Review Article

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Situs Inversus Totalis: A Narrative Review of Clinical Features, Diagnostic Advances, and Evolving Surgical Management

Surgery Section

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ABSTRACT

Situs Inversus Totalis (SIT) is a rare congenital condition where thoracic and abdominal organs are in complete transposition as mirror image with an estimated prevalence of 1/10000 births. Majority of the patients show no symptoms and SIT is usually identified incidentally during imaging, Electrocardiogram (ECG) or clinical examination. The symptomatic cases tend to be related to the associated pathologies, such as acute appendicitis, cholecystitis, or cardiac malformation, and will be atypical because the reversed anatomy of the organs. It is diagnosed by a combination of adequate history taking, physical examination, chest and abdominal imaging, echocardiography, and prenatal imaging and genetic testing are also becoming more important. Surgical treatment involves careful adaptation to the mirrored anatomy where it involves modified laparoscopic surgery but may also include Three-dimensional (3D)-assisted and robotic-assisted surgeries. New technologies, such as fluorescence cholangiography, AI-assisted imaging, and others, contribute to the high safety and accuracy of surgery and diagnosis. This narrative review article aimed to comprehensively summarise about embryology, clinical presentation, diagnostic modalities, associated anomalies as well as surgical considerations of SIT along with particular emphasis on recent technological advances such as fluorescence cholangiography and AI-assisted imaging which enhance diagnostic accuracy and operative safety.

Keywords: Artificial Intelligence-assisted imaging, Congenital anomaly, Dextrocardia, Fluorescence cholangiography, Robotic surgery

INTRODUCTION

The SIT is a very rare congenital disorder where both the thoracic and abdomen organs are located in an inverted mirror of the normal anatomy (Situs solitus) [1]. The heart (dextrocardia) is to the right of the chest, the liver on the left, the spleen and stomach on the right, and the lobation and division of the lungs and bronchial are reversed in people with SIT [1,2]. Although many patients remain asymptomatic, SIT can further present having atypical clinical manifestations resulting from reversed organ anatomy, which can result into diagnostic delays as well as surgical challenges, especially in the presence of congenital cardiac or other structural defects [3]. The incidence of SIT is estimated to be approximately 1 per 10,000 live births with some studies reporting slight predominance of male although overall sex distribution remains nearby equal [4]. The reported incidence rates of SIT also vary across various geographic populations and study cohorts [4].

Organ transposition as a phenomenon has been recognised for centuries [5]. The earliest documented human case was reported around 1600 by Girolamo Fabrizio, who described a reversal of the liver and spleen positions [4,5]. The first case of dextrocardia was reported in the year 1643 by Marco Aurelio Severino [5]. Clinicians could observe and establish visceral transpositions in vivo with the help of advancement of radiographic techniques in the late 19th century, beginning with Vehsemeyer in 1897 [5,6]. After these initial reports, hundreds of cases have been reported and the knowledge has grown with the insights into developmental genetics, embryology as well as the associated ciliary dysfunctions [5].

The establishment of left-right asymmetry during early embryogenesis is regulated process as well as disruption at this stage underlies development of SIT [7]. During gastrulation, motile monocilia at the embryonic Left-Right Organiser (LRO) produces a unidirectional leftward nodal flow which initiates asymmetric expression of key signaling molecules inclusive of NODAL, LEFTY, and PITX2, in the lateral plate mesoderm [7]. These molecular cascades further guide asymmetric morphogenesis also positioning of thoracoabdominal organs [7]. Genetic mutations which affects ciliary structure or function usually involving dynein arm-related genes such as DNAH5, DNAI1, CCDC11, and LRRD1 can impair nodal flow, thereby resulting into randomisation of organ laterality and complete mirror-image reversal seen in SIT [7,8]. SIT can occur as an isolated anomaly as well as in association with Primary Ciliary Dyskinesia (PCD) inclusive of Kartagener syndrome thereby also highlighting central role of ciliary dysfunction in laterality determination [8,9]. This narrative review aimed to give an overview of SIT and its clinical presentation, diagnostic improvement and current surgical management changes. It is also aimed at noting emerging technologies and plans that enhance the safety and the results of patients with this rare congenital condition.

Clinical Features and Symptomatology of SIT

The SIT in few cases is associated with PCD (including in Kartagener syndrome), and these individuals exhibit respiratory symptoms such as chronic sinusitis, bronchiectasis, along with recurrent pulmonary infections [10]. Among patients with PCD and concurrent SIT, clinical features inclusive of neonatal respiratory distress and chronic lung disease are usually determined by ciliary dysfunction rather than reversed organ arrangement [10]. In a case of idiopathic splenic infarction in an older patient with SIT, presenting symptom was acute abdominal pain, on further imaging it showed splenic infarcts in the setting of mirror-image viscera [11]. This demonstrates that rare complications (not only appendicitis or cholecystitis) have atypical symptoms because of the mirrored anatomy [11]. In another case, a 22-year-old woman with SIT had left hypochondriac and epigastric pain, nausea and occasional vomiting, endoscopy revealed that the stomach antrum and body were mirror imaged and the duodenal bulb of the stomach was opening on the left [12]. Symptoms characteristic of the cardiac defects may prevail in patients with SIT and cardiac malformations [13]. Patients having SIT and co-existing chronic cardiac conditions including rheumatic heart disease

can present with dyspnoea, palpitations, elevated jugular venous pressure, peripheral oedema as well as hepatomegaly; physical examination can demonstrate dextrocardia [13]. Clinical features and symptomatology in SIT are summarised in [Table/Fig-1] [2,4,10-16].

System/association	Clinical presentation	Underlying mechanism / explanation	Typical diagnostic clues	Reference (s)
Asymptomatic / Incidental detection	No specific symptoms; detected incidentally during imaging or clinical evaluation	Mirror-image arrangement of viscera without functional disturbance	Detected on chest X-ray, ECG (dextrocardia), or abdominal imaging	[2]
Abdominal pain due to acute appendicitis	Left lower quadrant abdominal pain	Reversal of viscera causes pain to manifest on the opposite side	Imaging reveals appendix on left-side	[14]
Cholecystitis	Left upper quadrant or epigastric pain, nausea, vomiting	Gallbladder located on left-side due to situs inversus	Ultrasound/CT showing left-sided gallbladder	[4,15]
Perforated duodenal ulcer	Epigastric pain and peritonitis localised to the left-side	Mirrored duodenal anatomy	CT abdomen showing reversed pathology	[16]
Primary Ciliary Dyskinesia (PCD) / Kartagener Syndrome	Chronic sinusitis, bronchiectasis, recurrent respiratory infections, neonatal respiratory distress	Defective ciliary motility affecting mucociliary clearance	High-Resolution Computed Tomography (HRCT) chest, nasal nitric oxide test, electron microscopy	[10]
Splenic infarction (rare association)	Acute abdominal pain; imaging shows splenic infarcts	Altered splenic position with possible vascular anomalies	CT abdomen revealing infarcted spleen in mirror position	[11]
Gastro-duodenal abnormalities	Left hypochondriac/epigastric pain, nausea, vomiting	Mirror-imaged stomach and duodenum	Endoscopy showing left-sided gastric and duodenal bulb anatomy	[12]
Cardiac malformations / Rheumatic heart disease	Dyspnoea, palpitations, elevated Jugular Venous Pressure (JVP), oedema, hepatomegaly	Associated congenital or acquired cardiac defects in dextrocardia	Echocardiography showing dextrocardia or structural anomalies	[13]

[Table/Fig-1]: Clinical features and symptomatology in Situs Inversus Totalis (SIT) [2,4,10-16].

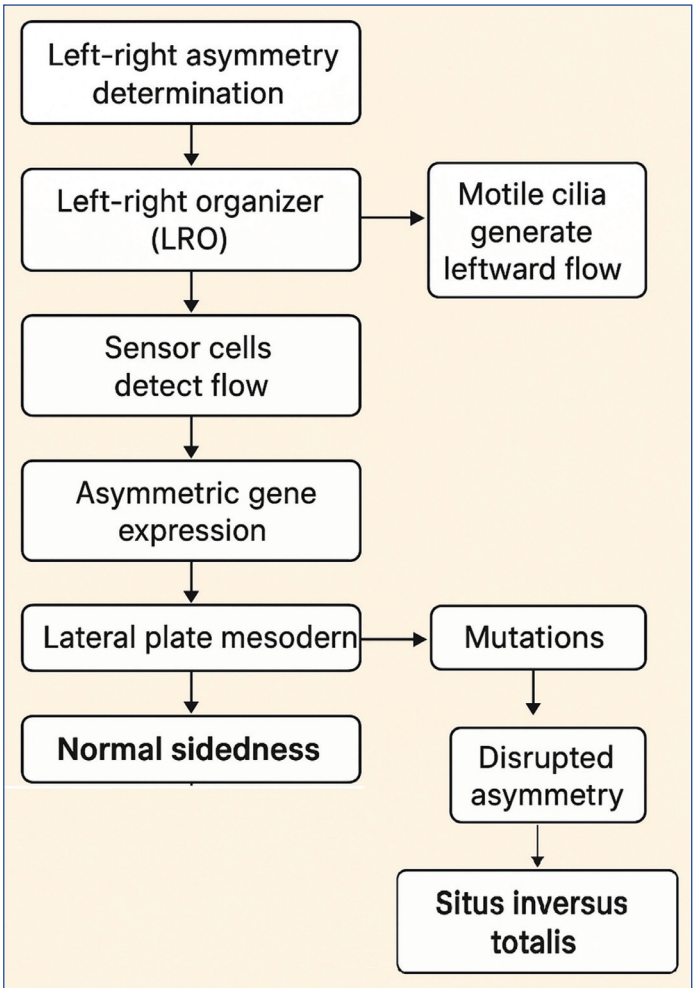
Pathogenesis of SIT

During early vertebrate embryogenesis, left-right asymmetry (laterality) is determined in molecular and biophysical events [17]. The formation of transient organiser structure called the LRO is among the first to occur [17]. Motile cilia cause a directional (leftwards) flow in the extracellular space at the LRO, which disrupts the symmetry in a uniform embryo and causes downstream asymmetric gene expression [17]. This flow is thereby detected by sensor cells (which may have non-motile or mechanosensory cilia), which leads to side-specific activation of signaling pathways (for example involving Nodal, Lefty, Pitx2) in the lateral plate mesoderm [17,18]. This leftward flow or detection are usually randomised by mutations that interfere with the motility of the nodal cilia, or structural or functional aspects of the sensory machinery [18]. In the event of disruption of this breaking of symmetry, mirror-image (or, in unstructured defects) organ repositions may occur i.e., Situs inversus (complete reversal) or, in less organised defects, heterotaxy/situs ambiguous [18,19]. Pathogenesis of SIT is depicted through [Table/Fig-2].

Approach to Diagnosis of SIT

Careful history taking and physical examination can initially create the suspicious (such as right-sided cardiac apex or pain in the "wrong" quadrant) [20]. The most common tests, which are readily available, include chest radiography, plain abdominal films, a 12-lead ECG (with axis and lead changes characteristic of dextrocardia), and abdominal/renal ultrasound which are often adequate to make a presumptive diagnosis since it shows mirror-image placement of thoracic and abdominal viscera [21]. An ultrasound or a chest X-ray will give the initial clear evidence that the clinician will need to interpret the ECGs and imaging with laterality in mind to prevent misdiagnosis [22].

The diagnosis is confirmed by cross-sectional and cardiac imaging, which defines related anomalies [20]. Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) provides appropriate anatomic localisation of thoracoabdominal organ situs and vascular anatomy and is known as modality of choice in cases where detailed preoperative assessment and trauma planning is needed [22]. The use of trans-thoracic echocardiography (and, when necessary, foetal or neonatal echocardiography) is very fundamental due to the fact that SIT can occur with a congenital cardiac malformation [23].



[Table/Fig-2]: Pathogenesis of Situs Inversus Totalis (SIT).

Prenatal diagnosis through the use of targeted obstetric ultrasound and foetal echocardiography has been well-reported and genetic testing (microarray or exome sequencing) is becoming more common in foetuses or neonates when further abnormalities have been observed [24,25]. Few other conditions (such as PCD and specific cardiac defects) frequently coexisting with laterality defects should be screened by the clinicians as well, and thus diagnostic work up of SIT should include both detailed imaging (CT/MRI and echocardiography) and targeted ancillary testing when necessary [23,26]. Diagnostic approaches for SIT are described in [Table/Fig-3] [20-26].

Diagnostic modality	Purpose / findings	Comments / clinical relevance	References
History and physical examination	Suspicion based on abnormal findings: right-sided cardiac apex, pain in "wrong" quadrant	Initial suspicion; guides further testing	[20]
Chest radiography	Mirror-image placement of thoracic organs, dextrocardia	Readily available, initial evidence	[21,22]
Plain abdominal X-ray	Mirror-image placement of abdominal viscera	Initial presumptive diagnosis	[21]
12-lead ECG	Axis and lead changes characteristic of dextrocardia	Must interpret with organ laterality in mind to prevent misdiagnosis	[21,22]
Abdominal /renal ultrasound	Mirror-image placement of abdominal organs	Often sufficient for presumptive diagnosis	[21].
CT/MRI	Detailed anatomical localisation of thoracoabdominal organs and vascular anatomy	Modality of choice for preoperative assessment or trauma planning	[22]
Trans-thoracic Echocardiography (TTE)	Screening for congenital cardiac malformations	Fundamental in all SIT patients; can extend to fetal/neonatal echocardiography	[23]
Prenatal targeted obstetric ultrasound and foetal echocardiography	Early detection of SIT and associated anomalies	Useful for prenatal counselling	[24]
Genetic testing (microarray / exome sequencing)	Detect underlying genetic abnormalities when other anomalies are observed	Increasingly used in fetuses/neonates with suspected SIT	[24,25]
Ancillary testing	Screening for coexisting conditions (e.g., Primary Ciliary Dyskinesia (PCD), specific cardiac defects)	Recommended based on clinical suspicion	[23,26]

[Table/Fig-3]: Diagnostic approaches for Situs Inversus Totalis (SIT) [20-26].

Advances in Imaging and Genetic Diagnostics of SIT

Emerging modalities in diagnostic procedures currently used in SIT are focused mostly towards high-resolution, 3D and functional images to define visceral orientation more precisely [27]. Multi-Detector Computed Tomography (MDCT) and 3D-MRI techniques enable visualisation of complicated cardiovascular and hepatobiliary anatomy in three dimensions, which is especially useful in the planning of surgery or interventional procedures [22,28]. On the same note, foetal Magnetic Resonance Imaging (fMRI) has become relevant in the prenatal detection techniques, which provides better soft-tissue contrast and confirmation of the visceral layout in cases where the ultrasonographic technique is inconclusive [29]. It has been reported that the diagnostic accuracy and reliance on the operator can be improved by the use of Artificial Intelligence-assisted (AI) image interpretation and automated organ-situs mapping algorithms in the CT and MRI datasets [27]. The diagnostic utility of Next-Generation Sequencing (NGS) and Whole-Exome Sequencing (WES) to detect pathogenic mutations in genes involved in control of ciliary motility and determination of left-right axis, including those in DNAH5, DNAI1, CCDC11, and ZIC3 [30]. These genetic panels make it easy to distinguish isolated SIT from similar manifestations like Kartagener syndrome as well as PCD [30].

Surgical Management and Emerging Techniques in SIT

The surgical treatment of SIT requires careful planning and accommodation to the mirrored anatomy to guarantee the safety and good outcomes [31]. During laparoscopic surgeries (like cholecystectomy), the surgeons usually alter the positions of standard ports and use the left-handed approach to fit the reversed positions of organs [31]. As an example, one study emphasised the application of a modified laparoscopic cholecystectomy procedure, which included the left-handed operation and port position adjustment, to treat one patient with chronic cholecystitis and many gallstones effectively [32]. Another study highlighted about the importance of meticulous preparation and intraoperative flexibility to address the specific challenges related to mirrored anatomy in SIT patients during laparoscopic surgical procedures [33]. The 3D laparoscopy-assisted surgery has been applied in case of associated abdominal surgeries with SIT, like in the treatment of gastric cancer [34]. Moreover, laparoscopic radical resection has been successfully applied to rectal cancer patients with SIT even with underlying diseases such as cerebral infarction and diabetes, indicating the benefits of surgery with proper preparation [35].

Emerging management strategies with regard to SIT are aimed at improving the accuracy of surgery and reducing complications by using high technologies and individual methods [36]. An example of this is fluorescence cholangiography which has been applied in laparoscopic cholecystectomy of patients with SIT to enhance the identification of biliary structures to minimise the risk of bile duct damage [36]. This technique implies the use of fluorescent dyes during surgery to visualise the biliary tree, and it provides a real-time representation that is especially useful in the case of reversed anatomy [36]. Also, robotic-assisted surgery is being integrated and is becoming popular which offer greater dexterity and 3D visualisation that are desirable in the treatment of SIT [37]. Such systems enable more accurate suturing and dissections which may have better surgical results and shorten the recovery process [37]. Nevertheless, the usage of robotic surgery on SIT cases demands a special training and equipment, which is not universally available [5,37]. Surgical approaches, advantages, and limitations in patients with SIT are depicted in [Table/Fig-4] [5,31-37].

Category	Approach/Technique	Details / Example	Advantages	Disadvantages	References
Standard laparoscopic surgery	Port position adjustment & left-handed operation	Modified laparoscopic cholecystectomy for chronic cholecystitis with multiple gallstones	Familiar technique; minimally invasive; adaptable to mirrored anatomy	Requires experienced surgeon; steep learning curve for left-handed approach	[31,32]
	Careful preparation & adaptability	Overcoming challenges of mirrored anatomy	Safer surgery; reduces intraoperative errors	Time-consuming planning; risk if not properly adapted	[33]
3D Laparoscopy-Assisted Surgery	3D laparoscopy-assisted surgery	Applied in abdominal surgeries like gastric cancer	Improved depth perception; better orientation in SIT	Requires 3D equipment; higher cost	[34]
	Distal radical gastrectomy	3D-assisted approach in SIT patient with gastric cancer	Precise dissection; safer margins	Limited availability; technical expertise needed	[34]
	Laparoscopic radical resection for rectal cancer	Successful in patients with comorbidities	Minimally invasive; faster recovery; feasible in complex cases	Requires skilled surgeons; longer operative time	[35]

Emerging management strategies	Fluorescence cholangiography	Enhances biliary structure identification during laparoscopic cholecystectomy	Reduces risk of bile duct injury; real-time visualisation	Requires fluorescent dye; added cost	[36]
	Robotic-assisted surgery	Offers dexterity, 3D visualisation, precise suturing and dissection	Precise; reduced fatigue; potentially faster recovery	Expensive; limited access; requires specialised training	[5,37]

[Table/Fig-4]: Surgical approaches, advantages, and limitations in patients with Situs Inversus Totalis (SIT) [5,20-26,31-37].

Surgical Feasibility, Outcomes, and Trends in SIT

Recent systematic analyses of minimally invasive procedures inclusive of laparoscopic and robotic gastrectomy in SIT patients have also documented favourable perioperative outcomes where careful preoperative imaging, operative planning as well as surgeon expertise are ensured [38]. In a systematic review including 30 SIT patients undergoing laparoscopic or robot-assisted gastrectomy, no perioperative mortality was reported also majority of procedures were performed safely with acceptable blood loss, lengths of hospital stay [38]. Only three postoperative complications were reported among laparoscopic cases out of which having only one possibly related to anatomical anomalies rather than inversion itself while the other two were attributed to procedural issues [38]. These results support about feasibility of both laparoscopic, robotic approaches in SIT when it is adapted to reversed anatomy, individualised surgical strategies [38].

Laparoscopic cholecystectomy remains mostly described surgical procedure in the SIT literature having numerous case reports demonstrating successful outcomes when mirrored operating room setup and modified trocar placements are used [39]. Multiple reports describe uneventful recoveries after cholecystectomy or other abdominal interventions such as bile duct reoperation in SIT patients thereby emphasising detailed preoperative identification of anatomy and team coordination as an important aspect for good outcomes [39,40]. Although the altered anatomy presents having technical challenges, most cases recover without complications reflecting improvements in imaging, operative planning as well as laparoscopic technique over time [39,40].

When comparing outcomes in patients having SIT with those showing normal anatomy, complication rates do not usually appear to be intrinsically higher when surgeries are done using appropriate adaptations [38]. In systematic analyses of laparoscopic and robotic procedures in SIT, morbidity was low (<5%) as well as no perioperative deaths were reported although a small number of adverse events occurred in laparoscopic cases but were mostly related to procedural errors rather than situs inversus itself [38]. Operative times in cases of SIT have shown a tendency to be longer than in typical anatomy, largely because of need for modified port placement, mirrored positioning as well as increased demands of intraoperative orientation [38]. Laparoscopic gastrectomy in patients having SIT had a mean operative duration of approximately 205 minutes which can be longer than standard times for similar procedures in patients having normal anatomy thereby reflecting additional complexity [38]. Similarly, some laparoscopic cholecystectomy case reports document extended surgery durations which is sometimes markedly longer than institutional norms thus attributable to the reversed anatomy requiring altered technique and surgeon adaptation [38,41].

Future Directions and Research Perspectives in SIT

Future studies on SIT should concentrate on improving the accuracy of diagnosing the disorder by improving the 3D and MRI imaging and the use of AI to assist in organ-situs mapping, and the genetic research should be further extended into the field of cilia motility and left-right axis determination genes [22,27]. Besides, it is important to examine the neurological implications of SIT including reversed brain asymmetry and also to examine possible factors that may affect the laterality [42]. The surgical innovations (such as robotic-assisted surgery and the use of fluorescence cholangiography) need additional development to achieve better results in patients with the mirrored anatomy [36,37]. In addition, prenatal imaging methods such as foetal MRI can facilitate early diagnosis, whereas extensive research into the relationship between SIT and other congenital defects will help increase general knowledge and management approaches [29].

CONCLUSION(S)

The SIT is an uncommon congenital disorder which is characterised by complete mirror-image transposition of thoracoabdominal organs. Although mostly asymptomatic, it may present with diagnostic and surgical challenges, especially in a case of cardiac defects as well as ciliary dysfunction. Surgical management is dependent on the use of detailed imaging, echocardiography and genetic testing; proper diagnosis depends on the use of modified laparoscopy, 3D-assisted and new robotic surgical approaches. Imaging, AI-assisted organ mapping, and prenatal detection can be performed in order to enhance outcomes. Further studies are required to develop diagnosis, surgical safety and knowledge of associated anomalies.

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