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Child and Adolescent Mental Health Service

# Moderators and Predictors of the Clinical Outcome After Hospitalization

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## Introduction

Clinical practice grounded in evidence-based medicine (EVB) is meant to obtain valid and reliable measures of outcomes of therapeutic intervention and to understand the underlying mechanisms leading to clinical benefits. The practice of EVB means drawing con-

sciously, explicitly, and judiciously from the best available external clinical evidence, from systematic research and integrating individual clinical expertise [1]. It allows clinicians to deliver the most efficient care known to date, while striving to respect their patients in their individuality. These considerations take on their full meaning especially when applied to children's and adolescent's mental health problems. More than 50% of lifetime psychiatric disorders have an onset in adolescence [2], but only a minority of adolescents have access to appropriate psychic care [3].

This study focuses on inpatient units (IPUs), which represent one type of care in child and adolescent mental health service (CAMHS). Stays in IPUs can be indicated for assessment and stabilization of disabling and acute psychiatric symptoms when outpatient settings can no longer contain the situation [4-6]. Although IPUs are known to be effective on the majority of young people [4, 7, 8], there are only a few studies measuring

the outcome after hospitalization in CAMHS (9) and it remains unclear which patient will benefit the most from hospitalization. To improve clinical outcomes and to better target personalized therapeutic interventions, it is crucial to understand the mechanisms behind behavior changes by examining predictors and moderators [10, 11].

Moderating factors specify the condition improving or reducing the effectiveness of the treatment [12]. For instance, boys (gender as moderator) have better treatment outcomes. In general, moderators refer to precursor of predictors and outcomes. In contrast, predicting factors are not differentially linked to treatment outcomes [13]. For example, significant pretreatment severity is related to better outcomes regardless of gender.

Studies of adolescent samples are rare. Some intrapersonal factors (stressful life events, gender, severity of treatment) or interpersonal factor (social functioning) have been identified as predictors and moderators

of both outpatient and inpatient treatment outcomes [14-17].

Mixed results have been observed regarding pretreatment symptom severity as a predictor in previous studies. A review of the literature [18] on inpatient and outpatient clinics for children and adolescents revealed that higher pretreatment depression severity was a predictor of poorer outcome for depression but not for anxiety. On the contrary, higher pretreatment symptom severity from various mental disorders was associated with greater improvement in clinical outcomes after inpatient treatment [10, 19, 20]. These discrepancies may be attributable to differences in study designs and sample characteristics.

A higher social functioning in youths is an important part of recovery and predicts better clinical outcomes after outpatient treatment among children and adolescents suffering from psychotic [21, 22] or mood [23] disorders. Likewise, a better premorbid family functioning predicted a better outcome after inpatient treatment [16, 24].

According to a literature review [25], a strong therapeutic alliance with an adolescent after inpatient and outpatient treatment is a modest but consistent factor predicting a better clinical outcome. More parental cooperation during the inpatient stay (i.e., family support and functioning and parents' involvement in treatment) translates into better treatment outcomes for youths with mental health problems [16, 19, 24, 26, 27]. A recent study based on an adolescent psychiatric out-

patient sample showed, that therapeutic alliance between patient and clinician is associated with a subsequent reduction in symptoms regardless of prior symptoms and pretreatment severity [28]. A study based on a sample of drug-using patients highlighted the existence of moderating effects of clinician-patient and clinician-parent alliances on the outcome of outpatient treatment. Indeed, the alliance with the parents was a moderator on the clinician-patient alliance related to the treatment outcome. Moreover, a better alliance with the patient predicted a decrease in symptoms at the end of the treatment and this was even more significant when the alliance with the parents was stronger [29].

Another literature review showed, that little is known about hospitalization against the will of children and adolescents as a predictor of treatment outcomes [30].

Stress from cumulative adverse childhood experiences is known to be a risk factor for developing psychological disorders in adolescence [31, 32]. In addition to the most well-known categories of stressful life events (SLEs), such as domestic violence, mental illness, incarceration of loved ones, and sexual, psychological or physical abuse [33], recent studies point out that other stressors, such as an unfavorable social environment [34], divorce, or exposure to a high number of SLEs [35], also promote the development of psychological disorders in adolescence.

To the best of our knowledge, no prior studies have examined the moderating effect

of gender and SLEs on the treatment outcome following hospitalization in IPU. Most outpatient studies did not observe any moderating effects of gender on treatment outcomes [18]. One study related to assertive community treatment [36] found that pretreatment severity had a greater influence on treatment outcome in youths confronted with many SLEs. Within the context of depression, outpatient studies reported that youths with a history of trauma had a lower twelve-week treatment response compared to those without trauma [37-39]. One study based on a child psychiatric outpatient sample found that quality of life was predicted by the presence of prior stressful life events and that this association was stronger for boys than for girls [40].

The aim of this study was to examine the weight of predictors and moderators of treatment outcome related to IPU for adolescents from a multiple informant perspective (i.e., clinicians and patients) in order to improve clinical care.

We assumed, that gender and SLE moderate the effect of predictors on treatment outcome. The impact of predictors on the outcome could differ between boys and girls. Among youths exposed to several SLEs, it was discovered that predictors known in the literature to be related to better treatment outcomes could have less impact. In this study, symptoms and psychosocial difficulties (i.e., clinical outcome) were assessed using the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) [41-43].

## Abstract

**Objective:** This study aims at determining the influence of several predictors and moderators of the clinical outcome following a hospitalization in a child and adolescent mental health service (CAMHS).

**Method:** The sample included 297 patients aged from 12 to 18 years. Patients and clinicians used the Health of the Nation Outcome Scales for Children and Adolescents (HoNOSCA) to rate clinical outcomes (i.e., symptoms and psychosocial difficulties).

**Results:** Hierarchical regression analyses revealed that patient alliance ( $p=0.003$ ), social functioning ( $p<0.001$ ), and parental cooperation ( $p=0.008$ ) were significant predictors of the clinical outcome. Moreover, gender (associated with pretreatment symptom severity;  $p=0.019$ ), parental cooperation ( $p=0.036$ ) and stressful life events (SLE; associated with social functioning;  $p=0.003$ ) moderated the clinical outcomes significantly. Higher patient alliance was related to lower symptoms and less psychosocial difficulties at discharge. In boys, lower parental cooperation and higher pretreatment symptoms severity were related to more symptoms and psychosocial difficulties at discharge. Finally, in youths exposed to several SLEs, social functioning had no influence on symptoms and psychosocial difficulties at discharge.

**Conclusions:** This study identified patient alliance, gender and SLEs as explaining factors of the clinical outcomes following the hospitalization in a CAMHS. These results could help clinicians to improve treatment strategies by allowing personalized care.

**Keywords:** HoNOSCA; adolescent; treatment outcomes; inpatient; mental health service; stressful life events; gender

## Methods

### Inpatient Stay

Data was collected from two adolescent IPUs in Switzerland (Lausanne and Sierre), between April 2016 and May 2018. Both IPUs consisted of ten beds. Participants were hospitalized either voluntarily (69.3%) or against their will (30.7%). The average length of stay was 24.59 days (standard deviation [SD]=19.8). Both units are primarily crisis resolution units for patients with psychiatric disorders. They consist of a multidisciplinary team and include a focus on networking with families, justice, schools, social services, and outpatient care units. Patients had two or three individual interviews and one family interview per week.

## Sample

All patients attending the two IPU were likely to participate in the study given that the HoNOSCA rating was part of the standard admission procedure. A total of 331 patients were admitted to the two units and data was collected for 297 patients aged 12 to 18 years ( $M=15.29$  years,  $SD=1.34$ ). Out of those, 58% were girls and 42% were boys. Also, 34 patients were not included due to the following exclusion criteria: (1) an inpatient stay less than seven days or (2) the inability to complete questionnaires because of insufficient language skills or mental retardation. Diagnosis was made according to the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [44]. The distribution of diagnoses within our sample is presented in table 1. Of note is that only a minority of adolescents (13.8%) did not report any SLEs.

Table 1: Diagnoses according to ICD-10 criteria

| Diagnoses                                                                                                | N (%)      |
|----------------------------------------------------------------------------------------------------------|------------|
| Mood disorders (F 30-39)                                                                                 | 123 (41.6) |
| Anxiety, stress-related and somatoform disorders (F 40-48)                                               | 74 (25.0)  |
| Behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F 90-98)   | 38 (12.8)  |
| Disorders of psychological development (F 80-89)                                                         | 16 (5.4)   |
| Disorders due to psychoactive substance use (F 10-19)                                                    | 13 (4.4)   |
| Disorders of adult personality and behavior (F 60-69)                                                    | 12 (4.1)   |
| Schizophrenia, schizotypal and delusional disorders (F 20-29)                                            | 11 (3.7)   |
| Mental and behavioral syndromes associated with physiological disturbances or physical factors (F 50-59) | 7 (2.4)    |

## Procedure

Every patient received oral and written information about the study at admission. After 24 hours, patients and their legal guardians (if younger than 14) decided whether to give their written consent to participate. The study procedure was approved by the Ethics Committee on Research Involving Humans from the Canton Vaud (#2015-00215).

The clinician in charge of the patient completed the HoNOSCA questionnaire (rating symptoms and psychosocial difficulties) at admission and at discharge, as well as noting sociodemographic information. Additionally, patients completed the HoNOSCA questionnaire at admission and at discharge.

## Measures

### Clinical Outcome

The HoNOSCA is a sensitive and valid measure of change for children and adolescents attending CAMHS [45, 46], covering a wide range of psychiatric symptoms and psychosocial difficulties independent of the diagnosis. Its psychometric properties and reliability are well established [45, 47, 48], especially in the

context of IPU [41-43]. The instrument is brief and easy to use by the clinician [49]. Of note, HoNOSCA offers one form for clinicians (HoNOSCA-CR) [48] as well as a self-report form for patients (HoNOSCA-SR) [41].

The clinicians were trained psychiatrists and psychologists. They used the French version of HoNOSCA-CR, which showed appropriate psychometric properties [50]. It is composed of 15 items scored on a five-point severity scale. For this study, only the first 13 items, which focus on patients' physical, social, and psychological difficulties, were considered. This allowed for better comparison of the results with the French version of HoNOSCA-SR for patients [42], which is composed by the same 13 items also rated on a five-point severity scale.

We computed the total HoNOSCA score by averaging responses on the 13 items. Higher scores meant more symptoms and psychosocial difficulties. The test was performed at admission and at discharge to diminish the bias generated by missing data. We considered multiple informant scores (patients and clinicians) in the regression analyses by averaging the scores of both type of raters ( $\rho=.165$ ,  $p=.016$ ). A multiple informant perspective improves the predictive value of clinical results [51]. Furthermore, this perspective provides complete information on the patient's progress as opposed to a single assessment [27].

### Moderators

Moderators were assessed by the clinicians. Patients' gender was registered in the sociodemographic information at admission. SLE refers to abnormal psychosocial situations according to the axis V of the ICD-10. During the anamneses, the following list of items was used to assess SLEs:

- Absence of distortion or maladjustment of the psychosocial environment.
- Abnormal intrafamilial relationship (e.g., lack of warmth in the parent-child relationship, discord between the adults).
- Mental disorder, deviance or handicap in the child's immediate environment, such as psychic disorders or behaviors deviance of a parent.
- Inadequate or distorted intrafamilial communication.
- Abnormal child-rearing patterns (e.g., parental overprotection, insufficient attention and supervision).
- Abnormal immediate environment (e.g., institutional upbringing, abnormal parental situation).

- Acute life events.
  - Social stressors (e.g., persecution, discrimination, migration, or social displacement).
  - Chronic interpersonal stress related to school or work environment.
  - Stressful events or situations resulting from the child's own disorder or disability.
- Each item is rated "1" if present. The assessment was supervised by a senior physician during the case review. Because a cumulative effect of SLE was associated with behavioral problems [42], the SLE score refers to the addition of the present items.

### Predictors

The type of admission at hospital was obtained by clinicians and indicated as either "voluntary" or "involuntary," meaning a hospitalization against the will of the patients, allowing the hospitalization of patients who do not adhere to a treatment while presenting symptoms deemed threatening to themselves or others and whose ability to discern is suppressed.

Pretreatment symptom severity was evaluated at admission using the French version of the Clinical Global Impression-Severity of Illness Scale (CGI-S) [53]. The CGI-S is a well-established, valid and sensitive rating instrument [54] that is known for its sensitivity to change, reliability, and brevity in completion [55-57]. The CGI-S describes patients' state as an overall impression and is assessed by the clinician using a single score to evaluate the severity of psychopathology relative to other patients with the same disease. The CGI-S score ranges from 1 to 7. A higher score correspond to a higher pretreatment symptom severity.

Social functioning was assessed at admission by the clinician using the French version of the Global Assessment of Psychosocial Disability Scale (GAPD-S). GAPD-S constitutes the sixth axis of the ICD-10 multiaxial presentation [58]. GAPD-S is a reliable and easy-to-use scale [59, 60]. It assesses functional disability during the disorder and three months prior to the assessment. The scale ranges from 0 to 8. A higher score corresponds to less social functioning.

The clinician assessed the cooperation of parents during the patients' hospitalization and at discharge. A single score was used ranging from 1 (minimal) to 5 (excellent). Similarly, the clinician assessed patients' cooperation and achievement of treatment objectives, using single scores also ranging from 1 (minimal) to 5 (excellent). The patients' cooperation score and achievement of treat-

ment objectives score were strongly correlated ( $\rho=.572$ ,  $p<.001$ ). Therefore, we computed a mean score between these two items to operationalize the patients' alliance. These items were rated by clinicians who were specifically trained and supervised by senior practitioners. Moreover, there were only a few evaluators, thus reducing inter-evaluator differences.

## Statistical Analysis

Since data distributions were not matching a Gaussian distribution, non-parametric tests (i.e., Wilcoxon) were used to assess admission-discharge differences. Spearman correlation coefficients between moderators, predictors, and the total HoNOSCA score were computed. We present the correlational analyses in a supplementary file (table S1, see supplementary file). The associations between gender, SLE, social functioning, voluntary admission, pretreatment symptoms severity, parental cooperation, patient alliance and the total HoNOSCA score were evaluated using linear regression models with backward elimination procedure. Backward elimination is a repetitive variable selection procedure. Starting with a model containing all variables the variable with the smallest coefficient is subsequently removed over each step. Here we present only the final solutions including the most relevant factors. Moreover, models were adjusted for age, duration of hospitalization, and for the provenance of the data (Lausanne and Sierre). Additionally, the moderating effects of gender and SLE for each predictor variable were added to the model by centering the data and multiplying them (e.g., gender x social functioning; gender x voluntary admission; gender x pretreatment symptoms severity; gender x parental cooperation; gender x patient alliance; SLE x social functioning; SLE x voluntary admission; SLE x pretreatment symptoms severity; SLE x parental cooperation; SLE x patient alliance). The examination of collinearity (i.e., variance inflation factor and tolerance) and distributions of residuals revealed no problems. Statistical significance was set, by convention, at  $p<.05$ .

## Results

### Admission vs Discharge

HoNOSCA scores from both perspectives were smaller at discharge than at admission suggesting less symptomatology in patients at the end of their hospitalization (table 2).

### Health of the Nation Outcome Scales for Children

|    | Discharge |      |
|----|-----------|------|
|    | Mean      | SD   |
| 75 | 1.02      | 0.68 |
| 54 | 1.01      | 0.50 |
| 52 | 1.05      | 0.51 |

## Regression Analysis

Table 3 sums up the results of the regression analysis.

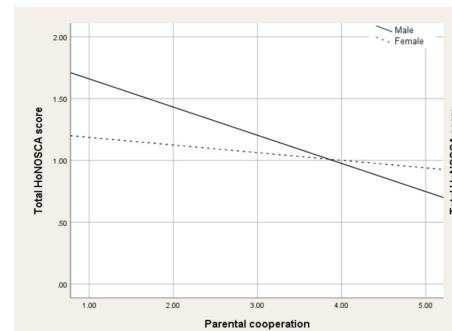
### moderators of the total HoNOSCA score

|            | Unstandardized Coefficient |      |         |       |
|------------|----------------------------|------|---------|-------|
|            | B                          | SE   | $\beta$ | t     |
|            | 2.39                       | 0.21 |         | 11.22 |
|            | -0.09                      | 0.02 | -0.26   | -3.98 |
|            | -0.14                      | 0.05 | -0.27   | -2.68 |
|            | -0.12                      | 0.04 | -0.19   | -2.98 |
| s severity | 0.08                       | 0.04 | 0.15    | 2.37  |
|            | 0.13                       | 0.06 | 0.20    | 2.11  |
|            | 0.07                       | 0.03 | 0.17    | 2.96  |

Outcome Scales for Children and Adolescents; SE: Standard error; SLE: Stressful life event.  
Regression analysis with backward elimination procedure.

### Anmerkung

The regression analysis computed on the total HoNOSCA score explained a significant part of the variance ( $F[6, 223]=13.51$ ,  $p<.001$ ,  $R^2=.272$ ). Patient alliance ( $p=0.003$ ), social functioning ( $p<0.001$ ), and parental cooperation ( $p=0.008$ ) referred to a significant predictor of the total HoNOSCA score at discharge. Moreover, the moderating effect of gender on a) pretreatment symptoms severity ( $p=0.019$ ) and on b) parental cooperation ( $p=0.036$ ) were related to the total HoNOSCA score at discharge. Pretreatment symptom severity and parental cooperation were related to the total HoNOSCA score at discharge more often in boys compared to girls. In addition, there was a moderating effect of SLE on social functioning ( $p=0.003$ ) (i.e., less influence of social functioning in adolescents with many SLEs) on the total HoNOSCA score at discharge. Figure 1 illustrates the moderation effects (gender x pretreatment symptoms severity; gender x parental cooperation; SLE x social functioning) on the total HoNOSCA score at discharge.



**Figure 1:** Moderation effects of gender on total HoNOSCA score at discharge and of stressful life events (SLE) on total HoNOSCA score at discharge (gender x pretreatment symptoms severity; gender x parental cooperation; SLE x social functioning).

Total HoNOSCA is the average of the HoNOSCA score completed by the patient and the HoNOSCA score completed by the clinician. HoNOSCA: Health of the Nation Outcome Scales for Children and Adolescents.

## Discussion

The aim of this study was to fill an important gap in the literature by determining predictors (i.e., pretreatment symptom severity, social functioning, alliance with the patient, cooperation with parents, the type of admission in hospital) and moderators (i.e., gender and SLEs) of the clinical outcome in adolescents after hospitalization in IPU. The results indicated a significant alleviation of symptoms and psychosocial difficulties from both perspectives (i.e., patients and clinicians). This is consistent with previous studies based both on clinician [6, 10, 20, 43] and on patient reports [20, 61]. The results support the notion that IPU-treatment in CAMHS is effective for many adolescents.

Correlation analyses showed that involuntary admission to IPU was associated with more symptoms and psychosocial difficulties at discharge. Although this result was not confirmed by the regression analysis, it should be considered in involuntary admitted admission by paying special attention, for instance, to therapeutic alliance with the patient as well as cooperation with the parents. Moreover, we observed (when controlling for other factors) that higher patient alliance was related to less symptoms and psychosocial difficulties at discharge, which is in line with previous studies [25].

The main finding of the current study was the identification of gender and SLE as important moderators of symptoms and psychosocial difficulties at discharge. We observed that boys with a higher pretreatment symptom severity or lower parental cooperation had more symptoms and psychosocial

difficulties at discharge. Moreover, in adolescents with many SLEs, social functioning had low influence on the treatment outcome.

### Moderating Effect of Gender and SLE

Our results showed that pretreatment symptom severity, measured by CGI-S, had a greater influence in boys compared to girls in predicting the clinical outcomes after an inpatient stay. We hypothesize that recognizing mental health problems is more difficult for boys than for girls [62]. This could lead to a lower demand for help and less acceptance of care, indicating a less effective treatment outcome, which could explain why pretreatment symptoms severity was associated with more symptoms and psychosocial difficulties in boys.

Parental cooperation was observed as an important factor affecting the treatment outcome, which is consistent with previous studies [16, 19, 24, 26, 27]. However, our findings indicate that parental cooperation has a greater influence on the clinical outcome in boys. Therefore, we can hypothesize that if parents present a lack of cooperation with the clinicians, their children will adhere less to the treatment. Consequently, these findings point to the need for gender-sensitive treatment [63]. Considering that boys generally present more externalized symptoms than girls [64], this could interfere more with the treatment leading to lower clinical outcomes. The role of co-parenting [65] and parenting style [66] in the development and persistence of externalized symptoms is well known. One study shows that reciprocal, coercive parent-child interactions are pertinent in the development and maintenance of externalized disorders [67]. Parent-child relationships degrade [68] leading to a lower investment of parents in their children and thus to less parental cooperation during hospitalizations. This hypothesis is reinforced by the therapeutic success of parenting programs (leading to parents' cooperation) in the reduction of externalized symptoms [69].

Our results revealed that when adolescents were confronted with several SLEs, social functioning did not influence treatment outcome. The developmental effects of trauma (i.e., development of insecure attachment and greater difficulties in interpersonal relationships) are more likely to occur when the victimization is repetitive and continuous [70]. Childhood trauma has been linked to several psychiatric disorders [71] by altering the capacity for emotional regulation [72]. Young people with many SLEs have experienced adverse relationships [73] limiting their trust in

others and the quality of social interactions. We could hypothesize that their history of difficult relationships reduces their ability to consider social links as a support to them resulting in a lower impact of the level of social functioning on the treatment outcomes compared to less traumatized youths.

### Clinical Implications

Our results allow the identification of patients with specific characteristics who could be targeted with more specific, effective and personalized treatment improving treatment their outcomes. The two main characteristics that should be considered are gender and SLE.

With male patients, it would be necessary to have a special focus on the development of the therapeutic alliance between the youth, their family, and the inpatient staff. For instance, psychoeducation could allow for better collaborative work between patients, their families, and caregivers. Collaborative work enables patients to make informed decisions concerning their care, which reinforces the patient's confidence and motivation [74].

Regarding the importance of SLE, the consequences of trauma could be better targeted by an adjusted treatment. An example of such a treatment could be mindfulness-based therapies that improve the healing of trauma-caused problems in adults [75] and young people [76, 77]. Mindfulness could allow patients to better regulate their emotional reactivity by increasing their tolerance to unpleasant emotional experiences leading to better social adaptation.

Mentalization-based therapy (MBT) or dialectical behavior therapy (DBT) should also be mentioned as effective therapeutic approaches to reduce externalized symptoms [78, 79] and self-harm [80, 81] in young patients. By teaching young patients new coping strategies, MBT or DBT can help improve their emotion-regulation skills promoting a decrease in self-harm behaviors and improving the quality of their social interactions leading to a decrease in aggressive behaviors.

### Strengths and Limitations

The design of our study offers specific and interesting strengths: (1) it includes hospitalized youths in a crisis context for whom increased and individualized attention and vigilance is needed; (2) it considers multiple informant perspectives; (3) it includes patients from two sites and from a large sample; (4) it explores a large number of factors known as predictors and moderators in previous literature; (5) the assessment of the clin-

ical outcome is based on clinically relevant instruments (i.e., HoNOSCA).

However, some limitations should be mentioned. First, this study took place in a naturalistic environment with a risk of methodological bias due to the lack of a control group. However, studies in naturalistic conditions consider the particularities of patients [82], have good external validity [83] and are often effective [84]. Therefore, our results are closer to the clinical reality and easier to generalize in the context of IPU. Second, the distribution of diagnoses in our results did not allow us to specify the impact of predictors or moderators on the outcome according to a specific diagnosis. In addition, we focused on the retained principal diagnosis using the ICD-10 general diagnosis groups (F1.x to F9.x). A more precise diagnosis categorization and consideration of secondary diagnoses should be used in future studies to refine these findings. Third, some constructs (e.g., SLE, patient alliance, parental cooperation) were not assessed using standard measures and were based on clinical objectification. Although there were only a few clinicians and they were trained and supervised in the assessment, some subjectivity remains. Further studies could use specific scores for these assessments, such as the Working Alliance Inventory [85] for alliance assessment and the Adverse Childhood Experience score for SLE assessment. This seems especially important as the definition of SLE evolves alongside the advances in psychiatric research [86]. In addition, the interactive effects of the parent-clinician alliance and the patient-clinician alliance could be considered to better define the impact of systemic work on the treatment outcome.

### Conclusion

This study confirmed a significant decrease in a wide range of symptoms and psychosocial difficulties from admission to discharge in IPU for adolescents. Moreover, our results identified patients' alliance, gender (associated with pretreatment symptom severity or parental cooperation) and SLE (associated with social functioning) as explaining factors of the clinical outcome after an inpatient stay in an IPU. The presence of these moderators should prompt clinicians to adjust their treatment approach and therapeutic plans to increase the likelihood of patients recovering following hospitalization in CAMHS and more specifically in IPU. As an example, personalized treatments could be offered to patients based on the presence or absence of one or more moderators.

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# Conflict of Interest Statement

No financial support and no other potential conflict of interest relevant to this article was reported.

# Author Contributions

MT: Conceptualization, data acquisition, statistical analysis, writing (original draft, review & editing), visualization. SU: Conceptualization, statistical analysis, writing (review & editing). MRC: Conceptualization, data acquisition, writing (review & editing). HDR: Data acquisition. SC: Data acquisition. CB: Data acquisition. VC: Data acquisition. CL: Data acquisition. GP: Data acquisition. KJP: Supervision, review & editing. LH: Supervision, project administration, conceptualization, review & editing. All authors reviewed and accepted the final version of the manuscript.

# Data Availability Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

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