuppressive therapy that, in the opinion of the investigator, would have decreased the subject's ability to eradicate the infection, including use of high-dose corticosteroids (eg, 40 mg or more prednisone or equivalent per day) or known diagnosis of acquired immunodeficiency syndrome (AIDS).
- Administration of intraoperative antibacterial irrigants or peritoneal antibacterial agents (eg, irrigants, antibiotic-impregnated sponges).
- Presence of infection requiring systemic antimicrobial therapy at a site other than the abdomen (eg, urinary tract).
- Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might increase the risk associated with study participation or investigational product administration or might interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
- Subjects who were investigational site staff members or relatives of those site staff members or subjects who were the Sponsor employees directly involved in the conduct of the study.
- Pregnant females; breastfeeding females; males and females of childbearing potential not using highly effective contraception or not agreeing to continue highly effective contraception for at least 28 days after last dose of investigational product.

Supplementary Table 2. Summary of MIC data for baseline isolates with number of subjects ≥5 for either antibiotic for the microbiologically evaluable (ME) population

	Tigecycline MIC (mg/L)					Imipenem MIC (mg/L)				
Baseline isolate	n	Min	Max	MIC_{50}	MIC_{90}	n	Min	Max	MIC_{50}	MIC_{90}
Escherichia coli	182	0.06	1	0.25	0.5	182	0.125	1	0.25	0.5
Klebsiella pneumoniae	25	0.25	4	0.5	2	25	0.25	16	0.5	1
Streptococcus anginosus	10	≤0.015	0.25	0.015	0.06	10	≤0.015	0.06	≤0.015	0.06
Enterococcus avium	10	0.03	0.25	0.06	0.25	10	0.03	1	0.25	1
Staphylococcus epidermidis	8	0.03	0.5	NA	NA	8	≤0.015	1	NA	NA
Pseudomonas aeruginosa	6	8	32	NA	NA	6	1	16	NA	NA
Bacteroides fragilis	5	0.5	8	NA	NA	5	0.25	1	NA	NA
B. thetaiotaomicron	5	0.25	16	NA	NA	5	0.25	1	NA	NA

Max, maximum; ME, microbiologically evaluable; Min, minimum; MIC, minimum inhibitory concentration (lowest concentration of drug at which the microorganism tested does not show visible growth); MIC_{50}, concentration of antibiotic that inhibits the growth of 50% of the isolates; MIC_{90}, concentration of antibiotic that inhibits the growth of 90% of the isolates; n, number of subjects with MIC values available for each baseline pathogen. For subjects who had multiple MIC values for one pathogen, the highest MIC value for the pathogen was used; NA, MIC_{50} or MIC_{90} values were not calculated for any pathogen with number of subjects less than 10.

Supplementary Table 3. Adverse events of special interest

Tier 1 AEs were pre-specified events of clinical importance and included nausea, vomiting, diarrhea, increased ALT, and increased AST.

- All-causality nausea, vomiting, diarrhea, increased ALT, and increased AST across treatment groups. Nausea occurred statistically more frequently in the tigecycline group (10.3%) compared to the imipenem/cilastatin group (4.3%) ($P = 0.0136$). No statistically significant differences in occurrence of other AEs of special interest between the 2 treatment groups were found.
- Treatment-related nausea occurred statistically more frequently in the tigecycline group (6.9%) compared to the imipenem/cilastatin group (2.2%) ($P = 0.0156$). Treatment-related vomiting also occurred statistically more frequently in the tigecycline group (5.2%) compared to the imipenem/cilastatin group (1.7%) ($P = 0.0443$). Treatment-related diarrhea occurred more frequently in the tigecycline group (1.7%) compared to the imipenem/cilastatin group (0.9%) but the difference was not statistically significant. Treatment-related ALT increases and AST increases occurred more frequently in the imipenem/cilastatin group (3.5% each) compared to the tigecycline group (1.3% each) but the difference was not statistically significant.
- The majority of events of special interest were mild to moderate in severity. Only 1 treatment-related event of vomiting was reported as severe in the tigecycline group.
- Median duration for all-causality nausea was 1.81 days (range: 0 to 15.9 days) for tigecycline-treated subjects and 1.06 days (range: 0 to 5.2 days) for imipenem/cilastatin-treated subjects. Median duration for all-causality vomiting was 1.16 days (range: 0 to 15.9 days) for tigecycline-treated subjects and 1.21 days (range: 0 to 15 days) for imipenem/cilastatin-treated subjects.
- There were 55 (23.7%) tigecycline-treated subjects and 35 (15.2%) imipenem/cilastatin-treated subjects who received concomitant therapy specifically to treat or prevent nausea or vomiting. The most common medication was metoclopramide, which was used in 29

(12.5%) tigecycline-treated subjects and 17 (7.4%) imipenem/cilastatin-treated subjects. The second most common medication reported was tropisetron, which was used in 7 (3.0%) subjects each in the tigecycline group and imipenem/cilastatin group.

Tier 2 events are events that were not tier 1 but are "common". A preferred term was defined as a tier 2 event if it was not a tier 1 event and there were at least 4 subjects with this event in any treatment group.

- In tigecycline-treated subjects, the most frequently reported all-causality tier 2 TEAEs were drug ineffective (21 [9.1%] subjects), postoperative wound infection (21 [9.1%] subjects) and pyrexia (18 [7.8%] subjects), while pyrexia (19 [8.2%] subjects), drug ineffective, hyperproteinemia, and cough (each experienced by 9 [3.9%] subjects) were reported most frequently in imipenem/cilastatin-treated subjects. In the tigecycline group, the number of subjects with both drug ineffective and postoperative infection was 6. The estimated risk difference (tigecycline minus imipenem/cilastatin) was 7.8% (9.1% versus 1.3%, 95% CI 4.1%, 12.3%) in postoperative wound infection, 5.2% (9.1% versus 3.9%, 95% CI 0.7%, 10.0%) in drug ineffective, 1.7% (1.7% versus 0, 95% CI 0.1%, 4.4%) in hypoalbuminaemia, −2.2% (0 versus 2.2%, 95% CI −5.0%, −0.5%) in increased urobilinogen urine and −2.6% (0 versus 2.6%, 95% CI −5.6%, −0.9%) in presence of urine ketone bodies.
- The estimated risk difference for treatment-related tier 2 TEAEs (tigecycline minus imipenem/cilastatin) was 5.16% (95% CI 1.2%, 9.6%) for drug ineffective and −1.7% (95% CI −4.4%, −0.1%) for increased urobilinogen urine.

Supplementary Table 4. Incidence of laboratory test abnormalities[a] in ≥10% of subjects in either treatment group in the safety analysis set

Parameter	Units	Criteria	Tigecycline 50mg n/N (%)	Imipenem/Cilastatin n/N (%)
Hematology				
WBC	$10^3/mm^3$	>1.5 × ULN	51/228 (22.4)	12/224 (5.4)
Lymphocytes (abs)	$10^3/mm^3$	<0.8 × LLN	27/218 (12.4)	42/213 (19.7)
Lymphocytes (%)	%	<0.8 × LLN	128/228 (56.1)	118/224 (52.7)
Total neutrophils (abs)	$10^3/mm^3$	>1.2 × ULN	99/228 (43.4)	56/224 (25.0)
Neutrophils (%)	%	>1.2 × ULN	27/228 (11.8)	25/224 (11.2)
Monocytes (abs)	$10^3/mm^3$	>1.2 × ULN	70/218 (32.1)	37/213 (17.4)
Monocytes (%)	%	>1.2 × ULN	38/228 (16.7)	17/224 (7.6)
Liver function				
Total bilirubin	mg/dL	>1.5 × ULN	30/228 (13.2)	21/224 (9.4)
Total protein	g/dL	<0.8 × LLN	25/228 (11.0)	13/224 (5.8)
Albumin	g/dL	<0.8 × LLN	72/228 (31.6)	47/224 (21.0)
Renal function				
Blood urea nitrogen	mg/dL	>1.3 × ULN	29/227 (12.8)	8/224 (3.6)
Electrolytes				
Calcium	mg/dL	<0.9 × LLN	32/226 (14.2)	15/222 (6.8)
Phosphate	mg/dL	<0.8 × LLN	22/222 (9.9)	48/216 (22.2)
Clinical chemistry (other)				
Glucose	mg/dL	>1.5 × ULN	29/226 (12.8)	26/221 (11.8)
Amylase	u/L	>1.5 × ULN	24/222 (10.8)	27/215 (12.6)

Values are n (%). Abs, absolute; LLN, lower limit of normal; n, number of subjects with a laboratory abnormality meeting specified criteria while on study treatment or from the end of treatment to test-of-cure; N, total number of subjects with at least 1 observation of the given laboratory test while on study treatment or from the end of treatment to test of cure; ULN, upper limit of normal; WBC, white blood cell.

[a] Hematology and chemistry, without regard to baseline abnormality.

Supplementary Table 5. Study center information

No	Study center and address	Principle investigator	Independent ethics committee at each study center that approved the study
1	Institute of Antibiotics, Hua Shan Hospital, Fudan University, Suite 12 Wulumuqi Zhong Road, Shanghai, 200040 CHINA	Jufang Wu	The Ethics Committee of Hua Shan Hospital, Fudan University, Shanghai, China
2	Department of General Surgery, the First Affiliated Hospital of Guangzhou Medical University, Number 151 Yanjiang West Road, Guangzhou, GUANGDONG 510120 CHINA	Jian Lei	The Medical Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China
3[a]	Renji Hospital, Shanghai Jiaotong University, School of Medicine, Department of General Surgery, 1630 Dongfang Road, Shanghai, 200127 CHINA	Zhiyong Wu	Shanghai Jiaotong University, School of Medicine, Renji Hospital Ethics Committee, Shanghai, China
4[a]	Zhongshan Hospital, Fudan University, Department of General Surgery, 180 Fenglin Road, Shanghai, 200032 CHINA	Wenhui Lou	The Medical Ethics Committee, Zhongshan Hospital, Fudan University, Shanghai, China
5	Department of General Surgery, Sichuan Provincial People's Hospital, Number 32 Section 2 West First Ring Road, Chengdu, SICHUAN 610072 CHINA	Ping Li	The Ethics Committee of Sichuan Provincial People's Hospital, Sichuan, China
6	The Third Xiangya Hospital of Central South University, Department of General Surgery, Number 138 Tongzipo Street, Hexiyuelu District, Changsha, HUNAN 410013 CHINA	Feizhou Huang	The Ethical Committee of the Third Xiangya Hospital, Central South University, Hunan, China
7	Peking University, Third Hospital, Department of General Surgery, 49 North Garden Road, Haidian District, Beijing, 100191 CHINA	Dianrong Xiu	Peking University, Third Hospital, Medical Science Research Ethics Committee, Beijing, China
8	Tianjin Union Medical Center, Department of General Surgery, Number 190 Jieyuan Road, Hongqiao District, Tianjin, 300000 CHINA	Yongjie Zhao	The Ethical Committee of the Tianjin Union Medical Center, Tianjin, China
9	The First Affiliated Hospital of College of Medicine, Zhejiang University, Hepatobiliary and Pancreatic Surgery Department, Number 79 Qingchun Road, Hangzhou, ZHEJIANG 310003 CHINA	Weilin Wang	The Medical Ethics Committees of the First Affiliated Hospital, College of Medicine, Zhejiang University, Zhejiang, China
10	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hepatic Surgery Department, Number 1095 Jiefang Road, Wuhan, HUBEI 430030 CHINA	Xiaoping Chen	The Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Hubei, China
11	Department of Hepatobiliary Surgery, Peking University People's Hospital, Number 11 Xizhimen South Street, Xicheng District, Beijing, 100044 CHINA	Jiye Zhu	The Medical Ethics Committee of Peking University People's Hospital, Beijing, China
12	Department of General Surgery, Peking Union Medical College Hospital, No.1 Shuaifuyuan, Dongcheng District, Beijing, 100730 CHINA	Taiping Zhang	The Ethics Review Committee of Peking Union Medical College Hospital, Beijing, China
13	The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou, JIANGSU 215004 CHINA	Chungen Xing	The Ethical Review Committee of the Second Hospital Affiliated to Soochow University, Jiangsu, China

14	Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, 1665 Kongjiang Road, Shanghai, 200092 CHINA	Yong Yang	The Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China
15	Tianjin Nankai Hospital Department of General Surgery, 122 Third Latitude Road, Nankai District, Tianjin, 300100 CHINA	Naiqiang Cui	Tianjin Nankai Hospital Medical Ethics Committee, Tianjin, China
16	Department of General Surgery, Tianjin Medical University General Hospital, No. 154 Anshan Road, Heping District, Tianjin, 300052 CHINA	Tong Liu	Tianjin Medical University General Hospital Medical Ethics Committee, Tianjin, China
17	Department of General Surgery, Beijing Shijitan Hospital, Capital Medical University, Number 10 Yangfangdian Tie Hospital Road, Haidian District, Beijing, 100038 CHINA	Nengwei Zhang	The Medical Ethics Committee of Beijing Shijitan Hospital, Capital Medical University, Beijing, China
18	The First Affiliated Hospital of Soochow University, General Surgery Department, No.188 Shizi Street, Suzhou, JIANGSU 215006 CHINA	Hong Zhao	The Medical Ethics Committee of The First Affiliated Hospital of Soochow University, Jiangsu, China
19	General Hospital of Chengdu Military Region of PLA, Department of Gastrointestinal Surgery, No.270 Rongdu Avenue, Jinniu District, Chengdu, SICHUAN 610083 CHINA	Yongkuan Cao	The Ethics Committee of the PLA General Hospital of Chengdu Military Region, Sichuan, China
20	The Third People's Hospital of Hainan Province, Department of General Surgery, Number 146 Jiefang 4th Road, Sanya, HAINAN 572000 CHINA	Lianchen Wang	The Ethics Committee of the Third People's Hospital of Hainan Province, Hainan, China
21	Jilin Province People's Hospital, Department of Gastrointestinal Surgery, Number 1183 Street of Workers and Farmers, Changchun, JILIN 130021 CHINA	Shoubai Li	The Ethics Committee of the People's Hospital of Jilin Province, Jilin, China
22	Yangzhou No.1 People’s Hospital, Department of General Surgery, Number 45 Taizhou Road, Guangling District, Yangzhou, JIANGSU 225001 CHINA	Qing Ni	The Ethics Committees of Yangzhou No.1 People’s Hospital, Jiangsu, China
23	The Central Hospital of Wuhan, ICU, Tongji Medical College, Huazhong University of Science and Technology, Number 26 Victory Street, Jiangan District, Wuhan, HUBEI 430014 CHINA	Li Yu	The Ethics Committee of the Wuhan Central Hospital, Hubei, China
24	Lishui People's Hospital, Intensive Care Unit, Number 15 Dazhong Street, Liandu District, Lishui, ZHEJIANG 323000 CHINA	Tianzheng Lou	The Ethics Committee of the Lishui People's Hospital, Zhejiang, China
25	Qinghai Provincial People's Hospital, Number 2 Gonghe Road, Chengdong District, Xining, QINGHAI 810007 CHINA	Yamin Guo	The Medical Ethics Committee of Qinghai Provincial People's Hospital, Qinghai, China
26	Affiliated Hospital of Guilin Medical University Hepatobiliary, Department of Surgery, Number 15 Lequn Road, Guilin, GUANGXI 541001 CHINA	Qian Chen	The Medical Ethics Committee of the Affiliated Hospital of Guilin Medical University, Guangxi, China
27	Shenzhen Second People's Hospital, Department of Hepatobiliary Surgery, 3002 Sungang Road West, Futian District, Shenzhen, GUANGDONG 518039 CHINA	Yongqiang Zhan	The Ethics Committee of Shenzhen Second People's Hospital, Guangdong, China
28[a]	Beijing Hospital, General Surgery Department, 1 Dahua Road, Dongdan, Dongcheng District, Beijing, 100730 CHINA	Junmin Wei	The Ethics Committee of Beijing Hospital, Beijing, China

29	Binzhou Medical University Hospital, Department of Gastrointestinal Surgery, 661 Huang He Er Road, Bin Zhou, SHANDONG 256603 CHINA	Yuming Li	The Ethics Committee of Binzhou Medical University Hospital, Shandong, China
30	Shanghai Fengxian District Central Hospital, Department of Surgery, 6600 Nanfeng Road, Fengxian District, Shanghai, 201400 CHINA	Yuanzhou Shan	The Ethics Committee of Shanghai Fengxian District Central Hospital, Shanghai, China
31	Hainan Provincial People's Hospital Number, 19 XiuHua Road, Xiuying District, Haikou, HAINAN 570311 CHINA	Kailun Zhou	The Ethics Committee of Hainan Provincial People's Hospital, Hainan, China
32	The First Affiliated Hospital of JiNan University, Department of General Surgery, Number 613 Huangpu Avenue West, Tian He District, Guangzhou, GUANGDONG 510630 CHINA	Yunlong Pan	The Ethics Committee of the First Affiliated Hospital of JiNan University, Shandong, China
33	The Affiliated Jiangyin Hospital of Southeast University Medical College, General Surgery Department, Number 163 Shoushan Road, Jiangyin, JIANGSU 214400 CHINA	Shuanghai Liu	The Ethics Committee of the Affiliated Jiangyin Hospital, College of Medicine, Southeast University, Jiangsu, China
34[a]	The Affiliated Hospital of Guizhou Medical University, Emergency Department, No 28 Guiyi Road, Yunyan District, Guiyang, GUIZHOU 550000 CHINA	Xiaohong Yu	The Ethics Committee of the Affiliated Hospital of Guizhou Medical University, Guizhou, China
35	China Meitan General Hospital, General Surgery Department, No. 29 Xibahe Nanli, Chaoyang District, Beijing, 100028 CHINA	Zheng Zhou	The Ethics Committee of China Meitan General Hospital, Beijing, China
36	The Navy General Hospital of the PLA China, General Surgery Department, No.6 Fucheng Road, Haidian District, Beijing, 100048 CHINA	Yuhong Wang	The Ethics Committee of Chinese PLA Navy General Hospital, Beijing, China
37	The Third Hospital of Changsha, Department of Surgery, Number 176 West Laodong Road, Tianxin District, Changsha, HUNAN 410015 CHINA	Zhiqiang Hu	The Ethics Committee of The Third Hospital of Changsha, Hunan, China
38	Qingpu Branch of Zhongshan Hospital Affiliated to Fudan University, Department of Surgery, No 1158 Gongyuan Road East, Qingpu District, Shanghai, 201700 CHINA	Weixing Shen	The Ethics Committee of Zhongshan Hospital Affiliated to Fudan University, Shanghai, China
39	Anqing City Hospital, Department of Surgery, 352 Renmin Road, Anqing, ANHUI 246003 CHINA	Mingyu Hu	The Ethics Committee of Anqing City Hospital, Anhui, China
40	Xiangya Hospital Central-South University, Department of General Surgery, Number 87 Xiangya Road, Changsha, HUNAN 410008 CHINA	Zhiming Wang	The Ethics Committee of the Xiangya Hospital of Central South University, Hunan, China
41	Baotou Central Hospital, General Surgery Department, Number 61 Huancheng Road, Donghe District, Baotou, INNER MONGOLIA 014000 CHINA	Lu Liang	The Ethics Committee of the Baotou Central Hospital, Inner Mongolia, China
42	Taizhou Hospital of Zhejiang Province 150 Ximen Street, Linhai, ZHEJIANG 317000 CHINA	Tienan Bi	Ethics Committee of the Taizhou Hospital, Zhejiang, China
43	The Second Hospital of Jilin University, Department of Gastrointestinal Nutrition and Hernia Surgery, No. 218 Ziqiang Street, Nanguan District, Changchun, JILIN 130041 CHINA	Xudong Wang	The Ethics Committee of The Second Hospital of Jilin University, Jilin, China

44[a]	Beijing Tongren Hospital, Capital Medical University, No.1 Dongjiaominxiang, Dongcheng District, Beijing, 100730 CHINA	Jixiang Wu	The Ethics Committee of Beijing Tongren Hospital, Capital Medical University, Beijing, China
	Beijing Tongren Hospital, Capital Medical University, Number 2 Western Ring Road South, Economic and Technological Development Zone, Daxing District, Beijing, 100176 CHINA		
45	The First Affiliated Hospital of Wenzhou Medical University, Department of Gastrointestinal Surgery, Nanbaixiang Street, Ouhai District, Wenzhou, ZHEJIANG 325000 CHINA	Guanbao Zhu	The Institutional Review Board of the First Affiliated Hospital of Wenzhou Medical University, Zhejiang, China
46	The First Hospital of Shantou University School of Medicine, Department of General Surgery, Number 57 Changping Street, Shantou, GUANGDONG 515041 CHINA	Wei Li	The Ethics Committee of the First Hospital of Shantou University School of Medicine, Guangdong, China
47	Zhangzhou Municipal Hospital of Fujian Province, the Second General Surgery Department, No. 59 Shengli West Road, Zhangzhou, FUJIAN 363000 CHINA	Mingzhi Cai	The Ethics Committee of Zhangzhou Municipal Hospital, Fujian, China
48	Zhongnan Hospital of Wuhan University, Intensive Care Unit, 169 Eastlake Road, Wuchang District, Wuhan, HUBEI 430071 CHINA	Zhaohui Du	The Medical Ethics Committee of Zhongnan Hospital of Wuhan University, Hubei, China
49	Zhongshan Hospital of Xiamen University, General Surgery Department, Number 201-209 Hubin South Road, Xiamen, FUJIAN 361004 CHINA	Guoyang Wu	The Ethics Committee of Zhongshan Hospital Xiamen University, Fujian, China
50	The First Hospital of Jilin University, Department of Surgery, No.71 Xinmin Street, Changchun, JILIN 130021 CHINA	Guangyi Wang	The Ethics Committee of the First Hospital of Jilin University, Jilin, China
51	First People's Hospital of Kunming, Department of Hepatobiliary Surgery, No. 504 Qing Nian Road, Xi Shan District, Kunming, YUNNAN 650011 CHINA	Gang Chen	The Ethics Committee of the First People's Hospital of Kunming, Yunnan, China
52	HaiKou Municipal People's Hospital, Department of Gastrointestinal Surgery, No. 43 RenMin Avenue, Haidian Island, Haikou, HAINAN 570208 CHINA	Bo Peng	The Ethics Committee of the HaiKou Municipal People's Hospital, Hainan, China

[a] Did not randomize patients.