Psychiatria Danubina, 2024; Vol. 36, No. 3-4, pp 386-390 https://doi.org/10.24869/psyd.2024.386 *Brief Report*

BLOOD DERIVED INFLAMMATORY MARKERS IN COMPLETED SUICIDE: RESULTS FROM A CASE-CONTROL STUDY

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Summary

Background: *It has been suggested that suicidal behavior may be associated with inflammatory processes. Several studies found altered blood count derived markers in suicide attempters. This study evaluated the potential association of inflammatory factors with completed suicide.*

Methods: *Data of in-patient and post-discharge suicide cases and matched controls were obtained from a preexisting data file. Blood count values with a focus on inflammatory parameters were compared.*

Results: *None of the blood count and inflammatory parameters assessed differed significantly between groups.*

Conclusions: *Previous indications of an association of blood count derived inflammatory factors with attempted suicide were not replicated in completed suicides.*

Keywords: *(completed) suicide, inflammation, biomarkers*

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INTRODUCTION

The search for biological markers for suicidal behavior is a long-lasting topic of interest in suicide research. On the one hand, such markers can aid in our understanding of the development of suicidal behavior, on the other hand robust biomarkers might be a valuable supporting tool for the assessment of the suicidal risk of an individual. However, research so far has not succeeded in the identification of any biological marker which is reliable and simply applicable for clinical use.

The best established biological correlate of suicidality is a decreased serotonergic turnover reflected by a low cerebrospinal fluid 5-hyroxyindole-acetic acid concentration (Åsberg et al. 1976). Further efforts in biological suicide research have focused on genetic markers (Bozorgmehr et al. 2018), the brain-derived neurotrophic factor (Pjevac & Pregelj 2012; Erbay et al. 2021), cortisol and the dysregulation of the HPA axis (Hernández-Díaz et al. 2020) as well as plasma lipids (Kulak-Bejda et al. 2021).

Recently, inflammatory processes and immunological alterations have found increasing scientific interest as biological correlates of mental illness (Pandarakalam 2022) and particularly suicidal behavior. Among others, pro-inflammatory interleukins (González-Castro et al. 2021), C-reactive protein (CRP) concentrations (Chen et al. 2020), immunoglobulins (Zhang et al. 2012) and white blood cell (WBC) increases (Keaton et al. 2019) were investigated. Most of this research, however, was done in suicide attempters or ideators.

In a study in patients with major depressive disorder with and without a history of attempted suicide, neutrophil-to-lymphocyte (NLR), monocyte-to-lymphocyte (MLR) and platelet-to-lymphocyte ratios (PLR) as indicators of the inflammatory status were assessed. In the final logistic regression model only the NLR increase in the suicide attempt group retained significance (Velasco et al. 2020). Somewhat counterintuitive to this, a study in patients hospitalized for a suicide attempt reported a significantly lower NLR in attempters who used a violent suicide method compared to those applying a nonviolent method (Capuzzi et al. 2022). Again in contrast, a study comparing suicide attempters with violent versus non-violent methods and healthy controls showed higher WBC counts, neutrophil percentages and NLRs in the violent suicide attempter group (Kara et al. 2019). Another investigation studied a number of inflammatory parameters in adolescents and found WBC counts, NLR and PLR increased in patients with major depressive disorder versus healthy controls and a higher MLR in patients with a history of suicide attempts (Puangsri & Ninla-aesong 2021). In a series of 4 cases of suicide attempts by hanging, elevated NLRs were observed (Arafat et al. 2021). However, not all investigations found a significant difference between suicide attempters and controls concerning

inflammation related blood cell counts (Gundogdu Meydaneri & Meydaneri 2018).

In two recent meta-analyses of studies comparing suicide attempt patients and controls in terms of various blood markers, increased levels of inflammation and neurotoxicity in patients with a current but not lifetime suicide attempt were reported (Vasupanrajit et al. 2021; Vasupanrajit et al. 2022). Focusing on peripheral CRP concentrations, another meta-analysis found higher CRP levels in individuals with suicidal ideation or a suicide attempt history (Miola et al. 2021).

With regard to completed suicide, however, there is considerably less data concerning a potential association with blood count derived inflammatory factors. In participants of a health check-up program with a mean follow-up time of 15.1 years an association of subsequent suicide risk with the highest quintile of WBC count but not CRP was found (Russell et al. 2021). In a similar study with a mortality surveillance span of 16.6 years, an association between WBC count and suicide risk was reported for women but not for men (Batty et al. 2018). In neither of these studies blood cell ratios were measured.

With the aim to investigate whether the hypothesis of an association between inflammation and suicidal behavior holds true for suicide completers, we utilized a preexisting data set of suicide cases and matched controls and linked it with the last available and thus relatively recent blood values.

SUBJECTS AND METHODS

The data file consisted of psychiatric and non-psychiatric suicide cases and controls matched for sex and age (for sub-samples also for diagnosis and day of admission or day of discharge, respectively) from studies investigating clinical suicide risk factors in psychiatric in-patients (Deisenhammer et al. 2020), psychiatric post-discharge patients (Deisenhammer et al. 2019) and non-psychiatric in- and post-discharge patients (data not published). Post-discharge suicides were defined as suicide deaths occurring within up to 12 weeks after discharge.

The respective last available plasma values of cases and corresponding values of controls were extracted from the electronic hospital register. Given the current or recent hospitalization it was possible to include values assessed relatively close to the time of death of the suicide cases.

The study procedure was approved by the Ethics Committee of the Medical University of Innsbruck.

Prior to the analysis, all metric variables were checked for normality by assessing their skewness, considering values >1 or <-1 as substantial deviations from a symmetric distribution requiring non-parametric testing. For comparing the two groups (suicide vs control) with regard to socio-demographics, we used the respective two-sample tests, i.e., the Chi-square test for the variable gender and Student's t-test for age. For group comparisons with respect to blood parameters, we applied the Mann-Whitney U-test throughout, as the majority of variables was not normally distributed.

RESULTS

The original data file comprised a total of 713 individuals. As the plasma parameters of interest were available to a varying degree, numbers of cases and controls included in the analyses differed (e.g., for leukocytes, 180 cases and 406 controls and for NLR, 86 cases and 264 controls). Demographic and clinical data of suicide cases and controls are displayed in Table 1. As expected due to the match design, there were no significant differences with regard to sex and age. The suicide method used most frequently was hanging. The mean time between blood draw and death was 50.1 ± 60.2 days.

Table 2 shows the results of blood count and inflammatory markers. None of the parameters differed significantly between suicide cases and controls.

When limiting the analysis to in-patient suicides and related controls only, thus reducing the period between blood draw and death even further (to 28.4 ± 36.8 days), statistical results remained basically the same.

DISCUSSION

In this study which compared blood count- and inflammation-related plasma factors assessed relatively shortly before death by suicide we found no significant differences between suicide cases and controls matched for sex, age and in part also diagnosis and day of admission/discharge.

This finding is in contrast with studies which found an alteration in one of these factors (either an increased NLR or an increased MLR) in patients with a previous suicide attempt. A history of attempted suicide is a major risk factor for suicide and therefore suicide attempter and suicide completer populations have many overlaps. However, there are considerable differences in terms of epidemiology and demographic and clinical risk factors. The incidence of non-fatal suicidal behavior peaks in adolescents and young adults while the risk for completed suicide increases with age. Similarly, there is a divergent

Table 1 – Demographic and clinical data

	Group			
	Cases (N=230)		**Controls (N=483)**	
	N	**%**	**N**	**%**
Sex				
Female	77	33.5%	159	32.9%
Male	153	66.5%	324	67.1%
Suicide method				
Hanging	77	33.5%		
Jumping from a height	46	20.0%		
Drug ingestion	26	11.3%		
Railway	25	10.9%	-	-
Firearm	24	10.4%		
Drowning	20	8.7%		
Cutting	8	3.5%		
Ingestion of other substances	4	1,7%		
	Mean	SD	Mean	SD
Age (years)	53.5	16.3	53.6	15.9
Time from blood draw to suicide (days)	50.1	60.2	-	-

No significant differences between cases and controls with regard to sex and age.

Table 2 – Comparison of cases and controls with regard to blood count and inflammatory markers

	Cases			**Controls**			**Statistics**	
	Mean	**SD**	**N**	**Mean**	**SD**	**N**	**Z**	**p-value**
CRP (mg/dl)	1.18	2.86	137	1.27	3.27	341	-1.657	0.098
Leukocytes (G/l)	8.54	9.29	180	8.24	5.95	406	0.551	0.581
% Neutrophils	62.34	13.75	88	60.78	14.60	264	0.950	0.342
% Eosinophils	2.48	2.09	88	2.48	2.43	263	-0.304	0.761
% Basophils	0.47	.36	83	0.51	0.45	257	0.309	0.758
% Monocytes	8.50	2.66	89	8.31	3.34	263	1.147	0.251
% Lymphocytes	26.52	13.52	86	27.46	13.48	264	-0.544	0.587
% Other Leukocytes	0.20	0.77	61	0.58	5.17	195	-0.029	0.977
Erythrocytes (T/l)	4.57	1.22	160	4.49	0.64	394	-0.257	0.797
Platelets (G/l)	240.18	92.39	158	235.61	82.51	390	-0.145	0.885
NLR	3.89	4.77	86	4.33	11.67	264	-0.667	0.505
MLR	0.44	0.36	86	0.43	0.50	263	-1.311	0.190
PLR	158.04	129.50	84	178.25	251.12	264	-0.569	0.569
Hemoglobin (g/l)	136.46	18.49	182	136.84	19.56	409	-0.449	0.654

CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio.
No significant differences between cases and controls in any of the laboratory parameters

pattern for gender. Women have higher rates of suicide attempts while, in most countries, suicide rates are higher in men. For completed suicides commonly highly lethal methods such as hanging or shooting are used while poisoning and cutting are the most prevalent methods used for suicide attempts.

Generally, biological and clinical markers for suicide and attempted suicide are studied in separate investigations making comparisons of their respective relevance difficult. A large-scale, register-based study from Denmark which investigated the association of infection-related clinical factors with suicidal behavior found a

significantly increased risk of deliberate self-harm in individuals who had been treated with an anti-infective agent and in those who had any hospital contact for an infection. For completed suicides, the risk was increased for patients who had been hospitalized only (Hansen et al. 2019). In general, apart from post-mortem studies, assessing biomarkers for completed suicide has to be done retrospectively with oftentimes large intervals between biomaterial sampling and death.

There are very few studies investigating blood derived inflammatory factors in completed suicide and the results of them are mostly inconclusive. They reported associations of one single factor in each case – either CRP (Batty et al. 2016) or total white blood count (Russell et al. 2021) – and, in one study, for women only (Batty et al. 2018). All of them were conducted in cohorts of the general population while in the present study data from an electronic hospital register were utilized. Mean CRP and leukocyte values in our sample were within the normal range in both the suicide and the control group. Unfortunately, in the previous studies, only quintiles or quartiles were given and no blood cell ratios were assessed. Further, they had a mean of up to 16.6 years of follow-up. In one study (Batty et al. 2016) only 25 suicide cases were identified. The present investigation is the first one using a case-control design with data of in-patient and post-discharge suicides. Another strength of our study is the considerably shorter time lag between last available blood assessments and death thus increasing the reliability of a potential association.

The limitations of our study include the possibility of a later death by suicide of a control participant, i.e. after study end, which, however, is immanent for this kind of studies. Further, particularly differential blood count values were not available for all individuals. In contrast to other studies where more homogenous groups of patients, predominantly with depressive disorders, were evaluated, diagnoses of suicides and controls, in particular those of the non-psychiatric patients, varied (although the majority of the psychiatric patients had had an affective disorder). And potential clinical confounders including medication and somatic conditions could not be assessed.

CONCLUSIONS

The findings of previous studies on NLR, MLR and other peripheral immunological parameters as potential biomarkers for suicide attempts and of investigations on total white blood count and CRP for completed suicide were not confirmed in this case-control study in suicide completers with a short time lag between blood assessment and suicide death. This result does not suggest that there is a solid relationship between peripheral inflammatory processes and completed suicide. Given the multiplicity of oftentimes complex effects on the immune system caution should be exercised when stating an association, even more so a causal one, between inflammatory markers and suicidal behavior, particularly completed suicide. More research in this field is clearly warranted.

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