JOURNAL OF SOCIAL SCIENCE
Printed ISSN: 2720-9938
Electronic ISSN: 2721-5202
jsss.co.id

# Understanding and Addressing the Challenges of Gastrointestinal Stromal Tumor (GIST): Towards Improved Diagnosis and Treatment Strategies

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**Keywords:**
Gastrointestinal Stromal Tumor (GIST), Early Diagnosis, Treatment Strategies

**ABSTRACT**
Gastrointestinal stromal tumor (GIST) is a prevalent mesenchymal tumor affecting the digestive tract, with the stomach being the most common location. While some GIST cases are sporadic with no known risk factors, certain factors such as age and genetic abnormalities increase the risk. Early diagnosis of GIST remains challenging due to atypical symptoms, leading to late diagnoses and reduced survival rates. This research aims to identify specific risk factors related to local populations, develop accurate early diagnosis methods, and formulate more effective treatment strategies. The study involved a retrospective observational approach, collecting data from medical records of GIST patients and analyzing risk factors and treatment outcomes. The results highlight the increasing prevalence of GIST globally, emphasizing the need for increased awareness and early diagnosis. Challenges in early diagnosis and treatment underscore the importance of public awareness, medical education, and collaborative efforts for better GIST management. This research offers implications for the development of diagnostic guidelines and more effective treatment approaches, ultimately improving the prognosis and quality of life for GIST patients.

## INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the digestive tract. GISTs can occur in various locations in the digestive tract, with the stomach being the most common location. Although most GISTs are sporadic with no known risk factors, some factors such as age and the presence of genetic disorder syndromes can increase the risk of GIST (Gheorghe *et al.* , 2021) . The diagnosis of GIST

can be made through imaging and endoscopic examination, and surgery is one of the treatment options (Ahmed, 2020) .

## METHOD

Methods and Procedures this literature review was prepared using various sources of scientific journal articles related to the topic discussed. The keywords used in the article search were "gastrointestinal stromal tumor", "Clinical manifestations", "Diagnosis", "Treatment", "Prevention". Article search procedures are carried out carefully and pay attention to their validity

## RESULTS

### A. Gastrointestinal Stromal Tumor

#### 1. Definition

Gastrointestinal stromal tumor (GIST) is a rare soft tissue sarcoma that can be found in all parts of the digestive tract. GISTs are most commonly found in the stomach, starting from the small intestine, large intestine and rectum. Initially, GISTs were misclassified as leiomyoma, leiomyosarcoma, and schwannoma. In its development, ultrastructural, immunohistochemical and molecular biology techniques have made it possible to recognize that GIST originates from interstitial cells of Cajal (ICC) or common progenitor cells. ICC are found throughout the digestive tract and act as *pacemaker cells* to regulate peristaltic movements. GIST can develop through oncogenic acquisition of functional mutations in the KIT or platelet-derived growth factor receptor (PDGFR) gene which plays a role in producing constitutive activation of the receptor tyrosine kinase (Mantese, 2019).

#### 2. Epidemiology

Gastrointestinal stromal tumor (GIST) is known to have an incidence of at least 14–20/1 million in population-based studies from Northern Europe. This estimate represents a minimum incidence, as subclinical GISTs are much more common. In the United States, approximately 5000-6000 new cases of GIST are diagnosed per year. Based on surveillance, epidemiology, and outcome databases, the incidence of GIST increased from 0.55/100,000 population in 2001 to 0.78/100,000 population in 2011. Another study published in 2006 showed that there was a 25-fold increase in the incidence of GIST in the US in the last 10 years since 1992. In Europe, the incidence of GIST varies from 6.5 to 14.5 per million per year (Miettinen and Lasota, 2013).

Soreide et al reviewed 29 studies consisting of 13,550 patients from 19 different countries with GIST between January 2000 and December 2014. Median age was 65 (range, 10–100) with a male to female ratio of 1:1. The highest incidence rates (19–22 per million per year) were recorded in Hong Kong, Shanghai, Taiwan, and Norway. The lowest incidence was recorded in the Shanxi

province of China with 4.3 per million per year. Eighteen percent (range, 5–40%) of GISTs are discovered incidentally ( Parab et al., 2019 ).

Most GISTs arise in the stomach (60–65%), followed by the small intestine (20–25%), rectum (3–5%), large intestine (1–2%), esophagus (1%) and other locations ( 8–10%). GISTs occur in young patients, children and young adults (<30 years) appearing mostly in the stomach (Blay et al., 2021). GISTs were found in the stomach (56%), small intestine (32%), colon and rectum (6%), esophagus (0.7%), and other locations (5.5%). About 10% to 30% of GISTs develop malignancy. GISTs that occur outside the stomach are associated with a higher malignant potential. Exophytic growth was noted in 79% of GISTs, while intraluminal or mixed growth occurred less frequently (Parab *et al.* , 2019).

## 3. Etiology and Risk Factors

Gastrointestinal stromal tumors (GIST) are generally sporadic with no known risk factors or causes, only around 5% of cases are caused by genetic factors in the family (Gheorghe *et al.* , 2021). Factors that are thought to increase the risk of GIST include age and the presence of genetic abnormality syndromes.

a. Age

One of the risk factors for GIST is age. The ages at risk of developing GIST are middle age to the elderly. This tumor is most often diagnosed in individuals aged between 50 and 70 years, while in terms of gender distribution, the ratio of men to women is more or less equal (Gheorghe *et al* ., 2021).

b. Genetic disorder syndrome

Genetic disorder syndromes are caused by gene mutations. Genetic disorder syndromes that can cause GIST include Carney–Stratakis syndrome (CSS), Carney triad, Neurofibromatosis type 1 (NF1), and primary familial GIST syndrome (Gheorghe et al., 2021 *)* .

1) Carney-Stratakis Syndrome (CSS)

Carney-Stratakis syndrome or Carney-Stratakis dyad is diagnosed in adolescents or young adults at an average age of 19-21 years. These patients usually have an association of GIST and paraganglioma (Gheorghe *et al.* , 2021).

This genetic disorder includes two types of tumors, pheochromocytoma (PHEO)/paraganglioma (PGL) and gastrointestinal stromal tumor (GIST) and is inherited in an autosomal dominant manner. This syndrome affects both men and women during childhood and adolescence. CSS is caused by mutations in the SDHB, SDHC and SDHD subunits, with subunits B and D mutated at higher frequencies. A study studied patients with CSS who developed gastrointestinal stromal tumors and identified germline mutations in SDHB, SDHC and SDHD. In addition, SDHA loss-of-function mutations have also been identified in patients with CSS ( Pitsava *et al.* , 2021 ).

2) Carney Triad Syndrome

Carney's Triad Syndrome was found in young women with GIST, pulmonary chondroma, and paraganglioma (Gheorghe *et al.* , 2021). Carney's triad is caused by SDH mutations, more specifically, SDHC (Pitsava *et al.* , 2021).

3) Neurofibromatosis type 1 (NF1)

GISTs associated with NF1 syndrome are localized to the small intestine in >70% of cases. These are usually multifocal tumors and have a low mitotic rate. Unlike sporadic GISTs, mutations in the PDGFRA and KIT genes are rare. GIST associated with NF1 syndrome has an incidence of 1 in 4000 in the general population and is an autosomal dominant genetic disease with a wide range of clinico-pathological features and an uncertain course. Mutations in the NF1 gene, which codes for neurofibromin, cause loss of function of the gene and result in Ras activation that promotes tumor formation. (Gheorghe *et al.* , 2021).

4) Primary familial GIST syndrome

Primary familial GIST syndrome is characterized by a tendency to early development of multiple tumors, located in the stomach or small intestine. This syndrome is caused by KIT or PDGFRA mutations. Patients with germline mutations in the KIT gene can have an association of paraganglioma, dysphagia or skin hyperpigmentation, and patients with a mutation in the PDGFRA gene can have an association of inflammatory fibroid polyps or intestinal fibromatosis (Gheorghe et al., 2021 *)* .

## 4. Pathophysiology

Uncontrolled ICC proliferation leads to GIST growth. The C-kit protooncogene located on chromosome 4q 11-12 encodes a transmembrane tyrosine kinase. Exon 11, which is the transmembrane domain, is involved in 90% of KIT gene mutations. KIT-activating mutations cause hyperplasia of ICC and GIST. This KIT gene mutation will activate tyrosine kinase, which is found in 75% of GIST cases.

The PDGFRA gene on chromosome 4q12 controls the production of PDGFRA which is part of the receptor tyrosine kinase (RTK) protein. The most commonly found PDGFRA mutation is the Asp842Val mutation in exon 18. Intragenic activating mutations in the PDGFRA gene with RTK production are found in 35% of GIST cases without KIT mutations. Therefore, the growth of GIST is based on mutations in the KIT gene, which covers 75% of GIST cases or mutations in the PDGFRA gene which covers 10% of GIST cases. The oncogenic mechanisms of these two mutations are mutually exclusive, meaning that only one of them can occur in one GIST case (Monjur Ahmed, 2020).

In 15% of cases, GISTs that do not have a KIT or PDGFRA mutation are called wild-type GISTs or pediatric GISTs. Wild-type GISTs need to be checked for mutations in the SDH gene. Clinically, these GISTs cannot be differentiated from KIT or PDGFRA mutation GISTs because they have the same morphology,

express high levels of KIT, and can appear anywhere in the GI tract. There are also other gene mutations found in *wild-type GIST,* including BRAF, HRAS, NRAS, and PIK3CA (Monjur Ahmed, 2020).

**5. Governance**

The standard treatment for localized GIST is surgery. The tumor and pseudocapsule must be removed to allow surgery with adequate margins because the primary goal is complete removal (R0). Given the fact that GISTs rarely metastasize to lymph nodes, resection of the lymph nodes is not necessary. The presence of metastases does not represent a contraindication to surgery for the primary tumor (Gheorghe et al., 2021).

Other treatment methods for non-metastatic GISTs are endoscopic techniques, such as enucleation, submucosal surgery, submucosal excavation, thickness resection, submucosal resection, and endoscopic cooperative surgery (Gheorghe et al., 2021).

Based on endosonography, GIST is grouped into four subtypes, depending on the location in the muscularis propria, including:

a. Type I: Tumors that enter the digestive lumen are slightly connected to the muscularis propria.
b. Type II: Tumors that protrude into the digestive lumen are mostly connected to the muscularis propria.
c. Type III: Tumor located in the middle of the stomach wall.
d. Type IV: Tumor that protrudes into the serosa of the stomach wall.

Endoscopic enucleation can be performed for type I GISTs and is possible for type II GISTs. Types III and IV may be more effective than the following endoscopic treatment techniques: submucosal surgery, submucosal excavation, complete resection, submucosal resection, laparoscopy, and endoscopic cooperative surgery (Gheorghe et al., 2021).

In cases where the KIT mutation status is unknown, alternative treatment can be chosen, namely using a kinase inhibitor. The presence of a mutation in PDGFRA D842V confirmed significant resistance to imatinib. Thus, avapritinib is recommended for patients with symptomatic or progressive disease and PDGFRA D842V mutation. However, in patients with mutations who are asymptomatic or have indolant disease (slowly growing tumors), regular monitoring is needed to decide on avapritinib administration. Other pharmacological treatment options for patients with the PDGFRA D842V mutation are ripretinib or dasatinib. In the INVICTUS demonstration study there was an increase in the survival rate of patients with advanced GITS given ripretinib as a *four-line* TKI. This study was conducted on 129 patients with advanced GIST, 10 patients showed *wild-type* KIT and PDGFRA mutation status (Gheorghe *et al.* , 2021).

**6. Prognosis**

Patient survival is related to a number of factors. The median survival of GITS patients is 60 months in those without evidence of metastasis, and this is

significantly reduced to approximately 19 and 12 months if there is advanced disease at onset or subsequent recurrence occurs (Zhang and Liu, 2020). Parameters to determine the prognosis of GIST are tumor size and mitotic ratio per 50 hpf. GISTs with tumor size ≤ 5 cm and mitoses ≤ 5/50 HPF have a good prognosis, with a risk of metastasis of 3-5%. (George Mantese, 2019). Meanwhile, a poor prognosis has a tumor size of >5 cm and mitosis with a total area of 5 mm2 (Alessandro *et al.,* 2019). Tumor location also seems to influence patient survival (Zhang and Liu, 2020). Patients with metastases and unresected tumors also have a poor prognosis (Gina *et al.,* 2021).

## 7. Complications

Complications that can occur with GIST include gastrointestinal bleeding and intestinal obstruction.

a. Gastrointestinal bleeding

Gastrointestinal bleeding is the most common and most dangerous complication, often requiring emergency surgery which also carries higher risks. GIST patients with chronic bleeding show symptoms of anemia, weight loss, and melena. In cases of acute bleeding, peritonitis and shock may occur. Most hemorrhagic stromal tumors are associated with an intact tunica serosa. Bleeding is triggered by mucosal ulceration due to tumor invasion of the blood vessels.

The causes of GIST intraluminal hemorrhage may be related to mucosal and submucosal damage by tumor growth, vascular invasion leading to vascular rupture, tumor necrosis, and the concerted action of digestive fluids, gastrointestinal peristalsis, and fecal transmission. GISTs are relatively fragile and highly vascularized compared to other common gastrointestinal tumors so bleeding occurs frequently. In general, by the time symptoms of gastrointestinal bleeding appear, the tumor has reached a relatively large size. The possibility of stromal tumor bleeding in the small intestine is much greater than in the stomach. This is related to differences in the size of the spaces in each digestive tract (Liu *et al* ., 2018).

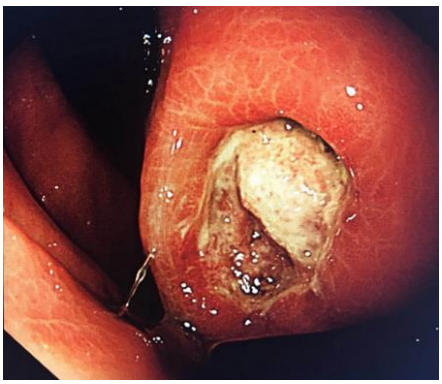

Figure 1. Endoscopic manifestations of GIST with ulceration and active bleeding

b. Intestinal obstruction

GISTs that occur in the duodenum and other parts of the intestine can show any growth pattern, but generally grow exophytically (growth that protrudes from the surface of the tissue). A frequently seen complication in small intestine and large intestine GISTs is cavitation. Mass effect can result in regional complications such as hydronephrosis and intestinal obstruction. Hydronephrosis can occur due to a mass in the intestine pressing on the ureter so that urine cannot flow to the bladder (Scola *et al.* , 2017).

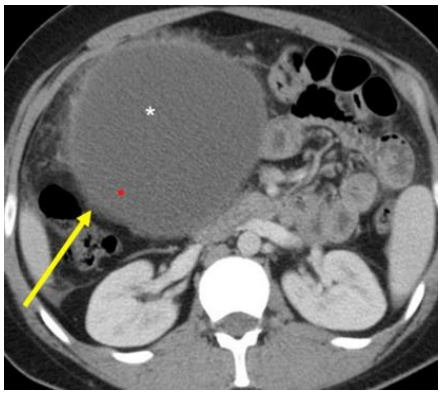

Figure 2. Obstruction due to GIST

## CONCLUSION

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the digestive tract. Risk factors for GIST include middle age to the elderly and the presence of genetic disorders such as Carney-Stratakis syndrome, Carney triad, Neurofibromatosis type 1 (NF1), and primary familial GIST syndrome. The diagnosis of GIST can be made through imaging and endoscopic examination, and surgery is one of the treatment options. Other treatment methods for non-metastatic GISTs are endoscopic techniques such as enucleation, submucosal surgery, submucosal excavation, thickness resection, submucosal resection, and endoscopic cooperative surgery. GIST prognosis is influenced by tumor size, mitotic rate, tumor location, presence of metastases, and the success of total tumor removal. Complications that can occur in GIST include gastrointestinal bleeding and intestinal obstruction.

## REFERENCES

Ahmed, M. (2020) 'Recent advances in the management of gastrointestinal stromal tumors', *World Journal of Clinical Cases,* 8(15), pp. 3142-3155. doi: 10.12998/wjcc.v8.i15.3142

Blay, J.Y. *et al.* (2021) 'Gastrointestinal stromal tumours', *Nature Reviews Disease Primers* , 7(1), pp. 1–22. doi: 10.1038/s41572-021-00254-5.

Gheorghe, G., Bacalbasa, N., Ceobanu, G., Ilie, M., Enache, V., Constantinescu, G., Bungau, S., & Diaconu, C.C. (2021). Gastrointestinal stromal tumors-a mini review. *Journal of Personalized Medicine* , *11* (8). https://doi.org/10.3390/jpm11080694

Halpern, AL, Torphy, RJ, McCarter, MD, Sciotto, CG, Glode, LM, & Robinson, WA (2019). A familial germline mutation in KIT associated with achalasia, mastocytosis and gastrointestinal stromal tumors shows response to kinase inhibitors. *Cancer Genetics* , *233–234* , 1–6. https://doi.org/10.1016/j.cancergen.2019.02.001

Liu, Q., Kong, F., Zhou, J., Dong, M., & Dong, Q. (2018). Management of hemorrhage in gastrointestinal stromal tumors: A review. In *Cancer Management and Research* (Vol. 10, pp. 735–743). Dove Medical Press Ltd. https://doi.org/10.2147/CMAR.S159689

Mantese, G (2019), "Gastrointestinal Stromal Tumor: Epidemiology, Diagnosis, and Treatment." *Current Opinion in Gastroenterology* , vol. 35, no. 6, pp. 555–59, doi:10.1097/MOG.0000000000000584.

Mazzocca, A., Napolitano, A., Silletta, M., Spalato, C, M., Santini, D., Tonini, G., Vincenzi, B., (2019), 'New frontiers in the medical management of gastrointestinal stromal tumours', *Therapeutic Advances in Medical Oncology,* 11. pp. 1-13. doi: 10.1177/1758835919841946

Miettinen, M., & Lasota, J. (2013). Gastrointestinal Stromal Tumors. *Gastroenterology Clinics of North America* , *42* (2), 399–415. https://doi.org/10.1016/j.gtc.2013.01.001

Parab, T.M. *et al.* (2019) 'Gastrointestinal stromal tumors: A comprehensive review', *Journal of Gastrointestinal Oncology* , 10(1), pp. 144–154. doi: 10.21037/jgo.2018.08.20.

Pitsava, G. *et al.* (2021) 'Carney Triad, Carney-Stratakis Syndrome, 3PAS and Other Tumors Due to SDH Deficiency', *Frontiers in Endocrinology* . Frontiers Media SA Available at: https://doi.org/10.3389/fendo.2021.680609.

Scola, D. *et al.* (2017) 'Getting the GIST: a pictorial review of the various patterns of presentation of gastrointestinal stromal tumors on imaging', *Abdominal Radiology* , 42(5), pp. 1350–1364. Available at: https://doi.org/10.1007/s00261-016-1025-z.

Sorour, MA, Kassem, MI, Ghazal, AEHA, El-Riwini, MT, & Abu Nasr, A. (2014). Gastrointestinal stromal tumors (GIST) related emergencies. *International Journal of Surgery* , *12* (4), 269–280. https://doi.org/10.1016/j.ijsu.2014.02.004

Zhang, H. and Liu, Q. (2020) 'Prognostic indicators for gastrointestinal stromal tumors: a review', *Translational Oncology*, 13(10), p. 100812. doi: 10.1016/j.tranon.2020.100812.