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Safety and efficacy of endoscopic ultrasound as a diagnostic and therapeutic tool in pediatric patients: a multicenter study

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Abstract

Background: Despite the well-established diagnostic and therapeutic applications of endoscopic ultrasound (EUS) in adults, data about its use in children are limited. In this study, we tried to assess the feasibility, safety, and clinical impact of EUS in pediatric patients.

Methods: Data of pediatric patients (<18 years) referred for EUS over a 3-year period to the endoscopy units of four Egyptian tertiary centers were retrospectively analyzed. Significant impact was defined as a new diagnosis or treatment attributed to the EUS procedure.

Results: Twenty-four diagnostic and five therapeutic EUS procedures were conducted in 29 children with a median age of 9 years. Indications for EUS included assessment of solid pancreatic mass ($n = 3$), pancreatic cyst ($n = 2$), suspected chronic pancreatitis ($n = 9$), pancreatic pseudocyst (PPC) ($n = 5$), recurrent hypoglycemia ($n = 1$), bile duct mass ($n = 1$), subepithelial lesion (esophageal, duodenal or anorectal) ($n = 4$), mediastinal mass ($n = 1$), pelvic mass ($n = 3$), and mass at splenic hilum ($n = 1$). Therapeutically, five patients underwent cystogastrostomy for symptomatic PPC with 100% technical and clinical success. EUS was able to diagnose 21 out of the other 24 patients. EUS-guided tissue acquisition was performed in 11 patients with definitive histopathological diagnosis in 10 patients (91%). There was no procedure-related major complication, while minor complications occurred in two cases (transient pain in one case, temporary fever, and vomiting in two cases).

Conclusion: Standard linear EUS equipment and accessories can be used safely and effectively in selected pediatric patients for diagnostic and therapeutic purposes.

Keywords: Egypt, endoscopic ultrasound, EUS, gastrointestinal disease, pediatric, safety, therapeutic

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Introduction

Endoscopic ultrasound (EUS) is a comparatively innovative tool for the evaluation of gastrointestinal (GI) diseases.[1] With an ultrasound transducer located at its tip, this modality permits the creation of high-resolution images of GI wall layers and adjacent organs such as the pancreas, liver, biliary tree, lymph nodes, kidney, and spleen. It also enables visualizing the extraluminal structures, including the mediastinum and retroperitoneum, which can be used to support the diagnosis and staging of extraluminal pathology and tissue acquisition.[2] EUS has been well-established as a diagnostic and therapeutic tool in adults, in whom it is safe, tolerable, feasible, and widely used. EUS also has a valuable therapeutic role in treating various GI or pancreatic lesions such as celiac plexus neurolysis, drainage of pancreatic fluid collection, and biliary drainage.[3]

In children, the most frequent indication of EUS is evaluation of the pancreaticobiliary tract, especially for common bile duct (CBD) pathology, evaluation of acute or chronic pancreatitis, and pancreaticobiliary anomalies.[4] Furthermore, EUS is an appropriate tool to differentiate the GI wall

layers, identify mucosal and submucosal lesions, and clearly distinguish between solid and cystic lesions and direct their management.[5]

Despite its benefits, the application of EUS and EUS-FNA/B in children is still limited, likely due to the lower frequency of GI tumors or pancreaticobiliary diseases in children, the limited awareness among pediatricians of EUS procedures, more incredible difficulty of intubation of the esophagus and duodenum in younger children due to the wide caliber of the scope, the absence of special pediatric endoscopes, and the need for deep sedation or general anesthesia among younger individuals.[6]

Although the literature reports that the application of linear echo-endoscopes may be feasible in patients weighing at least 15–25 kg, available data regarding this modality remain limited.[7] Moreover, to date, most studies have focused on the diagnostic role of EUS in pediatrics,[4,8,9] while studies evaluating its therapeutic role are fewer in number.[10,11]

The indication for EUS in this age group is expanding; thus, there is an unmet need to assess the safety and efficacy of EUS as a diagnostic and therapeutic modality in pediatric patients.

The present study aimed to evaluate the indications and safety of linear EUS as a diagnostic and therapeutic modality in pediatric patients. In addition, we tried to assess the clinical impact on pediatric GI and pancreaticobiliary disorders.

Patients and methods

In this study, we conducted a retrospective analysis of data of pediatric patients (<18 years) who presented with an indication for EUS from May 2017 to June 2020 to the endoscopy units of four Egyptian tertiary centers: Specialized Medical Hospital of Mansoura University, Theodor Biharz Research Institute, Kasr Elainy Hospital of Cairo University, and the Egyptian Liver Research Institute and Hospital.

Acceptable indications of EUS eligible for consideration in our study were assessing pancreaticobiliary diseases with and without tissue acquisition; the evaluation of submucosal lesions, mediastinal lesions, or pararectal lesions; and cystogastrostomy for pancreatic pseudocyst drainage. All EUS diagnostic maneuvers were conducted under deep sedation with intravenous midazolam, propofol, and fentanyl administration, while cystogastrostomy was performed in intubated patients under general anesthesia by an expert anesthesiologist. Highly experienced endosonographers performed EUS procedures in the four centers.

Pentax linear echo-endoscope EG-3870UTK (PENTAX Medical, Tokyo, Japan, insertion tube of 12.8 mm, biopsy channel of 3.8 mm), with a Hitachi–Aloka Avius processor (Hitachi, Tokyo, Japan) and Fujifilm EG-580UT Curved Linear Endoscopic Ultrasound scope (Fujifilm Global, Tokyo, Japan, insertion tube of 12.4 mm, biopsy channel of 3.8 mm with a small bending radius and short rigid section to enable easy access to targeted areas) with SU-1 were used. Fujifilm EG-580UT was used in most cases of cystogastrostomy and cases younger than 6 years. Under EUS-guidance with the assistance of Color Doppler to exclude intervening vasculature, tissue acquisition was performed using different types and sizes of needles (Echotip needle 19G, 22G and Procore needle 20 G, 22 G, Wilson-Cook Medical Inc., Winston-Salem, USA/Acquire needle 22-gauge; Boston Scientific, Natick, MA, USA). After applying Color Doppler, we targeted the lesion by EUS needle with to-and-fro movement within the lesion and fanning technique. We used the slow pull back technique during suction in most cases in case of insufficient material with the first pass. For cystogastrostomy, a 19-gauge EchoTip needle (Wilson-Cook Medical), 0.035 ERCP guidewire (Boston Scientific), 6-French cystotome (Cysto Gastro Set; Endo-flex, GmbH, Voerde, Germany), Souhendra dilator (10 mm; Wilson-Cook Medical), or Dilatation balloon of different sizes (Boston Scientific® CRE balloon), and finally a 10 or 7 French pigtail stent were used in each case.

When tissue acquisition (FNA/B) was performed, the gained material was processed by preserving the core/clotted material in a 10% neutral-buffered formalin fixative to create a tissue block. The remnant of the aspirated sample was to be smeared on a glass slide and fixed immediately in 95% ethyl alcohol for subsequent staining. An experienced cytopathologist analyzed all slides and core material.

The impact of EUS on the patients' subsequent treatment course and complications was reviewed and analyzed. The clinical impact of EUS was scored according to Bjerring *et al.*[12]

(0) No impact on diagnosis or management
(1) Establishment of a definitive diagnosis or exclusion of suspected pathological conditions
(2) Yield of new, relevant findings that subsequently altered the patient-management strategy
(3) Yield of relevant findings with subsequent adoption of an EUS-based therapeutic approach

All patients who underwent a diagnostic procedure were followed up after for 4–6 h post-procedure targeting early detection of any post-procedure complications. Patients who underwent cystogastrostomy were admitted and monitored for 24–48 h and followed up for 1 month to evaluate cyst size. Pathological, surgical, and radiological (including ERCP) data were recruited and correlated with EUS findings.

Ethical considerations

The study protocol was conducted according to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the ELRIAH Ethical Committee, Dakahlia, Egypt (Serial number: OR-2020-12). Signed informed consent forms were obtained from the parents or legal guardians of the pediatric study participants for participation in the study and for the publication.

Statistical analysis

The results were evaluated using descriptive statistics for nonparametric distribution with median values and minimum to maximum intervals. Analyses were performed using the Statistical Package for the Social Sciences version 20 software program (IBM Corporation, Armonk, NY, USA).

Results

Twenty-nine pediatric patients (19 males) with a median age of 9 years (range: 2.5–15 years), and a median weight of 28 kilograms (range: 13–45 kilograms), who underwent diagnostic ($n = 24$ cases) and therapeutic ($n = 5$) EUS procedures were included in this study. The demographic data, clinical presentation, complication and clinical impact of the EUS of the study population are presented in Table 1. PENTAX/linear device was used in 20 cases, while the remaining 9 cases were performed by Fujifilm/linear device. Persistent abdominal/epigastric pain was the most common presentation (13 patients, 44.8%), followed by recurrent abdominal/epigastric pain (8 patients, 27.6%), and tenesmus (4 patients, 13.8%), while dyspnea, mild dysphagia, obstructive jaundice, and recurrent fainting attacks were each presented by one patient. In all these cases, EUS was requested after the failure of cross-sectional imaging (CT/MRI) in providing a definite diagnosis.

In 13 patients, diagnosis has been achieved without tissue acquisition: chronic pancreatitis ($n = 7$), resolving pseudocyst ($n = 1$), rectal abscess with fistula ($n = 1$), duplication cysts ($n = 2$), and chronic pancreatitis was excluded in 2 cases with normal EUS imaging of the pancreas. On the contrary, 11 patients underwent EUS-guided tissue acquisition ($n = 5$ FNA and $n = 6$ FNB) with definitive histopathological diagnosis reached in 10 children while one case was inconclusive (diagnostic utility was 91%). The resultant histopathological diagnoses included four cases diagnosed as neuroendocrine tumors (three pancreatic and one mediastinal), four cases diagnosed as sarcomas (one biliary rhabdomyosarcoma, two pelvic rhabdomyosarcoma, and one pelvic Ewing sarcoma), one case of esophageal spindle cell tumor, and one pancreatic pseudocyst while one case of inconclusive finding. Final diagnosis detected by EUS and the histopathological findings are shown in Table 2. In addition, five patients had symptomatic pancreatic pseudocysts and cystogastrostomy was performed, with technical and clinical success achieved in all patients. The main cause of pancreatic pseudocyst in our patients was the asparaginase-associated pancreatitis (in four patients, being used as a treatment for acute lymphoblastic leukemia), while posttraumatic was the cause in one patient. Figure 1 shows the EUS examination of a pancreatic head mass with color flow doppler application, elastography, and EUS-guided FNB from the mass.

Pancreaticobiliary evaluation was the most common indication and required assessment site (16 cases, 55.2%), followed by rectal examinations (4 cases, 13.7%), while therapeutic interventions were performed in five cases (17.2%).

EUS examination was able to reach a diagnosis in 21 out of 24 patients (87.5%) (10 cases had histopathologically proven diagnosis, and 11 cases had the typical EUS criteria of a disease). The remaining 3 cases with indefinite diagnosis

Table 1. Demographic data of the study population and the clinical impact of EUS.

Case	Age/sex	Weight	EUS indication	EUS procedure	Final diagnosis	Procedure complication[a]	Clinical impact
1	9/F	28	Assessment of epigastric mass by imaging	TA/FNB by 20-gauge Procore needle	Pancreatic NET (rounded cell tumor)	Mild tolerable pain for 6 h	2
2	6/M	17	Assessment of anorectal lesion by imaging	Diagnostic/ assessment. Well-defined lesion where pus came out of the fistulous tract	Abscess	No	2
3	14/F	36	Periampullary bulge by EGD	Diagnostic/ assessment	Duplication cyst	No	2
4	15/F	45	Recurrent hypoglycemia	Diagnostic/ assessment	Normal pancreas	No	2
5	11/F	31.5	Assessment of epigastric mass by imaging	TA/FNA by 19-gauge EchoTip needle	Pancreatic NET	No	2
6	6/M	17	Assessment of pancreatic cyst by imaging	Diagnostic/ assessment	Resolving pan pseudocyst	No	2
7	12/F	32	Assessment of pancreatic mass by imaging	TA/FNA using 22-gauge EchoTip needle	Pancreatic NET	No	2
8	13/F	35	Assessment of the pancreas/CP	Diagnostic/ assessment	Normal pancreas	No	2
9	2.5/M	13	Assessment and drainage of pancreatic pseudocyst	Therapeutic Cyst drainage[b]	Cystogastrostomy	Vomiting, fever for 2 days	3
10	4/M	14	Assessment of pancreatic cyst by imaging	TA/FNA using 22-gauge EchoTip needle	Pancreatic pseudocyst Cyst resolve spontaneously on follow-up	No	2
11	6/M	20.5	Assessment and drainage of pancreatic pseudocyst	Therapeutic Cyst drainage[b]	Cystogastrostomy	No	3
12	7/F	23	Mediastinal mass	TA/FNB using 22-gauge Procore needle	Mediastinal NET	No	2
13	11/M	34	Esophageal SMT by EGD	TA/FNA using 19-gauge EchoTip needle	Esophageal spindle cell tumor	No	2
14	4/M	15.5	Assessment of CBD lesion by imaging	TA/FNB using 22-gauge Procore needle	Biliary Rhabdomyosarcoma	No	2
15	3/M	14	Splenic hilum mass	TA/FNA using 22-gauge EchoTip needle	Inconclusive biopsy	No	Missed follow-up
16	10/F	28	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic calcified pancreatitis	No	2

(Continued)

Table 1. (Continued)

Case	Age/sex	Weight	EUS indication	EUS procedure	Final diagnosis	Procedure complication[a]	Clinical impact
17	8/F	24	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic pancreatitis Gallbladder starry-sky appearance	No	2
18	10/M	32	Duodenal SMT by EGD	Diagnostic/ assessment	Duplication cyst	No	2
19	9/M	28	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic pancreatitis	No	2
20	8/M	26	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic calcified pancreatitis. Pancreatic duct stone	No	2
21	10/M	30	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic calcified pancreatitis	No	2
22	11/M	34	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic calcified pancreatitis pancreatic duct stone	No	2
23	9/F	32.5	Assessment of the pancreas/CP	Diagnostic/ assessment	Chronic calcified pancreatitis	No	2
24	12/M	31	Assessment and drainage of pancreatic pseudocyst	Therapeutic Cyst drainage[b]	Cystogastrostomy	No	3
25	12/M	32	Assessment and drainage of pancreatic pseudocyst	Therapeutic Cyst drainage[b]	Cystogastrostomy	No	3
26	9/M	26	Assessment of pelvic mass by imaging	TA/FNB using 22-gauge Acquire needle	Sarcoma	No	2
27	15/M	45	Assessment of pelvic mass by imaging	TA/FNB using 20-gauge Procore needle	Rhabdomyosarcoma	No	2
28	9/M	26	Assessment and drainage of pancreatic pseudocyst	Therapeutic/Cyst drainage[b]	Cystogastrostomy		3
29	7/M	19	Assessment of pelvic mass by imaging	Tissue acquisition/ FNB using 20-gauge Procore needle	Rhabdomyosarcoma		2

CBD, common bile duct; EUS, endoscopic ultrasound.
[a]No detected post-procedure-related major complication (bleeding, perforation, or severe pancreatitis).
[b]Using 19-gauge EchoTip needle, 6-Fr cystotome, balloon dilatation or Souhendra dilator and then 7- or 10-Fr pigtail stent.

included a case with inconclusive biopsy findings and two cases with normal EUS examination.

Regarding the follow-up of the interventions in the study, no recurrence was reported in any of the cases. One child spontaneously extruded/vomit the stent after 1 month of complete resolution of the cyst. The stents were removed in three cases 4–6 months after resolution of pancreatitis, while the last case is scheduled for stent removal after 24 months because of a suspected disconnected pancreatic duct syndrome.

Discussion

The current study reported the experiences of four Egyptian tertiary referral endoscopy centers in which pediatric patients were referred for EUS

Table 2. Final diagnosis detected by EUS ± histopathological examination.

Final diagnosis	Frequency (n)	Percentage (%)
Abscess	1	3.4
Biliary rhabdomyosarcoma	1	3.4
Chronic calcified pancreatitis/chronic pancreatitis	7	24.1
Cystogastrostomy	5	17.2
Duplication cyst	2	6.9
Esophageal spindle cell tumor	1	3.4
Inconclusive biopsy	1	3.4
Mediastinal NET	1	3.4
Normal pancreas	2	6.9
Pancreatic NET	3	10.3
Pancreatic pseudocyst	2	6.9
Pelvic sarcoma	3	10.3
Total	29	100.0

EUS, endoscopic ultrasound.

examination. Indications for referral included various pediatric pathologies involving the GI tract and pancreaticobiliary system.

Our study included 29 children ranging in age from 2.5 to 15 years, suggesting that the application of EUS and EUS FNA/B was safe and feasible, with substantial clinical impact on the management of pediatric GI and pancreaticobiliary disorders. EUS clearly elucidated the diagnosis in almost half of the included patients with no need for tissue acquisition. Still, 37.9% of the patients experienced EUS-guided tissue acquisition, which revealed a definitive diagnosis in all cases except one with persistent inconclusive results.

We also report here that the standard linear EUS equipment and accessories can be applied in pediatric patients to conduct different EUS therapeutic interventions and can be safely used in pediatric patients as young as 2.5 years old; ultimately, technical features of the echo-endoscope of concern, such as size and length of the distal rigid tip, were not limiting features.

Our work suggests that EUS plays a significant role in establishing a definitive diagnosis and in managing pediatric disorders, with an important clinical impact of more than 90%.

The most frequent indication for EUS in our study was the investigation of the pancreaticobiliary tract (69% of our cases), which was similar to the existing literature.[13] In a recent study from the United States about the use of EUS in pediatric age group, the most common indications were pancreatic-related disorders such as pancreatic fluid collections (18.4%), recurrent chronic and acute pancreatitis (14.3%), and acute pancreatitis characterization (13.3%).[14]

While EUS was beneficial in the diagnosis of seven patients with chronic pancreatitis, three patients with pancreatic NET, two with resolving pseudocyst, one biliary rhabdomyosarcoma, it has also a valuable role in excluding suspected chronic pancreatitis in two cases. Furthermore, successful drainage of symptomatic pancreatic pseudocyst was performed in five patients. In a Latin American study describing the diagnostic value of EUS in pediatric patients with pancreaticobiliary disorders, EUS showed abnormalities in 85% of patients.[15] The main indications of EUS in this study was the recurrent acute pancreatitis (54%). The main EUS findings were microlithiasis (25.9%), chronic

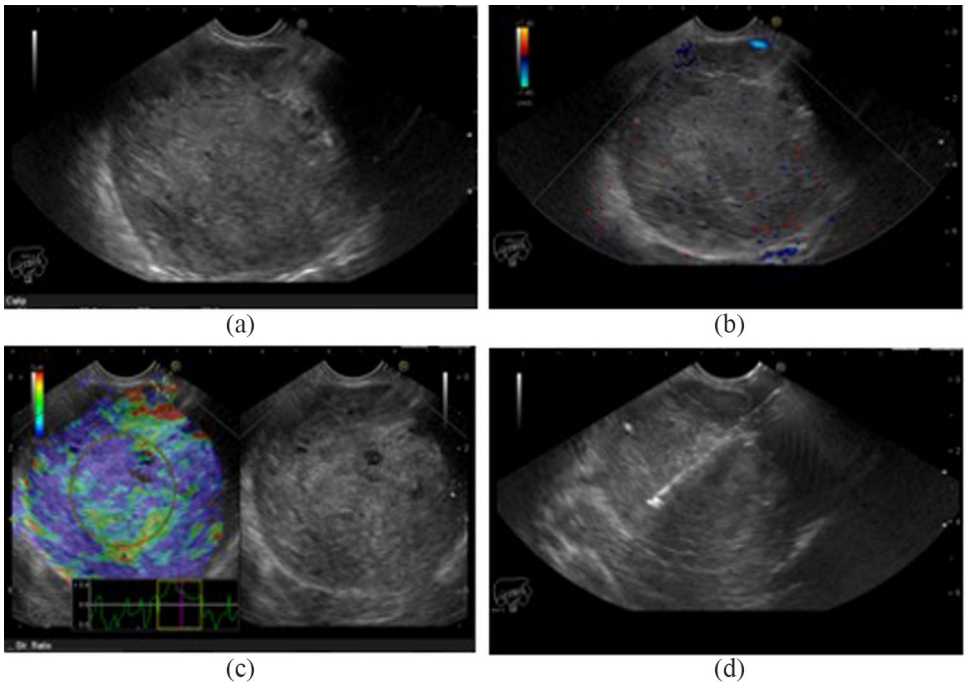

Figure 1. EUS examination of a pancreatic head mass: (a) Large isoechoic pancreatic head mass, (b) Color flow doppler, (c) Elastography (heterogeneous blue green) and strain ratio (8.9), and (d) EUS-guided FNB from the mass.

pancreatitis (16.7%), and pancreatic tumors in (11.1%) of patients.

In addition, rectal EUS can be performed safely and effectively. Three patients with pelvic sarcoma and one case of peri-rectal abscess were definitely diagnosed with rectal EUS. Data about the applicability and safety of EUS are scarce in literature and always limited to specific indications as pediatric inflammatory bowel disease.[16]

In 11 of our patients who underwent EUS-guided tissue acquisition ($n=5$ FNA and $n=6$ FNB) using different gauge echo tips and procore needles, the procedures were safely performed with no reported acute or delayed complications apart from mild tolerable transient pain in a single case. Ten lesions were reported as neoplastic diseases with sufficient tissue material, including four cases diagnosed as neuroendocrine tumors (three pancreatic and one mediastinal), four cases diagnosed as sarcoma (one biliary rhabdomyosarcoma, two pelvic rhabdomyosarcoma, and one pelvic Ewing sarcoma), one case of esophageal spindle cell tumor, while the findings of one were inconclusive. All diagnosed patients were subsequently directed to receive proper treatment. The feasibility, safety, and diagnostic utility of EUS-guided tissue acquisition in pediatrics with different indications were reported by a large Indian study including 76 cases.[17] The main indications for EUS in this report were solid pancreatic tumors (43.3%) and lymphadenopathy (44.7%). The authors confirmed the successfulness of all procedures without major complications. Minor adverse events included throat pain (10%) and abdominal pain (3%), and minor bleeding at puncture location (3%). Histopathological diagnosis was achieved in 88.1% of cases.

The most common cause of pancreatic cystic lesions in childhood is pseudocyst, which accounts for 75% of all cases.[18] Meanwhile, common causes of pancreatic fluid collection in children worldwide are trauma (50% of cases), gallstone, idiopathic, heredity, viral infection, or toxin-mediated pancreatitis.[19] In our study, EUS-guided pseudocyst drainage was safely performed in five children, culminating in successful pseudocyst resolution during the follow-up period with no post-procedure complications except vomiting and low-grade fever that were self-limited in one case within 2 days while managed with conservative treatment in the other case. These results were in concordance with those of Jia *et al.*,[20] who reported the safety of cyst gastrostomy

with 7-French stent replacement in two patients aged 6 and 17 years, respectively, with body mass index values of more than 18.5 kg/m^2. Also, our results were in agreement with those of Jazrawi *et al.*,[21] who reported successful outcomes of EUS-guided cyst gastrostomy in 10 pediatric patients ranging in age from 4 to 17 years.

Our study has some limitations including the retrospective nature of the study and the relatively small number of patients. However, this was the case of most published reports about the use of EUS in this age group because of the low frequency of GI tumors or pancreaticobiliary diseases in children, in addition to the limited awareness among pediatricians regarding the capacity and conduct of EUS procedures in this population.

In conclusion, standard linear EUS equipment and accessories can be used safely and effectively in selected pediatric patients to diagnose GI-related diseases, especially pancreaticobiliary, and therapeutic purposes, including EUS-guided cystogastrostomy.

Declarations

Ethics approval and consent to participate

The study protocol was conducted according to the ethical guidelines of the 2013 Declaration of Helsinki and was approved by the ELRIAH Ethical Committee, Dakahlia, Egypt (serial number: OR-2020-12). Signed informed consent forms were obtained from the parents or legal guardians of the pediatric study participants for participation in the study.

Consent for publication

Signed informed consent were obtained from the parents or legal guardians of the pediatric study participants for publication.

Author contributions

Khalid Mohamed Ragab: Conceptualization; Visualization.

Mohamed El-Kassas: Writing – review & editing.

Ahmad Madkour: Visualization; Writing – review & editing.

Hussein Hassan Okasha: Conceptualization; Data curation; Supervision; Visualization; Writing – review & editing.

Ramy Hassan Agwa: Data curation; Visualization; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data are available upon a reasonable request to the corresponding author.

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