Nutritional Status Alterations After Chimeric Antigen Receptor T Cell Therapy in Patients With Hematological Malignancies: A Retrospective Study

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Abstract

Purpose: The influence of innovative chimeric antigen receptor T cell (CAR-T) therapy for hematological malignancies on nutritional status remains unknown. Therefore, we aim to explore the alterations of nutritional status after CAR-T therapy in patients with hematological malignancies.

Methods: We retrospectively collected the data of patients with acute leukemia (AL), lymphoma and multiple myeloma (MM), who underwent CAR-T therapy at our hospital from 2018 to 2020. The serum albumin, triglyceride and cholesterol before and 7, 14 and 21 days after CAR-T cells infusion were compared and analyzed.

Result: A total of 117 patients were enrolled, consisting of 39 AL, 23 lymphoma and 55 MM patients. The baseline albumin, triglyceride and cholesterol were 37.43±5.08 mg/L, 1.63±0.74 mmol/L and 3.62±1.03 mmol/L, respectively. The lowest albumin level was found at 7 days after CAR-T infusion compared with baseline (P<0.001), while the levels of triglyceride increased at 14 and 21 days (P<0.001, P=0.036). The levels of cholesterol at 7, 14, 21 days after CAR-T infusion were lower than baseline (all P<0.05). Spearman correlation coefficient showed cytokine release syndrome grade was negatively correlated with the levels of albumin at 7 days and cholesterol at 21 days after CAR-T infusion (r=-0.353, P<0.001; r=-0.395, P=0.002).

Conclusion: Serum albumin and total cholesterol concentration decreased at the lowest level 7 days after CAR-T cells infusion, while triglyceride increased at 14 and 21 days after infusion. The levels of albumin and total cholesterol after CAR-T cells infusion were negatively correlated with the grade of cytokine release syndrome.

Introduction

Since the first batch of chimeric antigen receptor T (CAR-T) cells were recommended by Food and Drug Administration (FDA) in the United Stated in 2017[1], CAR-T therapy has achieved great progress and became a promising approach for cancers, especially in relapsed or refractory (r/r) hematological malignancies[2, 3]. In July 2020, FDA approved another CAR-T cell drug named Tecartus for treatment of adult patients diagnosed with mantle cell lymphoma (MCL). Adverse events, such as cytokine release syndrome (CRS) and tumor lysis syndrome, still are the main challenges in the clinical application of CAR-T cell[4, 5]. Though CAR-T cell therapy as an innovative treatment has the potential to be a dominated alternative for patients with hematological malignancies, the effectiveness and safety need to be determined in further studies[6].

Malnutrition may occur in 30% to 80% of patients with cancer[7, 8]. Nausea, diarrhea, constipation, and fatigue induced by chemotherapy or antineoplastic therapy and cachexia due to tumor-related metabolism abnormalities[9, 10] might eventually lead to malnutrition. It commonly manifested as weight loss, reduced muscle mass or body mass index (BMI), abnormalities in biochemical indices or ongoing high activity of inflammation. Studies have validated the effectiveness of various nutrition-related

indices, such as acute-phase reaction proteins (including albumin and immunoglobin)[11], biochemical parameters (including blood lipids, glucose and blood glucose, blood lipids and electrolytes) and calculated indices (including neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio)[12]. In addition, nutrition status evaluation scales, such as Patient-Generated Subjective Global Assessment[13], have been widely applied in clinical practice. As a key step in identifying cancer patients with malnutrition, nutrition screening provides the possibility of subsequent specific nutritional guidance or intervention.

Malnutrition in cancer patients has been proven to reduce response to treatment and increase treatment associated side effect[14], as well as influence on the quality of life, infection, relapse rate, longer hospital stays and higher healthcare costs[15-18]. Furthermore, being a major cause of cancer death, malnutrition could predict poor prognosis of patients[19]. Multiple studies have proven the relationships between malnutrition, metabolism, and immunity, especially concerning T cells[20, 21]. Regarding the crucial role of T cells in the effectiveness and safety of CAR-T therapy, the exploration of nutrition status alteration after CAR-T cells infusion is needed.

Since no studies have reported on the changes of nutrition status after CAR-T therapy, we aim to investigate the alterations of nutritional status after CAR-T therapy in patients with hematological malignancies in the present study and provide evidence for nutrition screening and intervention in such patients.

Methods

Study design and patients' selection

We retrospectively reviewed 117 patients who enrolled in phase 1/2 CAR-T cell therapy clinical trials conducted at our center from 2018 to 2020. Thirty-nine patients with acute lymphoblastic leukemia (ALL) were enrolled in CAR-T cell therapy either targeting CD19 (ChiCTR-ORN-16008948) or CD19/CD22 (ChiCTR1800015575), and 23 patients with non-Hodgkin's lymphoma (NHL) were treated with CD19-tageted CAR-T cell therapy (ChiCTR-OIC-17011310), moreover, 55 patients with multiple myeloma (MM) were administered with BCMA CAR-T cell (ChiCTR1800017404). These clinical trials were approved by the Medical Ethics Committee of the First Affiliated Hospital of Medical College, Zhejiang University, and performed according to the ethical principles of the Declaration of Helsinki.

The inclusion criteria were as follows: (1) age less than 75 years; (2) r/r CD19 positive ALL, r/r CD19 positive diffuse large B-cell lymphoma or follicular lymphoma, r/r MM with BCMA positive; (3) relapse after hematopoietic stem cell transplantation (HSCT) without evidence of graft-versus-host disease and not requiring immunosuppression therapy; (4) patients with adequate hepatic and renal function with an Eastern Cooperative Oncology Group performance status of 0–2; (5) measurable disease and adequate performance status and organ function. All patients were voluntarily participating in these trials and signed the informed consent form, and the informed consents were waived by the retrospective nature of this study.

Clinical protocol of CAR-T cell therapy

The protocol of CAR-T therapy was described previously[22]. Briefly, peripheral blood mononuclear cells were obtained from patients or donors by leukapheresis for CAR-T cell generation. T cells were transfected with CARs containing 4-1BB domain using lentivirus. Before CAR T-cell infusion, all patients received Fludarabine- (30 mg/m^2 on days -4~-2) and Cy- (750 mg/m^2 on day -3~-2) based lymphodepletion regimen. The expansion and persistence of CAR-T cells were elevated by flow cytometry and morphological analysis, and CAR DNA copy number was used as a complementary method.

Assessment of toxicities and efficacy

The grading of CRS is referred to a revised grading system[23]. While, other toxicities, including neurotoxicity and hematological toxicities were assessed referring to the National Institutes of Health Common Terminology Criteria for Adverse Events Version 5.0 (http://ctep.cancer.gov/). On day 28, the response of CAR-T cell therapy would be evaluated.

Data collection

The baseline data, including age, sex, BMI, smoking history, hypertension, diabetes and other comorbidities, residence, care-giver were collected. Nutritional status-related parameters, including triglyceride, cholesterol and albumin, were collected on the day of CAR-T cells transfusion and 7, 14 and 21 days after infusion. Cytokine release syndrome after CAR-T therapy were recorded, as well as the response of treatment.

Statistical analysis

SPSS 24.0 (SPSS Software Inc., Chicago, IL, USA) was used for statistical analyses, and GraphPad Prism 9.0.0 (San Diego, CA, USA) was used to draw the graphs. The continuous variables were presented as mean ± standard deviation and median (range). The categorical variables were presented as number (percentage). The parameters of multiple timepoints were compared by analysis of variance for repeated measurement. Mauchly's Test was used to determine whether the data were in line with the spherical hypothesis, and Greenhouse-Geisser method was used to for correction. Spearman correlation coefficient was used to analyze the correlation of serum albumin, triglyceride and total cholesterol with CRS. $P < 0.05$ was considered significant.

Results

Patients' characteristics

Among the 117 enrolled patients, the median age was 53 years (range, 14 to 74 years) with a BMI of 22.5±2.8 kg/m^2, and the majority were men (56.4%). The patients were mostly married (91.5%) and half of them came from urban residence. Nearly 80% patients received cares from spouses during hospitalization. The baseline demographics characteristics are summarized in Table 1.

Thirty-nine patients (33.3%) were diagnosed with acute leukemia, 23 (19.7%) with lymphoma and 55 (47.0%) with multiple myeloma, among which 33 (28.2%) had a history of hematopoietic stem cell transplantation (HSCT). Twenty-one patients complicated with hypertension and 14 with diabetes. Hepatitis B virus infection was found in 13 individuals (11.1%). The median length of hospital stay was 26 days (range, 7-90).

Alterations of serum albumin

The baseline albumin concentration was 37.43±5.08 mg/L. The prevalence of hypoalbuminemia was 35.9% (42/117) at baseline. The level of albumin concentration was 34.12±5.46 mg/L at 7 days after CAR-T cells infusion, which was significantly lower than baseline (mean difference: -3.84mg/L, P<0.001, Figure 1). The prevalence of hypoalbuminemia (<35 mg/L) was 59.8% (70/117). Subsequently, it increased to 37.89±4.99 and 38.45±5.46 mg/L with no significant difference found compared with baseline (P>0.999, P=0.259).

Alterations of serum triglyceride

The level of triglyceride at 7 days after CAR-T therapy was 1.68±1.23 mmol/L, which was similar with baseline (1.63±0.74 mmol/L, P>0.999). Nevertheless, it increased at 14 days (2.21±0.98 mmol/L, mean difference: 0.67 mmol/L, P<0.001, Figure 2) and remained at a high level at 21 days after CAR-T cell infusion (2.14±1.63 mmol/L, mean difference: 0.43 mmol/L, P=0.036). The prevalence of hypertriglyceridemia (>1.81 mmol/L) was 53.8% (63/117) at 14 days after CAR-T cells infusion.

Alterations of serum total cholesterol

The baseline total cholesterol concentration was 3.62±1.03 mmol/L. The lowest level was found at 7 days after CAR-T cells infusion (2.78±0.91 mmol/L, mean difference: -0.85 mmol/L, P<0.001, Figure 3). The prevalence of hypocholesterolemia was 91.5% (107/117). The total cholesterol concentration slightly increased at 14 and 21 days (2.98±0.84 mmol/L and 3.14±1.00 mmol/L, respectively), although the differences compared with baseline remained significant (mean difference: -0.79 mmol/L, P<0.001; mean difference: -0.47 mmol/L, P=0.003).

Correlation of serum albumin, triglyceride and total cholesterol with CRS

Thirty-five patients (30.0%) had Grade 0 or Grade 1 CRS, while 47 (40.1%) developed Grade 2 CRS and 28 (23.9%) developed Grade 3 CRS. Notably, 6 patients (5.1%) experienced a Grade 4 CRS but no death occurred.

Spearman correlation coefficient showed that CRS was negatively correlated with the level of serum albumin at 7 days (r=-0.353, P<0.001) and 14 days (r=-0.292, P=0.003), but not 21 days after CAR-T infusion (r=-0.104, P=0.421). Moreover, the negative correlations were found between total cholesterol levels and CRS at 7, 14 and 21 days after CAR-T therapy (r=-0.216, P=0.025; r=-0.310, P=0.002; r=-0.395,

P=0.002, respectively). However, no correlations were between triglyceride and CRS (all P>0.05). The details were presented in Table 2.

Effectiveness of CAR-T therapy

Sixty-nine (59.0%) patients achieved complete remission, and 27 (23.1%) achieved partial remission, leading to an objective response rate of 82.1%. The incidence of SCLS was 17.1% (20/117). Whereas, the association of nutrition-related parameters and prognosis of patients receiving CAR-T therapy was not significant (all P>0.05, data not shown), whether in univariate and multivariate analysis.

Discussion

In this retrospective study, the changes of nutritional status after CAR-T therapy were preliminarily explored. The finding showed the alterations varies across different indices, where serum albumin and total cholesterol decreased at the lowest level 7 days after CAR-T cells infusion, while the level of triglyceride increased at 14 and 21 days after CAR-T cells infusion.

The prevalence of hypoalbuminemia was 35.9% at baseline in this study, which was within the range of 30%-45% in previous studies based on hematological malignancies population[24-26]. In addition, the prevalence of hypocholesterolemia was 91.5% in this study, even higher than previous study reported[27]. Recently, a retrospective study including advanced hepatocellular carcinoma patients receiving anti-PD-1 immunotherapy reported that serum albumin concentration decreased distinctly after immunotherapy in disease progression patients[28]. In this study, the lowest level of serum albumin and TC concentration was found 7 days after CAR-T cells infusion and steadily climb back. Meanwhile, the level of TG after chemotherapy increased compared with pre-therapy[29, 30], which is similar in present study. Researchers have reported the influence of cytokines on the diet and metabolism of cancer patients[31, 32]. Cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha (TNF-α) together lead to decrease intake of food, increase glucose oxidation, increase synthesis of acute phase reactive proteins, decrease fatty acid uptake and increase resting energy expenditure, meanwhile affect metabolism by altering insulin, glucagon and corticosterone levels[32]. As studies revealed the onset-time of CRS was around 7-14 days[33], we supposed the decrease of albumin and TC to be correlated with CRS somehow. Subsequently, correlation analysis in this study showed negative correlations between serum albumin, total cholesterol with CRS, which preliminarily support the assumption. Further studies with larger sample size and concerning the mechanism of the influence of CRS on nutrition status are needed.

The effect of malnutrition on immunity remains appealing whether in cancer patients or healthy population. Relevant animal experiments proved that malnutrition could lead to a decrease in immune cells, especially T cells[20]. Similar findings were seen in human studies. Malnourished children had decreased CD4+ and CD8+ T cell numbers in whole blood compared to well-nourished children[34]. Yilmaz et al.[25] investigated the predictive performance of biochemical parameters in hematological malignancies patients and results suggested that serum albumin was a reliable index. Moreover, an observation study reported that lower albumin concentration pre-treatment was associated with toxic

induction deaths after chemotherapy in pediatric acute lymphoblastic leukemia patients[26]. Fang et al. [28] reported a correlation between serum albumin and the efficacy of anti-PD-1 immunotherapy, though the correlation was partial due to the small sample size. Nevertheless, the significant association of the level of serum albumin concentration and the prognosis of patients receiving CAR-T therapy was not found in our studies. We considered the frequent screening and active intervention might eliminate the effect, not to mention the small sample size and short follow-up.

The study had several limitations. Firstly, due to its retrospective nature, the selected bias and incomplete data were inevitable. In addition, limited follow-up data lead to the difficulty in exploring the effect of malnutrition on the prognosis of patients. Secondly, the sample size was relatedly small, which might result in the failure in the investigation of the risk factor of malnutrition. Finally, the evaluation of nutrition status in this study was insufficient. The application of other nutrition screening methods, such as muscle mass index, Patient-Generated Subjective Global Assessment and Nutrition Risk Index should be explored in further studies.

In conclusion, the alterations of different nutrition-related biochemical parameters varied after CAR-T therapy. Our findings revealed that serum albumin and total cholesterol concentration decreased at the lowest level 7 days after CAR-T cells infusion, while triglyceride increased at 14 and 21 days after CAR-T cells infusion. The levels of albumin and total cholesterol after CAR-T cells infusion were negatively correlated with cytokine release syndrome. Specific screening and intervention for malnutrition in patients receiving CAR-T therapy need to be explored in further studies.

Declarations

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Conflict of interest

The authors declare no conflict of interest.

Availability of data and material

Not applicable.

Code availability

Not applicable

Authors' contributions

Shuyi Ding, Lingxia Cai, Aiyun Jin, Xiaoyu Zhou, Jiali Yan, Tingting Wang designed the study and collected the data. Shuyi Ding, Linqin Wang, Houli Zhao analyzed the data and wrote the manuscript. Yongxian Hu designed the study and proof read the manuscript.

Ethics approval These clinical trials were approved by the Medical Ethics Committee of the First Affiliated Hospital of Medical College, Zhejiang University.

Consent to participate: Informed consent was obtained from all individual participants included in either study.

Consent for publication: Not applicable.

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Tables

Table 1. Characteristics of patients

Characteristics	Total (n=117)
Age, years, median (range)	53 (14-74)
Male, n (%)	66 (56.4)
BMI, kg/m^2, meanSD	22.5±2.8
Residence, n (%)	
Urban	59 (50.4)
Suburb	27 (23.1)
Rural	31 (26.5)
Married status, n (%)	
Unmarried	10 (8.5)
Married	107 (91.5)
Highest education, n (%)	
High school and below	89 (76.1)
College and above	26 (22.2)
Missing data	2 (1.7)
Care giver, n (%)	
Wife	62 (53.0)
Husband	36 (30.8)
Offspring	8 (6.8)
Parent	11 (9.4)
Diagnosis, n (%)	
Acute leukemia	39 (33.3)
Lymphoma	23 (19.7)
Multiple myeloma	55 (47.0)
Chemotherapy cycle, median (range)	7 (1-70)
History of HSCT, n (%)	
Yes	33 (28.2)
No	83 (70.9)

Missing data	1 (0.9)
Smoking history, n (%)	
Yes	20 (17.1)
No	97 (82.9)
Drinking history, n (%)	
Yes	20 (17.1)
No	97 (82.9)
Diabetes, n (%)	
Yes	14 (12.0)
No	102 (87.1)
Missing data	1 (0.9)
Hypertension, n (%)	
Yes	21 (17.9)
No	95 (81.2)
Missing data	1 (0.9)
HBV infection, n (%)	
Yes	13 (11.1)
No	104 (88.9)
Baseline ALB, mg/L, meanSD	37.43±5.08
Baseline TG, mmol/L, meanSD	1.63±0.74
Baseline TC, mmol/L, meanSD	3.62±1.03
Hospital stay, days, median (range)	26 (7-90)

SD: standard deviation; HSCT: hematopoietic stem cell transplantation; HBV: hepatitis B virus; ALB: albumin; TG: triglycerides; TC: total cholesterol

Table 2. Correlation of serum albumin, triglyceride and total cholesterol with cytokine release syndrome

Parameter	r	P
Albumin		
baseline	-0.184	0.049
7 days after CAR-T cells infusion	-0.353	**<0.001**
14 days after CAR-T cells infusion	-0.292	**0.003**
21 days after CAR-T cells infusion	-0.104	0.421
Triglyceride		
baseline	0.014	0.884
7 days after CAR-T cells infusion	0.164	0.089
14 days after CAR-T cells infusion	-0.017	0.868
21 days after CAR-T cells infusion	-0.083	0.534
Total cholesterol		
baseline	0.004	0.970
7 days after CAR-T cells infusion	-0.216	**0.025**
14 days after CAR-T cells infusion	-0.310	**0.002**
21 days after CAR-T cells infusion	-0.395	**0.002**

CAR-T: chimeric antigen receptor T.

Figures

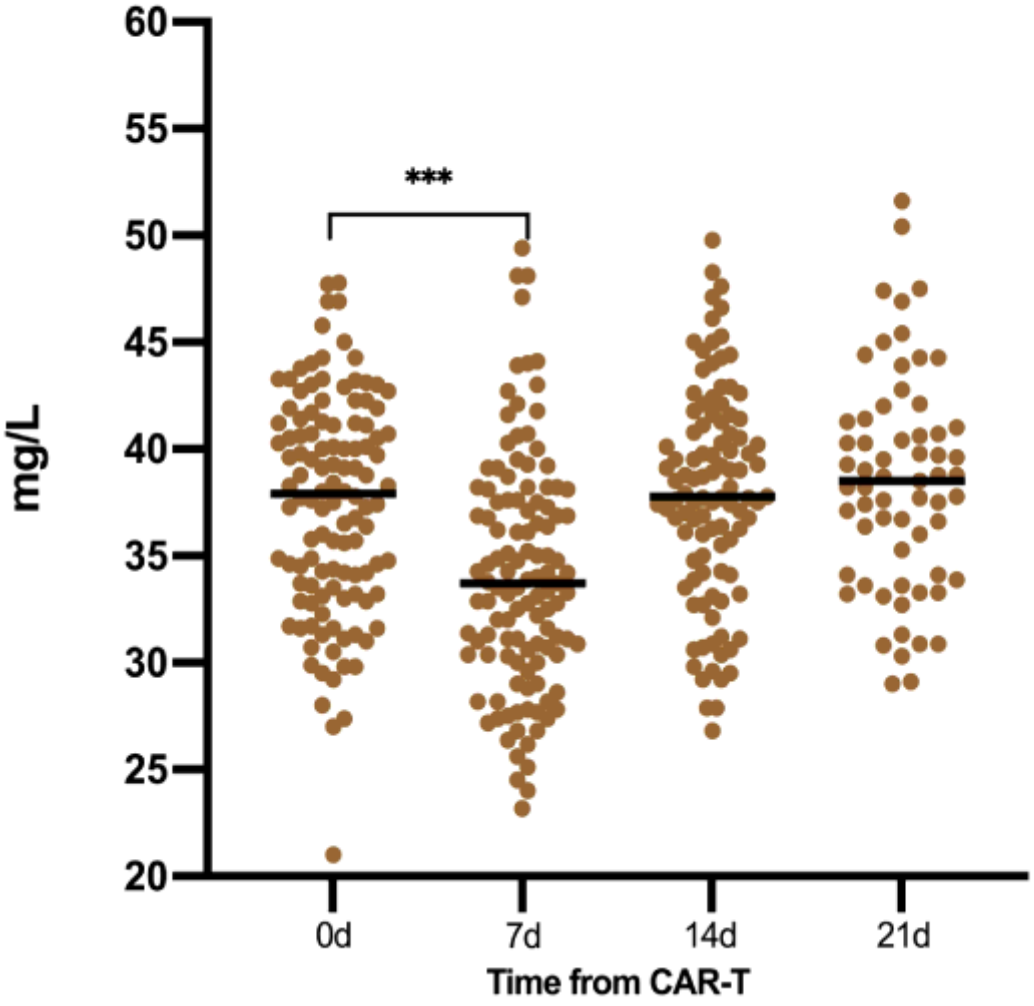

Figure 1

The albumin level at baseline and 7 days, 14 days and 21 days after CAR-T cell infusion. ***: P<0.001; **: P<0.01.

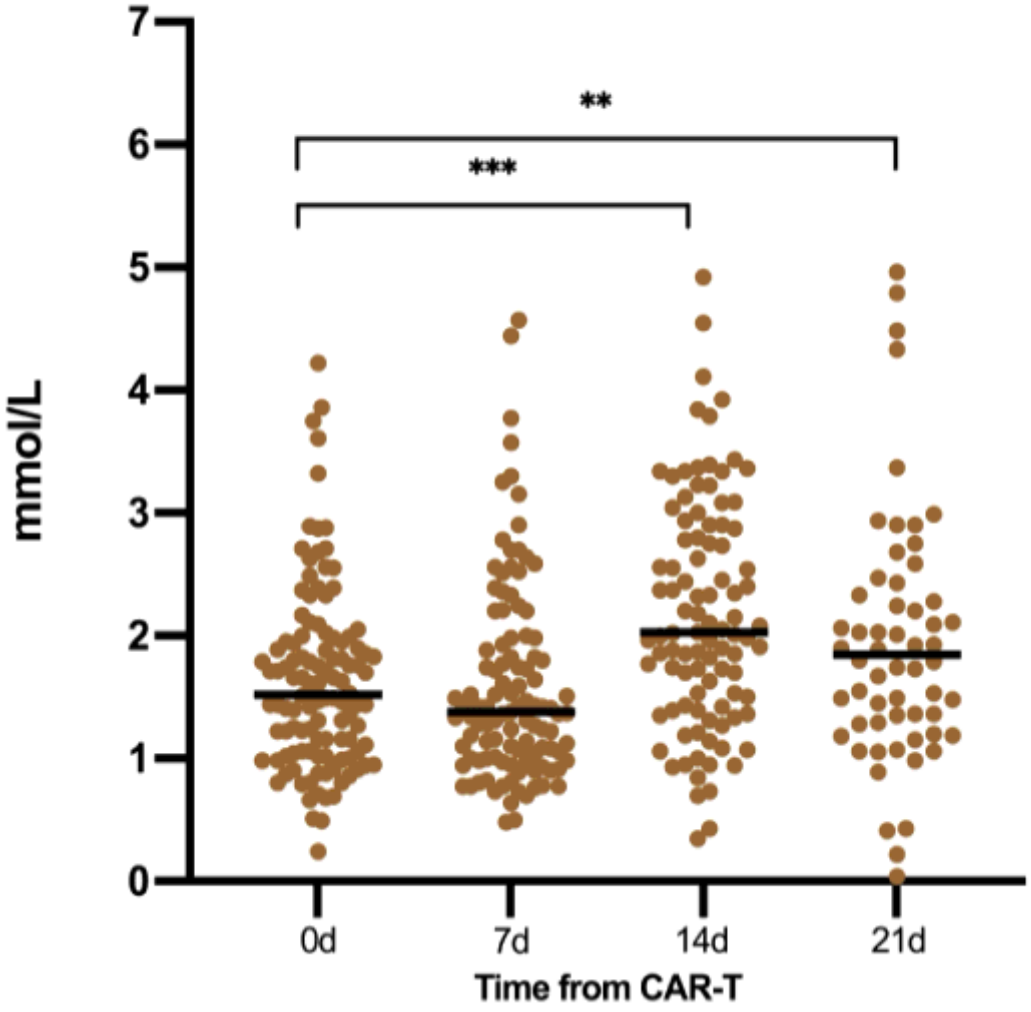

Figure 2

The total triglyceride level at baseline and 7 days, 14 days and 21 days after CAR-T cell infusion. ***: P<0.001; **: P<0.01.

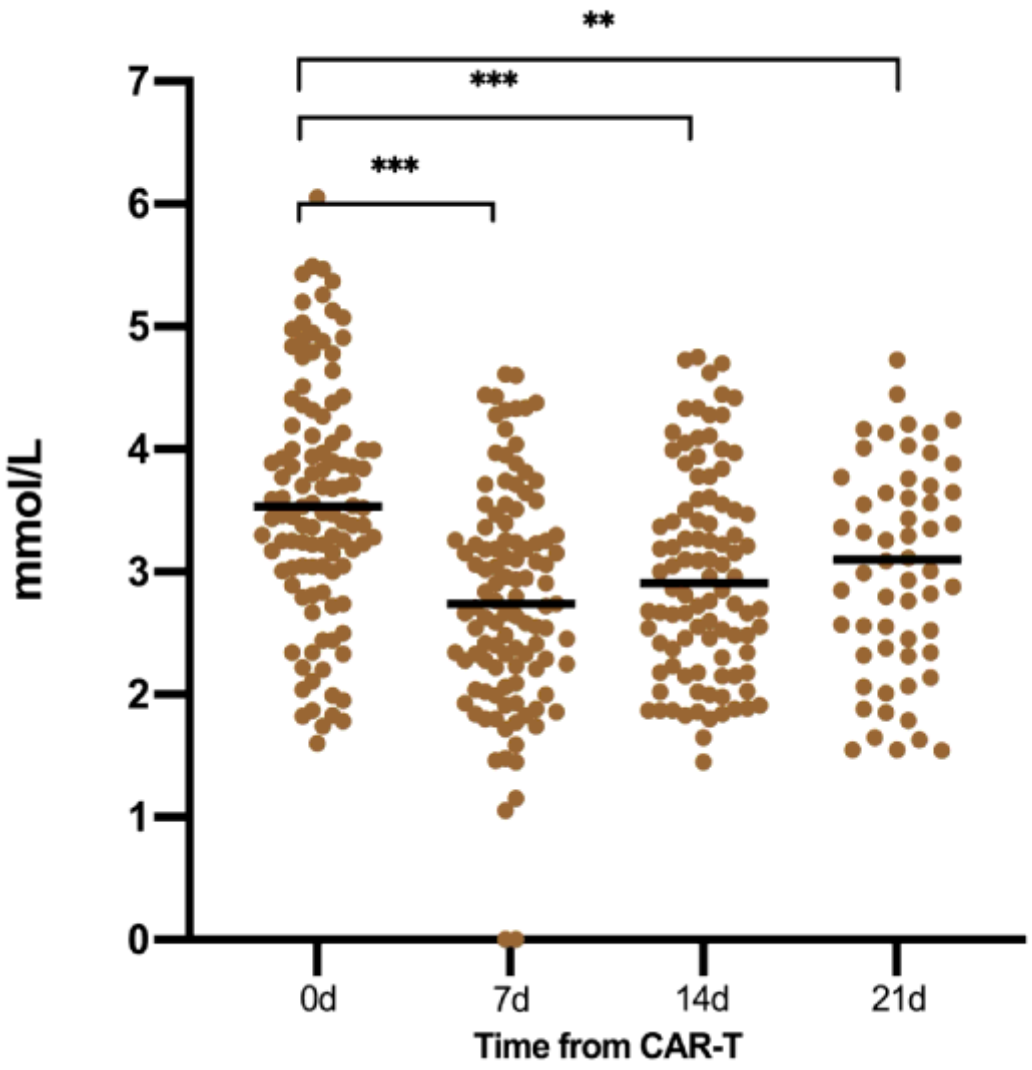

Figure 3

The total cholesterol level at baseline and 7 days, 14 days and 21 days after CAR-T cell infusion. ***: P<0.001; **: P<0.01.