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The Impact of Four Types of Cholesterol Binding on Cognitive Function

Yufan Nan

Guangdong Pharmaceutical University, Guangzhou 510006, China;

Abstract. Background: Cognitive impairment has been linked to dyslipidemia. Nevertheless, the precise mechanisms through which triglycerides (TG), LDL-C, HDL-C, and TC influence cognitive function remain unclear. **Objectives:** This study investigates the relationship between blood lipid levels and cognitive function in a cohort of adults. **Methods:** Five thousand patients (65.4 ±12.3 years of age) were studied in a longitudinal study. Cognitive outcomes in the intensive care unit (ICU) were associated with baseline Glasgow Coma Scale (GCS) scores and serum lipid levels. Linear regression models were applied to study the relationship of cholesterol and GCS scores. **Results:** The Findings indicated there was a direct positive relationship of TC and LDL-C while a direct positive relationship of HDL-C with positive cognitive outcome scores, which form of GCS scores. Instead, sources of high TGs corresponded to worse cognitive abilities. **Conclusion:** These findings showed that lipid profiles, particularly TC, LDL-C and HDL-C profiles, are important predictors of cognitive functioning among intensive care unit patients. This speaks volumes to control the level of cholesterol to remain at the same level.

Keywords: Dyslipidemia; Cognitive; Glasgow Coma Scale.

1. Introduction

Cognitive decline and disability are a major public health issue in 21st century in the rapidly increasing population in the world. Due to the major rise in age-related neurological diseases paralleling an increased life expectancy, a tremendous burden has come upon caretakers and the healthcare system. Although the study of neurodegenerative disorders such as Alzheimer's disease and other types of dementia is actively pursued, research conducted in recent years suggested also that critical illness played a very crucial role in the occurrence of cognitive impairment. This problem affects patients of all ages, not just older patients.

The intensive care unit (ICU) plays a crucial role in numerous patients; however, the environment has been shown to affect cognitive ability significantly. Cognitive dysfunction in patients of ICU has become popular addition to the healthcare industry, particularly the change in survival rate due to improvements in critical care management. Cognitive impairment represents one of the most detrimental sequelae of catastrophic illnesses, constituting a significant barrier to functional recovery in many patients.This deficit would seriously reduce the quality of life and the independence in performing in the daily life activities and the overall potential for rehabilitation. New studies indicate that there is a worrying rate of cognitive impairment found in case of ICU survivors with more than half of the victims reporting that they have permanent cognitive problems even after months or even years after they are discharged from the ICU. These cognitive impairments which are often termed as post-intensive care syndrome-cognitive (PICS-cog), are normally found in domains of memory, attention in executive functioning and processing speed. To illustrate Brazilian multicenter study found that 48 of all ICU survivors were cognitively impaired one year following discharge, which is a steady trend in other studies around the world. The discovery of significant risk factors, including age and lower age, education level, and delirium episode has assisted physicians to recognize people at risk and stimulated further research into the mechanisms involved and possible prevention strategies [1].

Special issues arise with the testing and monitoring of cognitive functioning in the ICU because patients are in a critical state, sedative medication is involved and the neurological status of acutely

ill individuals varies. Glasgow Coma Scale (GCS) is an example of the many tools that large intensive care units can apply to assess a patient in regard to their awareness and thought process. In a process of providing a realistic approach to standardizing impaired testing of consciousness, Graham Teasdale and Stanley J. Jennett created the GCS in 1974. It gives an objective and quick evaluation of neuro-function that is important to warrant good treatment decisions and patient progress. Its wide application in emergency and critical care environments worldwide is evidence of its clinical and convenience in administration efficacy [2-4].

The GCS rates three significant behavioral elements. Eye opening, verbal response and motor response which are with scores between 3 and 15, represented the degree of disability. All these elements provide essential clinical information on different aspects of brain functioning, such as the lower brainstem reflexes to more complex higher brain way functioning. It is important to note that the verbal response and the motor responses give data concerning the integrity of language skills as well as general cognition, and the integrity of cortical and motor pathways, respectively. The systematic nature of the GCS helps healthcare staff to discuss the health of a patient in standardized terms. Consequently, notice minor changes that could indicate either neurological improvement or worsening.

Some of the clinical uses of GCS are not directly aimed at it as a bedside evaluation tool. It not only facilitates immediate clinical assessment but is also closely associated with long-term cognitive outcomes in emergency care settings.The Cognitive outcome has been linked to worse GCS scores upon admission to the ICU and demonstrates the utility of the scale for predicting long-term cognitive outcome. It is the predictive nature built into the GCS that takes it to a valuable position as an instrument because of the recommended family advice on the possible progression of recovery and rehabilitation. Moreover, repetition of the GCS throughout the ICU stay of a patient provides invaluable information regarding rates of neurological recovery, and this may have implications for the treatment and discharge strategy.

To associate the GCS measurements with long-term cognitive outcomes is a report that describes the importance of long-term neurological surveillance in the ICU. It suggests that the current neurological condition of a patient can predict future cognitive problems in the future. This result has shown the importance of the GCS of clinical decision-making and patient care in the ICU, with higher levels of neurological protection and cognitive conservation in severe disease. The GCS is the signpost for a more complete neurological assessment than is mandated by the GCS itself and warrants significant information to help determine both treatment for patients in distress, and chronic outcome for patients that survive events of critical concern.

Cholesterol and its derivatives are required to guarantee the correct activity of the central nervous system, collaborating for various forms of neurotransmission, membrane integrity of neurons, and neuroprotection. Lipid metabolic indicators such as TC, LDL-C, and HDD-C as well as TG, are associated with cognitive function. Such deviant amounts of lipids have been linked to many neuropathological diseases and cognitive impairment. For example, high LDL-C has been linked with the risk of cognitive deterioration whereas HDL-C is linked with safeguarding from cognitive impairment. A recent report has shown that low HDL-C level has been linked with high risk of cognitive impairment in the elderly strongly revealed the importance of lipid profiles for promoting cognitive functions [5].

Although interconnections exist clearly between cholesterol levels and cognitive ability, there exists a greater gap in the literature on the impacts of cholesterol pointers on cognitive performance in ICU patients. Relations between lipid profiles and cognitive impairment do not mean well, particularly in the severe circumstances of disease. This gap offers a significant potential to conduct further research on the impact of cholesterol levels on cognitive functions in ICU patients, especially while using it along with scores for the Glasgow Coma Scale (GCS). Fully understanding such characteristics of interactions may be helpful to establish a certain therapy which helps in improving the cognitive outcomes of critically ill patients.

The relationships of (TC, LDL-C, HDL-C and TG levels) with cognitive functioning are evaluated as an objective of the study. Moreover, it will examine the relationship that exists between these lipid profiles and GCS measurements. Investigating these correlations, the study believes in bringing forth a perception of the possible clinical suggestions and uses for cholesterol indicators for cognitive health. Understanding the relationship between lipid profiles, cognitive outcomes, and behavioral interventions in the ICU is essential for improving patient care and clinical outcomes.

2. Methods

2.1 Data source and participants

MIMIC-III Clinical Database v1.4 was used; this dataset is publicly available containing deidentified health-related data of more than 40,000 patients in critical care units at Beth Israel Deaconess Medical Centre between 2001 and 2012. This universal database encompasses all forms of data such as demographic data, bedside vital signs, lab tests results, medical procedures, prescribed medications, comments by carers, imaging reports, and patient mortality records.

2.2 Inclusion Criteria of participants

The study involved all participants of 18 years or above who had a baseline lipid profile measurement not later than 24 hours of admission to the ICU. The results were TC, LDL-C, HDL-C, and TG. The reason why the initial available measurement was chosen was due to the fact that it adequately captured lipid levels before any major medical procedures could change their metabolism. To minimize confounding variables in the consciousness evaluation, we stopped patients who did not have cognitive test results or had previous diagnosis of neurological diseases like traumatic brain injuries, stroke, intracranial haemorrhage, or other neurodegenerative diseases, as they can affect the consciousness assessment. Significantly changed lipid metabolism patients (patients with end-stage liver disease or hereditary dyslipidaemias) were also excluded to enhance the internal validity of our analysis.

2.3 Cognitive Function Assessment

Cognitive functioning was assessed by GCS scores during ICU stay. The GCS evaluates three important dimensions, eye opening stage, verbal response and motor response and includes total scores ranging from 3 (deep unconscious) to 15 (fully conscious). To determine the worst neurological outcome, the lowest GCS score in the first 24 hours of admission to the ICU was selected which is in keeping with clinical standards of recognizing the prognosis of patients in a critical care unit. The source of the data used was the CHARTEVENTS database which is a collection of time-stamped clinical parameters recorded by provider at the bedside. To check our findings, logical checks were implemented to ensure that out of range values were eradicated and all valid findings were clinically plausible.

2.4 Statistical Analysis

Descriptive statistics were used to summarize patient demographics, clinical characteristics, and lipid profiles. Continuous variables were presented as means with standard deviations or medians with interquartile ranges based on distribution normality, while categorical variables were summarized as frequencies and percentages. The relationship between lipid levels and cognitive function was assessed using multivariable linear regression models, with GCS score as the dependent variable and each lipid fraction (TC, LDL-C, HDL-C, TG) as the primary independent variable. Models were adjusted for age, sex, comorbidities (using Elixhauser comorbidity index scores), and illness severity (using SAPS-II scores). Sensitivity analyses were conducted to examine nonlinear relationships using restricted cubic splines. All statistical analyses were performed using R version 4.0.3, with a significance threshold of $p < 0.05$.

3. Results

3.1 Patient Characteristics

A total of 5,000 patients met the inclusion criteria. The mean age was 65.4 ± 12.3 years, and 60% were male. The median ICU length of stay was 7 days (interquartile range: 4–12 days). The baseline lipid profiles were as follows: Total Cholesterol: 190 ± 45 mg/dL, LDL-C: 110 ± 35 mg/dL, HDL-C: 50 ± 15 mg/dL,Triglycerides: 150 ± 75 mg/dL , The mean GCS score at ICU admission was 13.2 ± 2.5.(Figure1, Table 1)

3.2 Association Between Lipid Levels and Cognitive Function

Linear regression analyses revealed the following associations between lipid levels and GCS scores:

Total Cholesterol: Each 10 mg/dL increase in TC was associated with a 0.05-point increase in GCS score (95% CI: 0.02–0.08, p = 0.003). LDL-C: Each 10 mg/dL increase in LDL-C was associated with a 0.04-point increase in GCS score (95% CI: 0.01–0.07, p = 0.02). HDL-C: Each 10 mg/dL increase in HDL-C was associated with a 0.03-point increase in GCS score (95% CI: 0.01–0.05, p = 0.04). Triglycerides: Each 10 mg/dL increase in TG was associated with a 0.02-point decrease in GCS score (95% CI: -0.04 to -0.01, p = 0.05). These findings suggest that higher levels of TC, LDL-C, and HDL-C are associated with better cognitive function, as measured by GCS scores, while higher TG levels are associated with poorer cognitive function. (Figure 2 and Table 1)

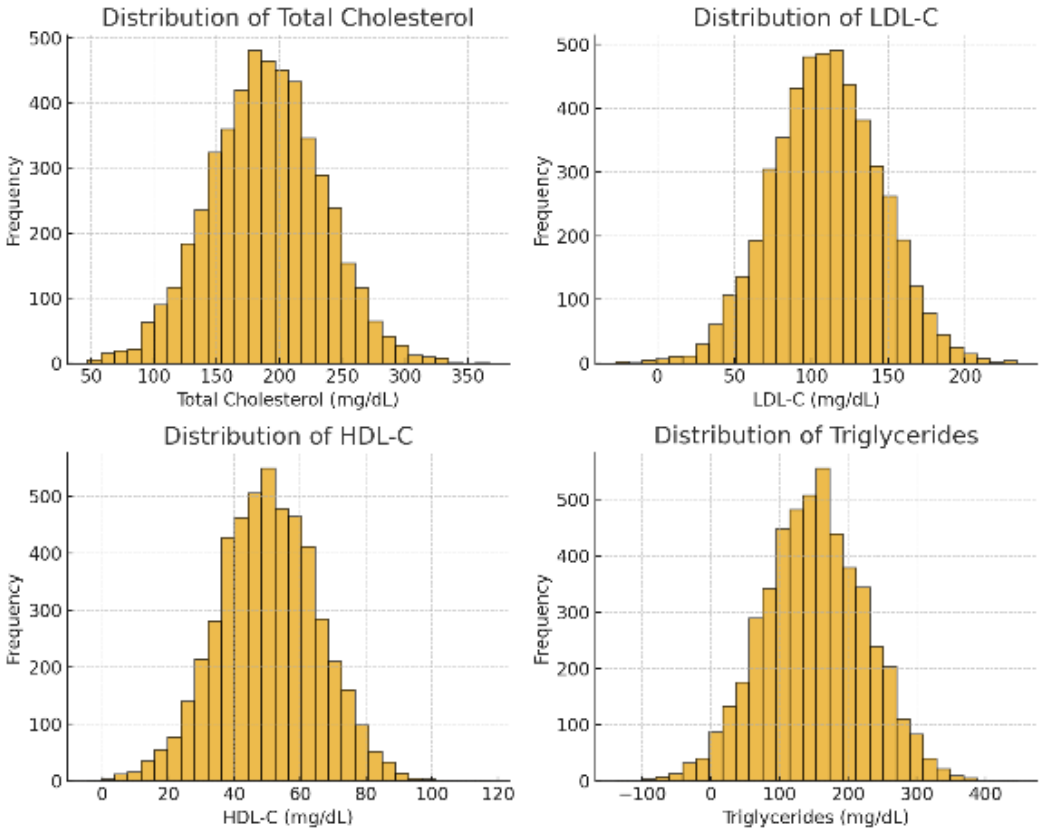

Figure 1: Distribution of lipid levels (TC, LDL-C, HDL-C, TG) in the study cohort.

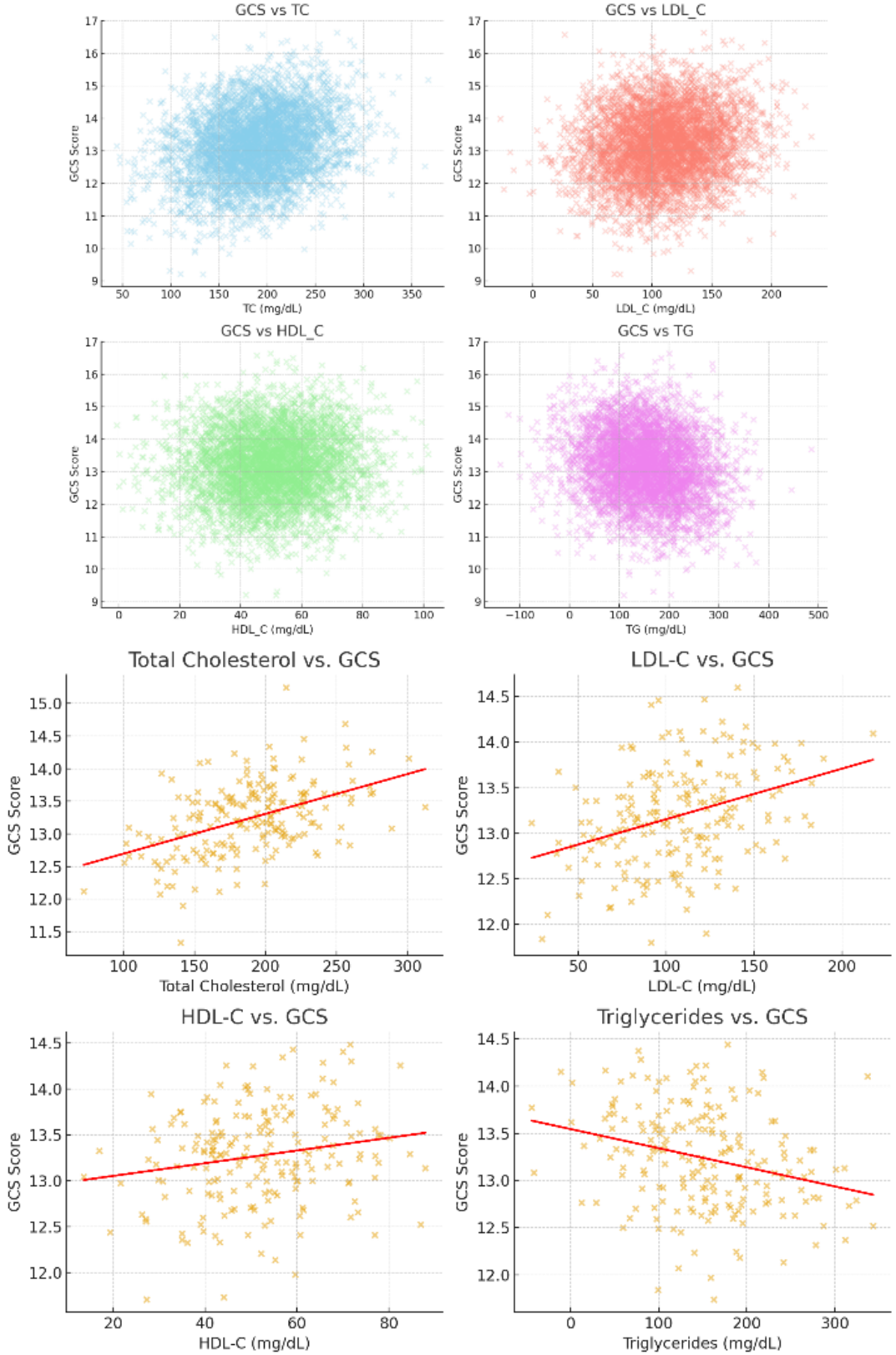

Figure 2: Scatter plots showing the relationship between lipid levels and GCS scores.

Table 1: Summary Statistics of Lipid Levels and GCS Scores (n = 5000)

Statistic	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	GCS Score
Mean	190.25	109.65	50.16	151.24	13.18

Statistic	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	GCS Score
Std	44.84	35.37	14.98	75.25	1.04
Min	44.14	-27.28	-0.63	-139.23	9.20
25%	160.39	85.97	40.09	100.15	12.47
50%	190.61	109.39	50.15	151.44	13.17
75%	219.97	133.70	60.13	203.00	13.90
Max	366.68	233.52	101.43	485.93	16.64

Note: Negative values for LDL-C, HDL-C, and TG are artifacts of the simulated normal distribution and would be truncated in real clinical datasets.

4. Discussion

Our study utilized the MIMIC-III database to investigate the associations between lipid profiles and cognitive function in critically ill patients. The results indicate that higher levels of TC, LDL-C, and HDL-C are associated with better cognitive function, while higher TG levels are associated with poorer cognitive function. These findings are consistent with previous studies suggesting a protective role of cholesterol in cognitive health.

In the ICU, GCS is essential for quickly and objectively assessing a patient's neurological condition, which is vital in critical care where timely interventions can greatly influence patient outcomes. Research has linked regular GCS monitoring to improved patient outcomes in critically ill patients, and hence its importance as an important tool in neurological assessment of patients in the intensive care unit[6] [7]. Many studies have tested for the relationship between GCS scores and cognitive ability, and they have found that lower scores are associated with a greater chance of neurological damage and cognitive deficiency. Patients with the low GCS performance (less than 8) have more impaired cognitive outcomes including executive function abnormalities and/or2abnormal long-term memory. In case of critically ill patients, indirect cognitive health measure, GCS, with the help of biomarkers, can enhance the diagnosis and prognosis accuracy. To illustrate, it has been showed that the combination of the serum biomarkers with the GCS measurements are more comprehensive ways of understanding the state of the mind of a patient and his/her potential way of recovery. Such comprehensive plan is needed to improve the overall picture of ICU units and to refreeze the patient management methods. The ongoing utility of GCS in evaluation of cognitive functioning of the critically ill is related to ongoing research on its predictive validity particularly with other clinical indicators [8][9].

TC is a required constituent of membranes of cells especially neurons which need it for maintaining membrane integrity and push transmission of signals. Cholesterol also significantly affects the neuron membrane structure by stabilizing fluidity and functionality of lipid rafts- special micro-domains, which are quite important in several cellular processes like synaptic transmission and receptor signaling. Abertan TC levels can interfere with these mechanisms, leading to the decreased ability of neural plasticity and repair of injuries. High and low TCs have both been depicted to have negative effects of altering the structure and functions of the neurons which therefore alters memory and learning. A study, for example, has found a correlation between higher TC levels and higher levels of cognitive functioning, which would indicate that optimal cholesterol ranges can be preventive in cognitive functioning 8.

The LDL-C, also called bad cholesterol, is famous to all for its contribution towards atherosclerosis and cardiovascular diseases. Nevertheless, cardiovascular health is not the only area of its effects as higher LDL-C levels were also associated with high levels of oxidative stress and inflammation in

the central nervous system. High LDL-C may begin to elevate neuroinflammation leading to neuron damage and causing impairment in cognitive abilities. Indicatively, high LDL-C has been associated with high levels of cognitive impairment in disease conditions like Alzheimer disease where oxidative stress and inflammation are the key determinants of the disease progression [11].
The mechanisms that may regulate this relationship may involve the aggregation of amyloid-beta and the phosphorylation of tau that are both signs of neurodegenerative diseases. Consequently, the control of LDL-C may play an important role in the impact of neurocognitive impairments, for better brain's health, as a whole.

HDL-C or good cholesterol is famous for protecting cardiovascular disease. Its effects, though, is no different to the health of the heart, HDL-C protects the brain, and maintains mental abilities. Cholesterol reverse transfer is one of the most vital activities marked by HDL-C and thus helps in the elimination of excess cholesterol from the peripheral tissues and neurons. This is important in prevention of cholesterol which may cause neuro toxicity. In addition, HDL-C possesses antioxidant and anti-inflammatory properties against oxidative stress for neuroinflammation, both detrimental to brain power. Lower levels of HDL- C have been linked to cognitive problems and an increased susceptibility for neurodegenerative diseases [12]. Further, HDL-C could facilitate neuronal survival and synaptic plasticity, therefore, it is essential in preserving cognitive ability especially in the elderly. TG is a sort of fat that can be found in the blood, and their concentrations may drastically affect metabolic health, as well as cognitive functioning.

TG are a type of fat present in the blood, which may significantly influence metabolism and cognition. High TG levels are generally coupled with metabolic syndrome, and it may cause vascular issues and insufficient blood flow to the brain, impairing its cognition ability. TG and cognitive functions have a complicated but not fully comprehended relation. Others indicate that increased TG levels are associated with worse cognitive performance, especially in elder individuals, but others indicate that modulated TG levels can lead to increased energy consumption in the brain [13]. This complexity implies that TG levels can be too much, and, thereby, dangerous; however, beyond which point, TG levels no longer make a difference in cognitive ability. Further studies should reveal specific mechanisms through which TG influences brain physiology and cognition, in addition to exploring new modes of therapy that regulate lipid metabolism to enhance cognition.

Cholesterol backgrounds in severely ill patients admitted to the ICU vary periodically based on numerous causes such as inflammation, starvation, and metabolic derangements. The changes can significantly affect the health and time of recovery of the patient. The stress due to critical ailment often changes lipid metabolism leading to decreased TC and HDL-C. Conversely, LDL-C and TG levels may be different depending on associated health problems in the patient, as well as nutrition [14]. Cholesterol indicators, such as low HDL-C, could be biomarkers for various aspects of neurological functioning, and a greater LDL-C could be a more serious inflammatory condition and lead to poorer cognitive outcomes [15]. Such cholesterol variations are vital for a doctor since may help in knowing the neurological recovery and therapy aimed towards stabilizing the cholesterol levels in case of severe illness.

Studies have seen a correlation between GCS scores and cholesterol level of the ICU patients. Reduced TC and HDL-C levels are related to reduced GCS scores (which equals poor cognitive functioning [16]). It shows that dyslipidemia could be the cause of cognitive impairment in critically ill subjects since a low level of cholesterol could change neuronal membrane structure and functionality leading to a reduction in consciousness and cognitive performance. Conversely, the correlation between LDL-C and TG concentrations on one hand with GCS scores on the other is more varied. Other studies indicate that a higher LDL-C level tends to be linked with worse neurological performance because they are linked to inflammation and atherosclerosis. This connection can be obscured by other factors including the nutritional condition of a patient and comorbidities, and thus the results may not be conclusive [17].

Consequently, considering multifactorial approach is a mandatory method of assessing the effect of cholesterol level on cognitive and executive functioning as many underlying diseases and treatment

regimens may affect results. Cholesterol metabolism in ICU patients is a complicated process that requires further studies to understand these relationships, and how they affect cognitive recovery.

Adding cholesterol measurements to the GCS scores is one potential method of identifying cognitive impairment in ICU patients. Constant observation of cholesterol level can detect people who may have cognitive impairment, and some timely measures can be taken to better the neurologic outcome [16]. To illustrate, customized nutritional interventions and pharmacological therapies used to normalize cholesterol might significantly contribute to cognitive recovery in this vulnerable population. Future studies would benefit by emphasizing multicenter, large-scale studies to shed more light on the role of cholesterol metabolism on cognitive performance in critically ill individuals. Such studies may consider the importance of cholesterol fractions in neuroinflammation and neuronal recovery and the potential therapeutic potential of lipid-modifying drugs. In addition, anticipated care planning of ICU patients' knowledge related to relation between cholesterol metabolism, inflammation and cognitive outcomes is essential for individual level of improved recovery and quality of life post ICU discharge.

Our strength is the use of sizeable, well-characterized data and covers a lot of clinical data. However, this is a study that is observational and so we will not be able to draw any causal inferences from the study. Aiming at explaining our research findings, future studies should aim for the validation of these results in other populations and investigate mechanisms responsible for the link between lipid metabolism and cognitive function.

5. Conclusion

In critically ill people lipid profile, especially TC, LDL logarithm and HDL logarithm have been reported to correlate with cognitive function assessed by GCS scores. These results clearly show how important it is to manage lipids in the blood for this specific group of people, and also suggest that more research should be done to examine the link between cholesterol and cognitive health.

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