

The Lancet

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--Manuscript Draft--

Manuscript Number:	THELANCET-D-20-02111
Article Type:	Article
Keywords:	coronavirus, COVID-19, lipid, cholesterol
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Manuscript Region of Origin:	CHINA
Abstract:	<p>Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel coronavirus COVID-19. Meanwhile, as the infection progressed, a large number of cases were also diagnosed in Wenzhou, China. The objective of the study is to describe the clinical laboratory features, especially lipid profile of the patients with COVID-19 infection in Wenzhou.</p> <p>Methods All cases were in a designated hospital in Wenzhou, and confirmed by positive virial nucleic acid detection through PCR assay. All clinical laboratory data were from the first test results after their admission. The unpaired t test was used for data analysis.</p> <p>Findings The absolute value of white blood cells, neutrophils and lymphocytes were lower than healthy controls ($P < 0.05$), more significantly, the patients had sharply decreased total cholesterol (TC), HDL-cholesterol and LDL-cholesterol levels ($P < 0.001$), 3.70 ± 0.09 mmol/L, 1.18 ± 0.03 mmol/L and 1.82 ± 0.08 mmol/L respectively, and increased monocyte/HDL-cholesterol ratio (0.37 ± 0.02 vs 0.28 ± 0.01 in healthy control). Among the patients, the primary infection cases showed the lower HDL-cholesterol levels (1.10 ± 0.04 mmol/L) and higher monocyte/HDL-cholesterol ratio (0.43 ± 0.03) than the secondary infection cases by person-to-person transmission ($P < 0.05$). Compared with the female patients, the male patients had higher levels of monocytes [$(0.46 \pm 0.02) \times 10^9$ /L], M/HDL-C ratio (0.44 ± 0.02), and lactate dehydrogenase (LDH, 257.6 ± 12.32 U/l).</p> <p>Interpretation Low serum cholesterol level in the patients with COVID-19 in Wenzhou, China. Altered serum cholesterol provide important information, and is meaningful to understand the disease.</p> <p>Funding Natural Science Foundation of Zhejiang Province</p>

Low Serum Cholesterol Level Among Patients with COVID-19 Infection in Wenzhou, China

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Abstract

Background A recent cluster of pneumonia cases in Wuhan, China, was caused by a novel coronavirus COVID-19. Meanwhile, as the infection progressed, a large number of cases were also diagnosed in Wenzhou, China. The objective of the study is to describe the clinical laboratory features, especially lipid profile of the patients with COVID-19 infection in Wenzhou.

Methods All cases were in a designated hospital in Wenzhou, and confirmed by positive viral nucleic acid detection through PCR assay. All clinical laboratory data were from the first test results after their admission. The unpaired t test was used for data analysis.

Findings The absolute value of white blood cells, neutrophils and lymphocytes were lower than healthy controls ($P < 0.05$), more significantly, the patients had sharply decreased total cholesterol (TC), HDL-cholesterol and LDL-cholesterol levels ($P < 0.001$), 3.70 ± 0.09 mmol/L, 1.18 ± 0.03 mmol/L and 1.82 ± 0.08 mmol/L respectively, and increased monocyte/HDL-cholesterol ratio (0.37 ± 0.02 vs 0.28 ± 0.01 in healthy control). Among the patients, the primary infection cases showed the lower HDL-cholesterol levels (1.10 ± 0.04 mmol/L) and higher monocyte/HDL-cholesterol ratio (0.43 ± 0.03) than the secondary infection cases by person-to-person transmission ($P < 0.05$). Compared with the female patients, the male patients had higher levels of monocytes [$(0.46 \pm 0.02) \times 10^9/L$], M/HDL-C ratio (0.44 ± 0.02), and lactate dehydrogenase (LDH, 257.6 ± 12.32 U/l).

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Introduction

A novel Coronavirus, COVID-19, named by WHO recently, has been identified as the causal pathogen of an ongoing epidemic. The first case was reported in last December 2019, in Wuhan, China, and now has since spread to other regions of China and other countries. Wenzhou, a city in southeast of China, also became one of the cities with COVID-19 outbreak in the past month.

COVID-19 is a new strain of coronavirus family, probably originated from bat and acquired the ability to infect humans due to genetic mutation, leading to this epidemic¹. Coronaviruses are a large family of viruses known to cause clinical symptoms ranging from the common colds to severe lung infections, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), which caused by SARS-CoV and MERS-CoV respectively. COVID-19 are enveloped, non-segmented positive-stranded RNA viruses, and known to be the pathogenic virus of Novel Coronavirus Infected Pneumonia (NCIP). As reported, the typical symptoms of the patients are persistent fever ($\geq 38^{\circ}\text{C}$), cough and short of breath. The imaging examination showed that the bilateral pneumonia, and multiple mottling and ground-glass opacity. Laboratory tests detection indicated that declined white blood cells and lymphocytes level in the patients with COVID-19 infection^{2,3}. However, there is no detailed description or assessment of lipid level in patients with COVID-19 infection, also in SARS-CoV or MERS-CoV infection.

Lipid play a key role in viral infection. The altered serum lipid levels, especially cholesterol level, have been reported to occur also during infection with viruses including human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Some proteins, such as SR-BI, a major receptor of high-density lipoprotein (HDL), were indicated to involve in HCV infection⁴. Moreover, membrane cholesterol has been indicated to be important component for the entering into host cells of pathogenic viruses⁵.

Therefore, in our current study, we want to analyze serum lipid profile of the patients with COVID-19 infection to reveal whether the viral infection cause the

changes in serum lipid. We hope our laboratory findings could be used to explain some clinical manifestations and provide the valuable information for future researches.

Method

1. Patients

We recruited 71 COVID-19-infected patients from Jan 2nd to Feb 2nd at Wenzhou Central Hospital, an admitted hospital of COVID-19-infection in Wenzhou. All cases were diagnosed according to the positive result of viral nucleic acid assay by PCR. For comparative study, we also recruited 80 age-matched healthy controls in healthy center of Wenzhou Central Hospital, excluding the subjects with dyslipidemia, diabetes, cardiovascular diseases and hypertension. Our study was authorized by Ethics Commission of Wenzhou central hospital.

2. Laboratory tests

For detecting serum lipid level, blood samples were collected from each subject after at least 12 hours of overnight fasting. Hematological parameters were analyzed on BC-5380 automatic blood cells analyzer (Mairui, China). Biochemical parameters were performed on AU5800 automatic biochemical analyzer (Beckman, USA). All laboratory assays had completed the standardization and certification program.

3. Statistical analysis

All data are expressed as the Mean \pm SEM. An unpaired t-test was used to compare results between the two groups. A *P* value of < 0.05 was determined to be significant. Statistical analyses were performed using the SPSS 17.0 statistical package and GraphPad Prime 6.

Results

1. Serum lipid levels generally decreased at the initial stage of infection

Compared with the healthy controls, the infected patients presented lower levels of

white blood cells, neutrophils and lymphocytes $(4.36\pm 0.17)\times 10^9/L$, $(3.38\pm 0.11)\times 10^9/L$ and $(2.04\pm 0.05)\times 10^9/L$ respectively ($P < 0.05$).

Meanwhile, the data showed that serum TC, HD-cholesterol and LDL-cholesterol levels in patients, which were $3.70\pm 0.09\text{mmol/L}$, $1.18\pm 0.03\text{ mmol/L}$ and $1.82\pm 0.08\text{ mmol/L}$ respectively, decreased sharply ($P < 0.001$), and monocyte/HDL-cholesterol (M/HDL-C) ratio, 0.37 ± 0.02 , was higher than 0.28 ± 0.01 in healthy control. No significant difference in other laboratory biochemical indexes were found between the two groups (Table 1).

2. More significant decline in cholesterol level in primary cases

We divided the patients into the two groups, the primary infection cases, who had been in Wuhan recently, and secondary infection cases, who had never been in Wuhan and infected by person-to-person transmission. The HDL-cholesterol results indicated that the significant lower levels, $(1.10\pm 0.04)\text{ mmol/L}$, in the primary infection cases than that, $(1.24\pm 0.04)\text{ mmol/L}$, in the secondary infection cases ($P < 0.05$). Moreover, the patients with primary infection had slightly higher level of monocytes than those with secondary infection cases. Therefore, the higher M/HDL-C ratio (0.43 ± 0.03) was found in the primary infection cases, comparing with the secondary infection groups ($P < 0.01$, Table 2). Other data showed in Table 2.

3. The changes of serum lipid are independent of gender and age

The patients were grouped by gender and age. Among the patients, the level of HDL-cholesterol in the male patients were significantly lower than that in the female patients, (1.07 ± 0.04) vs $(1.28\pm 0.05)\text{ mmol/L}$. Comparing with the female patients, the male patients had higher levels of monocytes [$(0.46\pm 0.02)\times 10^9/L$], M/HDL-C ratio (0.44 ± 0.02), and LDH ($257.6\pm 12.32\text{ U/L}$). There is no significant difference in other laboratory characteristics between the male and female patients, as well as, between the patients over and under 50 years old, even in other age groups (Table 3, Table 4 and

Supplementary data).

4. The serum lipid changes in a critically infection case

To evaluate the therapy, the blood biochemical indexes were monitored daily in a critically infection patient until she was discharged from the hospital, it was totally 16 days. As the figure 1 showed, the level of TC, HDL-cholesterol and LDL-cholesterol dropped persistently until the 9th day. With the adjustment of therapeutic regimen, the level of TC, HDL-cholesterol and LDL-cholesterol were starting recover until the 16th day, when she was discharged. Although the patient's serum cholesterol still remained low level on the day of her discharge, the TC, HDL-cholesterol and LDL-cholesterol return to high level, 5.70 mmol/L, 1.62 mmol/L and 3.24mmol/L respectively, on the 14th day after her discharge.

Discussion

To investigate the relationship between serum lipid levels and the infection in patients, we collected the first laboratory data when the patients were admitted and not treated clinically at that time. We found that serum lipid levels, especially TC, HDL-cholesterol and LDL-cholesterol in the patients with COVID-19 infection were significantly lower than the healthy controls ($P < 0.001$, Table 1). The changes were similar to those with HIV infection^{6,7}. More investigations indicate that HIV-infected patients, whether treated with antiviral therapy or not, developed dyslipidemia, which is defined hypocholesterolemia, low level LDL and hypertriglyceridemia⁸. Some study suggests that hypoalphalipoproteinemia is likely to be secondary to HIV infection itself⁹.

COVID-19 infection was firstly reported in Wuhan, and spread to other regions of China³, even other countries^{10,11}. However, both the infection rate and mortality are higher than other regions, there is no evidence to indicate whether it might be associated with the difference in the severity of primary infection and secondary infection, or not. Our data showed that HDL-cholesterol level was significantly lower in the patients with

SRAR-CoV-2 primary infection than secondary infection patients ($P < 0.05$), meanwhile, higher M/HDL-C ratio also were observed in these patients with primary infection ($P < 0.01$, Table 2). Although the main difference between the primary infection and secondary infection is serum HDL-cholesterol in the patients in our current study, more evidences are needed to reveal whether it is directly related to the severity of the viral infection. In addition, lower level of HDL-cholesterol and higher M/HDL-C ratio was found in the male patients, comparing with the female patients ($P < 0.05$ and $P < 0.01$ respectively, Table 3). The comparisons of the two series of grouped cases indicate that changes of HDL-cholesterol in patients is likely to be more sensitive to the infection than other serum lipids.

HDL mainly contains phospholipids, free cholesterol, cholesteryl ester, triglycerides, apolipoproteins (Apo A-I, Apo A-II), and other proteins. Generally, HDL is an anti-inflammatory lipoprotein with protective effects against oxidized lipids, and negatively regulates T cell activation and expression of inflammatory mediators in macrophages and dendritic cells^{12-14 15}. Whereas, during systemic inflammation HDL can be oxidized, becomes dysfunctional oxidized HDL (ox-HDL), including oxidized cholesterol^{16,17}. Oxidized HDL, and oxidized LDL, had been proved to upregulate immune activation^{18,19}.

As we know, the sharply elevated amounts of pro-inflammatory cytokines in serum of patients with COVID-19 infection indicated active systemic inflammation³. Huang et al. study suggested that the cytokine storm was associated with disease severity. They also found the increased cytokines that activate Th1 cells, i.e. IL1B, IFN γ , IP10, and MCP1, as well as increased cytokines secreted by Th2, IL4 and IL10, that suppress inflammation²⁰. In view of the immunomodulatory effects of HDL-cholesterol, we speculate that serum HDL-cholesterol was involved into the regulation of immune cells during COVID-19 infection, which might lead to the significantly dropped HDL-cholesterol level in the patients. However, it still remains to be verified by further studies to elucidate whether HDL and LDL is oxidized or not, whether they active or still negatively regulate immune cells during COVID-19 infection.

In vitro studies suggest that lipid rafts play a key role in coronavirus life cycle^{21,22}. Lipid rafts are microdomains of the eukaryote membrane, several enveloped viruses were known to contain lipid rafts on their membrane²¹. Lipid rafts contain high concentrations of cholesterol, sphingolipids, and proteins integral to signaling, protein transport, and adhesion. In the early stage of SARS-CoV entry into host cells, the spike (S) glycoprotein on SARS-CoV envelope bind to cellular receptor, angiotensin-converting enzyme 2 (ACE2)²³, localized on lipid rafts. In the case of SARS-CoV, lipid rafts could provide a platform to concentrate ACE2 as clusters on host cell membrane to anchor with the S glycoprotein efficiently²². Cholesterol on lipid rafts was proved to be required for the early stage of SARS-CoV replication and during the binding stage of SARS-CoV entering host cells²¹. Moreover, in a recent research, the findings revealed that membrane cholesterol promoted the binding and induced oligomerization of fusion peptide of SARS-CoV, which promote the entry of virions into host cells⁵. Thus, cholesterol plays an important role in viral infection, however, it is not unclear whether these changes in serum cholesterol in patients with COVID-19 are related to the fusion of virion with host cells and internalization.

Additionally, we monitored one of patient who was a female primary infection. As Figure 1 show, the changing curves of serum TC, HCL-cholesterol and LDL-cholesterol in the patient are similar. They all showed that cholesterol level continued to drop during the first few days of patient`s hospitalization, then gradually rose until she was discharged. Furthermore, on the 14th day after her discharge, the serum lipid returns to higher level. Taken together the clinical manifestations, the lipid changes indirectly indicate the effectiveness of the treatment regimens.

In a study in 2017²⁴, serum metabolomic analyses was performed in 25 recovered SARA patients 12 years after infection. Their data showed that the significantly higher level of TG and very low-density lipoprotein (VLDL) cholesterol than healthy controls. Similarly, some studies suggested that antiviral therapies caused severe dyslipidemia in HIV-infected patients⁶⁻⁸, as well abnormal serum lipid profile in HCV patient²⁵, which may contribute to cardiovascular diseases in the patients. Although there are no effective antiviral therapies until now, the specific antiviral drugs are currently

developing. Considering the life quality of the recovered patients, it is recommended to monitor serum lipid profile of COVID-19-infected patients during antiviral therapy.

Our study has several limitations: no information is available regarding COVID-19 viral load, or the life cycle of this novel virus. We also are unable to determine the activation of monocytes and T cells in peripheral blood. Moreover, the locality of the cases, mostly in Wenzhou, limit our study. We expect more reports and cases description from other regions to understand the disease.

Taken together, cholesterol play an essential role in not only virial replication, internalization, but also immune activation. Significant declined the serum cholesterol level of patients provide us important information for us to understand the COVID-19 infection, and also meaningful for future investigation.

Declaration of interests

We declare no competing interests.

Acknowledgement

This work is funded by Natural Science Foundation of Zhejiang Province (LQ18H020005).

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Figure 1 Serum cholesterol profile in a critically infection case

Table 1 Hematological parameters and serum lipid level in patients and healthy controls

Parameters		Control	Patients	<i>P</i> value
Gender	Male	n=42	n=38	
	Female	n=38	n=33	
Age (yr)		47.03±1.44	46.33±1.56	0.743
WBC (×10 ⁹ /L)		5.98±0.14	4.36±0.17	< 0.001
NE (×10 ⁹ /L)		3.38±0.11	2.95±0.15	< 0.05
LY (×10 ⁹ /L)		2.04±0.05	0.98±0.04	< 0.001
MNC (×10 ⁹ /L)		0.40±0.01	0.42±0.02	0.311
TG (mmol/L)		1.18±0.06	1.30±0.06	0.170
TC (mmol/L)		4.91±0.10	3.70±0.09	< 0.001
HDL cholesterol (mmol/L)		1.47±0.03	1.18±0.03	< 0.001
LDL cholesterol (mmol/L)		3.09±0.08	1.82±0.08	< 0.001
M/HDL-C ratio		0.28±0.01	0.37±0.02	< 0.001
TC/HDL-C ratio		3.41±0.09	3.24±0.09	0.174

WBC: white blood cell; NE: neutrophil; LY: lymphocyte; MNC: mononuclear; TG: triglyceride; TC: total cholesterol; HDL: high-density lipidprotein; LDL: low-density lipidprotein.

Table 2 Hematological parameters and lipid level in primary infection cases and secondary infection cases

Parameters	Primary infection cases (n=32)	Secondary infection cases (n=39)	<i>P</i> value
WBC ($\times 10^9/L$)	4.25 \pm 0.28	4.44 \pm 0.21	0.576
NE ($\times 10^9/L$)	2.98 \pm 0.26	2.92 \pm 0.17	0.827
LY ($\times 10^9/L$)	0.87 \pm 0.06	1.08 \pm 0.06	< 0.05
MNC ($\times 10^9/L$)	0.46 \pm 0.03	0.39 \pm 0.02	< 0.05
TG (mmol/L)	1.32 \pm 0.11	1.28 \pm 0.07	0.731
TC (mmol/L)	3.60 \pm 0.14	3.79 \pm 0.12	0.332
HDL cholesterol (mmol/L)	1.10 \pm 0.04	1.24 \pm 0.04	< 0.05
LDL cholesterol (mmol/L)	1.67 \pm 0.10	1.94 \pm 0.11	0.090
M/HDL-C ratio	0.43 \pm 0.03	0.33 \pm 0.02	< 0.01
TC/HDL-C ratio	3.37 \pm 0.16	3.13 \pm 0.11	0.204
CRP (mg/L)	24.61 \pm 3.56	26.62 \pm 4.45	0.733
LDH (U/L)	239.8 \pm 14.44	238.0 \pm 12.07	0.923

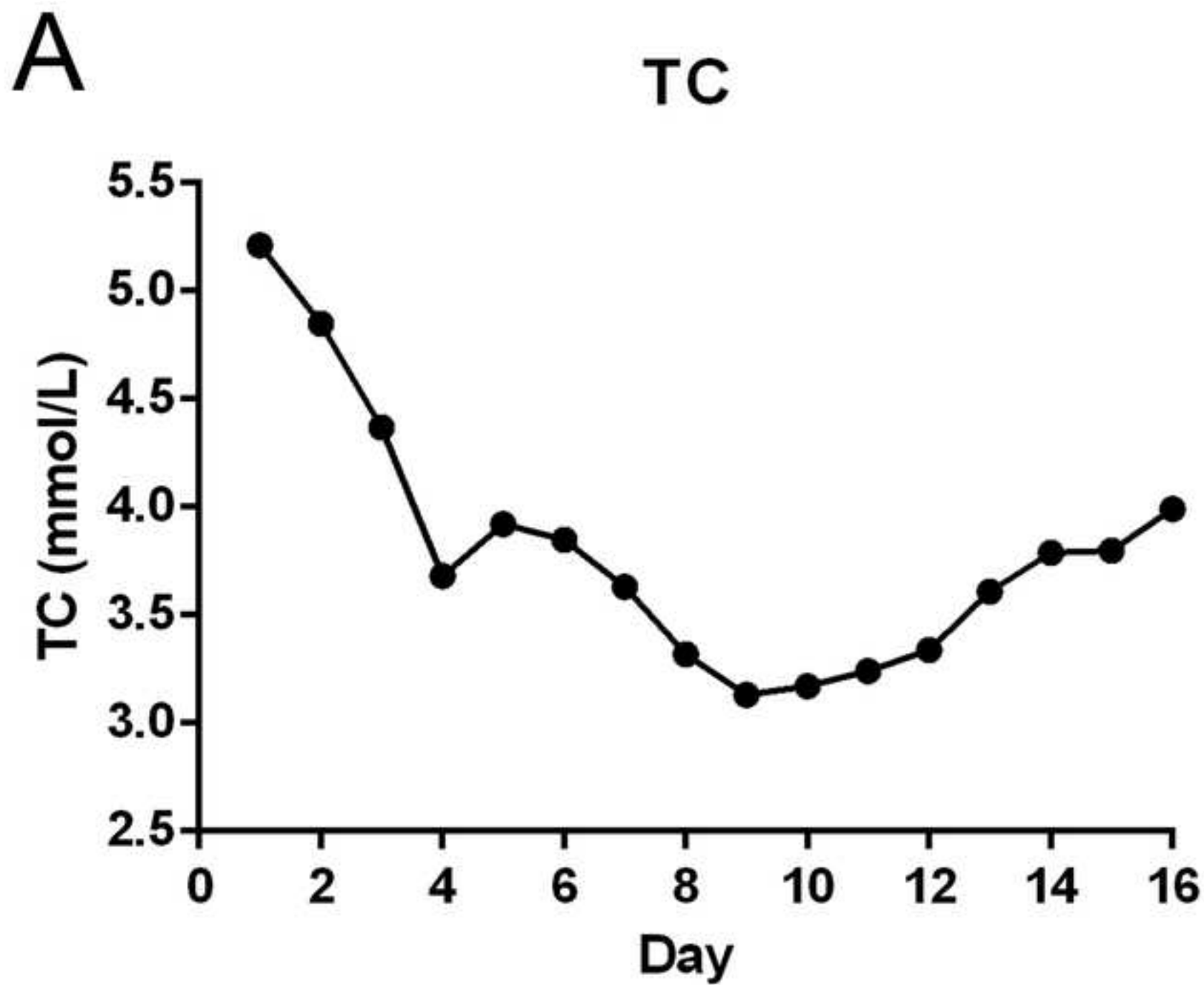
LDH, lactate dehydrogenase

Table 3 Hematological parameters and lipid level in male and female patients

Parameters	Male (n=38)	Female (n=33)	<i>P</i> value
WBC ($\times 10^9/L$)	4.33 \pm 0.24	4.38 \pm 0.25	0.900
NE ($\times 10^9/L$)	2.91 \pm 0.21	2.98 \pm 0.22	0.820
LY ($\times 10^9/L$)	0.97 \pm 0.06	1.01 \pm 0.06	0.657
MNC ($\times 10^9/L$)	0.46 \pm 0.02	0.37 \pm 0.02	< 0.01
TG (mmol/L)	1.39 \pm 0.08	1.19 \pm 0.09	0.108
TC (mmol/L)	3.63 \pm 0.12	3.79 \pm 0.14	0.400
HDL-cholesterol (mmol/L)	1.07 \pm 0.04	1.28 \pm 0.05	< 0.01
LDL-cholesterol (mmol/L)	1.74 \pm 0.10	1.91 \pm 0.12	0.290
M/HDL-C ratio	0.44 \pm 0.02	0.30 \pm 0.02	< 0.001
TC/HDL-C ratio	3.43 \pm 0.14	3.01 \pm 0.11	0.023
CRP (mg/L)	30.87 \pm 4.02	19.78 \pm 4.03	0.057
LDH(U/L)	257.6 \pm 12.32	217.2 \pm 13.08	< 0.05

Table 4 Hematological parameters and lipid level in the patients age above and under 50 year

Parameters	< 50 (n=40)	≥50 (n=31)	<i>P</i> value
WBC ($\times 10^9/L$)	4.26±0.23	4.48±0.26	0.537
NE ($\times 10^9/L$)	2.80±0.17	3.13±0.26	0.280
LY ($\times 10^9/L$)	0.99±0.05	0.98±0.08	0.890
MNC ($\times 10^9/L$)	0.40±0.02	0.45±0.03	0.131
TG (mmol/L)	1.26±0.07	1.35±0.11	0.476
TC (mmol/L)	3.66±0.11	3.77±0.16	0.556
HDL-cholesterol (mmol/L)	1.19±0.04	1.17±0.05	0.758
LDL-cholesterol (mmol/L)	1.83±0.10	1.81±0.12	0.898
M/HDL-C ratio	0.36±0.02	0.40±0.03	0.210
CRP (mg/L)	21.95±3.21	30.57±5.15	0.142
LDH(U/L)	222.6±11.18	259.8±14.80	< 0.05



B**HDL-cholesterol**