

Kinetics of FT4 serum concentrations in infants with congenital hypothyroidism differ during follow-up in the three severity groups

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INTRODUCTION

The goal of congenital hypothyroidism (CH) treatment is rapid normalization and maintenance of TSH and FT4 in the reference range. Recommended starting dose of levothyroxine (LT4) ranges from 10-15 mcg/kg/d. Hyperthyroxinemia can be accepted in the context of normal TSH and LT4 should only be reduced in case of symptoms or repeatedly increased FT4.

OBJECTIVES

- Perform retrospective data analysis on FT4 kinetics during the first six months of treatment for each CH severity group
- Quantify duration, maximum peak fold above upper FT4 reference limit and day of maximum peak fold of hyperthyroxinemic periods based on pharmacometrics model

METHODS

AVAILABLE DATA

- Retrospective longitudinal multi-center study during follow-up (first 180 days) with data from n = 56 infants (female 71%, GA 40.9 [38.6, 41.4] weeks)
- A total of 236 FT4 and 232 TSH measurements
- CH severity groups are defined based on FT4 level at diagnosis [1]:

Severe CH: FT4 < 5 pmol/l | **Moderate CH:** FT4 5-10 pmol/l | **Mild CH:** FT4 > 10 pmol/l

METHODS

- Simulation of FT4 kinetics for individual patients based on our recently developed mathematical pharmacokinetics model [2]

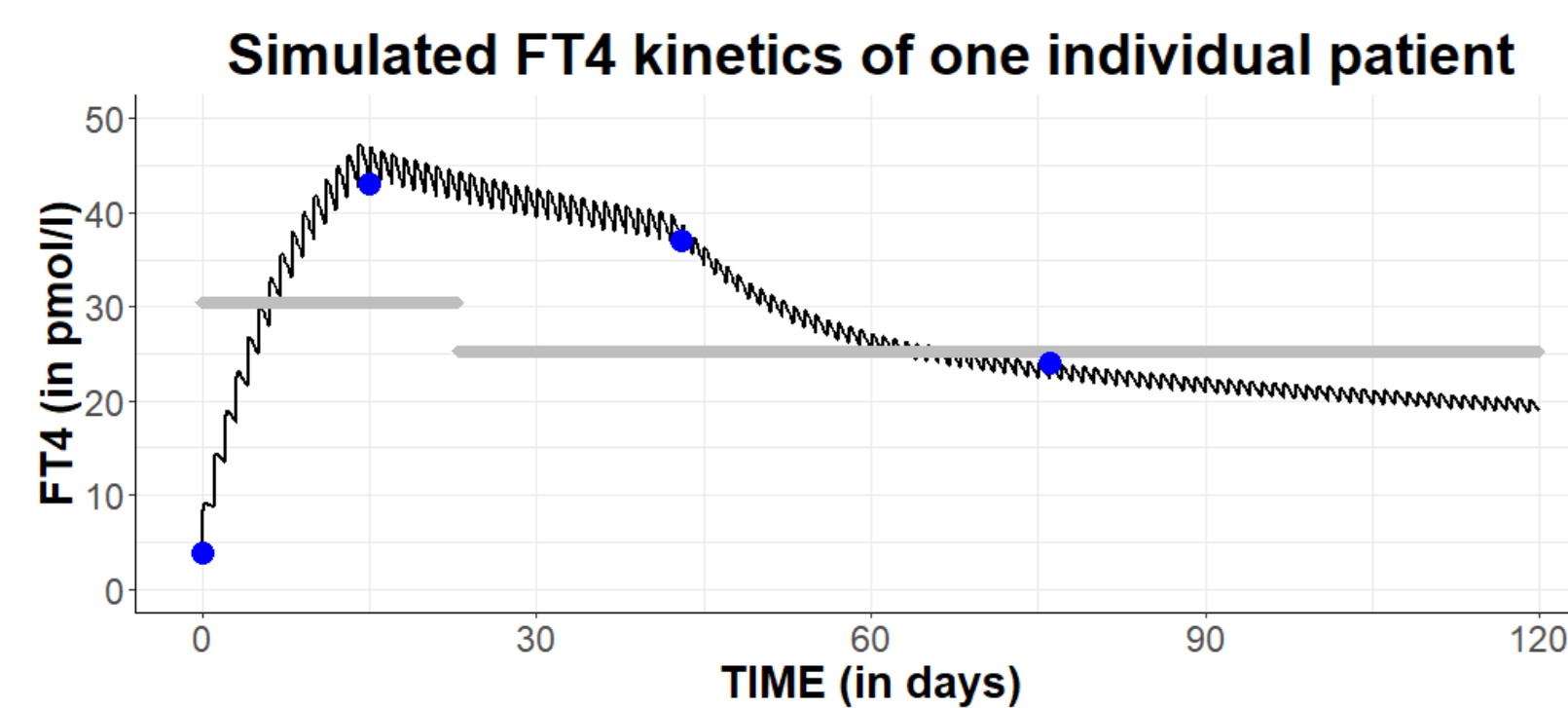


Figure 1. Example for the simulation of FT4 kinetics of one individual patient: Measured FT4 (blue points) together with simulated FT4 concentration (black curve) and upper age-specific FT4 reference limit (grey points).

- We defined patients as hyperthyroxinemic if they showed (based on our simulation) elevated FT4 concentration on at least two consecutive days.
- FT4 peak fold is defined as quotient of measured FT4 concentration and upper age-specific FT4 reference limit (97.5th percentile) [3].
- Hyperthyroxinemic periods are quantified in terms of (1) time duration above upper FT4 reference limit, (2) maximum peak fold above upper FT4 reference limit and (3) time point of the maximum peak fold (see Figure 2).

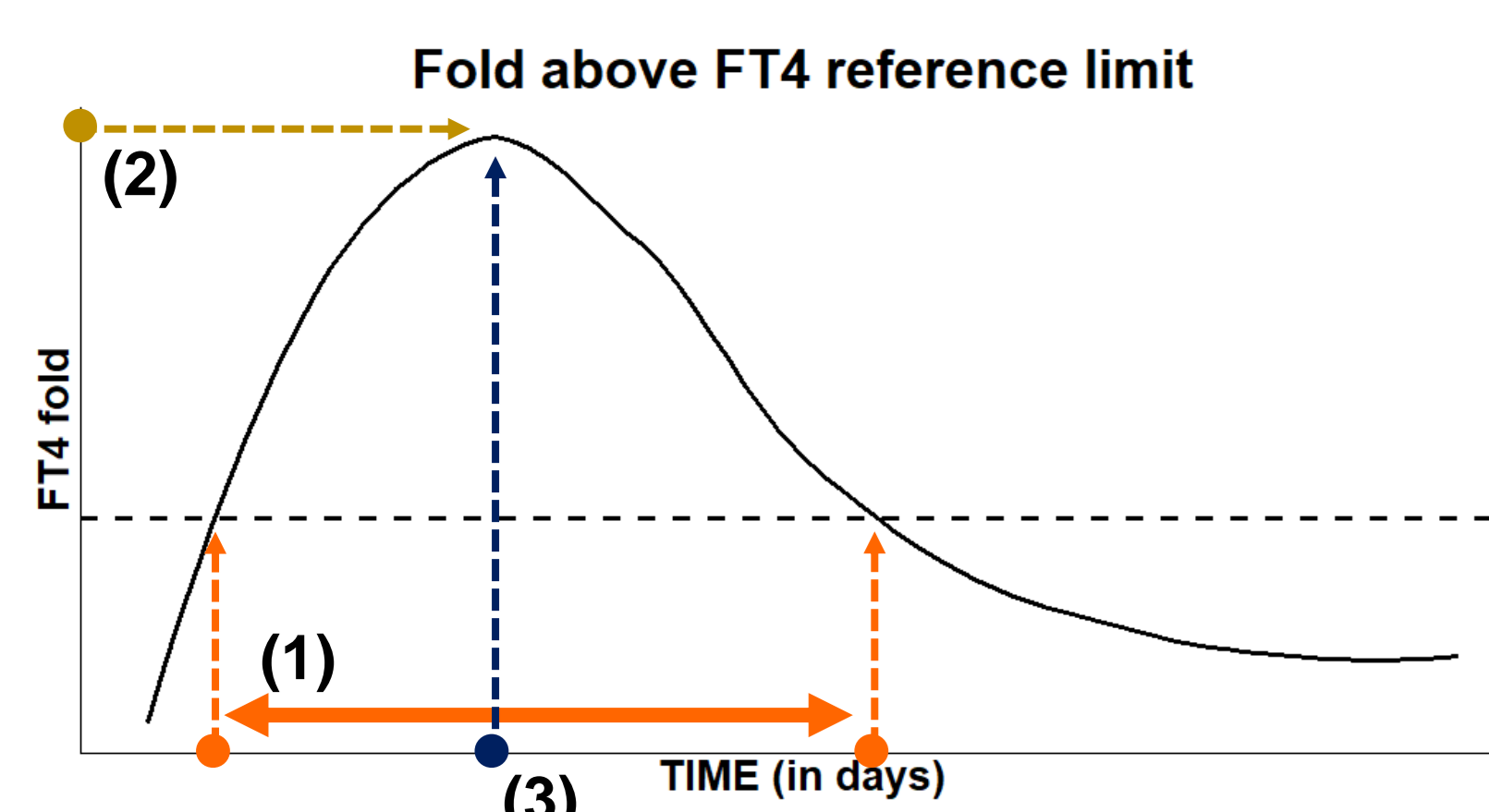


Figure 2. Quantification of periods of hyperthyroxinemia: (1) Duration [days] above reference range (orange arrow), (2) maximum peak fold above reference range (golden point), and (3) day of peak fold above reference range (dark blue point). The dashed grey horizontal line corresponds to FT4 equates upper FT4 reference limit (fold = 1.0)

RETROSPECTIVE DATA ANALYSIS

Summary of patient characteristics: Median [IQR]

	Severe CH	Moderate CH	Mild CH
Number of patients (% female)	25 (72%)	16 (75%)	15 (67%)
PNA (days) at diagnosis	7 [7, 8]	7 [6, 8]	7 [5.5, 52]
FT4 (pmol/l) at diagnosis	2.2 [1.2, 3.1]	7.2 [6.3, 7.7]	13.2 [11.7, 15.5]
TSH (mU/l) at diagnosis	415 [263, 540]	311 [220, 402]	28 [16, 194]
LT4 starting dose (mcg/kg/d)	10 [7.51, 14]	8.91 [7.1, 13.1]	7.06 [3.9, 8.6]
Number of consultations/180 days	4 [3, 5]	3.5 [2.5, 4.5]	4 [2.5, 5.5]

TSH at diagnosis per severity group

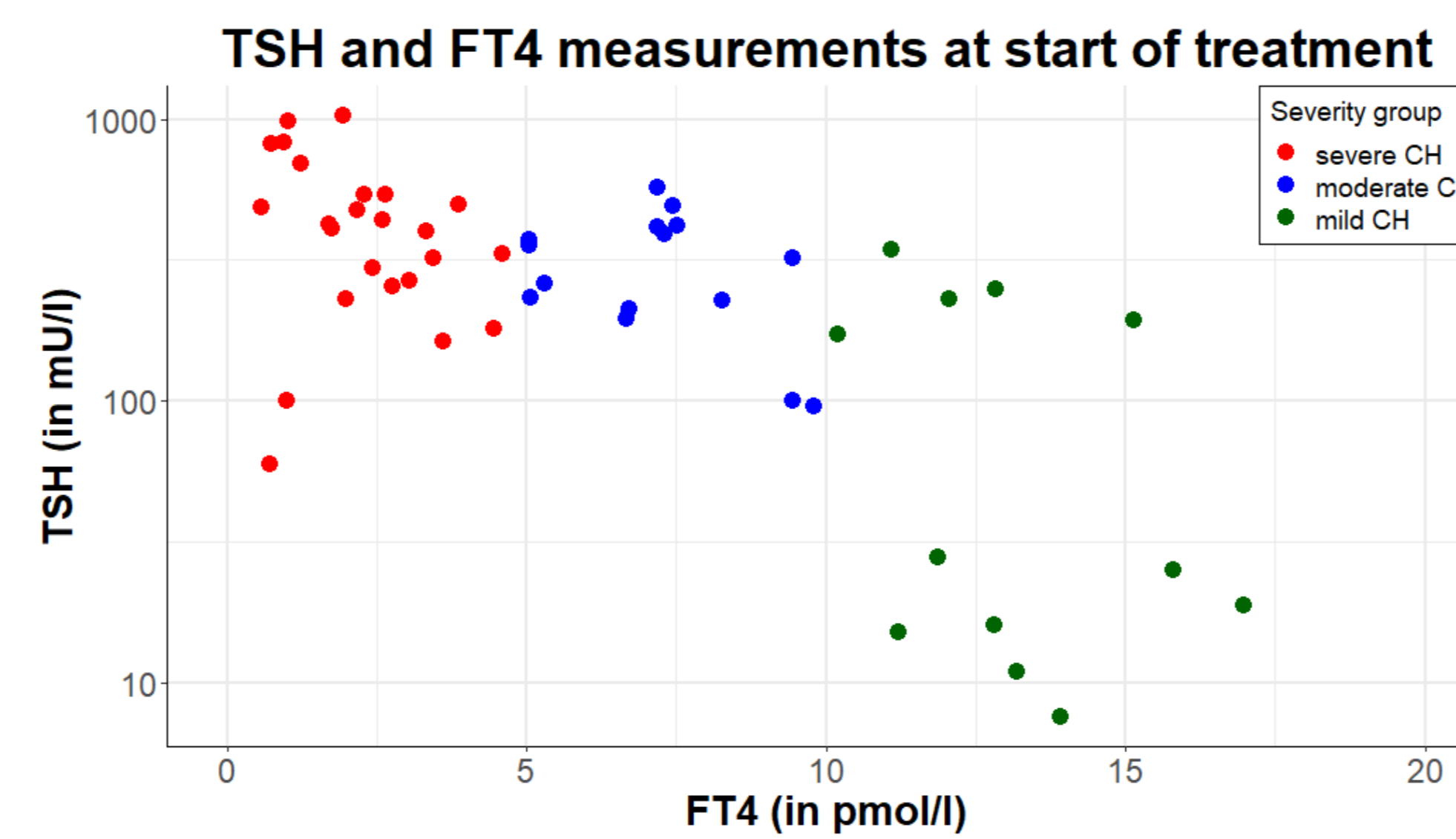


Figure 3. TSH measurements over FT4 measurements per severity groups: TSH over FT4 at diagnosis is shown with logarithmic y-axis; severe CH (red), moderate CH (blue) and mild CH (green).

- TSH levels at diagnosis were not significantly differing between moderate and severe CH.
- Severity groups had comparable numbers of consultations during follow-up.

COMPARISON OF LT4 STARTING AND MAINTENANCE DOSE

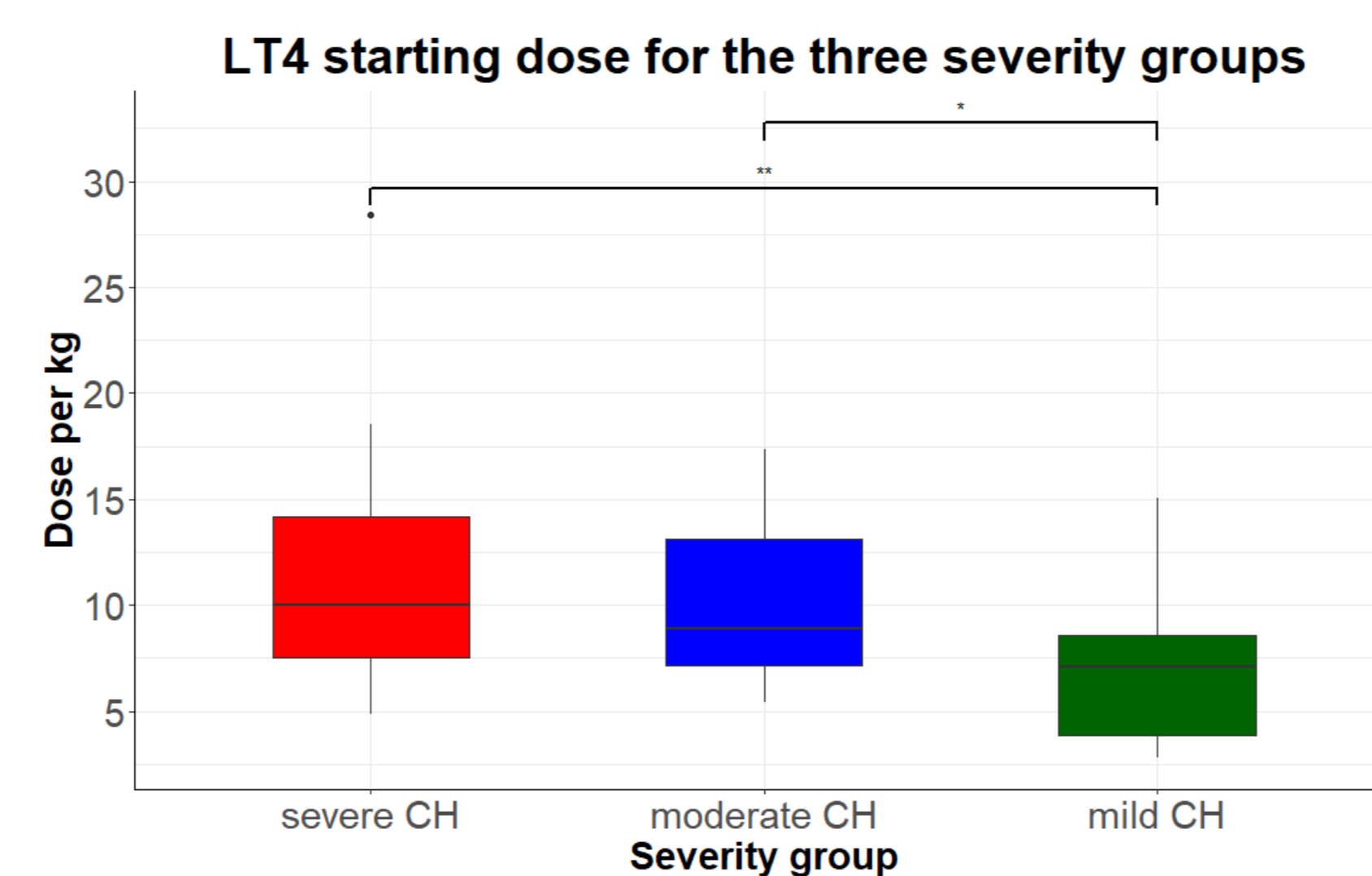


Figure 4. LT4 starting dose per severity group: Each boxplot displays LT4 dose (mcg/kg/d) at start of treatment; severe CH (red), moderate CH (blue) and mild CH (green). *P<0.05, **P<0.01

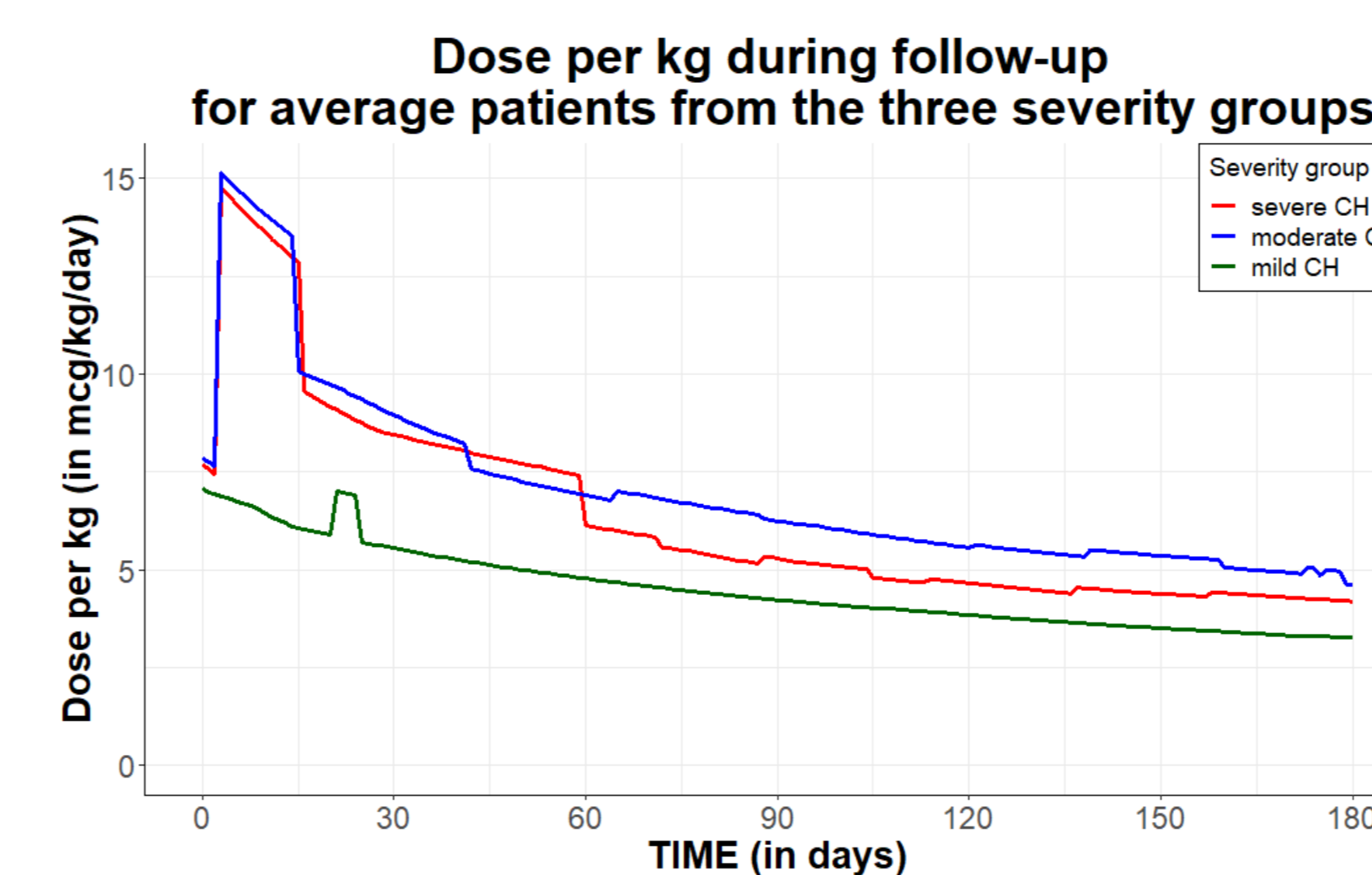


Figure 5. Median LT4 maintenance dose for average patient of the respective severity group: Each curve displays daily median dose per median weight during follow-up; severe CH (red), moderate CH (blue) and mild CH (green).

- Median LT4 starting doses for each severity group were lower than recommended by 2021 guidelines [1].
- Comparable LT4 starting doses for severe and moderate CH patients.
- Median LT4 maintenance dose per kg/d is comparable in moderate and severe CH patients and lower in mild CH patients.

RESULTS

QUANTIFICATION OF HYPERTHYROXINEMIA FOR INDIVIDUALS

Percentage of hyperthyroxinemic patients per severity group

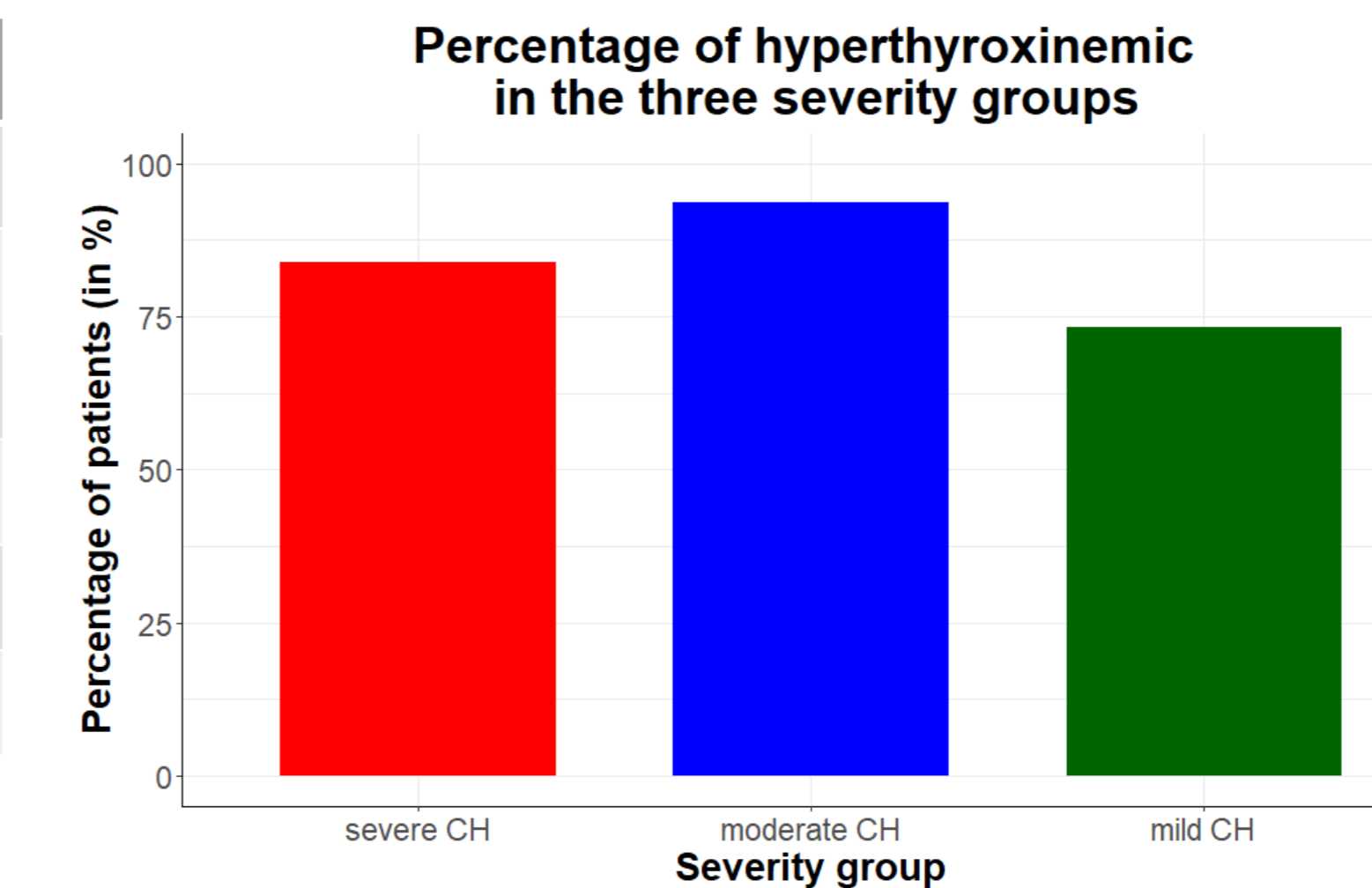


Figure 6. Percentage of patients showing repeatedly increased FT4 levels: The bars represent the percentage of individual patients per severity group with more than one day (based on our simulation) with increased FT4 levels during follow-up; severe CH (red), moderate CH (blue) and mild CH (green).

Duration and extent of hyperthyroxinemic periods per severity group

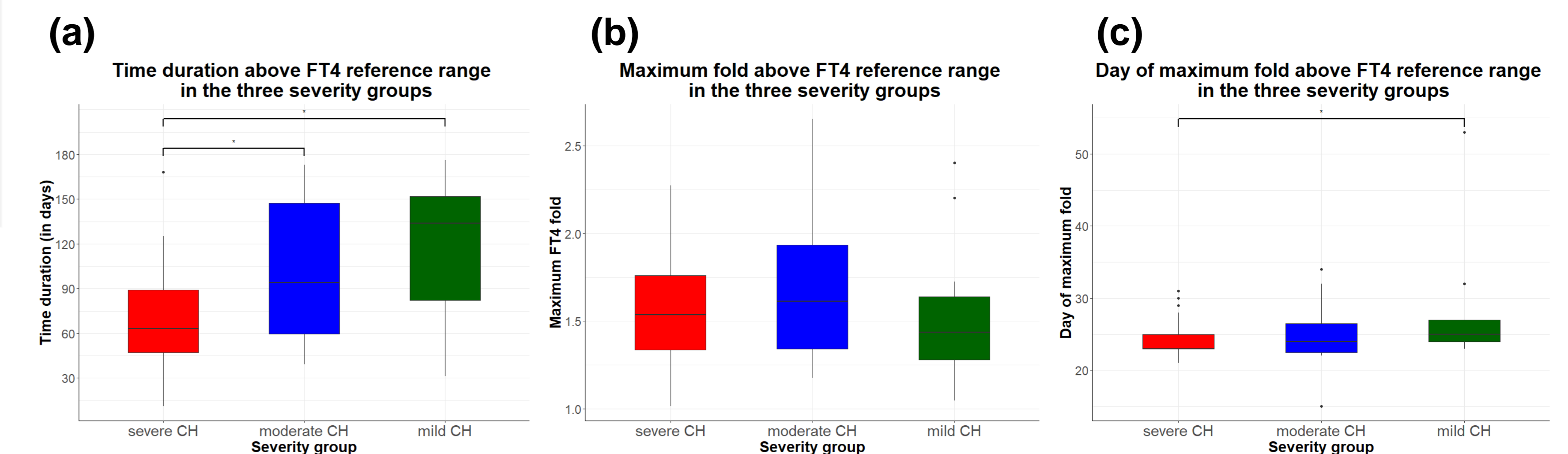


Figure 7. Comparison of hyperthyroxinemia per severity group: Each boxplot shows (a) Time duration above FT4 reference range, (b) Maximum peak fold above FT4 reference range, (c) Day of maximum peak fold above FT4 reference range; severe CH (red), moderate CH (blue) and mild CH (green). *P<0.05

- Duration [days] above age-specific FT4 reference range was significantly lower for severe vs. moderate and severe vs. mild CH patients.
- Maximum peak fold above age-specific FT4 reference range was comparable for all three severity groups.
- Day of maximum peak fold above age-specific FT4 reference range was significantly lower for severe vs. mild CH patients.

CONCLUSIONS

- Given available data, no significant difference in TSH at start of treatment and initial LT4 dosing for severe and moderate CH patients was found.
- Simulations revealed longer hyperthyroxinemic periods for moderate and mild CH patients compared to severe CH patients.
- From a pharmacological point of view, severity-based dosing during follow-up might help reducing duration and extent of hyperthyroxinemia.
- Prospective data are necessary to confirm these preliminary findings.

REFERENCES

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