# HEALTH RISK ANALYSIS IN EPIDEMIOLOGY

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## THE SIGNIFICANCE OF RISK FACTORS FOR ACQUIRING HEPATITIS B AND C VIRUS INFECTIONS IN CHILDREN WITH ONCOLOGICAL AND HEMATOLOGICAL DISEASES AND IMMUNODEFICIENCIES

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*Patients with oncological and hematological diseases are at high risk of nosocomial bloodborne infections (hepatitis B, hepatitis C, and HIV) due to their immunosuppressed condition and highly invasive treatment. The aim of our study is to identify the key risk factors of acquiring bloodborne infections among patients with hematological and oncological diseases and to determine the causes of uneven prevalence of hepatitis B and C among main clinical groups of patients.*

*The study was carried out from 2021 to 2023. The study cohort consisted of 500 patients, with 100 patients in each clinical group: primary immunodeficiencies PID), disorders of the blood and blood-forming organs (BD), hematological malignancies (HM), malignant solid tumors (MST), benign tumors (BT).*

*The median burden of invasive procedures per patient in the patients with HM, MST, BD, BT, and PID amounted to 10.9, 6.2, 5.1, 4.1, and 2.2 invasive interventions a day, respectively. The median infusion/injection burden was 8.3, 4.0, 2.7, 2.7, and 0.6 drugs a day, respectively. The median blood sampling burden amounted to 2.0, 1.7, 1.7, 1.3, and 1.6 samples a day, respectively. The median transfusion burden was 0.14, 0.07, 0.25, 0, and 0 units of transfused blood components a day, respectively. The median surgery burden was 0, 0.15, 0, 0.17, 0 surgical procedures a day, respectively. The medians for other medical procedures in all clinical groups amounted to 0.*

*The patients with PID representing a clinical group of patients with the highest prevalence of hepatitis B and C infections (2.5 % and 2.3 %, respectively) have the lowest level of invasive burden. It should be supposed that the major risk factor of acquiring HBV or HCV among patients with oncological and hematological diseases is the level of immunocompetence together with the impact of risk factors associated with invasive procedures such as blood transfusions, the use of venous catheters (for intravenous administration of drugs and blood sampling), and extensive surgeries.*

***Keywords:*** *risk factors, bloodborne infections, prevalence of HBV, prevalence of HCV, seroprevalence of HBV, seroprevalence of HCV, children with oncological and hematological diseases, transfusion-associated hepatitis, risk factors of acquiring nosocomial HBV and HCV infections.*

Patients with oncological and hematological diseases as well as patients undergoing hemodialysis are at high risk of nosocomial bloodborne infections (hepatitis B, hepatitis C, and human immunodeficiency virus (HIV)) due to their immunosuppressed condition associated with the underlying disease and specific treatment [1–8]. Factors



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most commonly considered to be involved in the transmission of bloodborne infections among patients with oncological and hematological diseases are blood transfusions, unsafe injections and infusions, surgeries and other invasive diagnostic and treatment procedures [9–19].

Testing for hepatitis C virus (HCV) infections of patients with oncological and immunological diseases admitted to the D. Rogachev NMRCPHOI of Ministry of Healthcare of the Russian Federation (hereinafter referred to as the Center) from different regions of Russia showed high prevalence of these infections among them. From 2014 to 2020, it amounted to 1.7 % which is 50 times higher than the average national prevalence reported for children. The prevalence of HCV infection among patients with different oncological and hematological diseases was found to be high in patients with PID (2.8 %), BD (2.2 %), MST (1.9 %), HM (1.6 %) [20].

**Materials and methods.** The aim of the study was to identify possible causes of uneven prevalence of hepatitis B virus (HBV) and HCV infections among patients with oncological and hematological diseases, namely causes of high HCV and HBV prevalence among patients with PID and other clinical groups of patients (BD, MST, and HM). The objectives of the study were to assess the burden of invasive procedures, to correlate it with the prevalence of HCV and HBV infections among patients from the main clinical groups and to hypothesize the possible causes and risk factors for acquiring these infections.

In our study, we assessed the burden of invasive procedures in patients who had undergone treatment at the Center from 2021 to 2023. The study sample included 500 patients (100 patients in each clinical group: PID, BD, HM, MST, BT). To analyze the burden of invasive procedures in the patients, we assessed the infusion burden (the number of drugs infused), the frequency of diagnostic blood sampling (the number of blood tubes collected), the burden of blood transfusions (the number of units of blood and blood components transfused), surgery burden (the number of surgeries), the frequency of bone marrow aspirations and lumbar punctures and diagnostic endoscopic procedures (the number of invasive procedures per patient per day).

In order to correlate the results of our assessment of invasive burden with the prevalence of HBV and HCV, we used the retrospective data on the prevalence of these infections among patients who had received treatment at the Center from 2014 to 2022 (13,500 patients). These retrospective data included the results of laboratory testing for HBsAg, anti-HCV, HCV RNA, and HBV DNA performed at admission to the Center. All patients with HCV and HBV from this retrospective cohort were infected before admission to the Center. There were no cases of HBV or HCV infections acquired at the Center during the analysis period.

The analyzed group of patients was characterized by prior hospitalizations at the place of residence, the need for complex and technologically advanced diagnostic and treatment modalities that are unavailable in other regions of the country, and severe condition at admission to the Center.

The statistical analysis was conducted using Microsoft Excel. The significance of differences in quality parameters was assessed by using contingency tables and the calculation of $\chi^2$ tests (95 % confidence intervals). A statistical comparison of the medians was made using the Mann – Whitney U test.

**Results and discussion.** It was revealed that the patients with HM experienced the highest burden of invasive procedures: the median daily burden among the patients with HM was 2 times higher than in the whole cohort of interest ($n$ = 500) (10.9 vs 5.4, $p < 0.001$). The lowest median burden of invasive procedures was observed among the patients with PID; it amounted to 2.2 invasive procedures per patient per day, which is 5 times lower than in the patients with HM ($p < 0.001$) and 2.5 times lower than the average burden of invasive procedures per patient per day in the whole cohort of interest ($p < 0.001$) (Table 1, Figure 1).

Table 1

The median number of invasive procedures per 1 patient per day (2022)

| Invasive procedures / Clinical diagnosis | Injections, infusions (drugs) | Blood sampling (tubes) | Blood transfusions (units) | Surgeries | Lumbar punctures/bone marrow aspirations | Diagnostic endoscopic procedures | Total burden |
|---|---|---|---|---|---|---|---|
| HM | 8.3 | 2.0 | 0.1 | 0 | 0 | 0 | 10.9 |
| MST | 4.0 | 1.7 | 0.1 | 0.15 | 0 | 0 | 6.2 |
| BD | 2.7 | 1.7 | 0.3 | 0 | 0 | 0 | 5.1 |
| BT | 2.7 | 1.3 | 0 | 0.17 | 0 | 0 | 4.1 |
| PID | 0.6 | 1.6 | 0 | 0 | 0 | 0 | 2.2 |
| All clinical groups | 3.3 | 1.6 | 0 | 0 | 0 | 0 | 5.4 |

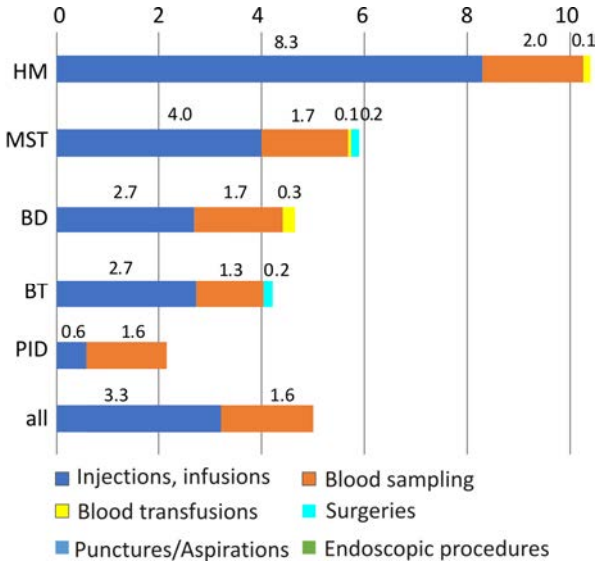


Figure 1. The median number of invasive procedures per 1 patient per day according to the type of procedures and clinical groups

We carried out a thorough analysis of each type of invasive interventions in all the clinical groups of patients. Parenteral administration of drugs was the most common invasive procedure in the patients with oncological and hematological diseases. To assess the burden of injections and infusions, we calculated the number of medications administered by the following parenteral routes: intravenous (IV) (intermittent (push or short) infusions and continuous infusions), subcutaneous (SC), intramuscular (IM), intrathecal (IT), and intraventricular (IVT).

The median number of medications administered to all patients from the cohort of interest was 3.3 per patient per day. The median number of medications administered per day to the patients with HM, MST, BD, BT, and PID was 8.3, 4.0, 2.7, 2.7, and 0.6, respectively. The patients with HM received the highest number of injections and infusions during treatment which is 2.5 times higher than the whole cohort of interest and statistically significantly higher than the patients from other clinical groups ($p < 0.05$). The patients with PID received the lowest number of parenteral medications, which is 14 times lower than the patients diagnosed with HM ($p = 0.00028$) and 6 times lower than the whole cohort of interest (Table 1, Figure 1).

At the Center, the most commonly used venous access for both intermittent and continuous infusions of medications was a central venous catheter (CVC).

The patients with HM received 5.1 medications per day administered as short infusions; the patients with MST, 3.3 medications; the patients with BT, 2.6; the patients with BD, 2.2; and the PID cases, 0.2. The patients with HM received the largest number of medications via short infusions which was twice as high as the median number of drugs administered this way at the Center (2.6). The patients with PID were given the smallest number of drugs as short intravenous infusions which was 16 times lower than the median number of medications administered this way at the Center, and 31 times lower than the number of drugs received by the patients with HM ($p = 0.00028$). The patients with HM received 2.8 drugs per day via continuous intravenous infusions, the patients with BD – 0.5 drugs, MST cases – 0.2, BT – 0, PID – 0 (Figure 2). The largest number of drugs administered via this route was given to the patients with HM.

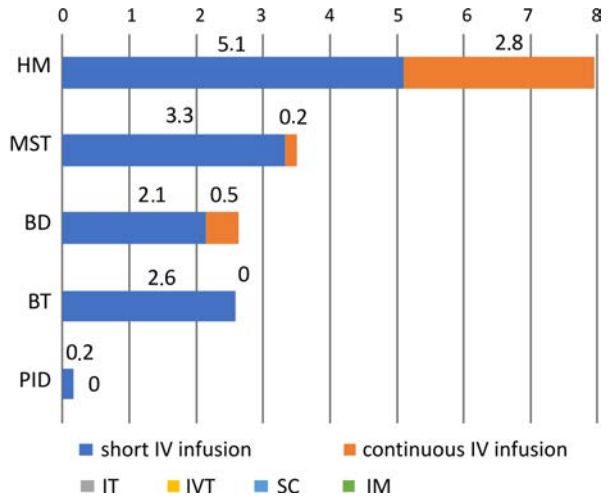


Figure 2. The median number of drugs per patient per day according to the disease and route of administration

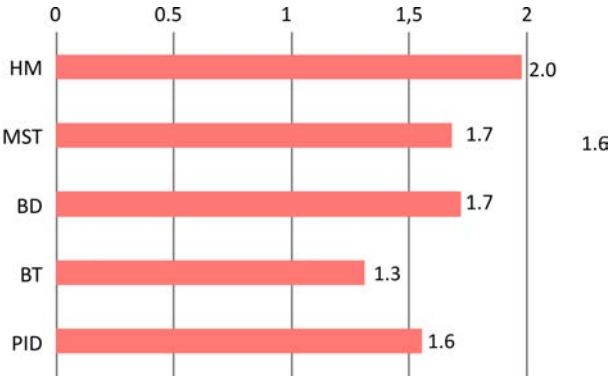


Figure 3. The median number of blood samples collected per patient per day according to the disease

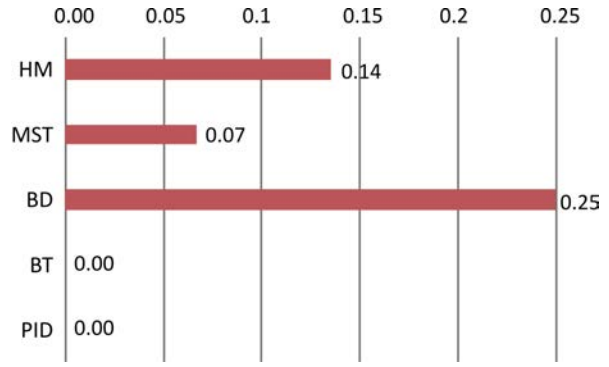


Figure 4. The median number of blood transfusions (doses of blood and its components) per patient per day according to the patient clinical group

The median number of drugs administered subcutaneously, intrathecally, intramuscularly and intraventricularly was 0 (Figure 2). Intrathecal and intraventricular routes were mostly used in the patients with HM.

The maximum burden of parenteral drug administration was registered in the patients with HM, with both the number of drugs and the route of their administration taken into account. Meanwhile, the patients with PID had the lowest injection/infusion burden.

Blood sampling was the second most frequent invasive procedure performed at the Center, after parenteral drug administration. In order to reduce the invasive and psychological burden in the patients, blood was collected from a central venous line in 89–99 % cases.

When assessing blood sampling burden, we discovered that the patients with HM underwent diagnostic blood testing more often than the others: the median number of blood specimens per patient per day was 2, and in the patients with PID this parameter was 1.3 times lower (1.6 vs. 2, $p = 0.017$) (Table 1, Figure 3). All the clinical groups experienced high invasive burden but the patients with HM were the most affected group.

The analysis of the burden of blood transfusions, namely, of the median amounts of transfused blood components, showed that the highest amount of blood was received by the patients with BD and HM: 0.25 and 0.14 doses of blood or its components per patient per day, respectively; while the patients with MST received 0.07 doses, and the patients with PID and BT – 0. The patients with BD underwent 1.8 times more blood transfusions than the patients with HM ($p > 0.05$) and 3.8 times more transfusions than the patients with MST ($p < 0.001$) (Table 1, Figure 4).

Since donor blood components with short shelf life (platelet concentrates, red blood cell containing components, granulocyte concentrates) are considered to be the most unsafe blood products, we decided to compare the number of transfusions of these components with that of quarantined ones among the different clinical groups. The patients with HM, MST and BD had the same median amount of transfused red blood cell containing components, namely, 0.06 dose. In the patients with HM and BD, the median amounts of transfused platelet concentrates were 0.03 and 0.06 doses per patient per day ($p = 0.89656$),

Table 2

The median number of doses of blood and its components transfused to 1 patient per day according to the patient clinical group and the transfused blood component

| Blood component / Clinical diagnosis | Platelet concentrate | Red blood cell containing components | Granulocyte concentrate | Plasma | **All the blood components** |
|---|---|---|---|---|---|
| HM | 0.03 | 0.06 | 0 | 0 | 0.14 |
| MST | 0 | 0.06 | 0 | 0 | 0.07 |
| BD | 0.06 | 0.06 | 0 | 0 | 0.25 |
| BT | 0 | 0 | 0 | 0 | 0 |
| PID | 0 | 0 | 0 | 0 | 0 |
| **All the patients** | 0 | 0 | 0 | 0 | 0 |

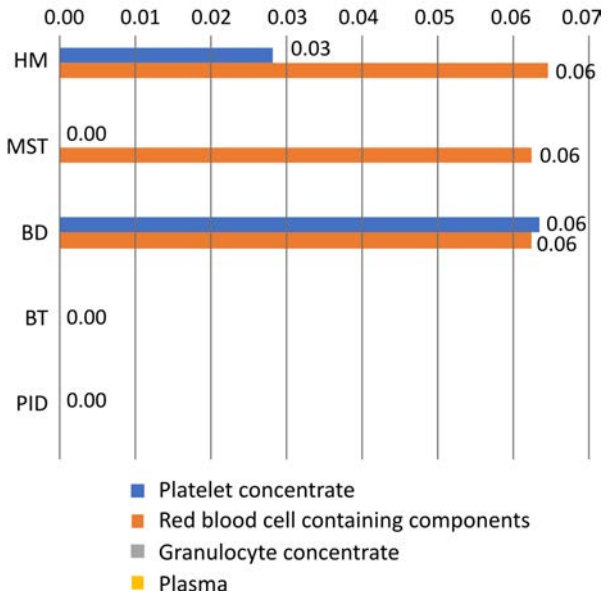


Figure 5. The median number of doses of blood and its components transfused to 1 patient per day according to the patient clinical group and the transfused blood component

respectively. The median amounts of other transfused blood components in the patients with HM, MST and BD as well as the median numbers of doses in the other groups (BT and PID) equalled 0 (Table 2, Figure 5). All the patient groups were at risk of acquiring bloodborne infections since most patients received blood components with short shelf life. The percentage of blood components with short shelf life transfused to the patients with HM was 83 %, the patients with MST – 79 %, BD – 83 %, BT – 74 %, PID – 95 %.

Thus, the highest burden of blood transfusions was registered in the patients with BD and HM, due to extensive replacement therapy with blood components that can potentially carry bloodborne pathogens.

Surgery burden assessment revealed that the median number of surgeries in the patients with MST was 0.15, while the patients with BT underwent a median of 0.17 surgeries per patient per day ($p = 0.5485$). In the other clinical groups, the median number of surgeries amounted to 0. The median number of surgeries undergone by the study cohort was also 0 (Table 3).

Since more extensive surgeries are associated with a higher risk of transmission of bloodborne infections, we analyzed the median numbers of surgeries stratified according to their complexity using the surgical complexity classification developed at the Center:

- Level I. Very low-risk surgeries: surgeries performed on the surface of the body without involving the inner structures;
- Level II. Low-risk surgeries: surgeries performed on the surface of the body with a few incisions, major surgeries without internal organ involvement, laparoscopy, oral surgeries, and limb reconstruction;
- Level III. Moderate-risk surgeries: surgeries on the internal organs and the intestines, open joint surgery, laparoscopy involving parenchymal organs, thoracoscopy, and microsurgery;
- Level IV. High-risk surgeries: extensive surgeries involving several organs or systems, surgery on the CNS;
- Level V. Extremely high-risk surgeries: surgeries on vital organs and systems in critically ill patients.

Table 3

The median number of surgeries per patient per day according to the clinical diagnosis and surgical complexity

| | Level I | Level II | Level III | Level IV | Level V | Total number |
|---|---|---|---|---|---|---|
| HM | 0 | 0 | 0 | 0 | 0 | 0 |
| MST | 0 | 0 | 0 | 0 | 0.08 | 0.15 |
| BD | 0 | 0 | 0 | 0 | 0 | 0 |
| BT | 0 | 0 | 0 | 0 | 0 | 0.17 |
| PID | 0 | 0 | 0 | 0 | 0 | 0 |
| All the patients | 0 | 0 | 0 | 0 | 0 | 0 |

An analysis of the number of surgeries stratified in accordance with their complexity showed that the median number of level V complexity surgeries was significant only in the patients with MST, amounting to 0.08 surgeries per patient per day. In the other clinical groups, the median number of surgeries of various complexity was 0 (Table 3).

Since the medians equalled 0, we had to analyze the distribution of the number of various complexity surgeries (Figure 6) in order to evaluate surgery burden in the different clinical groups. All the patients were shown to experience surgery burden to some extent but significant surgery burden was evident only in the patients with MST and BT, which was also demonstrated by the medians of the number of surgeries in these groups. Since the patients with MST underwent extensive level V complexity surgeries, the surgery burden in this group was judged to be higher than that in the BT patients. Fifty percent of the surgeries undergone by the patients with MST had level V complexity. The lowest surgery burden was registered in the patients with PID (Figure 6).

The median number of lumbar punctures and bone marrow aspirations was 0 in all the clinical groups. In this view, we set out to compare the distribution of the number of punctures/aspirations among the patient groups. The patients with HM were found to experience the highest burden of invasive procedures: 18 % of the patients underwent more than 0.1 punctures / aspirations per day (Figure 7).

The median number of endoscopic procedures was 0 in all the clinical groups. Our distribution analysis revealed that the highest number of endoscopic procedures was carried out in the patients with PID: 24 % of the patients underwent over 0.1 procedures per day (Figure 8).

Thus, the highest burden of endoscopy was registered in the patients with PID, while the patients from the other clinical groups experienced a minimal burden of invasive procedures.

When analyzing the prevalence of HBV and HCV in the main clinical groups of patients, we found that the most infected group was the one with the PID patients (HBV – 2.5 %, HCV – 2.3 %). HBV and HCV prevalence in the patients with PID was statistically significantly higher than in the patients with HM, BD and MST ($p < 0.05$). No significant difference in HCV prevalence was observed among the patients with HM, BD and MST (1.3 %, 1.3 %, 1.2 %, $p > 0.05$). There was no significant difference in HBV prevalence among the patients with HM and BD (0.9 %, 0.8 %, $p > 0.05$), but it was higher than in the patients with MST (0.2 %) ($p < 0.05$) (Figure 9).

Our analysis shows that invasive procedures have different significance depending on the clinical group of patients according to the special aspects of the organization of the D. Rogachev Center's work. Even though the results in other clinics may differ, our data can be taken into consideration when investigating cases of contracting bloodborne infections and instituting preventive and epidemic control measures among immunocompromised patients.

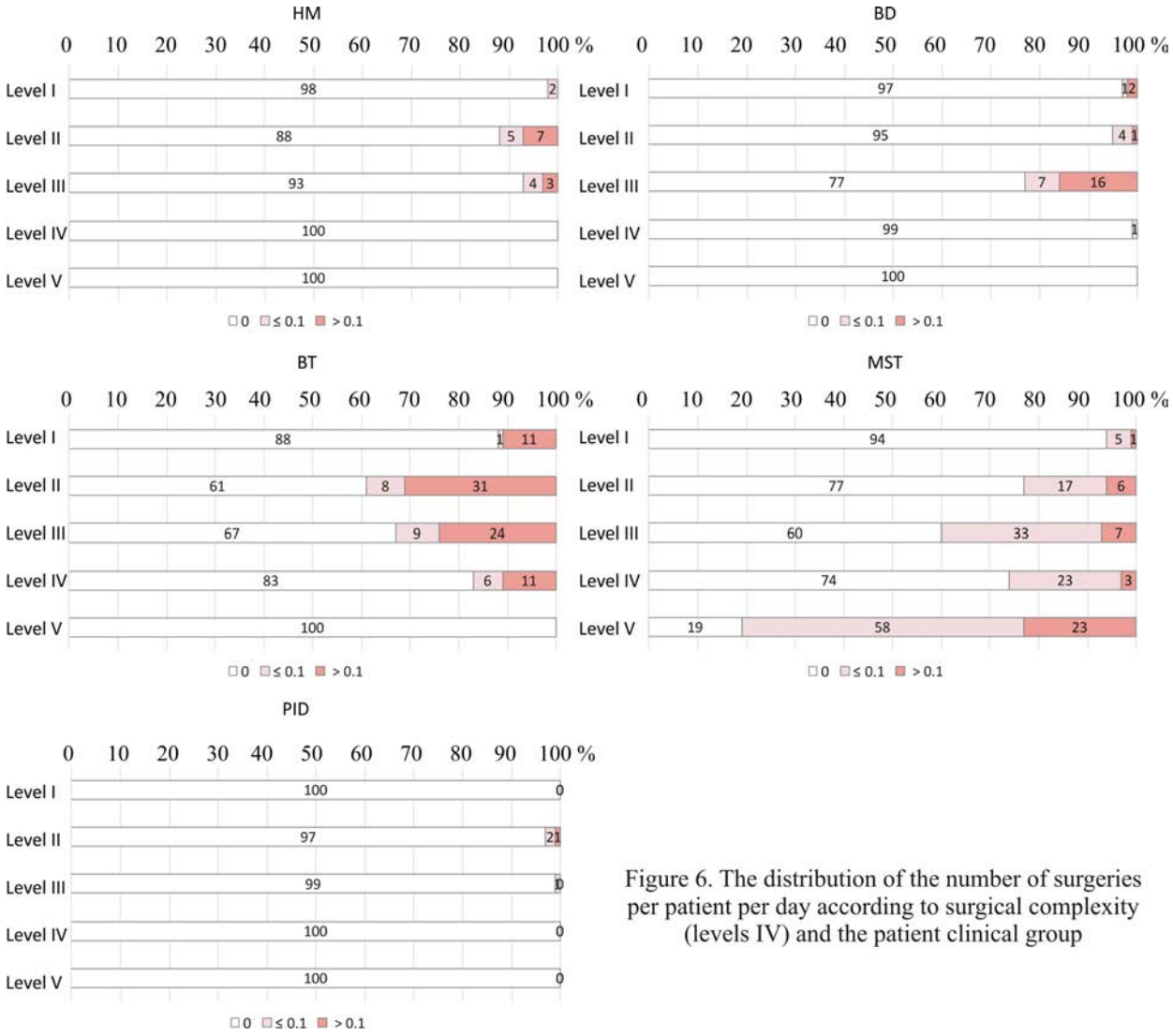


Figure 6. The distribution of the number of surgeries per patient per day according to surgical complexity (levels IV) and the patient clinical group

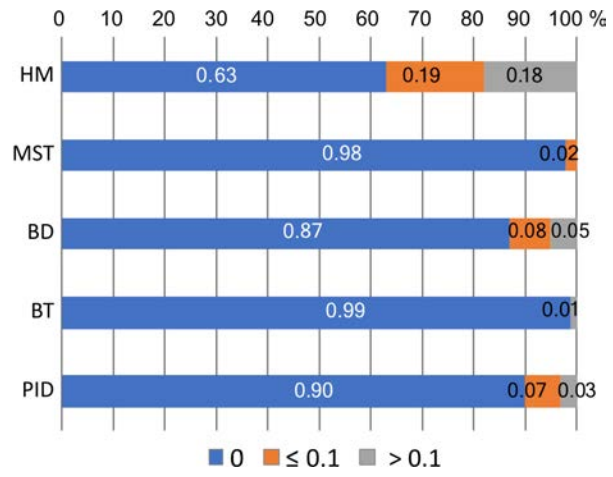


Figure 7. The distribution of the number of lumbar punctures and bone marrow aspirations per patient per day according to the clinical diagnosis

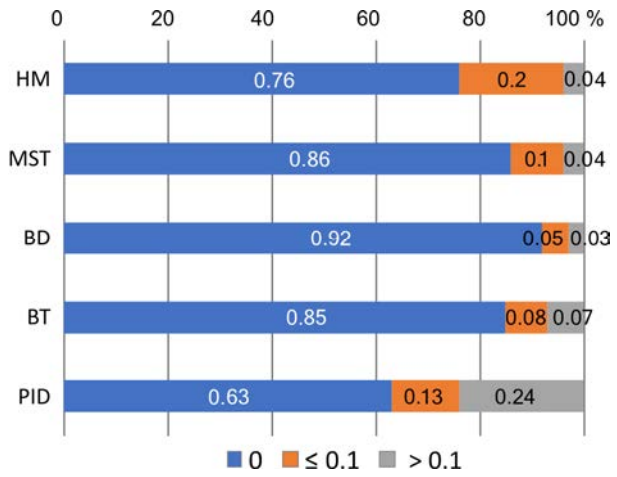


Figure 8. The distribution of the number of endoscopic procedures per patient per day according to the clinical diagnosis

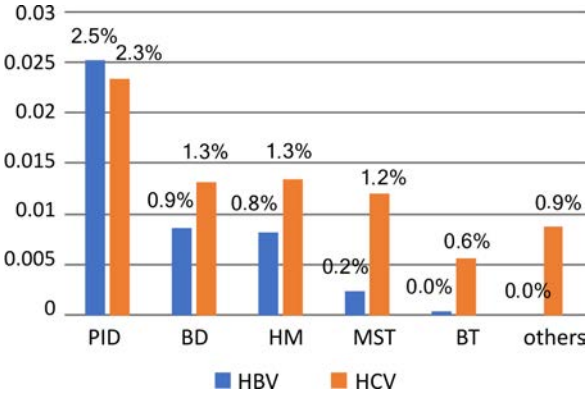


Figure 9. The prevalence of HBV and HCV infections in the main clinical groups of patients treated at the D. Rogachev NMRCPHOI, from 2014 to 2022 ($n$ = 13 500)

Our analysis showed that the highest burden of invasive procedures among the main clinical groups of patients with oncological and hematological diseases and immunodeficiency conditions was observed in the patients with HM which underwent 10.9 invasive procedures per day, while the patients with PID experienced the lowest burden of invasive procedures, 2.2 invasive procedures per day, which is 5-fold lower than in the patients with HM and 2.5-fold lower than the average burden of invasive procedures at the Center (5.4 invasive procedures per patient per day).

When assessing certain types of invasive procedures, we found that the patients with HM had the highest infusion/injection burden in terms of the number of drugs administered. Routes of drug administration have varying degrees of invasiveness and therefore the risk of bloodborne infection transmission. The highest risk of getting infected is observed in case of intravenous drug administration using a catheter by intermittent infusions, since it involves numerous procedures with both the catheter and secondary IV accesses. Thus, in the patients with HM, the largest number of drugs was administered by intermittent intravenous infusions.

Another type of invasive procedures associated with miltifactorial risks of transmitting bloodborne infections is blood sampling. During blood sampling, all clinical groups of patients experienced high burden of invasive procedures but the highest burden was observed in the patients with HM.

The patients with BD and HM had the highest burden of blood transfusions both in terms of the number of units of transfused blood components and their safety (the number of unsafe platelet concentrates and red blood cell containing components).

The highest surgery burden was observed in the patients with MST and BT; in addition, the patients with MST underwent a higher number of extensive surgeries than patients from other clinical groups. The percentage of the patients with MST who underwent level V surgeries was 50 %.

The largest number of lumbar punctures and bone marrow aspirations was carried out in the patients with HM.

The lowest infusion/injection burden was observed in the patients with PID and was 14 times lower than in the patients with HM and 6 times lower than in the whole cohort of interest. The patients with PID had 1.3 times fewer blood samples collected daily than the patients with HB. The median numbers of blood transfusions, surgical interventions, punctures/aspirations and endoscopic examinations were 0 in the patients with PID. According to our analysis of the distribution of the number of surgeries and lumbar punctures/bone marrow aspirations, among all the clinical groups of patients, the PID patients had the lowest invasive burden associated with surgeries and lumbar punctures/bone marrow aspirations and the highest invasive burden associated with endoscopic procedures.

Our retrospective analysis demonstrated a high prevalence of bloodborne infections among patients with oncological and hematological diseases and immunodeficiency conditions admitted to the Center from different regions of the country. HBV and HCV prevalence among the patients treated at the Center was high; the highest prevalence was observed in the group of patients with PID.

When correlating the results obtained by assessing the burden of invasive procedures with the level of HBV and HCV prevalence, we found that the patients with PID who

experienced the lowest burden of invasive procedures, had the highest prevalence of HBV and HCV. We can assume that a lower dose of an infectious agent is required to infect patients with PID due to their immunodeficiency state. Moreover, the analysis of medical records revealed that the patients with PID have a longer time to diagnosis in outpatient clinics compared with the patients with HM and MST: they undergo numerous invasive procedures during their long stay in clinics not specialized in the treatment of immunocompromised patients until a final diagnosis is established.

In the previous studies, blood transfusions and medical procedures were considered the leading risk factors for contracting bloodborne infections in patients with oncological and hematological diseases[1]. Based on the data obtained from our study, it can be assumed that the leading risk factor for contracting HBV and HCV in patients with oncological and hematological diseases is the level of immunocompetence of patients in combination with the influence of risk factors associated with invasive procedures.

The next highest prevalence of HCV was observed among the patients with HM, BD, MST, most likely due to the high burden of invasive procedures during drug administration and blood sampling. In patients with induced immunosuppression, there might have been infection control breaches in the preparation of infusions, blood sampling and the management of IV catheters (the most commonly used venous access devices for drug administration in these patients). There were additional risk factors for contracting infections: numerous lumbar punctures and bone marrow aspirations in the patients with HM and a large amount of extensive surgeries in the MST patients. Despite the absence of immunosuppressive and / or chemotherapy, HCV prevalence was 0.6 % in the patients with BT, which exceeded the prevalence in the general pediatric population. The leading risk factors for the patients with BT included high surgery and infusion burden, which emphasizes that there might have been infection control breaches in the procedures carried out in in- and outpatient clinics. High prevalence of HBV in the patients with BD and HM who received extensive replacement therapy with blood components implies a residual risk of contracting post-transfusion HBV which is able to escape the capabilities of diagnostic test systems due to the presence of mutant forms of the virus. Despite the absence of induced immunosuppression, the prevalence of HCV in the patients with BD was at the same level as in the patients with HM and MST. As regards the prevalence of HBV among the patients with BD, it was at the same level as in the patients with HM but higher than in the patients with MST. The leading risk factors in the patients with BD were as follows: a high burden associated with transfusions of unsafe blood components, infusion/injection burden, and blood sampling. The prevalence of HBV and HCV in the patients with BD shows that blood transfusions are associated with the risk of HBV transmission and implies the unsafety of medical procedures.

**Conclusions.** Invasive procedures and transfusions of unsafe blood components in patients with immunosuppression are factors that place patients with oncological and hematological diseases and immunodeficiency conditions at increased risk of contracting bloodborne infections. Such invasive procedures include intravenous administration of medications, blood sampling and extensive surgeries.

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**Competing interests.** The authors declare no competing interests.

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