ACCSCIENCE PUBLISHING

Tumor Discovery

SHORT COMMUNICATION

Mucosal Schwann cell hamartoma of the gastrointestinal tract: A benign and little-known entity

Kaijian Zhang*

Department of Pathology, The First Affiliated Hospital of Anhui Medical University, Hefei, Anhui, China

Abstract

Mucosal Schwann cell hamartoma (MSCH) is a rare neurogenic tumor occurring in the gastrointestinal tract composed of Schwann cell components. To investigate the clinical and histopathological features, immunohistochemical characteristics, diagnosis, and differential diagnosis of MSCH, we reviewed the gastrointestinal endoscopic biopsy cases in the past 3 years. Along with a re-examination of the histological patterns, immunohistochemical tests were performed to identify cases that met the diagnostic criteria for MSCH. The endoscopic and clinical data of the patients were collected. We found that MSCH is a clinically rare benign lesion of neurogenic origin of the gastrointestinal tract with non-specific clinical and endoscopic manifestations and is not associated with hereditary cancer syndromes. Therefore, the integration of morphological and immunohistochemical findings is crucial for making accurate diagnosis of this disease, which is essential to avoid unnecessary treatment.

Keywords: Mucosal Schwann cell hamartoma; Gastrointestinal tract; Diagnosis; Differentiation; Diagnosis

***Corresponding author:**
Kaijian Zhang
(kaijian_zhang2021@163.com)

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1. Introduction

Benign neurogenic tumors are relatively common lesions, frequently occurring in the skin and soft tissues of the trunk, with gastrointestinal tract involvement being relatively rare. Certain neurogenic lesions involving the gastrointestinal tract, such as neurofibromas and mucosal neuromas, are often closely associated with hereditary syndromes, particularly neurofibromatosis type 1 (NF1) and multiple endocrine neoplasia type 2B (MEN2B).

Small polyps consisting of Schwann cells in the lamina propria of the mucosa have not been systematically described and clearly named, and some scholars believe that they may be neuromas or neurofibromas lacking ganglion cells, regarded as benign, unclassified mucosal polyps at the time of diagnosis. Gibson and Hornick[1] conducted a retrospective analysis of 26 gastrointestinal polypoid lesions that had been previously diagnosed as "neuromas" or "neurofibromas," and found that these lesions were confined to the mucosal layer, consisted of simple S-100 protein-positive Schwann cells, and were not clinically accompanied by associated syndromes such as NF1, MEN2B, and other

related syndromes. To differentiate these lesions from the traditional hereditary syndromes associated with gastrointestinal neural tumors, Gibson and Hornick[1] suggested that these lesions be named "mucosal Schwann cell hamartoma." The mucosal Schwann cell hamartoma (MSCH) is rare (relatively low incidence), typically asymptomatic, and often detected incidentally during endoscopy as gastrointestinal polyps, with colorectal polyps being the most common.[2] Given the morphological similarities between MSCH and other polypoid lesions of mesenchymal origin in the gastrointestinal tract, these diseases are easily misdiagnosed as neuromas, neurofibromas, or classified as benign, unclassified mucosal polyps.[3] Thus, accurate diagnosis of MSCH may avoid overtreatment and may help to exclude hereditary neoplastic diseases. This article focuses on the clinicopathologic features, immunohistochemistry, and differential diagnosis of MSCH with the aim of improving pathologists' understanding of this group of diseases.

2. Materials and methods

2.1. Study cohort

Suspicious cases of endoscopic biopsy of digestive tract were retrieved from the electronic case system, and archived sections were subject to a re-examination of tumor cells' histomorphology and immunophenotype, to determine the cases that satisfy the diagnostic criteria for MSCH. Clinical data and endoscopic characteristics of the selected patients were gathered. Only secondary, anonymized data were utilized in this study; therefore, ethical approval was exempted. Given the fact that only routinely collected data were used in the analysis, the requirement for informed consent was also waived. The selected patients were followed up through telephone or review of their recent hospitalization records. The follow-up period ended in July 2025. This study was performed in accordance with the Declaration of Helsinki.

2.2. Immunohistochemical staining

All the histological and immunohistochemical sections were independently re-examined by two experienced pathologists. Immunohistochemical staining for each case was achieved using autostainer platforms (BenchMark ULTRA, Roche, Basel, Switzerland; BOND-MAX, Leica Biosystems, Wetzlar, Germany) using ready-to-use antibodies targeting S-100 (clone 4C4.9), SOX10 (clone MRQ-58), neurofilament protein (NF; clone MAB-0136), desmin (clone MX046), smooth muscle actin (SMA) (clone MX097), CD117 (clone YR145), DOG1 (clone MX067), and CD68 (clone KP1). All of these immunohistochemical antibodies were purchased from Fuzhou Maixin Bio-technology Development Co. Ltd. (China).

3. Results

3.1. Clinical characteristics of MSCH

Eight cases consistent with the diagnosis of MSCH were retrieved, consisting of four females and four males within the age range of 30–64 years (median: 59.5 years). Patients underwent gastroenteroscopy for abdominal pain (1 case), abdominal distension (1 case), blood in the stool (2 cases), and routine physical examination (4 cases), and neither the patients themselves nor their relatives had NF. According to the endoscopic examination results, one case is located in the gastric sinus and seven cases are located in the intestine (including five cases in the ileum and two cases in the rectum). Endoscopic findings revealed a solitary, broad-based, hemispherical polypoid elevation with well-defined margins. The surface mucosa remained regular in morphology, without evident vasodilatation. The lesions measured 0.3–1.0 cm in diameter. The surrounding mucosa appeared smooth, with a clear vascular pattern and no evidence of congestion, vesiculitis, ulceration, tumor formation, abnormal elevation, or intraluminal bleeding (Figure 1). Clinically, the lesions were diagnosed as polyps, and endoscopic biopsy or endoscopic submucosal dissection was performed. The patients were followed up by telephone for 5–23 months, and none of them experienced recurrence or malignant transformation.

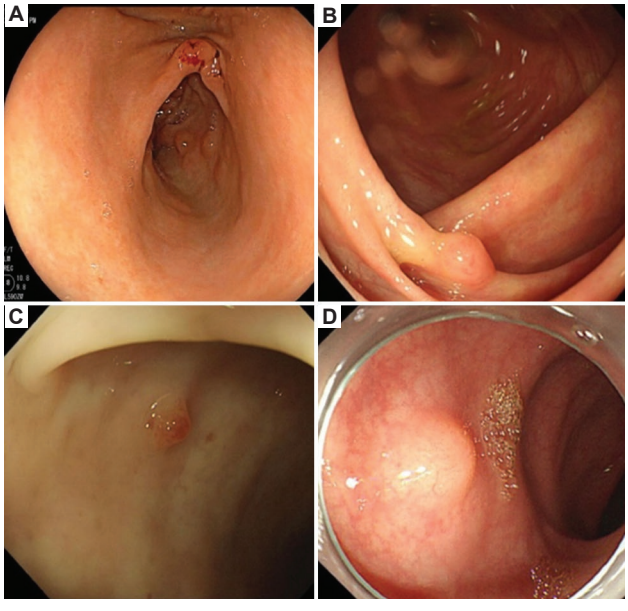

Figure 1. Representative endoscopic images of patients. (A) Multiple warty nodules are seen in the mucosa of the gastric sinus with surface congestion. (B) A polyp measuring 0.5 cm × 0.5 cm located in the ileocecal region. (C) A polyp measuring 0.4 cm × 0.3 cm located 10 cm from the anus. (D) A polyp measuring 1 cm × 0.8 cm located 15 cm from the anus.

3.2. Pathological features of MSCH

The lesion was confined to the lamina propria of the mucosa and lacked an envelope, with unclear boundary. Proliferating spindle cells were scattered around the crypts, and no obvious whorled, fenestrated or fascicular structure was observed. The spindle cells had unclear boundary, rich eosinophilic cytoplasm, elongated or wavy nuclei, fine chromatin, and occasional small and inconspicuous nucleoli. No obvious nuclear heterogeneity or nuclear division can be seen. The interstitium was infiltrated with scattered or focal lymphocytes, plasma cells, and eosinophils. In one case, large and irregular nuclei with degenerative atypical changes were seen in focal tumor cells (Figure 2). Eight cases of spindle cells showed diffuse and strong positivity for S-100 immunophenotype. Eight cases of spindle cells were negative for glial fibrillary acidic protein (GFAP), CD34, EMA, SMA, CD117, DOG1, CD68, desmin, calretinin, NSE, and seven cases were partially positive for SOX10 (Figure 3).

4. Discussion

Previously, there was no systematic description or definitive nomenclature for the small polyps in the lamina propria composed of Schwann cells. Some scholars believed they might be neuromas or neurofibromas lacking ganglion cells and classified them as benign, unclassified mucosal polyps. In 2009, Gibson and Hornick[1] conducted a retrospective analysis of 26 cases of gastrointestinal polyps previously diagnosed as "neuroma" or "neurofibroma." They found that these lesions were confined to the mucosal layer, composed purely of S-100 protein-positive Schwann cells, and were not clinically associated with syndromes such as NF1 or MEN2B. To distinguish them from traditional gastrointestinal neural tumors associated with hereditary syndromes, Gibson and Hornick[1] proposed the term "mucosal Schwann cell hamartoma" for these lesions.

In terms of clinical presentation, Gibson and Hornick[1] reported 26 cases of MSCH, which presented as broad-based polyps with a diameter range of 1–6 mm, with the majority of patients being asymptomatic. A review of literature in PubMed revealed that 77.9% of MSCH in 86 patients with a mean age of 60.2 years (47.7% male) occurred in the distal splenic flexure of the colon, especially in the sigmoid colon. Lesions in 81.0% of the patients were detected during routine physical examination by means of gastroenteroscopy, whereas the rest were detected gastroenteroscopically due to specific reasons such as bleeding, diarrhea, abdominal pain, and constipation.[4] Clinicians and pathologists also need to pay attention to some rare clinical features of this lesion when making a diagnosis; for instance, (i) MSCH may occur in young people, with 4 years old being the youngest age of onset reported in the literature; (ii) MSCH may be located outside the colorectum, with reported sites of occurrence in the duodenum, gastric sinus, gastroesophageal junction, and gallbladder; (iii) the lesions can be multifocal; and

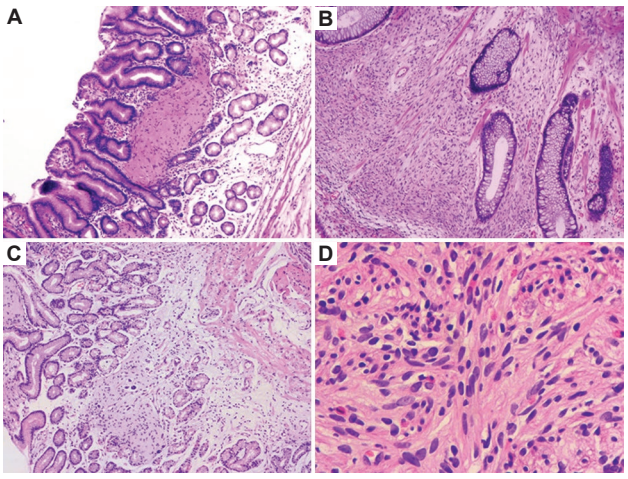

Figure 2. Representative histopathologic images of mucosal Schwann cell hamartoma (MSCH). (A) MSCH occurring in the gastric antrum with multifocal spindle cell proliferative lesions seen in the interstitium. The lesions are scattered and patchily distributed beneath the epithelium of the gastric lesser curvature, measuring approximately 25 mm × 20 mm. The surrounding mucosa exhibits sinus-type architecture and show changes consistent with mild to moderate chronic superficial gastritis. (B) MSCH occurring in the intestinal tract, with hyperplastic spindle cells scattered around the crypt. (C) MSCH occurring in the intestinal tract. The tumor cells exhibit abundant eosinophilic cytoplasm, with spindle- or ovoid-nuclei and indistinct cell boundaries. Some nuclei appear enlarged and irregular, displaying degenerative atypia. (D) Enlarged image of the spindle cells.

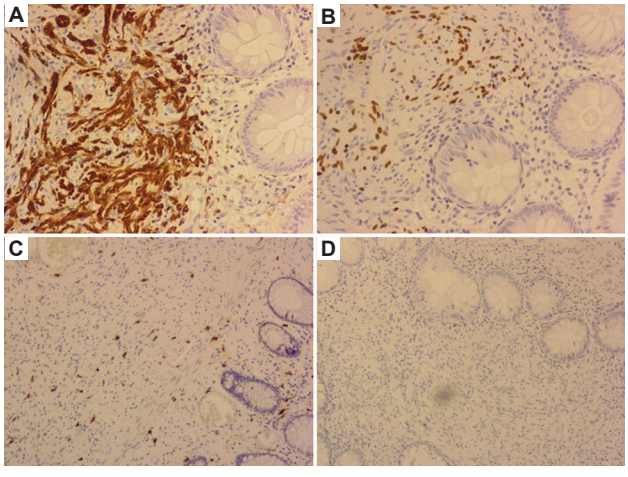

Figure 3. Representative immunohistochemical images of mucosal Schwann cell hamartoma. (A) Staining results showing S-100 positivity in spindle-shaped cells. (B) Staining results showing SOX10 positivity in spindle-shaped cells. (C) Staining results showing CD117 negativity in spindle-shaped cells. (D) Staining results showing DOG-1 negativity in spindle-shaped cells.

(iv) the size of the lesion can measure up to 1 cm.[5,6] In the present study, we performed a clinicopathological analysis of seven cases of MSCH occurring in the intestine and one case of MSCH occurring in the gastric sinus.

Histologically, diffusely proliferating spindle cells were located in the lamina propria and distributed around the crypts without a distinct spiral, fenestrated, or fascicular arrangement, and the lesion boundaries were indistinct. The morphology of the cells in the lesions was all similar, with elongated, wavy nuclei, abundant, dense, eosinophilic cytoplasm, and indistinct cell borders. Intranuclear chromatin was fine, and small, inconspicuous nucleoli were occasionally seen. Nuclear anisotropy, pleomorphism, and nuclear fission were not observed.[7] Several reports have found that the surface overlying epithelium of MSCH lesions appeared atrophic, while the surrounding normal mucosal overlying epithelium was intact,[1-7] consistent with the observations made in our case. The most superficial layer was atrophic mucosal dorsal epithelium, the middle layer was MSCH, and the deepest layer was residual crypt gland.

In addition to the above-mentioned common morphological features of MSCH, some rare morphological alterations of MSCH have been described in the literature. Li *et al.*[8] found that degenerative atypical alterations were present in parts of the tumor cells. In our case, we also found locally aberrant and enlarged nuclei of the tumor cells, but not accompanied by thickened chromatin and enlarged nucleoli. We believe that MSCH, which is composed of Schwann cells, may also show degenerative changes in cells such as "ancient" or "old" nerve sheath tumors. Among the cases included in the present study, one patient experienced degenerative atypia with abnormally enlarged nuclei seen in the focal lesion microscopically.

The most characteristic immunohistochemical feature of MSCH is the strong expression of S-100 protein in the cytoplasm and nucleus of tumor cells, which is attributed to the presence of Schwann cellular components in the tumor. Results of neurofilament immunostaining showed a generalized absence of axons, and the cells in the lesion did not express GFAP, EMA, claudin-1, CD34, EMA, GFAP, EMA, claudin-1, CD34, SMA, and KIT. These lesions are not associated with NF1 or other hereditary syndromes.[8,9]

While the pathogenesis of MSCH remains largely unclear, the prevailing hypothesis suggests that its occurrence is related to secondary repair and proliferation after local tissue injury, based on three primary justifications. First, as mentioned above, atrophy or disappearance of the overlying epithelium occurs on the surface of most MSCH. Second, MSCH lesions are mainly located in the superficial layer of the lamina propria of the mucosa, often immediately adjacent to the mucosal surface, suggesting that they are related to the response to external injuries. Third, MSCH mostly occurs in the sigmoid colon and the esophagogastric junction, which are the anatomical sites susceptible to mechanical injuries. In addition, Barreiro *et al.*[10] suggested that mechanical obstruction of the digestive tract and chronic inflammation may lead to proliferation of LGR5-positive intestinal stem cells, whose plasticity may lead to hypertrophy of nerve fibers in the gastrointestinal tract, which ultimately leads to the occurrence of MSCH. Therefore, it has been suggested that "mucosal Schwann cell hyperplasia" would be a more contextually appropriate nomenclature for this condition as compared to "Mucosal Schwann cell hamartoma," but their pathologic nuances need to be further verified.

The majority of patients with MSCH are asymptomatic, but some patients present with symptoms such as gastrointestinal bleeding, diarrhea, watery stools, abdominal pain with intermittent urgency, and epigastric pain. The prognosis of these patients who undergo polypectomy is often good, and no malignant changes or metastases have been reported. In addition, some of the larger lesions are easily misdiagnosed as other spindle cell tumors, which often lead to over-treatment of patients, as demonstrated by the cautionary tale of Hytiroglou *et al.*,[11] in which their patient was misdiagnosed with gastrointestinal stromal tumor (GIST), followed by the implementation of subtotal gastrectomy with additional lymph node dissection. Therefore, accurate identification of this type of lesion is extremely important. In the present study, we followed up eight patients for a duration of 5–23 months, and all patients experienced no recurrence or malignant changes. Long-term follow-up of bulk cases is necessary to decipher the pathogenesis of this lesion.

Differential diagnosis includes the following:

(i) Neurofibromas, which are prevalent in the population aged 20–30 years. According to the growth pattern, neurofibromas can be divided into plexiform, diffuse, and isolated/confined types. Plexiform neurofibromas are often accompanied by NF1. The tumor is characterized by low cell density, with elongated spindle-shaped cells in arranged in intertwined bundles. The stroma contains varying amounts of mucus and rope-like or "carrot filaments" collagen fibers. The tumor cells exhibit indistinct cell boundaries, pale pink-stained cytoplasm, and deeply stained nuclei. The nuclei are wavy, tapered at one end, giving a tadpole-like appearance. Overall cellular anisotropy is minimal, and mitotic figures are rare. Immunostaining shows patchy S-100 and SOX10 positivity, P16 positivity, and EMA expression along nerve bundle membranes, and NF positivity in the

axonal components. The primary distinguishable histologic feature of neurofibromas from MSCH is heterogeneous cellular composition, including Schwann cells, fibroblasts, and neural fasciculus cells, with visible axons, whereas MSCH has a homogeneous cellular composition, containing almost entirely Schwann cells based on the diffuse expression of the S-100 protein.[1] In addition, dispersed axons are observed in all colorectal neurofibromas, whereas axons are seen in only a small proportion of MSCH.

(ii) Ganglioneuroma, which are lesions composed of ganglion cells, nerve fibers, and Schwann cells. Ganglioneuroma usually occurs in the retroperitoneum and posterior mediastinum, and may also occur in the gastrointestinal tract, most commonly involving the colon and rectum. Gastrointestinal ganglioneuromas can be classified as polypoid ganglioneuromas, ganglioneuromatous polyposis, and diffuse ganglioneuromas, the latter two often associated with MEN2B and NF1. Hematoxylin-eosin (HE) staining shows scattered ganglioneuromas on the background of nerve fibers. Immunohistochemical staining shows that ganglion cells are positive for Syn, NF, and NSE; spindle cells are positive for GFAP and vimentin; and nerve fiber are positive for S-100.

(iii) Intramucosal neurofascial tumors. Frequently occurring in the distal part of the colon, intramucosal neurofascial tumors present as small broad-based polyps. Histologically, the tumor cells exhibit low-to-moderate density. Tumor cells may form indistinct mats or whirlpool-like structure and are often arranged spirally around blood vessels. In some areas, the cells can also be organized in layers. The tumor cells express EMA, but not S-100.

(iv) Schwannoma. This type of tumor is most common in peripheral nerves of the head, neck and limbs, and those occurring in the gastrointestinal tract mainly occur in the stomach but rarely occur in the colon. 10% of the cases are associated with NF type II, multiple meningiomas and other syndromes. Under low magnification, the tumor exhibits areas of both dense and loose cell arrangement. In the densely packed regions, the cells are in the shape of a long shuttle, while in some areas, they form irregular whirlpool with nuclei radiating toward the periphery, characteristic of the Verocay bodies. A distinct lymphocyte sleeve was seen around the tumor of nerve sheath tumor occurring in the gastrointestinal tract. Under high magnification, the tumor cells exhibit finely granular cytoplasm with indistinct cell borders; the nuclei of the cells are elongated, spindle-shaped, and wavy, tapering to a point at one end; the overall cell morphologic atypia is mild, with occasional nuclear atypia. Immunolabeling results show diffuse and strong S-100 positivity, SOX10 positivity, and CD117 and DOG1 negativity.[12] According to existing literature, MSCH should consist purely of S-100 protein-positive Schwann cells. However, it should be noted that in our series of eight MSCH cases, while all cases demonstrated diffuse S-100 positivity, seven cases exhibited focal SOX10 positivity. We speculate that this observation may be related to the specific antibody clone used or non-specific staining. These seven cases require careful differentiation from schwannoma. The reasons for not diagnosing these seven cases as schwannoma are as follows: first, all seven cases occurred in the stomach, whereas gastric schwannomas are exceptionally rare, making the location atypical for schwannoma. Second, these seven cases lacked the characteristic histological features of schwannoma. Furthermore, the immunohistochemical staining for SOX10 was only focally positive, which is inconsistent with the typical immunoprofile of schwannoma.

(v) GIST. This type of tumor is the most common mesenchymal tumors of the gastrointestinal tract, with 5–10% associated with Carney triad, Carney–Stratakis syndrome, and other syndromes. Microscopically, 70% of the tumor cells in GIST are spindle-shaped, posing a challenge for distinguishing them from MSCH cells under HE staining. Focused differentiation is required due to differences in treatment modalities. GIST typically exhibit moderate cellularity, with cells arranged in bundles and interwoven patterns. The cytoplasm is abundant with weak eosinophilia, and cell boundaries are indistinct. The nuclei are elongated and spindle-shaped, showing some paranuclear vacuoles, with mild nuclear atypia observed in a few cells. Immunophenotype for GIST tumor cell includes diffusely strong positivity for CD117 (KIT), DOG1 positivity, CD34 positivity in most cases, SMA, and S-100 negativity.[13-15]

(vi) Smooth muscle tumor. This type of tumor often forms a noticeable swelling. Microscopically, the cells are elongated and shuttle-shaped, with moderate eosinophilic cytoplasm. The nuclei are rod-shaped, slightly curved, rounded at both ends, and cigar-shaped. The tumor cells have low cell density and are arranged in an interwoven pattern. Immunolabeling results show positivity for SMA, desmin, h-Caldesmon, and other myogenic markers, as well as S-100 negativity.[16,17]

(vii) Inflammatory fibrous polyps, which are mesenchymal polyps commonly found in the stomach and small intestine. This type of lesion is usually located in the submucosal layer, and the boundaries of the surrounding tissues are clear. Microscopically, the

lesions exhibit low-to-medium density of spindle cells, with some spindle cells surrounding the blood vessels arranged concentrically, resembling the "onion skin." Some spindle cells are arranged in concentric circles around the blood vessels to form an "onion skin"-like structure, and wavy collagen fibers can be seen between the local spindle cells, and scattered eosinophilic infiltration can be seen in the background, and the immunohistochemical marker of vimentin, fascin, and CD34 is diffusely positive, while the expression of CD117 is negative.[18]

This study has several limitations. First, MSCH is relatively rare, and the sample size included in this study was only eight cases, without a control group for comparison. This limitation may affect the generalizability of the research findings. In addition, the follow-up period for MSCH patients in this study ranged from 5 to 23 months, which is insufficient to fully confirm the benign nature of the MSCH lesions. Future multicenter studies with extended follow-up durations are necessary. Second, while this study provides comprehensive histological and immunohistochemical analyses of MSCH and discusses key diagnostic and differential diagnostic points, it did not include genetic or molecular testing. Future research could benefit from molecular genetic studies on MSCH cases to further elucidate its molecular characteristics and its relationship with NF1 or MEN2B.

5. Conclusion

MSCH is a rare neurogenic lesion located in the mucosal lamina propria, which is mainly composed of spindle-shaped cells arranged in sheets between mucosal glands. The tumor exhibits low cell density, elongated tapering nuclei, abundant lightly stained cytoplasm, indistinct cell boundaries, and S-100 positivity on immunostaining. This lesion is most commonly found in the colorectum, and the available clinical data suggest that the prognosis is favorable. Accurate diagnosis by pathologists is crucial to prevent patient over-treatment of patients due to misdiagnosis.

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Conflict of interest

The author declares no conflict of interest.

Author contributions

This is a single-authored article.

Ethics approval and consent to participate

Only secondary, anonymized data were used in this study; therefore, ethical approval is exempted. The requirement for informed consent was waived because only routinely collected data were utilized in this study.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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