Efficacy and cost of double filtration plasmapheresis in severe hypertriglyceridemia-induced pancreatitis: A retrospective observational study

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Research Article

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Abstract

Background

The value of double filtration plasmapheresis (DFPP) in severe hypertriglyceridemia-induced pancreatitis (sHTGP) is controversial. This study aimed to investigate the efficacy of DFPP on clinical results in patients with sHTGP and the costs associated with the procedure.

Methods

Patients who underwent DFPP after admission between January 2016 and December 2021 were recruited. Data on lipid profile, clinical results, and costs were retrospectively collected and analyzed.

Results

Fifty sHTGP patients who received DFPP were enrolled. All of the lipid profile were significantly reduced and maintained a downward trend. The APACHE II score on admission was higher and the reduction after DFPP was more obvious ($P < 0.05$) in patients with higher triglyceride (TG) levels (≥ 33.9 mmol/L) than in patients with lower TG levels. More material fees were expended in the higher TG group due to more DFPP sessions ($P < 0.05$), but no significant differences existed in total hospital costs between the two groups.

Conclusion

DFPP could rapidly and effectively reduce TGs to a safe level. APACHE II score reduction was obvious in patients with TGs ≥ 33.9 mmol/L and was associated with lipid profile changes. DFPP may benefit sHTGP patients with a TG level higher than the current initiation threshold.

Background

Acute pancreatitis (AP) is a life-threatening disease resulting from various potential etiologies. Hypertriglyceridemia is the third leading cause of AP, accounting for approximately 7% of all cases. Severe hypertriglyceridemia-induced pancreatitis (sHTGP) differs from other causes due to its worse clinical course and outcomes(1). Severe hypertriglyceridemia, characterized by a triglyceride (TG) level ≥11.3 mmol/L, is thought to trigger sHTGP. The pathophysiology of sHTGP is presumed to involve lipotoxicity of TG breakdown and activation of the inflammatory response, and the severity and clinical course are associated with these mechanisms(2). Therefore, the primary management is to immediately decrease the TG level to the target of 5.65 mmol/L.

Extracorporeal apheresis is an effective option for sHTGP patients, which can eliminate cytokines and proinflammatory markers and improve clinical symptoms, morbidity, and mortality(3). Double filtration plasmapheresis (DFPP) is a selective plasma component separation therapy based on a two-type filter system that can also have a triglyceride-lowering effect. DFPP is the main modality in our center, resulting from the shortage of plasma and the desire to avoid transfusion adverse effects. To date, the efficacy and cost of DFPP for sHTGP patients is still controversial. The goals of this study were to describe lipid profile alterations after DFPP in sHTGP patients and to explore the relationship between these alterations and clinical improvement.

Methods

This retrospective observational study was approved by the ethics committee.

Patients

This study was conducted in the Department of General ICU from January 2016 to December 2021. Patients were recruited once AP was identified. Age < 18 years, pregnancy, other etiologies of AP, TG level 11.3 mmol/L, contraindication for DFPP, and incomplete data were the exclusion criteria.

DFPP

DFPP was conducted by a PlasautoΣ™ (Asahi Kasei, Japan) equipped with a plasma separator (Plasmaflo™ OP-08) and plasma component separator (Cascadeflo^{TM} EC-50 W). Vascular access was mostly through the femoral vein. An average of 1.5-time plasma volume was processed. The blood flow rate, plasma separation rate, and discarding rate were 100 mL/min, 20%, and 10%, respectively. Heparin was administered for anticoagulation during the entire procedure. Once the TG level (<5.6 mmol/L) was achieved, no additional sessions were delivered.

Data collection

Electronic medical records were reviewed for baseline characteristics, including demographic data, body mass index (BMI), comorbidities, time from onset to admission, BISAP score, Sequential Organ Failure Assessment (SOFA) score, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The lipid profile, including TG, total cholesterol (TC), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), was collected before DFPP, after the first session, and upon transfer/discharge. Clinical outcomes were depicted by APACHE II and SOFA scores after all sessions, local complications, mortality, and length of ICU and hospital stays. Hospital expenses were divided into total fees, professional fees and nonprofessional fees, and the latter item was divided into medication and material fees.

Statistical analysis

Patients were divided into higher and lower TG groups based on the TG level of 33.9 mmol/L (3 times the upper limit). Continuous variables with a normal distribution were described as the mean ± SD and were analyzed by t-test, while continuous variables with a nonnormal distribution were reported as the median (interquartile range) and were analyzed using the Mann–Whitney test. The association between lipid profile and APACHE II score changes was revealed using linear regression analysis. $P<0.05$ was judged to indicate statistical significance. Data were analyzed using SPSS 24.0 and GraphPad Prism 9.0.

Results

Patient characteristics

During this investigation, 63 patients were admitted and diagnosed with AP. Fifty sHTGP patients were recruited after exclusions (Fig. 1). The baseline characteristics are described in Table 1. The mean age was 37.7 ± 10.5 years (range: 21–65 years), and 39 (78.0%) patients were men. The average number of days from disease onset to admission were 1.2 ± 0.7 d. Sixteen (32.0%) patients had recurrent AP, and 20 (40.0%) patients had a past medical history of hyperlipidemia. Thirty (60.0%) patients were complicated with various risk factors, including diabetes (28.0%), alcohol abuse (24.0%) and medication history (26.0%). On admission, the average APACHE II score in the higher TG group was significantly higher than that in the lower TG group ($P< 0.05$).

Table 1
Baseline characteristics of the patients

Variables	All patients (n = 50)	Lower group (n = 24)	Higher group (n = 26)	P
Age, median (IQR), y	37.7(29.8–44.0)	37.0(28.0-43.8)	38.4(30.8–44.8)	0.719
Male, n (%)	39 (78.0)	21(87.5)	18(69.2)	0.123
BMI, mean ± SD, kg/m^2	27.2 ± 4.0	27.5 ± 3.7	27.0 ± 4.4	0.628
Recurrence, n (%)	16(32)	8(33.3)	8(30.8)	0.848
Preexisting comorbidities				
Hyperlipidemia, n (%)	20(40)	9(37.5)	11(42.3)	0.731
Diabetes, n (%)	14(28)	6(25.0)	8(30.8)	0.653
Alcohol abuse, n (%)	12(24)	4(16.7)	8(30.8)	0.248
Medication, n (%)	13(26)	7(29.2)	6(23.1)	0.627
Onset to admission, median (IQR), d	1.2(0.7-2.0)	1.3(1.0–2.0)	1.2(0.58–1.3)	0.368
Disease severity				
BISAP score, median (IQR)	2.1(2.0–2.0)	2.0(2.0–2.0)	2.15(2.0–2.0)	0.274
Before-APACHE II score, median (IQR)	11.5(7.0–14.0)	9.9(6.0-12.8)	13.0(9.0-17.3)	0.039
Before-SOFA, median (IQR)	3.1(1.0–4.0)	3.1(1.3–4.8)	3.0(1.0–4.0)	0.860

Lipid profile changes

In addition to adjunctive therapy, all patients underwent DFPP within 24 hours of admission without any complications. The majority of patients (n = 46, 92.0%) received fewer than 3 sessions, with 26 (52.0%) patients receiving only one session. Patients in the higher TG group experienced more sessions than those in the lower TG group (P< 0.01). The lipid profile presented a distinct difference after DFPP and remained stable (Fig. 2). The TG level was remarkably reduced by 71.9% on average (P< 0.01), and the levels of TC, HDL, and LDL all synchronously decreased (P< 0.05). Compared to the lower TG group, DFPP generated a stronger TG-lowering effect in the higher TG group (P< 0.01) after the first session but there were no significant differences in TC, HDL, or LDL levels (all P> 0.05).

Table 2
Therapy and lipid profile changes

Variables	All patients (*n* = 50)	Lower group (*n* = 24)	Higher group (*n* = 26)	*P*
Session, median (IQR), n	1.6(1.0–2.0)	1.3(1.0-1.8)	1.8(1.0–2.0)	0.003
Adjunctive therapy				
Somatostatin, n (%)	46(92.0)	21(87.5)	25(96.2)	0.265
Insulin, n (%)	26(52.0)	14(58.3)	12(46.2)	0.394
Fibrate, n (%)	41(82.0)	19(79.2)	22(84.6)	0.620
TG level				
Before DFPP, median (IQR), mmol/L	44.2(23.8–63.3)	24.3(19.2–30.4)	62.6(42.2–75.1)	0.000
First session, median (IQR), mmol/L	12.4(3.0-16.2)	6.0(2.7–5.9)	18.3(4.8–21.3)	0.001
TG reduction, median (IQR), mmol/L	31.8(18.8–42.1)	18.3(13.8–26.8)	44.3(33.8–53.8)	0.000
Transfer/discharge, median (IQR), mmol/L	3.7(2.7–4.4)	3.3(2.6–4.2)	4.0(3.3–4.8)	0.023
TC level				
Before DFPP, median (IQR), mmol/L	15.4(11.7–18.2)	12.5(9.5–15.2)	18.0(14.3–21.5)	0.000
First session, median (IQR), mmol/L	6.1(2.6–7.8)	3.7(1.9–5.4)	8.3(3.4–8.6)	0.000
TC reduction, median (IQR), mmol/L	9.3(6.2–11.1)	8.8(6.3–10.6)	9.8(6.2–11.9)	0.641
Transfer/discharge, median (IQR), mmol/L	2.9(2.2–3.4)	2.5(1.9–2.8)	3.3(2.8–3.6)	0.000
HDL level				
Before DFPP, median (IQR), mmol/L	2.6(1.5–3.2)	1.8(1.3–2.5)	3.3(1.9–4.4)	0.005
First session, median (IQR), mmol/L	1.2(0.7–1.3)	0.9(0.6–0.9)	1.6(0.7–1.8)	0.027
HDL reduction, median (IQR), mmol/L	1.3(0.4–1.9)	1.0(0.4–1.6)	1.7(0.3–2.9)	0.081
Transfer/discharge, median (IQR), mmol/L	0.7(0.5–0.9)	0.7(0.5–0.9)	0.76(0.6–0.9)	0.466
LDL level				
Before DFPP, median (IQR), mmol/L	4.3(3.2-5.0)	3.8(2.6–4.8)	4.9(4.0–6.0)	0.008

Variables	All patients (n = 50)	Lower group (n = 24)	Higher group (n = 26)	P
First session, median (IQR), mmol/L	2.2(1.1–2.9)	1.5(0.8–2.2)	2.8(1.6–3.5)	0.001
LDL reduction, median (IQR), mmol/L	2.2(1.3–3.1)	2.2(1.4–3.1)	2.1(1.2–3.2)	0.607
Transfer/discharge, median (IQR), mmol/L	1.3(0.9–1.5)	1.1(0.7–1.4)	1.5(1.1–1.8)	0.007

Clinical results and costs

Table 3 summarizes the main clinical outcomes and costs. The APACHE II score reduction was more obvious in the higher TG group, revealing a significant difference ($P < 0.05$). Other clinical outcomes, including the local complication rate and SOFA score, exhibited no difference between the two groups. No statistically significant differences existed in terms of ICU and hospital stays ($P > 0.05$). Except for material fees ($P < 0.05$), there were no notable differences in hospital charges.

Table 3
Clinical results and costs

Variables	All patients (*n* = 50)	Lower group (*n* = 24)	Higher group (*n* = 26)	*P*
Clinical outcome				
After-APACHE II score, median (IQR)	4.1(2.0-5.3)	4.8(2.0-5.8)	3.5(1.0-4.5)	0.185
After-SOFA, median (IQR)	1.76(0.0-2.3)	1.9(0.0–3.0)	1.7(0.0–2.0)	0.834
APACHE II reduction, median (IQR)	7.4(5.0–10.0)	5.1(3.0-7.5)	9.5(7.0–12.0)	0.000
SOFA reduction, median (IQR)	1.3(0.0–3.0)	1.3(0.0–3.0)	1.35(0.0–3.0)	0.875
Local complication, n (%)	5(10%)	2(8.3)	3(11.5)	0.709
Mortality, n (%)	2(4%)	1(4.2)	1(3.8)	0.954
ICU stay, median (IQR), d	4.1(2.0–4.0)	4.3(1.3-4.0)	3.9(2.0–4.0)	0.245
Hospital stay, median (IQR), d	15.5(9.0-17.3)	15.6(7.3–21.3)	15.4(10.8–17.3)	0.180
Cost				
Total fee, median (IQR), CNY	75871.1(30997.3-69063.3)	89243.1(28527.8-80806.5)	63527.7(41335.8-69063.3)	0.156
Professional fee, median (IQR), CNY	26542.8(12746.3-24366.3)	30036.5(12688.8-30591.5)	23317.8(13170.5-22648.3)	0.485
Non-professional fee, median (IQR), CNY	49328.3(17872.3-48537.8)	59206.6(16703.5-50513.5)	40209.9(24566.8-48537.8)	0.103
Medication fee, median (IQR), CNY	33658.2(8791.0-26805.0)	43837.2(7092.0-36378.8)	24262.3(11463.3-26405.3)	0.303
Material fee, median (IQR), CNY	15670.0(7967.8-17192.0)	15369.4(6940.0-16219.0)	15947.6(11444.3-17528.3)	0.019

Association between APACHE II score and lipid profile changes

Linear regression analysis was performed to reveal the relationship between APACHE II score and lipid profile alterations. The results demonstrated that clinical improvement was statistically associated with alterations in TG and TC levels in the higher TG group ($P = 0.014$, $P = 0.010$). However, the relationship was not obvious in the lower TG group (Table 4).

Table 4
Linear regression analysis of APACHE II score and lipid profile changes

Variables	Group	β	95%CI		*P*
			Lower	Upper	
TG	Lower	0.043	-0.016	0.192	0.554
	Higher	-0.112	-0.198	-0.025	0.014
TC	Lower	0.338	-0.374	1.051	0.333
	Higher	0.620	0.163	1.077	0.010
HDL	Lower	0.441	-1.294	2.176	0.601
	Higher	-0.436	-0.972	0.100	0.106
LDL	Lower	-0.918	-2.496	0.659	0.238
	Higher	-0.880	-2.015	0.254	0.121

Discussion

The goal of this study was to explore the changes in the lipid profile following DFPP and how they were related to clinical results in sHTGP patients. It is generally recognized that a higher TG level correlates with illness severity(4), so timely lowering of the lipid profile is a critical goal. To compensate for the slow effect of pharmacological therapies, DFPP was performed in sHTGP patients and has been proven effective for decades. The efficacy of DFPP was tested in 47 sHTGP patients by Zheng et al., who discovered that the parameters were altered dramatically on the first day after DFPP(5). This study revealed similar results, and the effect was maintained until discharge.

Despite its well-known TG-lowering efficacy, DFPP is not the recommended extracorporeal therapy in the guideline of the American Society for Apheresis(6). The potential mechanism of DFPP modulation in sHTGP is still unclear. Free fatty acids, identified as a critical mediator of organ failure, could not be removed by DFPP(7). However, DFPP could rapidly eliminate TG lipoproteins, theoretically limiting the accumulation of free fatty acid metabolized from TG. Elevated TG levels have been independently and proportionally associated with persistent organ failure(8). Consequently, the efficacy of DFPP in intervening in disease severity and clinical results in sHTGP patients has yet to be confirmed. Lu et al. conducted a propensity score matching analysis of DFPP and conservative treatment(9). They found that early implementation of DFPP could effectively reduce TG levels while manifesting no benefit on the clinical results of sHTGP patients. In this study, the TG levels on admission were 39.7 mmol/L and 31.1 mmol/L in the two groups. In the other study, Chang et al. reported that DFPP could eliminate inflammatory and oxidized lipoproteins and significantly reduce the incidence of complications when applied to patients with TG levels > 56.5 mmol/L (5000 mg/dL) (10). A TG level higher than the current

TG standard could be a better indication for DFPP and a better predictor of clinical outcomes. This hypothesis was partly verified by our research. The APACHE II score change was more obvious in the higher TG group than in the lower TG group, with a significant difference ($P < 0.05$). This clinical improvement was related to TG and TC reductions, according to linear regression analysis, but the potential mechanism required more investigation.

Moreover, it was controversial whether performing DFPP was associated with shortening hospital durations in previous studies(10). In Lu's study, DFPP imposed no effect on the length of hospital stay. However, Chang et al. inferred that DFPP could shorten the disease course and reduce hospital duration. This outcome was partly associated with the clinical improvement discussed above. In our study, the ICU and hospital stays in both groups were not significantly different (P = 0.245 and 0.180, respectively), contrary to previous expectations(11). Furthermore, due to the extra expenses, DFPP was reported to increase the hospital charges(9). However, except for material fees related to DFPP ($P = 0.019, < 0.05$), hospital expenses were not significantly different, including total, professional, nonprofessional, and medication fees. As mentioned above, it was reasonable to infer that DFPP could offset costs by alleviating disease severity and shortening the course of illness.

Limitations

This was one of the largest studies to evaluate the efficacy and cost of DFPP in sHTGP patients. However, this study possessed several shortcomings. First, some latent and confounding factors might exist in this retrospective observational study, which could influence patient outcomes. Second, relatively small sample sizes from a single center undermined the ability to measure some clinical results and reveal relationships. Therefore, further large-scale and multicenter prospective studies and randomized clinical trials are needed.

Conclusions

DFPP can rapidly and effectively reduce lipid profile, especially TG, to target levels. Early initiation of DFPP was associated with a decrease in the APACHE II score in patients with TGs ≥ 33.9 mmol/L. Although adding an extra material fee, DFPP may not increase the total hospital expense. DFPP may have beneficial effects on sHTGP patients with a TG level higher than the current threshold. Further studies are required to confirm the value of DFPP in the management of sHTGP.

Abbreviations

DFPP
Double filtration plasmapheresis
sHTGP
severe Hypertriglyceridemia-induced pancreatitis
AP

Acute pancreatitis
TG
Triglyceride
BMI
Body mass index
SOFA
Sequential Organ Failure Assessment
APACHE II
Acute Physiology and Chronic Health Evaluation II
TC
Total cholesterol
LDL
Low-density lipoprotein
HDL
High-density lipoprotein
IQR
Interquartile range
ICU
Intensive care unit

Declarations

This study was reported based on STROBE checklist.

Ethics approval and consent to participate

The research was in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Second Affiliated Hospital of Zhejiang University Medical School (ID: 20220039) and the necessity for informed consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Emails could be sent to the address below to obtain the shared data: zyeyzhicu@zju.edu.cn

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The study was designed by Xin Xu; Pan Han was responsible for analyzing the data and drafting the manuscript; The manuscript was reviewed by Chenyang Gao. All authors read and approved the final manuscript.

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Not applicable

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Figures

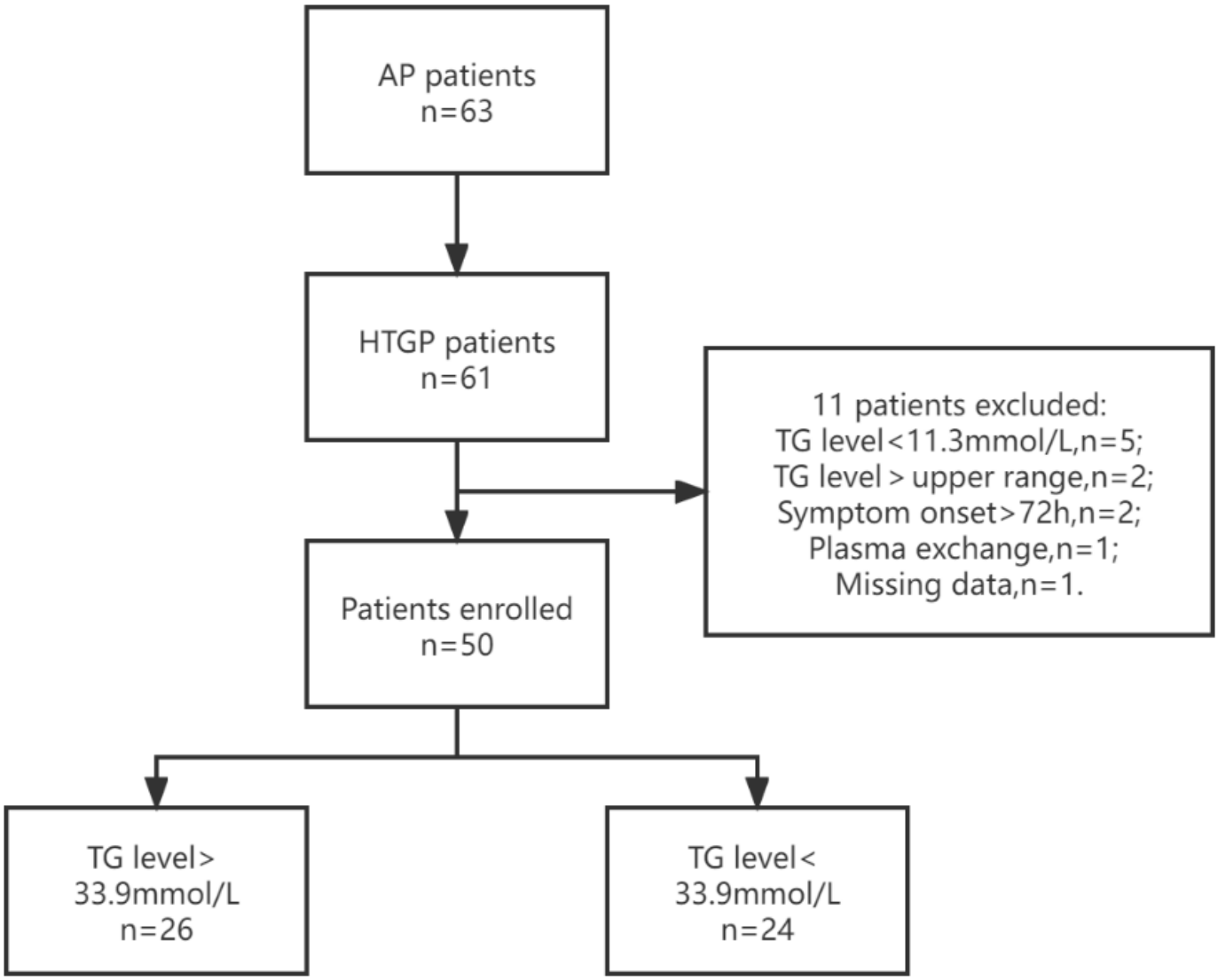

Figure 1

The study population was presented in the flow diagram. AP, acute pancreatitis; HTGP, hypertriglyceridemic-induced pancreatitis; TG, triglyceride

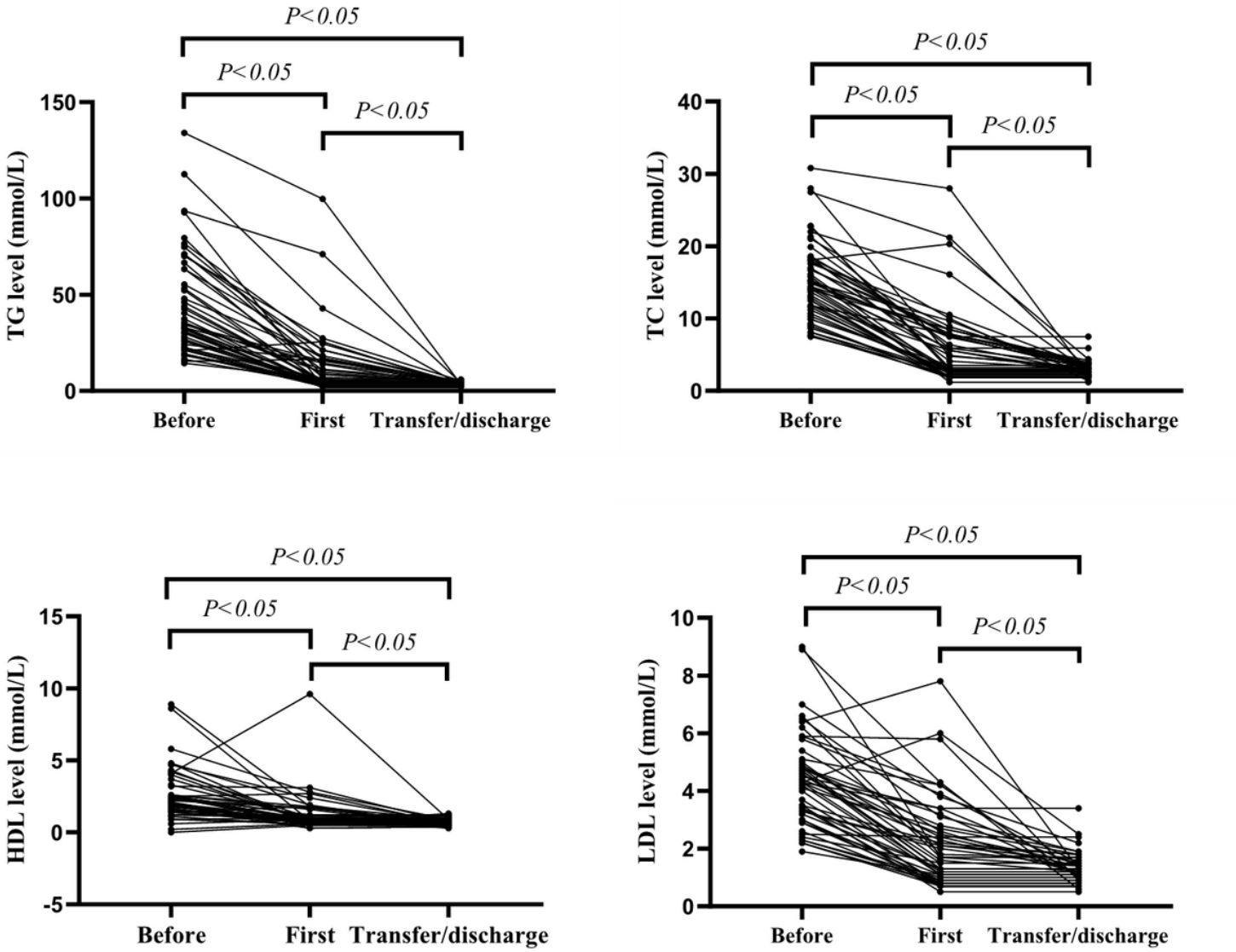

Figure 2

Lipid profile changes before DFPP, after the first session, and on transfer/discharge. The difference between the neighboring two sets of data was investigated by T-test.