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CASE REPORT

Swyer Syndrome Presenting as Dysgerminoma: A Case Report

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Abstract

Complete gonadal dysgenesis with 46,XY karyotype is a clinical condition characterized by the absence of testicular tissue but with the presence of typical Müllerian structures in a phenotypically female individual. The condition presents as primary amenorrhoea or delayed puberty. Eventually, malignant neoplasms may arise. We report a case of a 16-year-old Indian male with Swyer syndrome presenting with primary amenorrhoea and with an earlier diagnosis of a malignant dysgerminoma in the right ovary.

Key words: Swyer syndrome, dysgerminoma, amenorrhoea, gonadal dysgenesis

INTRODUCTION

Complete or pure gonadal dysgenesis (CGD) was first described by Dr. Gim Swyer in 1955, when he reported two women with tall stature, primary amenorrhoea, normal external genitalia, vagina and cervix, but with a karyotype of 46,XY.[1] The incidence of this eponymous condition is about one in 80,000. The process of testicular development, usually occurring in the second month of gestation, is regulated by several genes, the most crucial being SRY.[2] Inactivating mutations or deletion of SRY in the DNA-binding regions are present in approximately 15% of patients with Swyer syndrome.[3] Alterations in other genes, namely DAX1, WNT4, SOX9, SF1, and WT1, may also cause inhibition or mutation of SRY function,[4] resulting in streak gonads that do not secrete sex steroids or Anti-Müllerian Hormone (AMH). Hence, both the internal and external genitalia of such patients are phenotypically female. Patients with CGD and a 46,XY genotype are also at increased risk of developing gonadal tumours, namely, gonadoblastoma and dysgerminoma,[5] with an incidence of 20-30% and prophylactic gonadectomy is recommended.[6]

Dysgerminoma is the most common malignant germ cell tumour of the ovary. It can be found either in a pure form or mixed with other germinal elements.[5] The incidence of dysgerminoma is greater in younger women.[4] About 65% of dysgerminomas are at stage one at diagnosis; 85-90% of stage one tumours are unilateral, and 10-15% are bilateral.[5] Approximately five percent of dysgerminomas are found in phenotypic females with XY karyotype. Imaging of dysgerminoma shows multilobulated solid masses with well-defined fibrovascular septa and speckled calcifications.[7] On gross examination, they appear as firm, lobulated masses, while microscopically, they are composed of undifferentiated vesicular germ cells with clear cytoplasm and centrally placed regular nuclei. The morphology resembles that of a fried egg.[4]

We report a case of a 12-year-old phenotypical female presenting with dysgerminoma of the right ovary whose Swyer syndrome was recognized four years later.

CASE

A 12–year-old Indian female was referred to a local hospital due to a one month history of a gradually increasing, painless, right-sided abdominal swelling. There was no ulceration, fever, loss of body weight or impairment of function. On physical examination, her external genitalia were unambiguously female without any clitoromegaly and Tanner staging was prepubertal. Ultrasound of the abdomen revealed a large midline space-occupying lesion measuring 13 cm x 12 cm in the umbilical region, separate from the urinary bladder, having a heterogeneous echotexture and scattered echogenic specks (Figure 1). The contrast-enhanced computed tomography (CECT) scan of the abdomen was unremarkable. The laboratory results obtained are summarized in Table 1.

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Table 1. Baseline blood parameters

Laboratory parameters	Obtained value	Reference value/range
Haemoglobin (g/L)	105	116-150
Urea (mmol/L)	6.4	2.1-8.5
Creatinine (µmol/L)	57.47	53-97.2
Total Serum Bilirubin (µmol/L)	9.75	1.71-20.5
Serum Alkaline Phosphatase (U/L)	191	44-147
Alpha fetoprotein (µg/L)	1.41	10-20
Beta-hcG (IU/L)	4.30	<5
Carcinoembryonic antigen (µg/L)	1.90	0-2.5
CA-125 (kU/L)	67.2	<46
Lactate dehydrogenase (µkat/L)	10.27	2.33-4.67

Laparotomy was performed due to suspicion of malignancy. Intraoperative findings showed evidence of a tumour (15 cm x 12 cm x 10 cm) weighing 500 grams, arising from the right ovary and twisted from the right cornu. The left ovary was found to be very small for age. A gross histopathological examination of the resected specimen confirmed a right ovarian tumour, 14 cm in diameter. The tumour was solid with greyish-brown haemorrhagic, with infarcted areas (probably due to torsion), but with an intact capsule. On microscopy, the more significant part of the tumour was infarcted and showed ghost outlines of sheets, nests, cords and trabeculae of round or oval tumour cells. At the

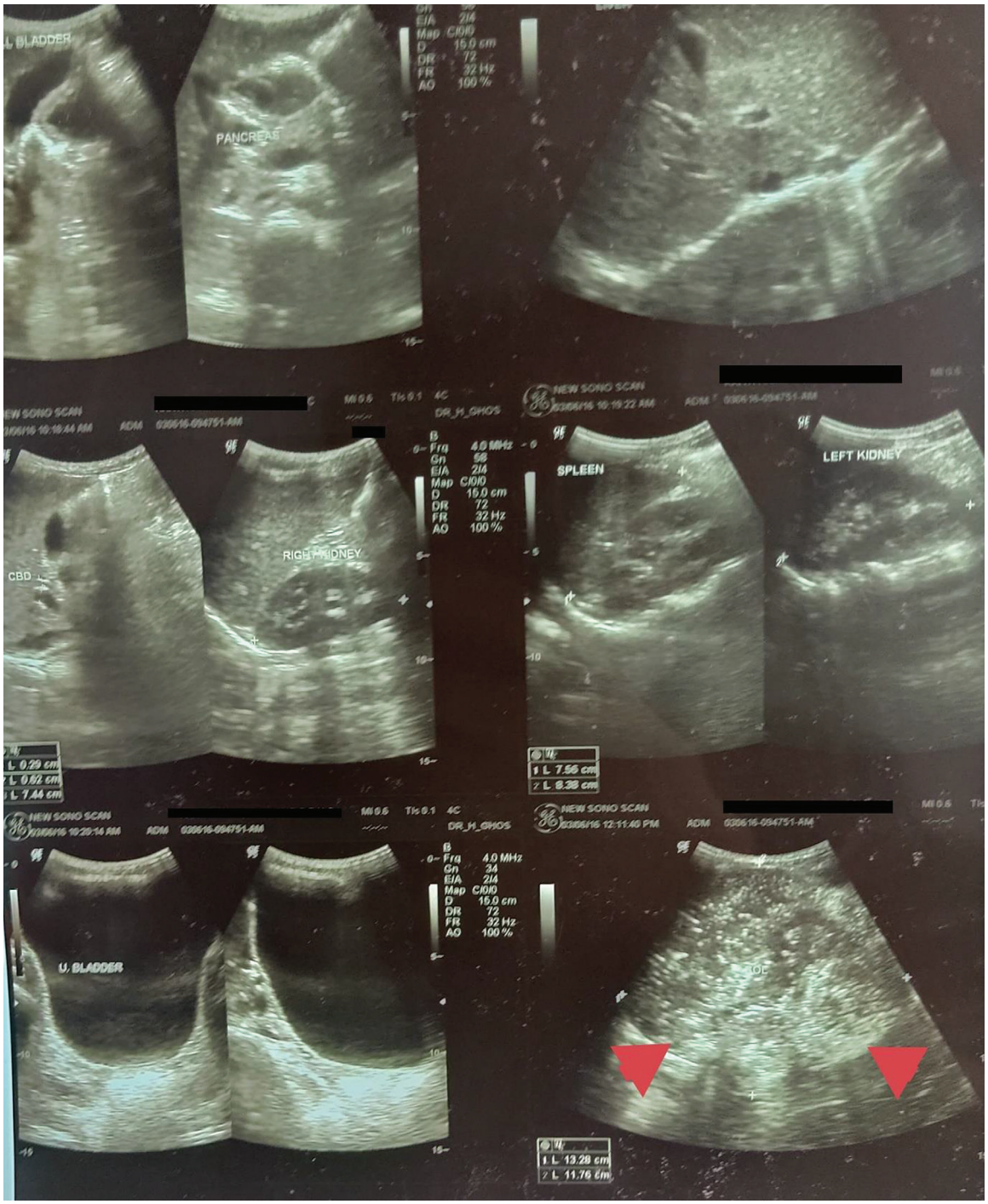

Figure 1. Ultrasound scan of abdomen of the 12-year-old patient. The red arrowheads indicate an area of increased echogenicity suggestive of a space-occupying lesion. The other organs appear normal.

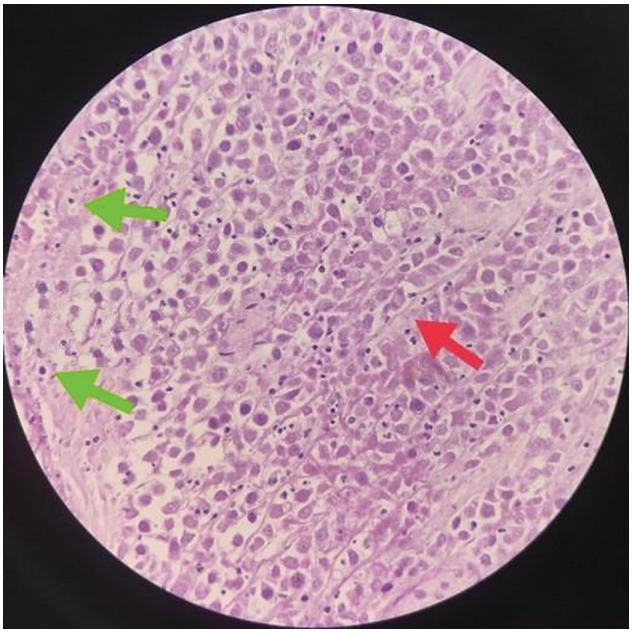

Figure 2. H&E stain of the resected specimen of the right ovary *(40x)*. The periphery is occupied by viable cells with distinct features *(green arrows)*. The central infarcted part of the specimen demonstrates ghost outlines of cells arranged in sheets and cords.

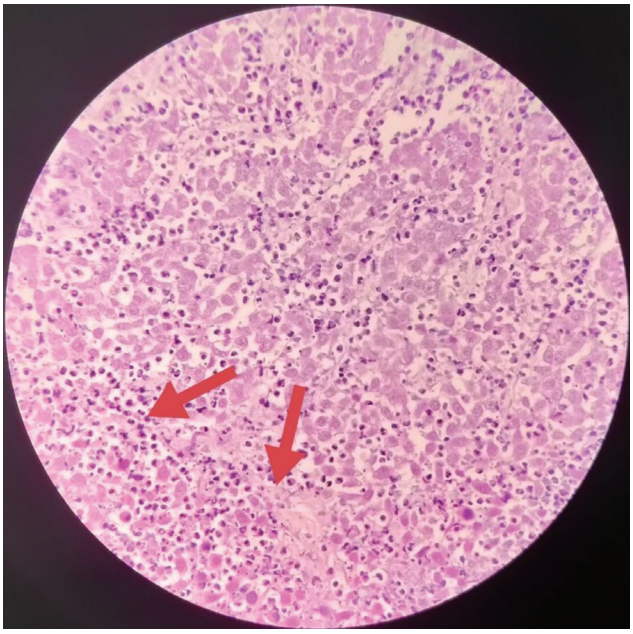

Figure 3. H&E stain of the resected specimen of the right ovary *(100x)*. The pale pink fibrous stroma is densely infiltrated with hyperchromatic inflammatory cells *(red arrows)*.

periphery, the viable tumour cells had round to oval vesicular nuclei, prominent nucleoli and amphophilic cytoplasm (Figure 2). The nests of the tumour were surrounded by a delicate fibrous stroma infiltrated by inflammatory cells (Figure 3). Extensive areas of haemorrhage and foci of calcification were seen. Lymphovascular and capsular invasions were found; however, metastatic deposits were absent. Immunohistochemistry was positive for Oct4 and CD117 focally and negative for CK and CD30. As a part of her treatment protocol, she received four cycles of intravenous bleomycin, etoposide and cisplatin (BEP) chemotherapy. The recovery was uneventful until the age of 16, when she was referred to our endocrinology department for evaluation of delayed puberty. On examination, her height was 1.61 m (75th percentile) and her arm span was 1.7 m. The findings of Tanner staging and examination of external genitalia were identical to previous records. The results of biochemical investigations are summarized in Table 2.

The whole abdominal ultrasound scan (USG) showed a left ovary (2 cm x 0.7 cm) with few tiny follicles, a uterine volume of 7.8 cc, and a non-visualized right ovary.

Table 2. Laboratory parameters after chemotherapy

Laboratory parameters	Obtained value	Reference value/range
Follicle-stimulating hormone (FSH) (IU/L)	89.4	2.5-10.4 (follicular)
Luteinising Hormone (LH) (IU/L)	56.7	1.9-12.5 (follicular)
Prolactin (µg/L)	6.3	1.9-25
Estradiol (pmol/L)	40.09	73-367 (follicular)
Inhibin B (pg/ml)	7.17	15-300
AMH (pg/ml)	2.18	0.9-9.5

Magnetic resonance imaging (MRI) scan of the abdomen and pelvis revealed a small, hypoplastic uterus (Figure 4). The right adnexal region showed no more lesions, and the left ovary was almost normal. However, cytogenetic studies revealed a 46,XY karyotype. No other gene sequencing studies were performed due to funding limitations. When the result was conveyed, the patient and her mother expressed wishes for a hysterectomy and total abdominal hysterectomy with left-sided salpingo-oophorectomy was performed. Histopathological examination of the resected left-sided adnexa revealed a streak gonad (Figure 5) with no evidence of malignancy.

The patient was initiated on 2 mg once daily oral estradiol valerate, to be continued till the age of menopause, along with calcium and vitamin D supplementation to help improve bone mineral density. Despite having a safer side-effect profile, transdermal estradiol could not be offered due to cost and availability constraints. There was no further indication for progesterone after the surgery. A bone mineral density testing was scheduled only after attainment of Tanner Stage 5 of pubertal development.

The mother and the patient were counseled about the condition's future social and psychological implications. The child identified more as a female; hence, her mother was advised to support the perspective through mental and emotional support. It was explained that regular sexual intercourse was possible; however, our patient would not be able to conceive. Potential options like pregnancy by donor egg could be explored. However, the success rate might be less owing to the inherent lack of estrogen and the presence of an infantile uterus.

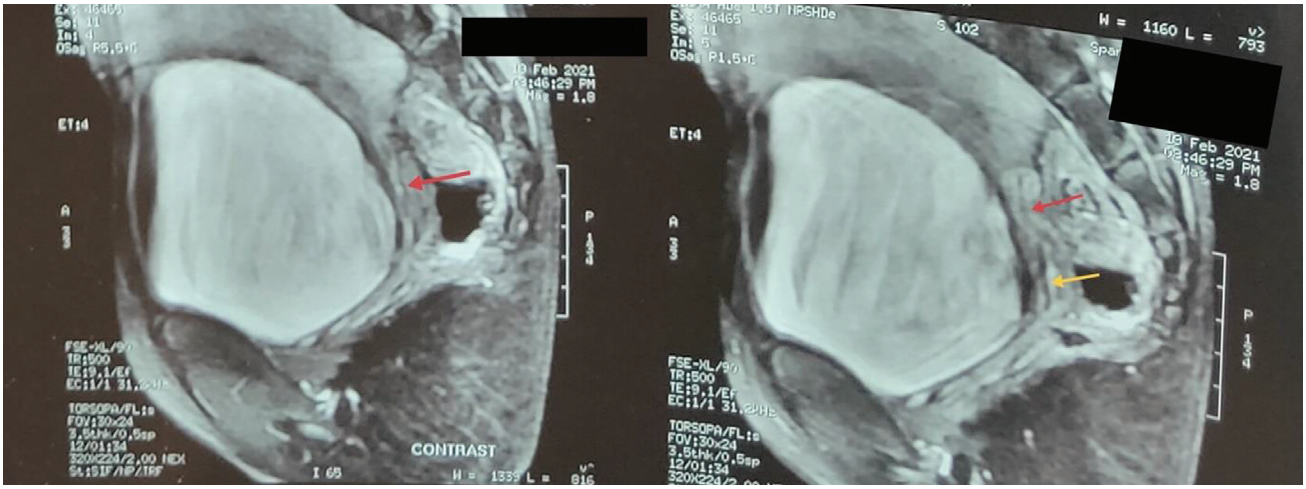

Figure 4. Sagittal cuts of MRI scan of the pelvis of the patient at the age of 16 years. The body of the uterus posterior to the bladder is hypoplastic with a slit-like uterine cavity *(red arrow)*. The length of the vagina is normal *(yellow arrow)*.

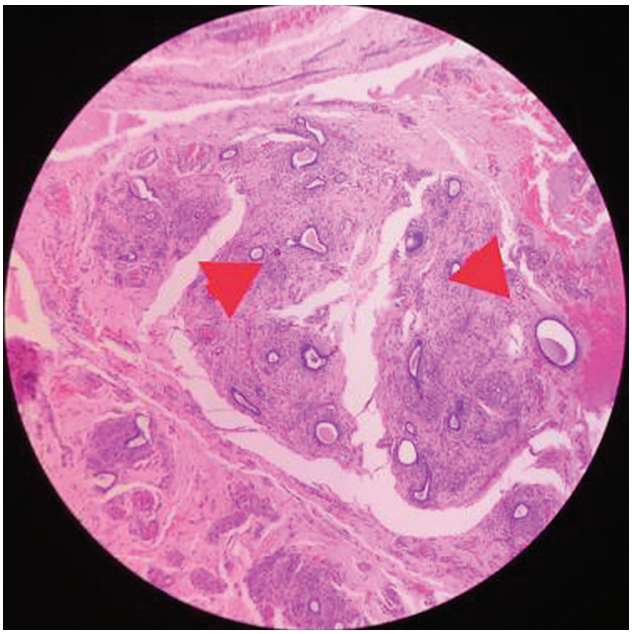

Figure 5. H&E stain of the left ovary *(100x)* obtained after total abdominal hysterectomy with left-sided salpingo-oophorectomy. Dense inflammatory infiltrates and atretic ovarian follicles containing colloid-like secretions dominate the field *(red arrowheads)*. Normal ovarian structures are replaced by a pale, fibrous stroma and narrow trabeculae. Dysplastic and anaplastic changes suggestive of malignancy are absent.

Follow-up was done six months after initiation of estradiol therapy. There were no significant complaints. On clinical examination, there has been a progression of pubertal features from Tanner stage B1 to B2.

DISCUSSION

Complete gonadal dysgenesis, a condition also called Swyer syndrome, is associated with a complete lack of androgenisation of the external genitalia and persistence of Müllerian structures,[3] owing to the lack of testosterone and AMH, the two testicular hormones involved in fetal sex differentiation. The gonads are usually hypoplastic without germ cells. The diagnosis is usually not suspected until puberty, when the patients complain of the absence of thelarche and menarche.

Our patient, a 12-year-old with phenotypically female external genitalia, presented with an enlarging abdomen, similar to the presentations observed by Caponetti et al.,[8] and Jonson et al.[9] The median age of diagnosis of Swyer syndrome is usually around 17 years.[10] In this patient, there were no features of virilisation (clitoromegaly, deepening of voice), as in the cases reported by Alam et al.,[11] Moreira et al.,[12] and Trovilion et al.[13] No other symptoms or signs such as confusion, pain, fever, were present in our patient, which contradicts the findings of Russo et al.,[14] where a 14-year old girl presented with lumbar pain and polyuria. Although rare, familial cases of Swyer syndrome have been reported previously.[15] Our patient, however, had no family history of consanguinity or other co-morbid conditions, as found in some other reports,[16,17] The patient's Tanner stage of was prepubertal which is typical of this syndrome.[6,18] However, spontaneous breast development and menstruation have also been reported as exceptions.[6,19,20]

Preoperatively, CA-125 was increased in our patient while the other tumour markers were normal, namely, b-hcG,[21] LDH[5] and AFP.[22] Although the excised ovarian tumour was unilateral and did not show any evidence of local spread or metastases, several cases of disseminated malignancy have been reported previously.[23,24]

Histopathological examination of the resected specimen revealed a dysgerminoma restricted to the right ovary, positive for Oct4 and CD117. In contrast to the finding reported by Anwar et al.,[25] it had not invaded the fallopian tube and did not show any other germ cell elements.[8] Despite placental alkaline phosphatase being a relatively specific marker for dysgerminoma as documented in several reports,[1] only serum total alkaline phosphatase

was performed in our patient, which was above the reference range.

Hypergonadotropic hypogonadism and hypoplastic female internal genitalia without testicular remnants have been unanimously reported in almost all cases of Swyer syndrome. Some reports have, quite peculiarly, demonstrated testicular remnants[26] and genotypic mosaicism in some patients suffering from the condition.[21] Our patient's clinical and biochemical status post-treatment has been unremarkable, and she is continuing her hormonal therapy. There have been some instances where there have been adverse outcomes in the form of persistently elevated tumour markers,[13] non-response to therapy,[27] emergence of a new pathology[26] and death.[15]

Differentiation of gonads occurs after the sixth week of gestation. They form testicular tissue under the influence of SRY, SF1, WT1 and SOX9 genes. However, in our patient the effects of the Y chromosome were probably overshadowed by genetic mutations, resulting in dysgenesis of the gonads in the undifferentiated stage to form ovarian structures. Masculine characteristics failed to develop, leading to the child being raised as female and the initial pelvic mass being suspected to be primarily an ovarian tumor.

The differential diagnoses of Swyer syndrome include complete androgen insensitivity syndrome and Mayer-Rokitansky-Kusterhauser syndrome. Complete androgen insensitivity was excluded as our patient had AMH levels towards the lower limit of normal, contrary to being well within the reference range.[4] Patients with androgen insensitivity syndrome have a female phenotype and normal breast development but with morphologically normal testes (which may be undescended) and no Müllerian structures. The absence of the uterus is also recently being considered as a criterion for diagnosing this condition.[28] Mayer-Rokitansky-Kusterhauser syndrome, another cause of primary amenorrhoea, affects 1 in every 5000 live females. The significant features of this syndrome are varying degrees of Müllerian duct and vaginal aplasia, along with a rudimentary uterus. However, their sexual characteristics and genotype are similar to that of a female.

Our patient manifested Swyer syndrome initially at the age of 12 years, which was not recognized till four years later. Thus, it emerged as a case of delayed diagnosis at late puberty, similar to previous reports where an opportunity for intervening at an earlier stage was overlooked. Hence, this adds to the existing cases warranting improvement in management strategies for the syndrome. It highlights the need to consider gonadal dysgenesis as a differential diagnosis in adolescent phenotypical females without thelarche, menarche, and adnexal masses.

CONCLUSION

Patients with complaints of delayed puberty and investigations revealing ovarian germ cell tumours should be promptly evaluated to rule out gonadal dysgenesis. Karyotyping should be mandatory even in other apparent causes of hypergonadotropic hypogonadism like chemotherapy.

Ethical Consideration
Patient consent was obtained before submission of the manuscript.

Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
SST: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **SC:** Methodology, Software, Investigation, Resources, Data Curation, Writing – original draft preparation, Visualization, Project administration; **ND:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **DH:** Conceptualization, Validation, Formal analysis, Investigation, Writing – review and editing, Supervision; **AB:** Conceptualization, Validation, Formal analysis, Writing – review and editing, Supervision; **PC:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **NS:** Conceptualization, Validation, Formal analysis, Writing – review and editing, Supervision,; **SG:** Conceptualization, Validation, Writing – review and editing, Supervision.

Author Disclosure
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