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# DYNAMIC CHANGES IN INFLAMMATORY INDICES AFTER LAPAROSCOPIC COMMON BILE DUCT EXPLORATION IN MALE AND FEMALE PATIENTS WITH COMPLEX COMMON BILE DUCT STONES

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Common bile duct stones (CBDS) are among the most prevalent biliary tract diseases, with a higher incidence in women, and pose a significant global health challenge. If left untreated, CBDS can lead to severe inflammatory complications, including cholangitis, pancreatitis, and biliary cirrhosis. Laparoscopic common bile duct exploration (LCBDE) followed by laparoscopic cholecystectomy (LC) has become a widely adopted treatment approach, alongside advanced endoscopic retrograde cholangiopancreatography (ERCP) techniques. However, managing cholelithiasis accompanied by difficult common bile duct stones (DCBDS) remains particularly challenging. The LCBDE + LC approach has been shown to minimize surgical trauma and systemic inflammatory response, leading to faster recovery in patients with cholelithiasis accompanied by DCBDS. Despite these advancements, sex-based differences in post-LCBDE + LC systemic inflammatory response remain largely unexplored. This study **aimed** to evaluate and compare the dynamic changes in inflammatory markers between male and female patients with cholelithiasis accompanied by DCBDS undergoing LCBDE + LC.

*Methods.* The study included 71 patients (24 males and 47 females) with cholelithiasis accompanied by DCBDS who underwent LCBDE + LC, with a mean age of 60.3 ± 1.9 years. White blood cell (WBC) counts and differentials were measured using a Mindray BC-2800 automatic hematological analyzer (Mindray, Shenzhen, China). Additionally, WBC-based inflammatory indices were calculated, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), and neutrophil-to-monocyte ratio (NMR). These indices were evaluated at three time points: before surgery, 24 h postoperatively, and upon discharge.

*Results.* Preoperatively, median inflammatory index values were significantly higher in female patients with cholelithiasis accompanied by DCBDS compared to males: NLR, PLR, and NMR were 1.4 times higher, while SII — by 1.6. 24 h post-surgery, systemic inflammatory indices followed distinct patterns in male and female patients. In males, the median values of NLR and LMR remained unchanged, whereas SII and NMR increased 1.2-fold, PLR rose 1.5-fold, and SIRI decreased 1.3-fold. In contrast, females exhibited a decline in the median values of NLR, SIRI, and SII by 1.2-, 1.7-, and 1.3-fold, respectively. PLR and NMR remained stable, while LMR increased 1.4-fold. At discharge, male patients showed a marked increase in median inflammatory index values compared to baseline, ranging from 1.8-

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to 2.5-fold. In contrast, females demonstrated either unchanged values or an increase of approximately 30% relative to baseline.

*Conclusions*. Female patients with cholelithiasis accompanied by DCBDS demonstrate a greater ability to resolve post-surgical inflammation compared to males.

***Key words:*** Difficult common bile duct stones; Laparoscopic common bile duct exploration; Inflammatory indices, Sex differences.

Endoscopic retrograde cholangiopancreatography (ERCP) combined with laparoscopic cholecystectomy (LC) is the standard treatment for cholecystolithiasis with choledocholithiasis [1]. However, this approach is often inadequate, particularly for managing difficult common bile duct (CBD) stones [2]. Difficult biliary stones refer to any stones within the common or hepatic bile ducts that cannot be removed in a single conventional ERCP session using biliary sphincterotomy and extraction attempts using balloon or basket catheters [3].

Laparoscopic common bile duct exploration (LCBDE) is widely recommended as the preferred treatment for difficult CBD stones in patients undergoing LC, as it generally leads to shorter hospital stays and faster recovery [4]. The clinical success of treating difficult CBD stones is strongly influenced by postoperative inflammation. Rather than focusing solely on gallstone clearance, minimizing the immune response triggered by surgical trauma may play a crucial role in optimizing treatment selection and improving surgical outcomes. Evaluating immunologic changes post-surgery requires an assessment of both hyperinflammation and immunosuppression during the immediate postoperative period [5].

Laparoscopic surgery causes minimal trauma, making it less disruptive to the immune system compared to open surgery. However, it still triggers both local (within the peritoneal cavity) and systemic inflammatory responses, including in procedures like LCBDE [6, 7]. Postoperative systemic inflammation plays a significant role in surgical outcomes, yet its impact on patient-centered outcomes remains largely unclear.

Additionally, there are notable sex differences in both immunity and inflammation. Inflammatory diseases vary significantly between men and women in terms of incidence, clinical presentation, severity, prognosis, and response to pharmacological treatments. Cholelithiasis is more prevalent in women [8].

Men and women also differ in their inflammatory stress responses. Males tend to produce higher levels of reactive oxygen species (ROS) while having less efficient antioxidant mechanisms. Furthermore, they exhibit higher baseline inflammation in the course of infectious diseases but a weaker immune response to inflammatory stimuli [9, 10]. This study **aimed** to evaluate and compare the dynamic changes in inflammatory markers between male and female patients with cholelithiasis accompanied by difficult CBD stones (DCBDS) undergoing LCBDE + LC.

## Materials and Methods

This retrospective study was conducted at the Department of Surgery with a Course in Emergency and Vascular Surgery at O.O. Bogomolets National Medical University in Kyiv, Ukraine. The study included 71 patients diagnosed with cholelithiasis accompanied by DCBDS: 24 males and 47 females with a mean age of 60.3 ± 1.9 years.

Abdominal ultrasound served as the primary diagnostic tool for detecting gallstone disease complicated by choledocholithiasis. In cases where ultrasound imaging provided insufficient visualization of the CBD and biliary tree, additional imaging modalities — such as contrast-enhanced computed tomography and magnetic resonance cholangiopancreatography (MRCP) — were employed. These advanced techniques were utilized in eight patients.

All patients underwent standard laboratory evaluations, including a complete blood count and liver function tests. Routine instrumental assessments included electrocardiography, chest X-ray, abdominal ultrasound, and esophagogastroduodenoscopy. The diagnosis of DCBDS was confirmed based on factors that complicated the endoscopic retrieval of CBD stones. The study was approved by the Ethics Committee of Kyiv City Clinical Emergency Hospital. Before participation, all subjects provided written informed consent, in accordance with the protocol set by the local ethical committee. All procedures were conducted in compliance with the ethical

standards of the institution and/or national research committee, as well as the principles outlined in the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical guidelines. LCBDE + LC were performed as described earlier [11, 12].

Hematological parameters were measured at three time points: 24 hours before surgery, 24 hours after surgery, and at discharge. Venous blood samples, anticoagulated with EDTA, were collected between 7:00 and 8:00 AM. Laboratory analyses were performed within 1.5 to 2.5 hours of sample collection. The white blood cell (WBC) count with a differential was conducted using a Mindray BC-2800 automatic hematology analyzer (Mindray, Shenzhen, China). In addition, various white blood cell-based inflammatory indices were calculated, including the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic inflammatory response index (SIRI), systemic immune inflammation index (SII), and neutrophil-to-monocyte ratio (NMR).

Prior to conducting other statistical tests, data were assessed for normality using the Shapiro-Wilk test [13]. All data are presented as median values with interquartile range (IQR). Statistical comparisons were made using the non-parametric Mann-Whitney U test, with a significance threshold set at $P < 0.05$. All statistical analyses were performed using IBM SPSS Statistics version 22.0.

## Results and Discussion

Biliary lithiasis is one of the most prevalent diseases worldwide, affecting the gallbladder and biliary tree in approximately 20% of the general population, though only a small percentage develop clinical symptoms [14]. Furthermore, up to 15% of individuals with cholelithiasis also experience concurrent choledocholithiasis [15]. The prevalence of choledocholithiasis in cholelithiasis patients increases with age, ranging from 8–15% in those under 60 years to 15–60% in individuals over 60 years [16]. About 15% of CBD stones are considered difficult [17]. The standard treatment for cholecystolithiasis with DCBDS involves a two-stage approach combining ERCP and LC. However, this method has certain limitations and drawbacks. Advances in laparoscopic techniques have led to the development of a single-stage approach for managing cholecystolithiasis with concurrent CBD stones, including DCBDS. The clinical success of treating DCBDS, including the LCBDE + LC approach, is highly dependent on perioperative inflammation. Perioperative inflammation in patients with DCBDS undergoing LCBDE + LC is triggered by two main factors. The first is the presence of challenging CBD stones themselves, which can cause varying degrees of inflammation, ranging from mild and asymptomatic to severe with pronounced immune responses [18]. The second trigger is the laparoscopic intervention. While laparoscopic surgery offers significant advantages over open surgery — including faster recovery, shorter hospital stays, and a quicker return to daily activities — it still induces a degree of trauma, albeit less severe for the immune system. Nonetheless, both local and systemic inflammatory immune responses are common after treatment and can significantly impact clinical outcomes [19]. Sex is a biological factor that influences immune system function, including the generation of inflammatory responses [20]. To our knowledge, this is the first report examining sex-related differences in perioperative inflammation in patients with DCBDS undergoing LCBDE + LC.

Perioperative inflammation was assessed using two sets of inflammatory markers. The first set included hematological parameters. Baseline WBC counts and differentials showed moderate differences between male and female patients with cholelithiasis accompanied by DCBDS (Table 1). In male patients, the median values of all hematological parameters remained within the normal range. In contrast, female patients exhibited a slightly elevated median neutrophil count and a slightly lower median lymphocyte count compared to the normal values. This suggests the presence of persistent systemic meta-inflammation in female patients, whereas no such trend was observed in males. Our findings align with well-documented evidence indicating that women tend to experience a more pronounced inflammatory response compared to men [20]. It is important to highlight the substantial individual variability in hematological parameters among study participants. Approximately 40% of patients, regardless of sex, exhibited significant baseline leukocytosis and neutrophilia, while the remaining patients had values within the normal range. A significantly reduced baseline lymphocyte count was observed in 66% of female patients and 40% of male patients.

At 24 hours post-surgery, a slight decrease in all parameters was observed in both male

*Table 1*

**Hematological parameters in male and female patients with CL and concomitant DCBDS undergoing LCBDE + LC ($\times 10^{-9}$/L)**

| | Basal | 24 h post-surgery | Upon discharge |
|---|---|---|---|
| Males ($n$ = 24) | | | |
| Total WBC count (4.0–9.0) | 7.7 [5.6; 13.2] | 7.5 [5.2; 9.1] | 8.1 [6.0; 9.5] |
| Neutrophil count (1.8–6.5) | 5.9 [3.8; 10.1] | 5.4 [4.0; 7.1] | 6.8 [5.1; 7.8] |
| Monocyte count (0.1–0.7) | 0.7 [0.3; 1.0] | 0.5 [0.3; 0.6] | 0.6 [0.3; 0.8] |
| Lymphocyte count (1.2–3.0) | 1.3 [0.7; 1.9] | 1.0 [0.6; 1.4] | 0.6 *# [0.4; 0.9] |
| Platelet count (180–360) | 189 [164; 295] | 233 [205; 274] | 231 [194; 298] |
| Females ($n$ = 47) | | | |
| Total WBC count (4.0–9.0) | 8.3 [6.8; 11.1] | 8.0 [6.7; 9.6] | 6.9 [5.9; 7.4] |
| Neutrophil count (1.8–6.5) | 6.9 [5.1; 9.1] | 6.3 [4.5; 7.5] | 5.7 [5.0; 6.4] |
| Monocyte count (0.1–0.7) | 0.6 [0.4; 0.8] | 0.5 [0.3; 0.8] | 0.5 [0.3; 0.6] |
| Lymphocyte count (1.2–3.0) | 1.0 [0.7; 1.3] | 1.0 [0.8; 1.5] | 0.6 *# [0.4; 0.8] |
| Platelet count (180–360) | 253 [196; 288] | 238 [205; 303] | 239 [208; 292] |

*Notes:* * — $P \leq 0.05$ as compared to lower value of reference range; # — - $P \leq 0.05$ as compared to baseline median value.

and female patients, except for platelet count, which showed a tendency to increase. Upon discharge, male patients exhibited mild neutrophilia accompanied by pronounced lymphopenia, whereas female patients showed only lymphopenia. This suggests a more pronounced residual systemic meta-inflammation in male patients at this stage.

Second set of inflammatory markers included WBC-based inflammatory indices. In recent years, there has been increasing use of inflammatory markers derived from complete blood count (CBC) results, such as the SII, NLR, and PLR etc., in the diagnosis and prognosis of various inflammatory diseases, including cholelithiasis and choledocholithiasis [21–23]. While these indicators may offer lower sensitivity and specificity compared to traditional disease markers, their cost-effectiveness and ease of calculation from widely available, low-cost measures make them valuable tools in clinical practice. The NLR is one of the most commonly used WBC-based inflammatory indices, reflecting the balance or imbalance between innate and adaptive immune responses, particularly in the context of inflammation and its resolution [23]. In our study, baseline NLR values were significantly elevated beyond the normal range reported in numerous clinical studies, with median values of 5.5 in males and 7.6 in females, compared to 1.88 and 1.68 in healthy individuals of the corresponding sex [24 (Fig. 1, *A*). At 24 hours post-surgery, median NLR values remained stable in male patients, while a slight decrease was observed in females.

However, at discharge, a significant increase in NLR values was observed in males, suggesting a persistent systemic inflammatory response. In contrast, NLR values in females at discharge showed no significant difference compared to admission levels. LMR values showed a trend of gradual decrease postoperatively in male patients, whereas no such trend was observed in female patients (Fig. 1, *B*). One potential reason for this difference could be a more pronounced decrease in monocyte count in males compared to females. This may be due to the migration of these cells to the site of

local inflammation, where they differentiate into tissue macrophages. These monocyte-derived tissue macrophages can either exacerbate inflammation or contribute to its resolution [25]. Preoperative PLR values were slightly elevated compared to normal levels as reported in the literature [26] (Fig. 1, *C*). In male patients, the median values of this index progressively increased postoperatively, and at discharge, PLR values were significantly higher than baseline levels. This indicates residual low-grade systemic inflammation. In female patients, there was only a trend toward an increase in PLR values postoperatively. Baseline SIRI values in all patients were 3.5 to 4 times higher than those in healthy individuals [27] and showed no significant change during the perioperative period in either sex (Fig. 1, *D*). Baseline SII values were twice the normal range in males and

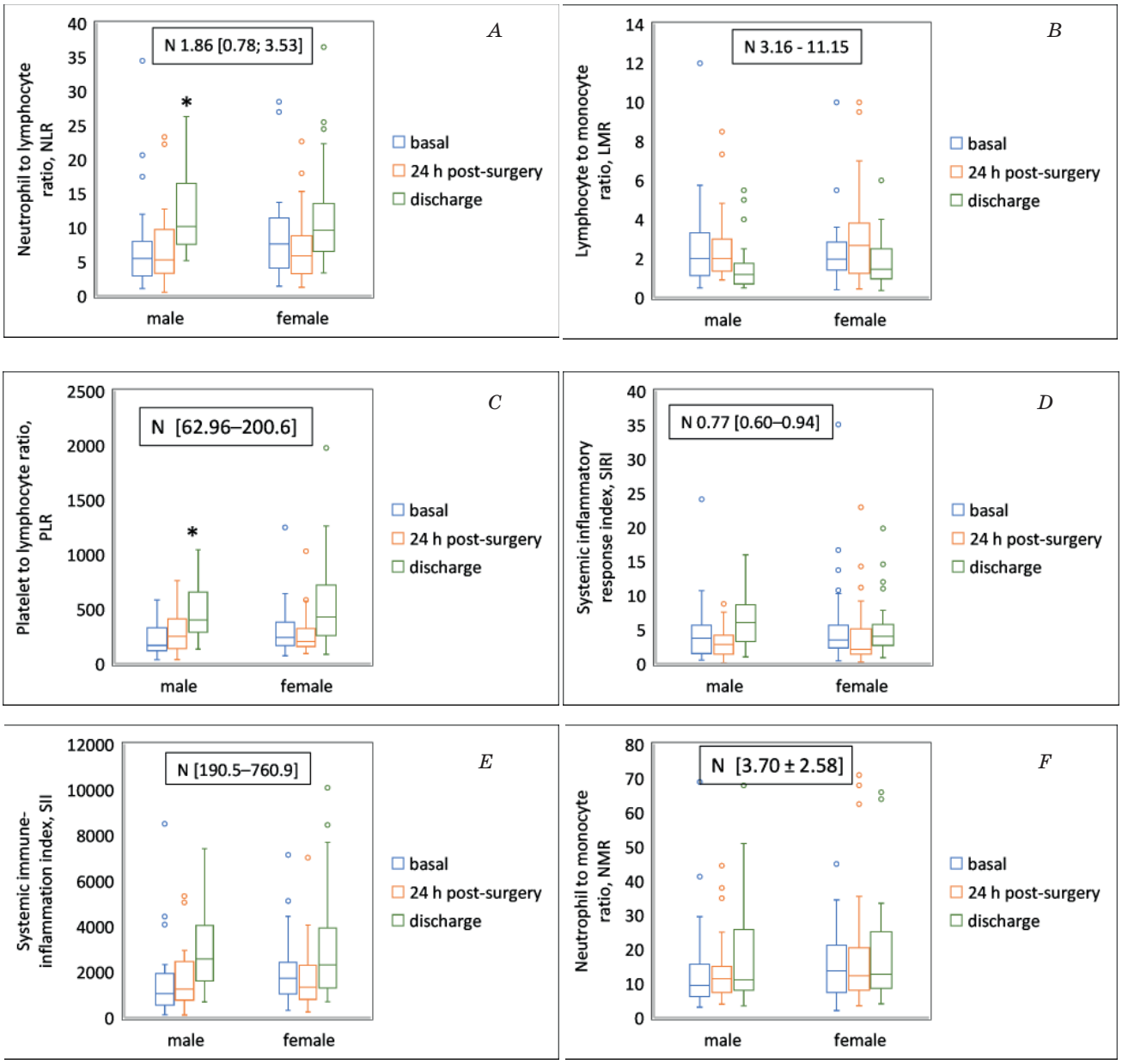


*Fig. 1.* **WBC-based indices of systemic inflammation in male and female patients with CL and concomitant DCBDS undergoing LCBDE + LC**

Data are expressed as medians with interquartile ranges (IQR) and were compared between groups using the Mann-Whitney U test.

* — $P \leq 0.05$ as compared to basal value.

three times higher in females (Fig. 1, *E*) [26]. However, upon discharge, a moderate increase in SII values was observed in males, but not in females. Baseline NMR values were elevated in all patients compared to healthy individuals [28]. No significant changes were observed throughout the perioperative period in female patients, and slight increase — in males.

## Conclusion

Thus, LCBDE + LC procedure did not induce immunosuppression or severe systemic inflammation in patients with CL and concomitant DCBDS. However, hematological markers of residual systemic inflammation were observed in male patients upon discharge. This suggests that female patients with CL and concomitant DCBDS exhibit a greater capacity for resolving post-surgical inflammation compared to males.

*Conflict of Interest*

The authors declare that they have no conflict of interest.

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*Author Contributions*

Y. Susak contributed to the study conceptualization, methodology, and writing — review and editing of the manuscript. V. Volkovetskii O. Lobanova, N. Puzyr, M. Maksimenko and A. Tkachenko were responsible for data curation, including the collection of imaging data and endoscopic scores. Larysa Skivka contributed to the study conceptualization, formal analyses and the writing of the original draft.

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# ДИНАМІЧНІ ЗМІНИ ПОКАЗНИКІВ ЗАПАЛЕННЯ ПІСЛЯ ЛАПАРОСКОПІЧНОЇ ХОЛЕДОХОЛІТОЕКСТРАКЦІЇ ТА ХОЛЕДОХОСКОПІЇ У ПОЄДНАННІ З ЛАПАРОСКОПІЧНОЮ ХОЛЕЦИСТЕКТОМІЄЮ У ЧОЛОВІКІВ ТА ЖІНОК ЗІ СКЛАДНИМ ХОЛЕДОХОЛІТІАЗОМ

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Конкременти загальної жовчної протоки (КЗЖП) є однією з найпоширеніших патологій жовчовивідних шляхів, з більш високою частотою випадків серед жінок, що становить серйозну глобальну проблему охорони здоров'я. За відсутності лікування КЗЖП можуть призвести до тяжких запальних ускладнень, зокрема холангіту, панкреатиту та біліарного цирозу. Лапароскопічна холедохолітоекстракція та холедохоскопія (ЛХХ) у поєднанні з лапароскопічною холецистектомією (ЛХ) стала широко використовуваним підходом до лікування КЗЖП, поряд із сучасними методами ендоскопічної ретроградної холангіопанкреатографії. Проте ведення пацієнтів із жовчнокам'яною хворобою (ЖКХ), ускладненою складним холедохолітіазом (СХ), залишається серйозним викликом. Метод ЛХХ + ЛХ дозволяє зменшити хірургічну травматизацію та системну запальну відповідь, сприяючи швидшому відновленню пацієнтів із ЖКХ, ускладненою СХ. Незважаючи на ці досягнення, статеві відмінності у системній запальній відповіді після ЛХХ+ЛХ залишаються недостатньо вивченими.

*Метою* цього дослідження було оцінити та порівняти динамічні зміни запальних маркерів у чоловіків і жінок із ЖКХ, ускладненою СХ після виконання ЛХХ+ЛХ.

*Методи.* Дослідження включало 71 пацієнта (24 чоловіки та 47 жінок) із ЖКХ, ускладненою СХ, яким було проведено ЛХХ+ЛХ, із середнім віком 60,3 ± 1,9 р. Лейкоцитарну формулу визначали за допомогою автоматичного гематологічного аналізатора Mindray BC-2800 (Mindray, Шеньчжень, Китай). Додатково розраховували індекси запалення на основі показників лейкоцитарної формули, зокрема: нейтрофільно-лімфоцитарний коефіцієнт (НЛК), лімфоцитарно-моноцитарний коефіцієнт (ЛМК), тромбоцитарно-лімфоцитарний коефіцієнт (ТЛК), індекс системної запальної відповіді (ІСЗВ), індекс системного імунного запалення (ІСІЗ), нейтрофільно-моноцитарний коефіцієнт (НМК). Ці показники оцінювали у трьох часових точках: до операції, через 24 години після втручання та на момент виписки.

*Результати*. До операції у жінок із ЖКХ, ускладненою СХ медіанні значення запальних індексів були значно вищими, ніж у чоловіків: НЛК, ТЛК та НМК перевищували відповідні показники у чоловіків у 1,4 раза, а ІСЗВ — у 1,6 раза. Через 24 години після операції системні запальні індекси мали різні тенденції у чоловіків і жінок. У чоловіків медіанні значення ТЛК та ЛМК залишалися незмінними, тоді як ІСІЗ та НМК збільшилися в 1,2 раза, ТЛК зріс у 1,5 раза, а ІСЗВ знизився в 1,3 раза. У жінок, навпаки, спостерігалося зниження медіанних значень НЛК, ІСЗВ та ІСІЗ в 1,2, 1,7 та 1,3 раза відповідно. При цьому ТЛК та НМК залишалися стабільними, а ЛМК збільшився в 1,4 раза. На момент виписки у чоловіків медіанні значення запальних індексів суттєво перевищували початковий рівень (в 1,8–2,5 раза), тоді як у жінок вони залишалися незмінними або зростали лише на 30% відносно вихідних значень.

*Висновки*. Жінки із ЖКХ, ускладненою СХ демонструють вищу здатність до усунення післяопераційного запалення порівняно з чоловіками.

***Ключові слова:*** складний холедохолітіаз, лапароскопічна холедохолітоекстракція та холедохоскопія, індекси запалення, статеві відмінності.