



# Comparison of inflammatory stress response between laparoscopic and open approach for pediatric inguinal hernia repair in children

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## Abstract

**Background** The aim of this study was to compare inflammatory stress response between laparoscopic percutaneous inguinal ring suturing (PIRS) and open modified Marcy technique for pediatric inguinal hernia repair.

**Methods** From May 2017 to April 2018, 32 male children with median age of 4.5 years undergoing inguinal hernia repair were included in randomized controlled trial. The patients were divided in two groups, by using random number generator, depending on surgical approach. The blood was tested in three time frames for white blood cells count (WBC), C-reactive protein (CRP), Interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- $\alpha$ ).

**Results** Significant increase in concentration for all inflammatory biomarkers, that occur over time, has been found ( $p < 0.001$  for all). Additionally, it was also found that the type of surgery significantly influenced the level of WBC, CRP, and IL-6 with Marcy showing a higher level of inflammatory response (WBC  $11.4 \pm 3.1 \times 10^9/L$ ; CRP 11.5 mg/L; IL-6 11.0 pg/mL) than the PIRS (WBC  $7.6 \pm 1.6 \times 10^9/L$ ; CRP 0.8 mg/L; IL-6 2.0 pg/mL) ( $p < 0.001$  for all). Similar pattern was also found for TNF- $\alpha$  (Marcy 16.8 pg/mL; PIRS 10.1 pg/mL), but correlation between surgery type and concentration of this biomarker was significant only at the 0.1 level ( $p = 0.055$ ). The mean operation time was significantly shorter ( $9 \pm 2$  min) in PIRS group compared to Marcy group ( $25 \pm 7$  min) ( $p < 0.001$ ). Significantly lower median of visual analog scale score (VAS) was found in PIRS group (VAS = 2) compared to Marcy group (VAS = 6) ( $p < 0.001$ ).

**Conclusions** Use of laparoscopic (PIRS) technique in children shows significantly lower surgical stress in comparison to open hernia repair.

**Keywords** Percutaneous internal ring suturing—PIRS · Inguinal hernia · Children · Interleukin 6—IL-6 · Tumor necrosis factor alpha—TNF- $\alpha$  · Surgical inflammatory stress response

Today, there are various surgical techniques for pediatric inguinal hernia repair. In many centers a modified Marcy repair, which includes high ligation and excision of hernia sac, with narrowing of the internal inguinal ring, is very popular for pediatric inguinal hernia repair, because it is associated with the lowest recurrence rates [1]. By

advancing of laparoscopic surgery, many successful laparoscopic inguinal hernia repairs were reported [2, 3]. After introduction of percutaneous internal ring suturing (PIRS) for pediatric inguinal hernia repair by Patkowski, this technique became very popular among pediatric surgeons [4]. It involves the percutaneous closure of the internal inguinal ring under the control of a laparoscope placed through the umbilical port [4, 5]. Advantages of laparoscopy are already well known but proper effects of laparoscopic surgery regarding inflammatory stress response in pediatric patients are not sufficiently investigated. The surgical stress response is the name given to the hormonal and metabolic changes which follow injury or trauma. This is part of the systemic reaction to injury which encompasses a wide range of endocrinological, immunological, and hematological effects. The responses to surgery have been of interest to scientists for many years. A high surgical stress is related

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with sympathetic nervous system activation, endocrine stress response, pituitary hormone secretion, insulin resistance, immunological and hematological changes, cytokine production, acute-phase reaction, neutrophil leukocytosis, and lymphocyte proliferation. All of the above-mentioned effects may affect postoperative course of the patient. Inflammatory stress response is associated with a hemodynamic response largely affected by endogenous mediators referred to as cytokines. The inflammation markers are mostly secondary to tissue injury [6]. Initial inflammatory response, stimulated by tissue trauma or sepsis, is characterized by the production of proinflammatory cytokines, in which IL-6 and TNF- $\alpha$  are regarded as important and influential as well as widely investigated [7]. IL-6 production is rapidly induced in the course of acute inflammatory reactions associated with injury, trauma, stress, infection, brain death, neoplasia, and stress situations [8]. The secretion of IL-6 correlates with the magnitude of the trauma, the duration of surgery, and the risk of postoperative complications [9]. IL-6 has been suggested as a mediator for immune monitoring in the damage control strategy. On the other hand, the increase in TNF- $\alpha$  level is seen in those with postoperative sepsis [10]. Thus, the increase in IL-6 but not TNF- $\alpha$  may show postoperative stress due to tissue trauma alone, which in turn, is dependent on operative time, blood loss, and the extent of tissue trauma [6]. Surgical inflammation stress response is also associated with a leukocytosis in peripheral blood and accumulation of granulocytes and macrophages in the damaged tissues [11]. Following surgical stress, leukocytosis is observed in the peripheral blood and while granulocytes accumulate in the area of injury [11, 12]. CRP is an acute-phase protein whose concentration rises non-specifically in response to inflammation. CRP is seen to increase as a result of the inflammatory process and is used as a marker or general diagnostic indicator of infections and inflammation, in addition to serving as monitor of patient response to pharmacological therapy and surgery.

The purpose of this study was to compare the level of postoperative inflammatory stress markers (WBC, CRP, IL-6, and TNF- $\alpha$ ), and pain between modified Marcy and PIRS techniques for inguinal hernia repair in children.

## Patients and methods

### Patients

A total number of 32 male children, 3–7 years of age, who underwent inguinal hernia repair between May 2017 and April 2018 in the Department of Pediatric Surgery, University Hospital of Split, were included in this randomized controlled trial. Informed consent was obtained from parents or legal guardians of all the patients and study protocol was

approved by the Ethics Committee of our hospital. Inclusion criteria were males 3–7 years of age with one-sided inguinal hernia. Exclusion criteria were patients with bilateral or recurrent hernia, patients who developed respiratory or any other infection during follow-up period, patients who used any medications, and patients with associated pathology.

### Randomization and sample size calculation

Sample size calculation was performed in the G\*power 3.1.9. software [13] with assumptions of the General Linear Model (GLM) for repeated measures and within-between interaction with two tested groups and three dependent variables, a level of significance of 0.05, a power of 80%, and a large effect size of Cohen's *d* of 0.60. Based on these assumptions, size of 30 subjects in total was calculated as minimally needed. Since the assumed effect size was large, in order to control whether the study had sufficient power to properly interpret its results, a post hoc analysis of study's power was performed. Observed power in all GLM models was above 90%, except for the analysis of the interaction between surgical technique and concentration of TNF- $\alpha$  for which the observed study's power was 57%.

Based on technique used for inguinal hernia repair, the patients were divided into two groups: Group I (Marcy; *n* = 16) and Group II (PIRS; *n* = 16). The allocation of participants in each group was done by using random number generator. The statistician who did not have any contact with the surgeons performed the randomization, with the probability of each participant entering any group of 50%.

### Study protocol

Patients are admitted to hospital on the day of surgery. Medical history and demographic data (age, sex, body height, body weight, BMI, and lateralization of the hernia) are recorded and noted in study protocol. Given the randomization number, the operation technique is determined for each child. The first blood sample is taken 1 h before the surgery, second is taken 24 h after, and the last sample 7 days after the surgery. After the surgery, duration of anesthesia, duration of surgery, operative findings, and intraoperative complications were recorded. Postoperative follow-up included postoperative complications, duration of hospital stay, amount of used analgesics, and pain intensity using VAS. All patients were discharged from hospital the day after surgery. The patients were followed-up at our outpatient clinics at the first and fourth week after surgery for detection of any complications. Sterile-strip or skin sutures were removed in the first-week visit. Follow-up program consisted of physical examination 6 months after surgery to assess the presence of late complications or recurrence of the hernia.

Study is registered in Clinical Trials (ClinicalTrials.gov) under ID: NCT03203343.

## Outcome measures

The primary outcome was postoperatively inflammatory stress response measured by levels of WBC, CRP, IL-6, and TNF- $\alpha$ . To determine superiority of one surgical technique in inflammatory stress response, we expected consistent and significant differences between the groups in all the listed outcome measures. The secondary outcomes were the postoperative pain level, duration of the surgery, hospital stay, and intraoperative and postoperative complications.

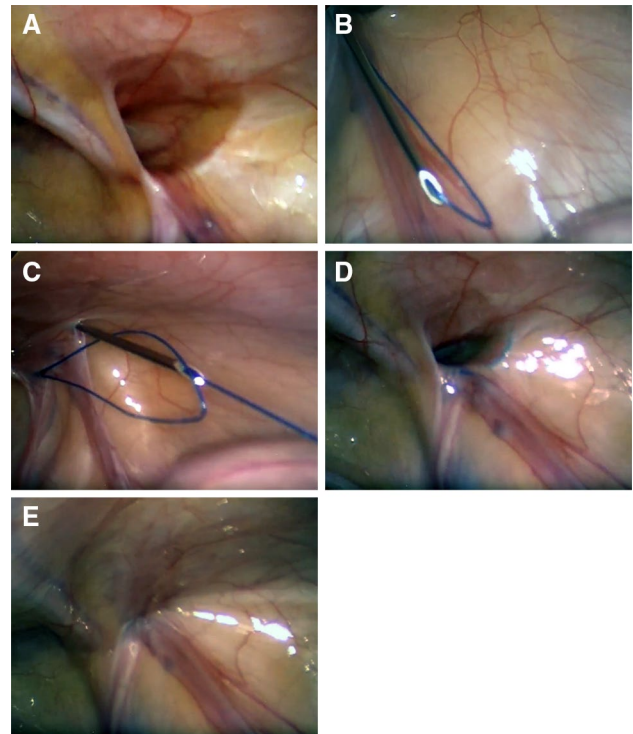
## Surgery

### Modified Marcy repair

Patients are placed in supine position with both arms tucked against their sides. Through the inguinal approach, incision of the aponeurosis of the external oblique abdominal muscle is performed horizontally 1 cm above the external inguinal ring, about 3 cm in length, along the cord, and up to the internal ring. The cord structures are dissected off the sac, and the transversal fascia is preserved intact. After high ligation of the sac with absorbable suture (Vicryl 3-0, polyglactin 910, Ethicon®, Cincinnati, Ohio, USA), the sac is resected. The cord structures are displaced laterally and one or more absorbable sutures are inserted through the fascial layers to reduce the size of the internal ring.

### PIRS

Through 3-mm supraumbilical incision, a Veress needle is used to achieve pneumoperitoneum of 6–10 mmHg, depending on patients' weight and age. A 3-mm port is inserted through supraumbilical incision. A 3-mm laparoscope is used to visualize open internal inguinal ring on side of hernia (Fig. 1A). Mini skin incision of 2 mm is performed in optimal position above the internal ring. A 20G spinal needle (ELDOR CSEN 38.4; Quincke Spinal Needle, Z.R.M.I. Co. Ltd. Jerusalem, Israel) is used for introduction of a non-absorbable monofilament nylon loop (Prolene™ 3-0, polypropylene, Ethicon®, Cincinnati, Ohio, USA) at one side of the internal ring, taking care not to enter peritoneal cavity multiple times or damage blood vessels and spermatic cord, but to take as much of the edge of entered side of internal ring (Fig. 1B). The loop is introduced into the peritoneal cavity and the spinal needle is taken out with care taken not to pull the loop out. The same needle was introduced at same skin incision but on the other side of the internal ring, again with care taken not to enter peritoneal cavity multiple times but to take as much of the edge of entered side of



**Fig. 1** PIRS technique: **A** right inguinal hernia—open internal inguinal ring; **B** introduction of a non-absorbable monofilament nylon loop through half of the inguinal ring; **C** the same needle was introduced at same skin incision but on the other side of the internal ring, and passed through the previously introduced loop and suture is pushed through the needle; **D** after removal of the needle, the loop was drawn out and the knot passed around internal ring; **E** closed internal ring

internal ring. The needle is then passed through the previously introduced loop and the same suture is passed through the needle (Fig. 1C). After removal of the needle the loop is withdrawn, catching the second suture, passing it out of the skin incision, tying it, and thus obliterating the internal ring (Fig. 1D). Successful repair is defined if occlusion of the hernia is visualized (Fig. 1E). Round gauze ball is placed on umbilical wound with sterile drape above it and mini inguinal wound is closed using braided adhesive sterile strips.

### Blood collection and preparation

Blood was drawn always by the same nurse with master in nursing with “butterfly needle” (BD Vacutainer® Push Button Blood Collection Set 0.8 × 19 × 178 mm) into two vials with clot activator (BD Vacutainer® CAT-Clot Activator Tube, 2.0 mL) and one vial containing anticoagulant K3 EDTA (BD Vacutainer® K3E 3.5 mg, 2.0 mL). Immediately after drawing, blood was taken to the Department of medical laboratory diagnostics of our hospital where vials containing clot activator were prone to centrifuge. From one of the mentioned vials, serum was divided into

two aliquots and stored on  $-80^{\circ}\text{C}$ . Serum from other vial was used to measure CRP. Blood taken into vial with K3 EDTA was used to analyze complete blood cell count. All blood samples were analyzed in the same biochemical laboratory following standard laboratory procedures.

## Measurement methods

WBC count was analyzed by hematology blood analyzer (Advia 2120, Bayer, Germany) using routine laboratory methods. CRP was analyzed using the Abbott Architect ci16200 (Abbott, GmbH Diagnostics, Wiesbaden, Germany) by immunoturbidimetric method. IL-6 was determined by electrochemiluminescence immunoassay “ECLIA” method (Elecsys e601 Analyzers, Roche Diagnostics GmbH, Mannheim, Germany). The assay linearity test ranged from 1.5 to 5000 pg/mL. TNF- $\alpha$  was assessed using an enzyme-linked immunosorbent assay (ELISA) test (DRG Instruments GmbH, Marburg, Germany) on the Elisys Duo Instrument (Human, Wiesbaden, Germany). According to the manufacturer’s data, the detection limit was 0.7 pg/mL. Intra and interassay variability for TNF- $\alpha$  ranged between 6.6 and 4.5% (for concentrations  $91 \pm 6$  and  $122 \pm 5$  pg/mL) and 6.3 and 3.3% (for concentrations  $526 \pm 33$  and  $431 \pm 14$  pg/mL).

## Statistical analysis

The data were analyzed using the SPSS 24.0 (IBM Corp, Armonk, NY) software. Arithmetic means and standard deviations were used for descriptions of distributions of quantitative variables in case no significant deviation from normal was observed, while the medians and ranges were used for asymmetrically distributed quantitative variables and for an ordinal variable—VAS scale. The significance of differences between the study arms in VAS levels or the process outcome measures (hospital stay, operation time, duration of anesthesia) was inferred by the *t* test for independent samples, or by its alternative—non-parametric test (Mann–Whitney U-test). The Chi-square test was used to assess differences in distribution of categorical data such as gender or lateralization of the hernia between the groups. The analysis of changes in an individual inflammatory biomarker within one subject at three time points, as well as the effect of the surgery type on the observed values of a marker, was conducted by the GLM for repeating measures with the surgery type as a factor. Post hoc GLM analysis and 95% confidence interval for the mean were used to infer on significance of difference in the concentrations of inflammatory marker between individual time points. All the tests were two-sided, and the significance level of 0.05 was used.

## Results

During the study period, a total of 32 male children, with median age of 4.5 (range 3–7) years were subjected to hernia repair, 16 were operated by PIRS, and 16 by open approach. There were no statistically significant differences between the groups in regards to age, lateralization of hernia, height, weight, and BMI (Table 1). The groups were also comparable in preoperative values of inflammatory biomarkers WBC, CRP, IL-6, except for TNF- $\alpha$  where statistical difference in basal values was found between the groups ( $p < 0.001$ ). Demographic and clinical data of the patients, and preoperative values of inflammatory biomarkers are summarized in Table 1. All included patients finished the study.

Overall, the type of surgery significantly affected the levels of WBC, CRP, and IL-6 (GLM-repeated measures, significant interactions between the type of surgery and an inflammatory marker, Wilks  $\lambda \leq 0.504$ ,  $p < 0.001$  for all listed markers) with Marcy showing greater level of inflammatory response than PIRS method (Table 2; Fig. 2A–C). Similar was found for TNF- $\alpha$ , but the interaction with this biomarker

**Table 1** Demographic and clinical data and preoperative values of inflammatory biomarkers

	Group I MARCY ( $n = 16$ )	Group II PIRS ( $n = 16$ )	<i>p</i>
Demographic and clinical data			
Age (years)	4	5	0.838*
Median (range)	(3–7)	(3–7)	
Lateralization <i>n</i> , (%)			
Left	5 (31.25)	6 (37.50)	0.710 <sup>†</sup>
Right	11(68.75)	10 (62.50)	
Height (cm)	$116 \pm 14$	$116 \pm 18$	0.974 <sup>‡</sup>
Mean $\pm$ SD			
Weight (kg)	18.0	19.5	0.956*
Median (range)	(14.0–42.0)	(14.0–43.0)	
BMI	$15.0 \pm 1.3$	$16.0 \pm 2.5$	0.147 <sup>‡</sup>
Mean $\pm$ SD			
Preoperative values of inflammatory biomarkers			
WBC ( $\times 10^9/\text{L}$ )	$7.3 \pm 1.3$	$7.4 \pm 1.9$	0.852 <sup>§</sup>
Mean $\pm$ SD			
CRP (mg/L)	0.3	0.4	0.381 <sup>§</sup>
Median (range)	(0.1–1.8)	(0.2–3.2)	
IL-6 (pg/mL)	1.5	1.5	0.831 <sup>§</sup>
Median (range)	(1.5–6.5)	(1.5–3.4)	
TNF- $\alpha$ (pg/mL)	4.4	8.8	$< 0.001$ <sup>§</sup>
Median (range)	(1.5–11.2)	(4.3–14.8)	

\*Mann–Whitney U-test

<sup>†</sup>Chi-square test

<sup>‡</sup>*t* test for independent samples

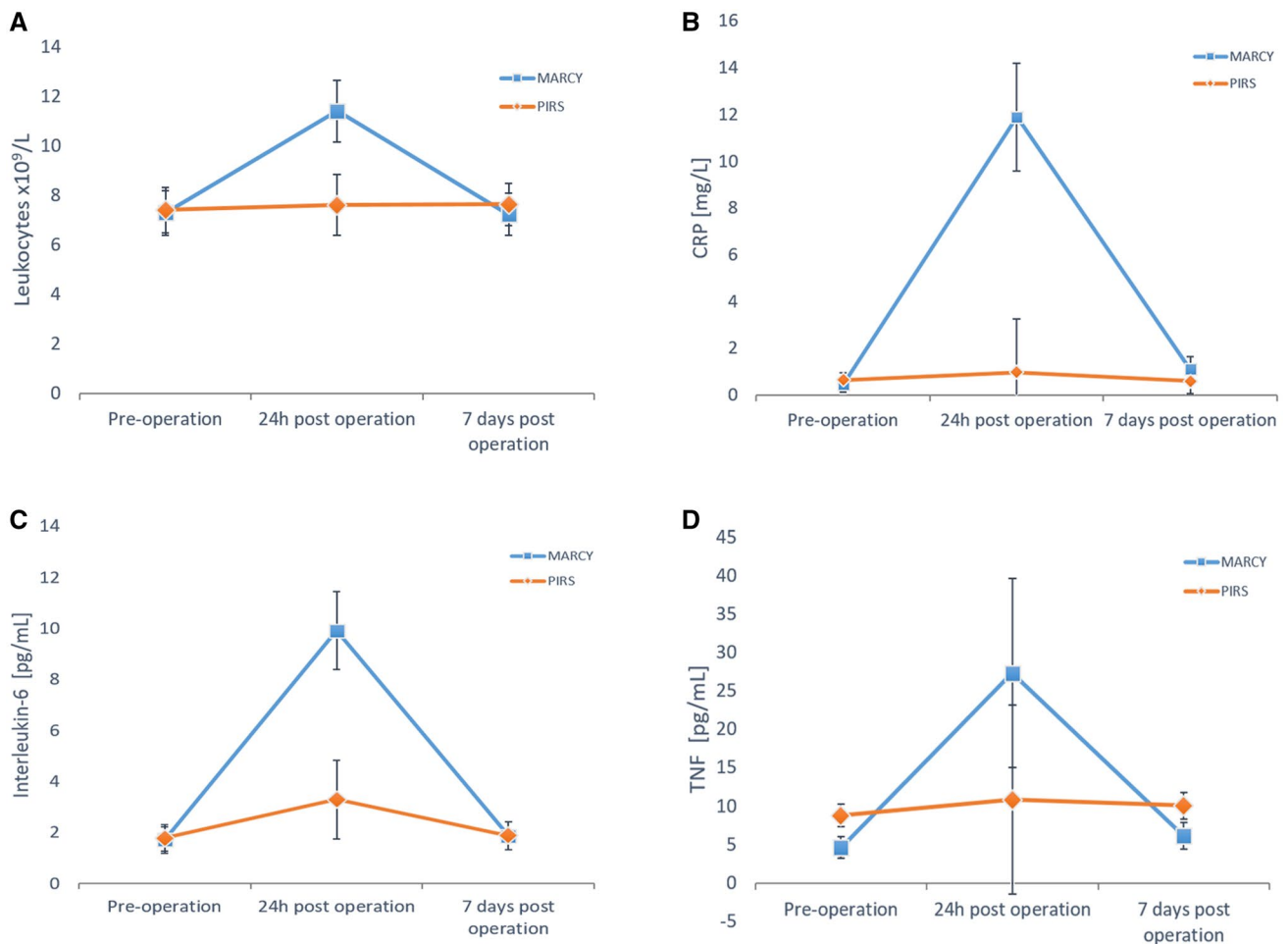
<sup>§</sup>GLM-repeated measures model



**Table 2** Postoperative changes in inflammatory biomarkers, 24 h and 7 days after surgery

	Group I MARCY (n=16)	Group II PIRS (n=16)	<i>p</i>
24 h after surgery			
WBC ( $\times 10^9/L$ ) mean $\pm$ SD	11.4 $\pm$ 3.1	7.6 $\pm$ 1.6	< 0.001*
CRP (mg/L)	11.5	0.8	< 0.001*
Median (range)	(2.3–24.5)	(0.3–2.1)	
IL-6 (pg/mL)	11.0	2.0	< 0.001*
median (range)	(4.7–14.9)	(1.5–9.8)	
TNF- $\alpha$ (pg/mL)	16.8	10.1	0.063*
Median (range)	(9.0–150.4)	(5.0–19.4)	
7 days after surgery			
WBC ( $\times 10^9/L$ ) mean $\pm$ SD	7.2 $\pm$ 1.8	7.6 $\pm$ 1.6	0.508*
CRP (mg/L)	0.5	0.5	0.191*
Median (range)	(0.2–4.8)	(0.2–1.4)	
IL-6 (pg/mL)	1.5	1.5	0.997*
Median (range)	(1.5–6.5)	(1.5–3.6)	
TNF- $\alpha$ (pg/mL)	6.2	10.2	< 0.003*
Median (range)	(1.3–13.1)	(3.9–16.0)	

\*GLM-repeated measures model

**Fig. 2** Comparison of serum concentrations of inflammatory biomarkers: **A** WBC; **B** CRP; **C** IL-6; **D** TNF- $\alpha$ ; between the study groups at three time points (before surgery, 24 h, and 7 days after surgery). Shown are means with corresponding 95% confidence intervals

was significant at the level of 0.1 (Wilks  $\lambda=0.819$ ,  $p=0.055$ ; Table 2; Fig. 2D). This finding was likely due to initial difference in TNF- $\alpha$  levels between the study groups as the baseline TNF- $\alpha$  concentration in lower inflammatory-response PIRS group was almost twice the concentration in Marcy group (Table 1).

Regarding the time point at which level differences of inflammatory markers between the study groups occur, GLM-repeated measures model showed that the groups were comparable with regard to levels of IL-6, WBC, and CRP, immediately before, and 7 days after the surgery ( $p \geq 0.191$  for all listed markers and time points); and that the only difference between the methods was observed 24 h after the surgery ( $p < 0.001$  for all listed markers). Exception to this pattern was TNF- $\alpha$  for which we found significant differences between the groups immediately before and 7 days after surgery, with the difference found 24 h after the surgery being significant only at 0.1 level ( $p=0.063$ ).

Concerning the dynamics of inflammatory response in each study group, a similar response pattern was observed in both groups. 24 h after the surgery, the values of inflammatory biomarkers' concentration significantly increased (post hoc GLM analysis for comparisons between preoperative and 24-h-after-the-surgery levels,  $p \leq 0.030$ ), whereas 7 days after the surgery these values dropped to preoperative levels (post hoc GLM analysis,  $p \geq 0.106$ ). Exception to this rule was observed for leukocyte concentration in the PIRS group which did not significantly change during time at all ( $p \geq 0.529$ ). Also, TNF- $\alpha$  levels more slowly dropped towards preoperative values. In Marcy group, TNF- $\alpha$  level measured at 7 days was still significantly higher than preoperative values (mean difference 1.5 pg/mL, 95% CI 0.5–2.6,  $p=0.007$ ), whereas in PIRS group the value of biomarker's concentration measured at same time point was still similar to the 24-h value ( $p=0.423$ ) and higher than preoperative values (mean difference 1.3 pg/mL, 95% CI from -0.2 to 2.7,  $p=0.083$  significant at the 0.1 level).

Process outcomes are presented in Table 3. Hospital stay was 1 day for all patients ( $p=0.999$ ). There were no intraoperative and postoperative complications recorded in both study groups. The mean operation time was significantly shorter ( $9 \pm 2$  min) in PIRS group compared to Marcy group ( $25 \pm 7$  min) ( $p < 0.001$ ). The median duration of the anesthesia was 20 min shorter in PIRS group, compared to Marcy group ( $p < 0.001$ ). Significantly lower median of VAS score was found in PIRS (VAS = 2) than in Marcy group (VAS = 6) ( $p < 0.001$ ) (Fig. 3).

## Discussion

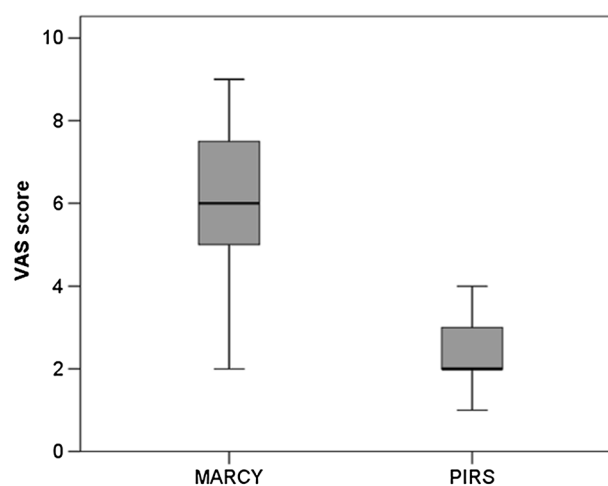
Inguinal hernia repair remains the most commonly performed surgery in children [14]. Advantages of both PIRS and modified Marcy techniques for inguinal hernia repair

**Table 3** Treatment outcomes in children undergoing inguinal hernia repair

Treatment outcomes	Group I MARCY (n = 16)	Group II PIRS (n = 16)	p
Hospital stay (days)	1	1	0.999*
Median (range)	(1–1)	(1–1)	
Operation time (min)	$25 \pm 7$	$9 \pm 2$	$< 0.001^\dagger$
Mean $\pm$ SD			
Duration of anesthesia (min)	40	20	$< 0.001^*$
Median (range)	(15–50)	(15–25)	
Pain intensity (VAS)	6	2	$< 0.001^*$
Median (range)	(2–9)	(1–4)	

\*Mann–Whitney U-test

$^\dagger$  t test for independent samples



**Fig. 3** Comparison of VAS score distributions between the study groups

are well known nowadays. Advantages and disadvantages of both techniques are well known and described in literature [1, 5]. The inflammatory stress markers response to elective surgery is well known and the response of inflammatory stress markers observed in this study is in agreement with previous studies [10, 12, 14, 15]. After acute stress, peripheral cytokines are released from T cells, and this results in increased proinflammatory cytokine production [10, 11]. Surgical stress is characterized by an induced production of WBC, CRP, and proinflammatory cytokines [10, 11, 16]. Monocytes in the area of injury release the proinflammatory cytokines IL-1, TNF- $\alpha$ , and IL-6. IL-6 stimulates the hepatic acute-phase protein synthesis with release of CRP and procalcitonin. Levels of IL-6 correlate with the magnitude of the injury, the duration of surgery, and the risk of postoperative complications [12]. TNF- $\alpha$  and IL-6 are two well-known proinflammatory cytokines which are thought

to be central mediators in the cytokine cascades, and also important cytokines for immune and inflammatory response. The changes in serum TNF- $\alpha$  and IL-6 concentration are sensitive indicators of the postoperative acute-phase inflammatory reaction and surgical stress [10, 17].

In presented study, these inflammatory biomarkers were used to evaluate surgical stress and injury between open and laparoscopic hernia repair in children. However, in current literature, there is no study evaluating in a comparative manner the possible effects of different surgical methods on the inflammatory stress markers response. The main advantage of this study is randomization, controlled measurement in three different time frames of three main inflammatory biomarkers, and two of them being proinflammatory cytokines. Also the stratification of study to the age group 3–7 years of age puts the study in special consideration.

The present randomized controlled trial investigated the perioperative time course of inflammatory markers in 32 children undergoing elective hernia repair in a matter of postoperative inflammatory stress response level. Our data demonstrate that inflammatory stress markers are significantly influenced by type of surgery used for hernia repair in children. As expected, after surgery, increase of all inflammatory biomarkers was shown in both techniques, PIRS and Marcy, but in children in open surgery group postoperative increase of all investigated inflammatory biomarkers was significantly higher than in laparoscopic group.

Possible explanation for this finding is that open hernia surgery may cause higher plasma inflammatory stress marker levels due to greater manipulation with tissue and tissue damage due to larger incision. Laparoscopic-assisted percutaneous method is related with two very small incisions and no manipulation with tissue and with no tissue dissection. Except larger incision, the hernia sac dissection and the separation of the funicular elements from hernia sac is a major part of the open hernia surgery in children. On the other hand, in presented laparoscopic percutaneous technique, there is no dissection of sac, the knot is just introduced and tied around the internal inguinal ring. All of these factors may result in higher increase of inflammatory marker level in open group.

A similar dynamics of all inflammatory biomarkers' was observed in both study groups. 24 h after the surgery the values of inflammatory biomarkers' concentration significantly increased, whereas 7 days after the surgery these values dropped to preoperative levels. The clinical significance of this finding correlated with degree of pain in children 24 h after surgery. Children in PIRS group had significantly lower pain level and received less analgesics compared to children in Marcy group. It has been hypothesized that a reduction in the surgical stress responses (endocrine, metabolic, and inflammatory) will lead to a reduced incidence of postoperative organ dysfunction and thereby to an improved

outcome. As afferent neural stimuli and activation of the autonomic nervous system and other reflexes by pain may serve as a major release mechanism of the endocrine metabolic responses and thus contribute to various organ dysfunctions, pain relief may be a powerful technique to modify surgical stress response. In this study, it has been shown that less invasive surgical technique was related with less cytokine response which correlates with less pain level in children compared to open technique.

In literature, there are no studies in pediatric population on the same pathology to compare our results with. Hao et al. investigated early postoperative stress response in order to evaluate surgical stress in children who underwent single-port and three-port laparoscopic varicocelectomy. The change in serum TNF- $\alpha$  and IL-6 concentrations pre- and postoperatively between the single-port group and three-port group was not statistically significant. Possible explanation is that they compared the same technique, just with difference in one introduced laparoscopic trocar and their sample was very small [6].

Redmond et al. demonstrated significantly increased TNF- $\alpha$ , chemotaxis, and WBC count in open cholecystectomy patients when compared to laparoscopy patients [18]. For these reasons, shorter operative time and hospital stay are important factors after surgery. Özçınar et al. also reported that longer operative time increases the levels of IL-6 and TNF- $\alpha$  [19]. As shown in our results, because there is no classic incision, and no dissection of the sac and separation of the funiculus, the operation time will be significantly shorter in laparoscopic group in hands of experienced laparoscopic surgeon.

Regarding the question of anesthetics and its implication in increase of inflammatory markers, we concur with Toft et al. that the effect of anesthetics on the inflammatory response is modest compared to the surgical stress [11]. Lower postoperative pain is a well-known advantage of minimally invasive surgery [20]. VAS was used for pain evaluation after surgery. Postoperative pain level was significantly lower in children operated laparoscopically, which correlates with lower values of inflammatory stress markers in laparoscopic group. Similar findings were reported in other studies [18, 19].

## Conclusion

This study demonstrates that host immune function, as assessed by a range of immunological parameters, differs in open versus laparoscopic surgery, whereas the stress and acute-phase protein responses were significantly higher in open group which was associated with longer duration of surgery and higher pain level. PIRS is a simple, safe, and effective method for treatment of pediatric inguinal hernia

and it satisfies all criteria of minimally invasive surgery, with significantly lower surgical stress and pain level compared to open surgery. Because of all the above-mentioned advantages, PIRS should be method of choice for inguinal hernia repair in children.

### Compliance with ethical standards

**Disclosures** Miro Jukić, Zenon Pogorelić, Daniela Šupe-Domić, and Ana Jerončić have no conflicts of interest or financial ties to disclose.

### References

- Pogorelić Z, Rikalo M, Jukić M, Katić J, Jurić I, Furlan D, Budimir D, Biočić M (2017) Modified Marcy repair for indirect inguinal hernia in children: a 24-year single-center experience of 6826 pediatric patients. *Surg Today* 47:108–113
- Thomas DT, Göcmen KB, Tulgar S, Boga I (2016) Percutaneous internal ring suturing is a safe and effective method for the minimal invasive treatment of pediatric inguinal hernia: experience with 250 cases. *J Pediatr Surg* 51:1330–1335
- Oral A, Karaca L, Ahiskalioglu A, Yildiz A, Yigiter M, Celikkaya ME, Chyndolotov T, Salman AB (2018) Effects of laparoscopic hernia repair by PIRS (percutan internal ring suturing) technique on testicular artery blood supply. *J Investig Surg* 2:1–5
- Patkowski D, Czernik J, Chrzan R, Jaworski W, Apoznański W (2006) Percutaneous internal ring suturing: a simple minimally invasive technique for inguinal hernia repair in children. *J Laparosc Adv Surg Tech A* 16:513–517
- Pogorelić Z (2018) Effects of laparoscopic hernia repair by PIRS (percutaneous internal ring suturing) technique on testicular artery blood supply. *J Investig Surg*. <https://doi.org/10.1080/08941939.2017.1423424>
- Hao W, Chan IH, Liu X, Tang PM, Tam PK, Wong KK (2012) Early post-operative interleukin-6 and tumor necrosis factor- $\alpha$  levels after single-port laparoscopic varicocelectomy in children. *Pediatr Surg Int* 28:281–286
- Hackam DJ, Rotstein OD (1998) Host response to laparoscopic surgery: mechanisms and clinical correlates. *Can J Surg* 41:103–111
- Song M, Kellum JA (2005) Interleukin-6. *Crit Care Med* 33:463–465
- Nast-Kolb D, Waydhas C, Gippner-steppert C, Schneider I, Trupka A, Ruchholtz S, Zettl R, Schweiberer L, Jochum M (1997) Indicators of the posttraumatic inflammatory response correlate with organ failure in patients with multiple injuries. *J Trauma* 42:446–454
- Kragstbjerg P, Holmberg H, Vikerfors T (1995) Serum concentrations of interleukin-6, tumor necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. *Eur J Surg* 161:17–22
- Toft P, Tonnesen E, Helbo-Hansen HS, Lillevang ST, Rasmussen JW, Christensen NJ (1994) Redistribution of granulocytes in patients after major surgical stress. *APMIS* 102:43–48
- Toft P, Tonnesen E (2008) The systemic inflammatory response to anaesthesia and surgery. *Curr Anaesth Crit Care* 19:349–353
- Faul F, Erdfelder E, Buchner A, Lang AG (2009) Statistical power analyses using G\*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods* 41(4):1149–1160
- Miltenburg DM, Nuchtern JG, Jaksic T, Kozinetz C, Brandt ML (1998) Laparoscopic evaluation of the pediatric inguinal hernia: a meta-analysis. *J Pediatr Surg* 33:874–879
- Naito Y, Tamai S, Shingu K, Shindo K, Matsui T, Segawa H, Nakai Y, Mori K (1992) Responses of plasma adrenocorticotrophic hormone, cortisol, and cytokines during and after upper abdominal surgery. *Anesthesiology* 77:426–431
- Novitsky YW, Litwin DE, Callery MP (2004) The net immunologic advantage of laparoscopic surgery. *Surg Endosc* 18:1411–1419
- van Berge Henegouwen MI, van der Poll T, van Deventer SJ, Gouma DJ (1998) Peritoneal cytokine release after elective gastrointestinal surgery and postoperative complications. *Am J Surg* 175:311–316
- Redmond HP, Watson WG, Houghton T, Condron C, Watson RG, Bouchier-Hayes D (1994) Immune function in patients undergoing open vs laparoscopic cholecystectomy. *Arch Surg* 129:1240–1246
- Özçınar B, Aksakal N, Yanar F, Ağcaoğlu O, Peker KD, Türkoğlu Ü, Mercan S, Özarmağan S, Erbil Y (2014) Increased interleukin 1 and tumor necrosis factor alpha levels after thyroid surgery. *Ulus Cerrahi Derg* 30:80–84
- Mimica Ž, Pogorelić Z, Perko Z, Sršen D, Stipić R, Dujmović D (2007) Effect of surgical incision on pain and respiratory function after abdominal surgery: a randomized clinical trial. *Hepatogastroenterology* 54:2216–2220