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Predictors of silent corticotroph adenoma recurrence; a large retrospective single center study and systematic literature review

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Abstract
Purpose Silent corticotroph adenomas (SCAs) are clinically silent and non-secreting, but exhibit positive adrenocorticotropic hormone (ACTH) immunostaining. We characterized a single center cohort of SCA patients, compared the SCAs to silent gonadotroph adenomas (SGAs), identified predictors of recurrence, and reviewed and compared the cohort to previously published SCAs cases.
Methods Retrospective review of SCA and SGA surgically resected patients over 10 years and 6 years, respectively. Definitions; SCA—no clinical or biochemical evidence of Cushing's syndrome and ACTH positive immunostaining, and SGA—steroidogenic factor (SF-1) positive immunostaining. A systematic literature search was undertaken using Pubmed and Scopus.
Results Review revealed 814 pituitary surgeries, 39 (4.8%) were SCAs. Mean follow-up was 6.4 years (range 0.5–23.8 years). Pre-operative magnetic resonance imaging demonstrated sphenoid and/or cavernous sinus invasion in 44%, 33% were > 50% cystic, and 28% had high ACTH levels pre-operatively. Compared to SGAs (n = 70), SCAs were of similar size and invasiveness (2.5 vs. 2.9 cm, p = 0.2; 44 vs. 41%, p = 0.8, respectively), but recurrence rate was higher (36 vs. 10%, p = 0.001) and more patients received radiation therapy (18 vs. 3%, p = 0.006). Less cystic tumors (0 vs. 50%, p < 0.001) and higher pre-operative ACTH levels (54 vs. 28 pg/ml, p = 0.04) were predictors of recurrence for SCAs.
Conclusion This review is unique; a strict definition of SCA was used, and single center SCAs were compared with SGAs and with SCAs literature reviewed cases. We show that SCAs are aggressive and identify predictors of recurrence. Accurate initial diagnosis, close imaging and biochemical follow up are warranted.

Keywords Silent corticotroph · Pituitary adenoma · Gonadotroph · Nonfunctioning · Cushing's disease

Introduction

First reported in late 1970s [1, 2], silent corticotroph adenomas (SCAs) are a distinct subtype of pituitary adenomas that represent approximately 20% of all corticotroph adenomas and approximately 5% [3] (3–19% depending on series) of non-functioning adenomas [4]. SCAs are defined as tumors with no biochemical hypercortisolism, no clinical evidence of Cushing's disease (CD), and evidence of tumor immunoreactivity for adrenocorticotropic hormone (ACTH). Since there is no evidence of hypersecretion syndrome, SCAs tend to present as larger tumors with mass effects, such as headache and visual symptoms [4]. They constitute a diagnostic challenge as most are diagnosed post-resection and confirmation of preoperative clinical ACTH hypersecretion status cannot always be ascertained.

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Published literature on clinical characteristics and outcome of SCAs is variable and cases include a range of different tumors, with variable clinical presentations and pathologic characteristics. Some studies, but not all, have demonstrated that SCAs have a more aggressive course with higher risk of recurrence than other non-functioning tumors [5–9].

Rigorous retrospective review of our center's pre-operative evaluation and diagnosis, characteristics and outcome of SCAs, determination of predictors of recurrences, comparison to a series of silent gonadotroph adenomas (SGAs) resected at our center, and comparison to previously published SCAs, is presented.

Patients and methods

A retrospective, Institutional Review Board approved analysis of patients who underwent resection of a pituitary adenoma at Oregon Health & Science University (OHSU) over 10 years (June 2006 to June 2016) was undertaken. Patients had been clinically assessed using a unified protocol.

Clinical characteristics and definitions

Charts were retrospectively reviewed by one neuroendocrinologist and if there was ambiguous diagnostic information, a second opinion from another neuroendocrinologist was obtained. Hormonal evaluation and clinical assessment were obtained at baseline preoperatively, repeated at 1–3 months postoperatively, and regularly at scheduled interval based on a unified protocol by a single neuroendocrinologist. Central adrenal insufficiency (AI) diagnosis was based on clinical evaluation, baseline morning cortisol, ACTH levels and/or abnormal response to 1 μg ACTH stimulation test (30 min stimulated cortisol < 16–18 μg/dL). Central hypothyroidism was defined as low free thyroxine and low or normal thyroid stimulating hormone (TSH). Central hypogonadism was defined in men as low testosterone and low or normal follicle stimulating hormone (FSH) and luteinizing hormone (LH), in premenopausal women as oligo- or amenorrhea, low estradiol, and low or normal FSH and LH, and in post-menopausal women as lower LH and FSH than the reference range for post-menopausal status. Growth hormone (GH) deficiency was based on low insulin-like growth factor 1 (IGF-1) in patients with multiple pituitary deficiencies. GH stimulation tests were not routinely performed unless there was clinical indication. Hyperprolactinemia was defined as prolactin elevation above the normal range for sex. Hypopituitarism was defined as presence of two or more deficiencies in adenohypophyseal hormones. Biochemical work-up for CD for patients with elevated ACTH preoperatively and all patients (in the absence of AI) postoperatively included either one or combination of tests; urine free cortisol (UFC), salivary cortisol, overnight dexamethasone (DEX) suppression test and DEX/corticotropin-releasing hormone (CRH) as a confirmatory testing in selected cases. Radiological invasion was defined as either cavernous and/or sphenoid sinus invasion. Postoperative evaluation also included magnetic resonance imaging (MRI) at 3 months post-surgery, and gross surgical cure was defined as no residual tumor on MRI. Recurrence was defined as progression of a residual tumor or new tumor growth after total resection.

Pathology was confirmed by one of three dedicated pituitary neuropathologists. We based tumor classification on immunochemistry. Adenoma immunohistochemical staining was performed using an automated immunohistochemical system (Benchmark XT, Ventana Medical Systems Inc., Tuscon, AZ, USA) with the following antibodies: ACTH, GH, PRL, Ki-67 (Ventana), SF-1 (ThermoFisher Scientific), cytokeratin CAM 5.2 (Beckton, Dickinson and Company, Franklin Lakes, NJ, USA) and SSTR2A (Gramsch Laboratories, Germany). ACTH, GH, PRL, SF-1 (from years 2011–2016), cytokeratin (CAM5.2), Ki-67 and p53 staining were routinely assessed; TSH and somatostatin receptor 2A (SSTR2A) were selectively stained as needed. Electron microscopy (EM) was available for selected cases.

Silent corticotroph adenomas

Patients were classified as having a SCA as follows; patient exhibited less than two signs or symptoms compatible with hypercortisolism, and most importantly, no biochemical hypercortisolism preoperatively. In patients found to have normal or elevated baseline ACTH levels, biochemical evaluation was pursued to exclude CD. Plurihormonal tumors were excluded. Cystic tumors were defined based on imaging as tumors with > 50% fluid content based on MRI T2 signal.

Silent gonadotroph adenomas

A group of patients with SGAs, resected at our center over 6 years (2011 to 2016; steroidogenic factor (SF-1) immunostaining was available only from 2011) by two dedicated pituitary neurosurgeons, was reviewed for comparisons with SCAs.

Literature review

A systematic literature search was undertaken using Pubmed and Scopus; using the following terms [silent/non-functioning, ACTH/corticotroph/Cushing's, adenomas/tumors] for articles published from 1970 to 2016. Cited references within articles were also searched for relevancy to the topic.

Clinical characteristics and outcome data of published cases were compared to our SCAs cohort.

Statistical analysis

A 2-tailed Student *t* test was used to perform parametric comparison between two variables with equal variances. Mann–Whitney rank sum test analyzed nonparametric comparisons for ACTH levels and Chi square test was used to compare categorical variables such as sex, cystic and invasiveness. A regression analysis was performed to define the relationship between variables for SCAs and SGAs. To analyze literature data, we used weighted average for continuous variables and percentage of occurrence of ordinal variables. Statistics were calculated using PASW 18 (IBM, Corp. Armonk, NY). P values were considered significant at <0.05.

Results

Retrospective review revealed 814 pituitary surgeries in the 10-year time period specified, 39 of which were SCAs; prevalence was 4.8%. Mean age at diagnosis was 50 ± 14 years with no gender predominance (54% female). Additional patient characteristics are presented in Table 1 alongside previously published data [1, 2, 5–65].

In our patient cohort, the majority presented with headaches (59%) and/or visual symptoms (49%). Pre-operative MRI demonstrated that 90% (35/39) were macroadenomas with a mean tumor size of 2.5 cm. Sphenoid and/or cavernous sinus invasion was described in 44% and a third were mostly cystic (>50% fluid content). Biochemical evaluation revealed that even though patients did not have biochemical evidence of hypercortisolism, 28% had elevated baseline ACTH. A quarter of the cohort also had mild hyperprolactinemia and 22% had hypopituitarism. The most frequent deficits were IGF-1 and gonadotrophins, as expected with macroadenomas. Baseline AI was present in only two patients and post-operatively, 23% developed new AI.

All tumors had low Ki-67 (<3%) and one tumor expressed p53 (with no recurrence). Only one patient had a transformation in tumor with high proliferation index of 6% and p53 positivity at its last recurrence (5th surgery). ACTH staining was strong in 6 tumors and weak in 17 tumors; for the others (16/39), ACTH immunostaining was reported as present.

SCA patients were followed for a mean of 6.4 ± 5.9 years. Only 42% of patients achieved gross surgical cure. 14 of 39 patients (36%) recurred at a mean of 44 ± 37 months (range 3–132 months) and 18% had multiples recurrences. Most recurrences (11/14) were treated surgically; six patients underwent a second intervention, three patients had three resections, one patient four surgeries and one patient underwent five surgical resections (over 16 years, the three last interventions were conducted at our center). Seven patients (18%) received adjuvant radiotherapy, and 2 (5%) patients received temozolomide-based chemotherapy; of those, one patient had an impressive reduction in tumoral mass with a 60% reduction in the first 3 months leading to visual

Table 1 Baseline characteristics and outcome

	OHSU (n = 39)	Literature (n = 736)[a]	P value
% SCA from total pituitary surgeries	4.8	6.8	0.6
Sex-female (%)	54	52	0.8
Age (years)	50.0 ± 14.2	46.3 ± 12.9	0.2
Tumor size (cm)	2.5 ± 1.2	2.5 ± 1.1	0.8
Cavernous/sphenoid sinus invasion (%)	44	49	0.5
>50% cystic (%)	33	N/a	–
Elevated ACTH (%)	28	39	0.06
Baseline hyperprolactinemia (%)	26	33	0.03
Pre-operative hypopituitarism (%)	22	25	0.7
Acquired post-operative adrenal insufficiency (%)	23	29	0.4
Headaches (%)	59	38	0.005
Visual symptoms (%)	49	55	0.001
Apoplexy (%)	2.6	12.5	0.006
Galactorrhea and/or amenorrhea (%)	5	21	0.001
Gross surgical cure (%)	42	50	0.007
Recurrence (%)	36	31	<0.001
Radiation (%)	18	27	0.002
Change in phenotype (%)	5.1	10.8	<0.001

[a]Total n value is 736; n may be smaller depending on the variable studied

improvement; the other patient died from another primary cancer in the following year. No patient died because of tumor progression, nor experienced transformation to a corticotroph carcinoma. During the follow-up period, one patient switched phenotype from a silent adenoma to CD 5 months after a first surgery and one patient had a previously secreting tumor that became silent on a fourth recurrence (9 years post-diagnosis) before receiving radiation therapy. Both patients also had recurrent tumors.

Compared to SGAs, SCAs had similar tumor size (2.5 vs. 2.9 cm; not significant) and invasiveness (44 vs. 41%; not significant) but a threefold higher recurrence rate (36 vs. 10%, p = 0.001). Radiation therapy was performed in 18% of SCAs versus 3% of SGAs (p = 0.006, Table 2).

When comparing recurrent SCAs versus non-recurrent SCAs, an association between recurrence and tumor size (3.2 vs. 2.1 cm, p = 0.019), and cavernous and/or sphenoid sinus invasion (79 vs. 25%, p = 0.001) was found (Table 3). Of note, on regression analysis, patients with cavernous sinus invasion were three times more likely to have recurrence (p = 0.006).

None of the patients with recurrent SCAs had cystic tumors (0 vs. 50%, p < 0.001), however, higher baseline ACTH levels were significantly associated with recurrence (54 vs. 28 pg/ml, p = 0.04). Although in our sample more recurrence occurred in males, this was not statistically significant, within our small recurrence sample (62 vs. 33%, p = 0.09). Likewise, there was no relationship with recurrence and age at diagnosis. Post-surgical AI onset was not found in patients with tumor recurrence compared to 35% of those with non-recurrent tumors (p < 0.001, Table 3).

Table 2 Clinical characteristics of SCAs compared to SGAs at OHSU

	SCA (n = 39)	SGA (n = 70)	*P* value
Sex-female (%)	54	38	0.1
Age (years)	50.0 ± 14.2	60.0 ± 15.1	0.001
Tumor size (cm)	2.5 ± 1.2	2.9 ± 2.0	0.2
Radiological invasion (%)	44	41	0.8
Recurrence (%)	36	10	0.001
Time to recurrence (months)	44 ± 37	61 ± 85	0.6
Number of surgeries (n)	1.5 ± 0.9	1.1 ± 0.4	0.006
Radiation (%)	18	3	0.006
Follow up (years)	6.4 ± 5.9	2.7 ± 2.8	0.001

Discussion

In this retrospective single institution cohort review with a uniform definition of silent tumors and long follow-up period, we confirmed that SCAs are aggressive tumors with a recurrence rate of 36% over 6 years. In studies with smaller number of patients and/or shorter follow up periods, recurrence rates are reportedly 25 to 42% [6–9, 34]. The review is unique in that new insights regarding predictors of recurrence are noted and discussed. Higher baseline ACTH levels and less cystic tumors are novel characteristics to make note of and may play an important role in patient management as they may indicate a worse prognosis in terms of recurrence. As noted, no cystic tumors were found to have recurred during follow-up. Interestingly, proliferation indices were not predictors of recurrence, as almost all tumors expressed low Ki67, concordant with previously published series data [5, 9]. Age was not identified as a predictor of recurrence, however mean age in the cohort (50.0 ± 14.2 years) was similar to the published literature, but older than the series by Cho et al., that showed that young patients (< 30 years of age) with SCA were most likely to recur [7]. Compared to SGAs treated in the same institution, SCAs were three times more likely to recur and had a sixfold increase in need for radiation therapy. Different follow-up periods could have influenced the observed outcome comparing SCAs to SGAs, however, clinically relevant differences and a shorter time interval to recurrence for SCAs versus SGAs were observed.

SCAs in this single institution cohort were slightly less prevalent than that reported in the literature (4.8 vs. 6.8%,

Table 3 SCA recurrent vs non-recurrent tumors characteristics

	Recurrent (n = 14)	Non-recurrent (n = 25)	*P* value
Sex-female (%)	33	62	0.09
Age (years)	49.7 ± 16.1	50.1 ± 10.7	0.96
Tumor size (cm)	3.2 ± 1.2	2.1 ± 1.0	0.019
Radiological invasion (%)	79	25	0.008
> 50% cystic (%)	0	50	< 0.001
Pre-operative ACTH (pg/ml)	54 ± 46; (n = 11)	28 ± 17; (n = 18)	0.04
Gross surgical cure (%)	14	58	0.004
New post-operative AI (%)	0	34.8	< 0.001
SCA subtype 1, strong ACTH staining (%)	38; (n = 8)	20; (n = 15)	0.04

respectively) but with a similar epidemiological profile (Table 1). The clinical presentations observed were mostly symptoms of mass effect (headaches and visual symptoms) and rarely oligomenorrhea/galactorrhea. Tumor size was large as previously published [4], however with the inherent bias of a surgical-based cohort where microadenomas are usually poorly represented. Only one patient presented with apoplexy, which is much less than that reported in previously published series (2.6 vs. 12.5% p = 0.006) [11]. We hypothesize that this difference could be due either to selection or reporting bias since most published cases were diagnosed during a symptomatic event such as acute apoplexy. The review we present included post-operative tumors in the contemporary setting of high definition imaging and increased detection, so a higher number were diagnosed during investigation of headaches or in completely asymptomatic patients. Moreover, fewer had elevated baseline ACTH levels compared to published cases and case-series, but clinical presentation of SCA in the literature review may be tainted by cases of subclinical CD.

In the cohort described, all patients defined as having a SCA had undergone a complete biochemical evaluation and CD had been ruled out prior to surgery. Since a SCA diagnosis is established post-operatively, it is possible that for some published cases mild early CD may have been present pre-operatively if a full biochemical work up was not completed. There also may be an overlap between silent ACTH and cyclical CD and some SCAs may be a form of CD with very low cyclicity or represent the controversial subcategory of cyclic and subclinical CD [66]. The longest intercyclic interval reported was 4.5 years [67]. Notably, we place emphasis on the clinical importance of measuring pre-operatively ACTH levels and on pursuing investigation of subclinical CD as needed. Diagnostic clarification is important as additional baseline investigations can help determine if the tumor secretes bioactive ACTH, thus modifying perioperative management and anticipating AI postoperatively. A more stringent sequential imaging and hormonal testing plan can also be made.

Notably, in our cohort of SCA patients, a wide spectrum of presentations was seen, from totally silent tumors with low secreting ability, to ACTH elevation without hypercortisolism, to very aggressive tumors requiring multimodal therapies. We hypothesize that SCAs, usually classified based on pathology as subtype 1 (strong ACTH immunostaining) and subtype 2 (weak ACTH immunostaining) are derived from two different populations.

On the one hand, preoperative ACTH levels indicate that one-quarter of SCAs secrete biologically inactive ACTH, and higher circulating ACTH levels could be a marker of a more aggressive subset of SCA. These tumors could represent poorly differentiated tumors arising from the Prop-1 lineage with less secretory ability, but with the potential for phenotypic change and recurrence over time. They may relate to SCA subtype 1 with strong ACTH immunopositivity, and previously reported to be more aggressive by Jahangiri et al. [34]. In our cohort, strong ACTH immunostaining was observed as twofold more prevalent in the recurrent compared to the non-recurrent group. Temozolomide might be an additional therapeutic option in very aggressive SCAs [68].

On the other hand, publications by Horvath and colleagues, suggest that SCA arise from the pars intermedia, as corticotrophs of the pars intermedia have low ACTH secretion activity [69], and Kasuki et al. showed that a high proportion of SCAs have a microcystic aspect [18, 70]. In our cohort, weak ACTH immunostaining was present in 12/15 (80%) of the non-recurrent group. In line with the results we present, some SCAs may originate from the pars intermedia cells, as one-third were predominantly cystic and none of these tumors recurred. This subgroup could account for more indolent tumors that may have the pathologic appearance of subtype 2 and weakly express ACTH immunopositivity (Fig. 1). In our cohort, as well as in a large German registry [3], SCA subtype 2 were 2–4 times more prevalent than their densely-granulated (subtype 1, more aggressive) counterpart.

Here we also show that SCAs have the potential to change phenotype over time, which is in agreement with previous publications [9, 13, 17, 27, 59, 60, 68], and as such requires further study. Many pathogenic processes have been identified and help explain SCA phenotype. First, low or absent biologic activity of ACTH can result from alteration in hormone processing, and more specifically from a deficit in prohormone convertase 1/3 (PC1/3) [34, 42, 45, 53]. Even in CD, larger tumors have been shown to less efficiently process proopiomelanocortin (POMC) to ACTH compared to microadenomas [28]. Righi et al. recently demonstrated that PC1/3 activity was acquired in tumors of patients changing from silent to active CD over time [47]. Another hypothesis is the secretion of fragments of ACTH-POMC, or high molecular weight ACTH, by the tumor, resulting in cross reactivity with the ACTH immunoassay [46, 58]. Fluctuation from silent to clinical disease has also been demonstrated in somatotroph adenomas resulting in silent to clinical acromegaly [71]. Changing phenotype has also been related to radiotherapy in some cases [40], this could be via direct radiation-induced changes in the tumor, or could also be an indirect relationship associated with more aggressive tumors. In our cohort, the change in phenotype cannot be attributed to radiotherapy, since the two patients who experienced a change in phenotype did not receive previous radiation therapy.

Role of tissue specific transcription factors, more specifically T-pit, has also been implicated in phenotypic silence. T-pit plays an important role in pathways of cellular

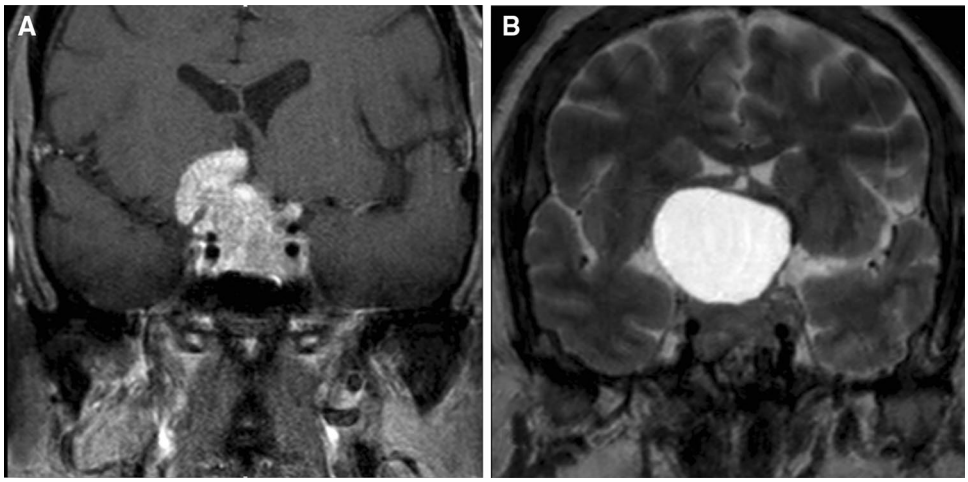

Fig. 1 Representative magnetic resonance imaging (MRI) SCAs cases. **a** MRI T1 gadolinium positive, recurrent SCA case in a 58 year-old male with a solid tumor, pre-operative ACTH 168 pg/ml, strong tumoral ACTH immunoreactivity and poorly differentiated corticotroph cells. **b** MRI T2, non-recurrent SCA case in a 46 year-old female with a cystic tumor, pre-operative ACTH 6 pg/ml, weak tumoral ACTH immunoreactivity, and pars intermedia-derived corticotroph cells

differentiation, directing cells towards corticotroph differentiation, and T-pit dysfunction could be an early abnormality leading to development of a SCA. However, T-pit testing yielded variable and inconclusive results in SCAs [72].

Some authors have hypothesized that silent ACTH tumors overlap with gonadotrophs, since they harbor SF-1 positivity, honeycomb golgi and increased mitochondrial density [22]. Others conclude that honeycomb golgi might be a non-specific marker of non-functionality [59, 73]. In our cohort, we have not been able to study SF-1 extensively (only routinely available from 2011), but SF-1 was absent in a third (0/13) of the SCA cohort tested, arguing against a common tumor origin.

Expression of genes implicated in tumorigenesis seems increased in silent ACTH tumors compared to their non-functional counterparts. Galectin-3 gene is mutated in a series of SCAs and its protein, functioning as an oncogene, promotes tumorigenesis and is associated with tumor aggressiveness (e.g. increased expression in carcinomas) [74, 75]. Other proteins implicated in extra-cellular matrix interaction have been associated with SCAs versus non-functioning pituitary adenomas; higher expression of beta 1 integrin and osteopontin (as determined by immunostaining), which promote cell motility and migration and high fibroblast growth factor receptor-4/matrix metallopeptidase 1 (FGFR4/MMP-1) profile has been related to more tumoral invasiveness [76]. With the advent of directed enzyme prodrug therapy, specific protein targeting could be a potential future therapeutic option.

Limitations of this study include the retrospective design in a tertiary center study with inherent referral bias. Specific tumor subtyping was not reported by neuropathologists until 2011. Transcription factors or mRNA measurements were not available as routine clinical studies, but ACTH staining was determined by dedicated neuropathologists. Study strengths are a unified clinical and biochemical evaluation for both hypopituitarism and CD by one dedicated neuroendocrinologist, routine follow-up protocol for all patients and MRI readings by dedicated neuroradiologists.

Conclusion

We show for the first time that patients with recurrent SCAs had less cystic tumors and higher pre-operative ACTH levels than those with non-recurrent SCA tumors. Furthermore, though SCAs are overall rare pituitary adenomas, they have potentially aggressive behavior and can switch phenotype over time, mandating accurate initial diagnosis, close imaging and biochemical follow up. Further large multicenter research studies are needed to elucidate the epidemiology and biology of SCAs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent The study was approved under an IRB approved data repository with waiver of consent.

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