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Persistent pro-inflammatory trait in elderly patients following treatment-resistant major depressive disorder: a longitudinal exploratory study

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ABSTRACT

Objectives: Considering that the remission rate for major depressive disorder (MDD) in elderly patients is below 50%, there is a compelling requirement for an enhanced comprehension of the underlying mechanisms. Chronic low-grade inflammation has been posited as one potential contributor to treatment-resistant MDD in the elderly. Accordingly, the objective of our study was to explore the longitudinal trends of systemic immune markers in elderly inpatients referred to electroconvulsive therapy due to an episode of treatment resistant unipolar MDD.

Methods: The study encompassed 64 elderly inpatients with unipolar MDD that had failed to respond to therapy in primary health care, and 18 non-depressed controls. Blood samples were collected at pre-treatment, mid-treatment, post-treatment and 12 weeks follow-up. We assessed 27 immune markers *via* multiplex assays. Depressive symptoms were evaluated using the Hamilton Rating Scale of Depression at these timepoints. For controls, the immune markers and depressive symptoms, were measured at baseline and eight weeks follow-up using identical methods.

Results: At follow-up, patients showed higher concentrations of 23 immune markers compared to controls, although the concentration of 19 immune markers decreased significantly from pre-treatment to follow-up. No differences in immune marker concentrations between treatment responders and non-responders were observed pre- and post-treatment in the patient group.

Conclusion: Our findings suggest that a pro-inflammatory trait persists in elderly after an episode of treatment resistant unipolar MDD. Thus, our study supports that chronic low-grade inflammation may characterise elderly with treatment-resistant unipolar MDD.

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Unipolar major depression; inflammation; cytokines; older adults; immune markers

Introduction

Low remission rates in major depressive disorder (MDD) in patients aged 65 years and older, regardless of the treatment modality, represent a well-documented challenge. Approximately one-third of these individuals reach remission post-initial antidepressant therapy [1], while half attain remission following electroconvulsive therapy (ECT) [2]. In this context, inflammation has been implicated in treatment-resistant depression among younger adults [3], and a recent nine years follow-up trial including 945 midlife adults reported that inflammation may predict MDD episodes [4]. However, the role of inflammation in elderly with treatment resistant unipolar MDD requires further evaluation. Hence, monitoring the patterns of immune markers in elderly inpatients with unipolar MDD towards remission of an episode could further elucidate the underlying involvement of inflammation as a mechanism that contribute to the persistence of depressive traits in this demographic.

A limited number of studies have examined immune markers in elderly inpatients with MDD [5–7]. We have previously documented that the cohort of elderly inpatients with unipolar MDD in this study exhibited significantly elevated levels of 22 immune markers, which included a spectrum of trophic, adaptive, and both pro- and anti-inflammatory cytokines, when compared to non-depressed controls at pre-treatment [7]. Thomas et al. (2005) identified a correlation between pro-inflammatory immune markers and the severity of depressive symptoms prior to treatment [5]. On the other hand, a longitudinal study with a sample of 10 patients found no significant relationship between interleukin-1 β (IL-1β), IL-6 or TNF and the severity of depressive symptoms [6].

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Typically, cross-sectional study designs are not optimal for investigating the role of inflammation in mechanisms contributing to varying remission rates. Similarly, the cited longitudinal study [6] encompassed merely ten inpatients, potentially lacking adequate power to detect associations between depression and inflammation. Despite this, outcomes from this longitudinal study suggest that the interplay between inflammation and depressive symptoms may be more intricate than the dose-response relationship suggested by Howren et al. (2009) [8].

In summary, to date, there exists only a single, limited scale longitudinal study investigating the link between inflammation and depression in hospitalized elderly with an episode of MDD. Consequently, a longitudinal evaluation of a broader array of immune markers in a more substantial cohort of elderly with treatment resistant MDD is warranted.

In Norway, elderly with MDD that has failed to respond to therapy in primary health care are admitted to hospital for ECT. ECT is deemed an advantageous treatment for elderly inpatients with MDD, and particularly those with multiple co-morbid physical conditions. The elderly population contains subgroups of frail individuals vulnerable to the adverse effects of antidepressant medications, as well as to dehydration and weight loss related to MDD itself [9,10]. Moreover, ECT is acknowledged as the most efficacious short-term intervention for MDD [11], yet the precise mechanisms of its therapeutic effects are not fully understood. One study documented a significant reduction in tumour necrosis factor (TNF) levels during ECT [12], in contrast to no change in TNF levels with antidepressant medication in adults with MDD [12]. Additionally, another study observed a decrease in interleukin-6 (IL-6) and no alteration in interleukin-1receptor antagonist (IL-1ra) levels during ECT in this patient population [13].

In this study, our objective was to explore the progression of systemic immune markers in elderly inpatients referred to ECT due to an episode of treatment resistant unipolar MDD.

Materials and methods

Study design

The present investigation is a longitudinal, exploratory study examining the trajectories of immune markers in elderly inpatients receiving ECT after failing to respond to treatment of unipolar MDD in the primary health care, and non-depressed elderly controls (Figure 1). It encompasses a subgroup of patients from a broader randomized controlled trial assessing the treatment efficacy [2] and cognitive effects of ECT in unipolar and bipolar MDD [14], registered with the identifier: NCT01559324 at the online clinical database ClinicalTrials.gov. The Regional Committee for Research Ethics in Norway and the Ombud for Patients' Rights approved this study prior to inclusion. Inclusions have been based strictly upon informed consent given and signed by the participants. We have prior published the baseline results included in this longitudinal study, comparing immune markers between patients and controls at pre-treatment [7].

Patient diagnostic procedure

Unipolar MDD was diagnosed according to the DSM-IV-TR criteria, and the 17-item Hamilton Rating Scale for Depression (HRSD)-17 were used to assess the depressive symptom score by three professional raters. Additionally, screening for psychiatric co-morbidities was performed in consensus between two independent senior consultants in geriatric psychiatry using the standardized clinical interview MINI-Plus version of the Mini-international Neuropsychiatric Interview [15,16].

Inclusion and exclusion criteria

Eligibility for participation required patients to meet the criterion for a current episode of unipolar MDD as outlined in the Diagnostic and Statistical Manual of Mental Disorders,

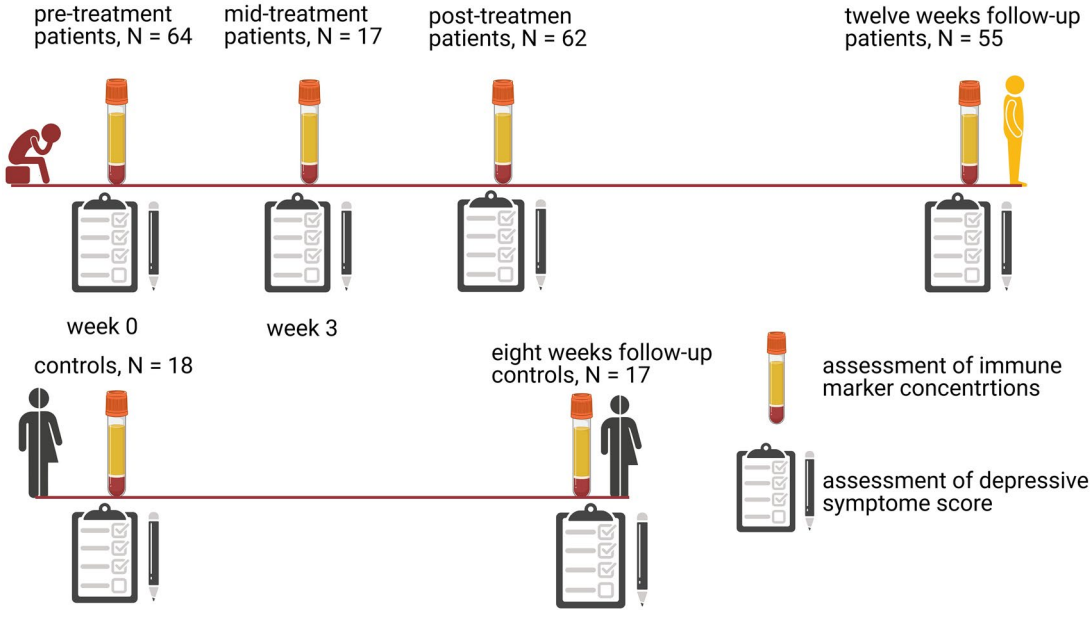

Figure 1. Measurements in patients and controls. [Created in BioRender. Gaarden, T. (2024) https://BioRender.com/p50h569]

Fourth Edition, Text Revision (DSM IV-TR) [17], and to exhibit a score of 18 or higher on the HRSD-17 [18,19]. Participants also had to demonstrate the capacity to provide informed consent and be aged between 60 and 85 years.

Exclusion criteria encompassed bipolar disorder, Parkinson's disease, schizophrenia, schizoaffective disorder, recent alcohol or substance abuse within the past three weeks, a Mini Mental State Examination (MMSE) [20,21] score below 24, any diagnosis of dementia, or any medical condition contradicting ECT, as well as those who had undergone ECT in the preceding six months.

Psychotropic drug use among participants was limited to the following maximum daily doses: oxazepam 15 mg, zopiclone 7.5 mg, olanzapine 20 mg, and quetiapine 200 mg.

Recruitment and health assessment of the patients and controls

Norwegian-speaking patients were recruited from the Department of Geriatric Psychiatry at Diakonhjemmet Hospital, a secondary care hospital in Oslo, Norway, between September 1, 2009, and May 1 2013. A total of ninety-seven patients with treatment resistant MDD referred to our department were assessed for eligibility during this timeframe (Figure 2). Of these, 23 were excluded based on the exclusion criteria, two did not met the inclusion criteria, six withdrew consent, and two had a change in diagnosis. Consequently, sixty-four patients were included in the study.

For the control group, we recruited 20 non-depressed, Norwegian-speaking elderly from a community senior citizen centre (Table 1). However, two controls were subsequently excluded due to an advanced stage of cancer, which aligned with the exclusion criteria applied to the patient group.

All patients and controls were subject to a comprehensive health evaluation. For the patient group, this included compiling a medical history with an emphasis on the cardiac, respiratory and nervous systems, primarily to prepare for anaesthesia for the included patients. Routine blood tests for laboratory analyses and depression symptoms using the HRSD-17 were also conducted. Medical history focused on systems pertinent to anaesthesia preparation. The average number of prescribed drugs was documented (mean 5.2, standard deviation [SD] 2.3) and body mass index (BMI) was calculated. Laboratory tests included blood sedimentation rate (SR), C-reactive protein (CRP), complete blood count with leukocytes, haemoglobin levels, electrolytes, creatinine, liver enzymes, thyroxine, HbA1c, and glucose. Additionally, the cumulative medical burden of physical illness was evaluated using the Cumulative Illness Rating Scale for geriatric patients (CIRS-G), excluding the

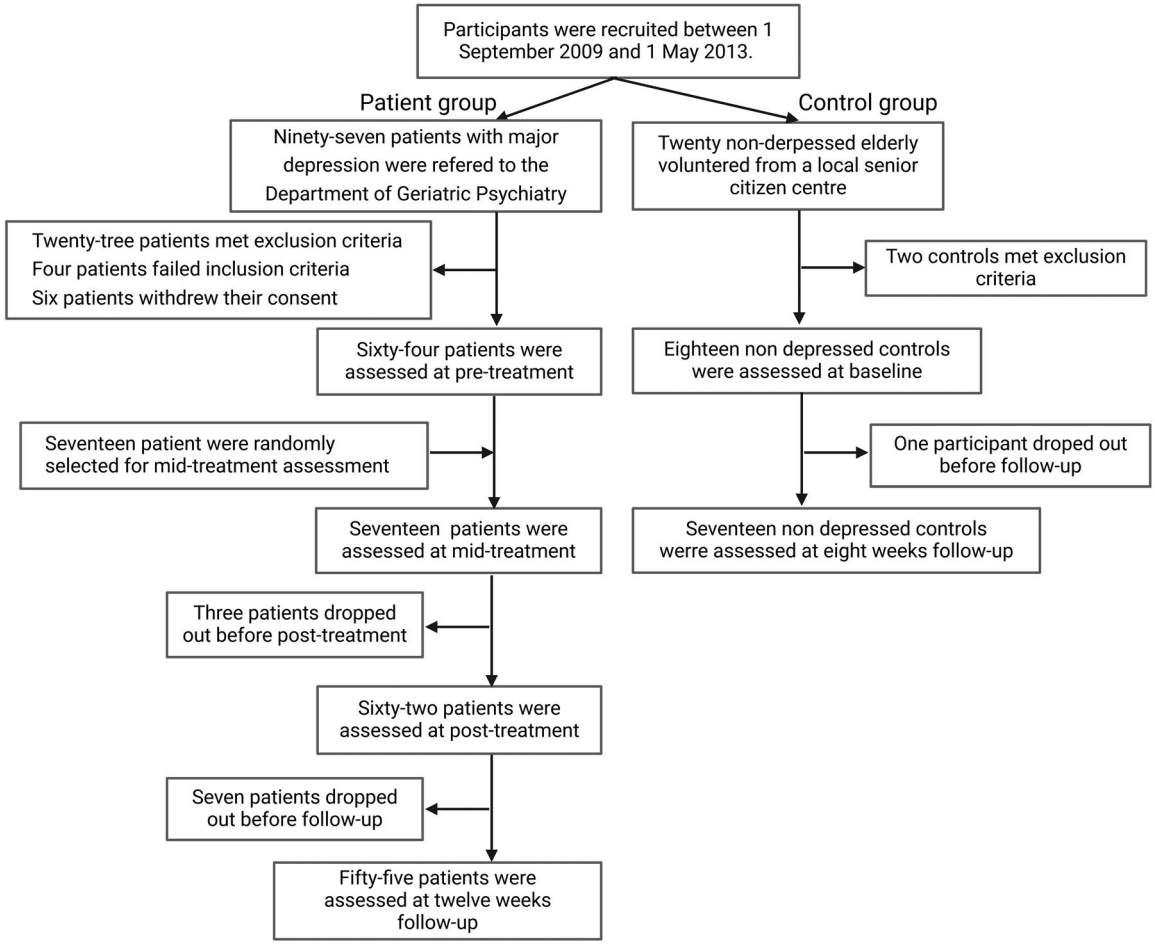

Figure 2. Flowchart of the study. [Created in BioRender. Gaarden, T. (2024) https://BioRender.com/v02z756]

Table 1. Characteristics of the patients and the non-depressed controls at baseline [7].

	Patients, $n = 64$	Controls, $n = 18$	P-value
Gender, female, n (%)	35 (54.7)	12 (66.7)	0.427[b]
Age, mean years (SD)	75.2 (6.3)	78.1 (4.8)	0.083[a]
Education, mean years (SD)	13.6 (3.0)	13.4 (2.8)	0.805[a]
MMSE, mean (SD)	27.7 (1.8)	28.2 (2.1)	0.432[a]
CIRS-G, mean (SD)	6.8 (3.6)	5.4 (2.4)	0.139[a]
BMI, mean (SD)	23.3 (4.6)	24.2 (4.1)	0.422[a]

[a]) Independent samples *t*-test; [b]) χ^2-test.
Abbreviations: BMI, body mass index; CIRS-G, Cumulative Illness Rating Scale for Geriatric Patients; MMSE, Mini Mental State Examination; n, number; SD, Standard Deviation.

psychiatric disorders [22] section, and any current or past physical conditions affecting immune system function (such as cancer, inflammatory diseases and infections) were recorded.

The health assessment for the control group encompassed blood sampling, evaluation of depressive symptoms using the HRSD-17, BMI measurement, and assessment of the cumulative medical burden of physical illness using the CIRS-G, excluding the psychiatric disorders component. The use of psychotropic drugs was not recorded for the control participants.

Electroconvulsive therapy

The patients underwent ECT twice every week until they met the remission, defined as an HRSD-17 score below 8, until no further improvement was observed as measured by the HRSD-17, or up to a maximum of 16 treatments. The Thymatron system IV (Somatics, LLC, Lake Bluff, IL, USA) was utilized, delivering square-wave, brief-pulse currents with a pulse width ranging from 0.5 to 1.0 milliseconds, a bidirectional current of 0.9 A, and a frequency of 10–70 Hz. Patients were randomized to bi-frontal or right unilateral electrode placements [2]. The average number of ECT sessions administered was 9.0 (SD 3.1); with an average charge of 327 milli Coulombs per session (SD 114), an average duration of motor seizure activity at 30 s (SD 10), and an average electroencephalography seizure duration of 43 s (SD 12).

Blood sampling

EDTA-plasma was collected from peripheral blood of patients between 08.00 and 10.00, and from controls between 10.00 and 11.00. For patients, blood was drawn at four distinct timepoints: pre-treatment, mid-treatment (72 h after the fifth ECT session), post-treatment (three days after the final ECT), and at 12-week follow-up post treatment. At mid-treatment, blood was collected from a subset of 17 patients chosen at random from the total of 64, while the remaining timepoints, all patients were sampled. For controls, blood was taken at study inclusion (baseline) and again at eight weeks follow-up. Patients were fasting only at the mid-treatment collection, while at other times, neither patients nor controls were fasting. Blood samples were centrifuged immediately at 4 °C at 3,000 x g for 15 min and subsequently stored in a local biobank at −80 °C. The study timeline and associated measurements are illustrated in Figure 2.

Laboratory analysis

The plasma samples were analysed using the multiplex cytokine assay (Bio-Plex Human Cytokine 27-Plex Panel; Bio-Rad Laboratories Inc., Hercules, CA, USA) which included the following 27 immune markers: IL-1β, IL-1 receptor antagonist (ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor (bFGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon (IFN)-γ, interferon-inducible protein (IP)-10, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, MIP-1β, platelet derived growth factor (PDGF)-BB, regulated upon activation T cell expressed and secreted (RANTES), TNF and vascular endothelial growth factor (VEGF). The samples were analysed on a Multiplex Analyzer (Bio-Rad Laboratories) at the Research Laboratory, Nordland Hospital Bodø, according to the instructions from the manufacturer.

Statistical analysis

Demographic and clinical characteristics are reported as group means and standard deviations for continuous variables, or as frequencies and percentages for categorical variables. Comparisons between patient and control groups were conducted using independent samples t-tests for continuous variables and χ^2-tests for categorical variables. Immune markers, being non-normally distributed, are presented as medians and interquartile ranges. Comparisons of immune marker concentrations between patients and controls, as well as between remitters and non-responders within the patient group, were performed using independent samples median tests. Logarithmic transformation was applied to the immune marker values in all subsequent analyses to correct highly skewed distribution.

To evaluate the temporal trend of each immune marker, linear mixed models with random intercepts were utilized. Because the models with fixed effects exhibited Due to convergence issues with models containing fixed effects for higher-order continuous time components, models incorporating fixed effects for each time point (dummy variables) were used instead. To explore the differences in immune marker changes from pre-treatment to post-treatment between remitters and non-responders, a linear mixed model with random intercepts, fixed effects for timepoints, group status, and their interaction was estimated. These models were adjusted for psychosis, antidepressant use, HRSD-17 scores, duration of the current MDD episode, BMI, CIRS-G, gender and age for patients, and for HRSD-17, BMI, CIRS-G, gender and age for controls. As the assessed immune markers are dependent [23], correction for multiple testing of the immune markers are not appropriate.

The temporal trend of HRSD-17 scores was analysed using linear mixed models with random intercepts and fixed effects for the time component up to the third-order for patients,

and linear time component for controls. The patient model was further refined to include adjustments for psychosis, benzodiazepine use, Montgomery and Asberg Depression Rating Scale (MADRS), duration of the depression, CIRS, and age; for controls, adjustments were made for MADRS and age. Model simplification was guided by the Akaike Information Criterion (AIC), with preference given to models with lower values. Results from the linear mixed models are reported as mean changes or mean differences in changes, accompanied by 95% confidence intervals and p-values. The IBM SPSS Statistics 25 software and SAS v.9.4 were used for statistical analyses. All tests were two-sided. Because the study had an explorative approach, we deemed the results with p-values below 0.05 to be statistically significant.

Results

Characteristics of the participants

The patient cohort exhibited a 28 weeks median duration of the assessed depressive episode, with the first and third quartiles being 13 and 77 weeks, respectively. At inclusion, the mean number of prescribed drugs were 5.2, (SD 2.3). We have prior published the baseline data in a cross-sectional study [7].

Measurement accuracies

The intra-class correlation between the raters using the HRSD-17 rating depressive symptom scores were 0.90 [2]. Immune marker measurements had lower detection limit in the range between 0.24 and18.84 pg/ml. The concentration of IL-1β, IL-5, IL-10 and IL-15 was below standard range in more than 20% of the patient cases at pre-treatment. At follow-up IL-1β, IL-2, IL-5, IL-9, IL-10, IL-13, IL-17, G-CSF, bFGF and VEGF were all below the standard range in more than 20% of the patient cases. In the controls, 14 and 22 immune markers had concentrations below the detection limit in more than 20% of the cases at baseline and at follow-up, respectively. Values measured below the lower detection limit were extrapolated beyond the standard range and values out of range were assigned the value 0.001 pg/ml in the statistical analysis.

The trends of immune marker concentrations during treatment and towards follow-up

We observed a decline in serum concentrations in 19 immune markers from pre-treatment to follow-up in the patient cohort, as detailed in Supplementary Table 1. Yet, at follow-up, the levels of 23 immune markers remained significantly elevated in patients when compared to non-depressed controls, as reported in Supplementary Table 1.

Throughout the treatment course, a significant decrease was recorded for all 27 immune markers in patients from pre- to mid-treatment, delineating a pronounced downward trend in immune markers concurrent with treatment. This pattern is exemplified by the trends of IL-6, TNF, PDGF-BB and MCP-1, which are graphically represented in Figure 3.

From mid-treatment to post-treatment, there was a significant increase of 23 immune markers (data not shown). The levels of the remaining four immune markers (IL-9, IL-13, IL-15 and MIP-1b) also rose, albeit not to a significant degree. Consequently, by the time of post-treatment assessment, the concentrations of nine immune markers TNF, IL-17, IFN-γ, PDGF-BB, IP-10, MCP-1, RANTES, IL-4 and GM-CSF did not differ significantly from their initial pre-treatment levels. Between the post-treatment assessment and the 12-week follow-up, the concentrations of 15 immune markers remained unchanged, while five increased and seven decreased significantly. These findings persisted even after adjusting for demographic and clinical characteristics.

Comparing the trends of immune markers between remitters and non-responders

At pre-treatment, the levels of TNF, IFN-γ and PDGF were significantly higher in non-responders than in remitters, as shown in Supplementary Table 3. From pre-treatment to post-treatment, the decrease in IL-12 concentration was significantly greater in non-responders as opposed to remitters, detailed in Supplementary Table 4. Following adjustment for demographic and clinical characteristics, the decrease in concentrations of TNF, IL-12, PDGF-BB and RANTES were significantly more pronounced in non-responders compared to remitters, though these particular data are not presented. At the post-treatment timepoint, the concentrations of all 27 immune markers showed no significant differences between remitters and non-responders, as indicated in Supplementary Table 4.

Change of the immune marker concentrations from baseline to follow-up in the controls

Within the control group, 11 immune markers did not exhibit significant changes from baseline to the eight-week follow-up, while 16 immune markers showed significant decreases in both unadjusted and adjusted analyses (data not shown).

The trends of depressive symptom score measured by HRSD-17 during treatment

The depressive symptom score, as quantified by the HRSD-17, exhibited a significant reduction from pre-treatment to mid-treatment ($p < 0.001$) and continued to decrease, though to a lesser extent, from mid-treatment to post-treatment ($p = 0.010$), as illustrated in Figure 4 and Supplemental Table 5. However, from post-treatment to the 12-week follow-up, the depressive symptom score experienced a no significant increase ($p = 0.439$), depicted in Figure 4 and Supplemental Table 3). In contrast, the control group's depressive symptom score showed a non-significant decline from baseline to the eight-week follow-up, as shown in Figure 4 and Supplemental Table 5. At the post-treatment assessment, 30 patients (47%) achieved remission, denoted by an HRSD-17 score of less than eight. Conversely, 21 patients (33%) were classified as non-responders, exhibiting less than a 50% reduction in the HRSD-17 score form pre-treatment. Among the non-responders, there was a 34% mean reduction in the depressive symptom score from pre-treatment to post-treatment.

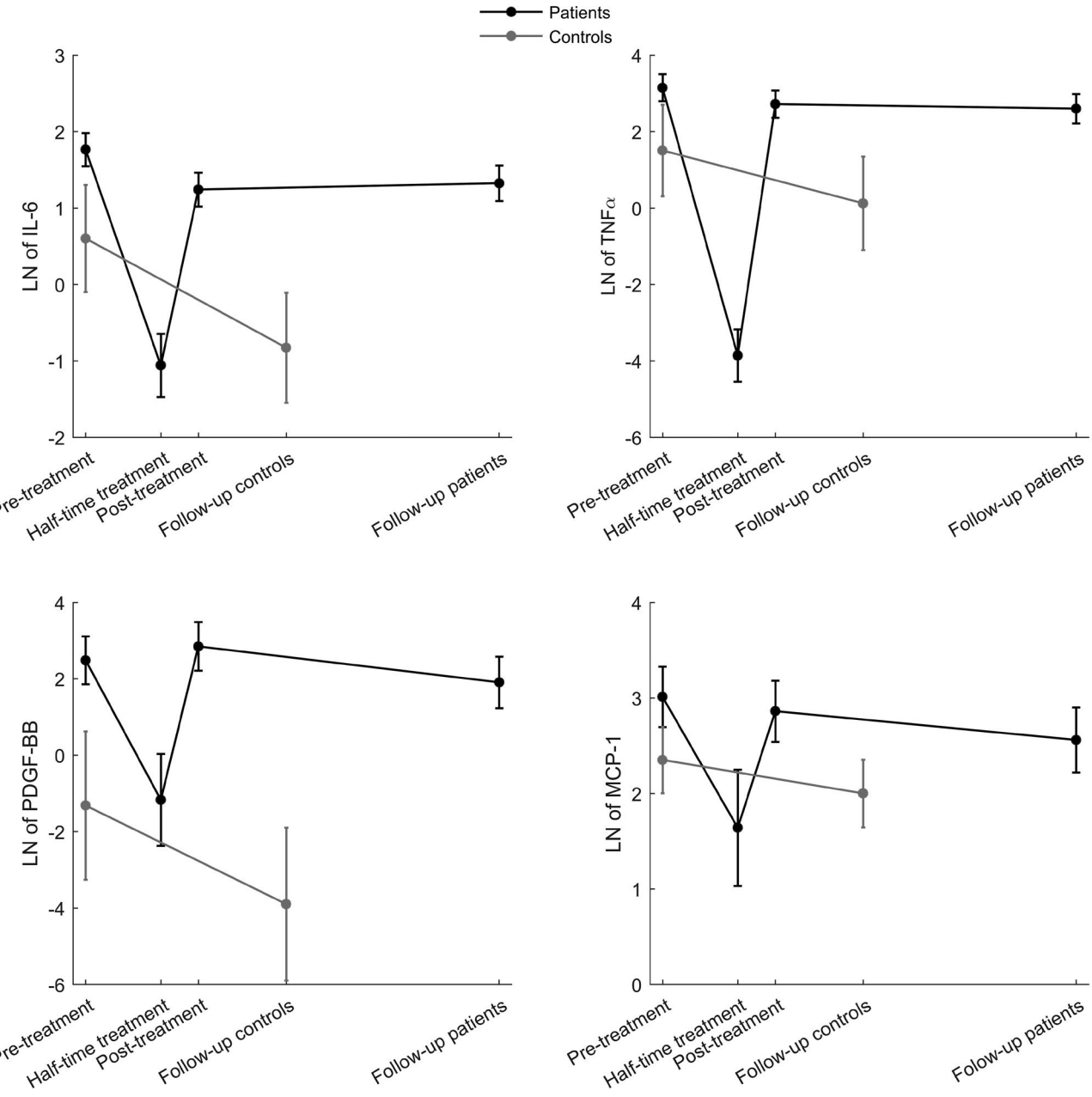

Figure 3. Trends for IL-6, TNF, PDGF-BB and MCP-1.
Abbreviations: IL, interleukin; PDGF, platlet derived growth factor-BB; MCP, monocyte chemotactic protein; LN, Natural logarithm.

Discussion

Our findings indicate a persistent higher concentration of 23 immune markers in the patients at follow-up compared to the controls. Additionally, our results demonstrate a decrease in serum concentrations of 19 immune markers from pre-treatment to follow-up. Contrasting our findings Brambilla and Maggioni (1998) reported no differences in immune marker concentrations between patients and controls after treatment and no change in immune marker concentrations during treatment [6]. However, our study benefits from enhanced statistical power relative to the aforementioned study [6] by Brambilla and Maggioni, which incorporated a sample size of ten patients and ten controls, potentially accounting for the discrepancies observed in the outcomes of the studies [6].

Concerning the correlation between depressive symptom scores and immune marker concentrations, we observed a significant reduction in depressive symptoms concomitant with the decrease in immune markers from pre-treatment to mid-treatment. This trend suggests a potential association between immune markers and depressive symptoms, corroborating with the findings of Howren et al. (2009), which suggested a dose-response relationship between depression severity and inflammatory processes [8]. However, our study documented a pronounced increase in the concentration of immune markers from mid-treatment to post-treatment, which was paradoxically associated with a further decline in depressive symptomatology.

Additionally, we observed that the trajectories of immune marker concentrations did not vary between treatment

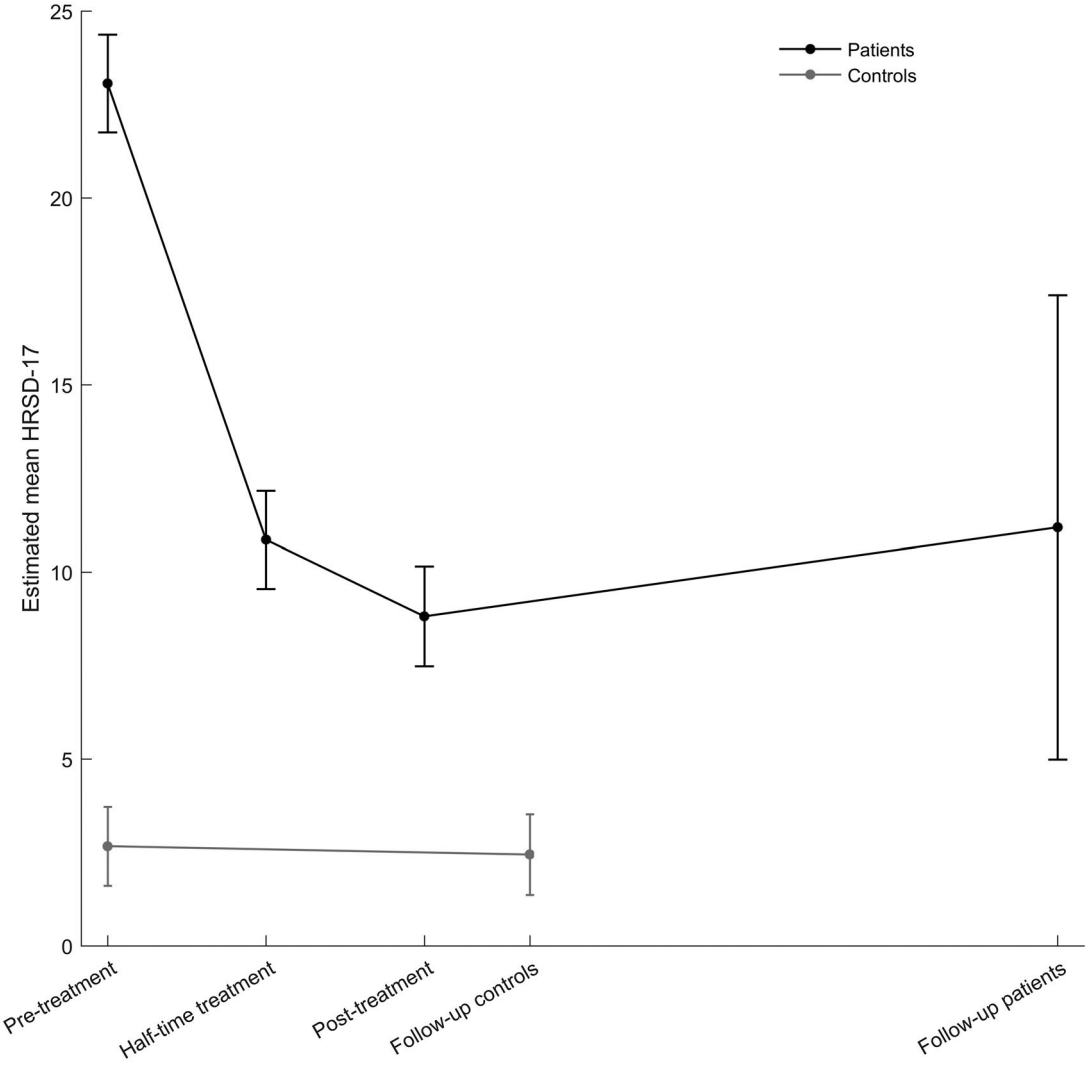

Figure 4. Trends of the depressive symptom scores measured by the HRSD-17 in the patients and the controls.
Abbreviation: HRSD-17, Hamilton Rating Scale of Depression.

responders (remitters) and non-responders within our cohort. This aspect of our results does not align with the theory of a positive association between inflammation and depression symptom scores as proposed by Howren et al. (2009) [8]. This inconsistency suggests that while inflammation may accompany MDD, it does not necessarily diminish in direct correlation with symptomatic improvement. Our findings imply that a dose-response relationship between depressive symptom severity and immune marker concentrations may exist transiently at the initial stages of treatment for a depressive episode.

Furthermore, the administration of ECT itself, along with its potential transient impact on immune marker concentrations, may also partially explain the results observed in our study. Accordingly, the reduction observed in 27 immune markers across the initial five sessions of ECT intimates that ECT might exert a considerable effect on immune system activity. However, it is important to note that during the mid-treatment measurement timepoints, patients were in a fasting state, in contrast to the non-fasting state at the pre-treatment, post-treatment and follow-up measurements. The potential influence of fasting on the decreased concentrations of immune markers cannot be disregarded. On the other hand, Dias et al. (2016) [24] have reported no significant differences between fasting and non-fasting blood concentrations of IL-1β, IL-6, IL-8 and TNF in 49 men (mean age 68 years) and 46 women (mean age 65 years). This could support that the pronounced and significant decrease in all 27 immune markers from pre-treatment to mid-treatment in our study is predominantly attributable to the effects of ECT. Thus, our findings propose that ECT may exert a transient but potent anti-inflammatory effect, which is consistent with the results reported by Hestad et al. (2003) [12] and Jarventausta et al. (2017) [13] who observed a reduction in TNF and IL-6 levels, respectively during ECT treatment.

In our control group, both depressive symptoms and immune marker concentrations remained relatively low at follow-up. This contrasts with the patient group, which differed significantly in terms of depressive symptoms and immune marker concentrations at this stage. Notably, several immune markers persisted at high concentrations in the

patient group at follow-up, distinctly different from those in the control group. Consequently, we cannot discount the hypothesis that these elevated immune markers levels may represent a characteristic trait of treatment resistant unipolar MDD in elderly.

Methodological considerations

Addressing required sample size to acquire sufficient statistical power, a meta-analysis by Yuan et al. (2019), indicated that a minimum of 70 participants is required to evaluate the correlation between the immune marker IL-6 and depression with an 80% statistical power and an alpha level of 0.05 [25]. Moreover, for the simultaneous analysis of 30 immune markers, a more stringent p-value of 0.016 is advocated, necessitating an increased sample size of 174 for adequate power concerning IL-6 [25]. However, immune markers are dependent variables [23], and make corrections for multiple testing misleading. A coinciding time-trend between the dependent immune markers, as in this study, may be an indicator of reliable results. Thus, the conclusions drawn by Yuan et al. (2019) suggest that our investigation may be close to sufficient powered regarding IL-6, still necessitating a prudent approach in the interpretation of our findings.

Concerning the methodological components of our investigation, multiplex cytokine assays are acknowledged for their proficient capability in measuring specific immune markers [26,27] and distinguishing between them effectively [26]. Nevertheless, the sensitivity to particular immune markers may be diminished when numerous markers are assayed concomitantly [28], which could have led to the reduced detectability of certain immune markers in our study. It should also be noted that the reliability between immune marker measurements is reported to be good among adults with MDD [29] but poor in healthy adults [27, 30]. This discrepancy suggests that caution should be exercised when interpreting the concentrations of immune markers in the healthy control group in our study. Notably, we found that within our control group, concentrations of 14 and 22 immune markers were below the detection limit at baseline and at follow-up respectively. Conversely, in our patient cohort, plasma concentrations of only four immune markers were below the detection threshold in more than 20% of the patients.

The age range of participants in this study spanned from 60 to 85 years, and some individuals presented with mild cognitive impairment, as the inclusion criterion was set at an MMSE score of 24 or higher. Consequently, the presence of mild cognitive impairment may have contributed to an elevated pro-inflammatory load in the study group. It is important to note that, in accordance with national guidelines, the included patients had previously undergone unsuccessful treatment with psychotropic drugs prior to study enrollment. At the time of inclusion, patients were still using moderate doses of psychotropic medications. This ongoing use may have influenced our results by potentially reducing the pro-inflammatory load in the patient group.

It warrants highlighting that the inter-rater reliability for the assessment of depressive symptoms using the HRSD-17 was good within our study, aligning with the findings of prior research [31].

Limitations and strengths

We must underscore the observational design of our study, which inherently does not control for potential confounders as robustly as a prospective, randomized, controlled and blinded trial would. Despite this limitation, we have statistically addressed confounding factors by employing a linear mixed model for each immune marker, adjusting variables such as depressive symptom score, presence of psychotic symptoms, use of antidepressant medications, duration of the current depressive episode, BMI, CIRS-G, gender and age. However, the behavioural diversity inherent in a population over a prolonged lifespan introduces a spectrum of possible confounders not accounted for in our analysis. It is important to note that this study may be constrained by the relatively small sample size, particularly with respect to the control group. This limitation primarily affects the comparative aspects of our findings rather than the longitudinal analysis of the patient cohort. Additionally, potential confounders including physical activity habits, smoking and alcohol consumption were not evaluated in our study. However, these factors have been reported by other studies to not significantly influence immune marker concentrations in elderly [32].

In summarizing the limitations of our investigation, emphasis should be placed on its observational and explorative nature, which is capable of generating, reinforcing, or attenuating hypothesis but not conclusively rejecting or confirming them. Furthermore, the relatively small sample size constrains our capacity to detect only moderate to large effect sizes of immune markers. Additionally, the extensive array of immune markers evaluated heightens the risk of false-positive findings.

Conclusion

In summary, our study lends support to the concept that the pro-inflammatory trait persists in elderly after a treatment resistant MDD episode, suggesting a low-grade continuous-load inflammatory process contributing to the pathogenesis of treatment resistant unipolar MDD in the elderly.

Acknowledgements

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Ethics approval and consent to participate

The Regional Committee for Research Ethics in Norway has approved the study. Inclusions have been based strictly upon informed consent given and signed by the patient.

Authors' contributions

TLG participated in recruiting patients and was a major contributor in writing the manuscript. KE participated in the planning of the study and was a major contributor in writing the manuscript. TMB participated in planning the study and recruiting patients and was a contributor in writing the manuscript. JŠB performed the statistical analyses and contributed in writing the manuscript. ML participated in recruiting patients and was a contributor in writing the manuscript. BL participated in the planning of the study and was a contributor in writing the manuscript. TEM participated in the planning of the study, interpretation of the data and was a contributor in writing the manuscript. AC participated in the planning of the study, interpretation of the data and was a major contributor in writing the manuscript. All authors have read and approved the final manuscript.

Name of the institution at which the research was conducted

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Availability of data and material

All data analysed during this study are included in this published article and its supplementary information files.

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