CNS Spectrums

www.cambridge.org/cns

Exploring the role of serum lipid profile and neutrophil-to-lymphocyte ratio in violent suicide attempters: a cross sectional study

Enrico Capuzzi[1*], Alice Caldiroli[1], Martina Capellazzi[2], Ilaria Tagliabue[2], Annamaria Auxilia[2], Giulia Ghilardi[2], Massimiliano Buoli[3,4] and Massimo Clerici[1,2]

[1]Psychiatric Department, Azienda Socio Sanitaria Territoriale Monza, Monza, Italy, [2]Department of Medicine and Surgery, University of Milan Bicocca, via Cadore, Monza (MB), Italy, [3]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Via F. Sforza, Milan, Italy, and [4]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy

Original Research

Cite this article: Capuzzi E, Caldiroli A, Capellazzi M, Tagliabue I, Auxilia A, Ghilardi G, Buoli M, and Clerici M (2022). Exploring the role of serum lipid profile and neutrophil-to-lymphocyte ratio in violent suicide attempters: a cross sectional study. *CNS Spectrums* **27**(3), 362–368.
https://doi.org/10.1017/S1092852920002199

Received: 29 September 2020
Accepted: 01 December 2020

Key words:
Biomarkers; lipid; mental disorders; NLR; suicide

Author for correspondence:
*Dr. Enrico Capuzzi, PhD,
Email: e.capuzzi1@campus.unimib.it

Abstract

Background. Suicidality is one of the most common complications of mental disorders, so that the identification of potential biomarkers may be relevant in clinical practice. To date, the role of serum lipids and neutrophil/lymphocyte ratio (NLR) has been explored albeit with conflicting results. To the best of our knowledge, no study has explored lipid levels concomitantly with NLR in relation to violent suicide attempts. Therefore, we aimed to investigate whether serum lipid levels and NLR might be associated with the violent method of suicide attempts.

Methods. The study group consisted of 163 inpatients who attempted suicide. Blood samples were collected at the beginning of hospitalization to measure total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein, very-low-density lipoprotein (VLDL), triglycerides, and NLR. Descriptive analyses of the total sample were performed. The included patients were divided into two groups according to violent/nonviolent method. Groups were compared in terms of lipid (MANCOVAs).

Results. Plasma levels of total cholesterol ($F = 5.66$; $P = .02$), LDL ($F = 4.94$; $P = .03$), VLDL ($F = 5.66$; $P = .02$), and NLR ($F = 8.17$; $P < .01$) resulted to be significantly lower in patients that used a violent method compared to patients who attempted suicide with a nonviolent method.

Conclusions. Low cholesterol, LDL, and VLDL levels as well as low NLR value were associated with a violent method of suicide attempt in patients with mental disorders. Further studies are needed to confirm these results.

Introduction

Several studies focused on the potential link between neurobiological factors and suicidal behaviors.[1] Of note, the possible role of lipids in modulating mental health was hypothesized according to the observations of an increased number of attempted suicides in subjects treated with lipid-lowering agents,[2] or conversely of an amelioration of mood symptoms in patients affected by major depression and taking statins.[3] In this regard, some studies suggested that statins may have some anti-inflammatory and antioxidant properties, possibly targeting the inflammatory and oxidative pathways associated with the pathophysiology of depression.[4] Furthermore, because patients using statins exhibit a limited risk of cardiovascular events, it cannot be ruled out that a better quality of life may be in turn associated with mood improvements.[5] Despite this, different neuropsychiatric adverse drug reactions such as violence, aggression, intentional injury, and mood changes were described in some observational studies as well as in pharmacovigilance databases regarding lipid-lowering drugs.[6] However, potential confounders in the association between lipid-lowering drugs and behavior modifications were often not taken into account. For instance, lack of exercise is related to higher risk of cardiovascular accidents and was found to be associated with depression. Because hyperlipidemic individuals having this risk factor could be more likely to assume statins than hyper-lipidemic individuals who practice physical exercise, not controlling for physical exercise should turn out to an apparent relationship between statin use and depression.[7] In light of these gaps, in the last years, a growing number of studies has investigated the possible relationship between lower serum lipid levels and suicidal behavior on the grounds that suicidal behaviors are more likely to be not a result of lipid lowering therapies, but basically of lower lipid levels.[8] In support of these clinical observations, some biological data show that low peripheral cholesterol and triglyceride levels might be associated with decreased lipids in synaptic membranes, leading to consistent changes in membrane viscosity and gene expression.[9] These variations, in turn, could result in a poor serotonergic activity in lipid rafts, possibly related to a limited suppression of impulsive violent

© The Author(s), 2020. Published by Cambridge University Press.

CAMBRIDGE UNIVERSITY PRESS

behaviors, such as suicidal conducts.[10,11] An inverse association of suicidality with serum cholesterol and triglyceride levels was also remarked in a recent systematic review and meta-analysis.[12] Even though subgroup analyses revealed a potential association between a lower serum total cholesterol and violent methods of suicide attempts, some studies reported opposite results.[12] As a whole, the studies exploring a possible interaction between lipid serum profile and suicidal behavior in subjects with mental disorders produced mixed results, possibly due to methodological heterogeneity.[13,14] The available data about this topic are also biased by confounding factors such as gender because males are more likely to use violent methods to commit suicide than women.[15] Furthermore, no robust evidence associates the severity of impulsivity with serum lipid profile,[16] partly due to the fact that other biological factors such as the amount of circulating neurosteroids[17] or severity of systemic inflammation[18] can both influence the cholesterol blood levels and the vulnerability to suicidal behaviors. In this regard, recent models included neuroinflammation as an important factor associated with the vulnerability to impulsive behaviors including suicide.[19] Recent studies identified neutrophil-to-lymphocyte ratio (NLR) as a measure of low-grade inflammation in different systemic diseases[20] as well as a potential biomarker related to the severity of psychiatric disorders and suicide.[21] Specifically, a recent meta-analysis reported higher levels of NLR in subjects with bipolar disorder (BD) and major depressive disorder (MDD) than healthy controls.[22] Further studies even suggest that NLR may be a trait marker of suicide vulnerability in patients with BD[23] or MDD,[21,24] although other findings contradicted these results.[25] Furthermore, two different articles[26,27] reported higher levels of NLR in subjects who attempted suicide with a violent method than the counterpart.

According to authors' knowledge, no study has explored till now the concomitant association of lipid serum levels and NLR with violent/nonviolent method of suicide attempt. Thus, in order to overcome gaps of previous research, purpose of the present study was to explore the possible roles of lipid serum levels and of NLR on the occurrence of violent suicide attempts in a sample of patients affected by psychiatric conditions.

Methods

This study was drawn up following the Strengthening the Reporting of Observational studies in Epidemiology Statement items.[28] The research project complied with the principles of the Declaration of Helsinki regarding medical research in humans, following local research ethical requirements.

Sample

A sample of 163 subjects aged ≥18 years was *cross-sectionally recruited in a Psychiatric Inpatient Unit (Desio Hospital, ASST Monza, Italy),* between January 2012 and December 2019. All patients were included if hospitalized for a suicide attempt occurred within the last 72 hours and if suffered from schizophrenia, BD type I or II (any acute phase), MDD and personality disorders according to ICD-10 (International Classification of Diseases) criteria. If patient had more than one psychiatric diagnosis, the main psychiatric condition was taken into account (ie, the disorder that conducted to hospitalization). Moreover, eligible subjects were medically stable, not needing treatment for any physical condition. We excluded subjects suffering from other mental disorders or mental retardation, and those with serious physical illnesses, including hepatitis B or C, and HIV infections (antiviral agents may modify lipid profile), or treated with thyroid hormone, antidiabetic, anticoagulant, antiplatelet, urate-, and lipid-lowering agents.

Assessments

All data were anonymously and retrospectively collected, not allowing subject identification. Standard demographic and clinical data (age, gender, nationality, occupational and marital status, characteristics of recent suicide attempts, diagnosis of mental disorders according ICD-10, ongoing psychopharmacological treatments, smoking status, co-occurring substance use disorders, and lipid profile) were retrieved from electronic health records. We considered as "suicide attempts," only self-injuries of people willing to die, while suicidal ideation or plans without any action, as well as low-lethal self-harm behaviors, were excluded.[24] We used standard definitions to distinguish violent (firearm, hanging, cutting, jumping, car exhaust, and other violent methods) from nonviolent (drug overdose and poisoning) methods for attempting suicide.[29] Information on lipid serum levels, including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low density lipoprotein (VLDL), triglycerides (TG), and NLR was retrieved from routine blood tests done in the first hours of hospitalization at 8.00 am, after an overnight fasting. We considered only serum blood tests carried out within 24 hours after the hospitalization. Serum lipid concentrations were examined using standard methods (enzymatic colorimetric ones) at the Department of Clinical Pathology of Desio Hospital, ASST Monza, Italy.

Statistical analyses

The data were analyzed using Statistical Package for Social Sciences —SPSS 26.0. Characteristics of the total sample were reported using mean and standard deviation for quantitative variables and frequencies and percentages for qualitative ones. Selected patients were divided into two groups according to the presence of violent or nonviolent suicide method. Quantitative and qualitative variables were respectively compared between the two groups by multivariate analyses of variance (MANOVAs) and Chi-square tests with eventual Bonferroni's post hoc analyses. Finally, multivariate analyses of variance, inserting gender, and psychiatric diagnoses as covariates (MANCOVAs) were performed to compare the two groups in terms of lipid profile and NLR.

A p value of $\leq .05$ was considered as statistically significant.

Results

A total of 163 patients hospitalized for a recent suicide attempt were included in the study. Almost a third of the sample had experienced a violent suicide attempt in the 72 hours before admission. As a whole, 17 individuals had schizophrenia, 19 BD, 37 MDD, and 90 a personality disorder. More than 40% of the subjects was treated with antidepressants. Moreover, more than half of the sample was a smoker while about one in five patients had a comorbid substance use disorder. Descriptive analyses of the total sample and of the groups divided according to the type of suicide attempts are reported in Table 1.

The groups of patients divided according to violent/nonviolent attempted suicide were significantly different in terms of gender

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press

Table 1. Clinical Characteristics of the Total Sample and of the Two Groups Identified According to the Method of Suicide Attempt.

Variables	Total Sample N = 163	Violent Method N = 51 (31.3%)	Nonviolent Method N = 112 (68.7%)	*P*-Value
Sociodemographic				
Age (years) mean (SD)	40.5 (12.2)	42.1 (14.1)	38.1 (13.1)	.23
Female gender	77 (47.2%)	15 (29.4%)	62 (55.4%)	**<.01**
Ethnicity (non-Caucasian)	16 (9.8%)	5 (4.5%)	11 (21.6%)	1.00
Unemployed*	70 (45.8%)	20 (42.6%)	50 (47.2%)	.60
Married*	45 (27.6%)	16 (32.6%)	29 (27.1%)	.57
ICD-10 primary diagnosis				
Schizophrenia	17 (10.4%)	8 (15.7%)	9 (8.0%)	.43
BD	19 (11.7%)	7 (13.7%)	12 (10.8%)	
MDD	37 (22.7%)	11 (21.6%)	26 (23.2%)	
Personality disorder	90 (55.2%)	25 (49.0%)	65 (58.0%)	
Medication before admission*				
FGA	11 (6.5%)	5 (10.0%)	6 (5.4%)	.32
SGA	41 (25.5%)	8 (16.0%)	33 (29.7%)	.08
Mood stabilizers	24 (14.7%)	6 (12.0%)	18 (16.2%)	.63
Antidepressants	66 (41.0%)	9 (18.0%)	57 (51.3%)	**<.001**
Smoking*	84 (52.0%)	31 (86.1%)	53 (66.2%)	**.04**
Comorbid substance use disorder*	31 (20.7%)	11 (22.9%)	20 (19.6%)	.67

Values are numbers (column %), unless stated. *P* values in bold indicate statistically significant differences between groups.
Abbreviations: BD, bipolar disorder; FGA, first generation antipsychotics; MDD, major depressive disorder; SD, standard deviation; SGA, second generation.
*There are missing values for some variables: the greatest number of missing values is for smoking and comorbid substance use disorder with 79 (48.4%) and 132 (81%) missing values, respectively.

($\chi^2 = 9.46$; $df = 1$; $P < .01$), antidepressant treatment ($\chi^2 = 15.85$; $df = 1$; $P < .001$), and smoking status ($\chi^2 = 4.90$; $df = 1$; $P = .04$). Indeed, male individuals were more likely to attempt suicide with a violent method than females. Furthermore, patients with a violent suicide attempt were more frequently smokers and were taking less antidepressant treatment than patients that attempted suicide in a nonviolent way. On the other hand, we did not find significant differences between the two groups in age ($F = 1.44$; $P = .23$), employment status ($\chi^2 = 0.28$; $df = 1$; $P = .60$), marital status ($\chi^2 = 0.50$; $df = 1$; $P = .57$), psychiatric diagnosis ($\chi^2 = 2.80$; $df = 3$; $P = .43$), first-generation antipsychotic treatment ($\chi^2 = 1.14$; $df = 1$; $P = .32$), second-generation antipsychotic treatment ($\chi^2 = 3.42$; $df = 1$; $P = .08$), treatment with mood stabilizers ($\chi^2 = 0.48$; $df = 1$; $P = .63$), and presence of a substance use disorder ($\chi^2 = 0.22$; $df = 1$; $P = .67$).

Finally, serum levels of total cholesterol ($F = 5.66$; $P = .02$), LDL ($F = 4.94$; $P = .03$), VLDL ($F = 5.66$; $P = .02$), and NLR ($F = 8.17$; $P < .01$) were significantly lower among patients using a violent method compared to patients with a nonviolent method of suicide attempt (Figure 1).

Similarly, lower HDL ($F = 0.006$; $P = .94$) and TG ($F = 0.05$; $P = .82$) serum levels were found in violent vs nonviolent suicide attempters, but these differences did not achieve statistical significance.

Discussion

Main findings

In this study, based on real world sample of inpatients with different mental disorders, we found that subjects who attempted suicide with violent method showed lower serum levels of total cholesterol as well as of LDL and VLDL subfractions compared to their counterpart. In addition, NLR was significantly lower in violent vs nonviolent suicide attempters.

Our results are consistent with a *previous meta-analysis by* Wu et al[12] and with a recent case–control study[30] which found lower serum total cholesterol and LDL levels in patients with high-lethality suicide attempts compared to low-lethality suicide attempters. Moreover, we found no differences in HDL and TG between nonviolent and violent suicide attempters similarly to previous studies.[31] However, the literature exploring a possible interaction between low lipid levels and the method of suicide attempt in subjects with mental disorders produced mixed results.[11,32] In particular, the high methodologically heterogeneity across studies due to the different assessment of suicide attempts,[30] the type of included mental disorders[33] as well as the role of possible confounders (ie, economic factors, dietary patterns, body mass index [BMI], physical conditions, infectious disease, medical treatments, other psychological characteristics, and current psychopharmacological treatment) should be taken into account.[14,30] Nevertheless, the different subfractions of cholesterol (pro-atherogenic lipids, ie, LDL, VLDL, and TG vs anti-atherogenic lipids, ie, HDL) may have distinct roles in brain function and therefore in influencing the risk of suicide, although no definitive answers to this question exist.[34] Thus, different possible explanations were suggested to account for the association between cholesterol and suicidal behaviors.[17] In particular, since violent suicide attempters usually have higher levels of aggressiveness and impulsivity, and more adult interpersonal violence and suicide risk than nonviolent attempters,[35] serum cholesterol might be more linked

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press

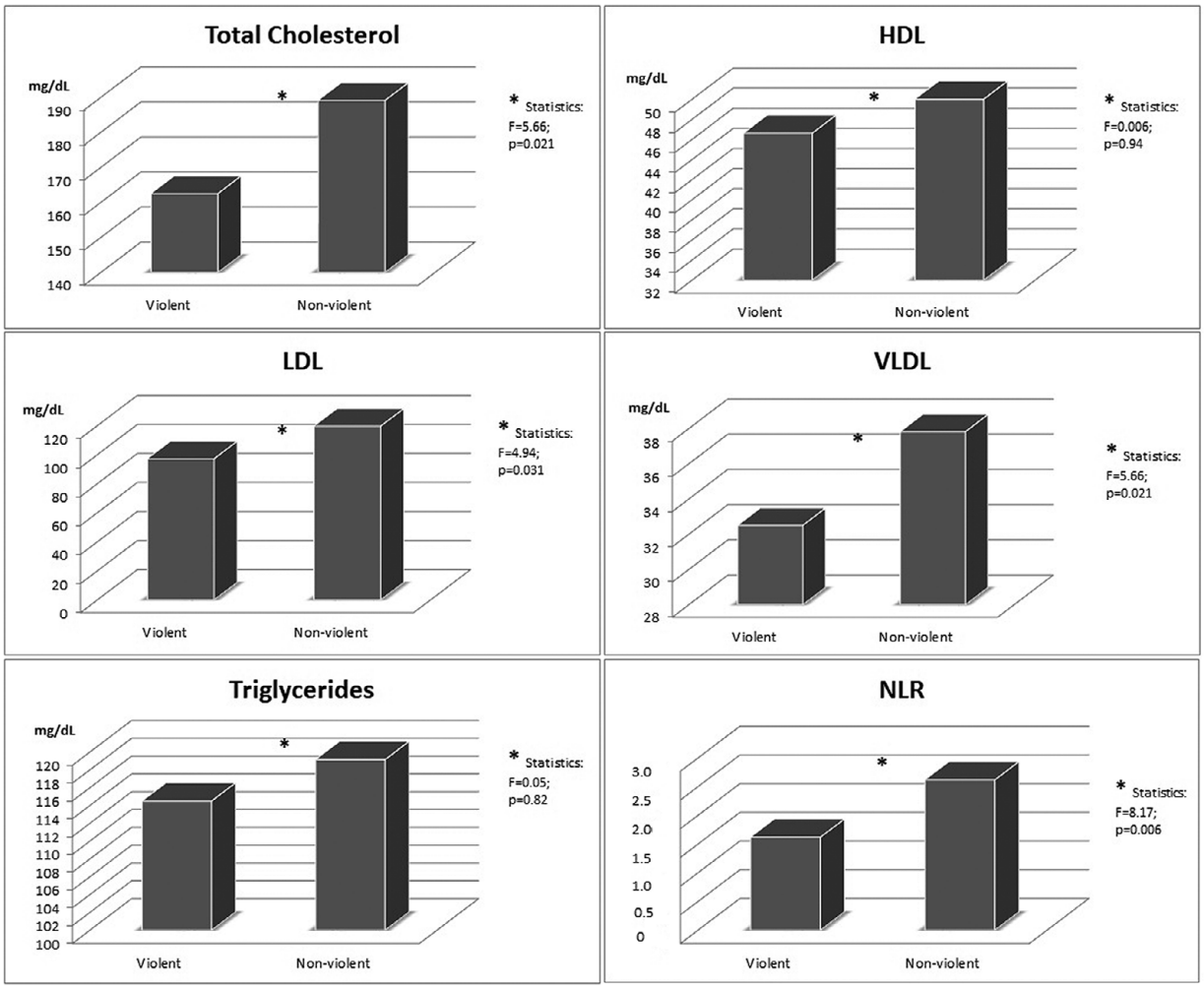

Figure 1. Lipid profile and neutrophil/lymphocyte ratio in violent vs nonviolent suicide attempts.
Multivariate analyses of variance adjusted for gender and diagnosis. Abbreviations: HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; NLR, Neutrophil/Lymphocyte Ratio; VLDL, Very-Low-Density Lipoprotein.

to the violence of suicide attempts than to suicide itself.[13] In support to this consideration, a correlation between infant exposure to violence and adult violent behaviors (ie, cycle of violence) was found in subjects with lower serum cholesterol levels.[36] Early life adverse experiences (ELAs), such as sexual or physical abuse and parental neglect, are distal events related to suicide behaviors.[37] ELAs may produce chronic psychological stress and epigenetic modifications of multiple genes including those implicated in regulation of cholesterol levels and stress responses.[36] In this regard, some studies reported that apolipoprotein E, that it is involved in the formation of synapses and prevention of neuronal death, might be associated with decreased lipid levels, which in turn might be related to the severity of suicidal behavior.[38,39] Nevertheless, some studies suggest that some cholesterol metabolites called oxysterols may cross the blood–brain barrier leading to modifications in central nervous system (CNS) cholesterol levels and lipid raft activity resulting in impairment of serotonin synaptic transmission.[19] As a consequence of altered phospholipid and cholesterol contents in CNS, a study reported that violent suicide completers may display a lower gray matter lipid content in both ventral prefrontal and orbitofrontal cortex than nonviolent suicidal people.[9] However, the debate in the relationship between serum lipids and suicide is still ongoing. For example, an alternative hypothesis is that low serum cholesterol levels are explained by the over-production of neurosteroids promoting self-harm behaviors in suicide attempters such as dehydroepiandrosterone sulfate.[40] Furthermore, serum lipids may just represent an epiphenomenon of suicide attempts, interplaying with more complex processes, specifically associated with the dysregulation of the hypothalamic–pituitary–adrenal axis, and inflammation.[41] In particular, interleukin-6 (IL-6), *is* hypothesized to be involved in the pathophysiology of suicidal behavior since it may promote inflammation with consequent astrocyte and microglial activation.[42] IL-6 may be overproduced by microglia or may enter in the brain from the periphery via a compromised blood–brain barrier.[43] In this regard, NLR is currently considered a reliable marker of low-grade systemic inflammation.[22] Our study found that individuals who committed a suicide attempt with violent method had a lower NLR compared to nonviolent ones. This result seems to conflict with two consecutive studies,[26,27] which found higher NLR values in violent suicide attempters in comparison to nonviolent suicide attempters and healthy controls. However, it appears to be difficult to compare our results with those reported by Orum[26] and Kara[27] since they excluded patients with a history of psychiatric treatments and with current psychiatric disorders, apart from those with major depression or anxiety, while we included a sample of patients affected by psychiatric disorders requiring hospitalization.

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press

As a whole, to our knowledge, few articles investigated the potential role of NLR in suicidal behavior and these studies present different methods and samples than our research.[25,44] Nevertheless, even though most studies reported higher levels of NLR in suicide *attempters than individuals* without suicidal behavior, these results can be discordant respect to our findings for the following reasons. First of all, the severity of depression and suicide may be related to distinct immune-biological profiles in peripheral blood.[45] This aspect is also supported by our findings as subjects with nonviolent suicide attempts were more frequently in treatment with antidepressants. In addition, a very recent study confirmed that the severity of depressive symptoms is linearly associated with LDL serum levels, but no changes in NLR.[46] Furthermore, suicidal behavior may be accompanied by an increased number of lymphocytes whereas depressed patients may be less likely to show elevated lymphocytes.[47] Similarly, distinct patterns of inflammation might be associated with a different impairment in self-regulation and consequently with a variable risk of impulsivity and violent suicide attempts.[48,49] Second, most studies about the association between inflammation and suicide considered the total count of white blood cells while just few studies examined lymphocyte subtypes. For instance, patients affected by post-traumatic stress disorder, a condition associated with high risk of suicide, can show a decreased number or a decreased *functional capacity of* natural killer cells as a result of the high glucocorticoid receptor expression on lymphocytes.[50] In addition, cortisol may promote the differentiation of regulatory T lymphocytes as well as repress the production of T-helper 1 and T-helper 17 lymphocytes.[41,51] Third, many possible confounders should be considered in the potential association between NLR and suicide attempts. In particular, our study found significant differences between nonviolent and violent suicide attempts in terms of gender, frequency of antidepressant treatment and smoking status. One study reported statistically significant differences in NLR between men and women[52] and another article found that the NLR is normalized by the antidepressant treatment in subjects affected by MDD.[53] Finally, smoking seems to affect NLR values[54] and a recent study, conducted on patients undergoing coronary intervention, reported that changes in the lipid profile influence the variability of NLR in the light of the inflammatory properties of atherogenic lipids.[55] Taken as a whole, in the light of the above mentioned considerations, we cannot fully exclude that lower serum levels of total cholesterol, LDL, and VLDL are concomitant with lower levels of NLR among patients using a violent method compared to patients with a nonviolent suicide attempt.

Limitations

There are some important methodological limitations in the present study and results should be interpreted cautiously. First, as this study was a cross-sectional one, we cannot definitively define whether the selected variables preceded or followed the suicide attempt. Consequently, we could not evaluate the direct causal relationship between suicidal behavior and lipid profile as well as NLR. Second, the sample size was relatively small and almost all subjects were Italian inpatients from one hospital, which limit the generalization of our findings. For the same reason, we were unable to stratify the sample according to the different type of mental disorders. Third, since data were retrieved from electronic medical charts, without information from face-to-face interviews, some variables including previous suicide attempts, poor adherence to medications, dietary habits, nutritional status, physical activity, and BMI were not available.[56,57] Fourth, we should consider that most subjects were treated with psychopharmacological agents, leading to a possible alteration of lipid serum levels and NLR. Indeed, it is widely known that both first- and second-generation antipsychotics as well as antidepressant treatments may cause lipid dysregulation, thereby contributing to the onset of the metabolic syndrome.[58-60] Moreover most mood stabilizers, including valproic acid, carbamazepine, lamotrigine and lithium could be typically associated with *alterations of Leukocyte Count,*[61] leading to possible change of NLR.[62] However, we excluded subjects with physical conditions or medical treatments, in particular lipid lowering agents, that may interfere with lipid metabolism and NLR values. Furthermore, we considered only certain mental disorders, excluding those conditions (ie, eating disorders, organic mental disorders, and mental retardation) that might confound the association between lipids, NLR, and suicidal behaviors.[63] Nevertheless, we cannot fully ruled out that part of our sample may be affected by subclinical conditions (eg, hypothyroidism, cardiovascular and *autoimmune diseases*, and infections) which in turn may translate into alterations of both lipid metabolism and NLR.[64-66]

Conclusions

Despite some limitations, the current study may support previous evidence of lower serum lipids in subjects with mental disorders and who attempted suicide with violent method as compared with nonviolent attempters. Moreover, low NLR levels might increase the risk of violent suicide attempts. To the best of our knowledge, no previous studies investigated lipid profiles concomitantly with NLR and other confounding factors in relation to the violence of suicide attempts. NLR could be a biomarker of clinical utility to stratify psychiatric subjects according to diagnoses or severity of symptoms.[67] Further studies should therefore focus on this parameter, including other important markers of inflammation such as glucocorticoids, cytokines, and *lymphocyte subpopulations*.[45] Longitudinal studies on larger samples of subjects, stratified by type of mental disorder, could better clarify the role of some biological pathways in the onset of suicidal behavior.

Disclosures. Enrico Capuzzi, Alice Caldiroli, Martina Capellazzi, Ilaria Tagliabue, Annamaria Auxilia, Giulia Ghilardi, Massimiliano Buoli, and Massimo Clerici have no conflict of interest with any commercial or other association in connection with the submitted article.

References

1. Kim S, Lee KU. Research on potential biomarker correlates for suicidal behavior: a review. *Asia Pac Psychiatry*. 2017;**9**(4):e12291. doi:10.1111/appy.12291.
2. Muldoon MF, Manuck SB, Mendelsohn AB, Kaplan JR, Belle SH. Cholesterol reduction and non-illness mortality: meta-analysis of randomised clinical trials. *BMJ*. 2001;**322**(7277):11–15. doi:10.1136/bmj.322.7277.11.
3. Köhler-Forsberg O, Otte C, Gold SM, Østergaard SD. Statins in the treatment of depression: hype or hope? [published online ahead of print, 2020 Jul 8]. *Pharmacol Ther*. 2020;**215**:107625. doi:10.1016/j.pharmthera.2020.107625.
4. O'Neil A., Sanna L., Redlich C., *et al.* The impact of statins on psychological wellbeing: a systematic review and meta-analysis. *BMC Med*. 2012;**10**:154. doi:10.1186/1741-7015-10-154.
5. Yang C, Jick S, Jick H. Lipid-lowering drugs and the risk of depression and suicidal behavior. *Arch Intern Med*. 2003;**163**:1926–1932. doi:10.1001/archinte.163.16.1926.

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press

6. Tatley M, & Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Saf*. 2007;**30**(3):195–201. doi:10.2165/00002018-200730030-00003.
7. Conklin SM, & Stanford MS. Premeditated aggression is associated with serum cholesterol in abstinent drug and alcohol dependent men. *Psychiatry Res.*. 2008;**157**(1–3):283–287. doi:10.1016/j.psychres.2007.02.006.
8. Leppien E, Mulcahy K, Demler TL, Trigoboff E, Opler L. Effects of statins and cholesterol on patient aggression: is there a connection? *Innov Clin Neurosci*. 2018;**15**(3–4):24–27.
9. Freemantle E, Mechawar N, Turecki G. Cholesterol and phospholipids in frontal cortex and synaptosomes of suicide completers: relationship with endosomal lipid trafficking genes. *J Psychiatr Res*. 2013;**47**(2):272–279. doi:10.1016/j.jpsychires.2012.10.019.
10. Vevera J, Fisar Z, Kvasnicka T, *et al.* Cholesterol-lowering therapy evokes time-limited changes in serotonergic transmission. *Psychiatry Res*. 2005;**133**(2–3):197–203. doi:10.1016/j.psychres.2004.11.005.
11. da Graça Cantarelli M, Nardin P, Buffon A, *et al.* Serum triglycerides, but not cholesterol or leptin, are decreased in suicide attempters with mood disorders. *J Affect Disord*. 2015;**172**:403–409. doi:10.1016/j.jad.2014.10.033.
12. Wu S, Ding Y, Wu F, Xie G, Hou J, Mao P. Serum lipid levels and suicidality: a meta-analysis of 65 epidemiological studies. *J Psychiatry Neurosci*. 2016;**41**(1):56–69. doi:10.1503/jpn.150079.
13. Atmaca M, Kuloglu M, Tezcan E, Ustundag B. Serum leptin and cholesterol values in violent and nonviolent suicide attempters. *Psychiatry Res*. 2008;**158**(1):87–91. doi:10.1016/j.psychres.2003.05.002.
14. Capuzzi E, Bartoli F, Crocamo C, Malerba MR, Clerici M, Carrà G. Recent suicide attempts and serum lipid profile in subjects with mental disorders: a cross-sectional study. *Psychiatry Res*. 2018;**270**:611–615. doi:10.1016/j.psychres.2018.10.050.
15. D'Ambrosio V, Salvi V, Bogetto F, Maina G. Serum lipids, metabolic syndrome and lifetime suicide attempts in patients with bipolar disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012;**37**(1):136–140. doi:10.1016/j.pnpbp.2011.12.009.
16. Shaker NM, Sultan M, Mohamed MY, Helal SA, Abd El Moneam MHE. Lipid profile and impulsivity in suicidal patients with major depressive disorder [published online ahead of print, 2020 Apr 6]. *Arch Suicide Res.* 2020;1–16. doi:10.1080/13811118.2020.1746456.
17. Cantarelli Mda G, Tramontina AC, Leite MC, Gonçalves CA. Potential neurochemical links between cholesterol and suicidal behavior. *Psychiatry Res*. 2014;**220**(3):745–751. doi:10.1016/j.psychres.2014.10.017.
18. Maes M, Smith R, Christophe A, *et al.* Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers. *Acta Psychiatr Scand*. 1997;**95**(3):212–221. doi:10.1111/j.1600-0447.1997.tb09622.x.
19. Capuzzi E, Caldiroli A, Capellazzi M, Tagliabue I, Buoli M, Clerici M. Biomarkers of suicidal behaviors: a comprehensive critical review. *Adv Clin Chem*. 2020;**96**:179–216. doi:10.1016/bs.acc.2019.11.005.
20. Howard R, Kanetsky PA, Egan KM. Exploring the prognostic value of the neutrophil-to-lymphocyte ratio in cancer. *Sci Rep*. 2019;**9**(1):19673. doi:10.1038/s41598-019-56218-z.
21. Ekinci O, Ekinci A. The connections among suicidal behavior, lipid profile and low-grade inflammation in patients with major depressive disorder: a specific relationship with the neutrophil-to-lymphocyte ratio. *Nord J Psychiatry*. 2017;**71**(8):574–580. doi:10.1080/08039488.2017.1363285.
22. Mazza MG, Lucchi S, Tringali AGM, Rossetti A, Botti ER, Clerici M. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in mood disorders: a meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;**84**(Pt A):229–236. doi:10.1016/j.pnpbp.2018.03.012.
23. Ivković M, Pantović-Stefanović M, Dunjić-Kostić B, *et al.* Neutrophil-to-lymphocyte ratio predicting suicide risk in euthymic patients with bipolar disorder: moderatory effect of family history. *Compr Psychiatry*. 2016;**66**:87–95. doi:10.1016/j.comppsych.2016.01.005.
24. Velasco Á, Rodríguez-Revuelta J, Olié E, *et al.* Neutrophil-to-lymphocyte ratio: a potential new peripheral biomarker of suicidal behavior. *Eur Psychiatry*. 2020;**63**(1):e14. doi:10.1192/j.eurpsy.2019.20.
25. Gundogdu Meydaneri G, Meydaneri S. Can neutrophil lymphocyte ratio predict the likelihood of suicide in patients with major depression?. *Cureus*. 2018;**10**(4):e2510. doi:10.7759/cureus.2510.
26. Orum MH, Kara MZ, Egilmez OB. Mean platelet volume and neutrophil to lymphocyte ratio as parameters to indicate the severity of suicide attempt. *J Immunoassay Immunochem*. 2018;**39**(6):647–659. doi:10.1080/15321819.2018.1529682.
27. Kara, M. Z., Orum, M. H., & Egilmez, O. B. Relationship between immune cells and violent/nonviolent suicide attempts and controls: what about the lymphocyte-related ratios and neutrophil-related parameters?. *Kaohsiung J Med Sci.* 2019;**35**(5):315–316. doi:10.1002/kjm2.12049.
28. von Elm E, Altman DG, Egger M, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;**61**(4):344–349. doi:10.1016/j.jclinepi.2007.11.008.
29. Nock MK, Borges G, Bromet EJ, Cha CB, Kessler RC, Lee S. Suicide and suicidal behavior. *Epidemiol Rev*. 2008;**30**(1):133–154. doi:10.1093/epirev/mxn002.
30. Aguglia A, Solano P, Giacomini G, *et al.* The association between dyslipidemia and lethality of suicide attempts: a case-control study. *Front Psychiatry*. 2019;**10**:70. doi:10.3389/fpsyt.2019.00070.
31. Bartoli F, Crocamo C, Dakanalis A, *et al.* Association between total serum cholesterol and suicide attempts in subjects with major depressive disorder: exploring the role of clinical and biochemical confounding factors. *Clin Biochem*. 2017;**50**(6):274–278. doi:10.1016/j.clinbiochem.2016.11.035.
32. Papadopoulou A, Markianos M, Christodoulou C, Lykouras L. Plasma total cholesterol in psychiatric patients after a suicide attempt and in follow-up. *J Affect Disord*. 2013;**148**(2–3):440–443. doi:10.1016/j.jad.2012.11.032.
33. De Berardis D, Marini S, Piersanti M, *et al.* The relationships between cholesterol and suicide: an update. *ISRN Psychiatry*. 2012;**2012**:387901. doi:10.5402/2012/387901.
34. Lutz PE, Mechawar N, Turecki G. Neuropathology of suicide: recent findings and future directions. *Mol Psychiatry*. 2017;**22**(10):1395–1412. doi:10.1038/mp.2017.141.
35. Stenbacka M, Jokinen J. Violent and nonviolent methods of attempted and completed suicide in Swedish young men: the role of early risk factors. *BMC Psychiatry*. 2015;**15**:196. doi:10.1186/s12888-015-0570-2.
36. Asellus P, Nordström P, Nordström AL, Jokinen J. Cholesterol and the "Cycle of Violence" in attempted suicide. *Psychiatry Res*. 2014;**215**(3):646–650. doi:10.1016/j.psychres.2014.01.009.
37. Zatti C, Rosa V, Barros A, *et al.* Childhood trauma and suicide attempt: a meta-analysis of longitudinal studies from the last decade. *Psychiatry Res*. 2017;**256**:353–358. doi:10.1016/j.psychres.2017.06.082.
38. Asellus P, Nordström P, Nordström AL, Jokinen J. Plasma apolipoprotein E and severity of suicidal behaviour. *J Affect Disord*. 2016;**190**:137–142. doi:10.1016/j.jad.2015.09.024.
39. Asellus P, Nordström P, Nordström AL, Jokinen J. CSF Apolipoprotein E in attempted suicide. *J Affect Disord*. 2018;**225**:246–249. doi:10.1016/j.jad.2017.08.019.
40. Chatzittofis A, Nordström P, Hellström C, Arver S, Åsberg M, Jokinen J. CSF 5-HIAA, cortisol and DHEAS levels in suicide attempters. *Eur Neuropsychopharmacol*. 2013;**23**(10):1280–1287. doi:10.1016/j.euroneuro.2013.02.002.
41. Walker DJ, Spencer KA. Glucocorticoid programming of neuroimmune function. *Gen Comp Endocrinol*. 2018;**256**:80–88. doi:10.1016/j.ygcen.2017.07.016.
42. Song K, Li Y, Zhang H, *et al.* Oxidative stress-mediated Blood-Brain Barrier (BBB) disruption in neurological diseases. *Oxid Med. Cell Longev*. 2020;**2020**:1–27. doi:10.1155/2020/4356386.
43. Pandey GN, Rizavi HS, Ren X, *et al.* Proinflammatory cytokines in the prefrontal cortex of teenage suicide victims. *J Psychiatr Res*. 2012;**46**(1):57–63.
44. Ucuz İ, Kayhan Tetik B. Can suicide behavior and seasonality of suicide be predicted from inflammatory parameters in adolescents? [published online ahead of print, 2020 Jul 4]. *Med Hypotheses*. 2020;**143**:110061. doi:10.1016/j.mehy.2020.110061.
45. Keaton SA, Madaj ZB, Heilman P, *et al.* An inflammatory profile linked to increased suicide risk. *J Affect Disord*. 2019;**247**:57–65. doi:10.1016/j.jad.2018.12.100.

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press

46. Buoli M, Caldiroli A, Guenzani D, *et al.*; DREAM Project Group. Associations Between Cholesterol and Fatty Acid Profile on the Severity of Depression in Older Persons with Non-dialysis Chronic Kidney Disease. 2020 *J Ren Nutr*; In press.
47. Barzilay R, Lobel T, Krivoy A, Shlosberg D, Weizman A, Katz N. Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior. *Eur Psychiatry*. 2016;**31**:8–12. doi:10.1016/j.eurpsy.2015.09.461.
48. Shields GS, Moons WG, Slavich GM. Inflammation, self-regulation, and health: an immunologic model of self-regulatory failure. *Perspect Psychol Sci*. 2017;**12**(4):588–612. doi:10.1177/1745691616689091.
49. Gassen J, Prokosch ML, Eimerbrink MJ, *et al.* Inflammation predicts decision-making characterized by impulsivity, present focus, and an inability to delay gratification. *Sci Rep*. 2019;**9**(1):4928. doi:10.1038/s41598-019-41437-1.
50. Gotovac K, Vidović A, Vukusić H, *et al.* Natural killer cell cytotoxicity and lymphocyte perforin expression in veterans with posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;**34**(4):597–604. doi:10.1016/j.pnpbp.2010.02.018.
51. Bellavance MA, Rivest S. The HPA - immune axis and the immunomodulatory actions of glucocorticoids in the brain. *Front Immunol*. 2014;**5**:136. doi:10.3389/fimmu.2014.00136.
52. Meng X, Chang Q, Liu Y, *et al.* Determinant roles of gender and age on SII, PLR, NLR, LMR and MLR and their reference intervals defining in Henan, China: a posteriori and big-data-based. *J Clin Lab Anal*. 2018;**32**(2):e22228. doi:10.1002/jcla.22228.
53. Demir S, Atli A, Bulut M, *et al.* Neutrophil-lymphocyte ratio in patients with major depressive disorder undergoing no pharmacological therapy. *Neuropsychiatr Dis Treat*. 2015;**11**:2253–2258. doi:10.2147/NDT.S89470.
54. Tulgar YK, Cakar S, Tulgar S, Dalkilic O, Cakiroglu B, Uyanik BS. The effect of smoking on neutrophil/lymphocyte and platelet/lymphocyte ratio and platelet ındices: a retrospective study. *Eur Rev Med Pharmacol Sci*. 2016;**20**(14):3112–3118.
55. Zhao L, Xu T, Li Y, *et al.* Variability in blood lipids affects the neutrophil to lymphocyte ratio in patients undergoing elective percutaneous coronary intervention: a retrospective study. *Lipids Health Dis*. 2020;**19**(1):124. doi:10.1186/s12944-020-01304-9.
56. Vogelzangs N, Beekman AT, van Reedt Dortland AK, *et al.* Inflammatory and metabolic dysregulation and the 2-year course of depressive disorders in antidepressant users. *Neuropsychopharmacology*. 2014;**39**(7):1624–1634.
57. Furuncuoğlu Y, Tulgar S, Dogan AN, Cakar S, Tulgar YK, Cakiroglu B. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. *Eur Rev Med Pharmacol Sci*. 2016;**20**(7):1300–1306.
58. Roohafza H, Khani A, Afshar H, Garakyaraghi M, Amirpour A, Ghodsi B. Lipid profile in antipsychotic drug users: a comparative study. *ARYA Atheroscler*. 2013;**9**(3):198–202.
59. Pillinger T, McCutcheon RA, Vano L, *et al.* Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;**7**(1):64–77. doi:10.1016/S2215-0366(19)30416-X.
60. Chokka P, Tancer M, Yeragani VK. Metabolic syndrome: relevance to antidepressant treatment. *J Psychiatry Neurosci: JPN*. 2006;**31**(6):414
61. Post RM, Ketter TA, Uhde T, & Ballenger JC. 2007; Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. *CNS Drugs*. **21**(1):47–71. doi:10.2165/00023210-200721010-00005.
62. Spuch C, López-García M, Rivera-Baltanás T, Rodrígues-Amorím D, & Olivares JM. Does lithium deserve a place in the treatment against COVID-19? A preliminary observational study in six patients, case report. *Front Pharmacol*. 2020;**11**:557629. doi:10.3389/fphar.2020.557629.
63. Diaz-Sastre C, Baca-Garcia E, Perez-Rodriguez MM, *et al.* Low plasma levels in suicidal males: a gender and body mass index-matched case-control study of suicide attempters and nonattempters. *Prog. Neuropsychopharmacol. Biol. Psychiatry*. 2007;**31**:901–905.
64. Xanthakis V, Sung JH, Samdarshi TE, *et al.* Relations between subclinical disease markers and type 2 diabetes, metabolic syndrome, and incident cardiovascular disease: the Jackson Heart Study. *Diabetes Care*. 2015;**38**(6):1082–1088. doi:10.2337/dc14-2460.
65. Liu XL, He S, Zhang SF, *et al.* Alteration of lipid profile in subclinical hypothyroidism: a meta-analysis. *Med. Sci. Mon Int Med J Exp Clin Res*. 2014;**20**:1432–1441. doi:10.12659/MSM.891163.
66. Onalan E, & Dönder E Neutrophil and platelet to lymphocyte ratio in patients with hypothyroid Hashimoto's thyroiditis. *Acta Bio-med Atenei Parmensis*. 2020;**91**(2):310–314. doi:10.23750/abm.v91i2.8592.
67. Brinn A, Stone J. Neutrophil-lymphocyte ratio across psychiatric diagnoses: a cross-sectional study using electronic health records. *BMJ Open*. 2020;**10**(7):e036859. doi:10.1136/bmjopen-2020-036859.

https://doi.org/10.1017/S1092852920002199 Published online by Cambridge University Press