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Oxytocin as a transdiagnostic biomarker of well-being in severe mental illness during the Covid-19 pandemic

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ABSTRACT

Individuals with severe mental illness (SMI) have been found to suffer a greater decline in psychological well-being compared to the general population in times of stress. The present study aimed to examine clinical and endocrine resilience factors of psychological well-being in SMI patients during the Covid-19 pandemic. Methods: After Covid-19 crisis outburst in Israel 112 participants, 69 outpatients, and 43 inpatients and day treatment patients were recruited. Outpatients signed an online informed consent and filled in questionnaires regarding their level of mental health symptoms (OQ-45), fear of Covid-19 (FCV), and psychological well-being (PWB). Inpatients answered the same questionnaires and in addition, went through a positive social interaction paradigm while providing three saliva samples to measure their s-IgA and oxytocin (OT) levels. Results: A strong negative correlation was found in the whole sample between reported mental health symptoms, fear of Covid-19, and well-being. Hierarchical regression did not find additional contribution of the fear of the pandemic in predicting well-being beyond the impact of symptomatology. For inpatients (N = 39) only, hierarchical regression found that oxytocin, but not s-IgA could explain 5% of the variance of well-being ($R^2 = 0.05$) in individuals with SMI regardless of their mental health symptoms ($R^2 = 0.46$) and their marital status ($R^2 = 0.21$). Conclusions: OT is suggested as a possible independent biological resilience factor of well-being in times of major stress among SMI patients. It is still unknown whether OT is a mediator that contributes to well-being or a biological marker that indicates the degree of beneficial social interactions.

1. Introduction

The Coronavirus-19 (Covid-19) pandemic had a vast impact on the mental health as well as on well-being of individuals worldwide (Salari et al., 2020). Patients suffering from severe mental illness (SMI) are more vulnerable to stress compared to the general population (Sukut and Ayhan Balik, 2021). A systematic review of studies on the impact of the Covid-19 crisis on SMI patients suggests that they are prone to suffer more from anxiety, depression, and stress in comparison to controls (Fleischmann et al., 2021). Most studies have focused on psychopathological symptoms as the sole outcome measure when evaluating health among individuals with SMI. Well-being of SMI patients, beyond psychiatric symptomatology, is central. Psychological well-being (PWB) has been defined as "a core feature of mental health, which includes hedonic (enjoyment, pleasure) and eudaimonic (meaning, fulfillment) happiness, as well as resilience (coping, emotion regulation, healthy problem solving)" (Tang et al., 2019). The importance of PWB is supported by the World Health Organization's current outlook which considers mental health as a goal, not just as the absence of a disorder (WHO, 2022).

Prior studies in clinical populations (de Vos et al., 2018; Weijers et al., 2021) found that the level of psychopathology is associated with a lower sense of well-being in SMI patients. Fear of Covid-19 (FCV) is related to an incline in anxiety, stress, and depression (Belen, 2022; Şimşir et al., 2021) as well as with lower levels of well-being (Ahuja et al., 2020; Paredes et al., 2021). Few studies evaluated symptom severity and well-being in SMI patients during the pandemic

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(Fleischmann et al., 2021). They focused on the role of symptom severity or various psychological factors in shaping the components of the "well-being" construct among SMI patients. Mueller-Stierlin et al. (2022) found that the "perceived control over dimensions of life (perceived empowerment)", a component of well-being, serves as a resilience factor for SMI patients when facing the negative consequences of the Covid-19 crisis. Little is known regarding the biological markers that act as resilience or risk factors in this population during the Covid-19 crisis.

Different endocrine systems have been suggested as potential biological correlates of well-being, particularly during stress. Immunoglobulin A (IgA) is a mucosal antibody secreted when the immune system is exposed to new potential threats (Bakema and Van Egmond, 2011). IgA secretion in human saliva (s-IgA) is a well-validated biomarker of immune-system activation (Engeland et al., 2019). Studies have shown that that levels of s-IgA are associated with higher levels of loneliness and depression (Dragoş & Tănăsescu, 2010; Engeland et al., 2016).

Oxytocin (OT) is a neuropeptide associated with bonding, affiliation, trust, and a general sense of well-being (Bakermans-Kranenburg & Van IJzendoorn, 2013). Oxytocin (OT) enhances the beneficial effect of social support in response to stress in healthy individuals (Heinrichs et al., 2003; Riem et al., 2020a) as well as in those who suffer from psychopathology such as major depression (Tsai et al., 2019). Social support, in turn, serves as a protective factor in coping with psychopathology and enhances well-being (Masten and Tellegen, 2012). Specifically, a study that assessed more than a thousand adults revealed that Covid-19-related fear was associated with a decrease in participants' mental well-being. Perceived social support was found to ameliorate both the mental well-being and the quality of life of the participants (Alyami et al., 2021). OT has well-known anxiolytic effects (Feldman et al., 2016) and induces a subjective feeling of relaxation and calmness that may increase an individual's sense of well-being, particularly during periods of elevated stress (Ishak et al., 2011).

The presented research is part of a larger project evaluating different aspects of the challenge the pandemic posed on SMI patients. In the previous arms of the project, we examined the course of psychiatric symptomatology of outpatients after the Covid-19 outbreak (Grossman-Giron et al., 2022) and then evaluated the protective effect of being in an inpatient unit during the outbreak (Bloch et al., 2022).

In the current study, we focused on the psychological well-being of SMI patients during the outbreak of the Covid-19 pandemic. We expected that the fear of Covid-19, beyond the general clinical symptoms, would have a detrimental effect on PWB. We hypothesized that s-IgA, as a biological marker of stress, will correlate negatively with PWB. In addition, we hypothesized that OT, serving as an indicator of social salience, will be able to explain changes in well-being beyond the contribution of the symptoms.

2. Methods

The institutional review board at Shalvata Mental Health Center gave its approval for the study (IRB approval number: 0007-20-SHA).

2.1. Participants

Participants were recruited between April 26th and June 6th, 2020, shortly after the first general Covid-19 lockdown was implemented in Israel. The sample consisted of 120 outpatients and 44 inpatients. The outpatients were recruited from a research project that addressed participants evaluated before the Covid-19 outbreak (Tzur Bitan et al., 2019). These participants were reassessed remotely during the lockdown. Inpatients were recruited through publications distributed to patients from 3 inpatient wards and one day-treatment program (a total of 217 patients at that time).

Inclusion criteria for the inpatient group were being registered in an inpatient ward or a day treatment program at the time of the study, completing the PWB questionnaire, and being able to provide a salivary sample. Out of the inpatients' respondents, one patient was removed after not completing the questionnaire. For the outpatient group, individuals needed to meet the criteria of being an outpatient (participating in psychiatric appointments or engaging in psychotherapy or group therapy sessions). The outpatients were required to complete the PWB questionnaire. Of the total 120 participants contacted by phone, 35 declined to participate or were unavailable. Of the 85 potential participants who signed informed consent, 16 respondents did not complete the PWB questionnaire. Sixty-nine outpatients and 43 inpatients were eligible for the study (Fig. 1).

Participants were 59.8% males, 38.5% females and 1.7% non-binary patients. Mean age was 34.18 (SD = 13.44) and most of the participants were born in Israel with a below-average socio-economic status. Seventeen participants (15.2% of the total sample) were diagnosed with a psychotic spectrum disorder. (Table 1).

2.2. Procedure

For the outpatients, online study questionnaires were answered after signing an online informed consent. Due to Covid-19 restrictions, we were not able to collect saliva samples from the outpatients. Inpatients had a face-to-face meeting with a researcher, during which they provided informed consent and completed questionnaires. After a 30-min period without eating or smoking, we obtained an initial saliva sample. Following this, patients participated in a 7-to-10-min conversation with a researcher, during which they planned an imaginary "best day ever" with a loved one. This paradigm is a widely accepted and validated approach for increasing OT levels in order to facilitate its measurement (Djalovski et al., 2021; Priel et al., 2019; Ulmer-Yaniv et al., 2018; Yirmiya et al., 2020). Due to Covid-19 restrictions, which limited family visits, we modified the task, so participants were instructed to imagine a "best day ever" with a loved one not in front of this person but in the presence of the researcher. Approximately 10 and 20 min after completing the conversation second and third saliva samples were collected respectively (Fig. 2).

2.3. Samples collection handling and assaying

The three saliva samples of 0.5ml–1.5 ml were collected into 5 ml tubes by passive drooling, kept child for less than an hour and kept at −20 °C for long-term storage.

Within a few months, these saliva samples underwent three freeze-thaw cycles, (−80 °C and 4 °C), followed by centrifugation at 4000×*g* for 30 min, in order to precipitate the mucus. The supernatant was collected and stored at −20 °C until assayed.

OT concentration was measured using a commercial OT Enzyme-Immuno- Assay (EIA) kit (ENZO, New York, USA). Measurement was done according to the kit's instructions. In-house high medium and low controls were added to each plate to verify the kit's sensitivity range. The intra-assay and inter-assay of samples and controls are less than 6.63% and 10.13%, respectively.

s-IgA concentration was measured using a commercial s-IgA- EIA kit (EUROIMMUN AG: 23560 Luebeck, Germany). Measurement was done according to the kit's instructions. The intra-assay and inter-assay coefficients of samples and controls are less than 3.79% and 7.50%, respectively.

2.4. Measures

The Outcome Questionnaire-45 (OQ-45) (Boswell et al., 2013): A commonly used self-report questionnaire in psychotherapy research. Its main objective is to evaluate the clinical condition of patients throughout the course of psychotherapy, without being limited by specific diagnoses. The questionnaire consists of 45 items. In the current

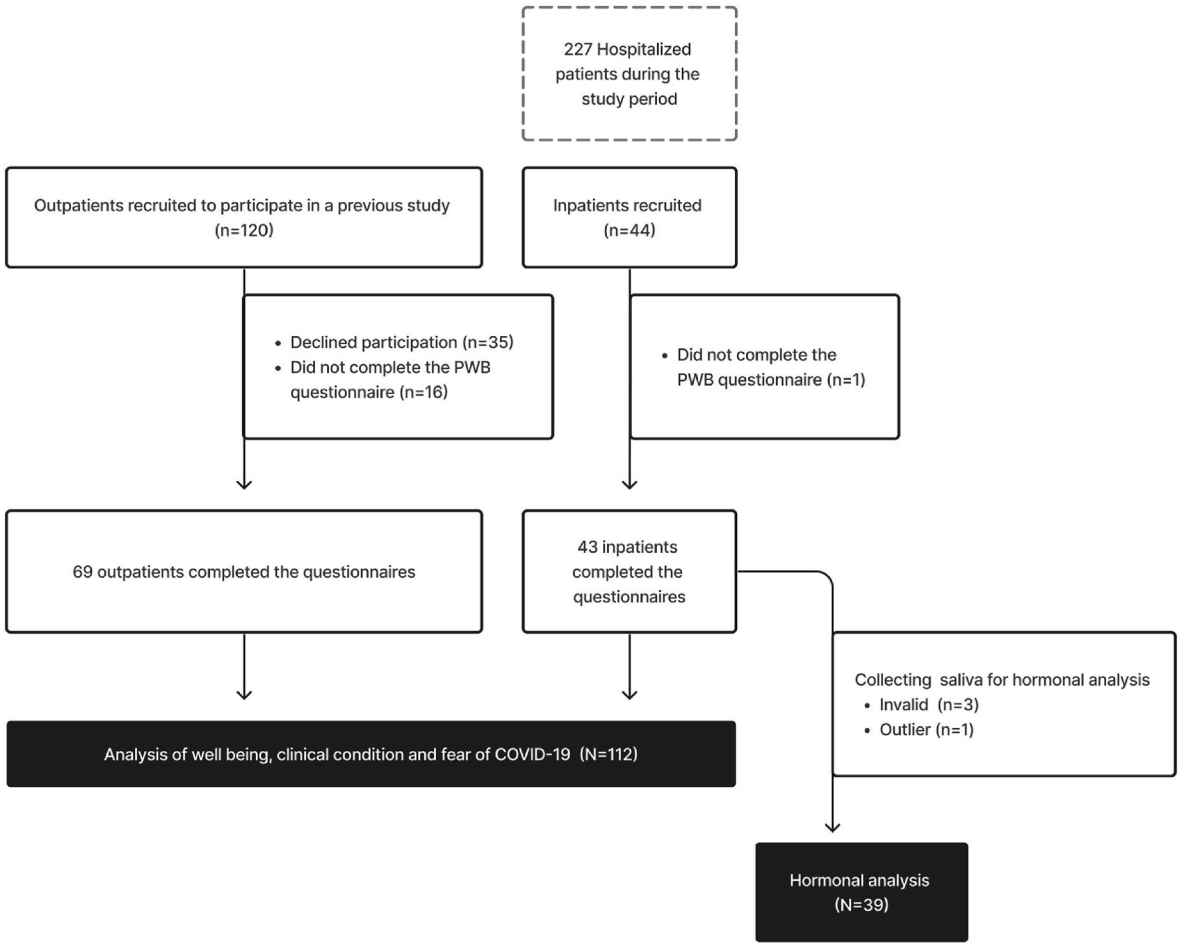

Fig. 1. The process of recruiting participants for the study
PWB= Psychological Well-Being.

study, the mean score of all the items was calculated, with higher scores indicating a more severe clinical condition. It had a good internal consistency (in our sample, Cronbach's alpha = 0.92), and test–retest reliability (r = 0.84) (Snell et al., 2001).

Psychological Well-Being Scale (PWB) (Ryff and Keyes, 1995): The purpose of this self-report questionnaire is to assess the psychological perception of well-being in relation to six distinct dimensions: personal growth, purpose in life, self-acceptance, environmental mastery, positive relations with others and autonomy. Respondents were asked to indicate the degree to which they agree with each one of the 54 items on a six-point Likert scale. Higher mean score of indicate a greater overall sense of well-being. The alpha coefficient of the PWB in the current sample indicated high internal reliability (Cronbach's alpha = .95).

Fear of Covid-19 (FCV–19S) (Ahorsu et al., 2022): A self-report scale aiming to evaluate the level of fear respondents experience regarding the Covid-19 pandemic. This questionnaire consists of seven items, rated on a five-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). Total sum score was computed with higher scores representing higher fear of the pandemic (i.e., Alijanzadeh et al., 2021),. The psychometric properties of this scale seem to be good among the Israeli population (Tzur Bitan et al., 2020). Furthermore, the current study shows high levels of internal reliability (Cronbach's alpha = .91).

***Measurement of Oxytocin and s-IgA*:** In order to establish a valid measure of oxytocin and s-IgA levels that takes into account the three samples, we performed a logarithmic transformation on the sample and then calculated the area under the curve (AUC; Pruessner et al., 2003). Oxytocin levels were missing for three of the forty-three participants while s-IgA levels were missing for only two out of these three patients. These three patients were not included in the sample calculations. An additional participant was excluded since his oxytocin levels were more than two standard deviations from the average of the sample (an outlier) (Fig. 1).

2.5. Statistical analyses

Demographic characteristics and their relation to PWB scores were assessed using independent t-tests in the case of birth country, marital status, and having a psychotic spectrum diagnosis, a One-Way ANOVA in the case of gender, socio-economic status, and education, and a simple Pearson correlation in the case of participants' age. Correlations between study variables were performed with a Pearson correlation matrix. Since the association between PWB and each individual study variable represents a distinct hypothesis, we did not conduct a correction test for multiple comparisons. Notwithstanding this, a sensitivity analysis for all statistical analyses mentioned above was performed and is presented in Appendix 1. In the case of hormonal analysis, to assess potential differences among the three saliva samples Repeated Measures, ANOVA test was utilized for both s-IgA and oxytocin. Finally, to estimate the independent contribution of our variables on PWB, we performed two hierarchical regression analyses. All statistical procedures were conducted using SPSS version 25.

Table 1
Demographic characteristics of the sample and their relation to Psychological well-being (PWB) scale.(N = 112).

Variable		Frequency (Value, %)	PWB Total mean (Mean; SD)	*p-value*
Gender	Males	67 (59.8%)	3.70 (0.79)	N.S.
	Females	43 (38.4%)	3.71 (0.80)	
	(Nonbinary)	2 (1.8%)		
Birth country	Israel	87 (77.7%)	3.67 (0.77)	N.S.
	Other	25 (22.3)	3.76 (0.84)	
Socio-economic status	Way below average	38 (33.9%)	3.53 (0.67)	N.S.
	Below average	30 (26.8%)	3.71 (0.90)	
	Average	26 (23.2%)	3.80 (0.81)	
	Higher than average	14 (12.5%)	3.83 (0.67)	
	Way higher than aver	4 (3.6%)	3.88 (1.22)	
Marital Status	Single	64 (57.1%)	3.51 (0.71)	*P < 0.01*
	Married or partnered	48 (42.9%)	3.94 (0.82)	
Education	Elementary and high school	63 (56.3%)	3.57 (0.77)	N.S.
	BA	36 (32.1%)	3.76 (0.77)	
	MA and PHD	13 (11.6%)	4.11 (0.80)	
Psychotic Spectrum Diagnosis	No	95 (84.8%)	3.64 (0.81)	N.S.
	Yes	17 (15.2%)	4.00 (0.60)	
		Mean; SD	PWB pearson correlation	*p-value*
Age		36.86 (13.99)	$r = 0.21$	*p=0.02*

3. Results

3.1. Symptoms, well-being and Fear of Covid-19 among all participants (N = 112)

3.1.1. Baseline demographics and their relationship to outcome variable (PWB)

PWB scores were not related to gender, place of birth, socioeconomic status, years of education, or having a psychotic spectrum diagnosis. An association between marital status and PWB was observed ($p < 0.04$), suggesting that participants who were married or in a partnership exhibited elevated PWB scores (Mean = 3.94; SD = 0.82) compared to single participants (Mean = 3.51; SD = 0.71). In addition, a positive relation was found between age and PWB scores indicating that older participants tended to report higher PWB scores ($r(112)=0.21$, $p < 0.05$). (Table 1).

3.1.2. Psychological well-being (PWB) and its correlation to symptomatology (outcome measure; OQ-45) and Fear of Covid-19 (FCV) scores

A Pearson correlation matrix was calculated to assess the interrelations between PWB, OQ-45, and FCV. A strong negative correlation was found between PWB and both FCV scores ($r(112)=-0.28$, $p < 0.01$) and OQ-45 scores ($r(112)=-0.82$, $p < 0.01$) indicating higher PWB scores were related to lower FCV and OQ-45 scores. In addition, OQ-45 and FCV had a strong positive correlation ($r(112) = 0.35$, $p < 0.01$).

3.1.3. Hierarchical regression analysis to evaluate the effect of Fear of Covid-19 (FCV) on psychological well-being (PWB) scores beyond symptomatology (outcome measure; OQ-45) scores

To assess the effect of FCV beyond the contribution of OQ-45 scores on PWB scores we conducted a hierarchical regression analysis, with PWB scores as the dependent variable and participants' marital status and age as covariates. We ensured that the necessary assumptions for conducting a linear regression were indeed met, including the normal distribution of our dependent variable, PWB (Skewness = −0.09). Age and marital status were introduced separately in the model because age is a straightforward demographic factor, while marital status encompasses both clear situational information and psychological nuances related to relationship-building abilities. In addition, since the OQ-45 questionnaire reflects a clinical state relevant beyond the pandemic, compared to the more specific pandemic-related fear, in this model OQ-45 score was introduced before the fear of Covid-19 score. The whole model was found significant, accounting for 67% of the variance in PWB scores ($F_{model}(4,107) = 57.79$, $p < 0.01$). Age entered in the first step, significantly contributed to PWB levels ($F_{step1}(1,110) = 4.92$, $p=0.03$) explaining 4% of PWB score variance. Subsequently, the inclusion of marital status in the analysis contributed a significant 5% to the explained variance, nullifying the relationship between age and PWB ($F_{change\ step2}(1,109) = 6.09$, $p = 0.02$). OQ-45, entered in the third step, predicted PWB scores ($F_{change\ step3}(1,108) = 201.35$, $p < 0.01$) adding 68% to the explained variance and eliminating the contribution of both marital status and age. In the fourth step, the inclusion of FCV scores did not contribute to the prediction of PWB scores or change the significance of OQ-45 in predicting PWB scores (Table 3).

3.2. Associations between oxytocin and s-IgA with well-being, symptoms, and Fear of Covid-19 analysis among inpatients with valid salivary samples (n = 39)

3.2.1. Descriptive data of oxytocin and s-IgA

Potential differences between the three saliva samples collected were assessed. The overall model was insignificant for both OT and s-IgA, indicating that there was no observable alteration in hormone levels across the three time points. Fig. 3 presents the average scores for each sample of oxytocin, which was used in further calculations.

The calculated mean of the AUC for OT, based on three samples, was 66.81 (SD = 0.62), and ranged between 48.46 and 87.64. Regarding the AUC of s-IgA, the mean score was 198.47 (SD = 15.91) and ranged between 163.83 and 227.96. Studied hormones seemed to be positively intercorrelated (r(39) = 0.40, p = 0.01) means higher OT levels tended to correlate with higher s-IgA levels.

3.2.2. Psychological well-being (PWB) and its correlation to hormonal levels

The correlation matrix containing PWB scores and OT showed a positive correlation ($r(39) = 0.32$, $p=0.04$) but not in the case of PWB and s-IgA.

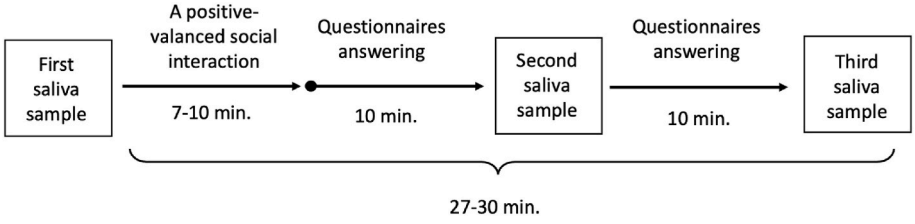

Fig. 2. Procedure timeline.

Table 2
Demographic characteristics of the sample and their relation to Oxytocin and s-IgA (N = 39).

Variable		Frequency (Value, %)	AUC s-IgA (Mean; SD)	*p-value*	AUC Oxytocin (Mean; SD)	*p-value*
Gender	Males	20 (51.3%)	196.05 (16.62)	N.S.	66.56 (9.84)	N.S.
	Females	17 (43.6%)	202.58 (14.14)		67.91 (9.78)	
	Nonbinary	2 (5.1%)	187.79 (23.14)		59.94 (5.51)	
Birth country	Israel	33 (84.6%)	197.41 (14.02)	N.S.	65.49 (9.22)	*p=0.04*
	Other	6 (15.4%)	203.74 (25.03)		74.07 (9.20)	
Socio-economic status	Below average	26 (66.7%)	198.95 (16.23)	N.S.	67.07 (10.23)	N.S.
	Average and above	13 (33.3%)	197.52 (15.80)		66.28 (8.65)	
Marital Status	Single	33 (84.6%)	197.69 (15.55)	N.S.	67.30 (9.51)	N.S.
	Married	6 (15.4%)	202.78 (18.72)		64.09 (10.68)	
Education	Elementary and high school	29 (74.4%)	199.55 (17.38)	N.S.	67.48 (9.09)	N.S.
	Academic education	10 (25.6%)	195.34 (10.70)		64.86 (11.33)	
Psychotic Spectrum Diagnosis	No	27 (69.2%)	195.05 (15.66)	*p=0.042*	64.79 (8.70)	*p=0.048*
	Yes	12 (30.8%)	206.17 (14.20)		71.36 (10.41)	
		Mean; SD	AUC s-IgA Pearson correlation	*p-value*	AUC Oxytocin Pearson correlation	*p-value*
Age		34.23 (13.61)	*r* = 0.34	*p=0.03*	*r=0.37*	*p=0.02*

AUC= Area under the curve.

Table 3
Summary of hierarchical regression coefficients of psychological well-being (PWB) by age, marital status, fear of Covid-19 (FCV), and psychopathology (OQ-45).

Predictor variable	Step 1		Step 2			Step 3			Step 4		
	B	t	B	t	β	B	t	β	B	t	β
Age	0.01	1.22	0.01	1.52	0.14	0.00	0.51	0.03	0.00	0.51	0.03
Marital status			0.37	2.47	0.23*	0.13	1.39	0.08	0.12	1.36	0.08
OQ-45						−0.02	−14.76	−0.80***	−0.02	−13.75	−0.80***
FCV									0.00	0.16	0.01
R^2 (ΔR^2)	0.04*		0.09 (0.05)*			0.68 (0.59)***			0.68 (0.00)		
***F* change**	4.92		6.09			201.35			0.02		

Note. *p < 0.05. **p < 0.01. ***p < 0.001.
PWB= Psychological well-being; OQ-45 = Outcome Questionnaire; FCV=Fear of Covid-19.

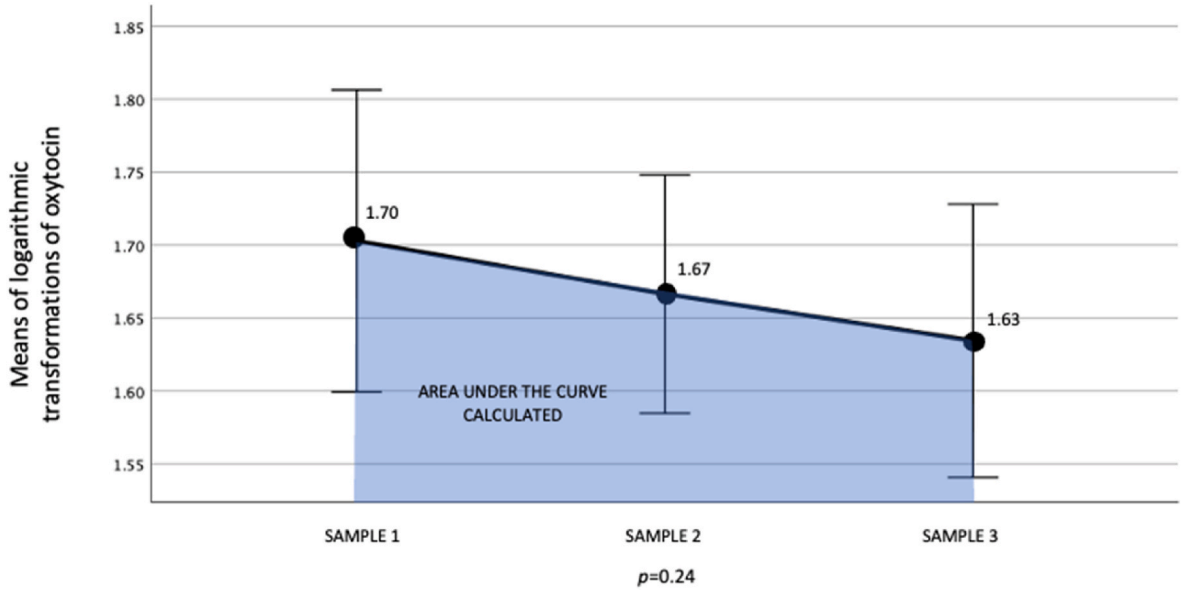

Fig. 3. Means of logarithmic transformations of oxytocin across three-time points and illustration of area under the curve calculated for each participant (p = 0.24).

3.2.3. Predicting psychological well-being (PWB)

To assess the effect of OT on PWB scores independently we conducted a hierarchical regression analysis, with PWB scores as the dependent variable and participants' marital status and age as covariates. The whole model was found significant, accounting for 72% of the variance in PWB scores ($F_{model}(4,34) = 21.70, p < 0.01$). Age, which was entered in the first step, significantly contributed to PWB levels ($F_{step1}(1,37) = 8.64$, p=0.01) explaining 19% of PWB score variance. In the second step, the inclusion of marital status into the model resulted in a non-significant impact. OQ-45, entered in the third step, predicted PWB scores adding 46% to the explained variance while canceling out the contribution of age but not the contribution of marital status (F_{change}

$_{step3}$ (1,35) = 49.10, $p < 0.01$). Finally, adding OT levels in the fourth step was significantly predictive along with marital status and OQ-45 scores ($F_{change\ step3}(1,34) = 5.49$, $p = 0.03$) explaining an additional 5% of the PWB variance (Table 4, Fig. 4).

4. Discussion

This study focused on the PWB of SMI patients during the Covid-19 pandemic. The idea of PWB goes beyond symptom relief. It focuses on attaining happiness and fulfillment (Tang et al., 2019). Consequently, PWB is currently considered a desired aim in both therapy and prevention for individuals with SMI. A study conducted among SMI patients revealed a strong correlation between PWB and the process of mental health recovery (Browne et al., 2017). Based on the significance of demographic, psychological, and biological correlates we identified factors that might be central to the understanding of PWB in SMI patients during the pandemic.

Our findings demonstrate that the well-being of psychiatric patients during the Covid-19 pandemic was negatively associated with the severity of symptomatology. This correlation was significant to the level that the fear of Covid-19, though correlated with well-being, had no additional effect in the regression model.

Evaluating both outpatients and inpatients (N = 112), only symptom severity remained significant in the regression model. This suggests that SMI patients are heavily affected by the symptoms. Some might argue that this finding diminishes the relevance of addressing PWB in SMI patients, as they appear to be entirely affected by the burden of their symptoms.

After examining the impact of hormones in the second regression model it turned out that other factors beyond the symptoms might influence SMI patient's PWB. Among the 39 inpatients, symptom severity remained the most significant factor affecting PWB. However, we also noticed that marital status played a significant role, and OT had a modest but noteworthy (5%) independent effect.

The emergence of marital status as a significant correlate to PWB is in line with the current literature. Studies in the general population show that being married or in partnership is associated with higher well-being (Dolan et al., 2008; Gómez-López et al., 2019). This applies to individuals with SMI as well, with married or cohabitating SMI patients reporting significantly higher quality-of-life scores (Bhattacharjee et al., 2023; Nyer et al., 2010). Both marital status and OT may emphasize the crucial role of social ties and social salience as resilience factors for PWB in SMI patients. While OT measurement is time-specific, marital status reflects a more longitudinal prosocial process, suggesting these two aspects complete each other. It is unclear why this factor became significant only after analyzing the biological data in the smaller inpatient group and not in the whole sample. One potential explanation is linked to the heightened disease severity observed among the inpatient group. Within this group, the majority were not in a relationship, suggesting that having a partner might indicate notable "social resilience" in the context of severe illness (Nyer et al., 2010).

The correlation of OT with well-being aligns with existing literature that associates OT with greater overall well-being and reduced fear in the general population (Ishak et al., 2011). A potential explanation for the OT's protective effect is the well-documented connection between OT and stress regulation (Matsushita et al., 2019; Olff et al., 2013) as well as the relation between experiencing lower levels of stress and enhanced mental well-being (Wersebe et al., 2018). In this context, it has been suggested that amplifying OT production can be a possible way to reduce the impact of stress in times of the Covid-19 pandemic (Gryksa and Neumann, 2022).

Another explanation could be that OT, beyond its stress-regulating function, may increase well-being by enhancing social salience. That means, by promoting prosocial behavior and a heightened awareness of social cues (Shamay-Tsoory and Abu-Akel, 2016). For instance, in a controlled trial, older adults who received OT reported increased feelings of gratitude and improved well-being (Barraza et al., 2013).

In addition, it has been argued that OT attenuates neurophysiological and autonomic avoidance responses by increasing attention to social cues. It is possible that this attenuation facilitates the formation of new social bonds and the experience of more social support, which in turn can result in promoting well-being (Wittfoth-Schardt et al., 2012). Perceived social support is a well-known resilience factor during exposure to different stressors (Ozbay et al., 2008), specifically in the case of Covid-19 related stressors (Mahamid et al., 2021; Ye et al., 2020).

In the current study, as the main point of interest was well-being, we emphasized the favorable impact of OT. Nevertheless, it's important to note that OT's influence is context-dependent (Kemp and Guastella, 2011; Shamay-Tsoory and Abu-Akel, 2016). This means that OT can also be associated with negative emotions, including aggression, envy, and anxiety, and not exclusively with positive ones (Duque-Wilckens and Trainor, 2022; Eckstein et al., 2014). Interestingly, this conceptualization of OT aligns with our findings, as OT was found to be related not only to PWB but also to s-IgA-a marker potentially associated with stress.

In our sample, s-IgA levels didn't correlate with participants' well-being. Perhaps our relatively small sample size and the fact that the task we used was not designed to amplify s-IgA made it difficult to detect differences in s-IgA changes. It is also possible that the s-IgA as an inflammatory marker has a more complex role in modifying stress and well-being.

It remains unclear whether OT is (1) a resilient factor, which through its crucial role in enhancing social connections and stress regulatory properties can affect SMI patients' well-being or (2) a biological marker of one's beneficial social relations. If these findings will be verified in larger longitudinal, prospective studies and the modest effect suggested in our study will be found to be of clinical relevance there is a potential for improving SMI patients' well-being through OT interventions. Either by administering it externally (Berends et al., 2019) or endogenously. Increasing social synchrony, or coordinated behavior during social interactions, can serve as a potential endogenously way to boost OT levels, as demonstrated in a few studies (Djalovski et al., 2021; Feldman et al., 2016; Levy et al., 2016).

Table 4
Summary of hierarchical regression coefficients of psychological well-being (PWB) by age, marital status, psychopathology (OQ-45) and oxytocin levels (AUC-g Oxytocin).

Predictor variable	Step 1		Step 2			Step 3			Step 4		
	B	t	B	t	β	B	t	β	B	t	β
Age	0.02	2.94*	0.02	2.40	0.38*	0.00	0.70	0.08	0.00	−0.09	−0.01
Marital status			0.11	1.08	0.17	0.17	2.70	0.28	0.17	2.83	0.28*
OQ-45						−0.02	−7.01	−0.73***	−0.02	−7.57	−0.75***
Oxytocin									0.02	2.34	0.23*
R^2 (ΔR^2)	0.19*		0.21 (0.03)			0.67 (0.46)***			0.72 (0.05)*		
***F* change**	8.64		1.16			49.10			5.49		

PWB= Psychological well-being; OQ-45 = Outcome Questionnaire; AUC-g = Area under the curve with respect to the ground.

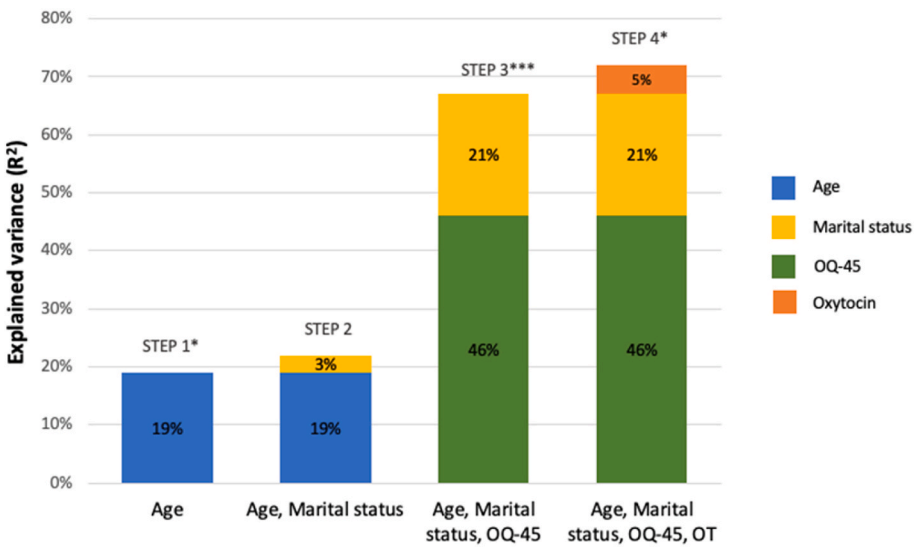

Fig. 4. Hierarchical regression presenting the four steps of the explained variance (R^2) in psychological well-being (PWB) as correlated with age, marital status, psychopathology (OQ-45), and oxytocin levels (AUC-g Oxytocin).
Note. *p < 0.05. **p < 0.01. ***p < 0.001.

4.1. Study limitations

Our study has several limitations. First, the findings presented are based on correlations, which make it hard to rule out the possibility that a third confounding variable affected both well-being and OT levels. For example, it is possible that social support raises both PWB and OT not through OT as a mediator. Since literature exists on the role of OT and social support in promoting well-being (Riem et al., 2020), our hypothesis regarding OT as a protective factor might be considered reasonable. Second, the sample size used in the final analysis of OT is somewhat small (N = 39), though this number is common in similar hormonal studies focused on this unique population (Bradley and Woolley, 2017). Third, the study lacks longitudinal follow-up which could have shed more light on the stability of our findings. Fourth, the effects of s-IgA and OT in the central nervous system may not be reflected accurately in saliva samples. Martins et al. (2020), for instance, claim that OT measurements are not steady enough to be reliable indicators of the OT system's function. In addition, the storage of saliva can bear the danger of confounding the results. Still, the field uses this method while being aware of these limitations. We considered that collecting three samples could be a possible way to validate the accuracy of our hormone measurement. In this sense, in contrary to our expectation, no differences were detected between the three OT samples. This finding could be attributed to the fact that subjects performed the task in a slightly modified way. Moreover, it is possible that when individuals engaged in conversation with an unfamiliar researcher during Covid-19 isolation, their OT levels reached a peak and remained constant throughout the entire interaction, resulting in a ceiling effect.

Declaration of Generative AI and AI assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT to improve readability and language. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author statement

According to IRB since these are small patient groups and the information is personal the research data is confidential.

Declaration of competing interest

None.

Appendix 1

Sensitivity analysis

To verify that our findings are independent of the specific analysis used, a sensitivity analysis was conducted. Concerning the baseline demographics and their relation to Psychological Well-Being (PWB), a Bonferroni post-hoc test for multiple comparisons was employed, leading to the annulation of the association between PWB and age. Nonetheless, the correlation between PWB and marital status maintained its statistical significance even after the Bonferroni post-hoc correction. In the case of the interrelationships among Psychological Well-Being (PWB), Fear of Covid-19 (FCV), and Outcome Questionnaire-45 (OQ-45), all the correlations observed remained significant after performing the Bonferroni post-hoc test.

Regarding the hormonal levels' analysis, none of the relationships between s-IgA, oxytocin, and any demographic variable remained statistically significant after the Bonferroni test. Finally, in the context of the interrelation between PWB, s-IgA, and oxytocin, only the association between s-IgA and oxytocin remained statistically significant after the Bonferroni post-hoc procedure.

In summary, the application of the Bonferroni post-hoc test revealed that the gathered demographic data showed no significant associations with both Psychological Well-Being (PWB) and hormonal levels, except for the notable linkage between PWB and marital status. Notably, the intercorrelations among the administered questionnaires (PWB, OQ-45, and FCV), along with the intercorrelations among the hormones (s-IgA and oxytocin), retained their statistical significance even following the post hoc tests.

Appendix 2

Baseline Demographics and Their Relationship to Hormonal Levels

We examined the relationship between the hormonal values and

clinical and demographic variables (Table 2). Out of the 14 comparisons that were conducted, birth country, psychotic state, and age were related to oxytocin. Psychotic state and age were found to be associated with s-IgA.

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