Clozapine Therapeutic Monitoring
Promoting effectiveness and safety in psychiatric patients

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Introduction

Therapeutic Drug Monitoring (TDM) in psychiatry is critical due to a significant impact of interindividual variability on the treatment effectiveness and to control drug related problems (DRP). Clozapine (CZP) is a widely used atypical antipsychotic, especially in the treatment of refractory schizophrenia and psychosis. CZP concentrations in blood are predictive for relapses and TDM may reduce the risk of relapse or recurrence. TDM can also guide the clinical team when CZP is used with inducers or inhibitors of metabolism, thus compromising the expected effect on symptom control.

According to European consensus guidelines of TDM in Neuropsychopharmacology, CZP monitoring is highly recommended (level 1) due to its variable pharmacokinetic profile. At drug concentrations in blood within the reported therapeutic reference range, highest probability of response or remission can be expected. At subtherapeutic drug concentrations in blood, the response rate is similar to placebo under acute treatment and there is a risk of relapse under chronic treatment. At supratherapeutic drug concentrations in blood, there is an increased risk of adverse drug reactions or outright toxicity. Ideal CZP range in blood is 350 - 600 ng/ml.

Purpose

This study evaluates clozapine blood levels both in outpatients and inpatients, the occurrence of DRPs and hospital staying duration.

Methods

This is a retrospective observational study of psychiatric inpatients and outpatients in our centre, between 2012 and 2021. Data was collected from the Electronic Health Records. Features collected include sex, age, diagnosis, date of dosing, daily dosage and length of hospital stay for inpatients. Statistical analysis was performed using Python 3.8.8 and Microsoft Excel 2019.
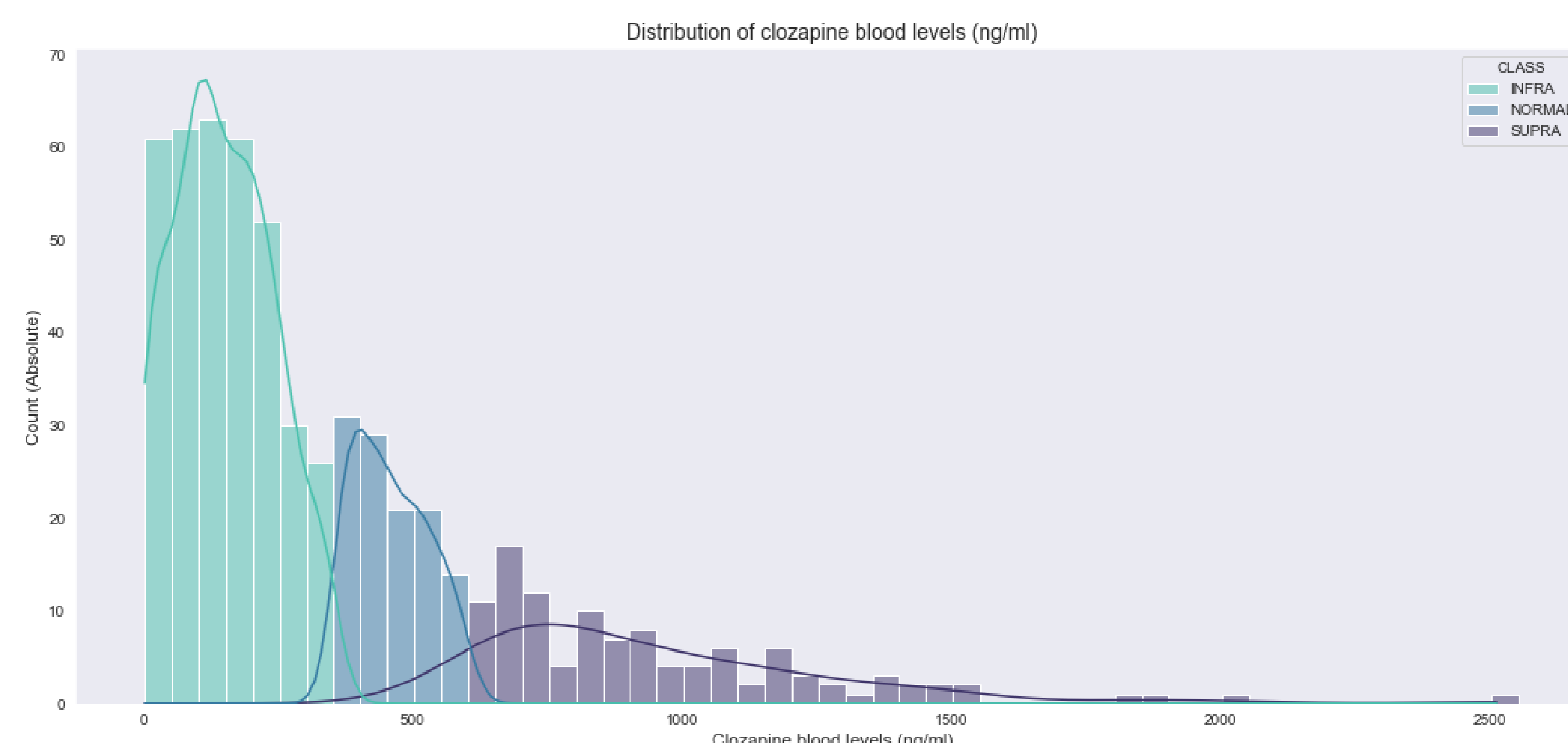
Results

The study included 181 patients, the majority being males (56%). The median age of the sample was 45 years (17-84) and 55% were outpatients. Schizophrenia was the most prevalent diagnosis (51%), followed by Non Otherwise Specified Psychosis (NOSP) and Bipolar Disorder (11%) (Fig 1). The analysis included 581 CZP measurements. There was no significant correlation between daily dosage and blood level (pearson = 0.26). Only 20% of TDMs were between the adequate range (median 250 ng/ml, 3 - 2511), 61% of patients had subtherapeutic levels of CZP and 19% presented supratherapeutic levels (Fig 2). The length of hospital stay was bigger for patients with levels higher than recommended, average of 169 days vs 84 days (p <0.05) (Fig 4). Schizophrenic and patients with NOSP had lower levels of CPZ comparing to other diagnosis (p < 0.01). Drug Related Problems were present in 23 patients, mainly sialorrhea (52%), constipation (17%) and extrapyramidal effects (13%).
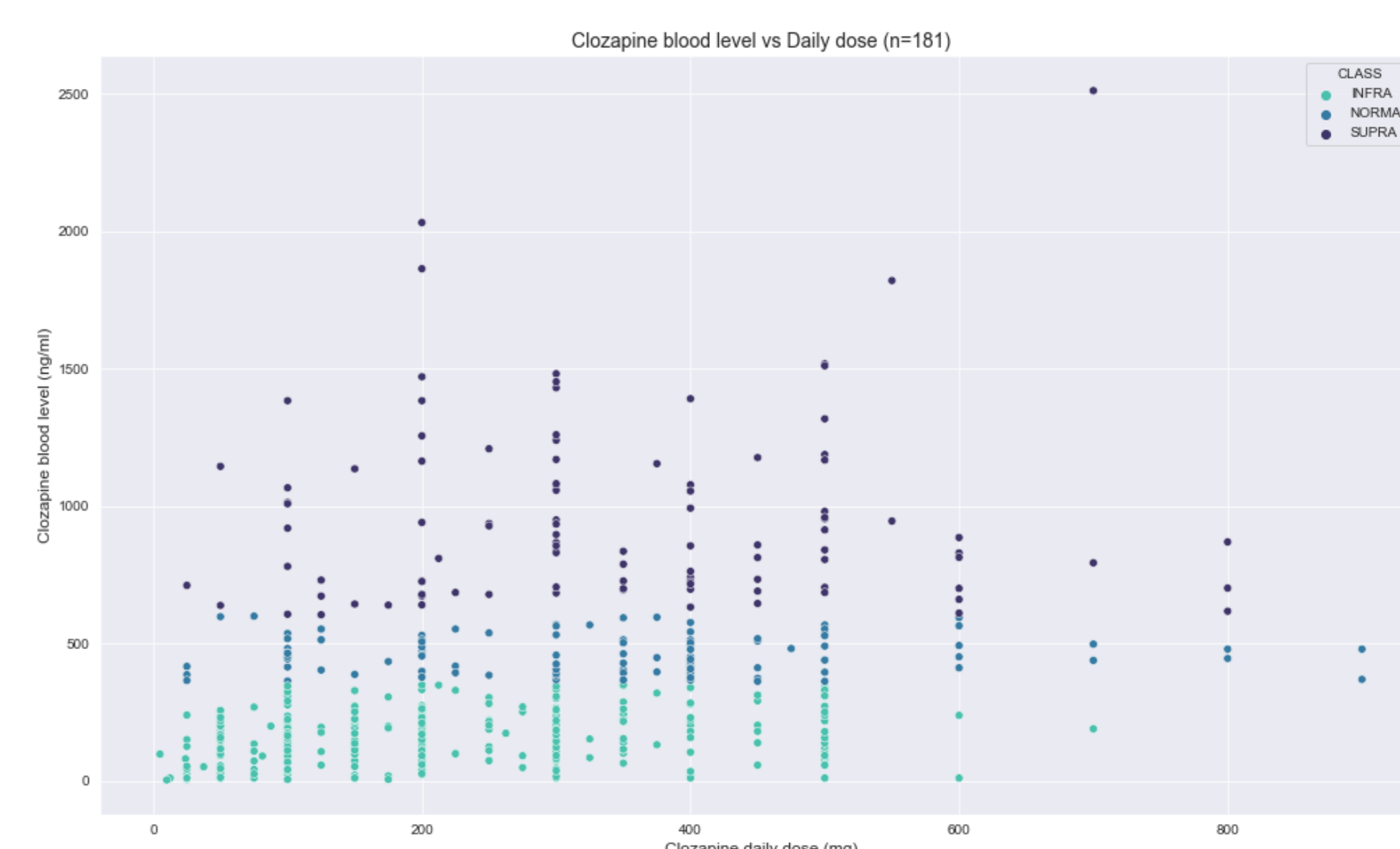

Fig.2 – Distribution of Clozapine blood levels (ng/ml)

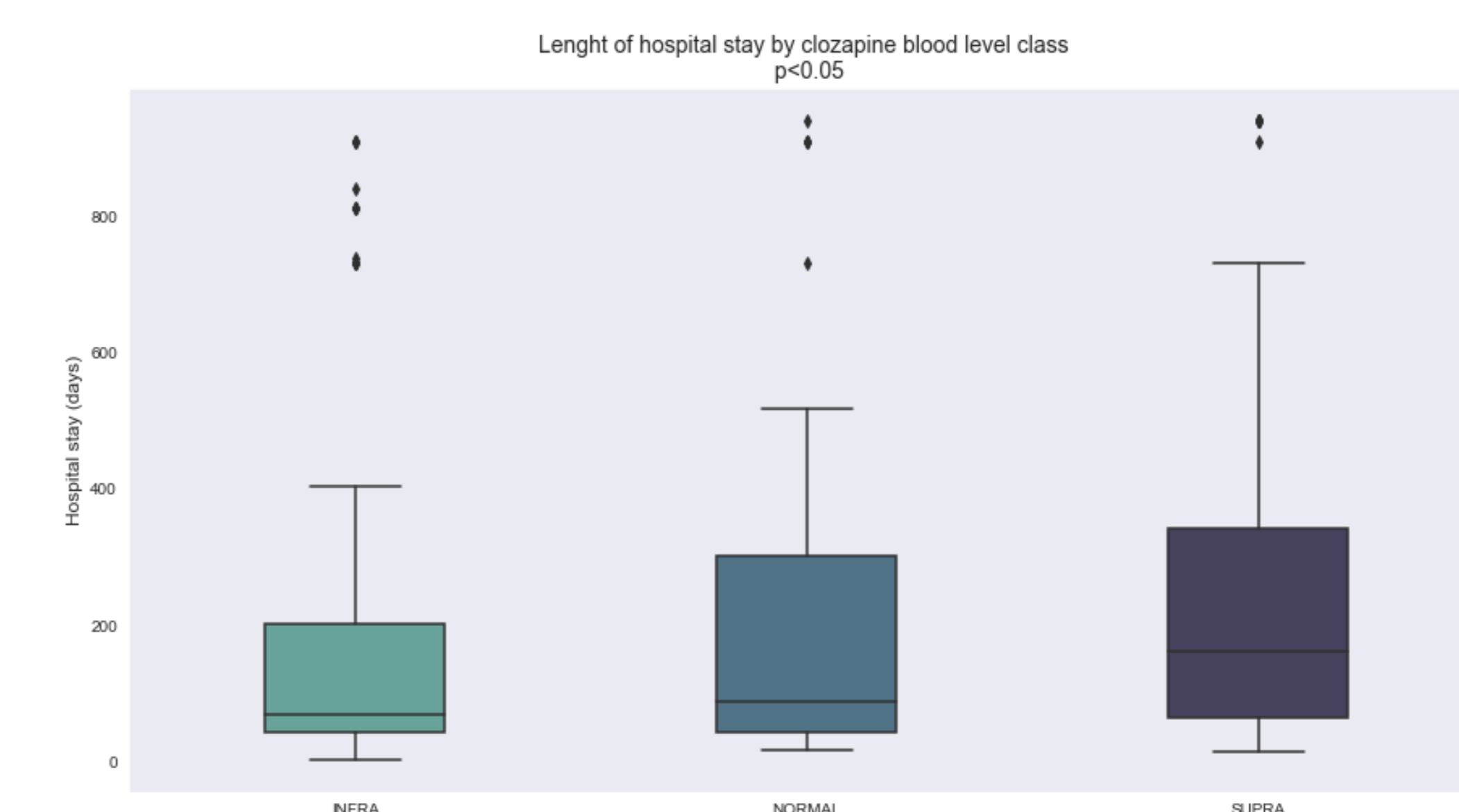**Fig.3 – Clozapine blood levels vs Daily dosage**
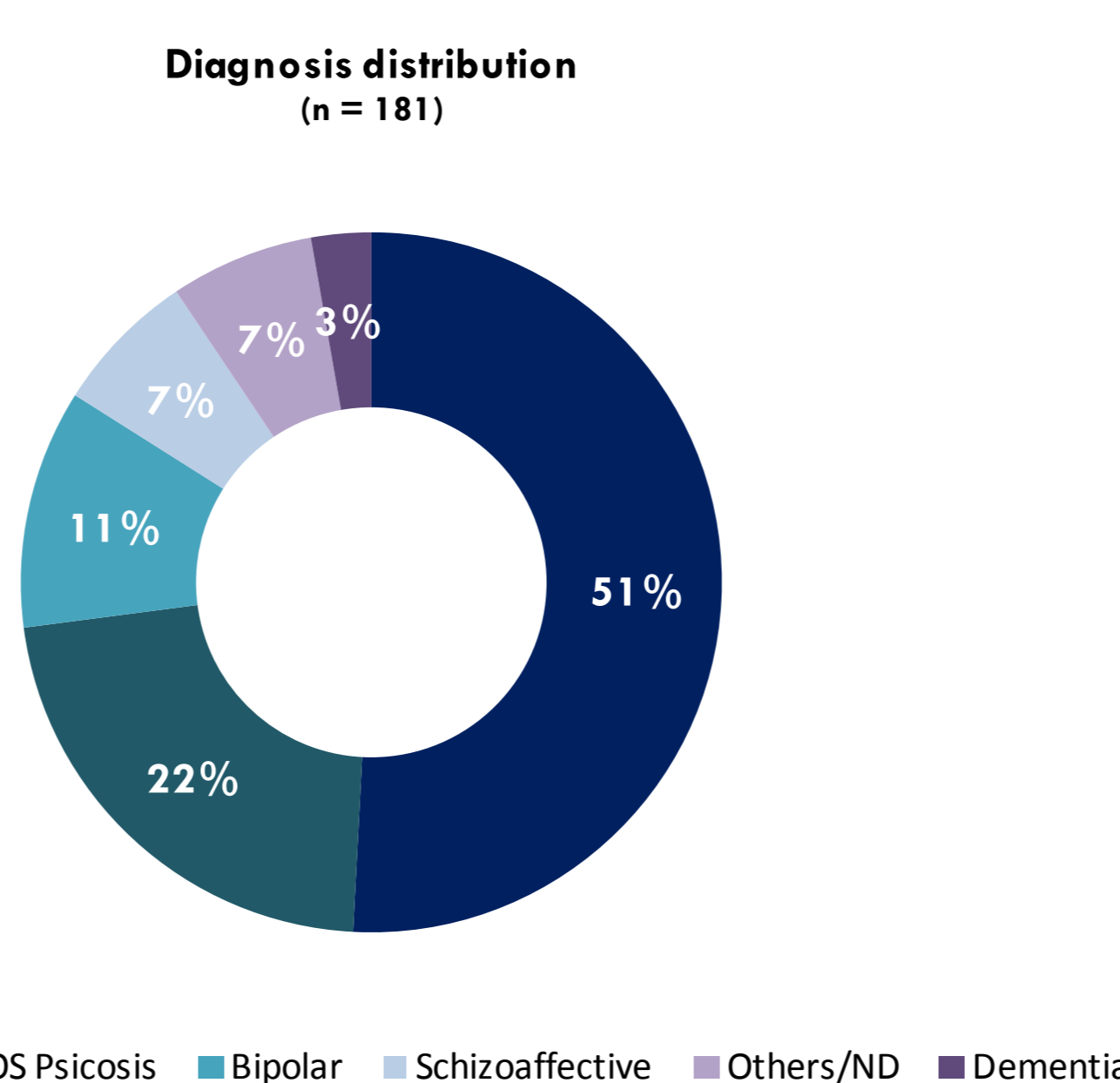

Fig.4 – Lenght of hospital stay

Fig.1 – Distribution of diagnosis

Conclusions

Despite the importance of maintaining adequate levels of CZP, the majority of psychiatric patients still present blood levels outside the recommended range. Pharmacists should recommend and evaluate TDM of antipsychotics to promote safety and increase effectiveness of treatment.

References

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