C-Reactive protein / prealbumin coefficient, as a new marker in diagnosis and monitoring of the treatment efficacy in patients with malignant obstructive jaundice, complicated by ascending cholangitis

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Abstract: preoperative ascending cholangitis is one of the main factors of unsatisfactory treatment outcomes and prognosis in patients with malignant obstructive jaundice. The aim of our study was to evaluate the diagnostic value of CRP / PA coefficient in preoperative ascending cholangitis diagnosis, the effectiveness of preoperative preparation and the possibility of infectious complications, which will improve the treatment quality and prognosis of this cohort of patients. The end points of the study were: to determine the reference rate of the CRP/PA coefficient; to evaluate the coefficient value for cholangitis and its severity at the stages of treatment; assess its importance in detecting postoperative infectious complications. A one-center prospective study of the treatment results of 84 patients who underwent biliary decompression in the preoperative period was conducted. All patients were diagnosed with preoperative ascending cholangitis according to the Tokyo Guidelines, 2018 criteria - I grade - in 48 (57.1%) patients, II grade - in 36 (42.9%) patients. It was determined that the median CRP/PA in healthy patients was 0.01 (0.01-0.02) of the main surgical intervention was significantly higher - 0.21 (0.13-0.45) and 0.02 (0.01-0.03) than in healthy individuals - 0.01 (0.01-0.02); p <0.001 and p = 0.004, respectively, we found a statistically difference between the medians of the CRP/PA level in patients with mild to moderate preoperative ascending cholangitis (p <0.001), which is confirmed by the correlation between the severity grade of cholangitis and CRP/PA value (r = 0.381, p <0,001). It was found that the preoperative biliary drainage increases the probability of reducing the CRP/PA level by 18% (R = 0.42, R2 = 0.18, p <0,001), increase CRP/PA level before drainage is associated with the presence of mixed biliary tract infection in 25% cases (R2 (Nagelkerke) = 0.25, p = 0.002) and it’s also associated with an increased the rate of infectious complications from postoperative wound by 18 .9% (R2 (Nagelkerke) = 0.189, p = 0.005). CRP/PA coefficient may indicate preoperative ascending cholangitis diagnosis and its severity in patients with malignant obstructive jaundice. Increase CRP/PA level before preoperative biliary drainage is associated with the presence of mixed biliary tract flora and possibility of infectious complications. The dynamics of the coefficient value can show the efficacy of preoperative preparation after biliary decompression and predict correct time for surgery, which improves the treatment prognosis in postoperative period.

Key words: cholangitis, jaundice, bile ducts, decompression, prealbumin
**Introduction**

Preoperative ascending cholangitis (PAC) is one of the main factors of unsatisfactory treatment outcomes and prognosis in patients with malignant obstructive jaundice (MOJ) (Pavlidis ET & Pavlidis TE, 2018, Ahmed, 2018). The gold standard for the PAC diagnosis is the Tokyo Guidelines 2018 recommendation, based on evidence of systemic inflammation, cholestasis and biliary obstruction, including assessment of the severity of acute cholangitis, and have prognostic value in the treatment and choice of appropriate method and time of invasive intervention (Adler & McEntire, 2018). Biliary infection is the most common complication of PAC and according to the literature review occurs in approximately 25% of cases (Muessle et al., 2018, Sulzer & Ocuin, 2019). The development of biliary infection in PAC increases the probability of mortality by almost 2.7 times, and its level can reach 24% (Wang et al., 2018, Darnell et al., 2021). Infectious inflammation of the biliary tract leads to cytotoxic damage to the liver parenchyma, accompanied by a decrease in its protein-synthesizing function, and systemic immunosuppression (Koch et al., 2015). Biliary tract inflammation leads to cytotoxic damage to the liver parenchyma, accompanied by a decrease in its protein-synthesizing function, and systemic immunosuppression (Koch et al., 2015 a). Untimely diagnosis of infected PAC contributes to the development of systemic endotoxemia and, as a consequence, decompensated multiorgan dysfunction, which worsens the clinical course and prognosis (Pavlidis et al., 2018 a). Therefore, early diagnosis of infected PAC is a key factor in improving the effectiveness of treatment of such patients. One of the main treatment methods of MOJ is biliary decompression, which reduces systemic and portal endotoxemia, restores phagocytic and immune function, improves the nutritional status of patients (Gouma et al., 1986, Scott-Conner & Grogan, 1994, Peter et al., 2001). However, the question of the feasibility of preoperative biliary drainage (PBD) is still debate, because, according to some authors, may increase the risk of infectious postoperative complications (Lee PJ et al., 2018, Lee H et al., 2018, Moole et al., 2016, Schuefele et al., 2017). At the same time, other studies have shown that PAC may be an independent etiological factor that worsens the prognosis of treatment, regardless of biliary decompression (Akashi et al., 2020, Endo et al., 2019). Recently, researchers have been paying attention to the study of additional criteria for early diagnosis and effectiveness of patients treatment with MOJ complicated by infected PAC. The role of the C-reactive protein/Prealbumin (CRP/PA) coefficient as a marker of the body’s systemic inflammatory response is being actively studied. Recent studies have shown that an increase in the PSA/PA ratio is observed within a few hours of the onset of infection and correlates with the severity of septic conditions (Salvetti et al., 2018, Lin et al., 2020). A systematic literature review did not reveal any studies devoted to the study of this marker as a diagnostic criterion for infected PAC in MOJ. In our opinion, given the peculiarities of the pathogenesis of the biliary tract infection in this pathology, which is associated with the development of systemic inflammation, the assessment of CRP/PA coefficient may be a new diagnostic marker for early diagnosis of biliary infection in this category of patients.

**Aim**

The aim of our study was to evaluate the diagnostic value of CRP/PA coefficient in PAC diagnosis, which can improve the quality and prognosis of patients treatment with MOJ.

**Materials and methods**

The study design- is a prospective single-center cohort study. The study included 84 patients with MOJ, who were treated at the clinical base of the Department of General Surgery №1, Bogomolets National Medical University, in the 2016-2021 periods.

**Inclusion criteria** - MOJ, morphological verification of the primary tumor, resectability of the primary tumor of the pancreatobiliary region, age of patients over 18 years, patient consent to participate in the study and subsequent outpatient monitoring. **Non-inclusion criteria** - carrying out any invasive interventions on the biliary tract for the underlying disease before hospitalization, history of cholecystectomy up to 6 months before diagnosis of the underlying disease, ASA V-VI surgery risk, IV clinical oncological patients group, acute surgical pathology not related to the underlying disease, decompensated comorbid pathology.
clusion criteria - the patient’s refusal of diagnosis and treatment at any stage of the study, the death of the patient, not related to the underlying disease. The diagnosis of ascending cholangitis was verified according to the Tokyo Guidelines, 2018 criteria, the severity of cholangitis was determined by TG18 calculator (https://www.mdcalc.com/tokyo-guidelines-acute-cholangitis-2018). The treatment plan was determined after discussion at a multidisciplinary conference, taking into account the results of preoperative examination. The main indications for biliary decompression were - acute ascending cholangitis, hyperbilirubinemia> 250 μmol /l, severe nutritional deficiency, delayed surgical treatment (Le Bian et al., 2018). All patients (n = 84) enrolled in the study underwent PBD- endobiliary stenting performed 56 (66.7%) patients, 28 (33.3%) patients underwent percutaneous-transhepatic biliary drainage. General characteristics of patients and the main tumor disease in the study group are shown in tables 1 and 2.

Table 1. Characteristics of patients in study groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PBD (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age *</td>
<td>62 (56-69)</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>50</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>24</td>
</tr>
<tr>
<td>BMI*, kg/cm²</td>
<td>26.4 (23.8-28.6)</td>
</tr>
<tr>
<td>Comorbidity, n (%)</td>
<td>45</td>
</tr>
<tr>
<td>ASA class</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>21</td>
</tr>
<tr>
<td>IV</td>
<td>60</td>
</tr>
</tbody>
</table>

Note. * Median (Q1-Q3); PBD - preoperative biliary decompression; BMI - body mass index; ASA (American Society of Anesthesiologists) - Physical Status Classification System

Table 2. Characteristics of the underlying tumor disease in the study groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PBD (n=84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histological type of tumor</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>84</td>
</tr>
<tr>
<td>Histological differentiation degree</td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>69</td>
</tr>
<tr>
<td>G3</td>
<td>15</td>
</tr>
<tr>
<td>Localization of the primary tumor</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>55</td>
</tr>
<tr>
<td>Choledohus</td>
<td>9</td>
</tr>
<tr>
<td>Papillae Fateri</td>
<td>16</td>
</tr>
<tr>
<td>Duodenum</td>
<td>3</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>5</td>
</tr>
<tr>
<td>T2</td>
<td>47</td>
</tr>
<tr>
<td>T3</td>
<td>28</td>
</tr>
<tr>
<td>T4</td>
<td>4</td>
</tr>
<tr>
<td>N0</td>
<td>56</td>
</tr>
<tr>
<td>N1</td>
<td>28</td>
</tr>
<tr>
<td>M0</td>
<td>84</td>
</tr>
<tr>
<td>Clinical staging</td>
<td></td>
</tr>
<tr>
<td>Stage I</td>
<td>17</td>
</tr>
<tr>
<td>Stage II</td>
<td>42</td>
</tr>
<tr>
<td>Stage III</td>
<td>25</td>
</tr>
</tbody>
</table>

Laboratory diagnostics was performed by the Roche/Hitachi cobas c 311 analyzer. The level of C-reactive protein (CRP) and prealbumin (PA) was determined by immunoturbidimetric method, reference values of CRP - <10 mg/l, PA-200-400 mg/l. The calculation of the CRP / PA ratio was carried out according to the formula:

\[
\text{Coefficient CRP/PA} = \frac{\text{CRP level}}{\text{PA level}}
\]

where, CRP - C-reactive protein, PA - prealbumin. To determine the reference rate of the CRP / PA ratio and compare the results obtained with PAC, we determined the value of this ratio in 30 healthy individuals aged 24 to 44 years. The co-
efficient in the study groups was determined at the time of PBD and before the main surgery. **Research endpoints** 1. Determine the reference rate of the CRP/PA coefficient; 2. Evaluate the CRP/PA coefficient in cholangitis and its severity at different stages of treatment; 3. Assess the significance of the CRP/PA ratio in the detection of postoperative infectious complications. **Statistical analysis** was performed using the U Mann-Whitney test, correlation Phi, V Cramer, Spearman analysis, logistic regression analysis using the statistical program SPSS 22.0 for Windows.

**Results**

The median CRP/PA coefficient in healthy individuals was 0.01 (0.01-0.02). The maximum value of this indicator was 0.03, the minimum - 0.0. The median CRP/PA at the time of decompression was 0.21 (0.13-0.45), and at the time of surgery - 0.02 (0.01-0.03). A comparative analysis of the mean values of the CRP/PA coefficient in healthy individuals and patients in group with PBD found that the median of this coefficient in patients with PAC at the time of drainage and major surgery was statistically significantly higher - 0.21 (0.13-0.45) and 0.02 (0.01-0.03) than in healthy individuals - 0.01 (0.01-0.02); p <0.001 and p = 0.004, respectively (Fig.1 and Fig. 2).

Using quadratic nonlinear regression, it was found that PBD increases the probability of reducing the CRP/PA coefficient by 18% (R = 0.42, R2 = 0.18, p <0.001). All patients (n = 84) who underwent PBD were diagnosed with PAC: I grade of severity - in 48 (57.1%) patients, II grade - in 36 (42.9%). In patients with mild cholangitis before PBD, the median CRP/PA levels was 0.16 (0.07-0.33), the minimum value was 0.03, and the maximum was 0.6. The CRP/PA levels in patients with moderate PAC corresponded to a value of 0.38 (0.19; 0.53): minimum - 0.05, maximum - 2.2. Using the U Mann-Whitney test for independent samples reveal, a statistically significant difference between the medians of the CRP/PA coefficient in study group patients for mild and moderate ascending cholangitis (p <0.001) (Fig. 5).

Correlation analysis using Phi and V Cramer coefficients showed a correlation between the severity of cholangitis and CRP/PA levels before drainage, the range of CRP/PA coefficient value was 0.03 - 2.2, and at the time of the main surgery - 0.001-0.1 (Fig.4).
Fig. 4. Distribution of CRP/PA levels depending on the treatment period

Fig. 5. Medians of CRP/PA coefficient depending on the severity of PAC

Fig. 6. Distribution of CRP/Prealbumin levels depending on the severity of PAC

Fig. 7. Distribution of the CRP/PA level depending on contamination degree

(r = 0.381, p < 0.001). In particular, the coefficient in the range of 0.03-0.6 was statistically more frequent in cholangitis of mild severity, and 0.6-2.2 - in cholangitis of moderate severity (Fig. 6).

Logistic regression analysis found that increasing the severity of PAC elevate the probability of raising the level of CRP/PA at the time of decompression by 24% (R^2 (Nagelkerke) = 0.24, p = 0.002). There was also a statistically correlation between the degree of contamination and the indicators of the CRP/PA value (r = 0.226, p = 0.038) in study group of patients. In particular, the coefficient in the range of 0.03-0.6 was statistically more often observed in monoflora, and 0.6-2.2 - in mixed infection (Fig. 7).

Discussion

CRP- protein synthesized by hepatocytes, mainly regulated by IL-6, is a sensitive and rapid marker, due to a short half-life of about 19 hours, confirming the presence of infection and inflammatory diseases. PA is a glycoprotein synthesized by the liver and is a direct indicator of damage to its parenchyma, its value also decreases with nutritional deficiency, the presence of infection (Xie et al., 2011). PA has a similar synthetic route as albumin, but has a much shorter half-life of about 2 days and higher sensitivity and specificity in assessing liver function and malnutrition. The level of serum PA is almost unaffected by infusion of albumin solution or blood transfusion (Devakonda et al., 2008). The study by Li, J et al., 2021 showed that preoperative serum PA levels, rather than albumin levels, were independently associated with early postoperative morbidity and mortality, as well as postoperative hepatic failure in

However, binary logistic regression showed that an elevate CRP/PA level before drainage was associated with an 18.9% increase the probability of postoperative wound infection complications (R^2 (Nagelkerke) = 0.189, p = 0.005).
patients who underwent liver resection for hepatocellular carcinoma. Shen et al., 2020 in multifactorial analysis defined that the level of PA <150 mg/l as an independent predictor of postoperative complications in patients with MOJ. PA is also a negative acute phase protein of the inflammatory processes. In this regard, in order to differentiate the inflammatory decrease in prealbumin concentration from nutritional deficiency, it is necessary to simultaneously determine another acute phase protein, such as CRP. If the CRP concentration is normal, then the low concentration of PA due to protein deficiency and on the contrary (conversely), with elevated CRP levels, low concentration of PA can not be regarded as a sign of eating disorders (Kishkun, AA., 2009). The value of the CRP / PA coefficient is more reliable in the diagnosis of the inflammatory process than each marker alone, and its definition is increasingly used in clinical practice (Wang et al., 2019). This coefficient is an indicator that correlates with the severity of sepsis. Pathophysiological changes that confirm this condition are: first, infection, hypoxia and ischemia, which stimulate the formation of large amounts of inflammatory cytokines and oxygen radicals and cause apoptosis of hepatocytes; secondly, liver proteins mainly synthesize acute phase protein against the background of systemic inflammatory response instead of plasma protein; third, hypermetabolism, malnutrition, and hepatic ischemia in patients with sepsis lead to impaired secretory and synthetic liver function (Lin, H., 2020). Prospective study of Pinilla et al., noted that the indicator correlates with the severity of multiple organ failure, and the high value of CRP / PA is associated with negative clinical results. After analyzing the high level of mortality and mortality in acute renal failure, a reliable relationship was found, which was also confirmed in the results of studies by Qiong Hong et al., (Pinilla et al., Qiong Hong et al.,1998 as cited in Xie et al., 2011 a). Li, L et al., 2017 found that the value of CRP / PA> 0.24 (sensitivity 82.1%, specificity 53.8%) is associated with increased mortality and length of hospital stay of patients in the intensive care unit. Analysis by Wang et al., 2019 a has shown a negative association of high rates with adverse outcomes in the treatment of acute coronary syndrome. Harriman et al., 2011 described the use of this marker as a predictor of gastrointestinal fistula closure, its value below 0.25 indicated the probability of fistula closure in 87% of cases, while a result greater than 1.0 indicated no tissue regeneration. Given the subject of our analysis- CRP / PA level may indicate the presence and severity of PAC, biliary tract contamination, the possibility of infectious complications, the coefficient dynamics after PBD may be an additional marker of treatment in the preoperative period. However, this study should be confirmed by further observations of a larger patients sample.

**Conclusion**

CRP/PA coefficient may indicate PAC diagnosis and its severity in patients with MOJ. Increase CRP/PA level before preoperative biliary drainage is associated with the presence of mixed biliary tract flora and possibility of infectious complications. The dynamics of the coefficient value can show the efficacy of preoperative preparation after biliary decompression and predict correct time for surgery, which improves the treatment prognosis in postoperative period.

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**Conflict of interest**

The authors state that there is no actual or potential conflict of interest regarding the results of this work with pharmaceutical companies and other organizations whose products and services may be related to the subject of the provided materials.

**Consent to publication**

The authors have agreed to publish this work from all patients related to the manuscript.

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A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of article
REFERENCES


Predictive value of the C-reactive protein-to-prealbumin ratio in medical ICU patients. Biomarkers in Medicine, 11(4), 329-337.


Коефіцієнт С-реактивний протеїн / преальбумін, як новий маркер у діагностиці та моніторингу ефективності лікування пацієнтів з обтураційною жовтяницею пухлинного генезу, ускладненою висхідним холангітом

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Анотація: Передоперacyjний висхідний холангіт є одним з основних факторів незадовільних результатів лікування та прогнозу у пацієнтів з обтураційною жовтяницею пухлинного генезу. Метою нашого дослідження було оцінити діагностичну значимість коефіцієнту СРП/ПА в постановці діагнозу ПВХ, в ефективності передоперацийної підготовки та можливості розвитку інфекційних ускладнень, для покращення якості та прогнозу лікування даної когорти пацієнтів. Кінцевими точками дослідження було: визначити релевантну норму коефіцієнту СРП/ПА; значення коефіцієнта при холангіті і ступеню його тяжкості на етапах лікування; оцінити його значимість у виявлений післяоператорних інфекційних ускладнень. Проведено одноцентрне проспективне дослідження результатів лікування 84 пацієнтів, яким у передоперационном періоді була виконана біліарна декомпресія. У всіх пацієнтів діагностовано передоперацийний висхідний холангіт згідно критеріїв Tokyo Guidelines, 2018- I ступеню - у 48 (57,1%) пацієнтів, ІІ ступеню - у 36 (42,9%) пацієнтів. Визначено, що медіана коефіцієнту СРП/ПА у здорових осіб склала 0,01 (0,01-0,02), Порівняльний аналіз середніх значень коефіцієнту СРП/ПА у здорових осіб та пацієнтів групи ПБД, показав, що медіана даного коефіцієнту на момент дренування та основного оперативного втручання була статистично значимо більшою - 0,21 (0,13-0,45) та 0,02 (0,01-0,03), ніж у здорових осіб - 0,01 (0,01-0,02); р<0,001 та r=0,004 відповідно, встановлено статистично значиму різницю між медіанами коефіцієнта СРП/ПА у пацієнтів з легким та середнім ступенем тяжкості передоперацийного висхідного холангіту (р<0,001), що підтверджено наявністю кореляційного зв’язку між ступенем тяжкості холангіту та показниками коефіцієнта СРП/ПА (r=0,381, р<0,001), виявлено, що виконання передоперацийного біліарного дренування підвищує вірогідність зниження рівня коефіцієнту СРП/ПА на 18% (R=0,42, R2 = 0,18, р<0,001), збільшення рівня коефіцієнту СРП/ПА до дренування пов’язано з наявністю мікст інфекції біліарного тракту у 25% випадків (R2(Nagelkerke)= 0,25, р=0,002), а також асоціюється з підвищенням ймовірності виникнення інфекційних ускладнень з боку післяоперацийної рані на 18,9% (R2(Nagelkerke)= 0,189, р=0,005). Коефіцієнт СРП/ПА підтверджує діагноз та ступінь тяжкості передоперацийного висхідного холангіту у пацієнтів з обтураційною жовтяницею пухлинного генезу. Підведення значення коефіцієнта СРП/ПА перед передоперацийним біліарним дренуванням пов’язане з наявністю мікст флори жовчі та можливістю розвитку інфекційних ускладнень. Динаміка значення коефіцієнта може покazaти ефективність передоперацийної підготовки після біліарної декомпресії та визначити точні терміни операції, що покращить прогноз лікування у післяоперационному періоді.

Ключові слова: холангіт, жовтяниця, обтураційна, декомпресія, С-Реактивний протеїн, преальбумін.