Thyroid function before, during and after COVID-19

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Abstract

Context: The effects of COVID-19 on the thyroid axis remain uncertain. Recent evidence has been conflicting, with both thyrotoxicosis and suppression of thyroid function reported.

Objective: We aimed to detail the acute effects of COVID-19 on thyroid function and determine if these effects persisted upon recovery from COVID-19.

Design: Cohort observational study.

Participants and setting: Adult patients admitted to Imperial College Healthcare National Health Service Trust, London, UK with suspected COVID-19 between March 9 to April 22, 2020 were included, excluding those with pre-existing thyroid disease and those missing either free thyroxine (FT4) or TSH measurements. Of 456 patients, 334 had COVID-19 and 122 did not.

Main Outcome Measures: TSH and FT4 measurements at admission, and where available, those taken in 2019 and at COVID-19 follow-up.

Results: Most patients (86·6%) presenting with COVID-19 were euthyroid, with none presenting with overt thyrotoxicosis. Patients with COVID-19 had a lower admission TSH and FT4 compared to those without COVID-19. In the COVID-19 patients with matching baseline thyroid function tests from 2019 (n=185 for TSH and 104 for FT4), both TSH and FT4 were reduced at admission compared to baseline. In a complete cases analysis of COVID-19 patients with TSH measurements at follow-up, admission and baseline (n=55), TSH was seen to recover to baseline at follow-up.

Conclusions: Most patients with COVID-19 present with euthyroidism. We observed mild reductions in TSH and FT4 in keeping with a non-thyroidal illness syndrome. Furthermore, in survivors of COVID-19, thyroid function tests at follow-up returned to baseline.

Key Terms: COVID-19, SARS-CoV-2, thyroid function, thyroid gland

Introduction

The COVID-19 pandemic continues to affect the global community, and as understanding of its pathophysiology deepens, so too does interest in the endocrine effects of its causative coronavirus, SARS-CoV-2. Coronaviruses are known to have direct effects on several endocrine glands, including the thyroid gland. In patients infected with SARS-CoV, the precursor to SARS-CoV-2, damage to the follicular and parafollicular cells of the thyroid was demonstrated at post-mortem (1). Additionally, coronaviruses have been detected in the pituitary gland at post-mortem (2), and reduced staining for thyroid stimulating hormone (TSH) has been observed in the anterior pituitary gland of patients infected with SARS-CoV (3). Furthermore, SARS-CoV-2 enters cells utilising the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in the thyroid gland (4). Thus, the hypothalamic-pituitary-thyroid axis may be susceptible to disturbance in patients with COVID-19. Currently there is contradictory evidence surrounding the effect of COVID-19 on thyroid function. Subacute thyroiditis presenting with overt thyrotoxicosis has been reported with COVID-19 (5–7). On the other hand, in a study undertaken in China of 50 patients with COVID-19, Chen et al. (8) observed a generalised reduction in TSH, total thyroxine (T4) and tri-iodothyronine (T3) more consistent with a non-thyroidal illness (NTI) pattern.

Whilst these studies provide useful information, they do have limitations. They have included incomplete data, for example measuring thyroid hormones only when TSH is out of range (6,7), or have failed to exclude confounding factors such as intercurrent steroid treatment (8). There is also limited knowledge of thyroid function in patients who have recovered from COVID-19. Given these conflicting results, we therefore undertook a large cohort observational study to understand if thyroid gland dysfunction is a frequent feature of patients with COVID-19.

Methods

Ethical Approval

The study was approved by the Imperial College London and Imperial College Healthcare NHS Trust governance team who confirmed that as we are reporting on routinely collected non-identifiable clinical audit data, no approval from a research ethics committee was additionally required under the UK policy framework for Health and Social Care.

Study Participants

All patients ≥18 years old admitted to Imperial College Healthcare NHS Trust (ICHNT) across three teaching hospitals, St Mary's, Charing Cross and Hammersmith, London, UK with a clinical suspicion of COVID-19 between March 9 to April 22, 2020 were included in this observational cohort study. Patients presenting with suspected COVID-19 underwent a standard set of blood tests, including full blood count, renal function, albumin, C-reactive protein (CRP), cortisol and thyroid function. Clinical and demographic data was extracted from patient records. Pre-selected demographics and co-

morbidities of interest (age, sex, history of diabetes, hypertension, chronic kidney disease (CKD), cardiovascular disease (CVD), endocrine disease, current diagnosis of cancer at time of admission, obstructive pulmonary disease including asthma and chronic obstructive pulmonary disease, current pregnancy) were recorded. A COVID-19 diagnosis was defined as a real time RT-PCR confirmation of infection from a nasopharyngeal swab (9). The COVID-19 negative patients were defined as those with clinical features inconsistent with COVID-19, a negative result from swabbing, and diagnosed with alternative conditions other than COVID-19. The first thyroid test from each admission episode was utilised for analysis. Cases were excluded from analysis if the measurement was not taken within 48 hours of admission or of diagnosis of COVID-19, if patients were documented with a previous history of thyroid disease and/or were taking thyroid hormones or anti-thyroid medications, if there were missing values of either free T4 (FT4) or TSH, or if they were taking glucocorticoids prior to admission. Mortality outcomes were recorded as of a database lock date of May 8, 2020. For longitudinal analysis of thyroid function tests, we searched the records of the patients included in the analysis for any thyroid function tests (free T4 or TSH) in 2019, prior to any cases of COVID-19 in the UK ('Base 2019') and for any follow-up tests after their index admission for COVID-19 up to Sep 1, 2020 ('follow-up').

Assay methodology

All analytes were measured at North West London Pathology, a UK Accreditation Service accredited laboratory, using Abbott Alinity series analysers. Cortisol, free T4 and TSH were measured by an Abbott Alinity ci-series analyser utilising chemiluminescent microparticle immunoassays. The precision of the cortisol assay was ≤10% total coefficient of variation (CV) for serum samples with cortisol ≥83 to ≤966 nmol/L, and the lower limit of detection was 22 nmol/L. The cross-reactivity of cortisone in this assay is minimal (2·7% at 1000 µg/dl). Free T4 and TSH assays are both two-step assays. The intra-laboratory precision of the TSH assay was ≤2.1% CV when tested at 0·09-30 mU/L. The lower limit of reporting is set at 0·01 mU/L (readings of <0·01 were set at 0·01 for data analysis). The cross-reactivity of FSH, LH and beta-hCG is ≤10% at up to 500 U/L, 500 U/L and 200,000 U/L respectively. The intra-laboratory precision of the free T4 assay was ≤3% CV when tested at levels of 8·5-33.6 pmol/L. The lower limit of detection and reporting is 5·4 pmol/L (if reported, readings of <5·4 were set at 5·4 for data analysis). The cross-reactivity of free T3 is ≤0·0035% at up to 18433 pmol/L.

Statistical Analysis

Data processing and statistical analysis were conducted using R 4.0.3 (R Foundation for Statistical Computing) and the packages “tidyverse 1.3.0”, “survival 3.2–7”, “ggpubr 0.4.0”, “rstatix 0.6.0”, “moments 0.14”. Data distribution was assessed using density and Q-Q plots, and a D’Agostino and Pearson test where required. Wherever appropriate, a log2-transformation was used to transform skewed distributions of measured parameters (e.g. of TSH, CRP, cortisol). Parametric data is presented as mean ± standard deviation (SD), whereas non-parametric data is presented as median with interquartile range (IQR). A p-value of <0.05 was regarded as statistically significant. An unpaired, two-tailed Student t-test was used to compare parametric continuous variables and a Wilcoxon rank-sum test for non-parametric continuous variables. For comparison of longitudinal data, a repeated measures one-way ANOVA for parametric data or a Friedman test for non-parametric data was used. Wilcoxon paired rank-sum tests with Bonferroni adjustment were used for pairwise comparison of TSH in the longitudinal data set. A Fisher exact test was used to test for differences in categorical distribution.

Results

Baseline characteristics

A total of 621 patients were admitted and had thyroid function tests at admission. Of the remaining 456 patients after exclusions, 334 (73·2%) were diagnosed with COVID-19 and 122 (26·8%) were not (Table 1). Mean (SD) age in the COVID-19 group was 66·1 (16·0) years and in the COVID-19 negative group was 63·8 (19·3) years. A male preponderance was observed in both the COVID-19 group (60·8%), and the control group (55·7%). By May 8, 2020, 40 (12·0%) patients with COVID-19 were admitted to intensive therapy units (ITU), and 95 (28·4%) patients had died, significantly higher than in the COVID-19 negative group.

Most patients admitted with COVID-19 are euthyroid

We classified patients into diagnostic categories according to their FT4 and TSH values (Table 2). Most COVID-19 patients were euthyroid (86·5%); none were overtly hyperthyroid (as defined by a low TSH and high FT4) and only a small number had overt hypothyroidism (0·6%). The proportions of patients in each category did not significantly differ between COVID-19 positive and negative

patients, nor did they significantly differ between COVID-19 survivors and non-survivors, and patients admitted to ITU vs those not admitted to ITU with COVID-19.

Admission with COVID-19 is associated with a lower TSH and FT4

Patients with COVID-19 had lower TSH with a median (IQR) of 1·03 (0·62, 1.71) mU/L vs those without COVID-19: 1·48 (0·79, 2·18) mU/L (Wilcoxon rank-sum test p=0·01). Patients with COVID-19 also had a lower mean (SD) FT4 at 12·60 (2·18) vs those without COVID-19 at 13.11 (2·33) pmol/L, p=0.037 (Figure 1A and B).

As the intra-individual variation in 'setpoint' FT4 and TSH is narrower than the population reference range, we examined the subset of COVID-19 patients who had had thyroid function tests in 2019 ('Base 2019'). 185 patients had a 'Base 2019' median (IQR) TSH of 1·59 (1·03, 2·24) vs 1·02 (0·6, 1·65) mU/L at admission (paired Wilcoxon signed-rank test p<0·0001). Of 104 patients with 'Base 2019' FT4 measurements, the mean (SD) was 12·94 (2·77) in 2019 vs 12·23 (2·14) pmol/L at admission (paired t-test p=0·015). In comparison, matched TSH and FT4 levels for patients without COVID-19 showed no significant difference between 'Base 2019' and admission measurements (n=62, p=0.72 and n=33, p=0.74 respectively). In other words, patients admitted with COVID-19 demonstrated reductions in TSH and FT4 levels compared to 'Base 2019' measurements. This phenomenon was not observed in COVID-19 negative patients.

In patients with COVID-19, those admitted to ITU had lower median TSH at 0·66 (0·48, 1·12) vs 1·10 (0·69, 1·75) mU/L (p=0.0012), although mean FT4 was not significantly different (Figure 1C and D). Interestingly, in COVID-19 survivors, the FT4 was slightly higher at 12·76 (2·18) vs non-survivors at 12·19 (2·14) pmol/L (unpaired Student t-test p=0·03), although there was no significant difference in TSH (Figure 1E and F). A Cox proportional hazards analysis for survival did not discern any significant univariable relationship of FT4 nor TSH to survival.

There was a highly significant negative correlation between serum cortisol and log-transformed TSH (Pearson R=-0·25, p<0·0001), but no correlation between serum cortisol and FT4. There were also significant correlations between CRP and TSH (R=-0·19, p=0·00063) and CRP and FT4 (R=0·15, p=0·0062). Serum albumin, which has previously been shown to be negatively associated with acute mortality from COVID-19 (10), was significantly lower in those diagnosed with COVID-19 (Table 1) but no significant correlations of FT4 and TSH were seen with albumin (Figure 2).

TSH recovers to the baseline on follow-up after COVID-19

A small subset of COVID-19 survivors (n=55) had follow-up thyroid function tests at a median (IQR) time since admission of 79 (52, 108) days. Most of the follow-up tests (47/55) were classified euthyroid. There were only two cases with mildly depressed TSH and normal FT4 ('subclinical hyperthyroid'), four with low FT4 and normal TSH ('secondary hypothyroid'), and two with normal FT4 and mildly elevated TSH ('subclinical hypothyroidism'). None had overt thyrotoxicosis. In 50 patients with complete sets of TSH measurements at baseline, admission and follow up, the median (IQR) baseline TSH was 1·59 (1·03, 2·21), at admission 1·05 (0·56, 1·62), and at follow-up 1·45 (0·98, 2·22) mU/L (Friedman rank sum test, p=0.0087). Pairwise comparisons showed significant differences in TSH comparing baseline vs admission (paired Wilcoxon signed-rank test p=0.004) and admission vs follow-up (p=0.034), but baseline vs follow-up values were not significantly different

(Figure 3). In 20 patients with complete sets of FT4 measurements, the mean (SD) baseline FT4 was 14·07 (4·74), at admission 12·41 (2·00) and at follow-up 12·61 (2·44) pmol/L with no significant differences seen (repeated-measures one-way ANOVA p=0.23, Figure 3).

Discussion

In this observational study, we investigated the acute effects of COVID-19 on thyroid function in the largest cohort of patients to date. Most patients were euthyroid at admission with COVID-19. We did however observe a small reduction in TSH and FT4 in patients with COVID-19 compared to non-COVID-19 cases. We confirmed with matched samples that there was a reduction in TSH and FT4 from 2019 baselines to admission with COVID-19, and this was not seen in patients admitted without COVID-19. Muller et al. recently reported overt thyrotoxicosis in 15% of patients admitted to a high dependency ITU with COVID-19 (6), compared to 2% in those treated in low intensity settings; however, this study defined thyrotoxicosis as TSH <0.28 mU/L and/or FT4 >21.9 pmol/L, reflecting the fact that TSH was the first-line thyroid function test and FT4 was only measured in 24% of their patients. We also note that in their study, TSH was routinely measured in all high dependency ITU patients but less frequently measured in all low dependency ITU patients, possibly introducing bias. Lania et al. similarly reported overt thyrotoxicosis in 10.8% of their cohort of 287 patients with COVID-19 who were treated outside of intensive care, but only measured thyroid hormones in 25% of patients (7). In contrast, our study included complete sets of FT4 and TSH measurements and the measurement of thyroid function was applied across the board as part of a standard workup. In our dataset we did not see any patients with overt thyrotoxicosis (utilising a conservative definition of TSH <0·30 and FT4 >23·0), even in our 40 cases of COVID-19 admitted to ITU. Therefore, in our cohort, there was no suggestion of a novel COVID-19 related thyroiditis/thyrotoxicosis.

The most likely explanation for the changes in thyroid function we observed is the NTI syndrome, initially characterised by a reduction in total and free T3 and a rise in reverse T3 (rT3) in the absence of a rise in TSH; more severe or prolonged illness causes global reductions in TSH, FT4, and FT3 (11). The suppression of TSH is most likely related to elevations in pro-inflammatory cytokines such as IL-6, which are negatively correlated with TSH. An additional factor may be cortisol, which is known to suppress TSH secretion, even at physiological levels (12). Chen et al. were unable to exclude exogenous glucocorticoids as a factor influencing TSH (8). No patient in our cohort received exogenous steroids, and we excluded any patients taking steroids prior to admission. Therefore, the marked elevations in endogenous cortisol secretion during COVID-19 may be an additional factor suppressing TSH (13). A possible third explanation may be a direct cytopathic effect of SARS-CoV-2 on thyrotrophs as the receptor for virion binding, ACE2, is expressed in the pituitary (14). Critically, whichever of these factors are responsible for the observed drop in TSH secretion, we found that on follow up TSH had returned to baseline, suggesting that the changes are reversible with recovery from COVID-19.

To our knowledge, this is the largest cohort of such patients with COVID-19 to have had assessment of thyroid function at presentation. Additionally, we have uniquely presented longitudinal data gathered both prior to the COVID-19 admission and at follow-up. Overt thyroid dysfunction is not characteristically observed in most patients presenting acutely with COVID-19 nor at follow-up in survivors. Although we did see a statistically significant reduction in FT4 and TSH between baseline and admission with COVID-19, the magnitude of the reduction was small and not likely to justify treatment. This data is limited by its single centre design, the absence of FT3 and rT3 measurement and characterisation of thyroid autoantibody status. However, we believe our data are sufficient to suggest that routine measurement of thyroid function in COVID-19 may not be necessary unless there are other specific indicators of thyroid disease. Further longitudinal studies including FT3 and rT3 measurement are now necessary to determine the full impact of COVID-19 on the hypothalamic-pituitary-thyroid axis.

Statements

Author Contributions: TT, BK, KM, ANC, AA and WSD conceptualised the study. SAC, EGM, BP, MM, MP, PCE, LT and ECA collected and recorded the demographic, clinical and laboratory data. TT and BK analyzed the data. TT, BK and EGM drafted the manuscript. BK, TT and WSD revised all subsequent versions of the manuscript. All authors read and approved the final manuscript.

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Data sharing: An anonymized dataset and data analysis code is available upon application to the corresponding author.

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Figure Legends

Figure 1: TSH and free T4 on admission to hospital. TSH and free T4 plotted with box indicating 25th and 75th centiles, whiskers indicating 5th and 95th centiles, line in box indicates median. (A,B) in all patients, classified by diagnosis of COVID-19. (C,D) in COVID-19 positive patients, classified by admission to ITU. (E,F) in COVID-19 positive patients, classified by survival to May 8, 2020. Wilcoxon rank-sum tests used for comparison of TSH, unpaired Student t-test for FT4.

Figure 2: Correlations of FT4 and log-transformed TSH with cortisol, CRP, albumin in COVID-19 positive patients. Scatterplots of log-transformed TSH (A, C, E) and free T4 (B, D, F) on the y-axes are plotted against log2 cortisol (A, B), log2 CRP (C, D) and albumin (E, F) on the x-axes. Pearson correlation is shown at the top with its associated p-value. Regression line (black line) and 95% confidence interval (grey shading) are plotted.

Figure 3: Longitudinal study of TSH and FT4 using 2019 baseline, admission and follow up measurements. Free T4 (A, n=20) and TSH (B, n=50) measurements are plotted against the timepoint they were taken (baseline in 2019, admission with COVID-19 and Follow up). Repeated measures one-way ANOVA or Friedman rank sum test performed as indicated. Pairwise comparisons of TSH were performed with paired Wilcoxon signed-rank tests, with Bonferroni adjustment.

Table Legends

Table 1: Characteristics of patients (n=456) diagnosed with COVID-19 and without COVID-19. COPD = chronic obstructive pulmonary disease. ITU = intensive therapy units. Categorical data shown as number (percentage). Continuous variables displayed as mean (SD) if parametric or median [IQR] if non-parametric. * p<0.05, ** p<0·01, *** p<0.001, **** p<0·0001 (two-tailed unpaired Student t-test); † p<0·05, †† p<0·01, †††† p<0·0001 (Fisher exact test); ‡ p<0.05, ‡‡ p<0.01, ‡‡‡‡ p<0.0001 (Wilcoxon rank sum test).

Table 2: Thyroid diagnostic categories in patients diagnosed with COVID-19 and without COVID-19. Patients were classified into diagnostic categories according to the pattern of results falling below, within or above the indicated reference ranges. P-values calculated using Fisher's exact test for the comparison between COVID-19 negative and positive patients, COVID-19 positive survivors and non-survivors, and COVID-19 patients admitted and not admitted to ITU are shown below. Euthyr, euthyroid; Hyper, hyperthyroid; Hypo, hypothyroid; SC, subclinical; Sec, secondary.

Tables

Table 1: Characteristics of patients (n=456) diagnosed with COVID-19 and without COVID-19. COPD = chronic obstructive pulmonary disease. ITU = intensive therapy units. Categorical data shown as number (percentage). Continuous variables displayed as mean (SD) if parametric or median [IQR] if non-parametric. * p<0.05, ** p<0·01, *** p<0.001, **** p<0·0001 (two-tailed unpaired Student t-test); † p<0·05, †† p<0·01, †††† p<0·0001 (Fisher exact test); ‡ p<0.05, ‡‡ p<0.01, ‡‡‡‡ p<0.0001 (Wilcoxon rank sum test).

COVID-19 status		**No**	**Yes**
Number (%)		122 (24·2%)	334 (73·2%)
Age (yr)		63·8 (19·3)	66·1 (16·0)
Age (stratified)	**<45**	25 (20·5%)	28 (8·4%)
	45–59	20 (16·4%)	92(27·5%)
	60–74	30 (24·6%)	84 (25·1%)
	≥75	47 (38·5%)	130 (38·9%)
Weight (kg)		73·1 (19·1)	79·9 (22·2)**
Sex	**Male**	68 (55·7%)	203 (60·8%)
	Female	54 (44·3%)	131 (39·2%)
Diabetes		30 (24·4%)	132 (39·5%)††
Hypertension		49 (40·2%)	162 (48·5%)
Current diagnosis of cancer		19 (15·6%)	29 (8·7%)†
COPD/asthma		25 (20·5%)	58 (17·4%)
Chronic kidney disease		17 (13·9%)	44 (13·2%)
Cardiovascular disease		33 (27·0%)	79 (23·7%)
Pregnancy		0	2 (0·6%)
Endocrine disease (other than thyroid)		2 (1·6%)	17 (5·1%)
Deaths (to May 8, 2020)		9 (7·4%)	95 (28·4%)††††
ITU admissions (to May 8, 2020)		3 (2·5%)	40 (12·0%)††
Free T4 (pmol/L)		13·11 (2·33)	12.60 (2·18)*
TSH (mU/L)		1·48 [0·79, 2·18]	1·03 [0·62, 1·71]‡
Cortisol (nmol/L)		537 [380, 708]	620 [454, 849]‡‡
CRP (mg/L)		39 [8, 125]	115 [58, 175]‡‡‡‡
Albumin (g/L)		32·9 (6·8)	30·3 (5·2)***

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	FT4 pmol/L	**TSH mU/L**	**All**	**COVID-19 Neg**	**COVID-19 Positive**				
	9·0-23·0	*0·30-4·20*			*COVID-19 Pos*	*Surv*	*Non-surv*	*Not ITU adm*	*ITU adm*
Euthyr	↔	↔	395 (86·6%)	106 (86·9%)	289 (86·5%)	211 (88·3%)	78 (82·1%)	258 (87·8%)	31 (77·5%)
Hyper	↑	↓	0	0	0	0	0	0	0
Hypo	↓	↑	2 (0·4%)	0	2 (0·6%)	2 (0·8%)	0	2 (0·7%)	0
SC hyper	↔	↓	26 (5·7%)	8 (6·6%)	18 (5·4%)	12 (5·0%)	6 (6·3%)	13 (4·4%)	5 (12·5%)
SC hypo	↔	↑	24 (5·3%)	7 (5·7%)	17 (5·1%)	9 (3·8%)	8 (8·4%)	15 (5·1%)	2 (5·0%)
Sec hyper	↑	↔	0	0	0	0	0	0	0
Sec hypo	↓	↔	9 (2·0%)	1 (0·8%)	8 (2·4%)	5 (2·1%)	3 (3·2%)	6 (2·0%)	2 (5·0%)
p-values				0·826		0·337		0·129	

Figure 1

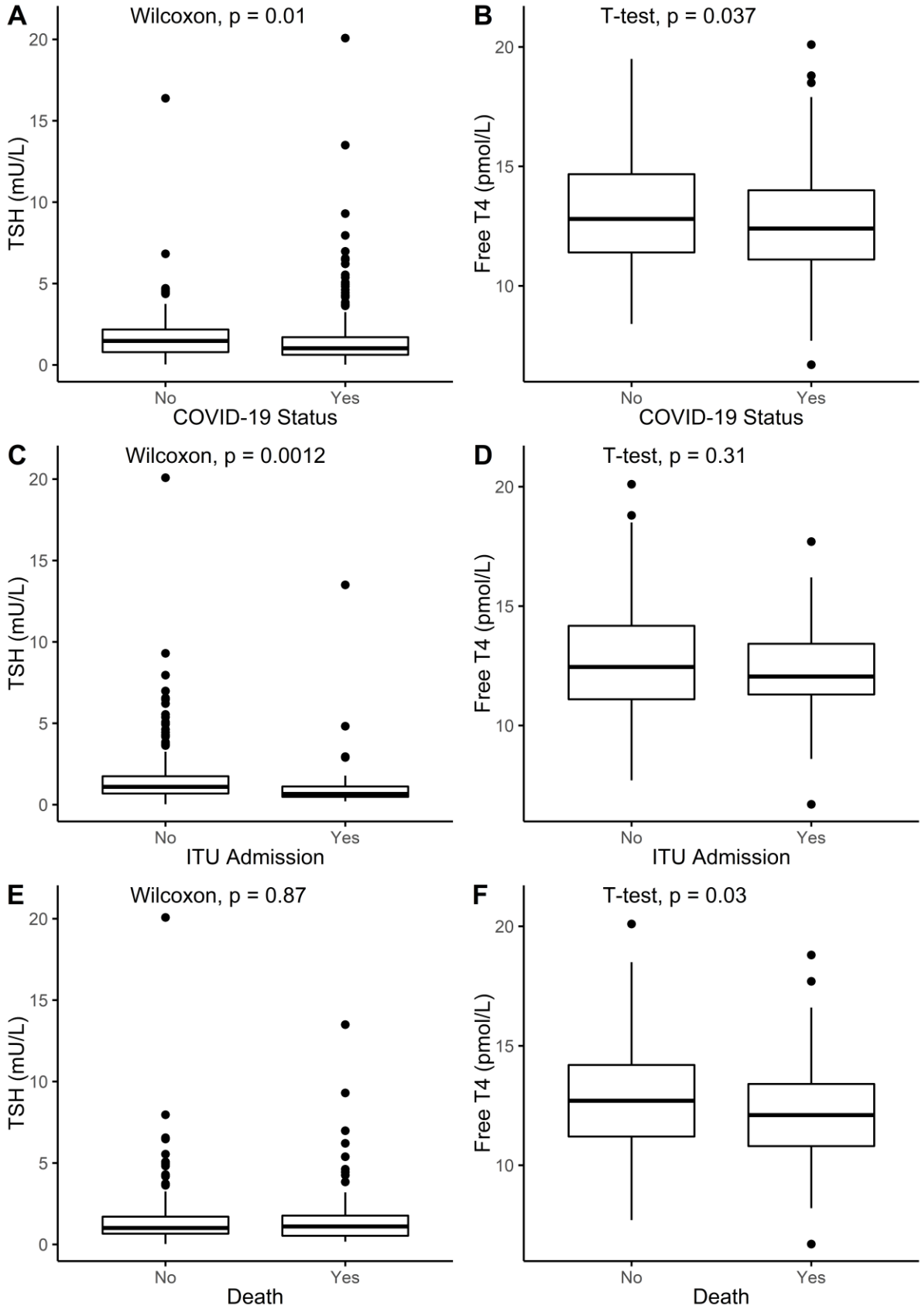

Figure 2

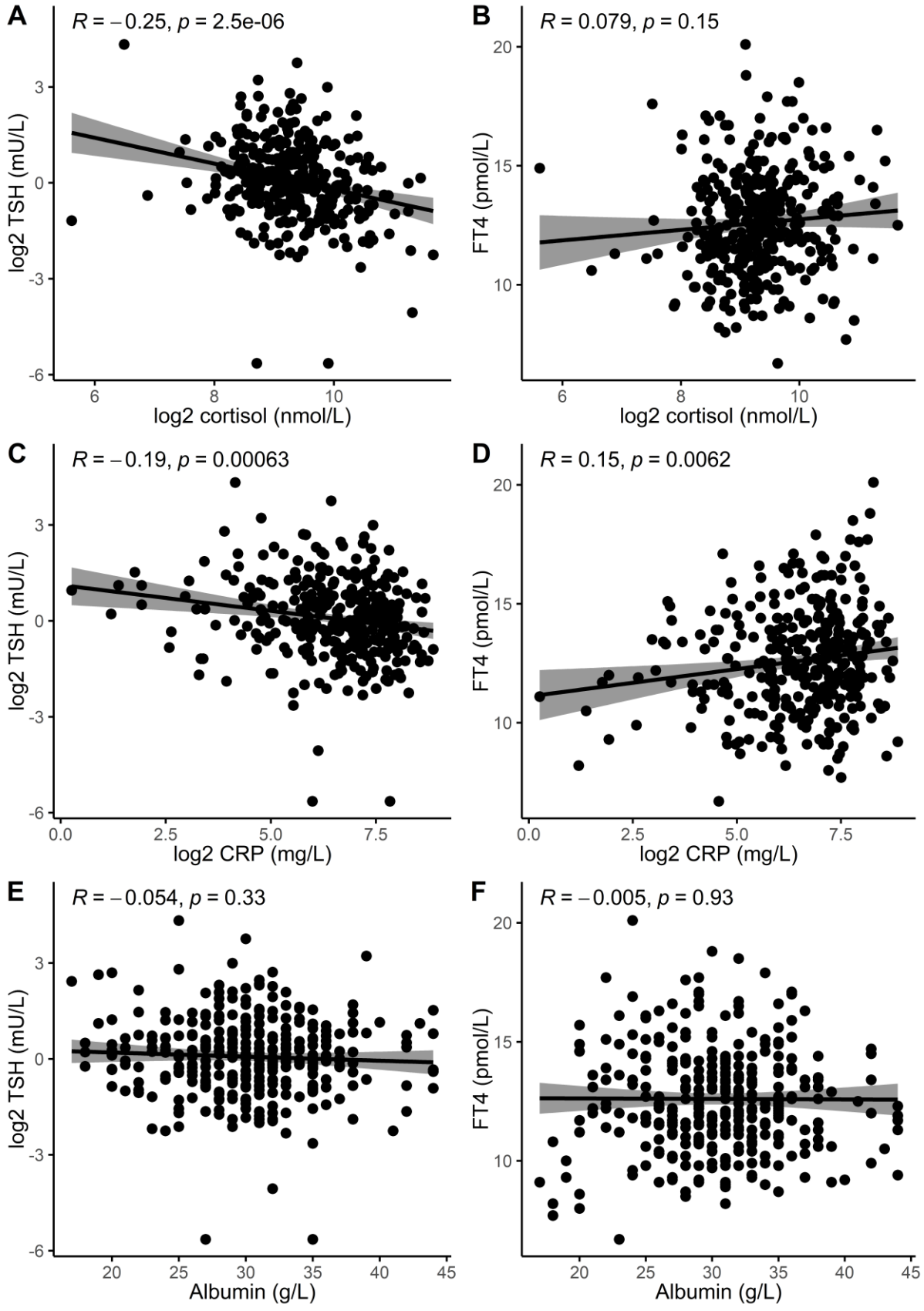

Figure 3