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Evaluating tertiary adrenal insufficiency in rheumatology patients on long-term systemic glucocorticoid treatment

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Abstract

Objective: Patients with rheumatic diseases are often treated with prolonged, high-dose systemic glucocorticoids which can cause hypothalamic-pituitary-adrenal (HPA) axis suppression and development of tertiary adrenal insufficiency. Adrenal insufficiency carries the risk of serious, potentially life-threatening adrenal crisis. Our study evaluated the prevalence, characteristics and recovery of patients with underlying rheumatology conditions who had received prolonged glucocorticoid treatment.

Design and patients: Retrospective, cross-sectional study. We evaluated 238 patients seen in outpatient rheumatology clinic, managed in accordance with current nationally and internationally accepted clinical guidelines.

Measurements: Data collected included patient demographics, historical steroid data, 09.00 h cortisol/short synacthen test (SST) results and follow-up data on those with repeat assessments.

Results: Overall, 65% of our cohort had a 09.00 h cortisol <350 nmol/L. On SST, 43% of patients demonstrated evidence of possible tertiary adrenal insufficiency.

Prednisolone equivalent dose at time of SST was significantly higher in the group who failed SST vs. those who passed; mean of 5.57 mg vs. 3.59mg (p = .005). 09.00 h cortisol result correlated with 30-min cortisol on SST (R^2 = .20, p = .002). 0-min cortisol on SST correlated more strongly with 30-min cortisol than 09.00 h cortisol (R^2 = .59, p-value < .001). Patients with 0-min cortisol >350 nmol/L, all passed their SST.

Patients who remained on prednisolone were more likely to recover (71%) vs. those switched to hydrocortisone (27%), P = .02. Peak steroid dose was predictive of recovery; significantly lower in those who recovered (mean of 22.3 mg vs. 33.8 mg, P = .03). Steroid duration was not found to be a predictor of recovery [recovery (64.2 months) vs. non-recovery (55.6 months), P = .58]. There was no correlation found to outcome on SST with age, sex, peak steroid dose, steroid duration, underlying rheumatological condition, additional exogenous steroid use or serum sodium.

Conclusions: Forty three percent of our patients demonstrated sub-optimal adrenal function on SST. Steroid dose at the time of SST was the only significant predictive risk factor for tertiary adrenal insufficiency. 09.00 h cortisol demonstrated good correlation with outcome on SST and could represent a valid screening test to reduce need for SST if 09.00 h >350 nmol/L. Further prospective data are required to further characterize risk factors, predictive features of recovery and establish optimal

management strategy of steroids (prednisolone vs hydrocortisone) to encourage adrenal recovery.

KEYWORDS
adrenal insufficiency, glucocorticoids, tertiary adrenal insufficiency

1 | BACKGROUND

Prolonged, high-dose systemic glucocorticoid (GC) treatment is key in managing numerous rheumatic diseases, in particular polymyalgia rheumatica (PMR), giant cell arteritis (GCA) and the large vessel vasculitides.[1–3] Prolonged exposure to glucocorticoid therapy at doses above physiological levels, approximately equivalent to a daily dose of prednisolone 5 mg, can lead to suppression of the intrinsic hypothalamic-pituitary-adrenal (HPA) axis.[4,5] This is termed tertiary adrenal insufficiency and can become clinically significant following withdrawal from chronic exogenous GC intake presenting as potentially fatal adrenal crisis, or more commonly in a mild form with a number of non-specific symptoms including fatigue, nausea/vomiting, muscle aches or dizziness leading to reduced quality of life.[6] There is also a significant cardiovascular risk as reported by Wei et al.[7]

Whilst steroids provide good symptomatic relief for the underlying rheumatological problem, it has been previously shown the potential for adrenal insufficiency is under-recognized and under-investigated in this patient population.[8] In particular, evaluating symptoms for evidence of adrenal insufficiency can prove challenging with many of these symptoms overlapping with the features of their underlying rheumatological condition. Furthermore, suppression of the patient's HPA axis leads to an inadequate physiological cortisol response to situations of stress including illness and surgery which could be potentially fatal if not recognized and managed appropriately.[9]

Despite the risks of adrenal insufficiency, there is relatively little published data in this domain to guide clinicians, particularly rheumatologists, in the day-to-day evaluation, investigation and management of patients in a safe clinical manner.[10–12] More data are available on managing respiratory patients,[13] requiring glucocorticoid therapies who also have potential risk of tertiary adrenal insufficiency.

Our study aimed to evaluate the prevalence, characteristics and recovery of adrenal insufficiency in patients who had received prolonged glucocorticoid treatment for rheumatological conditions at a large UK teaching hospital with a catchment population of around 800,000 people.

2 | METHODS

We retrospectively identified patients who had been seen in rheumatology outpatient clinics and evaluated for the possibility of adrenal insufficiency whilst attending for ongoing management of their underlying condition. Inclusion criteria included all patients over the age of 18 years of age, treated with glucocorticoid doses equivalent to a daily dose of prednisolone 5 mg or greater for at least 3 months, and who had an initial adrenal function assessment of either 09.00 h cortisol and/or short synacthen test (SST) between January 2014 and September 2019. Patients included in the study and the investigations evaluated are represented in Figure 1 (flowchart).

Using electronic hospital records and clinical letters, we collected a full data series including demographics, primary rheumatological diagnosis, co-morbidities, indication for assessment of adrenal function, symptoms if present, cortisol results, prednisolone treatment including duration, maximum dose and dose at time of adrenal function test. We also collected management and follow-up data for the patients. We recorded whether patients had been switched to hydrocortisone or remained on prednisolone treatment. We also evaluated the characteristics of recovery in those who had further, future assessments of adrenal function, usually following referral to the endocrinology department.

All results were reviewed by a consultant endocrinologist and categorized. For 09.00 h cortisol, values <350 nmol/L were typically deemed to require further assessment by SST. The threshold of 350 nmol/L was largely based on published data (Woods et al[13]) which demonstrated a normal cortisol response to SST in all cases if the 09.00 h cortisol was over 348 nmol/L.

Short synacthen tests were conducted as per local policy; following a basal (time 0-min) cortisol sample, 250 micrograms of synthetic tetracosactrin was administered either IM or IV and a further cortisol sample taken 30-min later. The local assay used is the ADVIA Centaur cortisol assay (Siemens). The assay has an analytical coefficient of variation of 4.5%. Manufacturer quoted cross-reactivity for the assay and prednisolone is 120%. The same cortisol assay was used for both 09.00 h cortisol and SSTs. Short synacthen tests were conducted in the morning, on either the specialist rheumatology or endocrine day units, predominantly between 08.30 and 10.00 h. These units conduct a large number of SSTs each year; all patients were advised to omit their prednisolone on the morning of the test and this was confirmed with each patient prior to testing. As the tests were carried out as part of routine clinical practice, mass spectrometry was not performed.

A post-synacthen administration (30-min) cortisol of 450 nmol/L was used as a threshold value for a normal or 'pass' response (>450 nmol/L) vs sub-optimal or 'fail' (<450 nmol/L) response.

2.1 | Statistical testing

Statistical analysis was carried out where appropriate for non-categorical data using Mann-Whitney's U test or unpaired *t*-test and

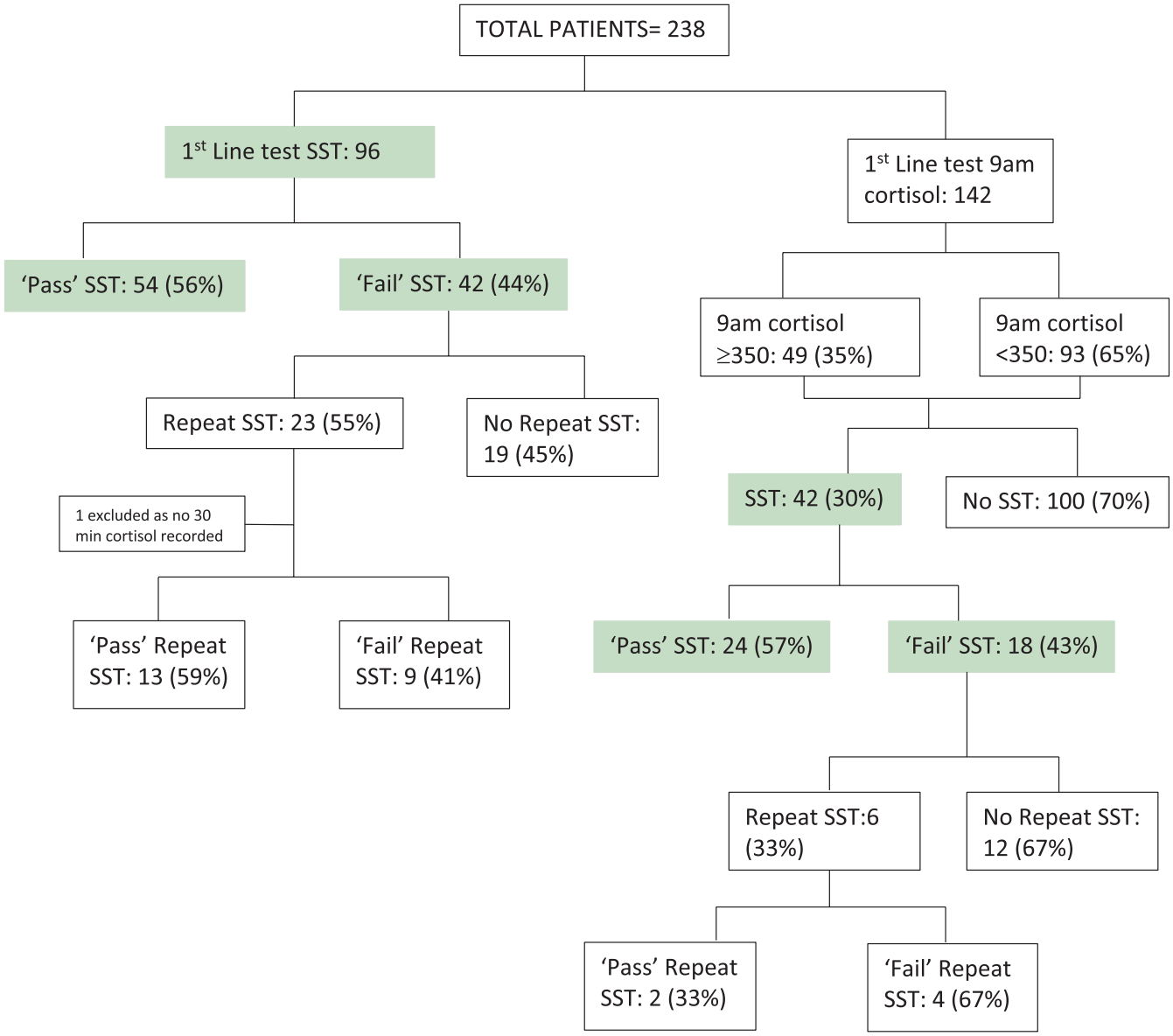

FIGURE 1 Flowchart demonstrating patients throughout study. SST, short synacthen test. Pass/Fail threshold on SST defined as 450 nmol/L. Pass/Fail threshold on 09.00 h cortisol defined as 350 nmol/L. Boxes highlighted green are those who had an SST as part of their 'initial' assessment for adrenal insufficiency (either as 1st line or within 6 months of 09.00 h cortisol result); total number of patients who had an initial SST = 138

categorical data was analysed using Fisher's exact test/Chi-squared chosen based on sample size using PRISM 8.3.1 (November 2019). Data were checked for normal distribution where relevant.

3 | RESULTS

As shown in Table 1, a total of 238 patients were included over the period of the study. There was a female preponderance (75% of patients were female), age range was from 24-92 years, with a mean age of 68 years. The single largest patient disease sub-group were those with PMR (45% total, Table 1), followed by GCA (21%), large vessel vasculitides (9%) and others (25% - comprising a range of other pathologies, fully detailed in Table 1, including rheumatoid arthritis and SLE).

Thirty seven percent of patients used another form of exogenous steroid treatment (19% inhaled therapies, 60% received injected treatment, 10% used topical steroids and 10% received more than one of the mentioned forms of steroid treatment).

3.1 | Assessing adrenal insufficiency

We evaluated all 09.00 h cortisol values and initial SSTs to assess for prevalence of adrenal insufficiency. An overview of these results is shown in Figure 1.

TABLE 1 Baseline demographics and characteristics of all study population, sub-optimal ('fail') SST group and optimal ('pass') SST group

	All (*n* = 238)	Sub-optimal SST (<450)	Optimal SST (>450)
Age	71 years (24-92)	70 years (34-92)	72 years (24-92)
Sex	179 female (75.2%) 59 male (24.8%)	44 female (73.3%) 16 male (26.7%)	61 female (78.2%) 17 male (21.8%)
Underlying condition	PMR 105 (44.1%) GCA 50 (21.0%) Vasculitides 22 (9.2%) Other 61 (25.6%): • Myositis/ dermatomyositis: 4 (6.6%) • SLE: 9 (14.8%) • Behcet's: 7 (11.5%) • Arthritis (psoriatic, IBD, erosive, uncharacterized): 11 (18.0%) • Rheumatoid Arthritis: 18 (29.5%) • Connective Tissue Disease: 6 (9.8%) • Ankylosing spondylitis: 1 (1.6%) • Sarcoidosis: 1 (1.6%) • Sjogren's: 3 (4.9%) • Still's disease: 1 (1.6%)	PMR 27 (45%) GCA 17 (28.3%) Vasculitides 6 (9.8%) Other 10 (16.7%): • Rheumatoid arthritis: 2 (20%) • Psoriatic arthritis: 2 (20%) • SLE: 3 (30%) • Behcet's: 2 (20%) • Dermatomyositis: 1 (10%)	PMR 41 (52.6%) GCA 19 (24.4%) Vasculitides 5 (6.4%) Other 13 (16.7%): • Rheumatoid arthritis 1 (7.7%) • Arthritis (psoriatric/ erosive): 2 (15.3%) • SLE: 3 (23.1%) • CTD: 2 (15.3%) • Behcet's: 2 (15.3%) • Ankylosing spondylitis: 1 (7.7%) • Sjogren's: 1(7.7%) • Still's disease: 1 (7.7%)
Peak steroid dose (mean ± SD)	29.2 ± 16.3 mg	27.7 ± 13.7 mg	30.1 ± 17.7 mg
Steroid duration (mean ± SD)	63.5 ± 53.4 months	67.4 ± 49.0 months	61.7 ± 59.9 months
Steroid dose at time of SST	4.5 ± 4.12 mg	5.57 ± 4.6 mg	3.59 ± 3.56 mg
Other exogenous steroids	88/238 (37%): Inhaled: 17/88 (19%) Injected: 53/88 (60%) Topical: 9 (10%) Multiple: 9 (10%)	25/60 (41.7%) Inhaled: 9 (36%) Injected:10 (40%) Topical:3 (12%) Multiple:3 (12%)	27/78 (34.6%) Inhaled: 5 (18.5%) Injected: 15 (55.6%) Topical: 5 (18.5%) Multiple: 2 (7.4%)
Sodium (mean ± SD)	140.5 ± 3.04 mmol/L	141.1 ± 2.87 mmol/L	140.3 ± 3.02 mmol/L

Of the 142 patients who had a 09.00 h cortisol as a first-line assessment of adrenal function, 93 (65%) had a <350nmol/L, our threshold value requiring further investigation for possible adrenal insufficiency. Of these patients who had a 09.00 h cortisol as the first-line test, 42 went on to have an SST with 18 (43%) demonstrating a sub-optimal response on SST.

Ninety six patients had an SST as the first-line test to investigate for possible adrenal insufficiency, with 42 (44%) responding sub-optimally. Thus, in total 138 patients had an SST to assess adrenal function, of these 60 (43%) were found to have sub-optimal adrenal response.

3.1.1 | 09.00 h cortisol

We evaluated the threshold value for a 09.00 h cortisol result that would require further assessment for possible adrenal insufficiency. This is represented in Figure 2. As shown, 80% of patients with a 09.00 h cortisol <100 nmol/L who had a subsequent SST, failed to reach a stimulated cortisol of >450 nmol/L. The failure rate on SST was shown to fall (p = .02) with each increasing cortisol range, down to 21% of those with a 09.00 h cortisol of 250-350 nmol/L failing subsequent SST. There was statistically significant correlation between 09.00 h cortisol as a predictor of 30-min cortisol level as

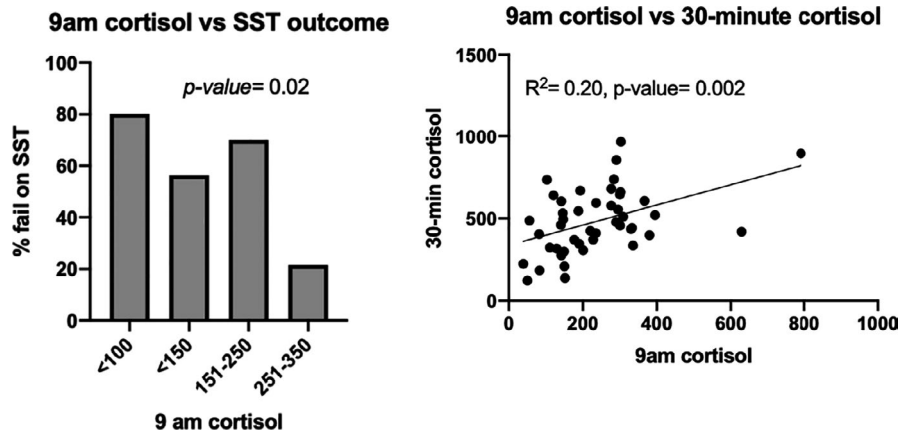

FIGURE 2 09.00 h cortisol as a predictor of 30-min cortisol level on SST and prevalence of adrenal insufficiency based on 09.00 h cortisol

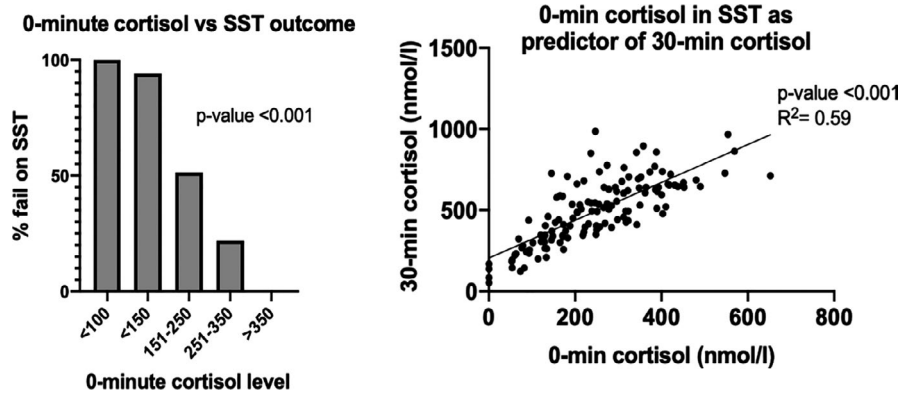

FIGURE 3 0-min cortisol as a predictor of 30-min cortisol level on SST and prevalence of adrenal insufficiency based on 0-min cortisol on SST

per Figure 2 (*p*-value = .002). No patients with a 09.00 h cortisol >350nmol/L had a subsequent SST.

3.1.2 | SST 0-min cortisol

As the 0-min cortisol on an SST was typically taken around 09.00 h, we also evaluated this to see if the results supported the 09.00 h cortisol cut-off of 350 nmol/L; similar results were demonstrated shown in Figure 3. With a 0-min cortisol <100 nmol/L, 100% of patients failed their SST. Again, increasing 0-min cortisol levels significantly correlated with falling failure rates on SST ($P < .001$). Of those with a 0-min cortisol >350 nmol/, none of the SSTs were abnormal. We also evaluated 0-min cortisol as a predictor of 30-min cortisol and found this correlated ($R^2 = .59$, *p*-value < .001), also shown in Figure 3.

3.2 | Assessing risk factors for adrenal insufficiency

3.2.1 | Age and sex

Thirty three male patients and 105 female patients had undergone an SST to assess adrenal function. 51.5% of the male patients had a pass result on SST vs. 58.1% of female patients ($p = .51$). The mean age (± standard deviation (SD)) of patients did not differ between the pass group 68.6 (± 14.5) years and the fail group 69.5 (± 12.5) years.

3.2.2 | Steroid use

We analysed historical steroid treatment data including maximum doses of steroid and duration of use. Glucocorticoid doses in this paper refer to prednisolone dose equivalent, patients on hydrocortisone had their doses converted to prednisolone equivalent (at a ratio of 4 mg hydrocortisone: 1 mg prednisolone). The mean peak dose (±SD) of glucocorticoid treatment amongst all 238 patients was 29.2 mg ± 16.3mg. The mean peak steroid dose in the fail group was 27.7 ± 13.7 mg vs. a mean of 30.1 ± 17.7 mg in the pass group, $P = .39$. Peak steroid dose was not correlated with 09.00 h cortisol ($P = .40$), 0-min cortisol on SST ($P = .32$) nor 30-min cortisol results ($P = .25$).

The mean duration of glucocorticoid treatment was 63 ± 53months across all patients. Just over half of the patients (52%) had been on steroids for 4 years or less.

We compared steroid duration vs. prevalence of adrenal insufficiency. There was no clear relationship between steroid duration

and rate of pass or fail on SST; the mean steroid duration (±SD) in the fail group was 67.4 ± 49 months and 61.7 ± 59.9 months in the pass group (*P* = .11).

We also evaluated pass/fail rate on SST vs. steroid dose at the time of the SST. In the fail group, there was a higher mean steroid dose (daily prednisolone equivalent) of 5.57 ± 4.6 mg compared with the pass group, mean 3.59 ± 3.56 mg (*P* = .005), as per Figure 4. Equally, increasing doses of prednisolone at the time of test showed increasing failure rate on SST as shown in Figure 4 (*P* < .001). With a dose of prednisolone <5 mg there was a 28.2% failure rate, increasing to 69.2% when dose was >7.5 mg.

3.2.3 | Disease group

We compared the SST outcomes across the various primary rheumatological conditions, listed in detail in Table 1. 68 patients with a primary diagnosis of PMR had an SST performed, of these, 39.7% had sub-optimal response on SST. Of the 36 patients with a primary diagnosis of GCA, 47.2% had sub-optimal response. 54.5% of the 11 patients with an underlying vasculitis had sub-optimal response and 43.5% other those with a diagnosis in the 'other' category failed SST. There was no relationship established between underlying condition and response on SST (*P* = .77).

3.2.4 | Serum sodium

We recorded patients' serum sodium level, closest to the date of SST (within 1 month), where available. Normal laboratory measurements on this assay were 133-145 mmol/L. Across the whole study patient population, the mean serum sodium was 140.5 (± 3.04) mmol/L. There was no correlation observed between serum sodium and SST outcome; mean of the pass group (± SD) was 140.3 ± 3.02 mmol/L vs. 141.1 ± 2.87 mmol/L in the fail group (*P* = .17).

3.2.5 | Other exogenous steroids

In total, 37% of the 238 patients were taking some other form of exogenous steroid (inhaled, injected, topical or a combination of more than one). There was no difference in pass/fail rate on SST seen between those on other exogenous steroids and those not, with 41.7% of patients with sub-optimal response on SST having taken other exogenous steroids vs. 34.6% of those who passed their SST (*P* = .40).

Thirty patients who received concurrent injected steroids in addition to oral glucocorticoids had an SST performed, with a 43% failure rate. 22 patients on other concurrent steroids (inhaled or topical) had an SST, with a failure rate of 55%. Those on no concurrent steroids who had an SST performed (86 patients) had a failure rate of 40.6% (*p*-value = .50).

3.2.6 | Recovery

Of the 60 patients who demonstrated sub-optimal adrenal response on SST, 42 (70%) of these patients were referred to endocrinology for further opinion on investigation and management of their potential adrenal insufficiency.

Twenty nine of the 60 patients (48.3%) had an SST repeated at least once following the initial test to assess potential adrenal recovery, 1 was excluded from further analysis as the post-synacthen result was incorrectly processed. 13 of these 28 repeat SSTs (46.4%) remained abnormal. Those who demonstrated optimal response to synacthen stimulation (>450 nmol/L) on repeat SST were deemed to be in the 'recovery' group.

We also evaluated patients' time to recovery through assessment of time between failure on first SST and passing repeat SST, indicating recovery. The average time to recovery was 23.1 ± 15 months.

The recovery group had a mean peak dose of steroid of 22.3 ± 11 mg vs. a higher mean peak dose in the non-recovery group of 33.8 ± 15 mg (*p*-value = .03). There were no statistical differences in steroid duration between the recovery group (64.2 ± 33 months)

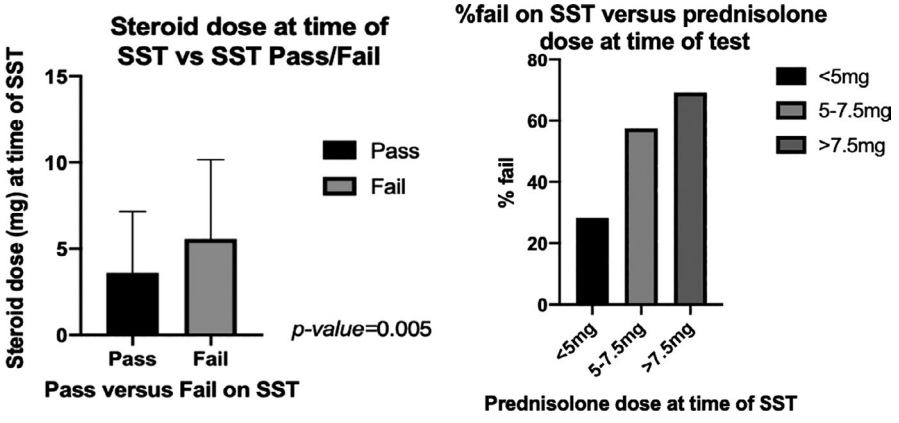

FIGURE 4 Pass/Fail on SST vs. mean steroid dose (daily prednisolone equivalent, mg) at the time that the SST was performed (± standard deviation) and grouping of prednisolone dose (mg) vs. failure rate on SST

and non-recovery group (55.6 ± 48 months), *p*-value = 0.58. (Figure 5).

Mean 30-min cortisol on initial SST in the non-recovery group was 318 ± 96 nmol/L vs. 325 ± 96 nmol/L in the recovery group (*p*-value = .84). Equally the 0-min cortisol on initial SST showed no significant difference between the two groups, 132 ± 81nmol/L in the non-recovery group vs. 159 ± 100 nmol/L in the recovery group (*p*-value = .44).

3.2.7 | Hydrocortisone vs. prednisolone

The recovery pathway described is represented by Figure 7. Of the 60 patients with abnormal initial SSTs, 14 were switched from prednisolone to hydrocortisone and 46 patients remained on prednisolone.

Of those who were switched to hydrocortisone, 11 had repeat SST performed with 3 (27%) demonstrating recovery. Initial 0-min cortisol on SST in those switched to hydrocortisone was 105 ± 73 nmol/L, mean 30-min cortisol was 239 ± 82 nmol/L. The average time to recovery was 23 ± 9 months.

Of the 46 patients who remained on prednisolone, 17 had a repeat SST to assess potential recovery of adrenal function. 12 (71%) of these patients showed recovery, with an average time to recovery of 22 ± 16 months. Initial 0-min cortisol on SST in those who remained on prednisolone was 155 ± 84 nmol/L, mean 30-min cortisol was 297 ± 99 nmol/L.

The initial SST 0-min and 30-min cortisol results may have been different between those switched to hydrocortisone and those who remained on prednisolone but numbers were small (*p*-value = .06 and .05 for 0-min and 30-min cortisol respectively). The difference in rates of recovery between the those who remained on prednisolone and those switched to hydrocortisone was significant, *p*-value = .02 (Figure 6).

4 | DISCUSSION

Based on SST results, our study demonstrated a prevalence of adrenal insufficiency of 43%, in patients with rheumatology conditions (mainly PMR, GCA, vasculitis and rheumatoid arthritis) treated with systemic glucocorticoids selected following routine investigation with 09.00h cortisol or SST. Only a few studies have previously investigated the prevalence and characteristics of tertiary adrenal insufficiency in this group of patients requiring long-term glucocorticoid treatment.

Although not specific to patients with rheumatological diagnoses, Broerson et al conducted a meta-analysis looking into prevalence of adrenal insufficiency and characteristics of patients who had received glucocorticoid treatment of any form. Of the total 74 articles included, with a total of nearly 4000 patients, prevalence ranged from 4.2% (nasal administration) to 52.2% (intra-articularly) which is not dissimilar to the prevalence seen in our group.[14]

More closely matching our patient population, one recent study looked at a smaller number of patients (*n* = 47) with PMR and/or GCA, and reported a lower prevalence of adrenal insufficiency of 11%-30% depending on disease group.[12] Another study investigating adrenal insufficiency in 150 patients with a diagnosis of GCA alone demonstrated a prevalence of 49%,[15] more closely supporting the prevalence seen in our study. Similar studies looking at other patient groups, for example those with respiratory disease taking systemic glucocorticoid treatment, reported prevalence of between 14% and 63%.[10]

Whilst many of the patients in our study were on other exogenous steroids, particularly intramuscular, in addition to oral systemic glucocorticoid treatment; no correlation was seen between the pass/fail rate on SST between those on additional exogenous steroids and those not. This suggests that it was primarily the use of oral steroids driving the patients' risk of tertiary adrenal insufficiency.

Age and sex do not seem to be relevant as risk factors for developing adrenal insufficiency. Interestingly, peak steroid dose did not correlate with a sub-optimal response on SST. Steroid duration did not show a clear correlation, but increasing prevalence of adrenal insufficiency was observed in those who had been on steroids for longer duration.

A higher steroid dose (daily prednisolone equivalent) at the time of SST did correlate with increased prevalence of adrenal insufficiency, with a mean daily dose of 5.57 mg in the fail group vs. 3.39 mg in the pass group. This indicates that patients on higher doses of daily

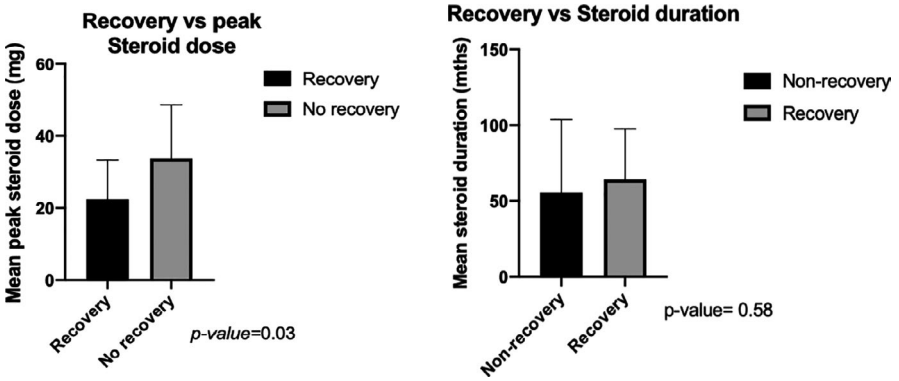

FIGURE 5 Peak steroid and steroid duration as predictors of adrenal function recovery

prednisolone are more likely to have sub-optimal adrenal function. Equally, patients who are able to successfully wean to doses less than 5mg appear to have a lower risk of adrenal insufficiency. Our data suggest that conducting an SST to assess for adrenal insufficiency when patients reach a daily dose of around 5mg, may be more clinically appropriate than conducting the test when patients are on higher doses.

Similar prevalence of adrenal insufficiency was seen in all disease groups, ranging from 40% with a sub-optimal response on SST in those with PMR to 55% in those with an underlying vasculitis. However, the type of primary rheumatological condition was not predictive of failure on SST. Serum sodium at the time of SST was also not predictive of prevalence of adrenal insufficiency.

Overall, in terms of predictive risk factors for adrenal insufficiency, steroid dose at time of SST was the only clear identified factor however further prospective data would be required to evaluate in greater detail.

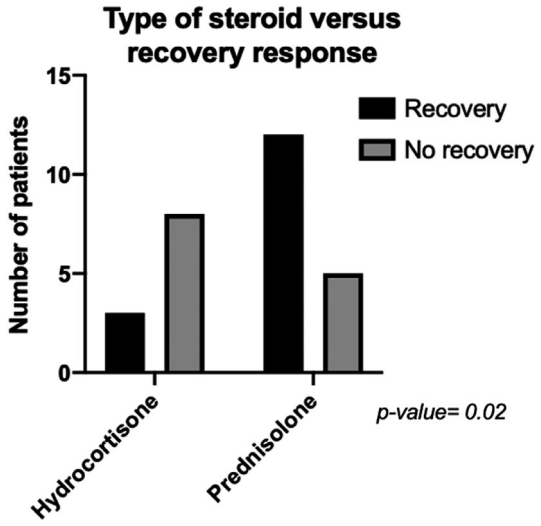

FIGURE 6 Hydrocortisone switch vs. remaining on prednisolone; rates of recovery

Woods et al[13] established that in respiratory patients at risk of tertiary adrenal insufficiency, a safe 09.00 h cortisol threshold was 348 nmol/L, with 100% of the patients with a 09.00 h cortisol over this value having normal response to synacthen during SST. Although our study used a different assay to Woods et al, a cut-off of 350 nmol/L was based on locally agreed practice for excluding possible adrenal insufficiency. From our results, this threshold of 350 nmol/L seemed valid, with reducing incidence of abnormal SST results as the 09.00 h cortisol moved towards 350nmol/L and all patients with a 0-min cortisol >350 nmol/L having a normal SST (Figures 6 & 7).

This would suggest that in terms of investigating patients, a 09.00 h cortisol result greater than 350 nmol/L, on the assay used in our study, should negate the need for further investigation such as SST or referral to endocrinology specialists when a daily prednisolone dose of 5 mg has been reached.

A key area in the management of these patients with confirmed tertiary adrenal insufficiency is establishing optimal management for recovery. There is very little data in this area. Recovery was defined in our cohort as patients with an initially sub-optimal SST result with subsequent testing at least 3 months later demonstrating a normal response (>450 nmol/L) to synacthen stimulation.

Switching patients to hydrocortisone may be appropriate in tertiary adrenal insufficiency in order to provide physiological glucocorticoid cover over a 24-h period and to better support 'steroid sick day rules'. Additionally, given the shorter half-life of hydrocortisone there may be a theoretical benefit in promoting HPA axis recovery. Our data showed that of the 28 patients who had repeat SST, those who remained on prednisolone had a greater rate of recovery (71%) compared with those who switched to hydrocortisone (27%), $P = .02$. This could suggest that, at least in this patient group, the switch to hydrocortisone provided no advantage, and remaining on prednisolone was actually better for adrenal recovery. However, 0-min and 30-min cortisol results on initial SST in the prednisolone group may be higher than those switched to hydrocortisone, and thus could

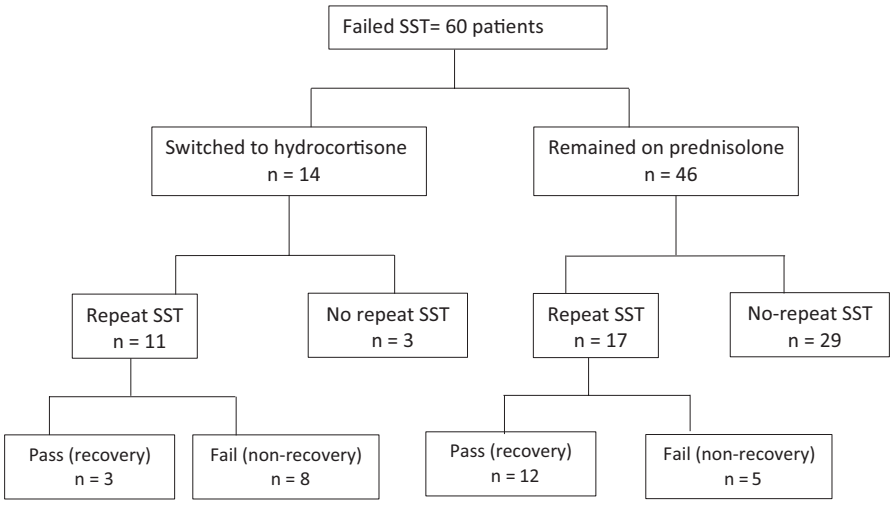

FIGURE 7 Flowchart demonstrating the pathway of potential adrenal recovery following initial failure of SST

represent a potential confounder. Numbers were relatively small in the recovery group and further data collected prospectively would be required to properly investigate management options for recovery. Additionally, given the retrospective nature of the study we were unable to accurately collect information of steroid tapering and how this would influence recovery. Although this was an interesting observation from the data collected, it was not the main focus of the study.

Our study supports the notion that the greater the peak dose of steroids, the less likely the chance of recovery, with a greater mean peak dose in the non-recovery group. A large initial prednisolone dose is common treatment in this patient cohort, with a dose of >40 mg prednisolone frequently used as first line in treatment guidelines including for GCA, the vasculitides and connective tissue disorders. Interestingly, we did not find a statistical difference between duration of treatment affecting adrenal recovery in the prednisolone vs. hydrocortisone groups. Again, this may relate to inaccuracies in data collection due to retrospective use of electronic patient records and thus prospective collection of the same data would be beneficial.

The greatest strength of our study was its size compared to existing published data. In addition, it provides an accurate representation of challenges facing rheumatologists in assessing and managing these patients in routine clinical practice. Additionally, our results suggest relatively few clear predictors for developing tertiary adrenal insufficiency and thus supports the need for a clear and robust protocol to aid rheumatologists in systematic evaluation of these patients.

The main limitation of our study is the retrospective nature of the design. In particular, steroid duration data may not be wholly accurate although has been collected as far as possible from a thorough electronic record system. We would also have ideally recorded total cumulative dose to see the impact on development of tertiary adrenal insufficiency and recognize that this is a limitation with the data. In addition, again given the retrospective nature of the study, there was an element of selection bias; with a large proportion of patients being investigated for possible adrenal insufficiency rather than routinely. Additionally, during this time period, 09.00 h cortisol was sometimes used preferentially due to a national synacthen shortage. Furthermore, ideally, we would have investigated the effect of cumulative steroid dose as a predictor of adrenal insufficiency but given the common practice of tapering steroid doses whilst managing the underlying condition, this could not be collected accurately and was therefore excluded. Finally, we have relatively few numbers in the recovery group and thus is difficult to establish true trends in the data.

Prospective data are required to further characterize the risks for adrenal insufficiency in this patient group. In addition to collecting further data in a prospective manner on the risk factors explored in this study, particularly with regards to cumulative steroid doses, other factors including blood pressure and specific symptom data would also be useful. Further data collection with greater numbers of patients to establish the best management strategy between careful tapering of prednisolone vs. switching to hydrocortisone to encourage adrenal recovery would also be a priority.

5 | CONCLUSION

Our study highlights the high prevalence of tertiary adrenal insufficiency as a result of glucocorticoid treatment of rheumatological conditions. With almost half of the patients in our study demonstrating some degree of lack of response to synacthen stimulation, there is an urgent need for establishing a standardized approach to the evaluation and management plan for these patients. Establishing presence of tertiary adrenal insufficiency in these patients is important both for the management of their underlying condition in terms of ongoing steroid treatment but also in providing timely and effective sick day rule education for patients to avoid the risk of an adrenal crisis.

There is a clear need for further prospective data in this area, to guide evaluation and assess the clinical consequences of tertiary adrenal insufficiency, to optimize management and predict recovery of endogenous adrenal function.

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RS and AA conceived the idea and designed the initial project. SM and AA refined the project design. SM, AVM and AA implemented protocols to facilitate data collection into clinical practice. RS collected data. RS and AA analysed and interpreted data. RS and AA wrote the first manuscript draft. SM, AVM and PS provided ideas and input for subsequent drafts. All authors contributed to the final manuscript.

CONFLICT OF INTERESTS

RS: Nothing to disclose. SM: Consultancy on behalf of her institution for Roche, Chugai, Sanofi; Support from Roche to attend EULAR conference in 2019; investigator on clinical trials for Sanofi, GSK; Patron of the charity PMRGCAuk. AM: Consultancy on behalf of her institution for Roche, Chugai, Sanofi and GSK for work unrelated to this manuscript. PS: nothing to disclose. AA: Nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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