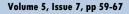


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# Comparison of the Effectiveness of Integrated Self-Analytic Approach Therapy and Acceptance and Commitment Therapy on Ego Strength and Emotion Regulation Difficulties in Individuals with COVID-19 Grief Syndrome

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#### ABSTRACT

**Objective:** Ego strength indicates an individual's capacity to endure stress without experiencing crippling anxiety and is related to a sense of competence and self-sufficiency in personal and social domains. Therefore, the aim of the present study was to investigate the effectiveness of therapy based on the integrated self-analytic approach on psychological capital, psychological well-being, ego strength, and emotion regulation difficulties in individuals suffering from COVID-19 grief syndrome.

**Methods and Materials:** The present research method was quasi-experimental, employing a pretest-posttest control group design with a two-month follow-up. The statistical population consisted of individuals with COVID-19 grief syndrome in Isfahan during the second half of 2022. Using a purposive sampling method, 30 eligible individuals were selected and randomly assigned equally to experimental and control groups. The experimental group received the integrated self-analytic approach therapy (Atashpour et al., 2021) and the acceptance and commitment therapy (Hayes, 2004), while the control group did not receive any intervention. Data collection tools included the Bart and Scott Grief Experience Questionnaire (1989), the Garnefski and Kraaij Emotion Regulation Scale (2006), and the Ego Strength Scale (PIES). Descriptive statistics (mean and standard deviation) and inferential statistics (mixed ANOVA with repeated measures) were used for data analysis. SPSS-26 software was used for conducting the statistical tests.

**Findings:** The calculated F-value for the between-group factor was significant at the 0.05 level (P<0.05). Consequently, there was a significant difference between the mean pretest, posttest, and follow-up scores of psychological capital in the experimental and control groups. Bonferroni post-hoc test results also indicated a significant difference between pretest and posttest, and pretest and follow-up scores of ego strength and emotion regulation difficulties in both experimental groups (P<0.05). However, the post-hoc test results showed no significant difference

between posttest and follow-up scores of the study variables (P>0.05). The Tukey post-hoc test also indicated no significant difference in the effectiveness of these two approaches (P>0.05).

**Conclusion:** The results demonstrated that both integrated self-analytic approach therapy and acceptance and commitment therapy were significantly effective in improving ego strength and reducing emotion regulation difficulties. These effects were sustained at the follow-up stage, and the effectiveness of the two approaches was identical.

**Keywords:** Integrated Self-Analytic Approach, Acceptance and Commitment Therapy, Ego Strength, Emotion Regulation Difficulties.

## 1. Introduction

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he COVID-19 pandemic has not only disrupted individuals' daily functioning but also led to fatalities caused by the disease. One of the primary challenges for survivors who have lost significant individuals to COVID-19 is the mourning process. Adhering to social distancing measures to prevent the virus's spread has disrupted traditional mourning processes, reducing emotional and social support from friends and acquaintances (Eisma et al., 2021). Therefore, it seems that the grief and sorrow resulting from the loss of loved ones due to COVID-19 have increased in a prolonged and debilitating manner, accompanied by symptoms of grief disorder (León & Guzmán-Saldaña, 2023).

Ego strength indicates an individual's capacity to withstand stress without experiencing crippling anxiety and is related to feelings of competence and self-sufficiency in personal and social domains. Since the ego is responsible for managing the psychological system, all psychological problems emerge when the ego fails to fulfill its responsibilities. Overall, our ability to cope with life, i.e., our psychological balance, depends on the ego's strength and capacity to overcome various pressures (Mishra, 2013). On the other hand, emotion regulation can mitigate the negative outcomes of COVID-19 and lead to better adaptation to feelings of loneliness and maintaining psychological wellbeing (Gubler et al., 2021). In general, emotion regulation can be defined as processes through which individuals influence what emotions they have, when they have them, and how they experience and express them (Panayiotou et al., 2021). Lower mental health is generally associated with fewer emotion regulation strategies, poor emotional clarity, and non-acceptance of emotions. Conversely, the ability to regulate emotions, considering that it involves behavioral control and self-acceptance, can be helpful (Vuillier et al., 2021).

Providing effective care and interventions for those grieving due to COVID-19 has become a global challenge (Eisma et al., 2021). One widely used psychological intervention is the integrated self-analytic approach therapy. This approach posits that the underlying layers of our insecurities and psychological pains are formed by fears and anxieties, making fear the root of all insecurities. At the upper layers of the psychological iceberg, emotions and feelings are generally conscious, and the disturbing emotions and pains individuals can talk about are at the peak. Beneath this peak, in terms of pathology, there is a type of insecurity that causes pain. These pains are cries that we sometimes eliminate from our awareness, suppress, or even convince ourselves that the pain does not exist. It is evident that the absence of pain by hiding, suppressing, or imagining it does not exist is very different. In such a situation, the individual is essentially fleeing. This escape starts from pain and leads to fear, and again from fear back to pain (Kelson et al., 2019). Another effective treatment in various situations is Acceptance and Commitment Therapy (ACT) (Zhao et al., 2021). ACT is rooted in a philosophical theory called pragmatism and is based on a research program on language and cognition known as Relational Frame Theory (Hayes, 2004). ACT involves six central processes that lead to psychological flexibility: acceptance, defusion, self as context, contact with the present moment, values, and committed action (Han et al., 2020; Kelson et al., 2019).

Given that grief disorder appears to be one of the common negative outcomes during the COVID-19 pandemic, providing interventions to enhance individual capacities can be helpful. Although the effectiveness of the integrated selfanalytic approach has been somewhat explored concerning psychological capital, psychological well-being, ego strength, and emotion regulation difficulties, there is still a gap in directly examining the effectiveness of this treatment on the mentioned variables in individuals with COVID-19 grief syndrome. Therefore, this study aimed to compare the effectiveness of the integrated self-analytic approach therapy on psychological capital, psychological well-being,



ego strength, and emotion regulation difficulties in individuals with COVID-19 grief syndrome.

### 2. Methods and Materials

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#### 2.1. Study Design and Participants

The present research method was quasi-experimental, using a pretest-posttest control group design with a twomonth follow-up. The statistical population consisted of individuals with COVID-19 grief syndrome in Isfahan during the second half of 2022. Using purposive sampling, 45 eligible individuals were selected and randomly assigned equally to experimental and control groups. Inclusion criteria included scoring above 27 on the Grief Experience Questionnaire and having passed six months since the death of their loved ones due to COVID-19. Exclusion criteria included taking medication and missing more than two sessions. The experimental group received the integrated self-analytic approach therapy, while the control group did not receive any intervention.

All members of the experimental and control groups completed the research questionnaires as a pretest before the intervention. Participants were informed about the study's purpose, the need to answer all questionnaire items, and the confidentiality of their responses, with coded data and the right to withdraw at any stage. After the educational sessions, the experimental and control groups completed the posttest questionnaires again. To follow up on the stability of the intervention's effectiveness, both groups were retested after two months.

## 2.2. Measures

## 2.2.1. Grief

This questionnaire was first designed and developed by Bart and Scott in 1989 to assess grief reactions in 34 items. It uses a five-point Likert scale (1 to 5) from never to always. The questionnaire has seven components: guilt feelings, attempts to justify and cope, physical reactions, feelings of abandonment, personal or others' judgment about the cause of death, embarrassment and shame, and stigma. Scores ranging from 34 to 68 indicate low grief experience, 68 to 102 moderate grief experience, and above 102 high grief experience (Barrett & Scott, 1989). The reliability of this tool was reported by Bart and Scott (1989) with a Cronbach's alpha coefficient of 0.90 for the total scale and 0.89, 0.69, 0.79, 0.87, 0.82, 0.82, and 0.87 for the respective components. The construct validity of the original questionnaire was confirmed through factor analysis. In Iran, Mehdi Pour et al. (2009) assessed its validity and reliability, reporting a Cronbach's alpha of 0.88 for the total questionnaire and 0.40 to 0.86 for the components. The convergent validity of the Persian version was confirmed, showing appropriate convergent validity with the depression and somatization subscales of the General Health Questionnaire (Mehdipour et al., 2009).

#### 2.2.2. Emotion Regulation

This 18-item scale assesses cognitive emotion regulation strategies in response to threatening and stressful life events on a five-point scale from one (never) to five (always), across nine subscales: self-blame, other-blame, rumination, catastrophizing, positive refocusing, planning, positive reappraisal, putting into perspective, and acceptance. Higher scores indicate greater use of that cognitive strategy. Alpha coefficients for the subscales ranged from 0.71 to 0.81, and test-retest reliability coefficients ranged from 0.48 to 0.61 over 14 days (Solimannejad et al., 2019). Self-regulation strategies can be considered along a continuum (cognitive coping) and divided into more adaptive (positive/efficient) and less adaptive (negative/inefficient) strategies. In Iran, alpha coefficients for the subscales ranged from 0.62 to 0.91, with test-retest reliability coefficients between 0.75 and 0.88 over one week. Factor analysis indicated a seven-factor structure: positive refocusing/planning, positive reappraisal/perspective taking, acceptance, other-blame, self-blame, rumination, and catastrophizing. Content validity was reviewed by eight psychology experts, with Kendall's agreement coefficients for subscales ranging from 0.81 to 0.92 (Solimannejad et al., 2019).

#### 2.2.3. Ego Strength

Developed by Markstrom et al. (1997), this 64-item scale measures eight ego strength points: hope, will, purpose, competence, fidelity, love, care, and wisdom, rated on a five-point Likert scale from strongly agree (5) to strongly disagree (1). Reverse scoring is applied to 30 items. The highest possible score is 300, and the lowest is 60, with higher scores indicating greater ego strength. Markstrom et al. (1997) confirmed its face, content, and construct validity, with a Cronbach's alpha coefficient of 0.68. In Iran, Altafi (2010) reported a Cronbach's alpha of 0.91 and a split-half reliability of 0.77. Parviz et al. (2016) reported a Cronbach's alpha of 0.64 (Parviz et al., 2016).



#### 2.3. Intervention

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#### 2.3.1. Integrated Self-Analytic Approach Therapy

The therapy sessions followed the protocol by Atashpour et al. (2021) (Einy et al., 2019).

Session 1: Pretest and Self-Worth Explanation

Introduction of members, conducting the pretest, explaining the objectives of the educational sessions, outlining rules and regulations, explaining the integrated self-analytic approach, and emphasizing the impact of loss and grief on psychological well-being and psychological capital during the COVID-19 pandemic.

Session 2: Attention to Human Existential Dimensions

Training in self-awareness through inner psychological considerations and interpersonal interactions, comparing the human psyche to an iceberg, focusing on personal history and existential fears, and assigning homework.

Session 3: Attention to Loss and Pain

Reviewing the previous session's homework, understanding emotional structures, the nature of frustration, loss and pain, improving distress, harmful emotional states, using related techniques, and assigning homework.

Session 4: Understanding Psychological Needs

Reviewing the previous session's homework, explaining the nature and necessity of fulfilling needs, identifying psychological needs such as survival, security, trust, competence, and assigning homework.

Session 5: Continuation of Psychological Needs Understanding

Reviewing the previous session's homework, understanding psychological needs such as growth and progress, attention and approval, connection, autonomy (independence), appropriate excitement (fun), solitude and introspection, spirituality, and self-worth, and assigning homework.

Session 6: Existential Fears

Brief review of the previous session, understanding the nature and types of fear, the damage from internal events, and assigning homework.

Session 7: Continuation of Existential Fears

Reviewing the previous session's homework, explaining that insecurity underlies human psychology, mechanisms of fear, types of fears, techniques for overcoming fears, and assigning homework.

Session 8: Life Stories

Reviewing the previous session's homework, explaining that life stories reflect experiences, and underlying misconceptions, and assigning homework. Session 9: Continuation of Life Stories

Reviewing the previous session's homework, providing and practicing techniques to correct misconceptions and improve unhealthy life stories, and assigning homework.

Session 10: Extreme-Compensatory Mechanisms

Reviewing the previous session's homework, explaining the emergence of compensatory mechanisms to couples, discussing and practicing major compensatory-defensive mechanisms, providing techniques to reduce harmful mechanisms, and assigning homework.

Session 11: From Worthlessness to Self-Worth

Reviewing the previous session's homework, explaining the nature of worthlessness and low self-esteem, the impact of worthlessness, characteristics of self-worthy individuals, positive components of self-worth and positive thinking, teaching and practicing self-worth and self-esteem techniques, and assigning homework.

Session 12: Power of Choice and Posttest

Summarizing and reviewing previous sessions, discussing human choice power, obtaining feedback from members about the sessions, addressing questions, and conducting the posttest.

#### 2.3.2. Acceptance and Commitment Therapy

The therapy sessions followed Hayes' (2004) protocol (Hayes, 2004).

Session 1: Introduction, Pretest, Goals, and Approach Explanation

Introducing members, conducting the pretest, explaining the objectives of the educational sessions, outlining rules and regulations, explaining the ACT approach and its goals, defining the research components, and explaining the purpose of the study to the participants.

Session 2: Creative Helplessness

Discussing experiences and evaluations, using efficacy as a measure, creating creative helplessness, controlling the problem, self as context, defusion, commitment to behavior change, initial values assessment, practicing mindfulness, and assigning homework.

Session 3: Acceptance

Practicing mindfulness, presenting acceptance strategies, using the swamp metaphor, chassis exercise, objectification practice, staying with problematic emotions, practicing facing the giant robot metaphor, and assigning homework.

Session 4: Defusion

Practicing mindfulness, reviewing the previous session, applying defusion strategies and exercises (e.g., milk



exercise), cognitive defusion: objectifying psychological content, practicing thoughts on cards, imagining the mind as a chatterbox, bus passengers metaphor, and assigning homework.

Session 5: Self as Context

Practicing mindfulness, reviewing the previous session, using self-as-context strategies: self as context metaphor, chessboard metaphor, other self-as-context metaphors, practicing self-observation, and assigning homework.

Session 6: Values and Commitment

Practicing mindfulness, reviewing the previous session, applying value clarification strategies: setting value-based goals and activity planning, creating larger and more sustainable committed actions, initial values assessment, questions about aspirations and dreams, value clarification exercises like the compass metaphor, setting value-based goals, and activity design, and assigning homework.

Session 7: Commitment

Practicing mindfulness, reviewing the previous session, using strategies for committed action towards values, and assigning homework.

Session 8: Mindfulness

Teaching mindfulness strategies: practicing mindfulness in daily activities, formal meditation exercises, mindfulness of thoughts and emotions, mindfulness of surroundings, reviewing the previous session, and assigning homework.

#### Session 9: Committed Action

Practicing mindfulness, reviewing previous sessions, creating larger committed actions, preparing clients for potential obstacles and distinguishing external from internal barriers, using mindfulness, acceptance, and defusion interventions, maintaining focus on value-driven processes, emphasizing the quality of committed actions over quantity, helping clients recommit in case of lapses, and assigning homework.

Session 10: Feedback and Posttest

Reviewing previous sessions, obtaining feedback from members about the sessions, addressing questions, and conducting the posttest.

#### 2.4. Data analysis

Descriptive statistics (mean and standard deviation) and inferential statistics (mixed ANOVA with repeated measures) were used for data analysis. SPSS-26 software was utilized for the statistical tests.

#### 3. Findings and Results

Descriptive indicators (mean and standard deviation) of psychological capital scores in the experimental and control groups at the pretest, posttest, and follow-up stages are presented below (Table 1).

#### Table 1

Descriptive Data of Scores in Experimental and Control Groups at Pretest, Posttest, and Follow-up Stages

Group	Variable	Indicator	Pretest	Posttest	Follow-up
Integrated Self-Analytic Approach	Ego Strength	Mean	161.87	180.00	184.27
		Standard Deviation	16.96	20.56	18.17
Acceptance and Commitment Therapy	Ego Strength	Mean	160.27	182.67	188.00
		Standard Deviation	18.85	18.31	13.18
Control	Ego Strength	Mean	160.27	157.60	159.73
		Standard Deviation	14.77	15.18	18.61
Integrated Self-Analytic Approach	Adaptive Emotion Regulation	Mean	22.53	31.87	30.67
		Standard Deviation	4.44	4.87	5.05
Acceptance and Commitment Therapy	Adaptive Emotion Regulation	Mean	22.67	31.60	30.53
		Standard Deviation	5.27	5.08	5.73
Control	Adaptive Emotion Regulation	Mean	23.47	23.07	24.80
		Standard Deviation	5.10	7.48	7.70
Integrated Self-Analytic Approach	Maladaptive Emotion Regulation	Mean	22.73	18.20	18.20
		Standard Deviation	4.77	4.26	5.33
Acceptance and Commitment Therapy	Maladaptive Emotion Regulation	Mean	23.27	12.93	14.67
		Standard Deviation	4.33	3.43	5.15
Control	Maladaptive Emotion Regulation	Mean	23.27	23.93	24.33
	-	Standard Deviation	4.46	7.05	5.79

As observed, the mean scores in the integrated selfanalytic approach and acceptance and commitment therapy groups increased at the posttest stage compared to the pretest stage. Based on the results in the table, it can be claimed that



the integrated self-analytic approach and acceptance and commitment therapy have increased ego strength and reduced emotion regulation difficulties in individuals with COVID-19 grief syndrome. Before conducting the mixed ANOVA with repeated measures, necessary assumptions were checked. The results of the Shapiro-Wilk test indicated that the significance levels for each research variable were

#### Table 2

greater than 0.05, confirming the normality of the variables' data at all three stages, allowing the use of parametric tests. Additionally, the results of Levene's test showed that the assumption of equal variances was met for all variables (p > 0.05). However, the results of Mauchly's test indicated that the assumption of sphericity was not met (p < 0.05). Therefore, the Greenhouse-Geisser correction was used.

Variable	Statistical Index	SS	df	MS	F	Sig	Eta Squared
Ego Strength	Test (Repeated Measures)	9511.60	1.54	6191.94	44.76	0.001	0.44
	Test*Group Interaction	4202.00	4.61	911.82	6.59	0.001	0.26
	Between Groups	8722.73	2.00	4361.36	4.31	0.01	0.19
Adaptive Emotion Regulation	Test (Repeated Measures)	1292.31	1.35	956.09	46.23	0.001	0.45
	Test*Group Interaction	671.43	1.35	497.45	31.29	0.001	0.36
	Between Groups	745.78	2.00	372.89	2.82	0.04	0.13
Maladaptive Emotion Regulation	Test (Repeated Measures)	483.69	4.06	119.28	5.77	0.001	0.24
	Test*Group Interaction	564.21	4.05	139.34	8.76	0.001	0.32
	Between Groups	1082.11	2.00	541.05	6.64	0.001	0.26

Table 2 shows that the calculated F value for the betweengroup factor is significant at the 0.05 level (p < 0.05). As a result, there is a significant difference between the pretest, posttest, and follow-up scores of psychological capital in the experimental and control groups. Additionally, Bonferroni post-hoc test results were calculated to examine the differences between means at the treatment stages, showing significant differences between pretest and posttest scores, and pretest and follow-up scores of ego strength and emotion regulation difficulties (p < 0.05). However, the post-hoc test results showed no significant differences between posttest and follow-up scores (p > 0.05).

#### Table 3

Tukey Post-hoc Test Results for Pairwise Comparison of Mean Scores in Three Groups

Variable	Comparison Groups	Mean Difference	Standard Error	Significance Level
Adaptive Emotion Regulation	Integrated Self-Analytic vs. ACT	0.27	2.32	0.99
	Integrated Self-Analytic vs. Control	8.80	2.32	0.001
	ACT vs. Control	8.53	2.32	0.001
Maladaptive Emotion Regulation	Integrated Self-Analytic vs. ACT	5.27	1.83	0.03
	Integrated Self-Analytic vs. Control	-5.73	1.83	0.01
	ACT vs. Control	-11.00	1.83	0.001
Ego Strength	Integrated Self-Analytic vs. ACT	-2.67	6.76	0.98
	Integrated Self-Analytic vs. Control	22.40	6.76	0.01
	ACT vs. Control	25.07	6.76	0.001

According to the results of the Tukey post-hoc test (Table

3), it can be concluded that the integrated self-analytic approach and acceptance and commitment therapy have a significant impact on ego strength and emotion regulation difficulties (p < 0.01), but there is no significant difference between the effectiveness of these two approaches (p > 0.05).

#### 4. Discussion and Conclusion

The present study aimed to compare the effectiveness of the integrated self-analytic approach and acceptance and commitment therapy on ego strength and emotion regulation difficulties in individuals with COVID-19 grief syndrome. The results showed that both therapies were significantly effective in enhancing ego strength and reducing emotion regulation difficulties, and these effects were sustained at the



follow-up stage. However, there was no significant difference between the effectiveness of the two approaches.

The findings regarding the effectiveness of the integrated self-analytic approach align with prior research (Lange, 2021; Solimannejad et al., 2019). In explaining these findings, it can be stated that in the process of the integrated self-analytic approach, counseling helps clients identify their limiting emotions and thoughts that cause distress, striving for balance, reasonable challenge, self-control, and prudent living. When the inner pains and cries of clients are well heard, empathy, affirmation, and trust-building occur as a reasonable bond between them and their therapist. Such dialogue is a bonding communication, which, like all bonds, is a dynamic flow of transformations. If the therapist creates effective and meaningful dialogue, the client's behavior and reasons will become apparent. Meaningful listening involves active attention, making clients feel understood, and facilitating the exchange of thoughts and behaviors freely. Without creating an environment filled with attention, affirmation, and neutrality (free from judgment), emotional release will be less successful. This process should be sought in active and effective listening. In such a process, a soft and smooth relationship is formed. Sometimes, in such listening, verbal expression of emotions is not even necessary; the resulting states and changes speak for themselves. It seems that in such a situation, a kind of freedom is formed, and there is no pressure to understand (Lange, 2021). A free process, a conversation without pressure, and an empathetic understanding will be formed, which will also be enjoyable. Creating such an environment facilitates the expression of pains, and a mechanism of internal self-regulation grows, allowing each party to speak without pressure or control. This approach believes that the underlying feeling of worthlessness or worthiness is central. If a person feels worthy, they will create the possibility of changing this process. In addition, they will accept their existential fears correctly and face them appropriately; by recognizing their recurring life story, making appropriate changes, and replacing suitable mechanisms, they will care for and quickly repair their emotional structure (Solimannejad et al., 2019).

The findings regarding the effectiveness of acceptance and commitment therapy align with prior studies (Ashrafi Alavijeh & Atashin Jabin, 2021; Bahramiabdolmalaki et al., 2021; Han et al., 2020; Hayes, 2004; Kelson et al., 2019; Otared et al., 2021; Zhao et al., 2021). Acceptance and commitment therapy (ACT) is a psychotherapy approach that emphasizes behavioral principles based on mindfulness. This approach helps individuals accept unpleasant feelings and experiences and learn commitment to their actions and values instead of resisting them. For individuals with COVID-19 grief, this approach can be very effective. COVID-19, besides its physical complications, has significant psychological impacts, including anxiety, increased stress, feelings of loneliness and isolation, increased anger, and insecurity. Additionally, some individuals may experience the loss of loved ones due to the disease (Bahramiabdolmalaki et al., 2021; Han et al., 2020). In this situation, ACT can help individuals face this unpleasant experience and expedite their psychological recovery. This approach focuses on mindfulness, increasing awareness of experiences and feelings, accepting them, and committing to actions and values that matter to the individual. It helps individuals understand themselves more deeply and cope with life changes, improving overall wellbeing. In this approach, individuals learn to accept negative feelings instead of resisting them, allowing them to engage with their emotions related to grief and COVID-19 anxiety. It also helps them avoid focusing on negative thoughts and self-concepts and instead commit to actions that improve life quality (Otared et al., 2021; Zhao et al., 2021).

#### 5. Limitations & Suggestions

The major limitation of this study is external validity, as the research population was a specific group (individuals with COVID-19 grief in Isfahan), limiting the generalizability of the results. Additionally, data collection was based on self-report scales, which may differ from actual behaviors and actions observed. Moreover, the research design was quasi-experimental, lacking the advantages of true experimental designs. Given the impact of the integrated self-analytic approach and ACT on individuals with COVID-19 grief, psychologists are encouraged to use these therapies extensively. Health and mental health professionals are recommended to design and apply suitable methods inspired by the integrated selfanalytic approach and ACT to enhance the mental health of individuals with COVID-19 grief. Further research involving psychologists and psychotherapists in various psychological and clinical centers is suggested to compare results and optimize the application of these therapeutic approaches. It is also recommended to train specialists to conduct educational workshops for vulnerable groups.

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## Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

## **Declaration of Interest**

The authors of this article declared no conflict of interest.

## **Ethics Considerations**

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants.

## **Transparency of Data**

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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## **Authors' Contributions**

All authors contributed equally.

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