Full Length Article

Higher rates of allergies, autoimmune diseases and low-grade inflammation markers in treatment-resistant major depression

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ABSTRACT

Only 30% of patients with major depressive disorder (MDD) reach full recovery or remission. Treatment-resistant depression (TRD) is MDD that does not respond to adequate treatment attempts with at least two antidepressants. TRD is associated more with immune activation than with treatment responsive depression. The current retrospective population-based cross-sectional study, utilizing data from a large nation-wide health maintenance organization in Israel which provides services to estimated 725,000 members, aimed to assess the clinical signs and laboratory markers of autoimmune comorbidity and low-grade inflammation, in patients with TRD. Included were participants aged 18–70 years, diagnosed twice within one year with ICD-9-CM MDD and two control groups, MDD responders (MDD-r) consisting of people with MDD and no TRD and a non-MDD group that included people with no MDD or TRD. The case (570 subjects in TRD group) to control ratio in both control groups (2850 subjects in MDD-r and 2850 subjects in non-MDD control group) was 1:5. Compared to MDD-r, the overall proportion of allergic diseases was higher among the TRD than among the MDD-r [OR 1.52 (1.19–1.94); p < 0.001]. Any systemic autoimmune disease was associated with increased likelihood of MDD-r [OR 1.52 (1.04–2.24); p = 0.03] or TRD [OR 2.22 (1.30–3.78); p = 0.003]. Higher rates of positive (>1:80) antinuclear antibodies [33 (5.79%)] were found among the TRD than among the MDD-r [98 (3.44%); p = 0.011]. More allergy and autoimmune comorbidities and presence of low-grade inflammation biomarkers, were found mainly in TRD.

1. Introduction

Patients with major depressive disorder (MDD) tend to manifest poor response to treatment and only 30% reach full recovery or remission (Kessler et al., 2003; Wang et al., 2005). The remaining MDD patients either respond without reaching remission (about 20%) or do not respond at all (50%) (Trivedi et al., 2006). Patients with MDD who did not respond to at least two prior antidepressants which were administered at adequate doses and durations are referred to as having treatment-resistant depression (TRD), but no comprehensively accepted working definition of TRD exists (Gaynes et al., 2020; Trevino et al., 2014; Trivedi et al., 2006).

MDD may represent a group of different disorders, with partly overlapping underlying biological pathways (Converge consortium, 2015; Postal and Appenzeller, 2015). One of the suggested etiologies is the inflammatory theory, which emphasizes the significance of dysfunction of macrophages (Smith, 1991). It is now generally accepted that patients with MDD have a dysfunctional cellular immunity, with high levels of pro-inflammatory cytokines (Liu et al., 2012) in addition to dysregulation of serotonin and dopamine pathways (Dantzer, 2012). Moreover, TRD seems to be associated more with immune activation than does treatment responsive depression (Chamberlain et al., 2019; Strawbridge et al., 2015). Epidemiological studies have indicated that presence of autoimmune comorbidities raises the likelihood of developing mood

disorders. Studies of the relationship between TRD and comorbid immune diseases are scarce. Moreover, most studies addressing this relationship are limited by small sample sizes and lack of correction for confounding factors (Benros et al., 2013).

This current observational study aimed to assess the clinical signs and laboratory markers of autoimmune comorbidity and low-grade inflammation in patients with TRD.

2. Materials and methods

The study used the electronic health record (EHR) database of Leumit Health Care Services (LHS) from the years 2016–2018. LHS is a health maintenance organization whose membership includes approximately 720,000 residents across Israel. LHS's database includes demographics of the members, their complete medical records, including visits to physicians and laboratory tests which were performed at a single centralized laboratory. The diagnostic codes used in the medical records follow the definition of the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Patients' diagnoses and laboratory results were collected using a unique patient identifier and data was cross-linked appropriately. Data capture was performed using IBM Cognos 10.1.1 BI Report Studio software. Results of queries were downloaded into Microsoft Excel (version 14) spreadsheets for analysis. The study was approved by the Asaf-haRofe Medical Center and the LHS institutional review committees. Due to the retrospective nature of this study, the need for informed consent was waived.

The LHS computerized database was reviewed retrospectively for the period of January 1, 2016 through December 31, 2018, for patients with MDD. Patient characteristics, medical histories, details of the diagnostic workup and medical treatment were retrieved. Detailed analysis of medication usage was also performed.

2.1. Study population

All patients aged 18–70 years, with a documented ICD-9-MC MDD diagnosis (codes 296.21–296.36 and 296.3), established twice in a one year period, by a board-certified psychiatrist were included in the study.

As per earlier mentioned definition, a patient was considered to have TRD if, according to the documentation in the EHR, there was only minimal improvement or no improvement at all with at least two different classes of antidepressants, tried at adequate doses and durations. The tried several antidepressants had to act on the monoamine systems and each had to be tried for 6 weeks and had to be documented as having been acquired for the whole trial period. It should be noted that none of the patients was treated with MAOIs.

In addition to the medications, an adequate course of evidence-based psychotherapy, (cognitive behavioral therapy, behavioral activation, or interpersonal therapy) of at least 10- to 12-weeks with a certified therapist was also required. The study group is here-on referred to as the TRD group.

Two control groups were included in the study. The MDD responder (MDD-r) group included MDD patients with no TRD, whose records reported improvement in symptoms following at most two attempts with different classes of antidepressant treatment. The non-MDD group - included LHS members without diagnoses of either MDD or TRD. Participants for both groups were selected randomly, from among the patients without TRD and matched for age and sex with the study group. A case to control ratio of 1:5 was maintained in each control group. The randomization was performed with the Epi Info 6 software (Atlanta, GA) using simple random sampling.

All blood tests, were taken by experienced nurses during the primary physician or psychiatrist visit during the preceding three months and performed in a single centralized laboratory of LHS.

Exclusion criteria consisted of pregnancy or lactation, malignancy, recent (<6 months) or current history of drug use disorder, noncompliance with treatment and lifetime history of psychosis. Other Axis I

comorbidities were not excluded. As previous electroconvulsive therapy (ECT) is not mandatory for the definition of TRD, we did not involve ECT as inclusion or exclusion criteria of the study. Patients with depression secondary to other diseases, such as Parkinson's disease, stroke, dementia, active and chronic infectious diseases were also excluded from this study.

Comorbidities were identified by ICD-9-CM codes documented by the attending board-certified physician, as follows: Allergic rhinitis −477.0–477.9; Diabetes - 250.00–250.93; Arterial hypertension - 401–405; Atopic dermatitis - 691.0–681.8, Contact dermatitis 692.9 and Asthma 493.0–493.2, 493.9. Body mass index (BMI) > 30 kg/m^2 was considered obese.

Systemic autoimmune diseases were identified by ICD-9-CM diagnostic criteria and corresponding codes documented by board-certified specialists as follows: rheumatoid arthritis 714.0–714.9, systemic lupus erythematosus 710.0, Sjögren's syndrome 710.2, polymyositis 710.4, dermatomyositis 710.3 and undifferentiated connective tissue disease 710.9.

The cumulative disease burden was calculated as the sum of all diseases during the study period and categorized into the following three key classifications: allergic diseases, systemic autoimmune diseases and organ-specific autoimmune diseases (Nguengang Wakap et al., 2020).

2.2. Statistical analyses

Differences in demographic and clinical characteristics between the study groups were determined by one-way analysis of variance, followed by post hoc t-test analysis. The multiple regression analyses adjusted for sex, age, smoking, and comorbidities (allergic rhinitis, arterial hypertension, obesity, diabetes, systemic autoimmune diseases) were used to estimate the odds ratios (OR) and 95% CI for the independent association between TRD and the autoimmune comorbidity. Statistical significance was defined as a two-sided p-value of 0.05. All statistical analyses were conducted using the Statistical Package STATA 12 software (StataCorp LP, College Station, TX).

3. Results

The initial analysis compared various demographic and clinical characteristics between the study group and the control groups. The LHS population was found to include 570 members with TRD during the study period. The two control groups (MDD-r and non-MDD) included 2850 age and sex-matched individuals who were randomly selected. The TRD group was characterized by a higher rate of divorced people. The three groups did not differ significantly in BMI values (Table 1).

Both MDD-r and TRD groups were characterized by higher levels of blood WBC, lymphocytes, platelets, C-reactive protein, ESR, C3 and C4 levels than the non-MDD group. In the TRD group there were higher levels of blood WBC (p < 0.001), lymphocytes (0.001), platelets (p = 0.001), MPV (p = 006), C4 (p < 0.001) and lower levels of blood IgE (p = 0.021) than in MDD-r group. Higher rates of positive (>1:80) antinuclear antibodies [33 (5.79%)] were found in the TRD group than in the MDD-r group [98 (3.44%); p = 0.011] (Table 1).

The rate of arterial hypertension was higher in the TRD group, than in the MDD-r group - %) - or non-MDD group (p = 0.006). MDD-r and TRD groups were also characterized by significantly higher rates of diabetes (p = 0.048), Ischemic heart disease (IHD) (p < 0.001), chronic heart failure (CHF) (p < 0.001), chronic obstructive pulmonary disorder (COPD) (p < 0.001) and renal disease (p = 0.031). There were no significant differences between the MDD-r and the TRD groups in the rate of these conditions (Table 2).

TRD was characterized by a higher rate of allergic rhinitis and asthma. The overall proportion of allergic diseases was higher in the TRD group than in the MDD-r group (p = 0.004) (Table 2).

While the overall rate of systemic autoimmune diseases was also higher in TRD than in the MDD-r group, (p = 0.026) the rates of the

Table 1
Demographic and laboratory characteristics of the three groups.

	MDD-r N = 2850	TRD N = 570	non-MDD N = 2850	P1	P2	P3	P4
Sex; Female, n (%)	1585 (55.61)	317 (55.61)	1585 (55.61)	0.996	0.466	0.500	0.466
Age; (years) (mean ± SD)	52.89 ± 16.12	52.74 ± 15.84	52.59 ± 16.11	0.781	0.419	0.241	0.419
Marital status							
Unmarried, n (%)	365 (12.81)	76 (13.33)	361 (12.67)	0.668	0.219	0.437	0.194
Married, n (%)	1447 (50.77)	290 (50.88)	1475 (51.75)	0.734	0.475	0.221	0.351
Widow, n (%)	72 (2.53)	14 (2.45)	63 (2.21)	0.473	0.108	0.217	0.229
Divorced, n (%)	213 (7.47)	48 (8.42)	153 (5.37)	0.001	0.227	<0.001	0.007
Unknown, n (%)	753 (26.42)	142 (24.91)	798 (28.00)	0.203	0.224	0.090	0.061
Body mass index, kg/m^2 (mean ± SD)	27.77 ± 5.91	27.68 ± 6.04	27.80 ± 5.76	0.998	0.372	0.423	0.331
Laboratory							
WBC, (cells × 10^9/L) (mean ± SD)	7.29 ± 2.29	7.68 ± 2.55	7.02 ± 2.16	<0.001	<0.001	<0.001	<0.001
Lymphocytes, (cells × 10^9/L, mean ± SD)	2.23 ± 0.74	2.29 ± 0.79	2.15 ± 0.72	<0.001	0.047	<0.001	<0.001
Eosinophils, (cells × 10^9/L) (mean ± SD)	0.20 ± 0.15	0.20 ± 0.14	0.19 ± 0.17	0.046	0.5	0.009	0.067
Eosinophils, (%) (mean ± SD)	2.82 ± 1.89	2.79 ± 1.87	2.79 ± 2.01	1	0.363	0.281	0.5
Eosinophils < 0.5 cells × 10^9/L, n (%)	148 (5.19)	32 (5.61)	151 (5.30)	0.917	0.344	0.429	0.382
Basophils (cell/mm^3) (mean ± SD)	0.05 ± 0.04	0.05 ± 0.03	0.04 ± 0.03	<0.001	0.5	<0.001	<0.001
Basophils, (%) (mean ± SD)	0.66 ± 0.35	0.64 ± 0.34	0.64 ± 0.35	0.078	0.101	0.016	0.5
Platelets, (cells × 10^9/L) (mean ± SD)	253.53 ± 73.68	260.55 ± 75.93	249.31 ± 67.97	0.001	0.021	0.012	0.001
MPV (fL) (mean ± SD)	10.79 ± 1.91	10.98 ± 1.56	10.79 ± 2.01	0.081	0.006	0.5	0.006
Glucose (mg/dL), (mean ± SD)	102.77 ± 32.24	103.98 ± 31.41	101.72 ± 28.51	0.186	0.202	0.096	0.056
TSH (0.35–4.94 mIU/L) (mean ± SD)	2.28 ± 2.46	2.43 ± 3.93	2.18 ± 1.93	0.050	0.190	0.044	0.069
C-reactive protein (mg/L) (mean ± SD)	7.39 ± 15.56	8.15 ± 18.58	5.82 ± 10.30	<0.001	0.180	<0.001	0.002
ESR (mm/h), (mean ± SD)	25.21 ± 20.84	26.56 ± 21.89	24.27 ± 18.78	0.025	0.087	0.037	0.010
C3 (g/dL), (mean ± SD)	133.99 ± 25.60	133.95 ± 21.91	139.25 ± 24.54	<0.001	0.484	<0.001	<0.001
C4 (g/dL), (mean ± SD)	35.31 ± 9.97	37.41 ± 11.19	36.38 ± 10.56	<0.001	<0.001	<0.001	0.021
Antinuclear antibodies positive (>1:80), n (%)	98 (3.44)	33 (5.79)	61 (2.14)	<0.001	0.011	0.002	<0.001
Rheumatoid factor (0–20 IU/ml), (mean ± SD)	14.94 ± 33.19	15.39 ± 13.25	14.12 ± 26.21	0.445	0.294	0.104	0.107
IgE (U/mL) (mean ± SD)	171.75 ± 277.25	147.71 ± 252.18	175.83 ± 342.75	0.135	0.021	0.311	0.012

MDD-r - Treatment Responsive Depression group, TRD - Treatment Resistant Depression group, non-MDD – Group without MDD, P1 – ANOVA, P2 – χ^2 between MDD-r and TRD groups, P3 – χ^2 between MDD-r and non-MDD groups, P4 – χ^2 between TRD and non-MDD groups.

Table 2
Comorbidity rates in the three groups.

Comorbidities	MDD-r N = 2850	TRD N = 570	non-MDD N = 2850	P1	P2	P3	P4
Arterial hypertension, n (%)	989 (34.70)	207 (36.32)	806 (28.28)	0.006	0.231	<0.001	<0.001
NIDDM, n (%)	546 (19.16)	112 (19.65)	443 (15.54)	0.048	0.394	0.011	0.058
Ischemic heart disease, n (%)	220 (7.72)	47 (8.25)	126 (4.42)	<0.001	0.337	<0.001	<0.001
Chronic heart failure, n (%)	105 (3.68)	25 (4.39)	63 (2.21)	<0.001	0.225	<0.001	<0.001
COPD, n (%)	248 (8.70)	53 (9.30)	130 (4.56)	<0.001	0.327	<0.001	<0.001
Renal disease, n (%)	80 (2.81)	17 (2.98)	52 (1.82)	0.031	0.411	0.007	0.063
Allergic diseases (pooled), n (%)	585 (20.53)	147 (25.79)	427 (14.98)	<0.001	0.004	<0.001	<0.001
Allergic rhinitis, n (%)	209 (7.33)	54 (9.47)	172 (6.04)	0.007	0.053	0.025	0.004
Atopic dermatitis, n (%)	28 (0.98)	7 (1.23)	22 (0.77)	0.494	0.311	0.197	0.175
Contact dermatitis, n (%)	28 (0.98)	10 (1.75)	21 (0.74)	0.068	0.091	0.157	0.038
Asthma, n (%)	320 (11.23)	76 (13.33)	212 (7.44)	<0.001	0.086	<0.001	<0.001
Systemic autoimmune diseases (pooled), n (%)	83 (2.91)	27 (4.73)	48 (1.68)	<0.001	0.026	0.001	<0.001
SLE, n (%)	6 (0.21)	2 (0.35)	5 (0.18)	0.701	0.296	0.381	0.249
Rheumatoid arthritis, n (%)	67 (2.35)	21 (3.68)	40 (1.40)	<0.001	0.056	0.004	0.003
Sjogren disease, n (%)	8 (0.28)	2 (0.35)	3 (0.11)	0.253	0.396	0.064	0.168
Systemic sclerosis, n (%)	0	1 (0.18)	0	0.091	0.158	0.5	0.158
Polymyositis/dermatomyositis, n (%)	2 (0.35)	1 (0.18)	0	0.165	0.281	0.078	0.158
Organ specific autoimmune diseases (pooled), n (%)	362 (12.70)	85 (14.91)	265 (9.29)	<0.001	0.086	<0.001	<0.001
IDDM, n (%)	19 (0.67)	5 (0.88)	8 (0.28)	0.054	0.307	0.017	0.069
Hashimoto's thyroiditis, n (%)	23 (0.81)	5 (0.88)	18 (0.63)	0.677	0.434	0.216	0.278
Graves' disease, n (%)	6 (0.21)	3 (0.53)	9 (0.32)	0.405	0.158	0.219	0.256
Celiac disease, n (%)	12 (0.42)	4 (0.70)	8 (0.28)	0.299	0.224	0.185	0.123
Vitiligo, n (%)	16 (0.56)	3 (0.53)	15 (0.53)	0.982	0.458	0.428	0.5
Alopecia areata, n (%)	1 (0.04)	0	2 (0.07)	0.716	0.158	0.281	0.079
Pemphigus vulgaris, n (%)	1 (0.04)	0	1 (0.04)	0.905	0.158	0.5	0.158
Psoriasis, n (%)	155 (5.44)	37 (6.49)	113 (3.96)	0.007	0.178	0.005	0.011
Chronic urticaria, n (%)	31 (1.09)	7 (1.23)	26 (0.91)	0.704	0.389	0.253	0.261
Dermatitis herpetiformis, n (%)	3 (0.11)	0	4 (0.14)	0.651	0.052	0.353	0.023
Pernicious anemia, n (%)	2 (0.07)	0	1 (0.04)	0.716	0.079	0.282	0.158
Ulcerative colitis, n (%)	17 (0.60)	3 (0.53)	13 (0.46)	0.770	0.419	0.235	0.415
Crohn's disease, n (%)	36 (1.26)	10 (1.75)	21 (0.74)	0.038	0.202	0.023	0.038
Immune thrombocytopenic purpura, n (%)	40 (1.40)	7 (1.23)	26 (0.91)	0.221	0.365	0.042	0.261

MDD-r - Treatment Responsive Depression; TRD - Treatment Resistant Depression.
P1 – ANOVA, P2 – χ^2 between MDD-r and TRD groups, P3 – χ^2 between MDD-r and non-MDD groups, P4 – χ^2 between TRD and non-MDD groups.

individual systemic autoimmune nosologies were similar in all three groups (Table 2). Multiple logistic regression analyses adjusted for sex, age and comorbidity revealed that presence of allergic diseases was positively associated with the likelihood of being with TRD [OR 1.52 (1.19–1.94); p = 0.001]. Additionally, presence of any systemic autoimmune disease was associated with the increased likelihood of being with MDD-r [OR 1.52 (1.04–2.24); p = 0.03] or TRD [OR 2.22 (1.30–3.78); p = 0.003] (Table 3).

Although the overall proportion of organ-specific autoimmune diseases was higher in MDD-r and TRD groups than in the non-MDD group [362 (12.70%), 85 (14.91%) and 265 (9.29%), respectively; p < 0.001], there were no statistically significant differences in any organ-specific autoimmune disease between the MDD-r and TRD groups (Table 2). Nevertheless, presence of organ-specific autoimmune diseases was associated with an increased likelihood of having MDD-r [OR 1.25 (1.04–1.49); p = 0.013] or TRD [OR 1.49 (1.12–1.97); p = 0.005] (Table 3).

4. Discussion

In this observational study, using matched patients with treatment responsive MDD and non-depressed controls, we quantified the odds ratios of allergy and autoimmune comorbidities and several biomarkers of low-grade inflammation in TRD. We report that more allergy and autoimmune comorbidities and existence of low-grade inflammation biomarkers were found mainly in TRD.

In recent years several epidemiological studies discovered an association between depressive disorders and chronic somatic diseases (Dijkstra-Kersten et al., 2017; Kendler et al., 2009; Rush et al., 2006; Tibubos et al., 2019; Whooley et al., 2008). The current study also demonstrated a higher rate of arterial hypertension, diabetes, chronic renal disease, and COPD in both the MDD-r group and the TRD group, and the rate was similar between the two groups.

Another finding of the current study is higher levels of circulatory WBC, platelets and MVP levels in TRD compared to MDD-r. Additional biomarkers of low-grade inflammation such as CRP, ESR, and C3 were higher in both the MDD-r and the TRD group compared to the non-MDD group. The difference between the MDD-r group and the TRD group, however, was not statistically significant. Our findings are in agreement with previous studies that found higher mean concentrations of peripheral inflammatory markers in subjects with depression compared to

controls without depression (Goldsmith et al., 2016; Haapakoski et al., 2015; Howren et al., 2009).

The link between low-grade inflammation and depression is clinically important. Lack of therapeutic benefit from antidepressant pharmacotherapy may be associated with the activation of the inflammatory immune system (Carvalho et al., 2013; Lanquillon et al., 2000). Several studies reported on higher CRP levels in people with TDR compared to those with MDD-r (Maes et al., 1997; Sluzewska et al., 1997). Low-grade inflammation is unlikely to be present in all patients with depression (Khandaker et al., 2017).

Low-grade inflammation is a risk factor for chronic cardiovascular diseases as well as renal and lung diseases and is associated with elevation of biomarkers such as CRP, WBC, C3, platelets and MPV (Hare et al., 2014; Khandaker et al., 2017). In the current study, the odds ratio for these inflammation biomarkers in patients with depression were compared to matched controls after adjusting for age, sex and comorbidities and no statistically significant associations were found.

Many studies have reported on the prevalence of inflammation in MDD using various CRP level thresholds to define inflammation, e.g. >3 mg/L or >1 mg/L. It should be mentioned that they were conducted in heterogeneous populations, e.g. inpatient, outpatient, population-based (Raison et al., 2013; Wium-Andersen et al., 2013; Shin et al., 2016). Therefore, the reported prevalence of low-grade inflammation differs widely among these studies and for CRP >3 mg/L it was reported to vary between 0% and 60% (Ma et al., 2010; Hannestad et al., 2013). Whereas according the meta-analysis, about a quarter of patients with MDD show evidence of low-grade inflammation (Fernandes et al., 2016; Osimo et al., 2019). Nevertheless, the role of anti-inflammatory agents in the treatment of MDD is uncertain and may be confined only to patients with MDD and evidence of inflammatory processes (Khandaker et al., 2017).

This study is consistent with previous population-based studies that demonstrated the potential association of allergic disorders with MDD (Cheng and Silverberg, 2019; Grosso et al., 2019; Sanna et al., 2014; Wufuer et al., 2020). The novel finding of the current study is that TDR is characterized by higher rates of overall allergic diseases than MDD-r. Meanwhile, MDD is characterized by T cell activation with a Th1 shift (Maes et al., 1990) with M1 microglia polarization (Kalkman and Feuerbach, 2016), however, allergic diseases are linked with the Th2 cell activation and microglia M2 polarization (Kalkman and Feuerbach, 2017). Previous studies found an association between changes in allergy symptom scores and changes in depression scores in MDD (Postolache et al., 2007). Furthermore, allergen-specific IgE with a specific environmental trigger can lead to exacerbation of depression in patients with MDD (Manalai et al., 2012). Further research is needed to clarify the mechanisms of allergy-related exacerbation of depression in MDD.

As in similar studies, the current study also found higher rates of systemic autoimmune diseases in MDD (Benros et al., 2013). In these diseases, dysregulation of Th1, Th2, and Th17 cell response leads to an increased Th1 and M1-macrophage-associated inflammatory cytokine secretion and to a decreased regulatory T-cell population in patients with MDD (Haapakoski et al., 2016; Toben and Baune, 2015). The results of this study indicate that TRD may be associated with immune dysregulation to a larger extent than MDD-r. This notion is supported by the finding of more frequent presence of positive antinuclear antibodies and lower levels of IgE in the TDR group.

An important strength of the current study is its large cohort and its generalizability, as the data stem from a nationwide database. The results of this study, however, should be interpreted with caution due to several methodological limitations including its retrospective nature and diagnostic code-based design. Additionally, the categorization of participants into the TRD and MDD-r groups was based on the number of different antidepressants that had been prescribed in the index period. This approach assumes that change of antidepressants was due to lack of response, rather than reasons like intolerability or non-adherence. This bias could have resulted in overestimation in the number of TRD participants.

Table 3
Multiple logistic regression model testing association of comorbidities with MDD-r or TRD adjusted to BMI and marital status.

	Association with MDD-r OR (95% CI)	P	Association with TRD OR (95% CI)	p
Somatic comorbidities				
Arterial hypertension	1.17 (1.03–1.33)	0.013	1.34 (1.08–1.67)	0.007
Type 2 Diabetes	1.07 (0.92–1.24)	0.368	1.32 (0.97–1.85)	0.058
Ischemic heart disease	1.44 (1.13–1.84)	0.003	1.27 (0.83–1.94)	0.256
Chronic heart failure	1.17 (0.83–1.65)	0.346	1.49 (0.86–2.56)	0.150
COPD	1.62 (1.29–2.05)	0.001	1.70 (1.18–2.44)	0.004
Renal disease	1.16 (0.80–1.69)	0.406	0.96 (0.49–1.87)	0.910
Category (pooled)				
Allergic diseases	1.24 (1.06–1.44)	0.006	1.52 (1.19–1.94)	0.001
Systemic autoimmune diseases	1.52 (1.04–2.24)	0.030	2.22 (1.30–3.78)	0.003
Organ specific autoimmune diseases	1.25 (1.04–1.49)	0.013	1.49 (1.12–1.97)	0.005

In conclusion, the study demonstrated higher allergy and autoimmune comorbidities as well as the presence of biomarkers of low-grade inflammation, mainly in patients with TRD. These results may point to higher degrees of immune dysregulation in TRD than in MDD-r. These findings warrant replication and further study in larger multi-national samples.

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5. Conflict of interest disclosure statement

None of the authors reports any conflicts of interest with regard to this study.

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