Predictors of adverse outcomes of steroids in patients with severe ulcerative colitis (systematic review and meta-analyses)

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ABSTRACT AIM: to identify predictors of steroid resistance among patients with severe ulcerative colitis (UC).
PATIENTS AND METHODS: the systematic review and meta-analysis were done, 18 observational case-control studies and 2545 patients with severe UC were included.
RESULTS: the rate of patients with effective steroid therapy was 69.5%, and steroid resistance occurred in 30.5%. Pancolitis (OR = 1.5; 95% CI: 1.1–2) and endoscopic picture on the UCEIS ≥ 7 points (OR = 4.5; 95% CI: 3.2–6.5) were predictors of steroid resistance. The levels of albumin and C-reactive protein before the start and on the 3rd day of steroid treatment were also significantly corresponded with adverse outcome of the treatment (p < 0.00001).
CONCLUSION: predictors of an adverse outcome are steroid resistance with pancolitis and endoscopic picture on the UCEIS scale ≥ 7 points. Hypoalbuminemia and high level of C-reactive protein were associated with the steroid resistance as well.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucous layer [1]. At the same time, a steady increase in morbidity and prevalence has been recorded in developed countries [2]. It is worth noting that in at least 30% of cases of disease onset, a severe UC attack occurs [2,3]. At the same time, during the first year after the manifestation of the disease, up to 40% of patients may be subjected to systemic steroid therapy in order to induce remission [3]. The primary effectiveness of steroid treatment in patients with severe UC does not exceed 70%, and about 40% of patients face an adverse outcome — the failure of steroid

therapy and the need for 'therapy or "rescue" surgery[4,5.] At the same time, among patients with severe UC attack resistant to steroid therapy, up to 40% may be subjected to radical surgical treatment [6]. Surgery in this situation, in turn, is associated with more than 60% risk of postoperative complications, which is probably due to the prolongation of steroid therapy and the progression of existing metabolic disorders [7].
For a long time, various predictors have been studied in the literature, potentially allowing predicting the failure of steroid therapy. Such factors include both history of the disease, laboratory tests reflecting the severity of the inflammatory process, and endoscopic signs assessed during colonoscopy before initiation of steroid therapy. Thus,

the purpose of the conducted systematic review and meta-analysis was to summarize the results of treatment and identify predictors of steroid resistance in patients with severe UC according to the literature.

MATERIALS AND METHODS

The systematic review and meta-analysis were performed in accordance with the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [8]. Literature was searched in PubMed and Google Scholar systems using the keywords as follows: ulcerative colitis [MeSH Terms]) OR ulcerative colitis AND severe OR acute severe AND outcomes OR colectomy OR surgery OR adverse effect OR treatment failure OR steroid resistance OR refractory AND predictive value OR predictors OR risk factors OR biomarkers OR albumin OR C — reactive protein OR endoscopy OR hemoglobin OR laboratory OR index. The keywords were selected based on a preliminary literature analysis. The search period was 10 years (2012–2022).

The first stage was the screening of titles and summaries of the found articles for compliance with a given topic and criteria for inclusion in a systematic review:

1. Adult patients with severe UC;
2. Articles with full text available;
3. Observational studies aimed at finding predictors of the failure of steroid therapy in patients with severe UC.

If the criteria were met, the full text of the selected articles was analyzed for the absence of possible restrictions. The articles were selected based on the fully described results of comparative and factor analysis of predictors of an adverse outcome of therapy with the presented values of quantitative variables and indicating the measure of central tendency and variability, as well as absolute figures for categorical data.

Statistical data processing when comparing the above treatment methods was performed in the Review Manager 5.3 program. The total value of the dichotomous data was described with a 95% coincidence interval (CI) in the form of an odds ratio (OR). Quantitative data were compared by calculating the difference of averages with a 95% coincidence interval. Statistical heterogeneity among the studies included in the meta-analysis was assessed using the χ^2-test and the heterogeneity index (I^2). At $p < 0.1$ and $I^2 > 50\%$, the results were considered statistically significantly heterogeneous. In the absence of average values in the articles, the calculation of the latter was carried out using a calculator of Wan's method.

Search Result

As a result of the query, 3,040 literature sources were found. The found works were screened for compliance with the inclusion criteria by title and resume. After the screening, 2,955 articles were excluded from the systematic review (Fig. 1).

The next stage was a detailed study of 85 original studies with the full text of the articles available. As a result, 67 studies were excluded from the further systematic review due to non-compliance with the inclusion criteria and lack of data necessary for the analysis. The reason for the exclusion was also the lack of the necessary results of statistical analysis: the absolute values of the outcome under study, as well as the values of categorical and quantitative variables. Ultimately, 18 studies were included in the systematic review and meta-analysis (Table 1).
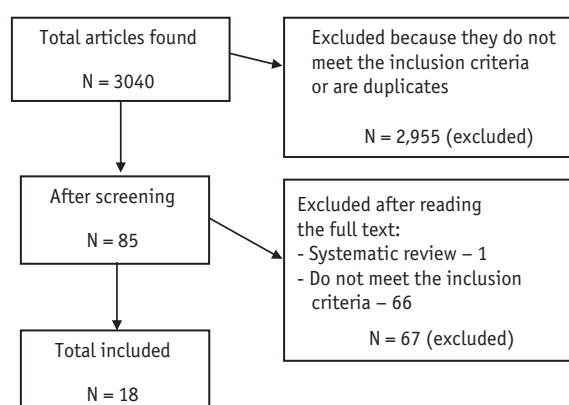
Figure 1. *Scheme of literature searching*

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Table 1. *Included studies*

| Author	Year	Samples	Studied predictors
Han et al. [9]	2014	62	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Corte et al. [10]	2015	89	Endoscopic picture
Gibson et al. [11]	2017	124	Albumin, C-reactive protein
Xie et al. [12]	2017	117	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Jain et al. [13]	2017	49	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Choy et al. [14]	2018	54	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Xie (2) et al. [15]	2018	92	Albumin, endoscopic picture
Dalal et al. [16]	2019	440	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Ghoshal et al. [17]	2020	263	Albumin, C-reactive protein, hemoglobin
Grant et al. [18]	2020	235	Albumin, C-reactive protein, hemoglobin
Atia et al. [19]	2021	153	Albumin, C-reactive protein
Sahu et al. [20]	2021	40	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Tanaka et al. [21]	2021	95	Albumin, C-reactive protein, hemoglobin
Syal et al. [22]	2021	63	Albumin, C-reactive protein
Jain S. et al. [23]	2021	76	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Baut et al. [24]	2021	270	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Adams et al. [25]	2022	131	Albumin, C-reactive protein, hemoglobin, endoscopic picture
Con et al. [26]	2022	94	Albumin, C-reactive protein

Getting Variables

The meta-analysis examined variables such as gender, age of the patient, duration of history of ulcerative colitis, extent of large intestine lesion, as well as levels of albumin, C-reactive protein and hemoglobin at the start of steroid therapy and on day 3, as the most important time for making decisions about the effectiveness of steroid therapy. In particular, the variables of the endoscopic picture were studied on the basis of the USEIS (7 points) and MES (3 points) scales evaluated before starting treatment with steroids.

Evaluation of Research Quality

A two-stage quality check of the studies included in the analysis was performed. The first stage at the time of the analysis of the full text of the articles was the assessment of quality for compliance with the criteria of the checklist for observational studies 'Strengthening the Reporting of Observational studies in Epidemiology' (STROBE Statement) [27]. Further, the quality of the included studies was evaluated in accordance with the criteria of Risk of bias in non-randomized studies — of Exposures (ROBINS — E) [28]. As a result of the analysis of the total risk of systematic error, it was revealed that only 1 (5%) of the 18 included studies had a high risk. 10 (55%) of the papers had

an average risk of systematic error. A low risk of bias was recorded in 7 (40%) studies (Fig. 2).
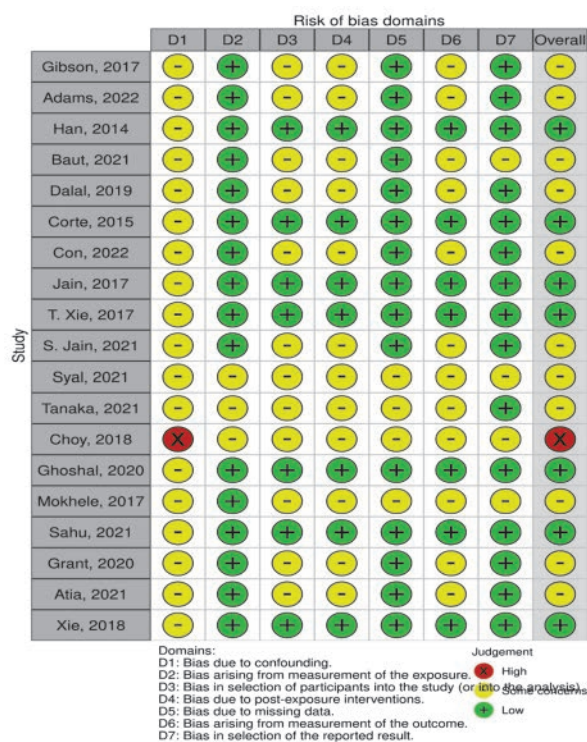
Рисунок 2. *Риск систематической ошибки в исследованиях*
Figure 2. *Risk of bias in studies*

Table 2. *Characteristics of patients*

Variable	Number of studies	Effect value	p	I²
Gender (male)	17	OR = 1.02; 95% CI: 0.84–1.24	0.8	0%
Age (years)	17	Mean difference = 0.58; 95% CI: −8–1.9	0.4	58%
Duration of medical history (years)	12	Mean difference = 0.13; 95% CI: −0.3–0.5	0.5	46%
Total lesion	11	OR = 1.5; 95% CI: 1.1–2	0.006	36%

RESULTS

Out of a total of 18 studies, 2,545 patients with severe UC attack were included in the systematic review and meta-analysis. As a result of treatment, a positive 'response' to systemic steroid therapy was noted in 1,769 (69.5%) patients — a group of effective conservative treatment. Hormonal resistance with the need for 'rescue therapy' or colectomy was established in 776 (30.5%) patients — the steroid resistance group.

The groups were checked for homogeneity. Thus, the UC groups did not differ significantly by gender, age, and time of the disease (Table 2).

It is worth noting separately that the factor variable of 'total lesion of the mucous layer of the large intestine', statistically significantly increases the probability of steroid resistance (OR = 1.5; 95% CI: 1.1–2; p = 0.006) and is a predictor.

A meta-analysis of a group of variables — potential predictors of an adverse outcome of steroid therapy — resistance was performed.
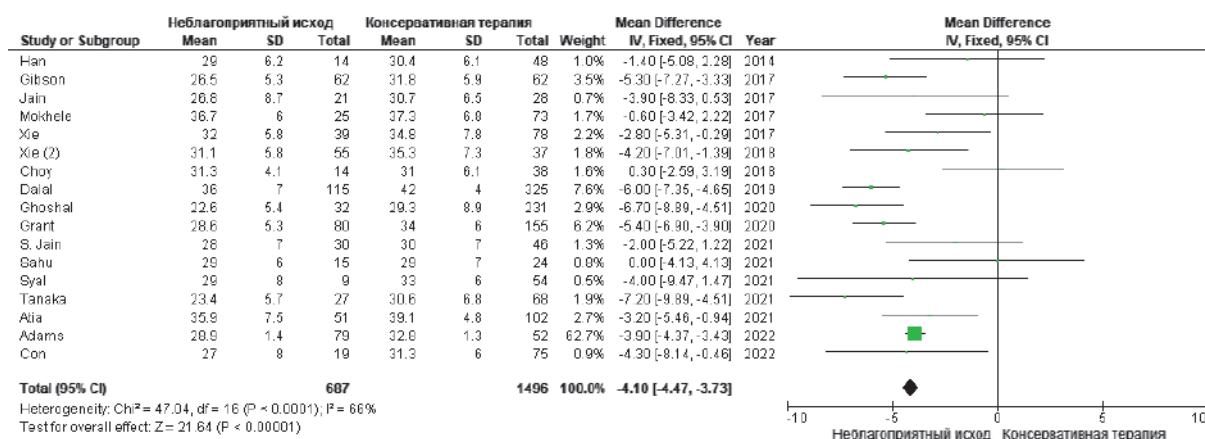
1) The albumin level at the time of initiation of steroid therapy was statistically significantly lower in the steroid resistance group, on average by 4.1 g/l (95% CI: −4.5 — −3.7), compared with the effective steroid therapy group, and amounted to 29 g/l and 33 g/l, respectively, p = 0.00001. The heterogeneity is statistically significant: (I²) = 66%, p < 0.0001 (Fig. 3).

On the 3rd day of treatment, the revealed trend in albumin levels persisted. Thus, in the steroid resistance group, the albumin level was statistically significantly lower by an average of 4.3 g/l (95% CI: −5.5 — −3.2) than in patients with effective steroid therapy: 25.5 g/l and 30 g/l, p = 0.00001. The heterogeneity was not detected: (I²) = 0%, p = 0.8 (Fig. 4).

2) The level of C-reactive protein before starting treatment in the steroid resistance group was higher than in the effective steroid therapy group by an average of 33.3 mg/l (95% CI: 29.9–36.7) and amounted to 74 g/l and 43 mg/l, respectively, p = 0001. The heterogeneity is statistically significant: (I²) = 90%, p < 0.00001 (Fig. 5).

On the 3rd day of treatment, the level of C-reactive protein differed, on average, by 24.8 (95% CI: 18.2–31.4) mg/l, compared with the group of effective steroid therapy: 49 mg/l and 25 mg/l,

Figure 3. *Level of albumin before treatment in groups.*

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respectively, *p* = 0.00001. No heterogeneity was detected: (I²) = 0%, *p* = 0.7 (Fig. 6).

3) The hemoglobin level at admission to the clinic was lower by an average of 8 g/l (95% CI: –10.1 — –5.8) in the adverse outcome group and amounted to 102.7 mg/l and 109 g/l, compared with the effective steroid therapy group, *p* = 0.00001. The heterogeneity is statistically significant: (I²) = 74%, *p* < 0.00001 (Fig. 7).

4) A meta-analysis of the effect of the endoscopic pattern on the development of steroid resistance was carried out. For this purpose, categorical data were extracted — the values of the UCEIS endoscopic scales ⩾ 7 points (yes/no) and MES = 3 points (yes/no). At the same time, it was revealed that the indicated

UCEIS value ⩾ 7 points were much more common in the group of the steroid therapy failure — in 135 (37%), versus 99 (15%) observations in the group of effective steroid therapy, *p* = 0.00001 (OR = 4.5; 95% CI: 3.2–6.5). The heterogeneity was not detected: (I²) = 0%, *p* = 0.6 (Fig. 8).

It should be noted that the endoscopic picture on the MES scale = 3 points was also statistically significantly more common in the adverse outcome group than in the effective steroid therapy group — in 116 (65%) and 204 (43%) cases, respectively, *p* = 0.00001 (OR = 2.9; 95% CI: 1.9–4.3). At the same time, the heterogeneity was statistically significant: (I²) = 76%, *p* = 0.005 (Fig. 9).
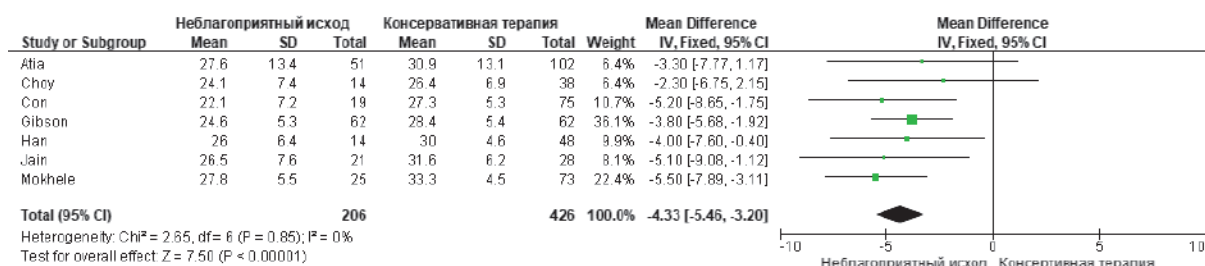

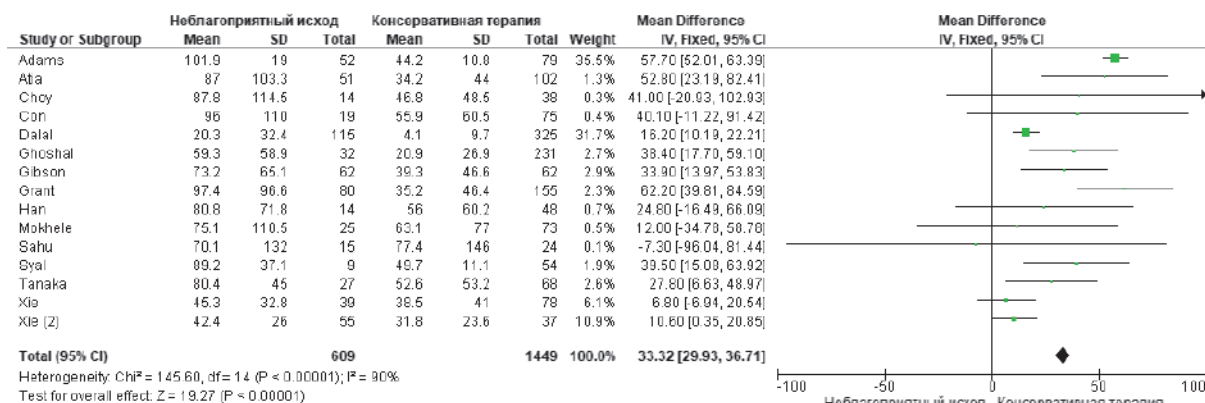**Figure 4.** *Level of albumin on day 3 of the treatment in groups*

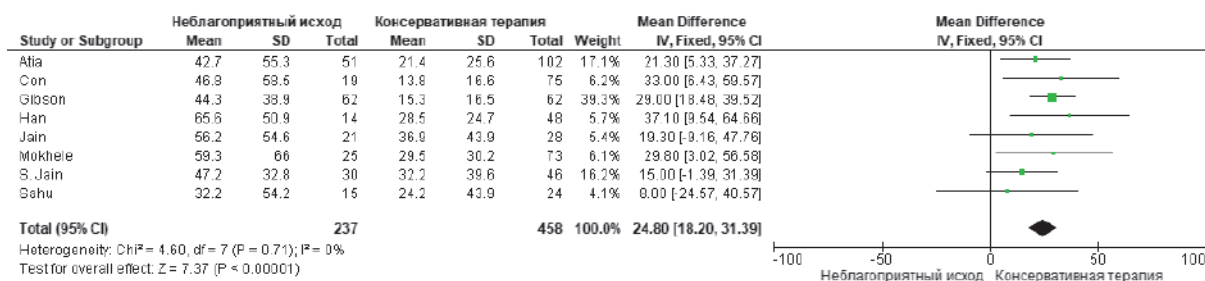**Figure 5.** *Level of C-reactive protein before treatment in groups*

Figure 6. *Level of C-reactive protein on day 3 of the treatment in groups*

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DISCUSSION

The relatively small number of published systematic reviews devoted to the study of predictors of the conservative treatment failure in patients with severe UC is likely due to the heterogeneity of the data. One of the few such papers is the meta-analysis by Dias et al., which included 20 retrospective studies published between 1988 and 2012. It was devoted only to comparing the characteristics of patients as predictors of the conservative treatment failure. The authors noted that it was not possible to evaluate laboratory parameters due to the sharp heterogeneity. One of the predictors of the therapy failure in this review was determined to be a total lesion of the mucous layer of the large intestine [29]. The extent of the lesion, along with the severity of inflammatory changes, is the most significant factor in the development of steroid resistance. Our meta–analysis also confirms the prognostic value of the fact of total lesion on treatment outcomes (OR = 1.5; 95% CI: 1.1–2). However, the main limitation of this parameter is that it is not always possible to estimate the extent of the lesion, especially in patients with acute severe UC, which does not facilitate the decision-making process.

In this regard, the systematic review pays considerable attention to the analysis of the influence of various laboratory parameters. One of these predictors is the level of albumin before and during steroid therapy. Thus, according to the results of the meta-analysis, the albumin level showed a statistically significant difference
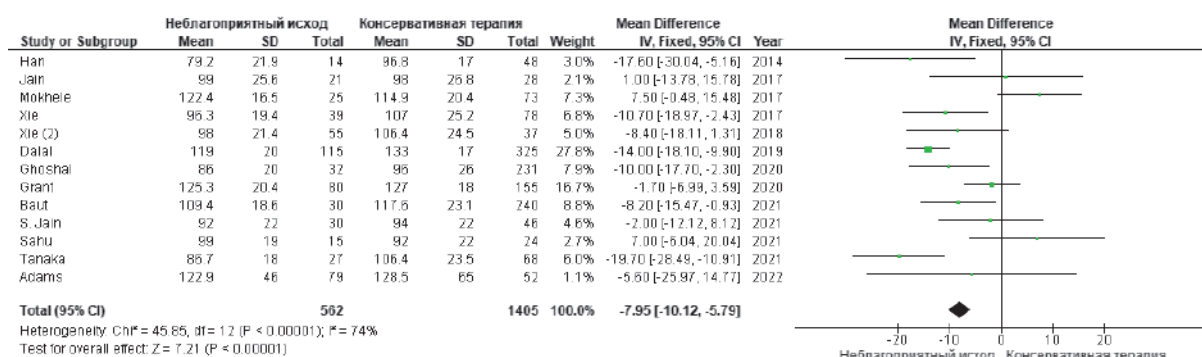

Figure 7. *Level of hemoglobin before treatment in groups*
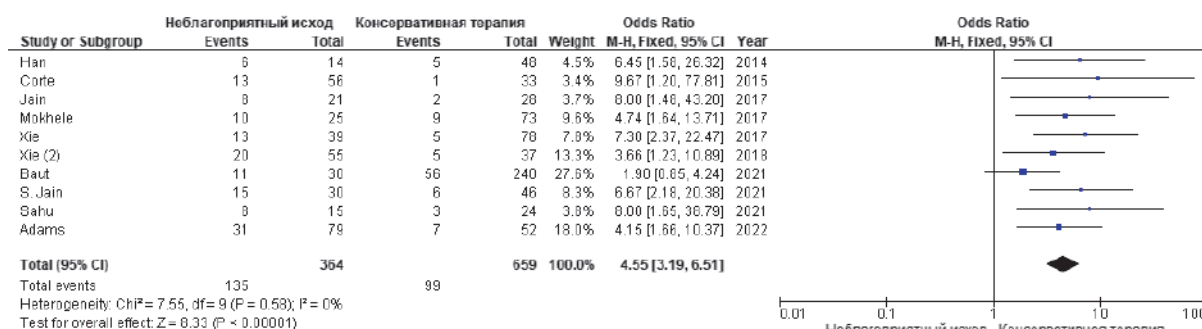
Figure 8. *Endoscopy based on UCEIS scale ≥ 7 points in groups*
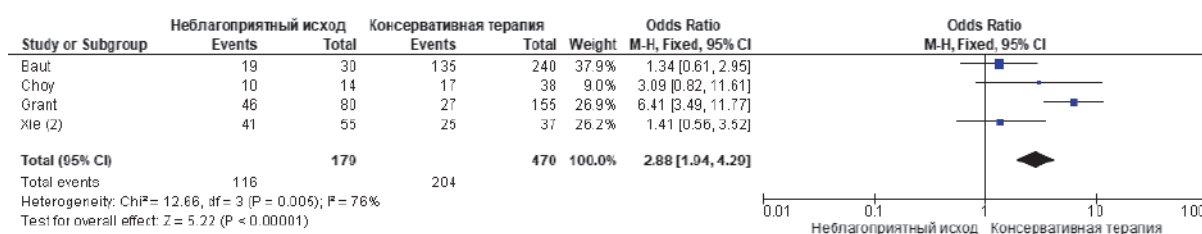
Figure 9. *Endoscopy based on MES scale = 3 points in groups*

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between the groups at the time of initiation of conservative treatment (mean difference = −4.1; 95% CI: −4.5 — −3.7). After 3 days (mean difference = −4.3; 95% CI: −5.5 — −3.2), it was also statistically significantly lower in the adverse outcome group. At the same time, the heterogeneity index of the research results included in the meta-analysis was 66%. But it is worth noting that on the 3rd day of the therapy, the heterogeneity of albumin values was completely leveled to 0%. The diagnostic value of albumin as a predictor of steroid resistance was confirmed in other studies not included in the meta-analysis due to non-compliance with the inclusion criteria. For example, an observational study by Lee et al. demonstrated a causal relationship between hypoalbuminemia during standard steroid treatment and the steroid therapy failure [30].

Similar to the level of albumin, the severity of inflammatory changes correlates with the level of C-reactive protein, which is a convenient indicator for monitoring the therapy effectiveness. Recently, some authors have proposed calculating the ratio of C-reactive protein/albumin (CAR). Thus, the study by Gibson et al., included in our meta-analysis, demonstrated a high prognostic value of the CRP/albumin ratio on the 3rd day of therapy. With a CAR value of more than 0.85 (area under the curve = 0.75, $p < 0.0001$), the relative risk of colectomy was almost 4 times higher (HR = 3.9; 95% CI: 2.1–7.2) [11]. Moreover, an observational study by Header et al. showed the applicability of the CRP/albumin ratio in relation to stratification of patients into a high-risk group of adverse therapy outcomes (area under the curve — 0.98, $p = 0.001$) [31]. Special attention should be paid to the assessment of the endoscopic picture of the mucous layer of the large intestine as the main criterion that must be taken into account first of all when forming treatment tactics for patients with severe UC attack. To date, the literature describes 2 main scales for assessing the severity of UC lesion during colonoscopy: UCEIS (8 points) and MES (3 points) [15]. In practice, the severity of inflammatory changes in the mucous layer

of the large intestine is directly correlated with the severity of the clinical picture and metabolic disorders. This fact is indirectly confirmed by the study by Zhang et al., which revealed a linear relationship between these indicators and the UCEIS scale value above 7 points ($r = 0.742$, $p < 0.001$) [32].

The issue of predicting the conservative treatment failure in patients with severe UC is also actively covered in the Russian literature. So, Golovenko, A.O. et al. have developed a prognostic model to determine the need for colectomy in patients with severe UC, including predictors such as hypoalbuminemia (< 30 g/l) and the presence of 'extensive ulcerative lesions with the formation of islets of the mucous layer'.

The risk of colectomy with a combination of these factors was 100% [33]. Previously, we presented a prognostic model — a nomogram based on retrospective data, in which a combination of an endoscopic picture of extensive ulcerative lesions, a decrease in albumin levels < 31 g/l and hemoglobin < 107 g/l predicted a 100% risk of colectomy [34].

The effect of the endoscopic picture on the 'prediction' of treatment outcomes was also confirmed in our meta-analysis. Thus, the maximum value of the UCEIS endoscopic scale corresponding to 'the presence of extensive ulcerative lesions with the formation of islets of the mucous layer' statistically significantly increased the likelihood of steroid resistance in patients with severe UC (OR = 4.5; 95% CI: 3.2–6.5) at $I^2 = 0\%$. In particular, the meta-analysis of the MES scale showed a statistically significant increase in probability (OR = 2.9; 95% CI: 1.9–4.3). However, only 4 studies were included in the analysis, and a high heterogeneity value was obtained ($I^2 = 76\%$).

It is worth mentioning separately that the hemoglobin level also demonstrated a statistically significant difference in the mean values before starting steroid therapy between the groups. However, the difference between the groups was about 8 g/l (95% CI: −10.1 — −5.8), which is clinically insignificant.

The conducted meta-analysis may have a number of systematic biases and limitations. First of all, it is worth noting once again that the works included in the systematic review are observational studies (cohort or case-control type). This is due to the prevalence of publications with an average risk of systematic error when evaluating the ROBINS-E checklist. This is due to the heterogeneity of the studied group of patients with a large number of anamnestic data, which is extremely difficult to trace and take into account. At the same time, one study had a high risk of systematic error.

CONCLUSION

Thus, taking into account the described limitations, as a result of a systematic review and meta-analysis, predictors associated with the development of steroid resistance were identified. They were 'the extent of lesionof the mucous layer of the large intestine', as well as the severity of changes during colonoscopy (UCEIS^{3}7 points). A direct relationship was also revealed between

hypoalbuminemia, high levels of C-reactive protein before and on day 3 of steroid treatment and the development of an adverse outcome — steroid resistance requiring 'therapy or surgery of rescue' in patients with severe UC attack.

AUTHORS CONTRIBUTION

Concept and design of the study: *Airat F. Mingazov, Sergey I. Achkasov, Oleg I. Sushkov, Tatiana A. Baranova, Bulat R. Kalanov*
Collection and processing of materials: *Airat F. Mingazov*
Statistical processing: *Airat F. Mingazov*
Text writing: *Airat F. Mingazov*
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