Effects of ω -3 polyunsaturated fatty acid-supplemented parenteral nutrition on postoperative complications for patients with Crohn's disease: a cohort study

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Research article

Keywords: Crohn's disease, ω -3 polyunsaturated fatty acid, parenteral nutrition, postoperative complications

Posted Date: August 27th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-55359/v1>

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Abstract

Background: Most patients with Crohn's disease (CD), a chronic inflammatory disease, need surgery but exhibit elevated postoperative complication incidences. ω -3 polyunsaturated fatty acids (PUFAs) are considered beneficial for nutrition, anti-inflammation, immunity and intestinal microflora balance in humans. This study assessed the effects of ω -3 PUFA-supplemented parenteral nutrition (PN) on postoperative complications in CD.

Methods: Overall, 186 CD patients undergoing bowel resection were eligible. Patient data were collected from a prospectively maintained database. After surgery, 103 patients received ω -3 PUFA-supplemented PN; 83 did not. Postoperative complications were compared between the groups. Complication risk factors were identified by univariate and multivariate analyses.

Results: Patients with ω -3 PUFA-supplemented PN after surgery had lower C-reactive protein levels (57.2 ± 5.3 mg/L vs 43.5 ± 3.9 mg/L, $P=0.047$) and shorter postoperative hospital stays (12.1 ± 1.1 days vs 9.3 ± 0.6 days, $P=0.041$) than those without. The ω -3 PUFA group exhibited significantly reduced incidences of overall complications (40.8% vs 24.1%, $P=0.016$) and major complications (23.3% vs 9.6%, $P=0.014$). Postoperative complications were associated with infliximab, ω -3 PUFAs, C-reactive protein, operative time, and laparoscopic surgery. Multivariate regression revealed that preoperative infliximab use and postoperative ω -3 PUFA-supplemented PN were independent risk factors in CD.

Conclusions: ω -3 PUFA-supplemented PN reduced post-surgery inflammatory response in CD patients, thus decreasing postoperative complications and accelerating recovery.

Trial registration: This trial was registered in ClinicalTrials.gov. Identifier was NCT03901937. The date of registration was 03/04/2019.

Introduction

Crohn's disease (CD) is considered to be a chronic inflammatory disease that affects all segments of the gastrointestinal tract. The bowel damage and disability of associated with CD occur due to the characteristic relapsing and remitting manner of the disease¹. It has been reported that almost 80% of patients need surgical therapy at least once during their lifetime, and that 10–37% of patients experience complications during recovery, especially infections^{2–5}. Thus, methods to improve postoperative outcomes in CD are urgently needed.

Postoperative negative nitrogen balance can cause poor healing of incisions and raise the risk of postoperative infection. Hence, patient nutrition must be optimized after surgery^{6–7}. As a conventional treatment, total parenteral nutrition (TPN) can improve postoperative patient nutrition, assist healing of incisions and relieve the suffering of CD patients^{8–10}. Moreover, ω -3 polyunsaturated fatty acids (PUFAs) have been shown to be effective in improving the nutritional status and immunity of patients after gastrointestinal surgery¹¹.

ω -3 PUFAs include α -linolenic acid (ALA; 18:3 ω -3), stearidonic acid (SDA; 18:4 ω -3), eicosapentaenoic acid (EPA; 20:5 ω -3), docosapentaenoic acid (DPA; 22:5 ω -3), and docosahexaenoic acid (DHA; 22:6 ω -3). The beneficial effects of ω -3 PUFAs in patients with myriad health conditions and diseases, such as cardiovascular diseases (atrial fibrillation, atherosclerosis, thrombosis, inflammation, and sudden cardiac death, among others), diabetes, cancer, depression and various other mental illnesses, age-related cognitive decline, periodontal disease, and rheumatoid arthritis, have been previously investigated^{12–13}. Many studies have also confirmed that ω -3 PUFAs can reduce the postoperative complications associated with gastrointestinal cancers, liver cancer and some other noncancerous gastrointestinal diseases^{14–15}.

In addition, ω -3 PUFA-supplemented parenteral nutrition (PN) has been proven to be safe, effective, and valuable for CD patients who do not undergo surgery^{16–19}. However, few studies have examined the effects of ω -3 PUFA-supplemented PN after surgery on postoperative complications for patients with CD. The purpose of this study was to explore the effects of ω -3 PUFA-supplemented PN on postoperative complications in CD patients by comparing patients with and without ω -3 PUFA supplementations.

Patients And Methods

Patients

We retrospectively reviewed a series of consecutive clinical records of CD patients who underwent bowel resection in the inflammatory bowel disease center of our hospital from January 2017 to May 2019. The inclusion criteria were as follows: (1) CD was definitively diagnosed according to the patient's history and imaging, endoscopy and pathology results; (2) the patient underwent bowel resection for bowel disease; and (3) TPN was used after the operation. To avoid bias due to of pre-existing factors, the exclusion criteria were as follows: (1) TPN was used less than 4 days after surgery; (2) the patient underwent emergency surgery; (3) the patient also had an other serious disease; and (4) the patient had incomplete data from follow-up over 30 days. Ultimately, 186 patients were enrolled in the retrospective analysis. This study was approved by the ethics committee of Sir Run Run Shaw Hospital. Written informed consent for the use of clinical records was obtained from each patient, as required by the Institutional Review Board at the hospital and in accordance with the ethical guidelines of the Declaration of Helsinki in 1964.

Perioperative Management

Elaborate case history analyses, normative physical examinations and routine preoperative laboratory measurements were performed for all participants. All patients above 50 years old were subjected to ultrasonic cardiography and pulmonary function, tests for evaluation of cardiopulmonary condition before surgery. Based on their preoperative and intraoperative conditions, patients were transferred to the intensive care unit for postoperative treatment when necessary. For all of the patients, reasonable perioperative management practices were implemented in line with the Enhanced Recovery After Surgery

(ERAS) program, including preoperative patient education about the disease, preoperative fasting time minimization, preoperative carbohydrate loading 2 hours before surgery, intraoperative use of minimally invasive techniques and opioid-sparing analgesia, avoidance of mechanical bowel preparation or oral antibiotics, perioperative fluid restriction for avoidance of overload, early postoperative drainage removal, off-bed mobilization and oral feeding until discharge.

Data Collection

Baseline characteristics, intraoperative data, postoperative treatment information, data on postoperative complications within 30 postoperative days, and laboratory data were collected from the database. The baseline characteristics included age, sex, BMI, American Society of Anesthesiologists (ASA) grade, comorbidities, and surgical indications. The intraoperative data included the operative time, type of surgery, surgical approach (open vs laparoscopy), stoma creation information, intraoperative blood transfusion information, intraoperative fluid use, and estimated blood loss. The laboratory data included the hemoglobin, hematocrit, preoperative C-reactive protein (CRP) and albumin levels.

PN was started on the first day after enterotomy through the central vein and was stopped when oral or enteral nutrition was able to supply 60% of the energy needs of the body. The total energy requirements of the subjects in this study were determined according to resting energy consumption rates calculated with an indirect energy meter. For homeostasis maintenance, the ratio of heat to nitrogen was 100–120 kcal:1 g. The dosage of ω -3 PUFAs (Juve, Huarui Pharmaceutical Company) was 0.1–0.2 g/kg/d. The postoperative complications included abdominal infection, postoperative intestinal obstruction, wound infection, anastomotic leakage, abdominal bleeding, fever, blood transfusion, secondary operation, etc. The complications were mainly classified based on the Clavien-Dindo scheme, in which a grade of I-II indicates a mild complication, a grade of III-IV indicates a major complication, and a grade of V indicates death²⁰. This study focuses on the postoperative complications of wound infection and abdominal infection.

Statistical Analysis

SPSS 20.0 (IBMCorp, Armonk, NY) was used to analyze the data. Continuous variables are presented as the mean $\pm$ SE or median (range), whereas categorical variables are presented as the number (%). Normally distributed and continuous variables were analyzed by Student's t test or the Mann-Whitney U test, and categorical variables were analyzed by Pearson's χ^2 test or Fisher's exact test. Variables with significant differences ($p < 0.05$) in univariate analysis were analyzed by multivariate logistic regression analysis to identify the independent predictors for postoperative complications. P values < 0.05 were considered to indicate statistical significance.

Results

Study Population And Baseline Characteristics

In total, 186 CD patients were enrolled (men : women = 115:71), of which 51.6% had terminal ileal lesions and 4.8% had colonic lesions, as shown in Table 1. A total of 73.7% of patients were diagnosed with structuring CD, and 36.0% were diagnosed with penetrating CD. Fifty-two patients (28.0%) had perianal lesions. A total of 62 patients (33.3%) had postoperative complications, with 30 (16.1%) having mild complications and 15 (14.9%) having major complications (Clavien-Dindo grade III to IV); 17 patients (9.2%) had both mild complications and major complications. Six patients (3.2%) had abdominal abscess, and 13 patients (7.0%) had wound infections. All of the patients with postoperative complications ultimately recovered uneventfully.

Table 1
Baseline characteristics of the study population.

Clinical variable	Control group (n = 103)	ω -3 PUFAs group (n = 83)	P value
Preoperative RBC	4.3 $\pm$ 0.1	4.2 $\pm$ 0.1	0.141
Preoperative WBC	6.2 $\pm$ 0.3	5.3 $\pm$ 0.2	0.051
Preoperative Hb	12.0 $\pm$ 0.2	11.8 $\pm$ 0.2	0.584
Preoperative PLT	255.5 $\pm$ 9.2	253.1 $\pm$ 9.4	0.860
Preoperative ESR	15.5 $\pm$ 1.5	18.4 $\pm$ 1.8	0.218
Preoperative ALB	36.7 $\pm$ 0.5	36.2 $\pm$ 0.6	0.511
Preoperative CRP	17.3 $\pm$ 3.6	14.1 $\pm$ 3.6	0.525
Preoperative Lymphocyte	1.2 $\pm$ 0.1	1.2 $\pm$ 0.1	0.768
Preoperative Hct	36.5 $\pm$ 0.5	36.0 $\pm$ 0.6	0.583
Operative time, min	190.7 $\pm$ 6.3	188.2 $\pm$ 6.2	0.779
Laparoscopic surgery	61 (59.2)	60 (72.3)	0.063
ASA $\geq$ 3	11 (10.7)	7 (8.4)	0.607
Postoperative CRP	57.2 $\pm$ 5.3	43.5 $\pm$ 3.9	0.047
Postoperative ALB	32.2 $\pm$ 0.4	33.1 $\pm$ 0.3	0.122
Postoperative WBC	6.5 $\pm$ 0.2	6.1 $\pm$ 0.2	0.242
Postoperative RBC	3.6 $\pm$ 0.1	3.6 $\pm$ 0.1	0.880
Postoperative Hb	10.2 $\pm$ 0.2	10.3 $\pm$ 0.2	0.666
Hb, Hemoglobin; CRP, C-reactive protein; WBC, White blood cells; RBC, Red blood cells; Hb, Hemoglobin; PLT, platelets; Hct, Hematocrit; ESR, erythrocyte sedimentation rate; ω -3 PUFAs, omega-3 polyunsaturated fatty acid.			

Comparison of Clinical Data between CD Patients in the ω -3 PUFA Group and CD patients in the Non- ω -3 PUFA Group

A total of 103 of the enrolled CD patients (55.4%) did not receive ω -3 PUFA, while 83 of the patients (44.6%) did receive ω -3 PUFA. Table 1 shows the demographic information, intraoperative data and laboratory data for each group. There were no significant differences between the two groups with regard to preoperative laboratory data or the proportion of postoperative mild complications. Postoperative serum CRP levels were significantly higher in non- ω -3 PUFA-receiving patients than in ω -3 PUFA-receiving patients (57.2 ± 5.3 vs 43.5 ± 3.9 , $P = 0.047$). Compared with ω -3 PUFA-receiving patients, non- ω -3 PUFA-receiving patients also had higher postoperative complication rates (40.8% vs 24.1%, $P = 0.016$), higher major complication (Clavien-Dindo grade III to IV) rates (40.8% vs 24.1%, $P = 0.016$) and longer postoperative hospital stays (12.1 ± 1.1 days vs 9.3 ± 0.6 days, $P = 0.041$) (Table 2).

Table 2
Postoperative complications in CD patients with and without -3 PUFAs

ω			
Characteristics	Control group (n = 103)	ω-3 PUFAs group (n = 83)	P value
Postoperative complications	42 (40.8)	20 (24.1)	0.016
Mild complications (Grade I to II)	29 (28.2)	18 (21.7)	0.313
Wound infection	10 (9.7)	3 (3.6)	0.105
Fever > 38.5oC after surgery	8 (7.8)	5 (6.0)	0.643
Diarrhea	2 (1.9)	2 (2.4)	0.827
Early postoperative bowel obstruction	4 (3.9)	6 (7.2)	0.316
Postoperative blood transfusions > 2U	4 (3.9)	1 (1.2)	0.242
Line sepsis	1 (1.0)	1 (1.2)	0.695
Major complications (Grade III to IV)	24 (23.3)	8 (9.6)	0.014
Gastrointestinal bleeding	3 (2.9)	2 (2.4)	0.832
Intra-abdominal bleeding	2 (1.9)	0 (0)	0.305
Anastomotic leakage	5 (4.9)	2 (2.4)	0.374
Abdominopelvic collection	2 (1.9)	1 (1.2)	0.688
Intra-abdominal abscess	4 (3.9)	2 (2.4)	0.567
Stoma complications	3 (2.9)	0 (0)	0.058
Septic shock	4 (3.9)	1 (1.2)	0.242
Sepsis	1 (1.0)	0 (0)	0.554
Grade V	0 (0)	0 (0)	-
Postoperative stay	12.1 ± 1.1	9.3 ± 0.6	0.041
CD, Crohn's disease; ω-3 PUFAs, omega-3 polyunsaturated fatty acid.			

Analysis Of Influencing Factors Of Postoperative Complications

According to the occurrence of postoperative complications, the patients were divided into a postoperative complications group and a non-postoperative complications group.

There were significant differences between the postoperative complications group and the non-postoperative complications group with regard to preoperative biological medication use, postoperative ω -3 PUFA use, preoperative CRP level, operative time and laparoscopic surgery, as shown in Table 3. The non-postoperative complications group had a lower incidence of preoperative biological medications use (12.9% vs 27.4%, $P = 0.015$), a greater incidence of postoperative ω -3 PUFA use (50.8% vs 32.2%, $P = 0.016$), a lower preoperative CRP level (10.2 ± 2.0 vs 27.3 ± 6.3 , $P = 0.001$), a shorter operative time (181.2 ± 5.3 vs 206.3 ± 7.7 , $P = 0.008$) and a greater incidence of laparoscopic surgery (71.0% vs 53.2%, $P = 0.017$) than the postoperative complications group.

Table 3
Univariate analysis of risk factors associated with postoperative complications.

Characteristics	Without complications (n = 124)	With complications (n = 62)	P value
Male/female	80/44	35/27	0.286
Age	39.3 ± 1.2	37.8 ± 1.7	0.482
BMI	19.2 ± 0.3	19.2 ± 0.4	0.877
Previous surgery	54 (43.5)	24 (38.7)	0.528
Motreal classification			
Age (years)			
A1 (≤ 16)	2 (1.6)	1 (1.6)	0.742
A2 (17–40)	68 (54.8)	39 (62.9)	0.294
A3 (> 40)	54 (43.5)	22 (35.5)	0.292
Location			
L1 (ileal)	62 (50.0)	34 (54.8)	0.534
L2 (colonic)	7 (5.6)	2 (3.2)	0.717
L3 (ileocolonic)	46 (37.1)	24 (38.7)	0.831
L4 (upper gastrointestinal)	9 (7.3)	2 (3.2)	0.442
Behavior			
B1 (inflammatory/failure of medical therapy)	6 (4.8)	2 (3.2)	0.898
B2 (stricturing)	93 (75.0)	44 (71.0)	0.556
B3 (penetrating)	43 (34.7)	24 (38.7)	0.589
P (perianal disease)	38 (30.6)	14 (22.6)	0.248
Preoperative medications			
5-ASA	29 (23.3)	17 (27.4)	0.548
Corticosteroids	9 (7.3)	5 (8.1)	0.845
Thiopurine	49 (39.5)	19 (30.6)	0.236
Infliximab	16 (12.9)	17 (27.4)	0.015
Others	21 (16.9)	4 (6.5)	0.080

Characteristics	Without complications (n = 124)	With complications (n = 62)	P value
Preoperative TPN	28 (22.6)	12 (19.4)	0.614
Postoperative TPN with ω -3 PUFAs	63 (50.8)	20 (32.2)	0.016
Preoperative RBC	4.3 $\pm$ 0.1	4.2 $\pm$ 0.1	0.807
Preoperative WBC	5.6 $\pm$ 0.2	6.1 $\pm$ 0.4	0.261
Preoperative Hb	12.0 $\pm$ 0.2	11.8 $\pm$ 0.3	0.520
Preoperative PLT	249.3 $\pm$ 7.9	264.6 $\pm$ 11.9	0.273
Preoperative ESR	15.8 $\pm$ 1.3	18.7 $\pm$ 2.2	0.253
Preoperative ALB	36.9 $\pm$ 0.5	35.7 $\pm$ 0.7	0.131
Preoperative CRP	10.2 $\pm$ 2.0	27.3 $\pm$ 6.3	0.001
Preoperative Lymphocyte	1.18 $\pm$ 0.04	1.11 $\pm$ 0.08	0.347
Preoperative Hct	36.5 $\pm$ 0.5	35.9 $\pm$ 0.7	0.502
Operative time, min	181.2 $\pm$ 5.3	206.3 $\pm$ 7.7	0.008
Laparoscopic surgery	88 (71.0)	33 (53.2)	0.017
ASA $\geq$ 3	11 (8.9)	7 (11.3)	0.599
BMI, body mass index; 5-ASA, 5-aminosalicylic acid; Hb, Hemoglobin; CRP, C-reactive protein; WBC, White blood cells; RBC, Red blood cells; Hb, Hemoglobin; PLT, platelets; Hct, Hematocrit; ESR, erythrocyte sedimentation rate; ω -3 PUFAs, omega-3 polyunsaturated fatty acid.			

Multivariate logistic regression analysis suggested that preoperative biological medication use was an independent risk factor for postoperative complications in CD patients (odds ratio (OR):2.644, 95% confidence interval (CI):1.137–6.152, P = 0.024) and that ω -3 PUFA-supplemented PN after surgery was an independent protective factor for against postoperative complications in CD patients (OR:0.492, 95% CI:0.249–0.974, P = 0.042), as shown in Table 4.

Table 4
Multivariate analysis of risk factors associated with postoperative complications.

Characteristics	OR	95% CI	P value
Preoperative medications with infliximab	2.644	1.137–6.152	0.024
Postoperative TPN with ω -3 PUFAs	0.492	0.249–0.974	0.042
Preoperative CRP	1.885	0.927–3.833	0.080
Operative time	1.780	0.897–3.531	0.099
Laparoscopic surgery	0.894	0.413–1.934	0.776
TPN, total parenteral nutrition; ω -3 PUFAs, omega-3 polyunsaturated fatty acid; CRP, C-reactive protein.			

Discussion

CD is a chronic inflammatory disease that can involve the whole digestive tract but especially involves the terminal ileum and right colon. The etiology of CD remains unknown, and there is still no specific radical treatment. Aminosalicylic acid preparations, glucocorticoids, and thiopurine drugs can be used for maintenance therapy during the active period and after drug-induced remission. However, surgical treatment is often needed. As reported previously, approximately 78% of patients who have CD for more than 20 years need surgical treatment^{1,21–23}. Surgical treatment can only address complications, such as obstructions, bleeding, perforations, abscesses, inflammatory masses, and internal and external intestinal fistulas; it cannot cure the primary disease. In addition, postoperative complications are still major problems after colorectal surgery that cause prolonged in-hospital stays, increase treatment costs, and worsen long-term survival. Malnutrition, preoperative drugs use, preoperative intestinal fistulas and abdominal abscesses can all increase the risk of postoperative complications^{24–26}. Hence, reliable treatments are needed to reduce postoperative complications in order to enable early and safe patient discharge, especially under the Enhanced Recovery after Surgery program.

In the current study, we analyzed the protective effects of ω -3 PUFA-supplemented PN after surgery against postoperative complications for patients with CD. The results revealed that CD patients who did not receive ω -3 PUFA after surgery were at higher risk of postoperative complications, exhibited higher postoperative serum CRP levels and experienced longer postoperative hospital stays after enterotomy than those who did receive ω -3 PUFAs. These findings indicate that ω -3 PUFA-supplemented PN after surgery can reduce the postoperative inflammatory response and reduce the incidences of postoperative complications, especially major complications, thus accelerating the recovery of CD patients. This study is the first to focus on the relationship between ω -3 PUFA-supplemented PN and postoperative rehabilitation for CD patients.

ω -3 PUFAs have been shown to be effective in enhancing nutritional status and immune function in gastrointestinal patients who have undergone surgery. ω -3 PUFA-supplemented PN has been proven to be

successful, safe, and effective and has good clinical applications and clinical value for CD patients without surgery^{27–28}. However, little is known about the relationship between the use of ω -3 PUFAs after surgery and clinical outcomes. The effects of ω -3 PUFAs in surgical patients are still controversial. One prospective randomized controlled study showed that ω -3 PUFAs could significantly ameliorate the postoperative inflammatory response in 48 patients with gastric cancer²⁹. Zhang et al.³⁰ found that ω -3 PUFA-supplemented PN could improve postoperative recovery, reduced postoperative complications, and shorten hospital stays after hepatectomy in patients with liver cirrhosis or liver cancer. A meta-analysis by Zhao et al.³¹ revealed that early application of ω -3 PUFAs in patients with gastrointestinal cancer could improve immunity, reduce the postoperative stress response, and attenuate metastasis or recurrence. However, other studies have shown that there is no significant correlation between ω -3 PUFAs and postoperative complications in colorectal or esophageal cancer patients^{12,32–33}. Our study suggests that ω -3 PUFA-supplemented PN can reduce the postoperative inflammatory response, promote the recovery of intestinal function, reduce the incidence of anastomotic leakage, and reduce the incidences of abdominal abscesses and other major postoperative complications in CD patients after enterotomy. However, the incidence of postoperative incision infection was not revealed to be significantly reduced in our study. CD is characterized by abnormal activation of the intestinal immune system and a major inflammatory response; however, application of ω -3 PUFAs after surgery can reduce the inflammatory response caused by surgical trauma stress, and further control the inflammatory response caused by CD itself³⁴.

The postoperative rehabilitation improvement mediated by ω -3 PUFAs may be due to regulation of the arachidonic acid pathway and control of the release of prostaglandins, thromboxanes, leukotrienes and other molecules, which reduces the levels of inflammatory molecules such as IL-6, IL-8, and TNF- α ^{35–37}; regulation of sterol regulatory element binding protein (SREBP-1), protein acylation reactions and calcium ion release, which maintains cell membrane integrity, stability, and fluidity, thus reducing the production and release of cytokines and ameliorating the postoperative inflammatory response³⁸; alteration of the phospholipid composition and function of T-cell membranes, which enhances the function of antigen-presenting cells and the cytotoxicity of natural killer cells and regulates the function of dendritic cells to affect immune function³⁹; and regulation of the intestinal flora and their metabolites, such as short chain fatty acids⁴⁰.

The current study had several limitations. First, it was a retrospective observational analysis, and the effects of residual confounding factors could not be fully excluded. Second, as this was a single-center study, the perioperative management strategies were dependent on our local experience, which may have influenced the outcomes⁴¹. Large multicenter prospective studies must be performed to verify the conclusions of the current study.

Conclusion

In summary, the findings of the current study confirm that ω -3 PUFA-supplemented PN after surgery can reduce the postoperative inflammatory response and the incidences of postoperative complications, especially major complications in CD patients. To optimize perioperative treatment measures, surgeons are advised to be aware of the benefits of ω -3 PUFA-supplemented PN after surgery. ω -3 PUFAs use can be considered for patients who receive TPN after surgery, as it is conducive to reducing postoperative complications and ultimately achieving accelerated rehabilitation.

List Of Acronyms And Abbreviations

CD: Crohn's disease; PUFAs: Polyunsaturated fatty acids; PN: Parenteral nutrition; ERAS: Enhanced recovery after surgery; SREBP: Sterol regulatory element binding protein.

Declarations

Acknowledgements: The authors gratefully acknowledge all of the investigators for their contributions to the trial, as well as Bin Chen, who provided medical writing assistance.

Author's contributions

Xiao-long Ge and Yan Wu made contributions to the conception, funding acquisition, investigation, and writing – review & editing. Hua-ying Liu made contributions to formal analysis and writing – original draft. Wei-lin Qi, Wei Liu, Sha-sha Tang, Ling-na Ye, Qian Cao, Xiaolong Ge and Wei Zhou were involved in collecting data, methodology, resources, and drafting the manuscript. All authors had read and approved the final manuscript.

Disclosure

The authors declare no conflicts of interest or financial ties to disclose.

Source of Funding: Supported by grants from National Natural Science Foundation of China (81800474).

Ethical approval

This study was approved by the Committee of Ethics of Sir Run Run Shaw Hospital of Zhejiang University, Hangzhou, China.

Data availability

Requests for materials and data should be addressed to Wei Zhou (zhouweisrrs@zju.edu.cn) or Xiaolong Ge (gxlmed@zju.edu.cn).

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