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**Title:**

**Impact of vascular risk factors on clinical outcome in elderly patients with depression receiving electroconvulsive therapy**

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## INTRODUCTION

Major depressive disorder is a common mental disorder, occurring across all world regions and at any age. With a worldwide prevalence of 4.4%, depressive disorders are ranked as the single largest contributor to non-fatal health loss in the world (WHO, 2017). Typically, the first line treatment consists of pharmacological medications using selective serotonin reuptake inhibitors. Antidepressant treatments are moderately effective, and only 30% of patients achieve remission to an initial antidepressant trial prescribed at the appropriate dose and duration and symptoms remain after a second line treatment in 50% of the cases (Fava, 2003). In the elderly, depression is one of the most common psychiatric disorder (Panza et al., 2010).

Late-life depression (LLD) is associated with significant morbidity and mortality with loss in functioning, dependence (Ferrari et al., 2013) and high rate of suicide (Raue et al., 2014). For several reasons, such as low tolerance to pharmacological treatments, drug-drug interactions, high rates of treatment-resistant depressive symptoms are observed in LLD (Mulsant and Pollock, 1998). Whatever the age, treatment-resistant depression is frequent in clinical settings. However, the number of treatment-resistant elderly depressive patients is estimated to one-third of the elderly depressed patients. In case of severe and/or treatment-resistant episode, the use of electroconvulsive therapy (ECT) is common in LLD (Socci et al., 2018). Although ECT is a safe, highly effective intervention with a response rate of more than 74% (Bahji et al., 2019) in patients with major depressive disorder, in the geriatric population, there is a large variability in response rates across individuals ranging from 55% to 92% (Antosik-Wójcińska and Świącicki, 2016; Kellner et al., 2016; Socci et al., 2018; van Diermen et al., 2018). Imaging studies report that MRI-defined vascular changes, such as deep white matter hyperintensities (WMHI), or cerebral atrophy could explain this heterogeneity, but the results remains inconsistent (Dols et al., 2017; Hickie et al., 1995; Oudega et al., 2020, 2014, 2011). In LLD, apathy syndrome, defined as diminished motivation for physical, cognitive or emotional activity, is frequently described (Groeneweg-Koolhoven et al., 2017; Oudega et al., 2020) and could be associated with poor prognosis and treatment response of depression (Husain and Roiser, 2018). It has also been proposed that response rate was related to medical comorbidities observed in the elderly. Among them, vascular risk factors (VRF), a common comorbidity in the elderly raised a particular interest (Allan et al., 2012; Sheline et al., 2010; Spaans et al., 2018).

To the best of our knowledge, only few studies have been designed to investigate the relationship between response rate to ECT and VRF in LDD. Recently, Spaans et al. explored the impact of VRF on response to treatment in depressed participants. Comparing pharmacological treatment to ECT,

they underlined the superior efficacy of ECT over pharmacotherapy in elderly patients with MDD, regardless the presence of VRF. Post-hoc analysis described non-statistical difference in ECT response rate between participants with one VRF compared to control group (Spaans et al., 2018). However, in another study, a significant difference was found when focusing on pharmacological treatment in LLD with or without VRF, with a lower response rate in patients with VRF (Bingham et al., 2015).

If the hypothesis of vascular depression is well described in the scientific literature, the impact of vascular burden on response rate to depression treatment remains unclear. The aim of this study was therefore to compare response rates to ECT in patients with LLD presenting with or without VRF. We hypothesized that the presence of VRF would predict a poorer treatment outcome to ECT. As a secondary objective, we evaluated the relationship between the severity of brain vascular burden measured with the Framingham score and the clinical improvement.

## **METHOD**

### *Participants*

Patients were recruited in a specialized ECT unit located in a psychiatric hospital, Hospital “Le Vinatier”, Lyon, France, between March 2016 and May 2018. All patients referred to our ECT unit with an age superior or equal to 55 years-old were considered for inclusion. Patients should present with a DSM-5 (American Psychiatric Association, 2013) unipolar or bipolar major depressive episode as assessed during a structural interview using the Mini International Neuropsychiatric Interview - MINI 7.0.2. The severity of the episode should be rated moderate to severe defined as a 10-item Montgomery–Åsberg Depression Rating Scale (MADRS<sub>10</sub>) score > 20 (Leucht et al., 2017). Exclusion criteria were: schizophrenia, schizoaffective disorder, delusional ideation, neurodegenerative disease or clinical conditions preventing the evaluation of the cognitive functioning (such as severe catatonia).

### *Assessment*

For each patient, a global assessment was realized before the first session of ECT and after the last one. The severity of depression was assessed by the MADRS<sub>10</sub> and the Beck Depression Inventory (BDI) scores. Maudsley Staging Method was used to define the resistance degree of depression (Fekadu et al., 2009). Cognitive functioning was assessed with the Montreal Cognitive Assessment (MoCA) (Moirand et al., 2018; Nasreddine et al., 2005). Other demographic and clinical

characteristics were also collected such as age, sex, duration of the illness, pharmacological treatments (table 1). Duration of the illness was calculated based on the medical records and reflects the duration between the first acute mood disorder and the beginning of the ECT course.

Patients were separated into two groups based on the presence of a high vascular risk. To be consistent with the scientific literature, a Risk Factor Composite Score were calculated and a score of 2 or more were considered to be reflecting a high vascular risk (Valkanova and Ebmeier, 2013a). Patients were thus included in the VRF group when 2 or more VRF were observed in their medical records among: hypercholesterolemia (LDL cholesterol > 4.91mmol/L), hypertension (systolic arterial pressure > 130 mmHg), tobacco smoking (current or in the last 6 months), diabetes mellitus (diagnosis), cardiovascular disease, and cerebral vascular accident/transient ischemic attack (diagnosis). Information in the medical records were considered only before the ECT course. Repartition of vascular risk factors in both groups is presented in Table 2.

Framingham score was calculated for each patient using the Framingham algorithm (D'Agostino et al., 2008). The Framingham risk score was calculated at baseline and represents a weighted sum of age, sex, antihypertensive treatment (yes or no), systolic blood pressure (millimeters of mercury), body mass index, history of diabetes (yes or no), and current cigarette smoking status (yes or no). It provides a 10-year probability of future cardiovascular events. Framingham score is correlated to cerebral vascular region and provide information about brain vascular burden (Rabin et al., 2018).

The presence or absence of white matter intensities was clinically determined by a radiologist on a T1-weighted magnetic resonance imaging (MRI). The MRI were acquired in a specialized hospital and only the clinical conclusions from the specialized radiologist were available. When the FAZEKAS score (Fazekas et al., 2002) was specified, the presence of WHI was determine as a score equal or superior to one.

#### *Administration of ECT*

ECT sessions were administered twice weekly using a Mecta Spectrum 5000Q (Mecta Corporation, Tualatin, OR, USA) and followed the NICE recommendations (NICE, 2009). Anesthetic agents were either propofol (1–1.5 mg/kg) or etomidate (0.15–0.2 mg/ kg). All patients were treated with bitemporal (BT) stimulation, some of them being switched to right unilateral (RUL) in the case of major cognitive effects (*e.g.*, disorientation or confusion). The seizure threshold (ST) was defined as the minimal electrical stimulus charge eliciting a generalized seizure lasting at least 20 s as measured with electroencephalography (EEG). ST was individually determined according to a titration schedule

during the first session, and treatment was administered at 2 times the ST for BT stimulation and at 6 times the ST for RUL stimulation (Sackeim, 1987). The pulse duration was brief (1ms) during BT stimulation and ultra-brief (0.3ms) during RUL stimulation. A specialized psychiatrist determined the duration of the ECT course according to mood assessments after the sixth ECT session and then every other 2 ECT sessions using the MADRS<sub>10</sub>. ECT was delivered until patients achieved remission or until there was no decrease in MADRS<sub>10</sub> scores between two assessments. A maximum of 20 sessions was delivered.

### *Response and remission to ECT*

Response was defined as an at least fifty percent decrease of the MADRS<sub>10</sub> score between the baseline assessment and the score obtained after the ECT course (Trivedi et al., 2009). Remission was considered for patients with a MADRS score < 10 (Hawley et al., 2002).

### *Ethical issues*

All patients signed an informed consent to receive ECT. They received individual information folder and opposition rights to record data. The database was approved and registered (record number MR-003-2017-002) by the French national commission for information technology, data processing and civil liberties (CNIL).

### *Statistical analysis*

Statistical analyses were processed with R (version 4.0.2). Statistical level of significance was set at  $p < 0.05$  (two-tailed). Descriptive statistics of baseline demographic and clinical characteristics of participants were calculated, and differences between the VRF and the non-VRF groups were investigated using chi-squared tests or Fisher's exact tests for categorical variables, two-sided Student's t-tests for continuous variables in cases of normal distribution, Mann-Whitney U-tests in cases of non-normal distribution.

Differences in response rate between the VRF and non-VRF groups were calculated using a Fisher's exact test.

Spearman correlation test was undertaken to evaluate the relationship between Framingham score and MADRS scores changes (measured as the difference between before and after ECT course).

Repeated-measures mixed ANOVA (rm-ANOVA) were conducted for MADRS scores with "time" (before and after treatment) as a within-subject factor and "VRF" (group with or without) as a between-subject factor. The assumption of sphericity was assessed using Mauchly's test.

## **RESULTS**

### *Demographics and clinical characteristics*

Among the 95 patients who received ECT between March 2016 and May 2018 in our unit, 59 were included according to our inclusion criteria. Among them, 56 completed the study and 3 patients were lost at the end of the ECT course and didn't show up for testing, therefore their data were not available for analysis. We excluded 4 patients that received only unilateral stimulation as they were most probably different from the rest of the population to be indicated for unilateral stimulation at the beginning of the ECT course. Among the 52 included patients, 20 were considered having a vascular burden ( $VRF \geq 2$ ). There was no significant difference between the two groups regarding age, sex, illness duration, MADRS scores, cognitive functions and white matter hyperintensities (Table 1) at baseline. A non-significant difference was found for BDI scores: patients with VRF declared lower scores on this auto-evaluation scale (20.5 +/- 9.1 in the non-VRF-group versus 14.0 +/- 6.5 in the VRF-group;  $p=0.04$ ). No difference was found between the groups regarding the number of ECT sessions delivered, the switch of electrode positioning during the course (*i.e.*, RUL or BT), the used anesthetic agent or the duration of the EEG seizures. Regarding concomitant pharmacological treatments, there was no significant difference between groups in terms of antidepressant, antipsychotic and benzodiazepine use. Mood stabilizer intake was more frequent in the VRF group.

***Insert table 1 about here.***

### *Patient with VRF versus without*

According to our hypothesis, response rate was significantly lower in patients presenting with a vascular burden than in patients without VRF. While 30 out of 32 non-VRF patients (94%) responded to ECT, only 12 out of 20 (60%) were responders in the VRF group ( $p = 0.004$ ) (see Figure 1).

Considering remission to ECT, 24 out of 32 non-VRF patients (75%) were in remission after the ECT course, while only 10 out of 20 (50%) were in remission in the VRF group, although this result is non-significant ( $p=0.065$ ).

***Insert figure 1 about here.***

The rm-ANOVA revealed a significant interaction between the group (VRF, non VRF) and the decrease of MADRS before and after ECT ( $F_{(1,50)} = 10.22$ ,  $p = 0.002$ ); no effect of group  $F_{(1,50)} = 0.319$ ,  $p = 0.575$ ); but a significant effect of time  $F_{(1,55)} = 279.1$ ,  $p < 0.001$ ). Post-hoc analysis found a significant difference in MADRS decrease between the non-vascular group ( $-28.9 \pm 9.5$ ) and the

VRF-group ( $-19.4 \pm 12.2$ ;  $p = 0.003$ ) with a significant smaller decrease in the VRF-group than in the non-VRF group.

As observed with the MADRS<sub>10</sub> scores, the rm-ANOVA with BDI scores revealed a significant interaction between the group and the decrease of BDI before and after ECT ( $F_{(1,17)} = 8.08$ ,  $p = 0.011$ ); no effect of group ( $F_{(1,17)} = 0.027$ ,  $p = 0.870$ ); and a significant effect of time ( $F_{(1,17)} = 16.97$ ,  $p < 0.001$ ).

Although BDI scores seems lower at baseline in the VRF-group ( $14 \pm 6.50$ ) than in the non-VRF group ( $20.53 \pm 9.07$ ), the opposite results were found after ECT regimen. Patients from the VRF-group displayed significant higher BDI scores at endpoint ( $10.8 \pm 5.2$ ) than patients from the non-VRF group ( $5.4 \pm 3.4$ ;  $p=0.003$ ).

#### *Correlation between Framingham and MADRS score*

A significant negative correlation between the Framingham score and the MADRS differences before and after ECT course was found,  $\rho = -0.42$  ( $p = 0.0039$ ) (see Figure 2).

*Insert figure 2 about here.*

#### *Sensibility analysis*

To determine the impact of important explicative variables on response to ECT a logistic regression model was conducted (Table 3). Independently to sex, age and depression type (bipolar or unipolar), response is decreased for patients presenting with a vascular burden with an OR = 0.06 (IC95%[0.01;0.034],  $p=0.004$ ). This result was similar when considering mood stabilizer instead of type depression (see Supplemental).

## **DISCUSSION**

The aim of the study was to compare response rate to ECT in elderly depressed patients presenting or not with VRF. According to our hypothesis, response to ECT was lower in patients with vascular burden compared to patients without vascular burden. It also seems that, based on Framingham score, the higher was the vascular burden, the lower was the MADRS change after ECT course. Our results are in line with those from Spaans et al. (2018) reporting that, although the difference did not reach significance, remission rate to ECT decreased from 80 to 58 in patients with at least one VRF as compared with patients without VRF (Spaans et al., 2018).

To the best of our knowledge, the current study is among the first studies designed to explore the impact of VRF on ECT outcome in LLD. Because of a high prevalence of major depressive disorder but also the increase of VRF in the elderly population, this subject is a major clinical concern. Our population is representative of severe elderly depressed participants, in terms of age and depression severity (Spaans et al., 2018; Steffens et al., 2001). We included both unipolar and bipolar depression as there is no difference in response rate to ECT between these two diagnoses described in the scientific literature (Daly et al., 2001; Dierckx et al., 2012; Narayanaswamy et al., 2014; Pinna et al., 2018). Results from the regression model suggests that the depression type did not influenced the impact of VRF on the response to ECT in our population. ECT protocols were realized according to guidelines with a sufficient duration of seizure. Patients received mostly bitemporal ECT stimulation, which is described as more efficient (The UK ECT Review Group, 2003). The high response rates observed in the current study (94% in non-VRF group *versus* 60% in VRF group) are in line with response rates reported in other studies on ECT, notably in older population, with a high proportion of women with unipolar disorder (Medda et al., 2009).

To explain the difference in response rate observed between the VRF and the non-VRF groups, one can hypothesize that vascular damages would alter affective brain networks that are involved in ECT response (Steffens et al., 2001). It has indeed been reported that micro-damage to small cerebral vessels may compromise the integrity of the frontal-subcortical circuits involved in mood regulation (Valkanova and Ebmeier, 2013b) and could precipitate, perpetuate, or predispose one to specific geriatric depressive syndromes (Aizenstein et al., 2016; Alexopoulos et al., 1997) also these results are inconsistent (Oudega et al., 2011). Defect in left superior longitudinal fascicle, cingulum bundle, and frontal projections to the corpus callosum, disrupting frontal and frontal-to-limbic white matter tracts have been shown in case of late-life vascular depression (Aizenstein et al., 2016). These white matter damages have been related to inflammatory mechanisms with a role of cytokines and other pro-inflammatory markers (Aizenstein et al., 2016; Alexopoulos, 2019). Reduction of gray matter in frontal, hippocampal and limbic regions have also been implied, as well as altered default-mode network following white and gray matter damages (Aizenstein et al., 2016; Jellinger, 2013). Recent meta-analyses showed that LLD increases the risk of Alzheimer's disease and vascular dementia compared to non-depressed older adults, therefore, resistant cognitive symptoms could also explain the poorer treatment response in LLD (Aizenstein et al., 2016).

#### *Limitations:*

We acknowledge some limitations of the current study. First, the study design is retrospective, based on collected data, with a moderate sample of patients with moderate to severe depression (N = 52,

baseline MADRS<sub>10</sub> > 20). However, our population is quite homogeneous with similar baseline characteristics in both groups. The observed difference could thus not be explained by difference between groups regarding age, gender, type of depression (bipolar *versus* unipolar), severity of depression (symptoms or cognition), illness duration, or the occurrence of comorbidities such as obstructive sleep apnea or alcohol use disorder (table 1). BDI scores at baseline seems different between the two groups, with a higher score in non-VRF group, but this difference were not significant. To explain this difference, one can hypothesize that patients in the VRF-group could displayed a more severe level of apathy than patients from the non-VRF group resulting in a reduced auto-evaluation of depressive symptoms. This is supported by evidence suggesting that apathy symptoms are well represented in LLD and are associated to vascular burden (Groeneweg-Koolhoven et al., 2017; Hollocks et al., 2015; Ligthart et al., 2012). Moreover, a lack of insight has been described in vascular depression and may also be taken into account to explain this difference (Aizenstein et al., 2016). ECT treatment have an impact on apathy symptoms in the context of depression which could explain the BDI decrease observed post-ECT (Carlier et al., 2018). It is also important to note that a large porportion of patients from the current study were not able to rate their mood with the BDI before receiving ECT. Thus, the BDI seems not to be a reliable tool to evaluate depression in our sample of patients with severe depression.

As we did not use a cut-off score at the MoCA scale to exclude patients with a pre-clinical stage of dementia in, we cannot rule out to have including some of such patients in the current study. Cognitive status based on rapid scales tends to improve after the ECT course, it is therefore not recommended to withhold ECT in older patients with severe depression in presence of pretreatment cognitive impairment (Obbels et al., 2019).

Add-on pharmacological treatment could also constitute a limitation. However, no significant difference was observed between groups regarding psychotropic medication intake in terms of antidepressant, benzodiazepine, first and second generation of antipsychotic. The observed difference between groups seems thus not linked with medication. It is important to note that a significant difference was observed for mood stabilizer with a higher consumption of mood stabilizer in the VRF group at baseline. This difference is not explained by the number of bipolar depressions in VRF group as both groups are not significantly different on this point. Moreover, VRF still decrease response to ECT when adjusting on depression type in the regression model. Patients with vascular depression could present atypical clinical features (Aizenstein et al., 2016). Some recent reviews propose that lithium could be used in association to antidepressant in this clinical context (Knöchel et al., 2015), which could explain the difference for mood stabilizer in our study. Mood stabilizer such as lithium and anti-epileptic drugs can interact with ECT outcomes. Combination of ECT and lithium is known to increase the risk of confusion and seizures length, but do not affect ECT outcome

(Zolezzi, 2016). In our study, the duration of seizure was comparable between the two groups. Confusion was not higher in VRF group (estimate by the use of unilateral stimulation in both groups). Concerning anti-epileptic drugs, combination with ECT could lead to difficulty eliciting seizure (Zolezzi, 2016) but do not affect ECT outcome (Rubner et al., 2009). As described in table 1, sufficient seizure length was obtained in both groups. The supplemental analysis also confirm that adjusting on mood stabilizer did not influence our results.

Findings from neuroimaging studies have been inconsistent regarding the impact of MRI-defined vascular changes, such as deep white matter hyperintensities (WMHI), and response to ECT (Dols et al., 2017; Hickie et al., 1995; Sheline et al., 2010; Spaans et al., 2018). In the current study, there is a lack of longitudinal precise neuroimaging to investigate this point. WMHI were investigated through a binary criterion (“WMHI” or “no-WMHI”) based on the radiologist’s conclusion. With this criterion, we observed no difference between VRF group and non-VRF group. These results were not surprising as low WMHI are very common in mid-life and older people (d’Arbeloff et al., 2019). Although each patient performed a cerebral imaging prior to ECT course, we were not able to measure standardized WMHI or hippocampus size scores and data were analyzed by several radiologists in multiple laboratories with different protocols. Further studies are needed to establish the relationship between WMHI, VRF and response rate to ECT.

Strikingly, although the response rate was significantly different between the groups, we did not observed a significant difference in regards of remission rate between the VRF-group and the non-VRF group. One may hypothesized that a study with a larger number of patients achieving remission is needed to detect a significant difference in remission rate.

#### *Consideration for future studies:*

Regarding limitations in our methodology, some advice should be considered for future studies. As none are found on this topic in literature, impacts of VRF on ECT outcome in LLD should be assessed with a prospective design. Association of well-validated VRF scores such as Framingham score (D’Agostino et al., 2008) with depression characteristics, cognitive features and imaging data could be useful to complete lacking answers of available literature. Impact of modifiable and non-modifiable VRF could offer some perspectives for therapeutic improvement. Also, prospective studies with survival analysis could monitor the impact of VRF duration on depression and treatment outcome. Automatically computed imaging rating scales should be used to determine anatomical cerebral impairment, as their visual measurement are poorly reproducible (De Guio et al., 2016;

Koikkalainen et al., 2019; Scheltens et al., 1997). Moreover, as it can act as a confusion factor, apathy should be assessed at baseline (Pavlovic et al., 2016; Yuen et al., 2014). It has been proposed that the brains of older depressed patients may take longer to respond to the antidepressant effects of ECT. Improvement may not be detected immediately after an acute course of ECT. Future studies may evaluate improvement at distance of the ECT course (Steffens et al., 2001).

*Prevention and treatment option in resistant late-life depression:*

Facing the lower response rate in the VRF group, we should discuss other therapeutic strategies that can be proposed to these patients. One option is to promote primary prevention, in general population but also in at-risk subgroups, as addressing modifiable risk factors since early mid-life may reduce the risk of vascular depression (Whyte and Rovner, 2006). Also, sufficient brain reserve, characterized by educational attainment, may counterbalance the effect of cerebrovascular burden with respect to depressive symptoms, thereby preserving mood in late life (Aizenstein et al., 2016). Moreover, as secondary prevention measure, in addition to the appropriate treatment for depression, screening and optimized management of risk factors for cardiovascular and cerebrovascular disease is necessary (Alexopoulos, 2019).

Neurobiologically based psychotherapies has also been proposed, focusing on barriers to “reward exposure” in three behavioral domains, known to be impacted in LLD, i.e., “negativity bias” (negative valence system dysfunction), “apathy” (arousal system dysfunction), and “emotional dysregulation” (cognitive control dysfunction) (Alexopoulos, 2019). More generally, as psychotherapy has been reported as efficient as pharmacotherapy, it should not be neglected (Pinquart, 2006). Augmentation strategy of antidepressants with either lithium, aripiprazole, methylphenidate has also been found effective in LLD unresponsive to an antidepressant and can be considered (Alexopoulos, 2019; Knöchel et al., 2015; Lenze et al., 2015).

Based on the hypothesis that the treatment of LLD requires stimulation intensities that can overcome prefrontal atrophy, a recent trial reported evidence for the efficacy and tolerability of high-dose deep repetitive transcranial magnetic stimulation for LLD (Kaster et al., 2018). Other therapeutic pathways targeting inflammatory or cerebral hemodynamic systems have also been explored, with a need of confirmation studies (Alexopoulos, 2019). Therefore treatment recommendations for elderly depressive patients favor a multimodal approach and optimization in psychotherapy, pharmacotherapy, biophysical therapy with an appropriate treatment of comorbidities is essential (Knöchel et al., 2015).

It is of importance to note that response rate to ECT, even in VRF context, is higher than medication (Sheline et al., 2010; Spaans et al., 2018). ECT is generally well-tolerated and can avoid severe

medication adverse effects such as serotonin syndrome, associated to multiple lines of antidepressant, in case of treatment-resistant depression (Jurek et al., 2019).

## **CONCLUSION**

In conclusion, although ECT is an effective and well tolerated treatment for LLD, this study discloses that VRF can impede response to ECT in elderly patients with moderate to severe major depressive disorder. Framingham scores were negatively correlated to MADRS changes across ECT course and could be a useful tool in clinical practice to estimate response to ECT. Further studies are needed to confirm our results and to better understand the impact of VRF on ECT outcomes but also its pathophysiology. Nevertheless, primary and secondary prevention of VRF is essential to prevent vascular depression and to improve ECT outcome.

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**TABLE :**

<i>Characteristics</i>	<i>No-VRF group N = 32</i>	<i>VFR-group N = 20</i>	<i>p-value<sup>1</sup></i>
<i>Age, mean years (SD)</i>	70 (9)	67 (7)	0.15
<i>Sex (%)</i>			0.14
<i>Female</i>	66%	45%	
<i>Male</i>	34%	55%	
<i>Duration of the illness, mean (SD)</i>	20 (18)	20 (13)	0.97
<i>Depression Type, n (%)</i>			
<i>Unipolar</i>	75%	55%	0.13
<i>Bipolar</i>	25%	45%	
<i>Treatment</i>			
<i>First generation Antipsychotic (%)</i>	16%	25%	0.48
<i>Second generation Antipsychotic (%)</i>	53%	45%	0.57
<i>Antidepressant (%)</i>	78%	80%	>0.99
<i>Tricyclic (%)</i>	31%	30%	0.92
<i>Mood Stabilizer (%)</i>	16%	45%	<b>0.020</b>
<i>Benzodiazepine (%)</i>	41%	35%	0.69
<i>Comorbidities</i>			
<i>Alcohol Use Disorder (%)</i>	13%	32%	0.15
<i>Obstructive Sleep Apnea (%)</i>	6.7%	15%	0.38
<i>Baseline evaluation</i>			
<i>BDI at baseline, mean (SD)</i>	21 (10)	14 (7)	0.070
<i>MADRS at baseline, mean (SD)</i>	38 (7)	35 (10)	0.13
<i>MOCA at baseline, mean (SD)</i>	21 (4)	23 (4)	0.15
<i>MAUDSLEY at baseline, mean (SD)</i>	10 (2)	9 (2)	0.85
<i>White matter hyperintensities (%)</i>	16 (59%)	7 (44%)	0.32
<i>ECT characteristics</i>			
<i>n of ECT sessions, mean (SD)</i>	14 (4)	14 (4)	0.84
<i>EEG seizure duration (sec), mean (SD)</i>	36 (11)	39 (16)	0.39
<i>Switch from bilateral to unilateral (%)</i>	28%	25%	0.80
<i>Unipolar stimulation ECT (mC), mean (SD)</i>	423 (223)	299 (132)	0.28
<i>Bipolar stimulation ECT (mC), mean (SD)</i>	397 (171)	408 (235)	0.84
<i>Anesthetic agent (%)</i>			
<i>Etomidate</i>	47%	40%	0.63
<i>Propofol</i>	53%	60%	

**Table 1. Characteristics of studied population.\* = p<0.05**

SD: Standard Deviation, VRF: Vascular Risk Factor, MADRS: Montgomery–Åsberg Depression Rating Scale, MOCA: Montreal Cognitive Assessment, BDI: Beck Depression Inventory, n: number, ECT: Electroconvulsive Therapy, EEG: Electro Encephalography

	<b>Non-VRF group (n=32)</b>	<b>VRF group (n=20)</b>
<b>Tobacco smoking, n (%)</b>	1 (3.1%)	8 (40%)
<b>Diabetes mellitus, n (%)</b>	3 (9.4%)	9 (45%)
<b>Hypertension, n (%)</b>	14 (44%)	16 (80%)
<b>Hypercholesterolemia, n (%)</b>	3 (12%)	8 (44%)
<b>History of cardio-vascular disease, n (%)</b>	2 (6.2%)	2 (10%)

**Table 2. Descriptive of vascular risk factors in both groups.**

Characteristic	OR <sup>1</sup>	95% CI <sup>1</sup>	p-value
<b>Depression Type</b>			
<i>Unipolar</i>	—	—	
<i>Bipolar</i>	5.47	0.84, 55.1	0.10
<b>Age</b>	0.96	0.85, 1.07	0.5
<b>Sex</b>			
<i>Women</i>	—	—	
<i>Men</i>	0.37	0.05, 2.00	0.3
<b>Vascular Risk Factor group</b>			
<i>No</i>	—	—	
<i>Yes</i>	0.06	0.01, 0.34	<b>0.004</b>

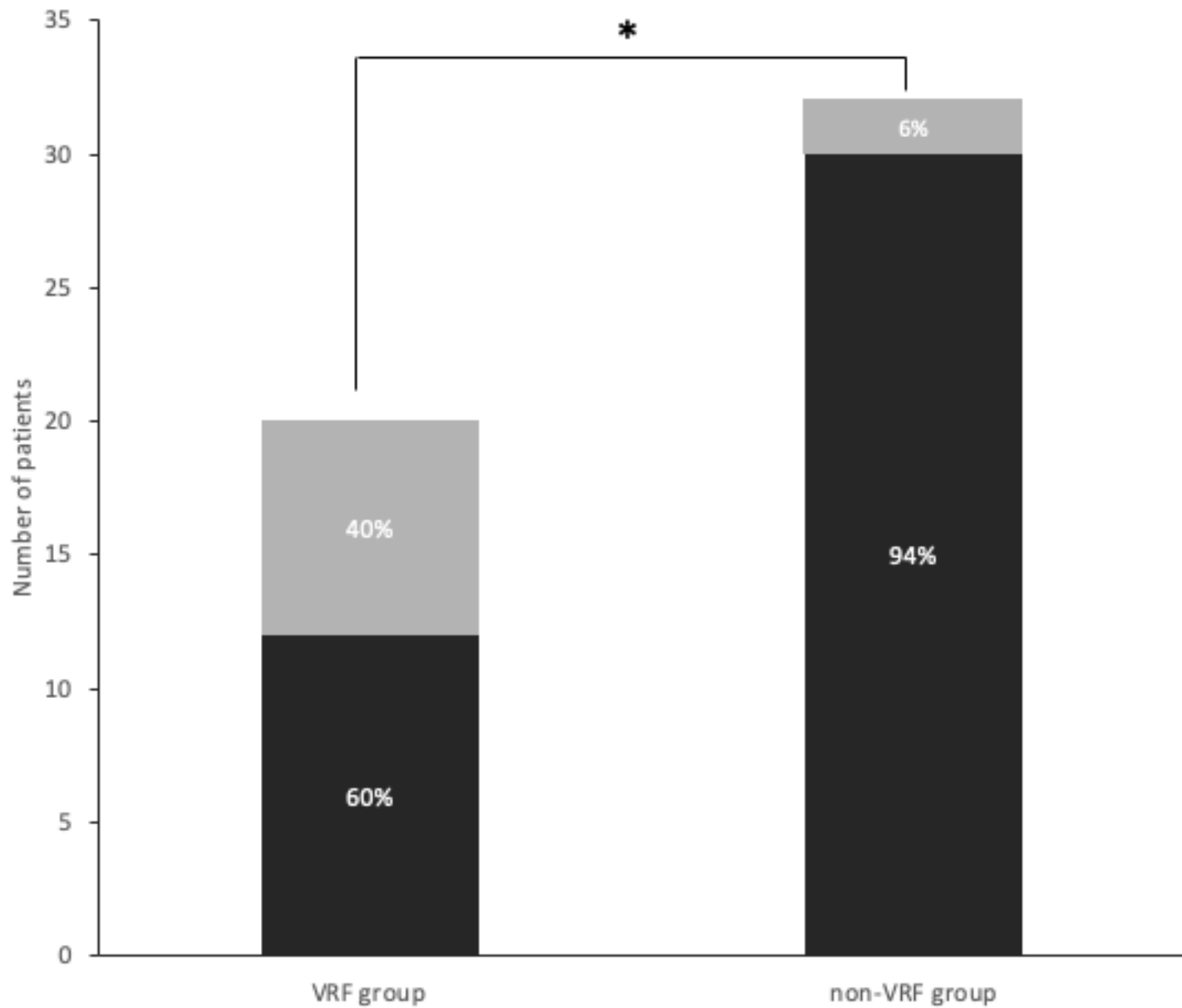
<sup>1</sup> OR = Odds Ratio, CI = Confidence Interval

**Table 3. Logistic regression analysis for response to ECT.**

**Figure 1. Number of responders to electroconvulsive therapy in the two groups: with and without vascular risk factors.**

\* =  $p < 0.05$  / VRF: group with Vascular Risk Factor; Non-VRF : group without Vascular Risk Factor

■ responder ■ non-responder



**Figure 2. Spearman correlation between Montgomery–Åsberg Depression Rating Scale difference (pre/post electroconvulsive therapy) and Framingham score.**  
MADRS: Montgomery–Åsberg Depression Rating Scale

