

Investigating the association of a selected inflammatory protein panel with suicide attempts in the PsyCourse Study: A pilot study

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ABSTRACT

Suicide is a significant global public health issue and expected to contribute increasingly to the global burden of disease over the coming decades. Suicide attempts are much more common than completed suicides and represent a major risk factor for and predictor of suicide. Increasing evidence links suicidal behavior to neuroinflammation, i.e., inflammatory processes in the brain. Therefore, in a subsample ($n = 155$) of the PsyCourse Study we investigated whether the circulating levels of 12 inflammatory proteins from the Olink® Explore 384 Inflammation Panel are associated with suicide attempts. We found significantly higher interleukin (IL)-1 β levels in suicide attempters than in non-suicide attempters. Our finding indicates that the IL-1 signaling pathway plays

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a critical role in suicidal behavior and suggests that targeting this inflammatory pathway may help prevent suicide. This finding needs to be replicated in a larger sample.

1. Introduction

Suicide remains a critical global public health challenge, accounting for 727,000 deaths annually (World Health Organization, 2023). It currently stands as the third leading cause of death among individuals aged 15–29 years, representing a significant loss of productive years of life worldwide (World Health Organization, 2023). Suicide is a multifaceted, multidimensional phenomenon with a wide range of biological, clinical, psychosocial, cultural, and environmental risk factors that interact in complicated ways (Aguglia et al., 2022). This complexity may explain why, despite recent advancements, the pathophysiological mechanisms underlying suicidality remain poorly understood (Aguglia et al., 2022).

Suicide attempts (i.e., involvement in self-harming actions with some degree of intent to die) are classified as nonfatal suicidal behavior that can occur at any age (Aguglia et al., 2022). Suicide attempts are the best predictor of and 20 times more common than completed suicides (Aguglia et al., 2022; Brundin et al., 2017).

The molecular mechanisms underlying the risk factors for suicidal behavior remain unclear; however, the associated pathophysiology is being increasingly linked to immune system dysfunction, and evidence is growing that neuroinflammation may play a key role in the pathogenesis of suicidality (Baldini et al., 2025; Brundin et al., 2017; Ganaça et al., 2016). Suicidal individuals may have more severe inflammation, and the levels of inflammation appear to be higher in the brains of people who died by suicide (Brundin et al., 2017). Furthermore, individuals with major depressive disorder who exhibit suicidal behavior were found to have higher levels of systemic inflammatory mediators, which are also thought to impact neurobiological pathways, such as serotonergic signaling, the hypothalamic-pituitary-adrenal (HPA) axis, and microglial activation (Black and Miller, 2015). We previously showed that the severity of mental disorders is associated with inflammatory pathways (Solomon et al., 2025).

To gain a better understanding of the neurobiological mechanisms involved in the pathophysiology of suicide, particularly among individuals with major psychiatric disorders (who are at an increased risk of suicide), the present study investigated the association between circulating levels of inflammatory mediators and suicide attempts in a subsample of participants from the PsyCourse Study. In this exploratory study, we employed a targeted proteomics approach using the Olink® Explore 384 Inflammation Panel to investigate a subset of 12 inflammatory proteins. This high-throughput methodology allows for the precise quantification of a pre-defined set of inflammatory mediators, providing a focused study of the immune landscape in individuals with a history of suicide attempts.

2. Method

2.1. Participants

From the PsyCourse Study sample, we selected a transdiagnostic subsample of 155 individuals with major psychiatric disorders (89 with schizophrenia [SCZ], 55 with bipolar disorder [BD], and 11 with major depressive disorder [MDD]) for whom proteomics (Olink) and suicide attempt data were available. Our study used cross-sectional data from the PsyCourse Study, version v6.0 (Heilbronner Urs et al., 2023). The multicenter, longitudinal PsyCourse study was performed in Germany and Austria and collected detailed phenotypic data and biomaterials from 1320 individuals with major psychiatric disorders and 466 healthy individuals (Budde et al., 2019). All participants provided written informed consent to participate. The study was performed in accordance

with the principles of the Declaration of Helsinki, and approval was obtained from the respective ethics committees at the study sites. More information about the PsyCourse Study sample and assessments can be found elsewhere (Budde et al., 2019; Heilbronner Urs et al., 2023).

2.2. Assessment of suicide attempts

For clinical participants in the PsyCourse study, a lifetime history of suicide attempts was assessed at baseline as part of the Structured Clinical Interview for DSM-IV (SCID-I). For the present study, we classified individuals with a history of suicide attempts as suicide attempters (SA; $n = 40$), and those without a history of suicide attempts as non-suicide attempters (non-SA; $n = 115$). Consequently, we dichotomized the data on suicide attempts as yes/no.

2.3. Assessment of protein levels and selection of inflammatory mediators

For proteomics analysis, we used the data from the Olink® Explore 384 Inflammation Panel, which quantifies 368 inflammatory proteins in serum and was performed for a subset of the PsyCourse Study sample (Solomon et al., 2025). Olink® Explore is a high-multiplex, high-throughput protein biomarker platform that combines proximity extension assay technology with an innovative new readout methodology based on next-generation sequencing (<https://olink.com>).

On the basis of the significant findings reported in a recent comprehensive review of studies on the association between inflammatory markers and suicidal behavior (Baldini et al., 2025) and on our own Olink data on the inflammation panel, we selected a panel comprising 12 inflammatory proteins, i.e., interleukin (IL)-1 β , IL-2, IL-4, IL-6, IL-10, IL-13, IL-17C, tumor necrosis factor alpha, interferon gamma, transforming growth factor beta, CXCL10, and CCL26.

2.4. Statistical analysis

The association of levels of the 12 inflammatory proteins with suicide attempt status (SA vs. non-SA) was analyzed by a logistic regression model in R version 4.3.0 (<https://www.R-project.org/>). The model included sex, age, diagnosis, duration of illness, body mass index (BMI), and medications (i.e., the number of antipsychotics, antidepressants, mood stabilizers, and tranquilizers being taken at the time of the interview) as covariates that were selected a priori based on their potential as confounders. Model performance was further evaluated using the Nagelkerke pseudo- R^2 and cross-validated receiver operating characteristic (ROC) analyses. Spearman correlation was used for exploratory analyses of duration of illness, frequency (i.e., the total number of lifetime suicide attempts), and recency (i.e., the time elapsed since the last suicide attempt). Additionally, multicollinearity among all covariates was assessed using the variance inflation factor (VIF). Results were considered statistically significant if the p value was less than 0.05, and Bonferroni corrections were used to adjust the results for multiple comparisons.

3. Results

The study included 40 SA and 115 non-SA. Table 1 presents the demographic and psychopathological data for all participants. Sex, age, BMI, diagnosis, and psychiatric symptoms at the time of interview were not significantly different between the two groups, but duration of illness was.

In this preliminary study of twelve inflammatory proteins, IL-1 β was the only marker that remained significantly associated with suicide

attempt status after applying a conservative Bonferroni correction. IL-1 β levels were significantly higher in the SA than in the non-SA group (odds ratio [OR], 1.96; 95% CI, 1.25–3.09; Bonferroni-adjusted p value, 0.039; Nagelkerke pseudo-R², 0.201; Fig. 1; Supplementary Table S1). No other proteins in the selected panel reached statistical significance after correction, suggesting that the inflammatory signal is primarily centered on the IL-1 pathway in our study. The logistic regression indicated that each two-fold increase in IL-1 β concentration is associated with a 96% increase in the odds of being in the SA group. Detailed descriptive statistics (mean, standard deviation, and sample size) for all 12 inflammatory proteins, stratified by group (SA vs. non-SA), are provided in Supplementary Table S2.

To evaluate the potential of IL-1 β as a biomarker for suicide attempt status, a 10-fold cross-validated ROC analysis was conducted. The model yielded an area under the curve (AUC) of 0.601 (95% CI: 0.50–0.70; Supplementary Figure 1) and a cut-off of 0.421 was identified. At this threshold, IL-1 β demonstrated a sensitivity of 35.0% and a specificity of 88.7%.

To assess whether the association between IL-1 β and suicide attempts was moderated by diagnosis, the interaction analysis between IL-1 β levels and diagnosis showed no statistically significant result (p value = 0.164). We also performed a subgroup analysis within the predominant diagnostic categories of the SA group (SCZ, n = 24; BD, n = 15), which showed that IL-1 β levels did not differ significantly between SA with SCZ and those with BD (p value = 0.36). Likewise, no significant correlation was observed between duration of illness and IL-1 β levels (r = -0.005, p value = 0.945), even though it was a relevant independent variable in our multivariate model (p value = 0.011).

In addition, to ensure model stability, we conducted the logistic regression analysis using a parsimonious model that adjusted for four main covariates (age, sex, diagnosis, and duration of illness; events per variable [EPV] = 10). The association between IL-1 β levels and suicide attempt status remained significant (Bonferroni-adjusted p value, 0.046) with an effect size (OR = 1.87) consistent with the fully adjusted model (OR = 1.96). Furthermore, all VIF values were below 2.0, indicating no significant multicollinearity between the covariates. These results show that the primary model is stable.

Additionally, correlation analyses within the SA group revealed that IL-1 β levels were not significantly correlated with either the frequency (r = -0.152, p value = 0.347) or the recency (r = -0.288, p value = 0.070).

4. Discussion

To investigate whether circulating levels of a selected panel of 12 inflammatory proteins were associated with a history of suicide attempts, the present study compared SA with non-SA in a transdiagnostic subsample of the PsyCourse Study. We found significantly higher IL-1 β levels in the SA group, suggesting a potential association with a higher lifetime risk of suicide attempts. However, given that IL-1 β was the only significant finding among the twelve proteins investigated, the results should be interpreted as hypothesis-generating, providing a framework for future targeted investigations into the IL-1 pathway. While these preliminary results align with existing theories of neuroinflammation, the cross-sectional design of our study precludes any causal inferences.

The pro-inflammatory cytokine IL-1 β is a member of the IL-1 family, which affects central nervous system function. Immune system dysregulation and inflammation appear to be associated with the severity of mental disorders and suicidal behavior (Baldini et al., 2025; Black and Miller, 2015; Solomon et al., 2025). In individuals with psychiatric disorders, an imbalance in the ratio of pro- to anti-inflammatory cytokines, e.g., due to chronic stress, infections, or vitamin deficiency, may lead to neurochemical, neuroendocrine, and behavioral abnormalities and trigger depressive symptoms, which are directly linked to suicidality (González-Castro et al., 2021).

Some studies found that IL-1 β blood levels were higher in individuals with SCZ, BD, and MDD (Baumeister et al., 2014) and that IL-1 β levels were higher in the post-mortem brain tissue of suicidal individuals (Pandey et al., 2012). Increased levels of inflammatory cytokines have been frequently associated with an increased risk of suicidal behavior due to their potential impacts on neurotransmitters, neuroplasticity, and stress response pathways (Baldini et al., 2025). Circulating IL-1 β can cross the blood-brain barrier (BBB), activate microglia in the central nervous system, which triggers a pro-inflammatory microenvironment through the excessive release of pro-inflammatory cytokines, reactive oxygen species, and glutamate excitotoxicity (Black and Miller, 2015; Han et al., 2017).

IL-1 β is known to damage the BBB, which facilitates the entry of immune cells into the brain and exacerbates neuroinflammation (Fetsko et al., 2024). Additionally, axon development, synapse formation, and oligodendrocyte proliferation may be adversely affected by IL-1 β (Vela et al., 2002). Biologically, IL-1 β acts as a critical neuroinflammatory mediator, bridging peripheral inflammation with central HPA-axis regulation and monoaminergic signaling (Brundin et al., 2017). Elevated levels of pro-inflammatory cytokines such as IL-1 β can disrupt

Table 1
Demographic and psychopathological data of the study participants.

Variable	Group	SA	Non-SA	Group differences		
				χ -squared	F value	P value
Participants, n		40	115			
Sex, % female		42.5	38.26	0.081		0.775
Age, mean \pm SD, y		47.3 \pm 11.07	42.96 \pm 13.33		3.423	0.066
BMI, mean \pm SD, kg/m ²		29.7 \pm 7.08	28.01 \pm 6.3		1.958	0.164
Duration of illness, mean \pm SD, y		18.6 \pm 11.42	12.55 \pm 9.88		10.25	0.001
Diagnosis, n	SCZ	24	65			0.498
	BD	15	40			(Fisher's exact test)
	MDD	1	10			
PANSS positive sum score, mean \pm SD		11.75 \pm 5.35	11.03 \pm 4.98		0.601	0.439
PANSS negative sum score, mean \pm SD		12.7 \pm 6.9	12.65 \pm 5.23		0.001	0.972
PANSS general sum score, mean \pm SD		26.85 \pm 9.33	25.27 \pm 7.5		1.142	0.287
IDS-C ₃₀ sum score, mean \pm SD		17.79 \pm 13.43	13.76 \pm 10.88		3.056	0.082
BDI-II sum score, mean \pm SD		11.71 \pm 12.25	12.09 \pm 10.17		0.032	0.859
YMRS sum score, mean \pm SD		3.22 \pm 4.55	3.49 \pm 5.51		0.072	0.788
ASRM sum score, mean \pm SD		2.62 \pm 3.08	2.2 \pm 2.81		0.6	0.44
MSS sum score, mean \pm SD		6.72 \pm 6.86	6.04 \pm 6.86		0.19	0.664

ASRM, Altman Self-Rating Mania Scale; BD, bipolar disorder; BDI-II, Beck Depression Inventory scale; BMI, body mass index; IDS-C₃₀, Inventory of Depressive Symptomatology scale; MDD, major depressive disorder; MSS, Self-Report Manic Inventory (German: Manie-Selbstbeurteilungsskala); Non-SA, non-suicide attempters; PANSS, Positive and Negative Syndrome Scale; SA, suicide attempters; SCZ, schizophrenia; YMRS, Young Mania Rating Scale.

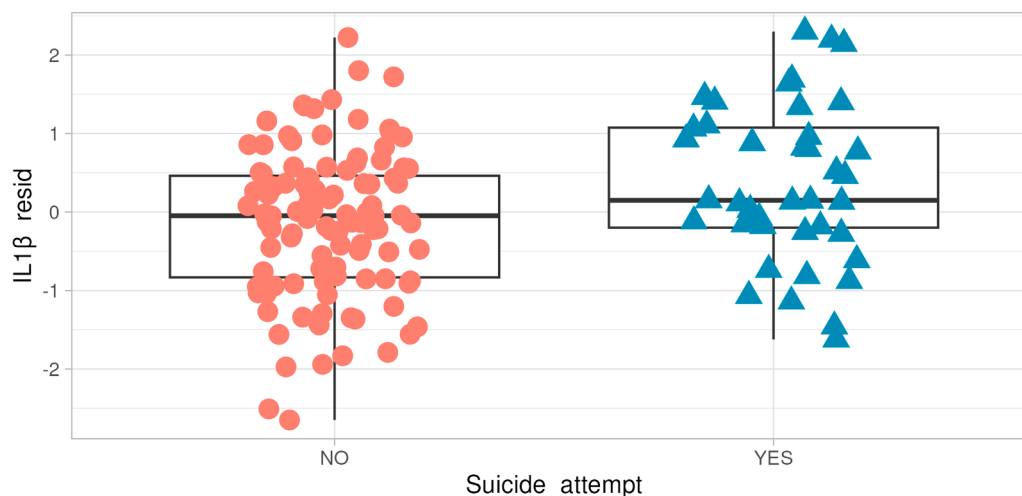


Fig. 1. Box plot and data points of serum levels of interleukin-1 β , the inflammatory cytokine differentially expressed in individuals with and without suicide attempts. IL-1 β resid, covariates-controlled residual values of interleukin 1 β .

tryptophan metabolism (by affecting specific kynurenine pathway enzymes), HPA axis functioning, and monoamine metabolism, and in susceptible individuals, these disruptions may have considerable effects on emotion and behavior and possibly culminate in suicide (Black and Miller, 2015; Brundin et al., 2017). IL-1 β may also contribute to glucocorticoid receptor resistance, which is linked to chronic psychological stress; notably, stress, HPA hyperactivation, and abnormal neurotransmitter levels are collectively associated with an increased suicide risk (Ganança et al., 2016). Previous research has also demonstrated that in cell culture models, IL-1 β increases the expression and activation of serotonin transporters (Zhu et al., 2006). By positioning our results within this framework, we highlight the possibility that IL-1 β is a key driver in the intricate immune-neuroendocrine interactions that may help to characterize the high-risk psychiatric phenotype.

Regarding diagnostic specificity, our findings suggest that the observed IL-1 β elevation is consistently associated with suicide attempts across the diagnostic subgroups in our sample rather than being a confounding reflection of the primary psychiatric diagnosis (a transdiagnostic framework). A recent meta-analysis found that IL-1 β is one of the most frequently increased pro-inflammatory cytokines in the peripheral blood of suicidal individuals (Black and Miller, 2015), but not all studies support this direction of changes in IL-1 β levels: Some found lower levels of IL-1 β (Coryell et al., 2018; Lu et al., 2019) or no association (Gabbay et al., 2009). While our findings regarding IL-1 β align with some previous post-mortem and peripheral studies (Black and Miller, 2015; Pandey et al., 2012), the lack of significance across the rest of our panel highlights the complexity of the neuroinflammatory signatures.

Regarding clinical utility, our findings suggest that while IL-1 β may not be suitable as a standalone screening biomarker, it has the potential for identifying a biologically distinct subgroup of high-risk individuals. In the context of complex psychiatric phenotypes, single biomarkers rarely achieve high discriminatory power. Our results highlight IL-1 β as a significant signal that may contribute to a broader, multi-marker inflammatory biosignature of suicide attempts.

The main limitation of our study is the small sample size, but another limitation is the unequal group allocation (SA, $n = 40$; non-SA, $n = 115$). Additionally, the PsyCourse Study data do not include information on the infection status of individuals at baseline. Given the limited number of suicide attempt cases overall as well as within the MDD subgroup, the results of the interaction between IL-1 β levels and psychiatric diagnosis should be interpreted with caution as the model may have been underpowered to detect subgroup-specific effects. In order to conduct a stratified analysis based on duration of illness, the

sample was heavily skewed toward long-term illness (>5 years), leaving the short-term (<2 years) and medium-term (2–5 years) subgroups underpowered for meaningful comparison. We must also acknowledge the potential confounding effect of general psychopathology. Larger-scale studies are needed to further dissociate the specific inflammatory signature of suicidality from the broader symptom severity of psychiatric disorders. While our exploratory analyses suggest that IL-1 β remains stable regardless of frequency or recency, the cross-sectional nature of this study limits our ability to definitively establish IL-1 β as a trait marker. Without longitudinal data, it is difficult to determine whether IL-1 β represents a stable vulnerability marker or a state-dependent correlate of suicidal behavior. If the proximity of suicide attempts to the blood sampling time influences IL-1 β levels, the heterogeneity in this regard may obscure or magnify any relationships. Thus, while IL-1 β emerges here as a candidate for further study, its stability over time and its potential clinical utility require validation in larger, longitudinal cohorts.

5. Conclusion

Suicidal behavior, one of the leading global causes of injury and death, has been reported to be linked to alterations in inflammatory pathways. Our study provides preliminary evidence suggesting that the IL-1 signaling pathway may be associated with a lifetime history of suicide attempts in individuals with major psychiatric disorders. These findings underscore the need for further research to determine whether IL-1 β can serve as a reliable biomarker or whether targeting the relevant pathways may be helpful in preventing or reducing suicidal behavior. Given the modest sample size of our study, the results should be considered preliminary and require replication in larger, independently powered cohorts.

CRediT authorship contribution statement

Mojtaba Oraki Kohshour: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Monika Budde:** Writing – review & editing, Resources, Data curation, Conceptualization. **Pierre Solomon:** Writing – review & editing, Resources, Data curation. **Kristina Adorjan:** Writing – review & editing, Data curation. **Maria Heilbronner:** Writing – review & editing, Data curation. **Alba Navarro-Flores:** Writing – review & editing, Data curation. **Daniela Reich-Erkelenz:** Writing – review & editing, Data curation. **Eva C. Schulte:** Writing – review & editing, Data curation. **Fanny Senner:** Writing – review & editing, Data

curation. **Volker Arolt:** Writing – review & editing, Data curation. **Bernhard T. Baune:** Writing – review & editing, Data curation. **Udo Dannlowski:** Writing – review & editing, Data curation. **Andreas J. Fallgatter:** Writing – review & editing, Data curation. **Christian Figge:** Writing – review & editing, Data curation. **Georg Juckel:** Writing – review & editing, Data curation. **Eva Z. Reininghaus:** Writing – review & editing, Data curation. **Max Schmauß:** Writing – review & editing, Data curation. **Jens Wiltfang:** Writing – review & editing, Data curation. **Peter Falkai:** Writing – review & editing, Data curation. **Jeremie Poschmann:** Writing – review & editing, Resources, Methodology, Data curation. **Sergi Papiol:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Urs Heilbronner:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Thomas G. Schulze:** Writing – review & editing, Supervision, Project administration, Data curation.

Ethical approval

The study was performed in accordance with the principles of the Declaration of Helsinki, and approval was obtained from the respective ethics committees at the study sites (Project number: 17–13 at the University Hospital Munich).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.psyneuen.2026.107862](https://doi.org/10.1016/j.psyneuen.2026.107862).

Data Availability

A unique feature of the PsyCourse Study is that it has been conceptualized as a continuously growing data resource available to the scientific community. Data sharing will be based on mutually agreed research proposals and within the Open Science framework of the PsyCourse Study (Please see psycourse.de/openscience-en.html).

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