Wydawnictwo UR 2024
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2024.4.15

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2024; 22 (4): 911–920

REVIEW PAPER

Valentino's syndrome – a systematic review of a life-threatening mimic of acute appendicitis

Sajad Ahmad Salati, Yasir Ahmed AlSalamah, Lamees Sulaiman AlSulaim

Department of Surgery, College of Medicine, Qassim University, Unaizah, Kingdom of Saudi Arabia

ABSTRACT

Introduction and aim. Valentino's syndrome is an atypical but potentially lethal presentation of a perforated peptic ulcer. It closely mimics appendicitis. Literature about this disorder is sparse due to its rarity. Hence, this article was compiled to gain an understanding of this disorder. This article was composed to review the profiles of patients with Valentino's syndrome reported in the recent literature.

Material and methods. A systematic literature search was conducted through electronic databases, including PubMed, ResearchGate, and Scopus, using the key words and terms "Valentino's syndrome," "perforated duodenal ulcer simulating acute appendicitis," and "perforated peptic ulcer mimicking acute appendicitis." Only English literature was considered for inclusion in this study, and the time frame was fixed between 2012 and 2023.

Analysis of the literature. Twenty-seven cases from both genders, ranging in age from 7 to 76 years, were included in the review. In 20 cases, the diagnosis was made at laparotomy for a presumed diagnosis of acute appendicitis. Six cases had undergone appendectomy as their first surgical operation, but their condition had worsened postoperatively and had undergone re-exploration at a delay of 3 to 10 days (mean 6±2.86 days; mode 3 days). One patient required a third abdominal exploration.

Conclusion. Valentino's syndrome has a very high rate of misdiagnosis. There is a need to increase awareness of this disorder among healthcare professionals so that it might be considered a differential diagnosis while a patient is being evaluated for acute abdomen

Keywords. appendicitis, Graham's patch, peptic ulcer, perforation, peritonitis, Valentino's syndrome

Introduction

One of the most common causes of right lower quadrant (RLQ) abdominal pain is acute appendicitis.[1] Typically beginning in the periumbilical region, the pain advances to the RLQ and is connected to anorexia, vomiting, and nausea.[1] However, a variety of common and uncommon disorders may have identical clinical manifestations. Valentino's syndrome [syn: Valentino appendix] is one such rare condition wherein a perforated peptic ulcer very closely mimics acute appendicitis.[2-4] As depicted in Figure 1, fluids leaking out of the perforated gastric or duodenal ulcer stream along the right paracolic gutter reach the RLQ, causing peritoneal and periappendiceal inflammation.

Although there are certain distinctions, the clinical signs and symptoms often follow a three-phase pattern that is comparable to a typical perforation of the peptic ulcer as follows:[5]

First Phase: Severe upper abdominal pain like a bolt from the blue, due to perforation of the ulcer and leakage of acidic contents for 0–2 hours after onset.

Second Phase: Abdominal pain shifting to the right lower quadrant within 2–12 hours after onset, as a result of tracking of the leaking fluid from the perforated ulcer

Corresponding author: Lamees AlSulaim, e-mail: dr.lameesz@gmail.com, l.alsulaim@qu.edu.sa

Received: 17.03.2024 / Revised: 15.05.2024 / Accepted: 20.06.2024 / Published: 30.12.2024

Salati SA, AlSalamah YA, AlSulaim LS. Valentino's syndrome – a systematic review of a life-threatening mimic of acute appendicitis. *Eur J Clin Exp Med.* 2024;22(4):911–920. doi: 10.15584/ejcem.2024.4.15.

along the right paracolic gutter, causing peritoneal and periappendiceal inflammation as depicted in Figure 1.

Third Phase: If not diagnosed and managed within 12 hours, generalized peritonitis sets in and manifests as diffuse abdominal pain and abdominal distension with acute circulatory collapse.

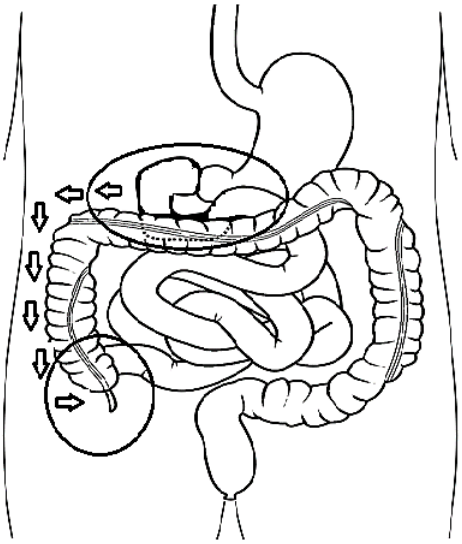

Fig. 1. Etiopathogenesis of Valentino's syndrome (Image credits: Sajad Ahmad Salati – author)

Historically, Valentino's syndrome (VS) is named after Rudolph Valentino, a well-known American actor who was born in Italy. He underwent an appendectomy in 1926, at the age of 31, after exhibiting symptoms and signs of appendicitis. He didn't get better, though, and after a week, he passed away due to peritonitis. The autopsy revealed that he actually had a perforated peptic ulcer.[2] This condition, if misdiagnosed and ignored, can have ramifications similar to those that Rudolph Valentino suffered a century ago.

Peptic ulcer perforations occur in around 2–15% of patients and have a mortality rate ranging from 1.3% to 25%. They are among the most uncommon complications related to the disease.[6] More than half of the cases are female; compared to males, they are older and have more comorbidities.[6–7] Numerous etiologic factors, such as the use of steroids, non-steroidal anti-inflammatory medicines (NSAIDs), smoking, *Helicobacter pylori*, and a diet high in salt, have been found to operate by influencing acid secretion in the stomach mucosa. In most patients, there are multiple factors present that tend to increase the ulcerogenic impact.[8]

Aim

Because VS is considered a rare manifestation of a perforated peptic ulcer and the majority of the relevant literature consists of solitary case reports, its exact epidemiology is still unknown, and healthcare professionals are not well-informed about it. Considering this, any analysis was undertaken to examine the recently published case reports of VS in order to gain a deeper comprehension of the characteristics of this rare disease that places patients at a significant risk of complications and death.

Material and methods

Methods

A systematic literature search was conducted through electronic databases, including PubMed, ResearchGate, Scopus, and Google Scholar, using the key words and terms "Valentino's syndrome", "perforated duodenal ulcer simulating acute appendicitis" and "perforated peptic ulcer mimicking acute appendicitis". The search was carried out by using individual keywords with a combination of Boolean logic (AND). Only English literature was considered for inclusion in this study. The time frame fixed was 2012–2023.

Criteria for considering studies

Articles, including case series and case reports, that provided a precise and comprehensive account of the variables were included in the review process.

Participants and outcome measures

Only those cases were included where the diagnosis of Valentino's syndrome had been established through surgical exploration. The ten variables (Table 1) reported and analyzed include: [i] age of the patient; [ii] gender; [iii] duration of symptoms; [iv] history of NSAID intake; [v] clinical features; [vi] provisional diagnosis on clinical assessment; [vii] findings on imaging; [viii] management; [ix] operative findings; and [x] H-pylori eradication status.

Exclusion

Excluded were the original studies, systematic reviews, or meta-analyses that offered condensed data without a comprehensive analysis of the variables. Additionally, non-English language articles were not included.

Risk of bias

The study analyzed articles that were obtained via Open Access, made available by Qassim University and Saudi Digital Library through institutional subscriptions, or else obtained through requests to the authors through the ResearchGate platform; consequently, it is possible that some articles that were not accessible through these sources may have got overlooked.

Methodological quality checking

For comparison with the checklist that was self-drafted for this study, checklist items from Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) and previously published peer-reviewed literature were used.

Data synthesis (extraction and analysis)

Data related to the nine variables was extracted and arranged in form of Tables 1 and 2. The collected data was then analyzed with Statistical Package for Social Sciences (IBM-SPSS version 27.0, Armonk, NY, USA) and Microsoft Excel (Office Version 16, Microsoft, Redmond, Washington, USA).

The characteristics of participants were described with descriptive statistical analyses such as simple frequencies, measures of central tendency, and measures of variability. Then, the information was presented using frequencies, summary measures, tables, and figures as shown in the results. $p<0.05$ and 95% confidence level were used as a difference of statistical significance. Moreover, the details of the included cases were provided in form of Table 1 and 2.

Analysis of the literature

Study selection

The electronic database search resulted in a total of 66 articles; 24 were identified in PubMed, 16 in ResearchGate, and 13 in Scopus. After excluding 18 duplicated articles, 35 were used to screen titles and abstracts, after which 31 potentially relevant articles in English were assessed for the eligibility criteria. Finally, 24 articles were included in the review after the inability to retrieve 4 articles and the detection of deficient data in 3 articles, as shown in Figure 2. No automation tools were used, and all the exclusion and inclusion of articles was undertaken by the authors manually.

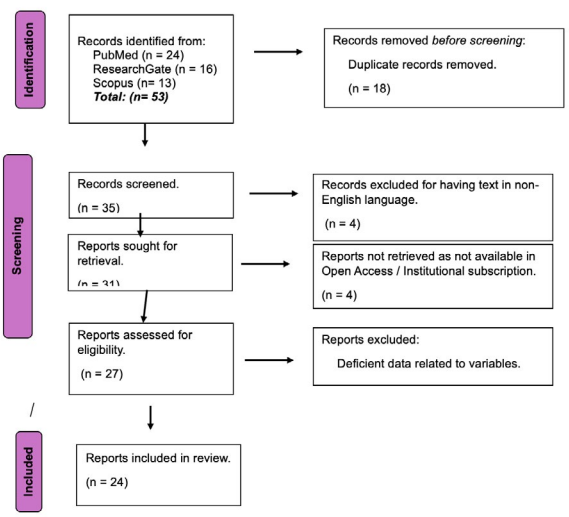

Fig. 2. Flowchart of the reviewed articles

There were 24 articles, including 22 case reports (each with a single patient) and 2 case series (with 2 and 3 patients). There were 27 cases (n=22; 81.5% males and n=5; 18.5% females), ranging in age from 7 to 76 years (mean 33±16.96 years). 4 (14.8%) cases had a positive history of prolonged NSAID intake, and 1 (3.7%) case had consumed a methylprednisolone course a week before this complication. For convenience in description, the included cases can be categorized into two types: type A (n=21, 77.8%) who had reported symptoms without any history of intervention, and type B (n=6, 22.2%) who had undergone appendectomy as their first surgical operation and got diagnosed when instead of recovery, their condition had worsened, leading to re-exploration. The duration of symptoms at presentation for cases of type A ranged from 4 hours to 7 days, and the majority of them (n=13; 48.1%) had reported within 24 hours. Six cases (type B) did not show expected improvement after appendectomy and deteriorated. Re-exploration was undertaken from 3 to 10 days (mean 6±2.86 days; mode 3 days) post-appendectomy. 2 cases were detected during prolonged index admission, and 4 cases were readmitted to the same or some other facility after being discharged home.

The clinical features cases included right lower abdominal pain/tenderness (n=21; 100%), pain in the upper abdomen with shift to the right lower quadrant (n=8; 35%), nausea/vomiting (n=14; 75%), and fever (n=6; 30%) in 21 type A. Type B cases had presenting features of peritonitis and sepsis in their second admission, whereas in the first admission, they had been managed as acute appendicitis on the basis of clinical presentation. The provisional diagnosis on the basis of clinical features was acute appendicitis (with or without perforation or lump formation) in 26 (96.3%) cases and peritonitis with viscus perforation in 1 (3.7%); in the second admission, all six Type B cases were diagnosed as peritonitis. In 3 female patients, ovarian pathology (Mittelschmerz, ovarian cyst, ovarian torsion) was considered a second differential diagnosis, whereas in 1 pediatric case, Meckel's diverticulitis was considered a differential diagnosis. The final diagnosis was perforated peptic ulcer in 26 (96.3%) cases and acute pancreatitis in 1 (3.7%) case.

As far as imaging is concerned, three modalities were used (alone or in combination) during the assessment, including a plain X-ray abdomen (with or without an X-ray chest), an ultrasound abdomen, and a CT scan of the abdomen. Plain X-rays were conducted in 11 cases (40.7%) and in 5 (18.5%); the images were within normal limits; pneumoperitoneum was detected in 5 (18.5%); and a sentinel loop in RLQ was seen in 1 (3.7%). Ultrasound Abdomen was conducted in 15 (55.6%), and intraperitoneal free fluid was found in 10 (37%), pneumoperitoneum in 5 (18.5%), features of acute appendicitis in 5 (18.5%), and ovarian cyst in 1 (3.7%) case. A CT scan of the abdomen had been advised in 11 cases (40.7%), and intraperitoneal free fluid was revealed in 10 (37%), intraperitoneal air pockets/pneumoperitoneum in 6 (22.2%), oral contrast leakage through the duodenum in 1 (3.7%), features of acute

Table 1. Study characteristics of the patients (demographics and preoperative assessment)*

Serial number	Series	Year of publication	Number of cases	Age (years)/ Gender (M-F)	Duration of symptoms (hours-h; days)-d	Presenting complaints	H/o NSAIDs intake	Provisional Diagnosis	Findings on imaging
1	Wijegoonewardene, et al.[2]	2012	1	30/F	4h	**RLQ abdomen pain /tenderness** * Got symptoms 4 hours after removal of intrauterine contraceptive device	-	Appendicitis	**USG:** Minimal free fluid in pelvis
2	Mahajan et al.[3]	2014	1	21/M	8 h	**-RLQ abdomen pain /tenderness** **-Nausea/vomiting** * Epigastric pain to start with and then shift to RLQ	Yes	Appendicitis	-
3	Mbarushimana et al.[4]	2014	1	12/M	4h	**RLQ abdomen pain /tenderness** **-Nausea/vomiting**	-	Perforated appendix/Meckel diverticulum	**Plain Xray:** Pneumoperitoneum
4	Sultan and Pal[9]	2015	3	48/M	7 d PA (Type B)	Abdominal distension and pain ; fever, bile discharge through appendectomy wound , peritonitis	-	Post appendectomy; Peritonitis	-
				28/M	10 d PA (Type B)	**- Nausea/vomiting** Abdominal distension and pain; septic shock ; peritonitis.	-	Post appendectomy; Peritonitis	-
				30/M	3d PA (Type B)	**Nausea/vomiting** * Type B ; Pain abdomen, High grade fever, dehydration, features of peritonitis	-	Post appendectomy; Peritonitis	**CT:** Oral contrast spillage in the duodenal area
5	Blundell et al.[10]	2015	1	14/M	12h	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** - Pain epigastrium shifting to RLQ; Fever ; positive family history of PUD.	-	Appendicitis; peritonitis	**X-Ray:** Pneumoperitoneum; Football sign
6	Hussain et al.[11]	2016	1	7/M	1d	**RLQ abdomen pain /tenderness** * Pain in epigastrium and umbilical areas	-	Appendicitis	-
7	Ramírez-Ramírez et al.[12]	2016	1	29/M	2d	**RLQ abdomen pain /tenderness**	-	Perforated Appendicitis	**-X-Ray:** Pneumoperitoneum
8	Chávez et al.[13]	2017	2	26/M	8h	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** **Fever**	Yes	Peritonitis	**- X ray:** Sentinel loop in RLQ **USG:** Free fluid in pelvis **CT:** Pneumoperitoneum, free fluid,
				76/M	8d PA (Type B)	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** Periumbilical pain that shifted to RLQ; fatigue, anorexia	-	1.Appendicitis; 2. Post appendectomy; Peritonitis	**X-Ray:** 8 days post-appendectomy, dilated bowel loops in RLQ and pneumoperitoneum **USG:** Pericaecal free fluid before appendectomy
9	Amann et al.[14]	2017	1	18/F	1 d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** * Pain upper abdomen; similar pain 12 days prior treated with H2-blockers	Yes	Appendicitis; Ovarian torsion	**CT:** Pneumoperitoneum within the greater sac and free
10	Sgro et al.[15]	2017	1	32/M	4h	**RLQ abdomen pain /tenderness**	-	Appendicitis;	-
11	Iloh et al.[16]	2018	1	45/M	3d PA (Type B)	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** - At onset, sudden epigastric pain shifting to RLQ; appendectomy undertaken followed by generalized abdomen pain after 3 days.	-	1-Appendicitis ; 2: Post appendectomy; Peritonitis	**USG:** Free fluid in peritoneal cavity
12	Yildiz et al.[17]	2018	1	17/M	-	**RLQ abdomen pain /tenderness** **-Nausea/vomiting**	-	Appendicitis	**X-ray:** Normal Study **USG:** Free fluid in RLQ

13	Mohan et al.[18]	2018	1	17/M	1d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** -Fever	-	Appendicitis	**X-ray:** Pneumoperitoneum **USG:** Free fluid in RLQ and pelvis **CT:** Free fluid in peritoneal cavity; no clear perforation
14	Brandon et al.[19]	2019	1	24/F	-	**RLQ abdomen pain /tenderness**	-	Appendicitis; mittelschmerz; ovarian cysts	**USG:** Transvaginal US showed fluid in cul-de-sac **CT:** Inconclusive; appendix not visualized
15	Phadnis et al.[20]	2019	1	42/M	4h	**RLQ abdomen pain /tenderness** **-Nausea/vomiting**	Yes	Appendicitis	**X-ray:** Normal **USG:** Free fluid with thick appendix (6mm)
16	Noussios et al.[21]	2020	1	51/M	6h	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** * Pain abdomen with positive signs of acute appendicitis; history of duodenal ulcer for 10 years with *H. pylori* eradication	Yes	Appendicitis	**X-ray**: Normal chest and abdomen Xray
17	Karthik et al.[22]	2020	1	60/M	3 d	**RLQ abdomen pain /tenderness** * Fever, pain in right groin, restlessness; H/O PPIs intake PUD for 10 years.			**X-ray**: Normal **USG:** "Probe tenderness" and fluid collection in the RLQ **CT:** Free air in the RLQ and paracolic gutter
18	Lopez-Casillas et al.[23]	2020	1	52/M	1d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** * Fever, dehydration,	-	Appendicitis	**USG:** Free fluid , increased fat echogenicity, a retrocecal 10 mm swollen appendix
19	Rodrigo et al.[24]	2022	1	31/F	5d PA (Type B)	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** * Appendectomy followed by clinical deterioration and bilious discharge through surgical site; re-exploration undertaken on 5th day. H/O steroid intake	-	Appendicitis	**USG:** Swollen appendix; a right-sided 4 cm × 4.5 cm ovarian cyst **CT:** Post appendectomy. CT showed multiple fluid collections, no pneumoperitoneum
20	Devi et al.[25]	2022	1	22/M	2d	**RLQ abdomen pain /tenderness** - Pain in right groin, fever	-	Pain in right groin, fever	**USG:** "Probe tenderness" and fluid collection in RLQ. **CT:** Air pockets over right kidney and the right paracolic gutter; fluid in Morrisons pouch
21	Arumugam et al.[26]	2022	1	28/M	4d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting**	-	Appendicular mass	**USG:** "Probe tenderness" in the RIF **CT:** Acute edematous pancreas with peripancreatic fluid collection suggestive of acute pancreatitis
22	Machaku et al.[27]	2023	1	23/M	7 d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** - Fever, guarded lower abdomen		Perforated appendix, perforated peptic ulcer	**USG:** Suggestive of perforated appendicitis
23	Villamil-Angulo et al.[28]	2023	1	59/M	3d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** Generalized abdomen pain shifted to RLQ, diarrhea	-	Appendicitis	-
24	Komatreddy et al.[29]	2023	1	50-/F	4d	**RLQ abdomen pain /tenderness** **-Nausea/vomiting** Pain started in epigastrium, then shifted to RLQ		Peritonitis due to Perforated Appendix	**X-ray :** Normal **USG:** Fluid collection in pelvis **CT:** Multiple loculated right subhepatic fluid collections with inflamed appendix

* type B – patient diagnosed only after appendectomy

Table 2. Study characteristics (management, operative findings and *H. pylori* status)

Serial number	Series	Number of cases	Management	Operative findings	Postoperative H. pylori eradication
1	Wijegoonewardene, et al.[2]	1	Exploratory laparoscopy; lavage; repair of prepyloric ulcer with falciform ligament patch	0.5 cm anterior prepyloric ulcer; turbid fluid in peritoneum; appendix normal	Yes
2	Mahajan et al.[3]	1	Exploratory laparoscopy, lavage and repair of DU perforation	Perforated ulcer in the first portion of duodenum with bile leak	-
3	Mbarushimana et al.[4]	1	Exploratory laparoscopy, lavage and repair of DU perforation	A large volume of turbid fluid tracking to the pelvis and a 0.5 cm perforation in the anterior wall of the first part of the duodenum	Yes
4	Sultan and Pal[9]	3	Exploratory laparotomy; lavage; Graham patch repair of duodenal ulcer ; postoperative active ventilation for 4 days , ICU care , hospitalization for 13 days.	Perforated duodenal ulcer (DU), anterior D1	-
			Exploratory laparotomy; lavage; Graham patch repair of duodenal ulcer; postoperative active ventilation for 5 days, ICU care, abdominal dehiscence management	Perforated duodenal ulcer (DU)	-
			Exploratory laparotomy; lavage; Graham patch repair of duodenal ulcer; postoperative active ventilation for 4 days , ICU care	Perforated duodenal ulcer (DU)	-
5	Blundell et al.[10]	1	Exploratory laparoscopy; lavage; modified Graham repair of duodenal ulcer	Duodenal ulcer perforation	-
6	Hussain et al.[11]	1	Laparotomy started with grid iron incision for appendectomy and then extended by Rutherford Morrison incision; repair of duodenal ulcer by Graham patch; lavage; appendectomy.	Lot of brownish-green fluid; normal appendix; perforation in the anterior wall of first part of duodenum	-
7	Ramírez-Ramírez et al.[12]	1	Exploratory laparoscopy; lavage; repair of duodenal ulcer with Graham patch; appendectomy	A 5 mm perforated duodenal ulcer on the anterior surface of the first part of the duodenum; hyperemic caeca appendix with fibrin and peri- appendicular fluid.	-
8	Chávez et al.[13]	2	Exploratory laparoscopy; lavage; modified Graham repair of antral perforation	Free fluid with gastric contents; 1 cm gastric antrum, 2 inches from the pylorus	-
			1st operation: laparoscopic appendectomy; 2nd operation: exploratory laparotomy Repair of duodenal perforation by Graham patch; lavage	1st operation: Purulent fluid along paracolic gutter and pelvis; inflamed mesoappendix 2nd operation: 5 mm perforation in anterior wall of 2nd part of duodenum.	-
9	Amann et al.[14]	1	Exploratory laparoscopy and Graham patch repair of DU perforation	Small, perforated ulcer in the first portion of duodenum	Yes
10	Sgro et al.[15]	1	Exploratory laparoscopy and Graham patch repair of DU perforation	Perforated ulcer anteriorly in the first portion of duodenum	-
11	Iloh et al.[16]	1	Exploratory laparotomy; lavage; primary repair of pre-pyloric ulcer with biopsy;	5 liters of purulent fluid; 3 mm anterior prepyloric ulcer	Yes
12	Yildiz et al.[17]	1	Exploratory laparotomy and repair of anterior gastric ulcer with pedicled omentum	Normal appendix, pus flowing from upper abdomen, perforated anterior gastric ulcer	-
13	Mohan et al.[18]	1	Exploratory laparotomy, lavage, Graham patch repair of perforated duodenal ulcer	Sero-purulent fluid collection, appendix normal, sealed anterior perforation in first part of duodenum	-
14	Brandon et al.[19]	1	Exploratory laparoscopy converted to minilaparotmy; lavage, repair of duodenal ulcer with Graham patch	Cloudy fluid in peritoneal cavity; normal appendix, pinhole perforation in the first part of the duodenum.	-
15	Phadnis et al.[20]	1	Exploratory laparoscopy converted to laparotomy; lavage; Graham patch repair of DU perforation	500 ml of bile-stained fluid, perforated ulcer in the first portion of duodenum	-
16	Noussios et al.[21]	1	Exploratory laparotomy; repair of perforated duodenal ulcer with omentoplasty	Retroperitoneal perforation of a duodenal ulcer	-
17	Karthik et al.[22]	1	Exploratory laparotomy; lavage, Graham patch repair of DU perforation	Bile-stained fluid and food particles in retroperitoneum, no intraperitoneal fluid; appendix normal; a retroperitoneal perforation (approximately 3 mm × 4 mm) of posterior wall of duodenum	-
18	Lopez-Casillas et al.[23]	1	Exploratory laparotomy, lavage, modified Graham patch repair (and biopsy) of perforated duodenal ulcer	150 cc seropurulent fluid collection, appendix edematous, anterior perforation in first part of duodenum	-
19	Rodrigo et al.[24]	1	1st: Open appendectomy and ovarian cystectomy done - 2nd: Exploratory laparotomy; lavage and repair of duodenal ulcer; patient got complicated with drain induced colonic perforation requiring re-laparotomy and intensive care.	Perforation at the posterior aspect of the junction of first and second part of the duodenum.	-
20	Devi et al.[25]	1	Exploratory laparotomy; lavage, Graham patch repair of DU perforation	Intraperitoneal fluid; 5 mm × 5 mm perforation of anterior wall of second part of duodenum	-
21	Arumugam et al.[26]	1	-	-	-
22	Machaku et al.[27]	1	Exploratory laparotomy, lavage, appendectomy and modified Graham patch repair of pyloric perforation	Free fluid in peritoneal cavity, gastric contents around appendix and cecum, fibrinous exudates, 0.5×0.2-cm perforation on the anterior pyloric antrum.	-
23	Villamil-Angulo et al.[28]	1	Exploratory laparoscopy; lavage; repair of pyloric antrum ulcer with Cellan Jones patch; appendectomy	Purulent fluid, appendiceal inflammation features, fibrinous exudate with 5mm ulcer over anterior pyloric antrum	-
24	Komatreddy et al.[29]	1	Exploratory laparotomy, lavage, modified Graham patch repair of perforated duodenal ulcer; appendectomy	Free intraperitoneal fluid and pus flakes; perforation in anterior wall of first part of duodenum	-

edematous pancreatitis in 1 (3.7%), and 1 study (3.7%) was inconclusive.

Surgical exploration was undertaken in 26 (96.3%) cases, and the patient with acute pancreatitis was managed conservatively. The surgical approach was open laparotomy in 19 (66.7%) and laparoscopic in 7 (24.9%). In 2 cases (7.4%), the approach was laparoscopic to start with but was converted into open due to difficulties during the operation, and in 5 cases (18.5%), laparotomy followed the index appendectomy as the second procedure.

The surgical steps in 26 cases that underwent surgical management involved thorough peritoneal lavage/toilet repair of ulcers in all and reinforcement with greater omentum utilizing techniques including Graham patch in 14 (53.8%), modified Graham patch in 7 (26.9%), and Cellan Jones in 1 (3.8%). In 1 case (3.8%) of pyloric ulcer, a falciform ligament patch was used. Appendectomy was undertaken in 6 (38.5%) of cases during surgical exploration, including the 4 cases (15.4%) that had appendectomy as the primary procedure. A biopsy of the ulcer was retrieved in 1 (3.8%) case, and 1 (3.8%) case required further re-exploration to treat colonic perforation caused by surgical drain-induced pressure necrosis. The majority of the perforated ulcers were located on the anterior surface of the first part of the duodenum (n=15; 57.7%), followed by the anterior surface of the stomach over the prepyloric region or antrum (n=6; 23.1%), the posterior surface (retroperitoneal) of the first part of the duodenum (n=3; 11.5%), and the anterior surface of the second part of the duodenum (n=2; 7.7%), as shown in Figure 3. Helicobacter pylori was tested and eradicated in only 4 (15.4%) cases.

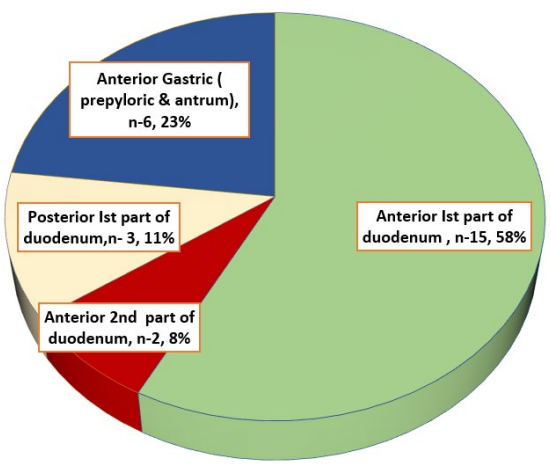

Fig. 3. Distribution of perforated peptic ulcers

Discussion

Despite improvements in diagnostic technology over the past century, cases of Valentino syndrome continue to be published, and in our review, all of the patients had acute appendicitis as a tentative diagnosis. Due to chemical peritonitis in RLQ, patients frequently experience abdominal tenderness and discomfort that is remarkably similar to peritonism induced by acute appendicitis.[27] Proper assessment and imaging can aid in diagnosis, when there is awareness about this possibility and the condition is suspected preoperatively. In this review, we found that, three modalities were used (alone/combination) during assessment including plain X-ray abdomen (with or without X-ray chest), ultrasound abdomen and CT scan of abdomen.

Plain X-rays were taken in 11 cases (40.7%), and in half of those, the pictures were considered normal; pneumoperitoneum was only found in 5 cases. Ultrasound abdomen was performed in 15 (55.6%), intraperitoneal free fluid was found in 10 (37%), pneumoperitoneum in 5 (18.5%), features of acute appendicitis in 5 (18.5%), and ovarian cyst in 1 (3.7%) case. An abdominal CT scan had been done in 11 cases (40.7%), and intraperitoneal free fluid was revealed in 10 (37%), intraperitoneal air pockets/pneumoperitoneum in 6 (22.2%), oral contrast leakage through duodenum in 1 (3.7%), features of acute edematous pancreatitis in 1 (3.7%), and 1 study (3.7%) was inconclusive. This data shows that a CT scan with contrast is most helpful in the detection of peptic ulcer perforation, but it has been ordered in only 40.7% of cases as the condition has not been suspected. Ansari et al. found that a CT scan with intravenous and oral contrast is the most valuable imaging technique to identify peptic ulcer perforation, and only in rare circumstances may surgical exploration be necessary for reaching the diagnosis.[30]

3 (11.1%) of the patients in this review had perforations in the duodenum's posterior wall, which resulted in retroperitoneal collections. Several manifestations that might be seen on a CT scan and indicate retroperitoneal perforation have been noted in the literature. These include retroperitoneal free air, mainly around the right kidney, known as the "veiled right kidney sign" a thickened duodenal wall, and free air around the duodenum.[3,21] Plain chest and abdominal x-rays may illustrate free intraperitoneal air under the right diaphragm or around the right kidney, pointing towards the possibility of perforation of the duodenum.[21] In a recent study, Wang et al. examined the correlation between CT scan results and the locations of perforated peptic ulcers and discovered that this modality gives gastrointestinal surgeons greater information.[31] According to Ishiguro et al., CT scans can help diagnose perforated peptic ulcers as well as predict the amount of accumulated intraperitoneal fluid in patients. This knowledge may be used to inform treatment choices and gauge the seriousness of postoperative complications.[32]

In this review, there are 6 cases in which an appendectomy served as the index procedure. The majority of these patients were sent home after their index operations but were readmitted after returning back in deteriorated

condition. Despite the fact that the patients' symptoms continued even after the appendectomy, the delay in re-exploration was 6±2.6 days. These startling statistics highlight the need to raise awareness of this ailment so that it can be suspected when patients behave in an unusual way.

Based on clinical signs and imaging, an appendectomy was performed in the case described by Chavez et al.[13] During the procedure, purulent fluid was discovered in the right paracolic gutter and cul-de-sac in addition to inflammation of the mesoappendix. After the surgery, the patient stayed in the hospital for an additional three days while experiencing severe epigastric pain (8/10 on the Visual Analogue Scale). Ketorolac was administered to control the pain. The patient reported back with features of generalized peritonitis, and a plain X-ray showed massive pneumoperitoneum. The patient underwent re-exploration, wherein a perforated ulcer was detected. The patient had a prolonged hospital stay. The appendix's histology report ruled out appendicitis. Similarly, the case reported by Rodrigo et al. also suffered due to misdiagnosis.[24] She underwent appendectomy for provisionally diagnosed acute appendicitis and, on the 4th postoperative day, reported back with fever, generalized abdominal pain, and purulent bile-stained discharge from the surgical site. A CT scan revealed multiple intraperitoneal fluid collections in the right lower quadrant and pelvis, and exploratory laparotomy was undertaken for thorough peritoneal lavage and repair of the duodenal ulcer. She got further complicated when the drain caused colonic perforation, requiring another laparotomy and prolonged intensive care. Similarly, the other four cases also had a stormy post-appendectomy course, but there was no reported mortality. Limiting surgical delay in patients with perforated peptic ulcers is of paramount importance, and every hour of delay from admission to surgery was found by Buck et al. to be associated with increased morbidity and an adjusted 2–4 percent increased probability of death.[33]

Only 4 (15.4%) of the cases had Helicobacter pylori testing, and this tendency is inconsistent with the suggestions made in the literature. In order to compare the long-term outcomes in terms of ulcer recurrence, Tomtitchong et al. searched the Cochrane Controlled Trials Register, Medline, and Embase for controlled trials of duodenal ulcer perforation patients using the simple closure method plus postoperative *H. pylori* eradication therapy versus simple closure plus antisecretory non-eradication therapy.[34] They found that *H. pylori* eradication after simple closure of duodenal ulcer perforation was better for the prevention of ulcer recurrence as compared to the operation plus antisecretory non-eradication therapy. They recommended testing for *H. pylori* infection in all patients with duodenal ulcer perforation and starting eradication therapy in all infected individuals.[34] In a randomized trial with comparable goals, Ng et al. discovered that in patients with perforated duodenal ulcers caused by *H. pylori*, eradicating *H. pylori* prevents ulcer recurrence and that in cases of generalized peritonitis, no immediate acid-reduction surgery is required.[35]

Gisbert and Pajares investigated *H. pylori* prevalence in perforated peptic ulcers and the effects of antibiotic therapy.[36] They discovered that whereas the percentage rises to 90–100% in cases of noncomplicated ulcers, the mean prevalence of *H. pylori* infection in patients with perforated peptic ulcers is approximately 65-70%. Patients with *H. pylori* infection is more likely to experience recurrent ulcer disease after peptic ulcer perforation, proving the importance of the bacteria in the condition. All patients with perforated ulcers caused by *H. pylori* should begin *H. pylori* eradication medication as soon as possible in the postoperative phase in order to avoid or at least lessen ulcer recurrence and ulcer perforation.[37] Regardless of prior NSAID use, Metzger et al.'s research revealed that 73.3% of patients with perforated peptic ulcers tested positive for *H. pylori*.[38] A timely and effective *H. pylori* eradication therapy for perforated peptic ulcers was also discovered to lower the relapse rate following straightforward closure without any acid-reduction surgery. They also discovered that a triple eradication procedure had a great response rate.

In this review, 1 (3.7%) case had taken a course of methylprednisolone a week prior to this problem, and 4 (14.8%) cases had a history of extended NSAID use. Due to their anti-inflammatory and analgesic effects, NSAIDs make up around 8% of all prescriptions worldwide and are widely accessible over-the-counter for a variety of reasons.[39] NSAIDS use, together with exposure to the *H. pylori* infection, is a significant risk factor for peptic ulcer perforation, along with smoking, chronic stress, alcoholism, old age, and cocaine use.[39,40]

No patient underwent any acid-reduction surgery, as is the norm currently, and management in 26 cases that underwent surgical management involved a thorough peritoneal toilet to remove collections and simple repair of the ulcer, reinforced with greater omentum utilizing techniques including Graham patch in 14 (53.8%), modified Graham patch in 7 (26.9%), and Cellan-Jones repair in 1 (3.8%). In 1 case (3.8%) of pyloric ulcer, a falciform ligament patch was used. These are standard procedures mentioned in the literature, and the methods adopted generally depend on the preference of the operating surgeon.[41] Depending on the patient's health and the surgeon's expertise, either an open or a laparoscopic method can be used.[42,43] In the review, open laparotomies were used in 19 (66.7%) and laparoscopic procedures in 7 (24.9%) patients.

There is one case in this review by Arumugam et al. that is likely the only one of its kind to have been recorded in the literature, where the patient reported having clinical signs indicative of appendicitis, but a CT scan revealed acute edematous and bulky inferior part of the head and

an uncinate process of the pancreas, with peripancreatic fluid collection noted in the infrapancreatic region, pancreaticoduodenal groove, and precaval region.[26] Blood work further confirmed acute pancreatitis, and the patient was managed conservatively. The imaging had been crucial in making the treatment decision; otherwise, he might have possibly ended up with surgical treatment for the suspicion of the appendicular abscess.

Conclusion

Valentino's syndrome is an atypical presentation of a perforated peptic ulcer that closely mimics appendicitis. The misdiagnosis rate for this condition is very high. Focused assessment and imaging studies can help in reaching the correct diagnosis. If the diagnosis is missed and an appendectomy is started, then the presence of bile-stained or turbid peritoneal fluid and the lack of an obviously inflamed appendix should trigger a search for a potential perforated peptic ulcer. After an appendectomy, if the patient doesn't get better or worsens, appropriate imaging should be undertaken to rule out Valentino's syndrome. There is a need to enhance the awareness level of this disorder among healthcare professionals so that it might be considered a potential differential diagnosis while a patient is being evaluated for pain in the right lower abdomen.

Declarations

Funding

The authors declares that this study has received no financial support.

Author contributions

Conceptualization, S.A.S.; Methodology, S.A.S.; Software, S.A.S.; Validation, S.A.S.; Formal Analysis, S.A.S.;, Investigation, S.A.S.; Resources, S.A.S.; Data Curation, S.A.S.; Writing – Original Draft Preparation, S.A.S. and L.S.AS.; Writing – Review & Editing, S.A.S.; Visualization, S.A.S.; Supervision, S.A.S.; Project Administration, S.A.S., Y.A.AS. and L.S.AS.

Conflicts of interest

No conflict of interest is declared by the author.

Data availability

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request.

Ethics approval

Not applicable.

References

1. Yeh B. Does this adult patient have appendicitis? *Ann Emerg Med*. 2008;52(3):301-303. doi: 10.1016/j.annemergmed.2007.10.023
2. Wijegoonewardene SI, Stein J, Cooke D, Tien A. Valentino's syndrome a perforated peptic ulcer mimicking acute appendicitis. *BMJ Case Rep.* 2012;2012:bcr0320126015--bcr0320126015. doi: 10.1136/bcr.03.2012.6015
3. Mahajan PS, Abdalla MF, Purayil NK. First report of preoperative imaging diagnosis of a surgically confirmed case of Valentino's syndrome. *J Clin Imaging Sci.* 2014;4(28):28. doi: 10.4103/2156-7514.133263
4. Mbarushimana S, Morris-Stiff G, Thomas G. Atypical presentation of perforated peptic ulcer disease in a 12-year--old boy. *BMJ Case Rep*. 2014;2014:bcr2014204716--bcr2014204716. doi: 10.1136/bcr-2014-204716
5. Chung KT, Shelat VG. Perforated peptic ulcer - an update. *World J Gastrointest Surg*. 2017;9(1):1-12. doi: 10.4240/wjgs.v9.i1.1
6. Thorsen K, Søreide JA, Kvaløy JT, Glomsaker T, Søreide K. Epidemiology of perforated peptic ulcer: age- and gender--adjusted analysis of incidence and mortality. *World J Gastroenterol*. 2013;19(3):347-354. doi: 10.3748/wjg.v19.i3.347
7. Thorsen K, Glomsaker TB, von Meer A, Søreide K, Søreide JA. Trends in diagnosis and surgical management of patients with perforated peptic ulcer. *J Gastrointest Surg*. 2011;15(8):1329-1335. doi: 10.1007/s11605-011-1482-1.
8. Lau JY, Sung J, Hill C, Henderson C, Howden CW, Metz DC. Systematic review of the epidemiology of complicated peptic ulcer disease: incidence, recurrence, risk factors and mortality. *Digestion*. 2011;84(2):102-113. doi: 10.1159/000323958.
9. Sultan R, Pal KMI. Valentino appendix: a report of 3 cases. *J Pak Med Assoc*. 2015;65(2):223-224.
10. Blundell S, Campbell A, Patel R, Besarovic S. Valentino's syndrome in an adolescent boy with peptic ulcer perforation simulating acute appendicitis. *J Pediatr Surg Spec*. 2015;9(4):40-42.
11. Hussain K, Munir A, Wahla MS, Masood J. Valentino's syndrome: Perforated peptic ulcer mimicking acute appendicitis managed through Rutherford Morrison incision. *J Coll Physicians Surg Pak*. 2016;26(8):727-728. doi: 2422
12. Ramírez-Ramírez MM, Villanueva-Saenz E. Valentino's syndrome: Perforated peptic ulcer with unusual clinical presentation. *Revista de Gastroenterología de México.* 2016;81:225-226.
13. González Chávez AM, García Vázquez AA, Gómez López JM, et al. Valentino's syndrome: the simulation of an appendicitis. *Int Surg J*. 2017;4(5):1813. doi: 10.18203/2349-2902.isj20171647
14. Amann CJ, Austin AL, Rudinsky SL. Valentino's syndrome: a life-threatening mimic of acute appendicitis. *Clin Pract Cases Emerg Med.* 2017;1:44-46.
15. Pata F, Sgro A, Petkar M, Benevento A. Valentino's syndrome: An unusual presentation of a perforated peptic ulcer. *Transl Surg*. 2017;2(4):106. doi: 10.4103/ts.ts_16_17
16. Iloh AA, Omorogbe SO, Osime OC. Surgeons beware: It may not be acute appendicitis. *Arch Int Surg*. 2017;7(4):139. doi: 10.4103/ais.ais_41_17

17. Akiş Yildiz Z, Ayyildiz HN. Valentino's syndrome in a child: Perforated peptic ulcer mimicking acute appendicitis. *Turk J Pediatr Dis*. 2018;12(4):287-288. doi: 10.12956/tjpd.2018.346
18. Mohan CP, Kabalimurthy J, Balamurugan E, Jayavarmaa R. A rare case of Valentino's syndrome. *International Surgery Journal*. 2018;5:2933-2935.
19. Cherry BH, Patel D, Ronaghan JE. A case of Valentino's syndrome presenting as possible appendicitis. *Int Surg*. 2019;104(11-12):540-541. doi: 10.9738/intsurg--d-17-00136.1
20. Phadnis RK, Sharma S, Patnala SL, Hussain F, Chigulapalli N. A Rare Case Of Valentino Syndrome- Case Report. *Int J Med Biomed Stud*. 2021;5(11). doi: 10.32553/ijmbs.v5i11.2301
21. Noussios G, Galanis N, Konstantinidis S, Mirelis C, Chatzis I, Katsourakis A. Valentino's syndrome (with retroperitoneal ulcer perforation): A rare clinico-anatomical entity. *Am J Case Rep*. 2020;21:e922647-1–e922647-4. doi: 10.12659/ajcr.922647
22. Karthik G, Naga, Bala, Naik A. Retroperitoneal duodenal ulcer mimicking appendicitis associated with Valentino's syndrome - A rare case report. *Journal of Advanced Clinical and Research Insights*. 2020;7(4):55-58. doi: 10.15713/ins.jcri.304
23. Lopez-Casillas N, Luna-Guerrero CE, Lopez-Rico LA, Vargas-Flores E. An Unusual Cause of Abdominal Pain: Valentino's Syndrome. A Case Report. *Japanese Journal of Gastroenterology and Hepatology*. 2020;4(2):1-3.
24. Rodrigo VEU, de Silva G, Jayasinghe DSH, et al. Valentino's syndrome: A rare and lethal differential diagnosis for acute appendicitis. *SAGE Open Med Case Rep*. 2022;10:2050313X2211320. doi: 10.1177/2050313x221132069
25. Devi T P, Selvi S M, Naveen B G, Kannan. *Indian Journal of Research* 2022;11(3):29-31. doi : 10.36106/Paripex.
26. Arumugam B, Giridharan B, Prabhakar, Shanmugasundaram. Syndrome Valentino from a DE Novo aetiology – acute pancreatitis. *Cureus*. 2022;14(1):e21360. doi: 10.7759/cureus.21360
27. Machaku D, Suleman M, Mduma E, Nkoronko M. Valentino's syndrome: a bizarre clinical presentation. *J Surg Case Rep*. 2023;2023(2). doi: 10.1093/jscr/rjad035
28. Villamil-Angulo CJ, Pérez Calvo D, Villamil Castro NA, Rey Chaves CE, Conde D. Valentino's syndrome: Simulation of acute appendicitis in the context of peptic ulcer perforation. Case report and literature review. *Int J Surg Case Rep.* 2023;105(108064):108064. doi: 10.1016/j.ijscr.2023.108064
29. Komatreddy GR, Gangam Venkat PR, Sai Teja K, Punyapu S. Valentino's syndrome: a formidably deceptive tale of peptic ulcer. *Int Surg J*. 2023;10(2):325-328. doi: 10.18203/2349-2902.isj20230277
30. Ansari D, Torén W, Lindberg S, Pyrhönen HS, Andersson R. Diagnosis and management of duodenal perforations: a narrative review. *Scand J Gastroenterol*. 2019;54(8):939-944. doi: 10.1080/00365521.2019.1647456
31. Wang SY, Cheng CT, Liao CH, et al. The relationship between computed tomography findings and the locations of perforated peptic ulcers: it may provide better information for gastrointestinal surgeons. *Am J Surg*. 2016;212(4):755-761. doi: 10.1016/j.amjsurg.2015.05.022
32. Ishiguro T, Kumagai Y, Baba H, et al. Predicting the amount of intraperitoneal fluid accumulation by computed tomography and its clinical use in patients with perforated peptic ulcer. *Int Surg*. 2014;99(6):824-829. doi: 10.9738/intsurg-d-14-00109.1
33. Buck DL, Vester-Andersen M, Møller MH. Surgical delay is a critical determinant of survival in perforated peptic ulcer. *Br J Surg*. 2013;100(8):1045-1049. doi: 10.1002/bjs.9175
34. Tomtitchong P, Siribumrungwong B, Vilaichone RK, Kasetsuwan P, Matsukura N, Chaiyakunapruk N. Systematic review and meta-analysis: Helicobacter pylori eradication therapy after simple closure of perforated duodenal ulcer. *Helicobacter*. 2012;17(2):148-152. doi: 10.1111/j.1523--5378.2011.00928.x
35. Ng EKW, Lam YH, Sung JJY, et al. Eradication of Helicobacter pylori prevents recurrence of ulcer after simple closure of duodenal ulcer perforation: Randomized controlled trial. *Ann Surg*. 2000;231(2):153-158. doi: 10.1097/00000658-200002000-00001
36. Gisbert JP, Pajares JM. Helicobacter pylori infection and perforated peptic ulcer prevalence of the infection and role of antimicrobial treatment. *Helicobacter*. 2003;8(3):159-167. doi: 10.1046/j.1523-5378.2003.00139.x
37. Bertleff MJOE, Lange JF. Perforated peptic ulcer disease: A review of history and treatment. *Dig Surg*. 2010;27(3):161-169. doi: 10.1159/000264653
38. Metzger J, Styger S, Sieber C, Vogelbach P, Harder F. Prevalence of Helicobacter pylori infection in peptic ulcer perforations. *Swiss Med Wkly*. 2001;131(7-8):99-103. doi: 10.4414/smw.2001.06118
39. Odisho T, Shahait AA, Sharza J, Ali AA. Outcomes of laparoscopic modified Cellan-Jones repair versus open repair for perforated peptic ulcer at a community hospital. *Surg Endosc*. 2023;37(1):715-722. doi: 10.1007/s00464-022-09306-7
40. Tai FWD, McAlindon ME. Non-steroidal anti-inflammatory drugs and the gastrointestinal tract. *Clin Med*. 2021;21(2):131-134. doi: 10.7861/clinmed.2021-0039
41. Kidwai R, Ansari MA. Graham patch versus Modified Graham patch in the management of perforated duodenal ulcer. *J Nepalgunj Med Coll*. 2017;13(1):28-31. doi: 10.3126/jngmc.v13i1.16409
42. Chou TC, Lee CH, Soong RS, Chen YC. A simple and effective technique for laparoscopic gastrorrhaphy: modified Graham's patch with barbed suture. *BMC Surg*. 2023;23(1):295. doi: 10.1186/s12893-023-02192-3
43. Chung KT, Shelat VG. Perforated peptic ulcer - an update. *World J Gastrointest Surg*. 2017;9(1):1. doi: 10.4240/wjgs.v9.i1.1