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Low-impact laparoscopic cholecystectomy is associated with decreased postoperative morbidity in patients with sickle cell disease

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Abstract
Background Laparoscopic cholecystectomy (LC) is one of the most frequent surgeries performed in patients with sickle cell disease (SCD). LC in SCD patients is associated with a particularly high postoperative morbidity. The aim of the present study is to assess the safety and feasibility of cholecystectomy performed by mini-laparoscopy with low- and stable-pressure pneumoperitoneum (MLC + LSPP) and to compare the rate of postoperative SCD-related morbidity with standard LC.
Methods Thirty-five consecutive SCD patients admitted between November 2015 and March 2017 for cholelithiasis requiring surgery were compared with an historical cohort of 126 SCD patients who underwent LC for the same indication. Operative variables, postoperative outcomes, patient and surgeon satisfaction, and costs were evaluated.
Results MLC + LSPP exhibited a mean operative time comparable to LC ($p=0.169$). Operative blood loss was significantly reduced in the MLC + LSPP group, and the suction device was rarely used ($p=0.036$). SCD-related morbidity (including acute chest syndrome) was significantly higher in the LC group compared with the MLC + LSPP group (18.3 vs. 2.9%; $p=0.029$). The mean times to resume ambulation ($p=0.018$) and regular diet ($p=0.045$) were significantly reduced in the MLC + LSPP group. The mean incision length (all trocars combined) was 28.22 mm for MLC + LSPP and 49.64 mm for LC patients ($p<0.0001$). Multivariate regression analysis demonstrated that the only significant predictor of postoperative SCD-related morbidity was the surgical approach (odds ratio: 9.24). Patient and surgeon satisfaction were very high for MLC + LSPP. The mean total cost per patient (surgery and hospitalization) was not different between groups ($p=0.084$).
Conclusion MLC + LSPP in SCD patients appears to be safe and feasible. Compared with LC, MLC + LSPP in SCD patients is associated with a significantly reduced incidence of postoperative SCD-related morbidity and more rapid ambulation and return to regular diet without increasing the total costs per patient.

Keywords Sickle cell disease · Micro-laparoscopy · Low-pressure pneumoperitoneum · Low-impact laparoscopy · Cholecystectomy

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Sickle cell disease (SCD) is a frequent monogenic disease worldwide, affecting more than 300,000 newborns each year [1]. In France, SCD is the most common severe autosomal recessive genetic disorder. In total, 80% of cases are diagnosed in the Ile-de-France region and overseas territories, where the frequency of the SCD genetic trait is estimated at 2.2 and 5.4–11% of the population, respectively [2, 3].

SCD is characterized by the substitution of valine for glutamic acid in position 6 of the b-globin chain, which results in an abnormal propensity of deoxy-hemoglobin (HbS) to polymerize. SCD refers to all genotypes containing at least one sickle gene, including homozygous SCA (HbSS) and compound heterozygotes for hemoglobin S and C (HbSC) or hemoglobin S and β thalassemia (HbSβThal) [4, 5]. When HbS polymerizes within the cell, erythrocytes have a great loss in their deformability, and they tend to acquire a sickle form [6].

Patients with SCD suffer from chronic hemolytic anemia and so they are at an increased risk of cholelithiasis. Indeed, cholelithiasis is observed in 30–70% of SCD patients [7–9]. Consequently, cholecystectomy is one of the most frequent surgical procedures performed both in the presence or absence of specific symptoms [3, 10].

Laparoscopic cholecystectomy (LC) is the gold standard treatment for gallstone disease [11–13]. However, in the frail subset of SCD patients, LC is associated with high peri- and postoperative morbidity (up to 38% [12, 14, 15]), including intra-operative desaturation, vaso-occlusive crisis (VOC), or acute chest syndrome (ACS), which is the most dangerous and an often fatal complication [10]. SCD-related morbidity following LC is mainly explained by the effects of CO_2 insufflation and postoperative pain in promoting metabolic acidosis, low O_2 saturation, and erythrocyte sickling [16–18].

Mini-laparoscopy and low-pressure pneumoperitoneum are emerging techniques of minimally invasive surgery that have been advocated as low-impact laparoscopy. Mini-laparoscopy involves the use of miniaturized scopes and instruments (via 3-mm ports) that contribute to further reduce perioperative pain, curtail morbidity, and enhance cosmetic results. Although the literature on the topic is limited, recent studies on mini-laparoscopic cholecystectomy (MLC) report significantly reduced postoperative pain and improved aesthetics compared with conventional techniques [19–24]. Similarly, low-pressure pneumoperitoneum (7–8 mmHg) has been proposed to reduce the impact of capnoperitoneum on cardiopulmonary complications and pain while providing satisfactory exposure and adequate working space [25]. Several studies and meta-analyses demonstrated that low-pressure pneumoperitoneum for laparoscopic cholecystectomy leads to reduced postoperative pain scores [26–28] without significantly increasing the operative time [27].

MLC has never been reported in SCD patients. Similarly, to the best of our knowledge, data about the role of low-pressure pneumoperitoneum, which may have a specific indication as a low-impact surgery in SCD patients undergoing cholecystectomy, are not available. Of note, the combination of mini-laparoscopy with low-pressure pneumoperitoneum has never been reported to date. Thus, the aim of the present study is to describe the safety and feasibility of cholecystectomy performed by mini-laparoscopy with low and stable pressure pneumoperitoneum (LSPP) in patients with SCD. Additionally, the surgical outcomes and healthcare costs of MLC + LSPP are compared with LC in a large cohort of SCD patients.

Materials and methods

Study population

The study population includes consecutive SCD patients admitted between November 2015 and March 2017 at the Unit of Digestive, Hepato-Pancreato-Biliary Surgery and Liver Transplantation of the Henri Mondor University Hospital of Creteil (France) for symptomatic or asymptomatic cholelithiasis requiring surgery. All patients with SCD were followed in the Adult Sickle-Cell Referral Center of the Henri Mondor University Hospital of Creteil (that serves about 3000 adults with SCD of all genotypes [29]). All patients underwent elective cholecystectomy by MLC + LSPP.

Study design

This is a single-institution study aiming at evaluating the safety and feasibility of elective MLC + LSPP in a sample of SCD patients. To further investigate the advantages of this emerging surgical technique, the operative and postoperative outcomes of MLC + LSPP were compared with those of elective LC with standard pneumoperitoneum performed for symptomatic and asymptomatic cholelithiasis in a historical cohort of SCD patients admitted to our unit. The LC patients underwent operation between January 2011 and November 2015.

The study was approved by the institutional review board and was conducted in accordance with the Helsinki Declaration for human research studies. Informed consent was provided by all participants.

Perioperative management

Patients with SCD were managed by a multidisciplinary team involving hematologists, anesthetists, and surgeons coordinated by the Sickle-Cell Disease Referral Center [3].

Prior to surgery, all patients underwent ultrasound examination or magnetic resonance imaging to detect gallstones and evaluate the biliary system. In selective cases with suspected choledocolithiasis, preoperative endoscopic retrograde cholangiopancreatography (ERCP) was also performed [14, 30, 31].

Patients were typically admitted 1 day before surgery. Antibiotic prophylaxis was not systematically administered. Based on standard protocols, patients received intravenous hydration with crystalloids at 1.5 times the maintenance rate upon admission, and the dosing continued postoperatively until resumption of full oral intake. During the postoperative period, patients were kept well oxygenated and pain-free and were trained to perform specific inspiratory muscle exercises by spirometry. To control pain, opioid analgesia was administered if needed. Discharge was allowed when ambulation, light diet intake, and pain were adequately controlled and according to the patient's will. All patients received follow-up in the outpatient clinic by both surgeons and hematologists. The surgical follow-up typically lasted 4 weeks postoperatively.

Red blood cell transfusion, an essential part of the management of acute complications of SCD in adulthood, can also be indicated as a preventive measure in preparation for surgery [3, 12, 29]. However, in our center, the transfusion strategy was restricted because of the frequency of delayed hemolytic transfusion reaction (DHTR) and the high DHTR-related morbidity [3, 32]. Therefore, since 2015, patients have been rarely transfused.

Surgical technique

For all cholecystectomies, the patient was placed in the supine anti-Trendelenburg position, and the pneumoperitoneum was established using an open trans-umbilical technique. The standard French technique with 4 ports was used [14, 33].

For MLC + LSPP procedures, an 8-mmHg pneumoperitoneum was induced and maintained stable using the AirSeal® System (Conmed Corp, Utica, NY, USA) through a 30° laparoscope inserted at the 12-mm umbilical AirSeal access port (consumable). Then, under direct visual control, three reusable 3-mm mini-laparoscopic ports (ABmedica s.a.s, Mery-sur-Cher, France) were placed in the left hypochondriac, epigastric, and right hypochondriac regions (Figs. 1, 2). Calot's triangle was dissected by bipolar forceps and scissors. The cystic duct and artery were controlled by placing 10-mm absorbable clips (Laproclip®, Coviden, Dublin, Ireland) through the AirSeal access port after obtaining direct visual control via a 3-mm optical device. Thus, two optical devices (10 and 3 mm) were used connected to the same camera of conventional laparoscopy (Karl Storz GmbH & Co KG, Tuttlingen, Germany). The gallbladder was dissected from the liver bed using bipolar forceps and scissors and placed in an impermeable bag for retrieval through the umbilical port. Whenever necessary, a 3-mm suction instrument was used. No drain was inserted. The umbilical fascial defect was closed with interrupted polydioxanone sutures. The mini-laparoscopic trocar skin incisions were closed using a simple adhesive, and the umbilical skin incision was closed by running absorbable sutures. All site ports were infiltrated with local anesthesia at the end of the procedure.

For conventional LC, 4 consumable ports were used (two 12-mm ports [Applied Medical, California, USA] in the periumbilical and left hypochondriac regions, and two 5-mm ports [Applied Medical, California, USA] in the epigastric and right hypochondriac regions) were used according to

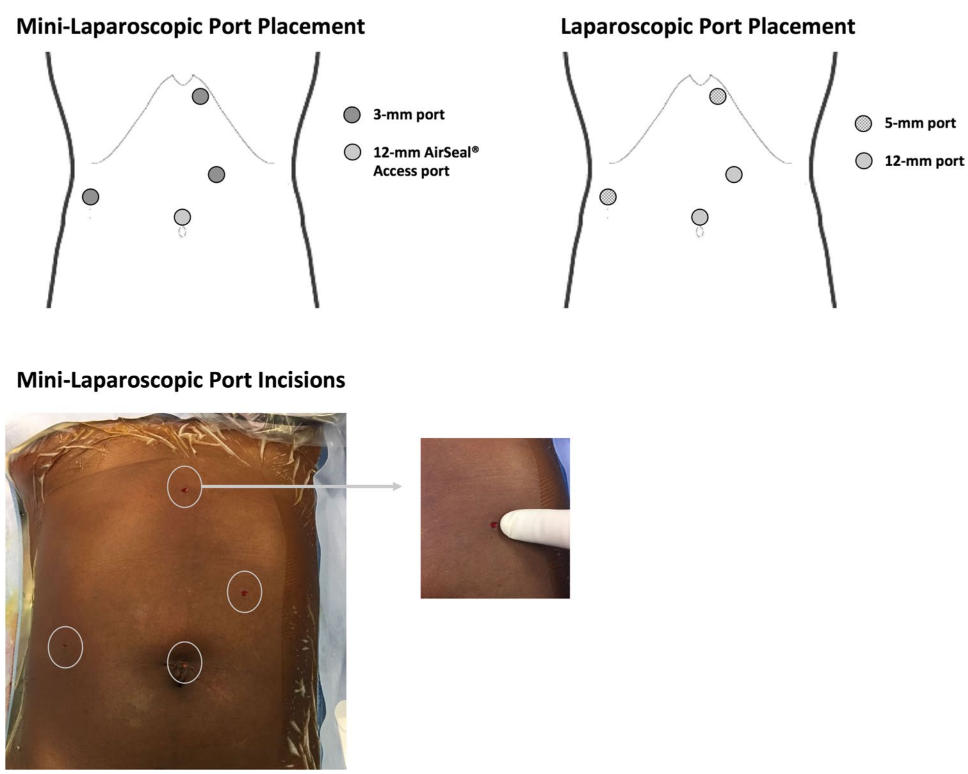

Fig. 1 Port placement for mini-laparoscopic cholecystectomy with low and stable pneumoperitoneum and for standard laparoscopic cholecystectomy

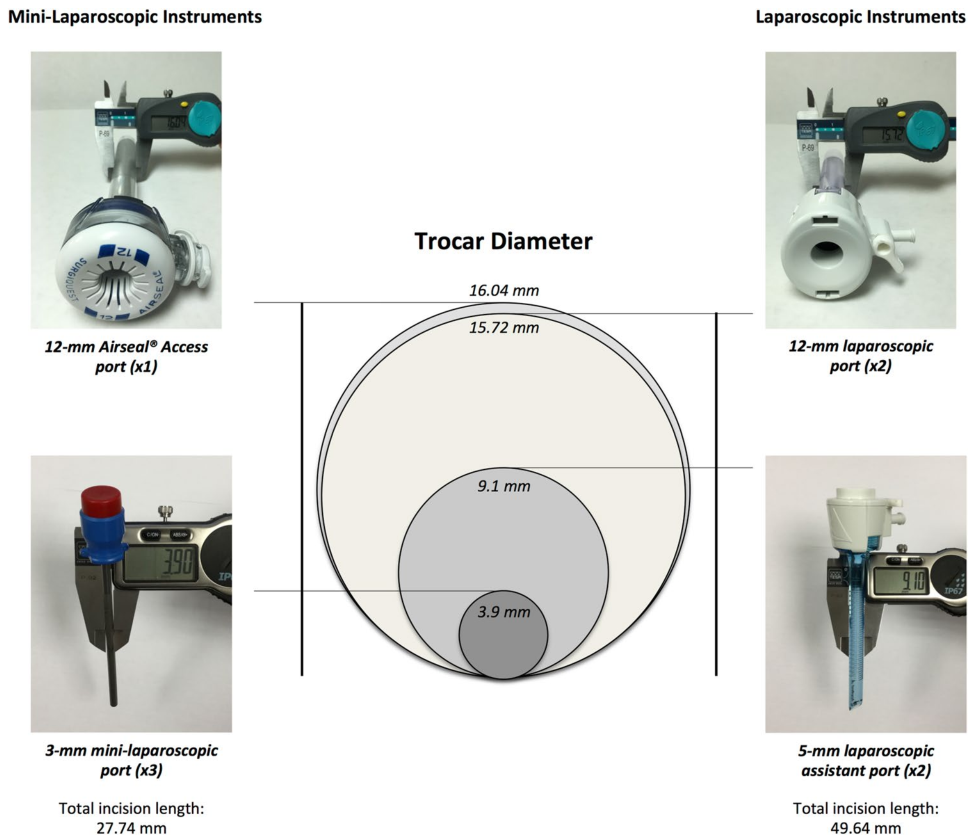

Fig. 2 Trocar diameter, instruments, and total incision length for mini-laparoscopic and laparoscopic cholecystectomy

the French technique. A pneumoperitoneum of 12 mmHg was maintained by standard laparoscopic insufflator (Figs. 1, 2) [12, 14, 30]. As described above, the gallbladder was dissected after cystic duct and artery clipping (Laproclip®, Coviden, Dublin, Ireland). The umbilical fascial defect was closed with interrupted polydioxanone sutures, and all skin incisions were closed with absorbable sutures.

All MLC + LSPP procedures were performed by the same surgeon (NdeA) experienced in minimally invasive surgery. LC procedures were performed by two surgeons (FB and NdeA) experienced in minimally invasive surgery (> 200 cholecystectomies). Of note, the MLC + LSPP and LC procedures were carried out following the same surgical steps.

Study outcomes

The study outcomes include surgical parameters and postoperative results. The surgical parameters recorded included operative time, blood loss, transfusion need, conversion rate (to laparoscopic ports or to laparotomy), number of additional ports used, intra-operative complications (e.g., gallbladder bleeding, accidental gallbladder perforation, and desaturation), and technical complications (e.g., failure to maintain an 8-mmHg pneumoperitoneum). The operative time was defined as the minutes between the skin incisions for the first port to skin closure of the last port. Gallbladder bleeding was defined as bleeding from the hepatic pedicle or gallbladder bed requiring use of aspiration/lavage.

Postoperative outcomes included postoperative morbidity and mortality (within 90 days after the operation), analgesia need, time to resume ambulation, time to resume regular diet, length of hospital stay, time to resume physical activities at the same level prior to the operation, and healthcare costs. Postoperative morbidity during the hospital stay comprised all types of postoperative complications that were categorized according to the Dindo–Clavien Classification [34]. More precisely, VOC was defined as pain affecting at least one part of the body, including limbs, ribs, sternum, head (skull), spine, and/or pelvis, not attributable to other causes and requiring analgesics [30, 35, 36]. The diagnosis of ACS was based on the association of a respiratory symptom (dyspnea or chest pain), an abnormal lung sound at auscultation, and a new pulmonary infiltrate on the chest radiograph [14, 30, 37, 38]. Other complications included wound infections, renal failure, and biliary leakage.

In addition, for SCD patients who underwent MLC + LSPP, postoperative pain and patient satisfaction were evaluated by using a visual analog scale (VAS, ranging from 0 to 10 cm). Pain was scored immediately after surgery; at 4, 8, 12, 24, and 48 h; and at discharge. The cosmetic results were assessed using the patient and observer scar assessment scale (PSAS and OSAS) [39]. The surgeon's satisfaction with exposure and instrument maneuverability was assessed immediately after surgery by filling a predefined questionnaire using a Likert scale of 1–5 (1 = very difficult, 5 = easy). Five different steps of MLC + LSPP were considered, including exposure of fundus and body of the gallbladder, exposure and dissection of Calot's triangle, exposure during separation of gallbladder from the liver bed, and dissection of the gallbladder from the liver bed. The scores of each step were summed to obtain the overall surgeon's satisfaction score [40, 41].

Statistical analysis

Descriptive statistics were used to describe the study population. Data are presented as number and percentage and mean and standard deviation (or median and range). For bivariate two-sided comparisons between the MLC + LSPP group and the LC group, Chi-squared test or Fisher's exact test were used for categorical variables, whereas the Mann–Whitney U test was applied for continuous variables. Multivariate regression analysis was performed to evaluate the role of covariates as predictors of postoperative complications. Patients who required conversion were retained in their original group based on an intention-to-treat analysis. For pain score analysis within the MLC + LSPP group, a repeated measures ANOVA was used.

For the healthcare cost analysis, the total cost per patient, including surgery-related costs (e.g., costs of disposable materials, instruments, clips and sutures) and hospital stay costs (e.g., days of hospital stay), was estimated and compared between the MLC + LSPP and LC groups. Independent (fixed) costs, such as facility maintenance, electricity or anesthesia, were not considered.

Statistics were performed using SPSS (Statistical Package for Social Science, IBM SPSS Statistics, Version 23 for Macintosh; IBM Corp., Armonk, NY, USA). A p value ≤ 0.05 was considered statistically significant.

Results

During the study period, 35 consecutive SCD patients underwent operation via MLC + LSPP. This group was compared with a historical cohort of 126 SCD patients who underwent operation via LC. The demographic and clinical characteristics of the MLC + LSPP and LC groups are displayed in Table 1. In the MLC + LSPP group, 26 (74.3%) SCD patients had HbSS, 8 (22.9%) HbSC, and 1 (2.9%) HbSβThal. In the LC group, 98 (77.8%) SCD patients had HbSS, 23 (18.3%) HbSC, and 5 (4%) HbSβThal ($p = 0.804$). The mean preoperative hemoglobin S (Hb-S) was 68.7% in the MLC group and 67.2% in the LC group ($p = 0.839$). The mean preoperative hemoglobin F (Hb-F) was 5.9% in the MLC group and 6.2% in the LC group ($p = 0.772$). Preoperative transfusion was performed in 2 (5.7%) MLC + LSPP patients and 19 (15.1%) of LC patients ($p = 0.254$).

Operative and postoperative outcomes are presented in Table 2. MLC + LSPP presented a mean operative time comparable to LC ($p = 0.169$). In one MLC + LSPP patient, an additional 5-mm port was required to favor the Calot's dissection in the presence of hepato-splenomegaly, and the pneumoperitoneum was concomitantly elevated at 12 mmHg. In two MLC + LSPP patients, a mini-laparoscopic port was substituted with a conventional laparoscopic port. Precisely, in one patient, a mini-laparoscopic port was substituted with a 5-mm port in the left hypochondriac region due to technical problems with the 3-mm bipolar forceps, whereas the mini-laparoscopic port was substituted with a 12-mm port in the left hypochondriac region due to technical problems with the 3-mm optical device in another patient. No conversion to open surgery was necessary in either group. The postoperative period of converted patients was uneventful.

The mean operative blood loss was significantly reduced in the MLC + LSPP group, in which the suction device was rarely used, compared with the LC group. Overall, 27 patients (16.7%) developed postoperative complications. Of these, SCD-related morbidity (including ACS, limb and abdominal VOC) was observed in 24 patients. The incidence of SCD-related morbidity was significantly higher in the LC group compared with the MLC + LSPP group (18.3 vs. 2.9%; $p = 0.029$). No biliary tract injury occurred. The majority of postoperative complications were classified as Dindo–Clavien grade I or II, and no differences between groups were noted ($p = 0.395$). The mean times to resume ambulation and regular diet were significantly reduced in the MLC + LSPP group, whereas a trend toward a significant difference was observed for the duration of the hospital stay in favor of the MLC + LSPP ($p = 0.069$). No mortality was observed. The mean overall incision length (all trocars combined) was 28.22 mm for MLC + LSPP and 49.64 mm for LC patients ($p < 0.0001$) (Fig. 2).

Multivariate regression analysis demonstrated that the only significant predictor of postoperative SCD-related morbidity was the surgical approach (LC versus MLC + LSPP, odds ratio: 9.24). A preoperative Hb level < 7 g/dL and SCD HB-SS displayed a trend towards statistical significance (Table 3).

Postoperative pain was prospectively evaluated by all SCD patients who underwent the MLC + LSPP procedure using a visual analog scale (VAS, 0 to 10 cm). The mean (SD) postoperative pain intensity was 3.14 (1.95) early after surgery and 0.5 (1.35) at discharge, and a linear decrease was noted over time ($p < 0.0001$). A significant decrease in pain scores was observed at 12 h postoperatively ($p = 0.001$)

Table 1 Demographic and clinical characteristics of patients with sickle cell disease operated on by mini-laparoscopic cholecystectomy with low and stable pneumoperitoneum (MLC + LSPP) or conventional laparoscopic cholecystectomy (LC) ($n = 161$)

	MLC + LSPP ($n = 35$)	LC ($n = 126$)	p value
Gender (F/M) [n]	12/23	62/64	0.129
Age (year) [median (range)]	32 (16–67)	32 (20–63)	0.783
BMI (kg/m^2) [median (range)]	23.2 (18–43.10)	22.5 (15.2–36.3)	0.240
Obesity (BMI ≥ 30 kg/m^2) [n (%)]	4 (11.4)	11 (8.7)	0.742
ASA score I/II/III [n]	15/15/5	39/70/17	0.367
Diabetes [n (%)]	1 (2.9)	1 (0.8)	0.389
Cardiopulmonary diseases [n (%)]	4 (11.4)	30 (23.8)	0.159
Kidney diseases [n (%)]	3 (8.6)	13 (10.3)	1
Liver diseases [n (%)]	1 (2.9)	8 (6.3)	0.685
Smoking [n (%)]	1 (2.9)	10 (7.9)	0.459
Preoperative hemoglobin (g/dL) [mean (SD)]	9.19 (1.38)	9.57 (1.79)	0.373
Preoperative leukocytes (10^9/L) [mean (SD)]	9.23 (2.98)	9.55 (3.44)	0.777
Preoperative platelets (10^3/mm^3) [mean (SD)]	307.16 (98.41)	308.69 (11.41)	0.884
Preoperative RCP (mg/L) [mean (SD)]	7.22 (8.33)	7.55 (18.41)	0.247
Preoperative alanine aminotransferase > 40 UI/L [n (%)]	5 (14.3)	20 (15.9)	1
Preoperative aspartate aminotransferase > 40 UI/L [n (%)]	12 (34.3)	49 (38.9)	0.696
Preoperative serum bilirubin > 50 µmol/L [n (%)]	4 (11.4)	23 (18.3)	0.447
Previous upper abdominal surgery [n (%)]	1(2.9)	11 (8.7)	0.465
Indication for surgery [n (%)]			0.768
Asymptomatic cholelithiasis	18 (51.4)	52 (41.3)	
Biliary colic	10 (28.6)	34 (27)	
Antecedent cholecystitis	5 (14.3)	25 (19.8)	
Antecedent stone migration	1 (2.9)	6 (4.8)	
Antecedent biliary pancreatitis	0	4 (3.2)	
Gallbladder polyp	1 (2.9)	5 (4)	

BMI body mass index, *ASA* American Society of Anesthesiology, *RCP* reactive C protein

and continued at 24 h ($p = 0.053$), 48 h ($p < 0.0001$), and discharge ($p < 0.0001$).

The surgical cosmetic results were evaluated using the OSAS and PSAS scales at the first follow-up visit. The median OSAS and PSAS scores were 18.5 (range 7–29) and 15.1 (6–26), respectively, corresponding to a low impact of the scar. Patient satisfaction was very high [mean VAS score 9.2 (2.3)]. The surgeons' satisfaction scores for MLC + LSPP are presented in Table 4.

The mean cost per intervention was 514.4 euros for MLC + LSPP and 157.2 euros for LC ($p < 0.0001$). The mean hospitalization costs were significantly reduced for the MLC + LSPP (5015.3 euros (SD: 1485) vs. 6182.1 euros (SD: 4417.9); $p = 0.013$). The mean total cost per patient (surgery and hospitalization) was 5528.7 euros (SD: 1485) for MLC + LSPP and 6339.3 euros (SD: 4417.9) for LC, and statistical significance was not obtained ($p = 0.084$).

Discussion

The findings of the present study support the safety and feasibility of MLC + LSPP in SCD patients. While maintaining the same surgical procedural steps of a conventional LC (e.g., number of laparoscopic ports, port placement), MLC + LSPP is associated with a significantly lower incidence of postoperative SCD-related morbidity (e.g., VOC, ACS). Moreover, the application of miniaturized instruments does not appear to increase the total cost per patient.

To the best of our knowledge, this is the first study evaluating low-impact laparoscopy (i.e., MLC + LSPP) in adult SCD patients. This innovative and minimally invasive surgical technique may find a specific indication in SCD patients who are prone to develop VOC following LC. Previous studies have reported incidence rates of SCD-related morbidity post-LC ranging from 7.3 to 38% [12, 14, 15, 42–51] (Table 5), which in some studies were significantly higher than after open cholecystectomy [14, 37, 52], thus challenging the safety of LC in SCD patients [14]. Although

Table 2 Operative and postoperative outcomes of patients with sickle cell disease operated on by mini-laparoscopic cholecystectomy with low and stable pneumoperitoneum (MLC + LSPP) or conventional laparoscopic cholecystectomy (LC) (*n* = 161)

	MLC + LSPP (*n* = 35)	LC (*n* = 126)	*p* value
Operative time (min) [median (range)]	55 (40–120)	55 (40–95)	0.169
Need of additional port (one 5-mm port) [*n* (%)]	1 (2.9)	0	0.217
Conversion [*n* (%)]			
To laparotomy	0	0	NA
To laparoscopy (one 3-mm port to 5-mm port)	1 (2.9)	NA	NA
To laparoscopy (one 3-mm port to 12-mm port)	1 (2.9)	NA	NA
Failure to maintain LSPP (at 8 mmHg) [*n* (%)]	1 (2.9)	NA	NA
Accidental opening of gallbladder [*n* (%)]	1 (2.9)	11 (8.7)	0.465
Operative blood loss (mL) [median (range)]	0 (0–50)	20 (0–90)	***0.036***
Number of transfused patients [*n* (%)]	0	3 (2.4)	1
Patients with postoperative complications [*n* (%)]	2 (5.7)	25 (19.8)	0.07
Patients with SCD-related postoperative morbidity [*n* (%)]			***0.029***
Vaso-occlusive lower limb crisis	1 (2.9)	23 (18.3)	
Vaso-occlusive abdominal crisis	0	3 (2.4)	
Acute chest syndrome	0	2 (1.6)	
Wound infection [*n* (%)]	1 (2.9)	2 (1.6)	0.523
Dindo–Clavien classification [*n* (%)]			0.395
I	1 (2.9)	9 (7.1)	
II	1 (2.9)	12 (9.5)	
III	0	2 (1.6)	
IV	0	2 (1.6)	
Reoperation [*n* (%)]	0	0	NA
Time to resume ambulation (hours) [mean (SD)]	13.3 (5.77)	13.94 (9.02)	***0.018***
Time to resume regular diet (hours) [mean (SD)]	17.52 (8.59)	25.93 (8.05)	***0.045***
Hospital stay (days) [mean (SD)]	3.71 (1.1)	4.58 (3.27)	0.069
Mortality at 90 days [*n* (%)]	0	0	NA
Readmission within 60 days [*n* (%)]	0	0	NA

Significant *p* values are indicated in bold italics

BMI body mass index, *ASA* American Society of Anesthesiology, *RCP* reactive C protein

the precise effects remain to be elucidated, CO_2 insufflation might result in hypercapnia and respiratory acidosis that subsequently promotes sickling of erythrocytes in the perioperative period causing VOC and ACS [17]. Moreover, altered splanchnic perfusion following the induction of pneumoperitoneum might be exacerbated by the patient's position, procedure duration, and degree and stability of intra-abdominal pressure [18, 30, 53, 54]. For conventional LC, CO_2 is insufflated at room temperature (20–25 °C) under dry conditions (0–5% relative humidity), and these factors may contribute to operative and postoperative complications [25, 55, 56]. For these reasons, some authors recommended great care when operating on SCD patients, suggesting operating with low-pressure pneumoperitoneum, minimizing pain, facilitating early mobilization, and extending the hospital stay beyond 3 days for ACS surveillance [14, 30]. The application of MLC + LSPP may address all these recommendations.

In the present study, MLC was performed with a stable pneumoperitoneum of 8 mmHg. Of note, standard LC procedures are typically performed with an intra-abdominal pressure of 12–15 mmHg to obtain a satisfactory visualization and manipulation of instruments. However, lowering the intra-abdominal pressure significantly reduces CO_2 insufflation-related risks on the surgical peritoneal environment [25] as well as postoperative pain and hospital stay [27, 57, 58]. The feasibility and safety of cholecystectomy are preserved under lower pneumoperitoneum [28], as confirmed in the present study. Indeed, the high surgeon's satisfaction regarding the exposure and maneuverability obtained with the miniaturized instruments can also be considered as a proxy of a satisfactory visualization of the working space. Moreover, the AirSeal® system allows maintaining a stable intra-abdominal pressure and continuously evacuates smoke. The system senses the intra-abdominal pneumoperitoneum pressure in real time and recirculates CO_2 through its valve-free AirSeal Access port and its 0.01-micron triple lumen

Table 3 Assessment of predictors of postoperative SCD-related morbidity in the study population ($n = 161$) based on multivariate regression analysis

Predictors	Coefficient B	Wald χ^2	p value	Odds ratio (95% CI)
Age	− 0.001	0.003	0.959	0.99 (0.94–1.05)
Gender (M)	− 0.04	0.70	0.401	0.66 (0.26–1.71)
BMI	0.006	0.011	0.918	1 (0.90–1.12)
Surgical approach (LC vs. MLC + LSPP)	2.224	4.285	***0.038***	9.24 (1.12–75.92)
Homozygotic sickle cell disease trait (HB-SS)	1.2	2.41	0.120	3.33 (0.73–15.23)
Preoperative Hb < 7 g/dL	1.53	3.17	0.075	4.64 (0.85–25.12)
Preoperative total bilirubin > 50 µmol/L	0.056	0.007	0.931	1.05 (0.29–3.79)
Previous upper abdominal surgery	− 1.024	0.84	0.358	0.35 (0.04–3.19)
Operative time	− 0.01	0.23	0.625	0.98 (0.94–1.03)
Blood loss	− 0.009	0.35	0.553	0.99 (0.96–1.02)
Postoperative blood transfusion	1.78	1.87	0.171	5.93 (0.46–75.95)

Significant p values are indicated in bold italics

BMI body mass index, *CI* confidence interval, *Hb* hemoglobin, *LSPP* low and stable pneumoperitoneum, *M* male, *MLC* mini-laparoscopic cholecystectomy, *SCD* sickle cell disease

SVD spleen vein diameter, *PSVT* portal or splenic vein thrombosis, *SE* standard error

Table 4 Surgeons' satisfaction scores for mini-laparoscopic cholecystectomy with low and stable pressure pneumoperitoneum

Surgical steps	Score (Likert scale: 1 = poor or difficult, 5 = good or easy)
Exposure of fundus and gallbladder body	4.1 (0.51)
Exposure of Calot's triangle	3.74 (0.65)
Dissection of Calot's triangle	3.9 (0.53)
Exposure during separation of the gallbladder from the liver bed	4.7 (0.64)
Dissection of the gallbladder from the liver bed	4.5 (0.61)
Maneuverability of mini-laparoscopic instruments	4.57 (0.5)
Total score	25.6 (2.21)

tube set components. Recirculation and filtration of the intra-abdominal CO_2 contribute to maintaining a more stable patient body temperature during surgery and a certain level of moisture within the abdominal cavity [59–61]. These features contribute to minimize the risk of hypothermia, the irritating effects of CO_2, and the injury and stretching of the peritoneal and diaphragmatic tissues. In addition, by controlling CO_2 desufflation, the risk of residual pockets of gas in the abdominal cavity after surgery is drastically reduced [62]. These technical advantages translate into operative and postoperative improvements in terms of a significantly reduced incidence of SCD-related morbidity, pain, and hospital stay (trend) compared with conventional LC. Moreover, avoiding hypothermia is crucial in SCD patients to prevent sickling and subsequent SCD-related morbidity (i.e., VOC and ACS) [30].

Of note, MLC + LSPP and LC were associated with comparable operative times. Long operative times are a potential contributory factor of surgery- and anesthesia-related complications, especially postoperative lung complications [14, 30]. In this study, the mean operative time ranged from 40 to 120 min for MLC + LSPP procedures and from 40 to 95 min for LC, whereas the median value was 55 min for both techniques. These findings are consistent with the operative times reported for LC in SCD patients [12, 14, 30] and support the notion that MLC + LSPP is not associated

Table 5 Summary of relevant studies on the outcomes of LC in adult SCD patients ($n > 10$)

Study (year)	Country (period)	*n*	Mean age (range)	Gender (M:F)	Mean preop-Hb (range)	Preoperative Transfusion (%)	Mean OT (range)	Conversion to open (%)	Morbidity (%)	VOC /ACS	Mean LOS (range)	Mortality (%)
Muroni et al. (2015) [43]	France (2000–2014)	103	n/a	28:75	n/a	25 (24.2)	n	4 (3.9)	17 (16.5)	5/4	n/a	0
Al-Mulhim et al. (2012)# [42]	Saudi Arabia (2004–2008)	73	n/a	n/a	n/a	n/a	62 (18.3)**	1 (1.4)	2 (2.8)	n/a	3.1 (0.92)*	0
Aziz et al. (2011) [65]	South Arabia (2006–2009)	40	26.6 (6–53)	16:24	n/a	16 (40)	n/a	2 (5)	5 (12.5)	3/1	2.8 (1–8)	0
Rachid et al. (2009) [44]	Niger (2004–2008)	47	22.4 (11–46)	16:31	n/a	27 (57.4)	64 (42–103)	2 (4.3)	6 (12.8)	4/1	3.5 (1–9)	0
Dan et al. (2009) [30]	Trin-Tobago (2003–2008)	19	21.5 (9–37)	2:17	8.2	0	27.9 (20–45)	0	4 (21.1)	2/1	2.5 (1.5-7)	0
Al-Mulhim et al. (2009) [12]	South Arabia (1994–2006)	427	21 (14–34)	187:240	8.7 (6.5–11.4)	393 (92)	76 (35–240)	21 (4.9)	31 (7.3)	19/8	2.6 (1–9)	0
Diarra et al. (2008) [14]	France (1990–2005)	47	25.5 (99.7)**	29:18	10.7 (1.9)**	37 (78.7)	71.4 (18.9)**	n/a	n/a	2/5	7.7 (1.7)**	0
Plummer et al. (2006) [15]	Jamaica (1999–2004)	16	28.5 (13–45)	4:12	8.08 (1.07)**	0	108 (70–150)	4 (25)	6 (42.9)	1/4	5.5 (1–13)	1 (6.2)
Leff et al. (2006) [45]	U.K (1997–2004)	14	34.5* (18–42)	6:8	9* (6.9–12.7)	0	n/a	1 (7.1)	5 (35.7)	–/1	4.57 (4.84)	0
Al-Mulhim et al. (2002) [31]	South Arabia (1994–1998)	35	19 (12–30)	9:26	7.2 (6.5–11.2)	27 (77.1)	130 (45–240)	2 (5.7)	6 (17.1)	1/–	5.3 (3–12)	0
Al-Abkari et al. (2001) [51]	South Arabia (1994–1998)	36	25 (14–52)	14:36	8.9 (6.3–11.7)	27 (75)	104	4 (11.1)	9 (25)	2 / -	3.9* (2–7)	0
Bonatsos et al. (2001) [46]	Greece (1991–1999)	13	34.7 (18–57)	5:08	10.6	9 (69.2)	n/a	n/a	1 (7.7)	0	3.3 (2–6)	0
Leandros et al. (2000) [47]	Greece (1991–1998)	41	24 (17–47)	22:19	11.8 (91–141)	n/a	64.2 (45–90)	2 (4.9)	2 (4.9)	0	2.7 (2.5)**	0
Meshikhes et al. (1998) [48]	South Arabia (1992–1996)	71	25 (13–58)	42:29	9 (6.3–13.5)	55 (77.5)	80 (40–270)	4 (5.6)	10 (14.1)	1/–	2.5* (1–10)	1 (1.4)
Alaud-Din et al. (1998) [49]	South Arabia (1993–1996)	36	(6–30)	25:11	n/a	18 (50)	n/a	n/a	3 (8.3)	1/–	n/a	0
Meshikhes et al. (1995) [50]	South Arabia (1992–1993)	30	26 (15–44)	23:07	9.7 (8.6–12)	19 (63)	75 (60–100)	1 (3.3)	3 (10)	1/–	2* (1–5)	1 (3.3)

= Only included data from the most recent 5-year period; *= median ;**= Standard deviation

M/F male/female; preop-Hb, preoperative hemoglobin (g/dL), *OT* operative time, *VOC* vaso-occlusive crisis, *ACS* acute chest syndrome, *LOS* length of stay with longer operative time if performed by an experienced laparoscopic surgeon [27, 28, 58]. However, with the exception of using miniaturized instruments and applying a LSPP, no changes were made in the operative technique, such as number of ports or port placement, to perform standard and reproducible cholecystectomies. This feature minimized or even avoided the eventual learning curve of the surgeon and thus, maintained the operative time in the typical ranges. As further support, no differences were observed between MLC + LSPP and LC in terms of conversion rate and intra-operative complications (e.g., biliary injury). In the two MLC + LSPP patients who required conversion, conversion involved the substitution of a mini-laparoscopic port with a conventional laparoscopic port. This substitution was essentially due to technical problems with the mini-instruments that may be more fragile and subject to wear during multiple sterilization processes. Despite these features, the latest generation of mini-instruments has rigidity and resistance that guarantee proper visualization and adequate tension for safe tissue dissection. Indeed, in the majority of the MLC + LSPP patients, no suction instrument was used given that no bleeding occurred. Although very low in both groups, intra-operative blood loss was significantly reduced in MLC + LSPP patients compared with LC patients. This may be explained by the extreme precision and delicateness during tissue dissection dictated by the use of miniaturized instruments.

Another important factor that may impact postoperative morbidity in SCD patients is the intensity of postoperative pain [3, 14]. Reducing abdominal pain might have a cardinal impact given that intensive pain during shallow breathing is the major cause of postoperative hypoxemia and pulmonary complications. In the present study, only the MLC + LSPP patients evaluated postoperative pain prospectively using a VAS scale. Thus, no comparison can be made with the LC group, but very low pain (mean score 3.1) lasting less than 48 h was reported. These findings are consistent with previous reports [20] and are likely related to the small diameter of the instruments used [24, 63, 64]. Indeed, incision size is an important determinant of postoperative pain that should be minimized as much as possible in SCD patients to facilitate normal ventilation, early mobilization, and thus more rapid recovery [24]. Incision size also drastically impacts cosmetic results and patient satisfaction, as observed in the present study.

Together with the abovementioned advantages, MLC + LSPP appeared to be associated with a significantly reduced incidence of SCD-related morbidity, especially ACS, compared with LC. This reduction was confirmed in the multivariate regression analysis, in which the surgical technique was identified as the only predictor of SCD-related morbidity. This main finding can be explained by the use of miniaturized laparoscopic instruments during the LSPP operation, but specific and adequate pre- and postoperative management of SCD patients remains essential for achieving good surgical outcomes [3, 30]. These practices include optimal hydration, intensive spirometry, effective analgesia, and management of hemoglobin levels with blood transfusion when necessary [3]. In the present study, a restricted protocol for red blood cell transfusion was applied and only a low proportion of patients received preoperative blood transfusions in order to avoid the risk of alloimmunization and DHTR [3, 29, 32]. Indeed, the postoperative outcomes support that surgery in SCD patients is safe even without preoperative blood transfusion [65].

Regarding all newly introduced techniques, the cost-effectiveness of MLC + LSPP must be verified. A simple cost analysis comparing the mean total cost per patient for MLC + LSPP versus LC revealed no significant differences despite the higher costs of the surgical materials for the MLC + LSPP procedures. This lack of a difference is a direct consequence of the reduced hospitalization costs for MLC + LSPP compared with LC. However, further studies are required to better evaluate the cost-effectiveness of MLC + LSPP by taking into account the amortization time and the depreciation of instruments.

The present study has some limitations. MLC + LSPP was evaluated in a relative small sample of SCD patients and compared with a historical cohort. Subsequently, the outcomes of MLC + LSPP observed in the present study cannot be generalized without caution. Moreover, it is not possible to weight the impact of the single components of the low-impact laparoscopy protocol (i.e., miniaturized instruments or low-pressure pneumoperitoneum) on the operative and postoperative outcomes. A randomized controlled trial with multiple arms would have been helpful to address this question. However, in patients with a relative rare disease, such as SCD, a randomized study appears hardly feasible in a reasonable time frame [66, 67].

In conclusion, the present study is the first to demonstrate that cholecystectomy by mini-laparoscopy with low and stable pneumoperitoneum is a valuable option in SCD patients given that it is associated with a significantly reduced risk of SCD-related morbidity compared with LC.

Compliance with ethical standards

Disclosure Nicola de'Angelis, Solafah Abdalla, Maria Clotilde Carra, Vincenzo Lizzi, Aleix Martínez-Pérez, Anoosha Habibi, Pablo Bartolucci, Frédéric Galactéros, Alexis Laurent, and Francesco Brunetti have no conflicts of interest to disclose with regard to the results of this study.

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