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ORIGINAL ARTICLE

The Clinical Application Value of Blood Lipid Levels in Multiple Myeloma

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SUMMARY

Background: **This study aimed to investigate the significance of serum lipid concentration in patients with multiple myeloma (MM) at different clinical stages and types, and the relationship between the change of serum lipid concentration before and after treatment, and to evaluate the application value of serum lipid index in MM disease.**
Methods: **Retrospectively, 130 patients who visited Shaoxing People's Hospital from July 2022 through July 2024, diagnosed with MM and meeting the inclusion criteria, were collected as the MM group. Additionally, 130 healthy individuals were collected as the NMM group. The study examined indicators such as triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) in both groups.**
Results: **Statistical analysis showed that TG, TC, HDL, and LDL concentrations in the MM group were lower than those in the NMM group ($p < 0.05$). In ISS staging, TC, LDL, and HDL concentrations were higher in stage I patients than in stage II and III patients, with a statistically significant difference ($p < 0.05$), and the difference in TG concentrations was statistically nonsignificant ($p > 0.05$). Among the common clinical subtypes, the TC and LDL concentrations of patients with light chain type were higher than those of patients with IgG type and IgA type, and the difference was statistically significant ($p < 0.05$); the TC and LDL concentrations of patients with IgG type were higher than those of patients with IgA type, and the difference was statistically significant ($p < 0.05$); and the differences between the different subtypes of the rest of the indicators were statistically nonsignificant ($p > 0.05$). In the remission group, MM patients showed increased TC, TG, HDL, and LDL concentrations after treatment compared to before, with statistically significant differences.**
Conclusions: **The serum TG, TC, HDL, and LDL concentrations of MM patients were lower than those of normal controls. The serum TC, HDL, and LDL concentrations of MM patients negatively correlated with the clinical stage of the disease (ISS stage), suggesting that the concentration of blood lipid can be used as a reference index for the clinical stage of multiple myeloma. Serum lipid indicators showed statistically significant differences among different protein subtypes (IgA, IgG, light chain type) in MM, indicating that combining lipid concentrations with MM clinical staging can help assess the progression of the disease. In the remission group, serum lipid concentrations in MM patients increased after treatment, which is significant for the monitoring of treatment efficacy in MM.**
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KEYWORDS

multiple myeloma, lipid concentration, clinical staging, different M protein types

INTRODUCTION

Multiple myeloma (multiple myeloma, MM) is the second most common malignancy of the hematological system, with an increasing incidence worldwide [1]. MM is a malignant tumor involving plasma cells (clonal plasma cells, PC), typically characterized by the presence of monoclonal immunoglobulin (M protein, the hallmark of MM). It is defined as having ≥ 10% clonal plasma cells in the bone marrow (or a plasma cell neoplasm confirmed by biopsy). The typical clinical symptoms are "CRAB" (hypercalcemia, renal insufficiency, anemia, and osteolytic lesions) [2]. Despite the emergence of more effective treatments over the past two decades, which have significantly extended the survival of MM patients, the disease remains incurable. This is because most patients experience recurrence or develop refractory conditions, severely impacting their quality of life [3]. It is well known that the clinical course of MM depends not only on the tumor potential of the clone but also on the tumor (usually bone marrow) microenvironment. Bone marrow adipocytes (bone marrow adipocytes, BMA) occupy 70% of the volume of the bone marrow microenvironment and have been recognized as an important component of the tumor microenvironment. Recent studies have shown that myeloma cells interact with bone marrow adipocytes and are intricately linked to MM development [4].

In recent years, the role of lipids in malignant neoplastic diseases has received increasing attention, as scholars have studied lipids in depth. Increasing evidence suggests that dysregulation of lipid metabolism plays a key role in various malignant tumors, including MM [5,6]. In MM patients, total cholesterol (total cholesterol, TC), high-density lipoprotein cholesterol (high-density lipoprotein cholesterol, HDL), and low-density cholesterol (low-density lipoprotein cholesterol, LDL) concentrations are significantly lower and can be used as an auxiliary diagnostic and prognostic markers of MM [7,8]. Although the relationship and correlation between blood lipid and MM have been paid more and more attention in recent years [9,10] and some achievements have been made in its clinical and basic research [11], the relationship between lipids and various clinical prognostic stages and risk stratification remains to be elucidated. In view of this, the study of the relationship between lipid indices and clinical staging may not only contribute to the clinical assessment of prognostic value but also contribute to a more in-depth understanding of the mechanism of tumorigenesis in MM. Therefore, the aim of the present study was to evaluate the application value of lipid indices in MM disease staging and survival prognosis assessment to serve the auxiliary diagnosis of MM.

MATERIALS AND METHODS

Objects of study

Basic information and clinical data were collected from 130 cases of multiple myeloma patients who first visited Shaoxing People's Hospital from July 2022 through July 2024 and met the inclusion criteria, including 78 men and 52 women. At the same time, 130 healthy people with age, gender, and body mass index (body mass index, BMI) matched with MM patients and without hyperlipidemia were included as normal control group.

Inclusion criteria: 1) The patient is initially diagnosed with multiple myeloma or relapsed after diagnosis; bone marrow smear and bone marrow biopsy indicate that the proportion of myeloma cells is greater than or equal to 10%; or confirmed plasmacytoma by biopsy of bone-related lesions (such as lytic destructive lesions, pathological fracture sites) or extramedullary tissues (such as liver, spleen, lymph nodes, soft tissues, etc.) (reference to "Chinese Guidelines for the Diagnosis and Treatment of Multiple Myeloma (2024 Revision)"). 2) Patients had not been treated with antitumor therapy prior to the diagnosis; they had been tested for lipids, and there were complete relevant clinical data. 3) The selected study subjects were those who had complete data of all assessment indexes and stable vital signs.

Exclusion criteria: 1) Abnormal thyroid function, including hyperthyroidism and hypothyroidism. 2) Nephrotic syndrome or proteinuria (urinary protein excretion > 0.5 g/24 hours). 3) Malnutrition (BMI < 18) or obesity status (BMI > 24). 4) Suffering from familial hyperlipidemia or taking medications affecting lipid metabolism (cholestatic metabolism). 5) Comorbidity with other malignancy or hematologic disease. 6) Diagnosis of unknown significance, such as smoldering multiple myeloma, primary amyloidosis, or isolated extramedullary plasmacytoma.

Research subgroups

The MM patients and the physically healthy population were divided into MM and NMM groups, and the patients within the MM group were further divided into ISS-I stage group, ISS-II stage group, and ISS-III stage group (Table 1). Patients within the MM group were categorized into IgA-type, IgG-type, and light chain-type based on M protein type.

Data collection

General information of the patients was collected, such as age, gender, laboratory test results, and past medical history and medication. Lipid indexes included TG (triglyceride, TG), TC, HDL, and LDL, and the values of each index were collected from the results of patients' whole blood biochemistry examination. Blood samples were collected twice; the first time was when the patient was admitted to the hospital after diagnosis and the sec-

ond time was after the patient reached the clinical discharge standard after clinical treatment. The blood specimens were collected with a strict fast for at least 8 hours. After centrifugation, the blood lipid concentration of the collected whole blood sample was measured. The data collected in this study have been approved by the Ethics Committee of Shaoxing People's Hospital. The reference ranges of normal lipid concentrations were as follows: total cholesterol TC ≤ 5.2 mmol/L, triglyceride TG ≤ 1.7 mmol/L, high-density lipoprotein (HDL) cholesterol HDL ≥ 1.1 mmol/L, and low-density lipoprotein (LDL) cholesterol LDL < 3.4 mmol/L.

Instruments and reagents

Instrument: the automatic biochemical analyzer (Beckman Coulter AU 5800) is used for quantitative detection and quantitative analysis.

Reagents: the kit for triglyceride, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol was provided by Meikang Biology.

Statistical analysis

Data were statistically analyzed using GraphPad Prism 10 software, and the Shapiro-Wilk test was applied to determine whether the data conformed to normal distribution. Measurement data conforming to normal distribution were expressed as mean ± standard deviation ($\bar{x} \pm s$), an independent samples *t*-test was used for comparison between two groups, and one-way analysis of variance (ANOVA) was used for comparison between multiple groups; measurement data with skewed distribution was expressed as median (P25, P75) and non-parametric rank-sum test was chosen. $p < 0.05$ was considered a statistically significant difference.

RESULTS

Comparison of lipid concentration in MM patients of different ages before treatment

The 130 patients with MM were age-segmented: 17 (13.08%) patients were 40 - 49 years old, 43 (33.8%) patients were 50 - 59 years old, 56 (43.08%) patients were 60 - 69 years old, and 14 (10.77%) patients were 70 - 79 years old. The lipid concentrations of patients in different age groups were compared, and the results showed that the serum TG concentration ($t = 6.439$, $p < 0.0001$) and HDL concentration ($t = 4.214$, $p < 0.0001$) of MM patients were statistically significant in some age groups. There was no statistically significant difference between TC concentration and LDL concentration of patients with MM in terms of age ($p > 0.05$) (Table 2).

Comparison of lipid concentrations between MM group and NMM group before treatment

Comparative analysis of lipid concentrations in the MM group and the NMM group showed that serum TG concentration ($t = 6.439$, $p < 0.001$), TC concentration ($t = 9.404$, $p < 0.001$), HDL concentration ($t = 4.214$, $p < 0.001$), and LDL concentration ($t = 2.584$, $p < 0.05$) were lower than those of the normal control group, and the differences were statistically significant (Figure 1).

Comparison of lipid concentrations in MM patients with different clinical stages

The 130 patients with MM were staged according to ISS staging: 43 (33.08%) patients with stage I, 62 (47.69%) patients with stage II, and 25 (19.23%) patients with stage III. Lipid concentrations of patients with different ISS staging were analyzed, and the results showed that the TC, HDL, and LDL concentrations were higher in patients in stage I than in patients in stages II and III. The difference was statistically significant ($p < 0.05$); however, the difference was statistically nonsignificant when comparing patients in stages II and III ($p > 0.05$). Also, the differences in TG concentration among the three stages were not statistically significant ($p > 0.05$) (Table 3).

Comparison of lipid concentrations in MM patients with different M protein types

The 130 MM patients were typed according to M protein type: 34 (26.15%) patients with IgA type, 73 (56.15%) patients with IgG type, and 23 (17.69%) patients with light chain type. Lipid concentrations of MM patients with different M protein types were analyzed, and the results showed that the TC and LDL concentrations of patients with light chain type were higher than those of patients with IgG type and IgA type, and the difference was statistically significant ($p < 0.05$); the TC and LDL concentrations of patients with IgG type were higher than those of patients with IgA type, and the difference was statistically significant ($p < 0.05$); and the difference between the remaining indicators of the different types was statistically nonsignificant ($p > 0.05$) (Table 4).

Comparison of lipid concentrations before and after treatment in MM patients in the relief group

After treatment, 130 MM patients were divided into remission and non-remission groups based on whether they met the clinical discharge criteria (including complete remission, very good partial remission, and partial remission). Among them, 112 patients were in the remission group and 18 patients were in the non-remission group. The results showed that after treatment, the concentrations of TC, TG, HDL, and LDL in the remission group increased compared to before treatment, with statistically significant differences (Figure 1).

Relief-related indicators after treatment of MM patients:

Complete remission (complete remission, CR)

Negative for serum and urine immunofixation electrophoresis, disappearance of soft tissue plasmacytoma, and plasmacytes in the bone marrow < 5%; for patients who rely solely on serum FLC levels to measure lesions, in addition to meeting the abovementioned CR

Table 1. International Staging System (International Staging System, ISS) staging criteria [12].

Installments	International Staging System (ISS) standards
ISS-I	Serum beta$_2$ microglobulin level < 3.5 mg/L and serum albumin level > 3.5 g/L
ISS-II	Patients not eligible for stage I and stage III
ISS-III	Serum beta$_2$ microglobulin levels > 5.5 mg/L

Table 2. Comparison of lipid concentration in MM patients of different ages before treatment.

Blood lipid	40 - 49 years (n = 17)	50 - 59 years (n = 43)	60 - 69 years (n = 56)	70 - 79 years (n = 14)	p-value
TG (mmol/L)	1.66 (0.74, 2.13)	0.97 (0.64, 1.68)	1.23 (0.66, 1.97)	0.88 (0.61, 1.64)	p = 0.0103
TC (mmol/L)	3.44 ± 0.91	3.46 ± 0.93	3.69 ± 0.95	3.15 ± 0.79	p = 0.0579
HDL (mmol/L)	1.17 ± 0.24	1.15 ± 0.29	1.08 ± 0.23	0.91 ± 0.16	p = 0.0154
LDL (mmol/L)	2.18 ± 0.51	2.14 ± 0.57	2.24 ± 0.46	2.55 ± 0.24	p = 0.3268

Table 3. Comparison of lipid concentrations in MM patients with different ISS stages.

Blood lipid	ISS I (n = 43)	ISS II (n = 62)	ISS III (n = 25)	p-value (I vs. II)	p-value (I vs. III)	p-value (II vs. III)
TG (mmol/L)	1.31 (0.68, 2.13)	0.93 (0.61, 1.58)	1.14 (0.72, 1.64)	p = 0.0576	p = 0.0829	p = 0.1013
TC (mmol/L)	4.16 ± 0.98	3.31 ± 0.84	3.09 ± 0.67	p = 0.0036	p = 0.0005	p = 0.1090
HDL (mmol/L)	1.22 ± 0.21	0.99 ± 0.25	1.07 ± 0.26	p = 0.0003	p = 0.0131	p = 0.3125
LDL (mmol/L)	2.46 ± 0.45	2.19 ± 0.43	1.97 ± 0.54	p = 0.0027	p = 0.0002	p = 0.0593

Table 4. Comparison of lipid concentrations in MM patients with different M protein types.

Blood lipid	TG (mmol/L)	TC (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
IgA (n = 43)	0.86 (0.63, 1.48)	3.06 ± 0.72	1.04 ± 0.19	2.10±0.52
IgG (n = 62)	1.10 (0.68, 1.66)	3.43 ± 0.81	1.12 ± 0.27	2.20 ± 0.43
Light chain (n = 25)	1.27 (0.81, 2.07)	4.53 ± 0.85	1.09 ± 0.31	2.55 ± 0.55
p-value (IgA vs. IgG)	p = 0.1444	p = 0.0226	p = 0.0941	p = 0.0288
p-value (IgA vs. Light chain)	p = 0.0648	p < 0.0001	p = 0.3661	p = 0.0026
p-value (IgG vs. Light chain)	p = 0.2793	p < 0.0001	p = 0.7007	p = 0.0020

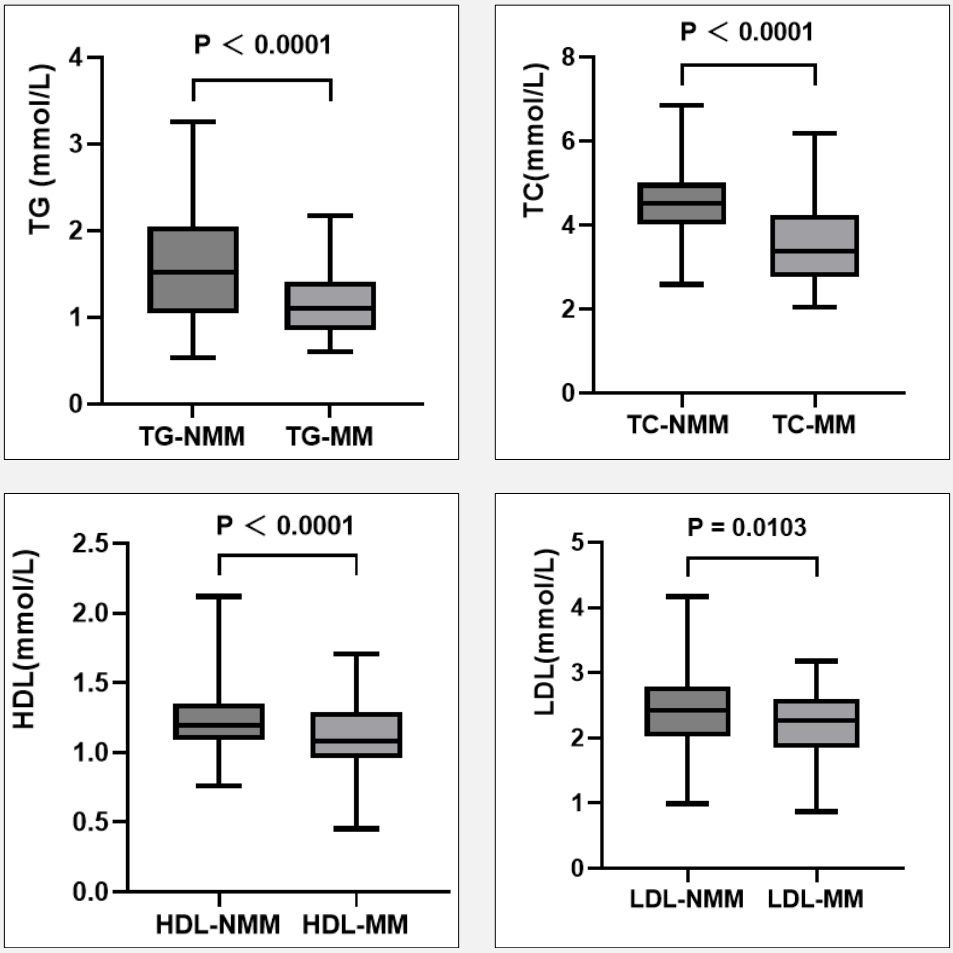

Figure 1. Comparison of lipid concentrations between MM and NMM groups before treatment.

criteria, it is also required that the ratio of serum FLC returns to normal in two consecutive assessments. Note that the use of daratumumab may interfere with the determination of IgG kappa-type CR.

Very good partial remission (very good partial remission, VGPR)

No M protein detected by serum protein electrophoresis, but positive for serum and urine immunofixation electrophoresis; or M protein reduced by ≥ 90%, with urinary M protein < 100 mg/24 hours; in patients who rely solely on serum FLC as a measure of disease, in addition to meeting the abovementioned VGPR criteria, it is also required that the difference between two consecutive serum FLC values of affected and unaffected sites be reduced by > 90%.

Partial remission (partial remission, PR)

1) Serum M protein decreased by more than 50%, 24-hour urine M protein decreased by more than 90% or decreased to < 200 mg/24 hours.
2) If M protein cannot be detected in serum and urine, the difference between affected and unaffected serum FLC should be reduced by at least 50%.
3) If serum and urine M protein and serum FLC are not measurable and the baseline bone marrow plasma cell proportion is greater than or equal to 30%, then the number of plasma cells in bone marrow should be reduced by more than 50%.
4) In addition to the aforementioned criteria, if there is a soft tissue plasmacytoma at baseline, it is required that the sum of the maximum vertical diameters of measurable lesions decreases by ≥ 50%. Both serum and urine M protein levels must be assessed twice consecutively, with no evidence of new bone lesions or progression of existing bone lesions.

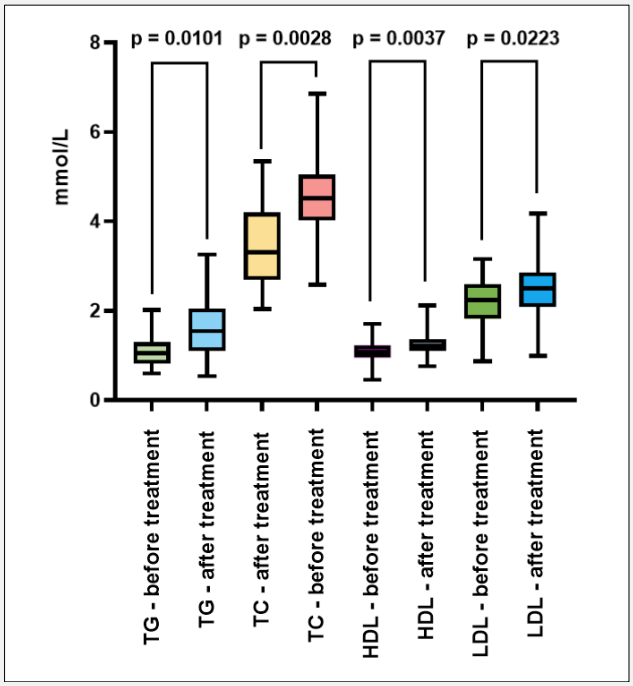

Figure 2. Comparison of lipid concentrations before and after treatment in MM patients in the relief group.

DISCUSSION

In this study, we explored the close association between multiple myeloma and serum lipid concentrations and investigated the significance of TG, TC, HDL, and LDL concentrations in different clinical stages and subtypes and the changes of MM patients lipid concentration before and after treatment, which can help to assess the value of serum lipid indices in MM disease.

Currently, the diagnosis of MM patients includes serum electrophoresis, blood calcium, immunoglobulins, free light chains, imaging, renal function, bone marrow smears, and biopsy of plasma cells, as well as common MM prognostic evaluation systems used in clinical practice. Despite this, the prognosis of MM patients is highly variable and precise stratification systems for their prognosis are still under continuous research and exploration. Lipid concentrations can reflect the metabolic state of lipids in the body; commonly referred to as lipids, these primarily include TC, TG, HDL, and LDL. Initially, attention to lipids was mainly focused on their application in cardiovascular diseases. In recent years, with deeper research into lipids, their role in cancer has received increasing attention. Abnormally proliferating tumor cells not only consume large amounts of lipids but also disrupt lipid metabolism, leading to a state of reduced lipid concentrations. Given the importance of metabolic disorders in MM patients and the practicality of predicting prognosis, studying the prognostic value of various lipid indicators may not only aid clinical decision-making but also contribute to a deeper understanding of tumor development in MM. Therefore, this study aimed to evaluate the application value of various lipid indicators in the staging and typing of MM, providing new insights for clinical diagnosis and treatment.

By studying serum lipid concentrations, we found that in MM patients the differences in TG and HDL concentrations were statistically significant in some age groups, while the differences in TC and LDL concentrations were statistically nonsignificant. The TG, TC, HDL, and LDL concentrations in the MM group were lower than those in the NMM group, which is basically in line with the literature [8] and with other hematologic neoplasms, suggesting an association between lipid concentrations and multiple myeloma [13,14]. Whether lipid variability can act as a risk factor for MM has not yet been proven. Based on the data published to date, lipid metabolism may influence the development of MM. However, it is not clear whether abnormal lipid metabolism causes MM or whether MM causes abnormal lipid metabolism.

We believe that the decrease in TC may be due to the fact that almost all of the increased TP is derived from

abnormal globulins secreted by proliferating myeloma cells, which need to consume a large amount of nutrients such as albumin and cholesterol to proliferate, resulting in a significant decrease in the concentrations of TC. The reason for the decrease in TG may be that when the malignant degree of tumor cells is increased, the proliferative and metastatic abilities of the tumor cells are also enhanced, and the demand for and uptake of cholesterol increases, leading to a decrease in peripheral blood cholesterol concentrations. It was confirmed in a large cohort study in Choi that lower lipoprotein concentrations are associated with an increased risk of developing MM [5]. In addition, the decrease of cholesterol in MM patients may be due to the consumption of cholesterol by its participation in the composition and function of cell membranes in proliferating myeloma cells, as well as the redistribution of serum cholesterol in the body [15]. The decrease in HDL concentrations may be due to the fact that HDL is the most ApoE-containing lipoprotein, whereas aberrant globular hyperplasia consumes a large amount of albumin, which decreases the synthesized ApoE, thus causing the low serum concentrations of HDL. On the other hand, MM cells can also autocrine or stimulate the bone marrow MSC pathway to secrete a number of cytokines, among which interleukin 6 (interleukin-6, IL-6) can alter the activity of TG lipase, which in turn affects HDL metabolism, resulting in a decrease in the concentration of HDL in the organism. Therefore, low HDL concentrations may also be the result of a precancerous state. The association of low HDL with an increased risk of plasma cell neoplasia suggests that HDL may be critical in regulating the homeostasis of the hematopoietic system and its proliferation, and that low concentrations of HDL may increase malignant development. The low LDL plasma concentrations observed in MM patients may be a result of increased LDL uptake by myeloma cells [16].

The results of ISS staging analysis showed that there were differences in TC, HDL, and LDL concentrations between different ISS stages and no differences in TG between different stages. Stage II and III patients had lower serum TC, HDL, and LDL concentrations than stage I patients, suggesting that lipid concentrations were higher in early-stage than in late-stage patients with early MM and that lipid concentrations can be used to some extent to guide disease staging.

The results of M protein typing analysis showed that the TC and LDL concentrations of light chain type MM patients were significantly higher than those of IgG and IgA type patients, and the TC and LDL concentrations of IgG type patients were significantly higher than those of IgA type patients, while the rest of the lipid-related indexes did not show statistically significant differences between different classes of MM. This may be due to the fact that light chain type MM tumor cells have the lowest degree of differentiation and proliferate rapidly, thus affecting lipid metabolism, suggesting that there are differences in lipid concentrations between MM patients of different types, and that lipid concentrations can be used as an auxiliary means of MM typing.

In addition, it has been documented that the lipid-lowering drug statin shows some therapeutic effect in MM patients [17], which involves a new pathway of fatty acid catabolism and uptake by adipocytes induced by myeloma cells [18,19]. Fatty acids are responsible for stabilizing cell membranes and are an important component of long-term energy reserves, and fatty acids from myeloid adipocytes can maintain the survival and proliferation of myeloma cells. Myeloma cells also increase fatty acid-binding proteins (fatty acid-binding proteins, FABP), which may promote tumor growth, implying that blocking the uptake of free fatty acids by myeloma cells could serve as a potential target for myeloma therapy [20].

Overall, with the research on MM, lipid concentrations have become an increasingly important indicator. By triggering abnormalities in lipid metabolism, not only does it directly affect the function of bone marrow adipocytes, but it may also accelerate the pathologic progression of MM. However, more large-scale studies are needed to validate our findings and to further clarify the exact mechanism of the role of serum lipid concentration in the pathophysiology of MM. The present study analyzed the clinical significance of serum lipid concentration in patients with MM, providing a new perspective to explore the relationship between MM and serum lipid concentration as well as efficacy monitoring. In MM patients, serum lipids can serve as an indicator of disease activity. Therefore, combining changes in lipid concentration with the clinical staging and typing of multiple myeloma helps to monitor disease progression.

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Declaration of Interest:
All authors declare that they have no competing interests.

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