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- МЕТОДОЛОГИЧЕСКИЕ ОСНОВЫ ПРОВЕДЕНИЯ ОЦЕНКИ ДОСТОВЕРНОСТИ НАУЧНЫХ ДАННЫХ С ПОМОЩЬЮ СИСТЕМЫ КЛАССИФИКАЦИИ, ОЦЕНКИ, РАЗРАБОТКИ И ЭКСПЕРТИЗЫ РЕКОМЕНДАЦИЙ GRADE
- РЕЗУЛЬТАТЫ РОССИЙСКИХ ФАРМАКОЭКОНОМИЧЕСКИХ ИССЛЕДОВАНИЙ

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PHARMACOECONOMIC ASSESSMENT OF HEPATOPROTECTORS USED FOR PREVENTION OF DEVELOPING POST-RESECTION ACUTE LIVER FAILURE AFTER EXTENSIVE HEMIHEPATECTOMY DUE TO COLORECTAL CANCER METASTASES

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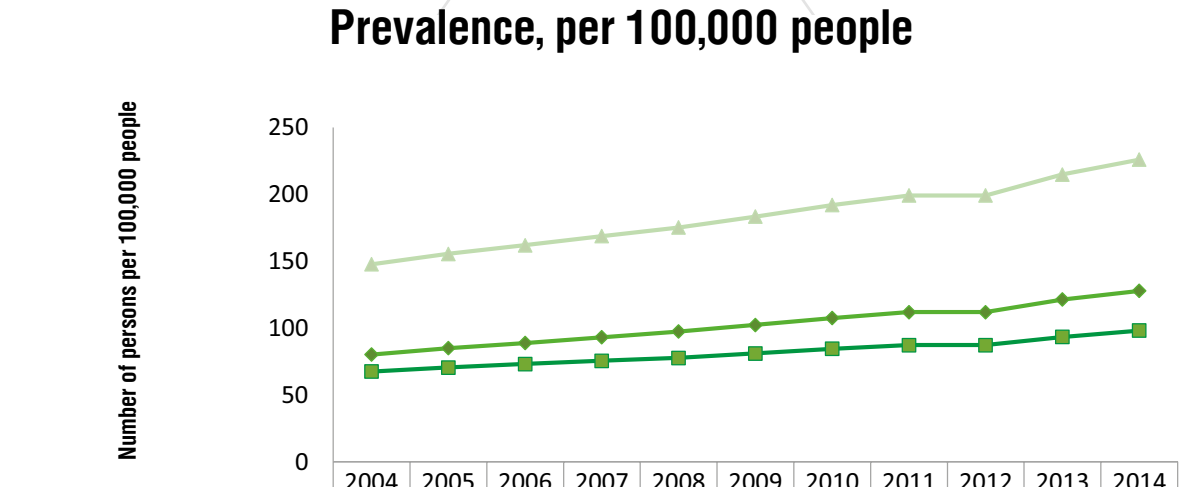
Resume:
During the current study, a pharmacoeconomic assessment of liver failure prevention after using Remaxol® (succinic acid, N-methylglucamine, inosine, methionine, nicotinamide – hereinafter SMIMN) vs. ademetionine was performed in patients with extensive liver resection. As a primary efficacy endpoint, a number of patients needed to treat (NNT) to reach a Child-Pugh Grade A liver functional state was used while analyzing therapeutic efficacy. In the clinical study, Khoronenko et al. demonstrated, that efficacy of SMIMN was higher than ademetionine in restoring liver functional state. On Day 5 and 12 after liver resection cost-effectiveness ratio measured in SMIMN vs. ademetionine groups was 39,624 vs. 96,634 Rub and 34,661 vs. 55,236 Rub, respectively, favoring conclusion that use of SMIMN exhibiting higher efficacy is a dominant approach for preventing acute liver failure (ALF) after extensive liver resection. Budget Impact Analysis revealed that budget savings after treatment with SMIMN vs. ademetionine were 11,831,861 Rub per 1,083 patients, and within a fixed budget, it allowed additionally to treat up to 427 patients.

Key words: *Remaxol®, succinic acid, N-methylglucamine, (meglumine), inosine, methionine, nicotinamide, ademetionine, pharmacoeconomics, acute liver failure, liver resection, colorectal cancer metastases, effectiveness analysis, cost analysis, cost-effectiveness analysis, Budget Impact Analysis.*

Introduction

Colorectal cancer is one of the most common cancers that holds a fourth place among oncologic diseases. Annually, up to 600,000 new cases are recorded worldwide [1], whereas in 2014 it reached up to 227 persons per 100,000 people in Russia, virtually exceeding it in 2013 by 5% (Figure 1). 2014 Russian statistics data registered 35,089 and 26,786 new cases of colon cancer and rectal cancer, respectively. Upon that, 27.7% and 23.5% patients with colon cancer and rectal cancer, respectively, were diagnosed at stage IV of the disease, whereas each third patient had distant metastasis mostly localized in the liver [1,4,5]. During the first year after diagnosing, mortality rate related to colorectal cancer reaches up to 30% (Figure 2). Average patient life expectancy with confirmed colorectal cancer does not reach even 2-3 years, whereas detected metastases shorten it down to 2-10 months [1, 26, 27].



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Colon cancer	80.2	85	88.8	93.1	97.5	102.3	107.5	111.9	111.9	121.4	127.8
Rectal cancer	67.5	70.5	73.1	75.6	77.7	81.1	84.5	87.3	87.3	93.4	98.2
Colorectal cancer	147.7	155.5	161.9	168.7	175.2	183.4	192	199.2	199.2	214.8	226

Figure 1. Prevalence of colorectal cancer in Russian Federation

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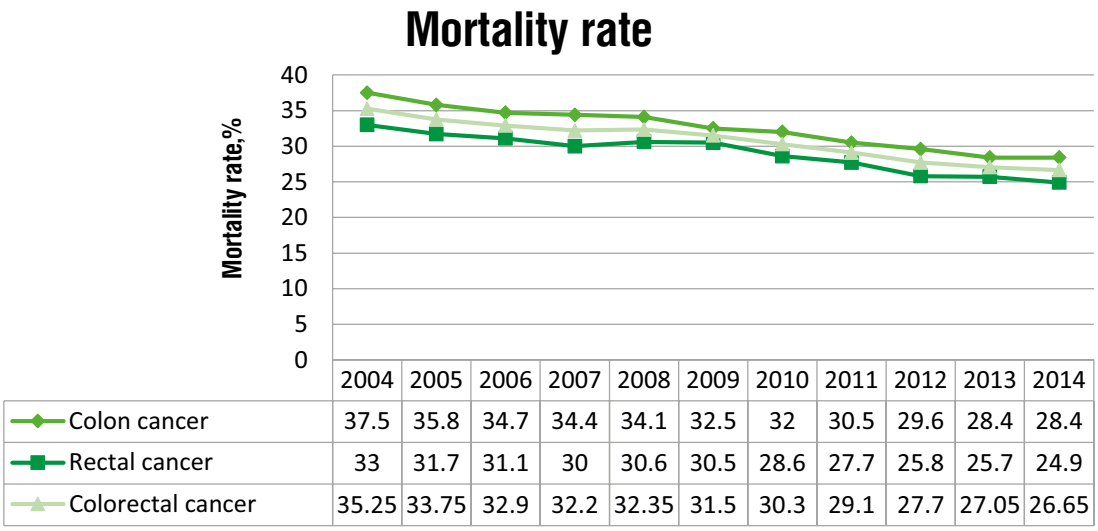

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Colon cancer	37.5	35.8	34.7	34.4	34.1	32.5	32	30.5	29.6	28.4	28.4
Rectal cancer	33	31.7	31.1	30	30.6	30.5	28.6	27.7	25.8	25.7	24.9
Colorectal cancer	35.25	33.75	32.9	32.2	32.35	31.5	30.3	29.1	27.7	27.05	26.65

Figure 2. Colorectal cancer mortality rate in Russian Federation

In 2014, approx. 61,874 new cases of colorectal cancer were recorded in the Russian Federation. Almost 25% patients with colorectal cancer had metastases in the liver, but were recommended for surgical removal only in 7% patients. Thus, approx. 1,083 patients in Russian Federation require surgical resection of liver metastases and potentially may be considered for undergoing liver failure prevention [1,4, 14, 25] (Figure 3).

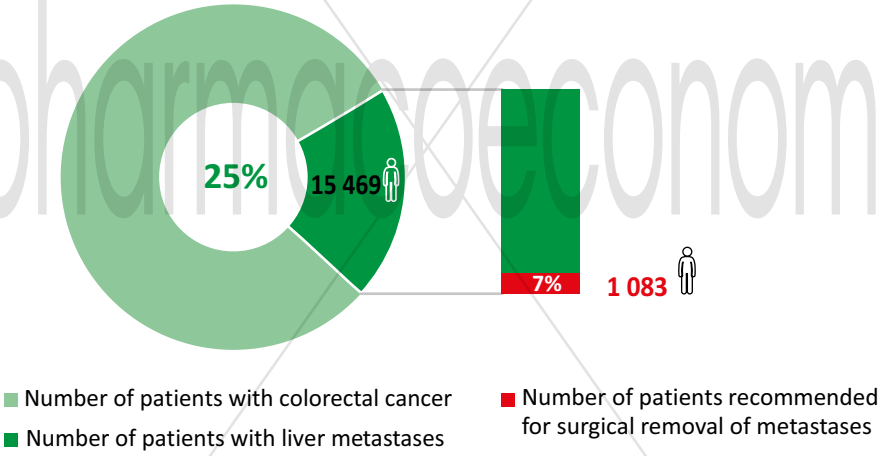

Figure 3. Predicted number of patients with liver resection due to colorectal cancer metastases

A five-year survival rate may be achieved in 30-50% patients underwent resection of metastases [1], but high mortality risk is still observed in 56-77% cases due to developing post-resection acute liver failure (ALF) in post-surgical period [14]. Conditionally, according to Khoronenko et al. preventive methods may be divided into surgical and anaesthetic measures. The former is based on precisely estimated extent of selected surgery and use of blood-saving techniques during operation, whereas the latter approach implies selection of anaesthetic support with dosing and application of components highly safely acting on the liver. In addition, hepatoprotectors, which have recently been more extensively applied in protocols of infusion therapy to avoid various sequelae, can be used to prevent developing ALF [14].

In 2009, drug Remaxol® (succinic acid + N-methylglucamine + inosine + methionine + nicotinamide – hereinafter SMIMN) exhibiting hepatoprotector activity, which is manufactured in the Russian Federation, was issued a certificate of pharmaceutical product. Remaxol® contains active ingredients with antioxidant, antihypoxant and immunomodulatory properties [3,13, 14, 22]. A pharmacoeconomic analysis of SMIMN is of particular interest for healthcare system of the Russian Federation given its multi-faceted mode of action and high efficacy confirmed in various clinical studies [7-11] by comparing it with other common hepatoprotector agents. Ademetionine included into the Vital and Essential Drugs List [20] was the main comparator agent used virtually in all studies assessing safety and efficacy of SMIMN [7-11]. Therefore, current study was aimed at performing pharmacoeconomic evaluation of SMIMN vs. ademetionine as a preventive therapy of developing ALF in patients with extensive liver resection due to colorectal cancer metastases.

Materials and Methods

During the current study, an analytical decision-making model was created by using software MS Excel that allows to perform pharmacoeconomic evaluation of ALF prevention after using SMIMN vs. ademetionine in patients with extensive liver resection due to colorectal cancer metastases.

During the current pharmacoeconomic study, an information retrieval method was applied for determining efficacy endpoints of the compared methods for prevention of liver failure by searching for a number of key words in databases Pubmed, eLibrary, Central Scientific Medical Library as well as search engines Google and Yandex: Remaksol, yantarnaya kislota, N-metilglyukamin, riboksin, metionin, nikotinamid, ademetionin, pechenochnaya nedostatochnost', rezektsiya pecheni, kolorektal'nyy rak, metastazy pecheni (all words written in Russian), Remaxol, succinic acid, N-methylglucamine, riboxinum, methionine, nicotinamide, ademetionine, liver insufficiency, hepatectomy, colorectal cancer, liver metastasis.

During the current study, only direct medical costs were calculated, which have the following pattern (Figure 4):

- Postoperative Costs:
  - Hepatoprotector therapy-related costs;
  - Concomitant therapy-related costs;
  - Stay at ICU;
  - Hospital observation.

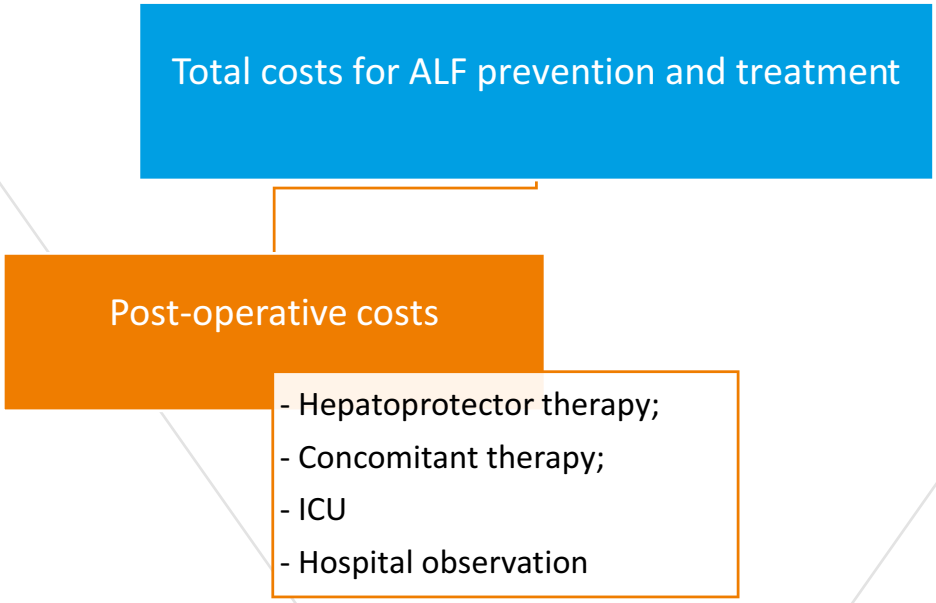

Figure 4. Pattern of costs related to ALF treatment and prevention

The following formulas were used to calculate direct costs:

Price per 1mg active ingredient contained in medicinal product (MP) used in concomitant therapy was calculated as follows:

$$Price(G) = \frac{\sum_{i=1}^{n} C/(Q \times N)}{n}, \text{ where:} \quad (1)$$

Price (G) – average price per 1mg active ingredient contained in MP, Rub;
C – Price per MP package, Rub;
Q – Amount of active ingredient contained in lyophilized form (LF) of MP, mg;
N – Amount of LF contained in MP package, pieces;
n – Amount of MP dosage forms.

Per-patient costs related to concomitant therapy:

$$Cost(G) = \sum D(G) \times D \times Price(G), \text{ where:} \quad (2)$$

Cost (G) – Per-patient costs related to MP course therapy, Rub;
D (G) – Daily MP dose, mg;
Price (G) – Price per 1mg MP, Rub;
D – Duration of course therapy, days.

Cost of hepatoprotector-containing vial was calculated as follows:

$$Price(G) = \sum_{i=1}^{n} C/(Q), \text{ where:} \quad (3)$$

Price (G) – per-MP vial average price, Rub;
C – Price per MP package, Rub;
Q – Amount of MP vials per package, pieces;

Hepatoprotector therapy-related costs were calculated as follows:

$$Cost\ (Hep) = \sum Price\ (G)*D, \text{ where:} \quad (4)$$

Cost (Hep) – Hepatoprotector therapy-related costs, Rub;
Price (G) – Price per one vial, Rub;
D – Average course dose per single administration.

Budget Impact Analysis was performed based on the number of patients with colorectal cancer. It was noted above that in the Russian Federation approx. 1,083 patients require surgical resection of liver metastases (Figure 3) [4,26], who may potentially undergo ALF prevention. No expenditure discounting was applied, as preventive measures mediated by the investigational products lasted for less than one year.

Results

Effectiveness Analysis

Current pharmacoeconomic study was based on the results from the randomized comparative clinical study performed by Khoronenko et al. [14] that assessed efficacy of SMIMN for ALF prevention during extensive hemihepatectomy due to colorectal cancer metastases. According to this, efficacy and safety of treatment were assessed by measuring major clinical and biochemical parameters of patients' peripheral blood. Liver dysfunction was assessed according to the Child-Pugh score, first time used more than 50 years ago [14]. Major feature of this classification is that it allows to predict mortality risk and complications related to liver cirrhosis [14]. Total score presented as a sum assigned in accordance to magnitude of clinical and biochemical blood parameters results in calculating degree of liver failure. Therefore, Grade A corresponds to score 5-6 (no liver failure); Grade B – score 7-9; Grade C – score 10-15. According to the Child-Pugh scale, patients with Grade C liver failure have 70% mortality risk [14].

During the study performed by Khoronenko et al., Child-Pugh scale allowed to assess degree of hepatocellular insufficiency occurred after direct liver resection due to colorectal cancer metastases. Results of clinical examination were evaluated on Day 5 and Day 12 in both comparison groups (Table 1).

A number of patients needed to treat (NNT) resulting in Grade A liver functional state according to the Child-Pugh scale was used as a primary efficacy endpoint. Thus, it may be concluded that SMIMN vs. ademetionine was more efficient in ALF prevention due to contributing to accelerated recovery of liver function.

Table 1. Results of clinical examination (Khoronenko et al.)

Effectiveness analysis	Day 5	Day 12
Child-Pugh scale (score)		
SMIMN	8	7
Heptral	11	8
NNT*		
SMIMN	1,429	1,25
Heptral	2,5	1,429

Comments: *NNT – a number of patients needed to treat (NNT) resulting in Grade A liver functional state according to the Child-Pugh scale.

Cost Analysis

Hepatoprotector Therapy-related Costs

While estimating hepatoprotector therapy-related costs, there were used the data from clinical studies, when investigational products were applied for ALF prevention after excessive liver resection as follows: SMIMN was administered 800 ml once on Day 1 after surgery, and then 400 ml twice a day for four days; and ademetionine – 800 mg once a day on Day 1, and then 400 mg once a day for four consecutive days.

Estimation of hepatoprotector therapy-related costs relied on average wholesale prices, which were calculated according to the database containing major Russian pharmaceutical distributors (fbr.info). Thus, average wholesale price per one SMIMN 400-ml vial was 362 Rub. At the same time, cost of a comparator drug ademetionine per 10-ml vial containing 400mg active ingredient was 335 Rub. By taking into consideration administration regimen it was found that for entire course (5 days) SMIMN vs. ademetionine therapy-related costs were 3,622 and 3,351 Rub, respectively (Table 2).

Table 2. Hepatoprotector therapy-related costs

INN	Unidose (ml/mg)	Number of vials per day	Number of vials per treatment	Cost of one vial, Rub	Daily expenses, Rub	Treatment expenses, Rub
SMIMN	400	2	10	362	724	3,622
Ademetionine	400	2	10	335	670	3,351

ICU Costs

According to the randomized clinical trial designed by Khoronenko et al., patients underwent liver resection were transferred to ICU for monitoring major vital signs. The data obtained revealed that length of stay at ICU was shorter in the group treated with investigational drug compared to group of ademetionine therapy, which corresponded to 1.9 and 2.6 days, respectively [14]. ICU costs for both groups were 8,360 and 11,440 Rub, respectively.

Costs of Hospital Treatment

After patients' condition was stabilized, they were transferred from ICU to a specialized department. To calculate costs of hospital treatment, a cost per bed-day was taken into account that reached 418 Rub [31]. Duration of stay at hospital also differed between both groups that was shorter for patients treated with SMIMN. In particular, patients from study group were observed for 9.1 days, whereas in control group – for 10.4 days [14]. Costs of hospital treatment were 3,807 and 4,351 Rub, respectively.

Costs of Concomitant Therapy

During the treatment, patients were administered with medicinal preparations of various groups, which should be also taken into consideration during cost analysis. Average wholesale prices for the drugs were obtained from the database enlisting major pharmaceutical distributors, whereas dosing regimen and duration of treatment were obtained from the approved directions for use of relevant drugs as well as data reported by Khoronenko et al. [14].

Similar concomitant therapy (pain relief, low-molecular-weight heparins, and laxatives) was applied in both groups. However, it should be noted that high efficacy of SMIMN on recovery of liver protein synthesis resulted in lowering use of quarantine fresh-frozen plasma (QFFP) virtually by 50% or 537ml compared to patients treated with ademetionine [14]. Thus, after performing proper re-evaluation estimating amount of QFFP consumption in both groups it was found that up to 537ml QFFP was used in treatment group, whereas in control group of patients treated with ademetionine – 1,074ml QFFP, that subsequently had an impact on total expenses (Table 3).

Table 3. Expenses related to concomitant therapy

Concomitant therapy	SMIMN, Rub	Ademetionine, Rub
A complex solution of Sodium Chloride*	29	29
Lornoxicam*	153	153
Calcitonin*	3,124	3,124
Dalteparin Sodium*	701	701
Lactulose*	362	362
QFFP**	7,572	15,143
Total	11,940	19,512

Comments: * – price information was retrieved from the database fbr.info.ru; ** – price information was retrieved from the information portal primspk.ru

The data presented demonstrate that expenses related to concomitant therapy were lower in treatment group that received SMIMN, which was accompanied with 7,572 Rub per patient cost reduction (Table 3).

After summing up all calculated expenses it was found that aggregate cost related to treatment and prevention of ALF in patients with liver resection due to colorectal cancer metastases was lower by 10,925 Rub in treatment group that received SMIMN vs. ademetionine, that determines reduction of budget funds upon administering combined hepatoprotector agent by 28.3 % (Table 4).

Table 4. Aggregate cost related to treatment and prevention of ALF in patients with extensive liver resection

Expenses	Prevention, Rub	Concomitant therapy, Rub	ICU, Rub	Hospital, Rub	Total, Rub
SMIMN	3,622	11,940	8,360	3,807	27,729
Ademetionine	3,351	19,512	11,440	4,351	38,654
Difference, Rub	-271	7,572	3,080	544	10,925
Difference, %	-8.1%	38.8%	26.9%	12.5%	28.3%

The data obtained evidence that high efficacy of the investigational drug multi-component hepatoprotector SMIMN vs. ademetionine results in budget savings related to stay at ICU, hospital as well as size of infusion-transfusion therapy (Table 4).

4. 3. Cost-effectiveness Analysis

While performing cost-effectiveness analysis, the data reported by Khoronenko et al. were used [14]. As a primary efficacy endpoint, a number of patients needed to treat (NNT) to reach a Child-Pugh Grade A liver functional state was used. To calculate cost-effectiveness ratio there were determined expenses based on duration of course therapy at time points chosen to estimate effectiveness. Thus, cost-effectiveness ratios were calculated on Day 5 and Day 12 of post-operative period (Table 5).

Table 5. Cost-effectiveness analysis

Groups	NNT, Day 5	NNT, Day 12	CER (NNT, Day 5)	CER (NNT, Day 12)
SMIMN	1.429	1.25	39,624	34,661
Ademetionine	2.5	1.429	96,634	55,236

It was demonstrated that use of SMIMN vs. ademetionine was accompanied with low value of cost-effectiveness ratios (Table 5), and that in order to reach a Child-Pugh Grade A liver functional state it costed 39,624 and 34,661 Rub for patients treated with SMIMN. At the same time, given that SMIMN was more efficient than ademetionine its use predominates in ALF prevention.

Budget Impact Analysis

During Budget Impact Analysis, it was found that treatment expenses were lower for SMIMN vs. ademetionine comprising 30,030,140 Rub per 1,083 patients (Table 6).

Table 6. Budget Impact Analysis for treatment of 1,083 patients

Groups	Prevention, Rub	Concomitant therapy, Rub	ICU, Rub	Hospital, Rub	Total, Rub
SMIMN	3,922,201	12,930,897	9,053,880	4,123,162	30,030,140
Ademetionine	3,629,248	21,131,048	12,389,520	4,712,185	41,862,001
Difference, Rub	-292,954	8,200,151	3,335,640	589,023	11,831,861
Difference, %	-8.1%	38.8%	26.9%	12.5%	28.3%

It was found that use of SMIMN vs. ademetionine results in budget savings up to 11,831,861 Rub for treatment of 1,083 patients with liver resection due to colorectal cancer metastases (Table 6). It should be noted that budget savings associated with SMIMN treatment are directly due to higher efficacy regarding recovery of liver functions, which is accompanied by shortened stay at ICU and hospital as well as decreased amount of required QFFP (Figure 5).

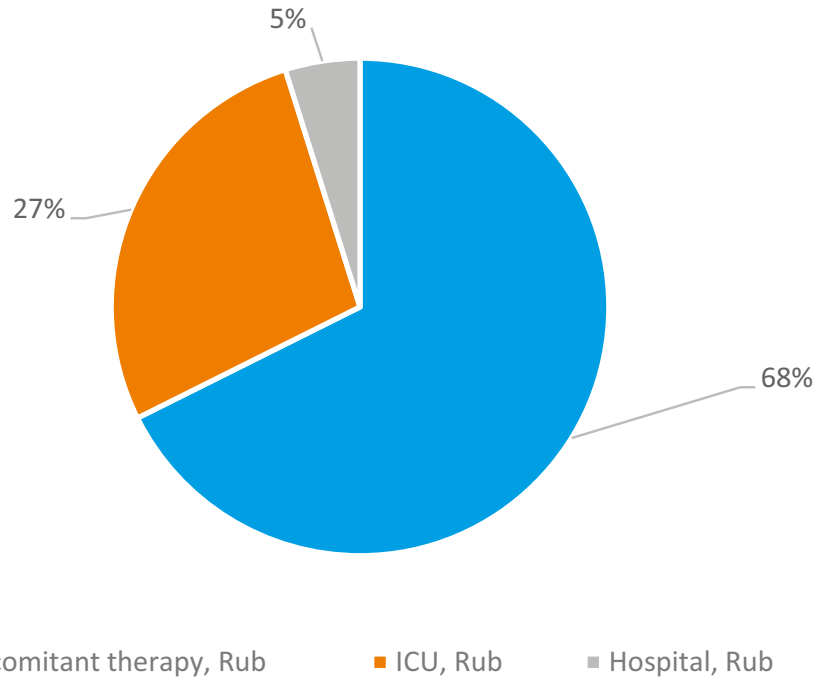

Figure 5. Costs distribution for budget saving measures associated with administration of SMIMN vs. Ademetionine

It was demonstrated that concomitant therapy, particularly use of QFFP, accounted for up to 68% of total budget savings, and it was the most prominent expenditure item resulting in budget savings (Figure 5). By shortening stay at ICU it comprises up to 27%, whereas stay at hospital – up to 5 % total budget savings.

Analysis of lost opportunities was conducted to determine directions for rational use of the obtained budget savings. It was found that by switching from ademetionine-to-SMIMN-therapy within a fixed budget it allows to additionally treat up to 427 patients.

4.5. Sensitivity Analysis

A Univariate Sensitivity Analysis was performed to determine sustainability of the obtained results. The following variable parameters were calculated: hepatoprotector therapy-related cost, cost of QFFP, size of QFFP consumption in both groups as well as duration and cost of stay at ICU and hospital (Table 7). A 30%-uncertainty level was set for cost parameters, whereas limit values with regard to standard deviation that was reported by Khoronenko et al. [14] were applied for length of stay at ICU and hospital.

Table 7. Maximum and minimum values of parameters used for Sensitivity Analysis

No.	Parameter	Lower limit	Higher limit
1	Price of SMIMN	253.5	470.8
2	Price of Ademetionine	1,172.9	2,178.2
3	Price of QFFP	9,870	18,330
4	Volume of QFFP in SMIMN group	376	698.1
5	Volume of QFFP in Ademetionine group	752	1,396.2
6	Days at ICU (SMIMN)	1.2	2.6
7	Days at ICU (Ademetionine)	1.5	3.7
8	Cost of ICU per day	3,080	5,720
9	Days at hospital (SMIMN)	8.6	9.6
10	Days at hospital (Ademetionine)	9.9	10.9
11	Bed-day cost	292.9	543.9

The results of Sensitivity Analysis were assessed in terms of budget savings, which at deterministic value of all parameters reached 11,831,861 Rub. When each separate parameter was changed to lower or higher limit, a corresponding budget savings due to SMIMN was obtained (Table 8).

Table 8. Impact of changed parameters on budget savings due to SMIMN

No.	Variable parameter	Lower limit	Higher limit	Difference
1	Days at ICU (Ademetionine)	6,590,141	17,073,581	10,483,440
2	Volume of QFFP in Ademetionine group	6,911,770	16,751,951	9,840,181
3	Days at ICU (SMIMN)	15,167,501	8,496,221	6,671,280
4	Price of SMIMN	15,754,062	10,655,200	5,098,862
5	Price of QFFP	9,371,815	14,291,906	4,920,091
6	Volume of QFFP in SMIMN group	14,291,906	9,371,815	4,920,091
7	Price of Ademetionine	10,743,086	12,920,635	2,177,549
8	One-day ICU cost	10,831,169	12,832,553	2,001,384
9	Days at hospital (Ademetionine)	11,424,075	12,239,646	815,570
10	Days at hospital (SMIMN)	12,058,408	11,605,313	453,095
11	Bed-day cost	11,655,154	12,008,568	353,414

A tornado diagram depicting expenditure items most pronouncedly influencing eventual outcome (shown at the top) was drawn, according to the data obtained (Figure 6).

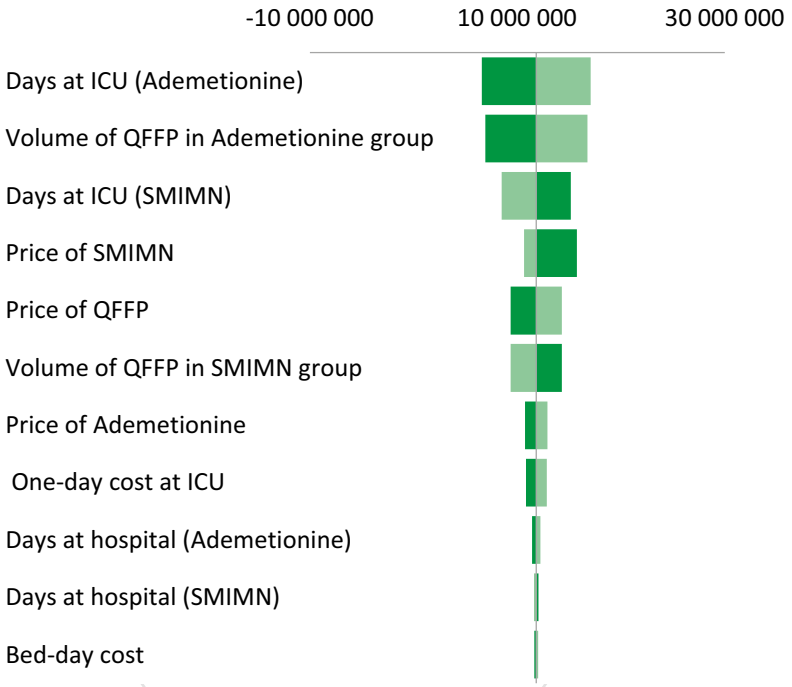

Figure 6. A tornado diagram

Thus, according to the data obtained after performing Sensitivity Analysis, it may be concluded that several parameters exhibited the strongest impact on study result: number of days at ICU, size of QFFP consumption in ademetionine group, length of stay at hospital, and price for QFFP and SMIMN. At the same time, it was demonstrated that by altering these parameters it did not affect sustainability of study results, and therapy by SMIMN was the most preferable method for ALF prevention in patients with liver resection due to colorectal cancer metastases.

Conclusions

1. Effectiveness analysis showed that ALF prevention with SMIMN vs. Ademetionine was more efficient based on value of NNT parameter required to reach Child-Pugh Grade A liver functional state.

2. Cost analysis revealed that use of SMIMN results in budget savings up to 10,925 Rub per patient and budget reduction related to treatment and prevention in these patients by 28.3 %.

3. Cost-effectiveness analysis demonstrated lower magnitude of cost-effectiveness ratios in SMIMN group, which together with its higher efficacy favors conclusion that use of SMIMN is a dominant method for ALF prevention due to extensive liver resection.

4. Budget Impact Analysis revealed that a course therapy by SMIMN vs. ademetionine budget savings reached 11,831,861 Rub per 1,083 patients. Analysis of lost opportunities demonstrated budget savings, which resulted from using SMIMN vs. ademetionine therapy in 1,083 patients that allowed additionally to treat up to 427 patients within a fixed budget.

5. A univariate Sensitivity Analysis demonstrated sustainability of the obtained results.

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