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Features of Gastrointestinal Bleeding in Patients with HIV-Related Infections

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Gastrointestinal hemorrhage is about 1.3 times more common in HIV-infected patients than in HIV-negative ones. At the same time the structural and etiological causes of hemorrhage in HIV differ in many ways from the main population which is undoubtedly due to the use of modern antiretroviral therapy, opportunistic infections and comorbidities.
Aim: to study the factors which are aggravating the course and influencing the structure of gastrointestinal bleeding in patients with HIV infection on the background of immunosuppressive disorders in comparison with HIV-negative patients.
Material and methods. To achieve this goal a multicenter retrospective cohort study of three groups of patients with gastrointestinal hemorrhage was conducted. Five hundred patients participated in the study: $n = 111$ — the main group (42 in Group 1 — HIV^+, $CD4^+ > 200$; 69 in Group 2 — HIV^+, $CD4^+ < 200$); $n = 389$ — in the control group (Group 3 — HIV-negative status).
Results. It was found that the comparison groups differ in age, the presence of previous hematological pathology (anemia, thrombocytopenia) as well as the sources of gastrointestinal bleeding. It can be noted that in all comparison groups endoscopic hemostasis methods were effective in about half of the cases (50.0 %, 42.0 % and 49.7 %), in the remaining findings hemostatic therapy was effective and sufficient (47.6 %, 33.3 % and 39.7 %). Surgical treatment was much more often required (statistically significant) in the group of patients with low immune status (29.0 %), and the need for it was associated with "rare sources" of bleeding: tuberculous intestinal ulcers, cytomegalovirus intestinal ulcers and decomposing Kaposi's sarcoma of various parts of the digestive tract. The overall survival rate of HIV-infected patients with low immune status and gastrointestinal bleeding was statistically lower than in HIV-negative patients or patients with satisfactory immune status.
Conclusion. Gastrointestinal bleeding in HIV-positive patients has a number of significant features, that directly affect severity of blood loss, treatment methods and patient survival.
Keywords: HIV infection, gastrointestinal bleeding, anemia, tuberculous ulcer, cytomegalovirus ulcer, immune status
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Особенности желудочно-кишечных кровотечений у больных ВИЧ-ассоциированными инфекциями

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Среди ВИЧ-инфицированных пациентов желудочно-кишечные кровотечения встречаются чаще примерно в 1,3 раза, чем среди ВИЧ-негативных пациентов. При этом структурно-этиологические причины кровотечений при ВИЧ во многом отличаются от основной популяции, что, несомненно, связано с использованием современной антиретровирусной терапии, оппортунистическими инфекциями и сочетанными заболеваниями.
Цель: изучить факторы, отягощающие течение и влияющие на структуру желудочно-кишечных кровотечений, у пациентов с ВИЧ-инфекцией на фоне иммуносупрессивных расстройств в сравнении с ВИЧ-негативными больными.
Материал и методы. Для достижения поставленной цели было проведено многоцентровое ретроспективное когортное исследование трех групп больных с желудочно-кишечными кровотечениями. В исследовании участвовали 500 пациентов: 111 чел. — в основной группе (42 в группе 1 — ВИЧ+, $CD4^+ > 200$; 69 в группе 2 — ВИЧ+, $CD4^+ < 200$); 389 чел. — в группе контроля (группа 3 — ВИЧ-негативный статус).
Результаты. Было установлено, что группы сравнения отличаются по возрасту, наличию предшествующей гематологической патологии (анемия, тромбоцитопения), а также источникам желудочно-кишечного кровотечения. Можно отметить, что во всех группах сравнения эндоскопические методы гемостаза оказались эффективны примерно в половине случаев (50,0 %, 42,0 % и 49,7 %), в остальных наблюдениях эффективной и достаточной оказалась гемостатическая терапия (47,6 %, 33,3 % и 39,7 %). Статистически значимо показано, что оперативное лечение было чаще необходимо в группе пациентов с низким иммунным статусом (29,0 %), что связано с «редкими источниками» кровотечений: туберкулезные язвы кишечника, цитомегаловирусные язвы кишечника и распадающаяся саркома Капоши различных отделов пищеварительного тракта. Общая выживаемость ВИЧ-инфицированных пациентов с низким иммунным статусом и желудочно-кишечным кровотечением статистически значимо ниже, чем у пациентов без ВИЧ-инфекции или пациентов с удовлетворительным иммунным статусом.
Заключение. Желудочно-кишечные кровотечения при ВИЧ-инфекции имеют ряд существенных особенностей, которые непосредственно влияют на тяжесть кровопотери, методы лечения и выживаемость пациентов.
Ключевые слова: ВИЧ-инфекция, желудочно-кишечное кровотечение, анемия, туберкулезная язва, цитомегаловирусная язва, иммунный статус
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Introduction

Gastrointestinal bleeding (GIB) firmly holds one of the leading positions in the structure of urgent surgical diseases. This is largely due to the variety of diseases and conditions that directly caused the bleeding [1, 2]. Mortality in GIB averages 4.87–11.24 % and increases significantly with recurrent bleeding — 28.3–82.5 % [3]. Unfortunately, according to statistics, the incidence of bleeding from various parts of the gastrointestinal tract is only increasing, which is directly related to the widespread prevalence of hepatic cirrhosis in the population (leading to portal hypertension), inflammatory intestine diseases (granulomatous colitis, ulcerative colitis), acute ulcerative lesions of the gastrointestinal tract (against the background of the use of medications drugs), tumors of the esophagus, stomach and intestines [4, 5]. Timely diagnosis of gastrointestinal bleeding, the use of endoscopic or surgical hemostasis methods, replacement of blood loss, as well as the treatment of diseases that caused hemorrhagic complications is a priority task of modern clinical medicine.

The structure of etiological factors of GIB development is quite well known. Thus, the upper gastrointestinal tract bleeding (80 %) is most often directly related to ulcers of the duodenum and/or stomach (45 %); erosive and ulcerative lesions of the mucous membrane (stress, drug, azotemic and others ulcers or erosions) — 20 %; esophagus veins varicose — 15 %; Mallory — Weiss syndrome — 10 %; tumors of the esophagus, stomach, pancreas and large duodenal papilla — 5 %; other causes (vascular malformations, burns, etc.) — 5 % [2, 6, 7]. Bleedings from the lower gastrointestinal tract are much less common (20 %). Their occurrence caused by hemorrhoids, diverticulosis with diverticulitis, tumors and polyps of the colon, congenital dysplastic angiomatosis, ulcerative colitis and Crohn's disease, as well as some rare infectious diseases (typhoid fever, amoebiasis, tuberculosis, etc.) [8].

By the end of 2021, there are more than 1.5 million people living with HIV in the Russian Federation. Among this group of patients, gastrointestinal bleeding was more common than

among HIV-negative patients [9]. According to E. Bratton et al. (2017), the prevalence of GIB among people with HIV was 1.3 times higher than in patients with HIV-negative status (9 and 6.9 %, respectively) [10]. At the same time, the structural and etiological causes of bleeding in HIV differ in many ways from the general population, which is undoubtedly due to the use of modern antiretroviral therapy (ART), opportunistic infections and comorbidities. As a consequence, the approach to the diagnosis and treatment of hemorrhagic complications in diseases of the gastrointestinal tract in people with HIV infection should be individual and take into account many factors.

Currently, the number of studies devoted to the problems of bleeding in HIV-positive patients is small, and such studies are rare in the Russian literature [11, 12]. To fill the gap in this scientific and clinical field, we tried to analyze and compare the etiological factors of GIB in people living with HIV and patients without HIV infection, taking into account the immune status of patients, the severity of blood loss and the presence of concomitant HIV-related infections.

Aim of the sturdy: to research the factors aggravating the course and affecting the structure of gastrointestinal bleeding in patients with HIV infection on the background of immunosuppressive disorders in comparison with HIV-negative patients.

Material and methods

To achieve this goal, a multicenter retrospective cohort study of three groups of patients with gastrointestinal bleeding was conducted (the documentation under study was an inpatient medical record, Form 003) in the period from 2020 to 2022 on the basis of Clinic No. 2 of the Moscow Research and Clinical Center for Tuberculosis Control of the Moscow Government Department of Health and Moscow Regional Hospital named after Professor V.N. Rozanov.

Study participants:

1. The main group included HIV-positive patients of Clinic No. 2 of the Moscow Research and Clinical Center for Tuberculosis Control of the Moscow Government Department of Health (Groups 1–2). Inclusion criteria: age over 18; diagnose of GIB in combination with HIV infection, confirmed by immune blotting. Exclusion criteria: pregnancy, HIV-negative status. The immunograms of each HIV-positive patient were examined which reflected the state of the immune system against the background of antiretroviral treatment or without therapy for HIV infection. The number of helper T-lymphocytes in 1 mL of blood ($CD4^+$) above 200 was considered an acceptable immune indicator, at which the risk of developing opportunistic infections is minimal; on the contrary, the number of $CD4^+$ cells below 200 per mL was defined as immunosuppression with a high risk of secondary diseases [13]. Thus, we assessed the expediency of dividing all HIV-positive patients into two groups with satisfactory (Group 1, $CD4^+ > 200$) and low (Group 2, $CD4^+ < 200$) immune status. Patients of the groups described above were hospitalized in the Moscow Research and Clinical Center for Tuberculosis Control of the Moscow Government Department of Health with suspected tuberculosis of the respiratory system, which was subsequently confirmed in 92 (82.9 %) cases. The examination revealed hepatitis C markers in 27 (24.3 %) patients, hepatitis B markers in 38 (34.2 %) and the combination of these markers was confirmed in 7 (6.3 %) cases.

2. The control group consisted of HIV-negative patients of the Moscow Regional Hospital named after Professor V.N. Rozanov (Group 3). Inclusion criteria: age over 18 years; proven diagnosis of gastrointestinal bleeding; HIV-negative status.

The study analyzed the results of diagnosis and treatment of all three groups of patients. The preliminary diagnosis of gastrointestinal bleeding was determined on the basis of anamnestic data, clinical picture of hypovolemia (presence of tachycardia, tachypnea, pallor, sweating, oliguria, mental confusion), symptoms of anemia (pallor, sweating), as well as direct laboratory parameters (decrease in hematocrit and hemoglobin levels, decrease in the number of erythrocytes 1 μL). The final diagnosis was made by imaging the source of bleeding during esophagogastroduodenoscopy (EGDS), colonoscopy, intraoperative or rectal examination. Following WHO recommendations, anemia was considered to be present with a decrease in hemoglobin levels below 120 g/L in men and below 110 g/L in women; and thrombocytopenia was understood as a decrease in the number of peripheral blood platelets of less than 50 thousand per mL.

Additionally, the following laboratory tests were performed in the group of patients with HIV infection: identification of the causative agent of tuberculosis in sputum and other biological fluids by polymerase chain reaction (PCR) and using cultural-based and bacterioscopic methods; quantitative determination of cytomegalovirus DNA (CMV DNA) in blood; as well as determination of the genetic material of toxoplasma and pneumocysts in biological material using PCR-based diagnostics. Apart from that, biopsies obtained during endoscopic examinations using histological, molecular genetic and cultural-based methods of

laboratory diagnostics were studied. In cases of fatal outcomes, histological examinations obtained during autopsy were used to confirm the diagnosis.

The diagnosis and treatment of patients were carried out in accordance with the International Clinical Guidelines for the management of patients with non–varicose bleeding from the upper gastrointestinal tract (2005), the Clinical Recommendations of the Russian Society of Surgeons "Ulcerative gastroduodenal bleeding" (Moscow – Voronezh, 2014), Clinical Recommendations of the Russian Society of Surgeons for the treatment of bleeding from varicosity of the esophagus and stomach (Voronezh, 2014), Clinical Recommendations of the Russian Society of Colorectal Surgeons [14–16].

The severity of acute blood loss was assessed using the classification of blood loss proposed by M.I. Lytkin and V.V. Rumyantsev in 1972. This classification helps specialists to quickly assess the amount of blood loss based on fairly simple but very informative physiological indicators [17]:

– *Mild severity.* The condition is satisfactory. A single vomiting or a single formed stool of black color. Heart rate 80–100 per minute; systolic blood pressure > 100 mmHg; diuresis > 2 L/day.

– *Moderate severity.* A patient's condition is of moderate severity. Repeated vomiting of blood or melena. Heart rate 100–110 per minute; systolic blood pressure 100–120 mmHg; diuresis < 2 L/day.

– *Severe degree of blood loss.* The condition is severe, possible impairment of consciousness up to coma. Repeated vomiting with little-changed blood, liquid tarry stool or stool with little-changed blood. Heart rate > 120 per minute; systolic blood pressure < 90 mmHg. Oliguria, metabolic acidosis.

Statistical processing of the results was carried out through computer data analysis using Python (Python 3.11.). Quantitative data were evaluated for compliance with the normal distribution using the Shapiro – Wilk criterion. The median was calculated as the center of distribution and quartiles (*Me* [Q1; Q3]) as indicators of variation. The Mann – Whitney *U*-test was used to compare two unrelated samples. The results of qualitative characteristics are expressed in absolute numbers with fractions (%). The comparison of the nominal data in the groups was carried out using Pearson's χ^2 criterion. In cases where the number of expected observations in any of the cells of the four-field table was less than 10, Fisher's exact criterion was used to assess the significance of the differences. The confidence interval for the fractions is calculated by the Wilson method. The survival function and cumulative probability of the analyzed event are calculated using the Kaplan – Mayer method. The survival function was compared using the Log Rank criterion. The analysis of patient survival was carried out using the method of univariate and multifactorial Cox regression. The Harrell concordance index (C-index) and Time-dependent ROC-AUC were used as the estimated metric of the survival model. The differences were considered statistically significant at $p < 0.05$. The sample size was not calculated in advance.

To conduct the study, permission was obtained from the independent Ethics Committee of the Moscow Research and Clinical Center for Tuberculosis Control of the Moscow Government Department of Health (Protocol No. 3.6 dated January 15, 2023).

Results

The study involved 500 patients, 111 of them in the main group (Group 1 – $n = 42$, HIV^+, $CD4^+ > 200$; Group 2 – $n = 69$, HIV^+, $CD4^+ < 200$); 389 patients comprised the control group (Group 3, HIV-negative status). Among patients with satisfactory immune status 39 (92.9 %) received antiretroviral therapy (ART) while patients with low immune status did not receive ART (100 %).

The gender and age composition of the studied groups is presented in Table 1, the analysis of which shows that the groups did not significantly differ in gender ($p = 0.301$), but statistically significantly differed in age ($p < 0.001$).

The analysis of the gastrointestinal bleeding cases, the severity of the course and outcomes in the studied groups of patients was carried out. The main focus of our study was on some pathophysiological features that affect the severity of blood loss and determine the possible disease outcome. We attributed thrombocytopenia and anemia preceding bleeding to such factors. Analyzing clinical data, it turned out that thrombocytopenia was observed in the majority of HIV-positive patients – mainly in the group of people with low immune status, while in the group of HIV-negative patients, thrombocytopenia was statistically significantly less common ($p < 0.05$) – in about one in ten patients. We also observed the largest number of patients with anemia of varying severity initially in groups of patients with HIV infection (more than half of the patients), while among patients with HIV-negative status their number did not exceed 25 % ($p < 0.05$) (Table 2).

An analysis of hospital records revealed that among patients with HIV-negative status there was a statistically significant predominance of bleeding from the upper gastrointestinal tract (79 %), whereas in the groups of patients with

Table 1. Gender composition of the study groups
Таблица 1. Гендерный состав исследуемых групп

Parameter ***Показатель***	**Group 1 (HIV+; CD4⁺ > 200)** ***Группа 1 (ВИЧ+; CD4⁺ > 200)*** **(*n* = 42)**	**Group 2 (HIV+; CD4⁺ < 200)** ***Группа 2 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 69)**	**Group 3 (HIV-neg.)** ***Группа 3 (ВИЧ-нег.)*** **(*n* = 389)**	***p*** **Pairwise comparison** ***Попарное сравнение***
Gender / *Пол*				$p_{1-2} = 0.526$ $p_{1-3} = 0.155$ $p_{2-3} = 0.428$
male / *мужской*	23 (55.0 %)	42 (61.0 %)	256 (65.8 %)	
female / *женский*	19 (45.0 %)	27 (39.0 %)	133 (34.2 %)	
Age, years *Возраст, лет* *Me* (Q_1; Q_3)	38.5 [36.0; 46.75]	39.0 [33.0; 44.0]	48.0 [38.0; 61.0]	$p_{1-2} = 0.278$ $p_{1-3} < 0.001$* $p_{2-3} < 0.001$*

Note (hereinafter in Tables): ** — statistically significant differences where p < 0.05.*
Примечание (здесь и далее в таблицах): ** — наличие статистически значимых различий при p < 0,05.*

Table 2. Distribution of patients by the presence of initial changes in hemograms
Таблица 2. Распределение пациентов по наличию исходных изменений в гемограммах

Hemogram ***Гемограмма***	**Group 1 (HIV+; CD4⁺ > 200)** ***Группа 1 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 42)**	**Group 2 (HIV+; CD4⁺ < 200)** ***Группа 2 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 69)**	**Group 3 (HIV-neg.)** ***Группа 3 (ВИЧ-нег.)*** **(*n* = 389)**	***p*** **Pairwise comparison** ***Попарное сравнение***
	% (95 % ДИ) / % (95 % CI)			
Thrombocytopenia *Тромбоцитопения*	28.6 % (17.2–43.6)	50.7 % (39.2–62.2)	13.9 % (10.8–17.7)	$p_{1-2} = 0.022$* $p_{1-3} = 0.012$* $p_{2-3} < 0.001$*
Anemia *Анемия*	59.5 % (44.5–73.0)	59.4 % (47.6–70.2)	24.9 % (20.9–29.5)	$p_{1-2} = 0.991$ $p_{1-3} < 0.001$* $p_{2-3} < 0.001$*

Table 3. Frequency of registration of various sources of bleeding
Таблица 3. Частота регистрации различных источников кровотечения

Source of bleeding ***Источник кровотечения***	**Group 1 (HIV+; CD4⁺ > 200)** ***Группа 1 (ВИЧ+; CD4⁺ > 200)*** **(*n* = 42)**	**Group 2 (HIV+; CD4⁺ < 200)** ***Группа 2 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 69)**	**Group 3 (HIV-neg.)** ***Группа 3 (ВИЧ-нег.)*** **(*n* = 389)**	***p*** **Pairwise comparison** ***Попарное сравнение***
	n (%)			
Upper gastrointestinal tract *Верхние отделы ЖКТ*	25 (60.0 %)	36 (52.0 %)	307 (78.9 %)	$p_{1-2} = 0.450$ $p_{1-3} = 0.005$* $p_{2-3} < 0.001$*
Lower gastrointestinal tract *Нижние отделы ЖКТ*	17 (40.0 %)	33 (48.0 %)	82 (21.1 %)	

HIV-positive status, bleeding from the same sources ranged from 52 to 60 % ($p < 0.001$). In patients with low immune status (Group 2), hemorrhages from the upper and lower gastrointestinal tract were recorded with approximately equal frequency (52 and 48 %, respectively) (Table 3).

In patients with HIV-negative status (Group 3), the predominant sources of bleeding were duodenal ulcers (36.2 %), bleeding from polyps and malignant neoplasms of the esophagus, stomach, and large duodenal papilla (3.3 %), as well as from polyps and malignant tumors in the left sections of the large intestine (8.2 %). In this patient cohort, rare angiodysplasias of various segments of the gastrointestinal tract were observed more frequently (3.6 %), as well as inflammatory intestine diseases (2.1 %). Among HIV-positive patients, we recorded an increase in the incidence of acute ulcers and erosions in the upper gastrointestinal tract, which were the cause of bleeding (Group 1 — 29.0 %; Group 2 — 20.0 %; compared to 16.5 % in Group 3). According to our observations, hemorrhoids are one of the most frequent sources of bleeding from the lower digestive tract,

Table 4. Sources of gastrointestinal bleeding in comparison groups
Таблица 4. Источники желудочно-кишечных кровотечений в группах сравнения

Source of bleeding ***Источник кровотечения***	**Group 1 (HIV+; CD4⁺ > 200)** ***Группа 1 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 42)**	**Group 2 (HIV+; CD4⁺ < 200)** ***Группа 2 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 69)**	**Group 3 (HIV-neg.)** ***Группа 3 (ВИЧ-нег.)*** **(*n* = 389)**	***p*** **Pairwise comparison** ***Попарное сравнение***
	n (%)			
Varicose veins of the esophagus and stomach *Варикозные вены пищевода и желудка*	3 (7.0 %)	7 (10.0 %)	42 (10.8 %)	$p_{1-2} = 0.256$ $p_{1-3} < 0.001$* $p_{2-3} < 0.001$*
Acute ulcer of the upper gastrointestinal tract *Острая язва верхних отделов пищеварительного тракта*	12 (29.0 %)	14 (20.0 %)	64 (16.5 %)	
Tumors and polyps of the upper gastrointestinal tract *Опухоли и полипы верхних отделов пищеварительного тракта*	1 (2.0 %)	1 (1.0 %)	13 (3.3 %)	
Mallory — Weiss tears *Синдром Мэллори — Вейсса*	4 (10.0 %)	8 (12.0 %)	33 (8.5 %)	$p_{1-2} = 0.256$ $p_{1-3} < 0.001$* $p_{2-3} < 0.001$*
Duodenal ulcer or stomach ulcer *Язва ДПК или желудка*	5 (12.0 %)	6 (9.0 %)		
Angiodysplasia of the upper gastrointestinal tract *Ангиодисплазии верхних отделов пищеварительного тракта*	0 (0 %)	0 (0 %)	14 (3.6 %)	
Hemorrhoids *Геморроидальные узлы*	12 (29.0 %)	9 (13.0 %)	29 (7.5 %)	
Tumors and polyps of the intestine *Опухоли и полипы кишечника*	1 (2.0 %)	3 (4.0 %)	32 (8.2 %)	
Kaposi's sarcoma *Саркома Капоши*	1 (2.0 %)	2 (3.0 %)	0 (0 %)	
Tuberculous intestinal ulcer *Туберкулезная язва кишечника*	3 (7.0 %)	13 (19.0 %)	0 (0 %)	
Cytomegalovirus ulcers of the intestine *Цитомегаловирусные язвы кишечника*	0 (0 %)	6 (9.0 %)	0 (0 %)	
Diverticular disease of the colon *Дивертикулез толстой кишки*	0 (0 %)	0 (0 %)	6 (1.5 %)	
Angiodysplasia of the lower gastrointestinal tract *Ангиодисплазии нижних отделов пищеварительного тракта*	0 (0 %)	0 (0 %)	7 (1.8 %)	
Inflammatory bowel disease *Воспалительные заболевания кишечника*	0 (0 %)	0 (0 %)	8 (2.1 %)	

however, hemorrhoidal bleeding was recorded much more often in patients with HIV infection (Group 1 — 29.0 %; Group 2 — 13.0 %), while in HIV-negative patients they accounted for 7.5 % of cases. Such common causes of bleeding in the population as varicose veins of the esophagus (7.0 %, 10.0 % and 10.8 %) and Mallory — Weiss syndrome (10.0 %, 12.0 % and 8.5 %) were also recorded in the studied groups of patients with approximately the same frequency. At the same time, among HIV-positive patients the following causes were identified as sources of bleeding that we did not find in HIV-negative patients: Kaposi's sarcoma (Group 1 — 2.0 %; Group 2 — 3.0 %), tuberculous intestinal ulcers (Group 1 — 7.0 %; Group 2 — 19.0 %), cytomegalovirus ulcers of

Table 5. Severity of blood loss and frequency of blood transfusions in comparison groups
Таблица 5. Тяжесть кровопотери и частота гемотрансфузий в группах сравнения

Blood loss degree ***Степень кровопотери***	**Group 1 (HIV+; CD4⁺ > 200)** ***Группа 1 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 42)**	**Group 2 (HIV+; CD4⁺ < 200)** ***Группа 2 (ВИЧ+; CD4⁺ < 200)*** **(*n* = 69)**	**Group 3 (HIV-neg.)** ***Группа 3 (ВИЧ-нег.)*** **(*n* = 389)**	***p*** **Pairwise comparison** ***Попарное сравнение***
	% (95 % ДИ) / % (95 % CI)			
Mild *Легкая*	57.1 % (42.2–70.9)	31.9 % (22.1–43.6)	58.2 % (53.3–63.1)	$p_{1-2} = 0.019$* $p_{1-3} = 0.26$ $p_{2-3} < 0.001$*
Moderate *Средняя*	38.1 % (25.0–53.2)	52.2 % (40.6–63.5)	29.6 % (25.3–34.4)	
Severe *Тяжелая*	4.8 % (1.3–15.8)	15.9 % (9.1–26.3)	12.1 % (9.2–15.7)	
Blood transfusion *Гемотрансфузия*	45.2 % (31.2–60.1)	66.7 % (54.9–76.6)	42.5 % (37.7–47.5)	$p_{1-2} = 0.026$* $p_{1-3} = 0.736$ $p_{2-3} < 0.001$*

the intestine (Group 2 — 9.0 %). Table 4 shows the frequency of registration of various sources of bleeding in the analyzed patient groups.

The analysis showed that the studied groups of patients differed statistically significantly in the severity of blood loss and the need for transfusion of blood components (erythrocyte mass or suspension). Thus, in patients with HIV-negative status (Group 3), moderate blood loss was recorded in 29.6 % of cases, and severe blood loss was observed only in 12.1 % of patients, which required hemotransfusion in 42.5 % of cases. We observed a similar pattern in patients with satisfactory immune status (Group 1). On the contrary, in Group 2, severe blood loss was recorded in 16.0 % of patients, and moderate blood loss was observed in 52.0 % of cases, which required hemotransfusion in 67.0 % of patients (Table 5). Thus, according to the severity of blood loss, HIV-negative patients did not significantly differ from HIV-infected patients with satisfactory immune status.

Mild and moderate blood loss occurred with almost the same frequency in patients with satisfactory immune status and patients without HIV infection, while in patients with low immune status, in most cases we recorded severe and

Table 6. Overall survival rate depending on various influencing factors
Таблица 6. Общая выживаемость в зависимости от различных влияющих факторов

Parameter ***Показатель***	***Overall survival* / Общая выживаемость**	
	10-day survival probability median (95 % CI) ***Медиана вероятности 10-дневной выживаемости (95 % ДИ)***	***p*** **(log rank)**
Thrombocytopenia / *Тромбоцитопения*		$p < 0{,}001$*
no / *нет*	0.959 (0.930–0.976)	
yes / *есть*	0.807 (0.714–0.872)	
Chronic anemia / *Хроническая анемия*		$p < 0.001$*
no / *нет*	0.964 (0.934–0.980)	
yes / *есть*	0.852 (0.783–0.900)	
Endoscopic hemostasis / *Эндоскопический гемостаз*		$p = 0.234$
ineffective / *не эффективен*	0.911 (0.861–0.944)	
successful / *успешный*	0.935 (0.895–0.961)	
surgical treatment is needed *необходимо оперативное лечение*	0.735 (0.598–0.832)	$p < 0.001$*
Packed red cell transfusion / *Переливание эритроцитарной массы*		$p < 0.001$*
not required / *не требуется*	1.0 (1.0–1.0)	
is needed / *необходимо*	0.855 (0.802–0.895)	
Blood loss degree / *Тяжесть кровопотери*		$p < 0.001$*
mild / *легкая*	0.996 (0.970–0.999)	
moderate / *средняя*	0.964 (0.922–0.984)	
severe / *тяжелая*	0.565 (0.430–0.679)	

moderate-severe blood loss, which can be explained by the initial comorbid and HIV-associated hematological disorders.

Endoscopic hemostasis and conservative methods of bleeding control were effective in the vast majority of patients and only one in ten cases required surgical treatment. At the same time, in the group of HIV-negative patients, surgery was required in 10.6 % (95% CI: 7.9–14.0) of patients, in 4.8 % (95% CI: 1.3–15.8) of HIV-positive patients with satisfactory immune status, and in the group of patients with low immune status, surgery was necessary in 29.0 % (95% CI: 19.6–40.6) of observations. Accordingly, mortality in the comparison groups was statistically significantly different. If in Groups 1 and 3 it was 4.8 % (95% CI: 1.3–15.8 %) and 7.2 % (95 % CI: 5.0–10.2), respectively, then in HIV-positive patients with low immune status, mortality was recorded at the level of 18.8 % (95 % CI: 11.4–29.6), which exceeded the average rate by almost 3 times.

Considering individual aggravating comorbid factors, it can be noted that the overall survival of patients with previous thrombocytopenia was statistically significantly different from the survival of patients without thrombocytopenia ($p < 0.05$). The probability of 10-day survival in the group of patients with thrombocytopenia was 80.7 % (95% CI: 71.4–87.2), and without thrombocytopenia — 95.9 % (95% CI: 93.0–97.6).

The survival rate of patients with chronic anemia was statistically significantly different from that of patients without chronic anemia ($p < 0.05$). The probability of 10-day survival in the group of patients with previous chronic anemia was 85.2 % (95% CI: 78.3–90.0), and without anemia — 96.4 % (95% CI: 93.4–98.0). The lowest 10-day survival was recorded for bleeding from

Table 7. Overall survival rate depending on the source of bleeding
Таблица 7. Общая выживаемость в зависимости от источника кровотечения

Source of bleeding ***Источник кровотечения***	***Overall survival* / Общая выживаемость**	
	10-day survival probability median (95 % CI) ***Медиана вероятности 10-дневной выживаемости (95 % ДИ)***	***p*** **(log rank)**
Varicose veins of the esophagus and stomach *Варикозные вены пищевода и желудка*	0.901 (0.779–0.958)	$p = 0.008$*
Acute ulcer of the upper gastrointestinal tract *Острая язва верхних отделов пищеварительного тракта*	0.891 (0.799–0.942)	
Tumors and polyps of the upper gastrointestinal tract *Опухоли и полипы верхних отделов пищеварительного тракта*	0.783 (0.465–0.925)	
Mallory — Weiss tears *Синдром Мэллори — Вейсса*	0.955 (0.830–0.988)	
Duodenal ulcer or stomach ulcer *Язва двенадцатиперстной кишки или желудка*	0.973 (0.929–0.990)	
Angiodysplasia of the upper gastrointestinal tract *Ангиодисплазия верхних отделов пищеварительного тракта*	0.917 (0.539–0.988)	
Hemorrhoidal bolus *Геморроидальные узлы*	1.000 (1.000–1.000)	
Tumors and polyps of the intestine *Опухоли и полипы кишечника*	0.921 (0.710–0.981)	
Kaposi's sarcoma *Саркома Капоши*	1.000 (1.000–1.000)	
Tuberculous intestinal ulcer *Туберкулезная язва кишечника*	0.813 (0.525–0.935)	
Cytomegalovirus ulcers of the intestine *Цитомегаловирусные язвы кишечника*	0.667 (0.195–0.904)	
Diverticular disease of colon *Дивертикулез толстой кишки*	1.000 (1.000–1.000)	
Angiodysplasia of the lower gastrointestinal tract *Ангиодисплазия нижних отделов пищеварительного тракта*	0.857 (0.334–0.979)	
Inflammatory bowel disease *Воспалительные заболевания кишечника*	0.875 (0.387–0.981)	

tuberculous intestinal ulcers — 81.3 % (95% CI: 52.5–93.5), polyps and malignant neoplasms of the upper gastrointestinal tract — 78.3 % (95% CI: 46.5–92.5) and cytomegalovirus ulcers of the small and large intestine — 66.7 % (95% CI: 19.5–90.4). Table 6 presents the overall survival in the comparison groups depending on the influencing factors.

The study showed that overall survival statistically significantly depends on the source of bleeding. Thus, the highest survival was found among patients with the following sources of bleeding: hemorrhoids, colon diverticulosis and Kaposi's sarcoma, and the lowest — among patients with cytomegalovirus intestinal ulcers, tumors and polyps of the upper gastrointestinal tract, tuberculous intestinal ulcers (Table 7).

A study of the factors significantly influencing survival rate showed that the identified factors do not significantly correlate with each other ($|R| > 0.7$). Statistically significant factors ($p < 0.05$) identified in the univariate analysis were included in the multivariate Cox regression analysis, which demonstrated that the age of patients, the presence of thrombocytopenia, the fact of surgical treatment, the severity of blood loss, duodenal or gastric ulcer and cytomegalovirus intestinal ulcers (as a source of bleeding) are risk factors affecting the prognosis of overall hospital survival of patients with gastrointestinal tract bleeding ($p < 0.05$). When assessing the quality of the constructed multifactorial model, a sufficiently high Harrell Concordance Index of 0.931 was obtained. Time-dependent ROC-AUC of 0.908 indicates a high prognostic quality of the model for the entire hospital observation period (Table 8).

The table shows the hazard ratios (HR) with 95 % confidence interval and p values of risk factors in the multivariate Cox regression model. As

Table 8. Single-factor and multifactorial regression analysis of Cox depending on various factors affecting the survival of patients with bleeding

Таблица 8. Однофакторный и многофакторный регрессионный анализ Кокса в зависимости от различных факторов, влияющих на выживаемость пациентов с кровотечениями

Parameter ***Показатель***	**Univariate analysis** ***Однофакторный анализ***			**Multivariant analysis** ***Многофакторный анализ***		
	B 95 % CI ***95 % ДИ***	**HR 95 % CI** ***95 % ДИ***	***p***	**B 95 % CI** ***95 % ДИ***	**HR 95 % CI** ***95 % ДИ***	***p***
Age *Возраст*	0.364 (0.188–0.539)	1.438 (1.207–1.715)	<0.001*	0.395 (0.172–0.617)	1.484 (1.188–1.853)	
Thrombocytopenia *Тромбоцитопения*	1.684 (1.057–2.311)	5.385 (2.877–10.081)	<0.001*	0.856 (0.175–1.536)	2.353 (1.192–4.646)	0.014*
Chronic anemia *Хроническая анемия*	1.180 (0.545–1.814)	3.253 (1.725–6.134)	<0.001*			
Nonsurgical treatment *Консервативная терапия*	–1.368 (–2.304:–0.432)	0.255 (0.100–0.649)	0.004*			
Surgical treatment *Оперативное лечение*	1.581 (0.973–2.189)	4.859 (2.645–8.924)	<0.001*	0.670 (0.032–1.308)	1.953 (1.032–3.697)	0.040*
Blood loss degree *Степень кровопотери*	2.224 (1.661–2.787)	9.240 (5.262–16.225)	<0.001*	2.047 (1.447–2.647)	7.744 (4.250–14.108)	
HIV+, $CD4^+ > 200$ *ВИЧ+, $CD4^+ > 200$*	–0.976 (–2.400–0.447)	0.377 (0.091–1.564)	0.179			
HIV+, $CD4^+ < 200$ *ВИЧ+, $CD4^+ < 200$*	0.605 (–0.070–1.279)	1.831 (0.933–3.593)	0.079			
Tuberculous intestinal ulcer *Туберкулезная язва кишечника*	0.241 (–0.970–1.452)	1.272 (0.379–4.272)	0.697			
Kaposi's sarcoma *Саркома Капоши*	1.645 (0.218–3.072)	5.182 (1.244–21.582)	0.024*			
CMV-intestinal ulcers *ЦМВ-язвы кишечника*	1.637 (0.454–2.820)	5.140 (1.574–16.783)	0.007*	1.373 (0.065–2.681)	3.946 (1.067–14.596)	0.040*
Ulcer duodenum or stomach *Язва ДПК или желудка*	–0.985 (–1.849:–0.121)	0.373 (0.157–0.886)	0.025*	–1.631 (–2.569:–0.692)	0.196 (0.077–0.501)	0.001*

can be seen from Table 8, the presence of HIV infection in a patient (including immune status parameters) does not statistically significantly affect the overall hospital survival rate of patients with gastrointestinal bleeding. At the same time, low immune status determines such a possible source of bleeding as cytomegalovirus intestinal ulcers, pancytopenia (anemia and thrombocytopenia) and other aggravating factors, which in turn determine the low survival rate of patients with bleeding.

The graph (Fig.) shows the B coefficients with 95 % confidence interval and p values of risk factors in the multivariate Cox regression model, which clearly shows that such a source of bleeding as a duodenal or gastric ulcer is a prognostically favorable factor for survival in GIB, while the other indicated factors to the right of the dividing line, on the contrary, aggravate the prognosis of such survival to varying degrees.

Discussion

The conducted study allowed to demonstrate that patients who came to hospitals with gastrointestinal bleeding have significant differences depending on the presence of HIV infection and different immune status. First of all, there are noticeable intergroup age differences in patients, which is undoubtedly associated with different life expectancies in the comparison groups and the presence of comorbid diseases. Thus, among HIV-negative patients, up to 26 % are patients over 61 years old, other age groups are represented in approximately equal proportions (24 % — 31–40 years old; 22 % — 41–50 years old; 19 % — 51–60 years old). The severity of blood loss and the severe course of the disease in elderly people is largely explained by the presence of a comorbid background (diabetes mellitus, chronic anemia, ischemic heart disease, cancer, etc.), which, along with blood loss, determines mortality from gastrointestinal bleeding [18, 19]. In our study, lethal outcome in elderly patients was 18.2 %, which is comparable to the overall mortality among patients with low immune status.

Despite the wide coverage of antiretroviral therapy (ART) in country the Russian Federation, approximately 40 % of patients either do not receive ART or have interrupted treatment on their own volition, which directly affected the immune status and life expectancy in the cohort of HIV-positive patients. The emergence of effective antiretroviral drugs in the early 2000s and adherence to therapy determine the age of patients with HIV infection, in the group of which we did not observe patients over 61 years old. The main contingent in Groups 1 and 2 is represented by young patients (under 30 years old — 5 and 10 %; 31–40 years old — 52 and 46 %; 41–60 years old — 43 and 43 %, correspondingly). Probably, over time, due to the development of new drugs for the treatment of HIV infection and the widespread coverage of ART among various segments of the population, life expectancy in the groups will equalize.

Chronic anemia preceding the development of blood loss has a significant impact on overall survival rate and the severity of bleeding. And if among HIV-negative patients anemia as a comorbid background is more common in elderly people (44.8 % of cases in people over 60 years old), then in patients with HIV infection it dominates in groups with both low and satisfactory immune status in all age groups (approximately 60 % of patients). According to C. Durandt et al. (2019), A. Marchionatti (2021), HIV can directly or indirectly affect the survival and function of hematopoietic stem/progenitor cells located in the bone marrow. In addition, drugs used for ART, inflammatory mediators released during HIV infection and coinfections or opportunistic infections can also affect the proliferation and differentiation of progenitor cells and reticulocytes during hematopoiesis [20, 21]. A meta-analysis conducted in 2022 evaluated population studies from different regions of the world, and the authors of the work statistically proved that anemia among HIV-infected individuals largely depends on the gender and ethnicity of patients (genetic dependence — African Americans and women of any nationality are more prone to anemia), diet (lack of iron in the diet and impaired absorption), and ART drugs (toxic effect of zidovudine on erythropoiesis) [22, 23].

Thrombocytopenia accompanying bleeding largely determines the risk of its occurrence and the severity of blood loss. In the population of HIV-negative patients, thrombocytopenia was observed in approximately every tenth patient and was more often detected in individuals of the older age group (40.7 % of cases in patients over 60 years). In the cohort of HIV-infected patients, we recorded thrombocytopenia 3 and 5 times more often in all age groups, which is largely explained by immune-mediated destruction of platelets by circulating immune complexes, direct infection of megakaryocytes, and the toxic and myelosuppressive effect of ART [24–26]. According to our data, thrombocytopenia occurred in approximately half of patients with low immune status and in one third of patients receiving ART, therefore, in the second case it was probably due to the myelotoxic effect of the drugs used [27].

According to our observations, the disease outcome was significantly affected by the method of permanent hemostasis. It can be noted that in all comparison groups, endoscopic methods of

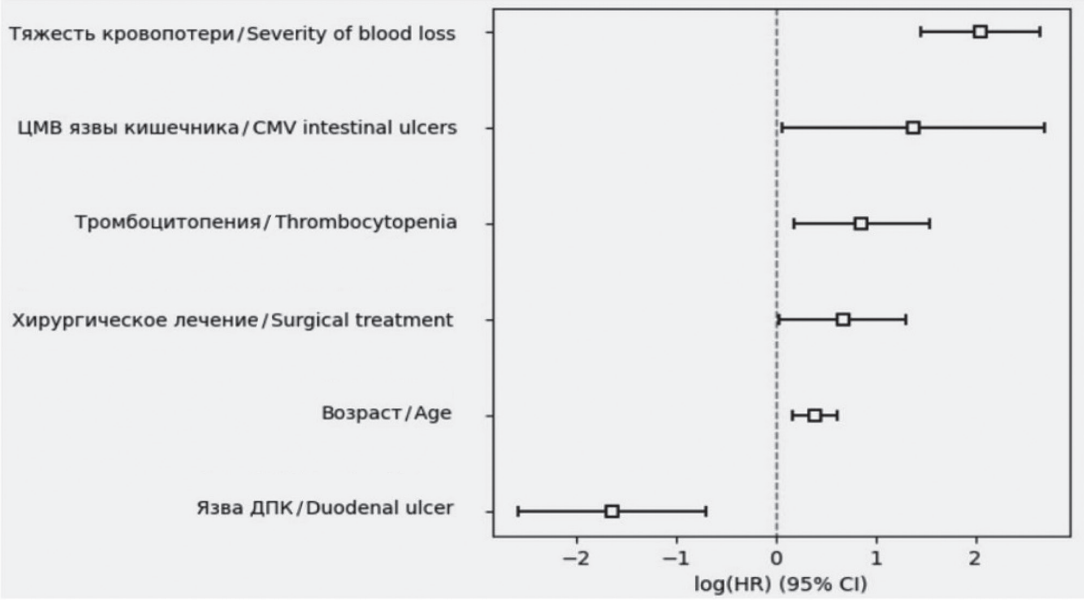

Figure. Overall survival analysis coefficients for patients with HIV and gastrointestinal bleeding (multivariate Cox regression model)

Рисунок. Overall survival analysis coefficients for patients with HIV and gastrointestinal bleeding (multivariate Cox regression model)

hemostasis were effective in approximately half of the cases (50.0 %, 42.0 % and 49.7 %), in the remaining observations, conservative hemostatic therapy was effective and sufficient (47.6 %, 33.3 % and 39.7 %). This is largely explained by the prevalence of "traditional" sources of bleeding, such as ulcers of the upper gastrointestinal tract, varicose veins of the esophagus, hemorrhoids and others, for which treatment tactics have been developed. Surgical treatment was significantly more often justified in the group of patients with low immune status (29.0 %) and its necessity was associated with "rare sources" of bleeding: tuberculous intestinal ulcers, cytomegalovirus intestinal ulcers and disintegrating Kaposi's sarcoma of various parts of the digestive tract [28, 29].

The study was limited by its retrospective nature.

Conclusion

The conducted study clearly showed that gastrointestinal bleeding in HIV infection has a number of significant etiopathogenetic features that directly affect the severity of blood loss, treatment methods and patient survival rate.

1. The source of gastrointestinal bleeding in HIV-positive patients and the severity of blood loss directly depend on the initial immune status of the patient.

2. The severity of blood loss in HIV-infected patients is determined by the initial comorbid hematological disorders (anemia and thrombocytopenia), which are more common in individuals with a low immune status ($CD4^+ < 200$) and less common in patients with satisfactory immunogram parameters. Severe blood loss and the need for transfusion of gas-transporting blood components in gastrointestinal bleeding are most relevant for HIV-positive individuals with low immune status.

3. In patients with $CD4^+ < 200$, tuberculosis and cytomegalovirus intestinal ulcers, as well as disintegrating Kaposi's sarcoma, are found as sources of bleeding in one third of cases, which requires "open" hemostatic resection surgeries.

4. Overall survival of HIV-infected patients with low immune status and gastrointestinal bleeding is lower than that of patients without HIV infection or HIV-positive patients with satisfactory immune status, which is due to the severity of blood loss, more frequent need for surgical hemostatic interventions.

Thus, people living with HIV and gastrointestinal bleeding are a complex and, unfortunately, frequent category of patients whose diagnostic features and approaches to treatment require further attention of the surgical community and the development of individualized rational treatment and diagnostic tactics.

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