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POLYPHARMACY, THERAPEUTIC INERTIA, AND ADHERENCE OF HEART RECIPIENTS TO DRUG THERAPY

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Heart transplantation remains the gold standard treatment for end-stage heart failure. Lifelong immunosuppressive and adjuvant therapy requires constant medical follow-up in order to optimize treatment regimens and increase the adherence of heart recipients to treatment. **Objective:** to study and adapt a method for systematic assessment of the complexity of treatment regimen using the MRCI index, and its link to long-term prognosis in heart recipients. **Materials and methods.** Results of the study were obtained by analyzing the data of heart recipients observed at the Consultative & Diagnostic Department, Shumakov National Medical Research Center of Transplantology and Artificial Organs (Shumakov Center). The Medication Regimen Complexity Index (MRCI) was used to assess drug therapy. In our study, polypharmacy was defined as taking five or more medications, and high-risk polypharmacy was defined as the use of more than eight medications. The heart recipients were divided into two groups based on how many medications they received daily. **Results.** The study included patients observed at the Consultative & Diagnostic Department, Shumakov Center from January 2008 to December 2017. The number of drugs taken by the patient at year 5 of follow-up was 9.2 ± 4.2. During the conducted data analysis, the mean total MRCI score was 48.72 ± 19.15 (from 32 to 70); medications used to treat comorbidities accounted for 42.9% of the total MRCI score, and immunosuppressive therapy accounted for 28.7%. The total MRCI score in the high-risk polypharmacy group was 58.49 ± 17.41; medications used to treat comorbidities accounted for 50.27% of the total MRCI score. The analysis revealed a correlation between the total MRCI score and the frequency of hospitalizations. **Conclusions.** Patient adherence to prescribed treatment is a predictor of favorable prognosis of event-free long-term survival, but low adherence and therapeutic inertness are associated with decreased quality of life, more frequent hospitalizations and higher risk of adverse events. With proper outpatient follow-up of this patient cohort, there were no significant differences in survival in the polypharmacy and high-risk polypharmacy group.

Keywords: heart transplantation, polypharmacy, comorbidity, immunosuppressive therapy, outpatient follow-up.

INTRODUCTION

In the past decade, the number of heart transplant (HT) recipients requiring dynamic outpatient follow-up has increased, driven by the rise in transplant activity. This follow-up is essential to monitor immunosuppressive therapy, assess graft function, address complications from long-term immunosuppressant use, and manage and prevent concomitant conditions [1].

Currently, the consultative and diagnostic department at the Shumakov National Medical Research Center of Transplantology and Artificial Organs (Shumakov Center) oversees more than 1500 HT recipients from various regions across the Russian Federation [2]. With the extensive experience and personalized care approach developed, long-term survival rates have significantly improved, now exceeding an average of 12 years [3].

Managing HT recipients involves lifelong immunosuppressive therapy combined with medications to prevent the side effects of long-term immunosuppression, as well as adjuvant therapies for treating concomitant conditions [4]. The long-term follow-up of HT recipients is influenced by factors such as interaction between the transplanted organ and the recipient, quality of immunosuppressive therapy and its side effects, and external factors, as well as the patient's genotype and cognitive abilities [5]. In this regard, evaluating both the adequacy of prescriptions and the patient's adherence to medication becomes crucial.

The term "medication regimen complexity" refers to the multiple characteristics of a patient's prescribed medication regimen [6]. Studies have shown that noncompliance with immunosuppressive therapy among HT recipients is as high as 19%, with medication administ-

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ration errors for adjuvant therapy exceeding 43%. These issues are primarily due to the need for daily administration of a large number of medications [7].

A quantitative assessment of medication regimen complexity can be performed using the Medication Regimen Complexity Index (MRCI), based on a specific patient's treatment plan. According to several studies, the MRCI has shown potential as an effective tool for preventing adverse events in HT recipients experiencing polypharmacy [8–10].

The **objective of our study** was to investigate and adapt a systematic approach for assessing treatment regimen complexity using the MRCI, and to explore its relationship with long-term outcomes in HT recipients.

MATERIALS AND METHODS

The results of the study were based on analysis of outcomes in HT recipients under follow-up care at the Shumakov National Medical Research Center of Transplantology and Artificial Organs (Shumakov Center). Outpatient monitoring was conducted by cardiologists from Shumakov Center's consultative and diagnostic department in collaboration with healthcare providers in the patients' place of residence. When necessary, remote consultations were organized through the Shumakov Center's telemedicine system to provide support to local physicians. Adjustments to drug therapy were made on an outpatient basis based on clinical and instrumental examination data. In cases where hospitalization was warranted, patients were admitted to the cardiology ward of Shumakov Center.

All patients underwent routine follow-up examinations, which included clinical evaluations, complete blood counts, biochemical assays, monitoring of blood levels of immunosuppressive drugs, echocardiography, as well as annual coronary angiography and endomyocardial biopsy.

Socio-demographic data – including region of residence, living conditions, marital status, and educational level – along with case histories and outpatient records from patients followed at Shumakov Center, were collected retrospectively. Recipients included in this study were treated in accordance with established clinical guidelines [11].

An adapted and modified version of MRCI was used in this study. To calculate the index, medications prescribed to HT recipients were categorized into three primary groups (Table 1).

Non-pharmacological supplements and herbal preparations were excluded from the analysis and were not recommended for patient use.

All patients received multicomponent immunosuppressive therapy, which typically included a calcineurin inhibitor (tacrolimus) in combination with an antimetabolite (mycophenolic acid or mycophenolate mofetil) or a proliferation signal inhibitor (everolimus), as well as methylprednisolone. The dosage of immunosuppressive drugs was based on the post-transplant period and the assessed risk of graft rejection.

Therapeutic drug monitoring was conducted to maintain target serum levels of immunosuppressive medications. The levels were measured using a Cobas e411 analyzer (Roche, Switzerland) via electrochemiluminescence immunoassay.

According to the literature, polypharmacy is defined as the concurrent use of five or more medications, while high-risk polypharmacy refers to the intake of more than eight medications [12]. Based on the number of medications received daily, HT recipients were divided into two groups: Group 1 included patients receiving 5 to 8 medications per day, and Group 2 included recipients taking 9 or more medications daily [13].

Patients were classified as comorbid if they had two or more coexisting medical conditions, irrespective of their primary diagnosis (ICD-10 code Z94.1, denoting heart transplant status).

MRCI was calculated for all medications self-administered by the patient or taken once daily. The MRCI score represents the cumulative total of points derived from three components evaluated for each individual medication: dosage form, frequency of administration, and any information about the drug. Table 2 summarizes the scoring criteria used to determine the total MRCI score [6].

Table 1

Groups of medications used in recipients after heart transplantation

Group 1 Immunosuppressive drugs	Group 2 Additional drugs (prevention of complications of immunosuppressive therapy)	Group 3 Drugs for the treatment of comorbidities
Cyclosporine/Tacrolimus Everolimus Methylprednisolone Mycophenolate mofetil/ Mycophenolic acid	Calcium/Vitamin D Statins Acetylsalicylic acid Antibacterials Antivirals Antacids Proton pump inhibitors Osteoporosis medications	Antidepressants Antihypertensive drugs Antiarrhythmic drugs Diabetes mellitus medications (oral) Anticoagulants Diuretics Others.

Table 2

MRCI sections

Section A: Dosage form and drug administration route

Administration route	Dosage forms	Score
Oral	Capsules/tablets	1
	Mouthwashes	2
	Chewable lozenges	2
	Powders/pellets	2
	Suspensions	
	Sublingual sprays/tablets	2
Local use products	Cream/gel/ointment	2
	Solutions	2
	Medicated dressings	2
	Medicated pastes	3
	Plasters	2
	Sprays	1
Eye, nose and ear products	Ear drops/creams/ointments	3
	Eye drops	3
	Eye gels/ointments	3
	Nasal sprays	2
	Nasal drops/creams/ointments	3

Administration route	Dosage forms	Score
Inhalation use	Metered-dose inhalers	4
	Nebulizer	5
	Turbuhalers	3
	Accuhalers	3
	Aerosols	3
	Oxygen concentrator	3
	Dry powder inhaler	3
Others	Enemas	2
	Ampoules/vials	4
	Gizzards	3
	Suppositories	2
	Injectable dosage forms	3
	Vaginal creams	2
	Dialysate	5
	Different types of analgesia administered by the patient alone (patient-controlled analgesia)	2

Section B: Dosing frequency

Dosing frequency	Score
Once a day	1
Once a day if required	0.5
Twice a day	2
Twice a day if required	1
Three times a day	3
Three times a day if needed	1.5
Four times a day	4
Four times a day if needed	2
Every 12 hours	2.5
Every 12 hours as needed	1.5
Every 8 hours	3.5

Dosing frequency	Score
Every 8 hours as needed	2
Every 6 hours	4.5
Every 6 hours as needed	2.5
Every 4 hours	6.5
Every 4 hours as needed	3.5
Every 2 hours	12.5
Every 2 hours as needed	6.5
Use of medications as needed	0.5
Use of oxygen concentrator as needed	1
Oxygen use <15 hours per day	2
Oxygen use >15 hours per day	3

Section C: Additional directions

Additional administration directions	Score
Crush	1
Dissolve tablet/powder	1
Administer multiple tablets/inhalations simultaneously	1
Administer within a specified time interval	1

Additional administration directions	Score
Take with food	1
Take with liquids to wash down	1
Take as directed	2
Reduce/increase dose	2
Alternate dose depending on the time of day	2

The minimum possible MRCI score for a patient is 1.5, which corresponds to a single tablet or capsule taken once daily as needed. The maximum MRCI score varies and is individually determined based on the patient's specific medication regimen.

Descriptive statistics are presented as arithmetic mean ± standard deviation (M ± SD). Kaplan–Meier survival analysis was employed to assess event-free survival, with statistical computations performed using IBM SPSS Statistics v23. Comparative analysis between groups was conducted using the log-rank test, Mann–Whitney U test, median test, Kruskal–Wallis test, Kolmogorov–Smirnov test, and Jonckheere–Terpstra test. For all statistical tests, results were considered significant at $p < 0.05$.

RESULTS

Between January 2008 and December 2017, a total of 771 HTs were performed at Shumakov Center. The study excluded cases involving retransplantation, in-

hospital mortality, and recipients under 18 years of age. So, 607 adult HT recipients under outpatient follow-up at Shumakov Center were included in the final analysis.

At the time of the study, recipient mean age was 47.84 ± 11.83 years. The mean follow-up period post-transplant was 8.2 ± 2.8 years, with a range from 2 to 15 years (Table 3).

The distribution of medications taken by HT recipients at different follow-up periods is presented in Table 4.

As shown in Table 4, by the end of the first year of follow-up, the average total number of medications taken by HT recipients had decreased slightly compared to the number prescribed at hospital discharge – 6.8 ± 4.2 versus 8.9 ± 2.7, respectively. However, by year 5 of follow-up, this value had increased to 9.2 ± 4.2 ($p < 0.05$).

When analyzing the average number of medications by drug group, it was observed that in Group 1, the number of immunosuppressive agents used decreased by year 5 ($p = 0.02$).

There was no statistically significant increase in the number of group 2 medications used during the follow-up period of 1 to 5 years ($p = 0.42$). However, a significant increase in the use of group 3 medications was observed by year 5 ($p = 0.001$). The average number of drugs prescribed for the management of comorbid conditions increased from 1.2 ± 1.3 at the end of year 3 to 4.3 ± 2.5 by year 5 of follow-up.

In assessing multicomponent therapy, MRCI was calculated for all recipients included in the study (Table 5).

The mean total MRCI score among the HT recipients was 48.72 ± 19.15, with individual scores ranging from 32 to 70. Medications prescribed for the management of comorbidities accounted for 42.9% of the total MRCI score, while immunosuppressive therapy contributed 28.7%.

To evaluate the prevalence of polypharmacy and high-risk polypharmacy, recipients were stratified into two groups based on the number of self-administered and single-use medications, and the groups were compared as presented in Table 6.

In the high-risk polypharmacy group, there was a significantly higher prevalence of arterial hypertension, diabetes mellitus, lipid metabolism disorders, and varying degrees of obesity compared to the lower-risk group ($p < 0.05$, Fig. 1).

To evaluate the treatment regimen complexity, the MRCI score was calculated for both groups. In the high-risk polypharmacy group, the mean total MRCI score was 58.49 ± 17.41, with 50.27% of the total complexity attributed to medications prescribed for the management of comorbid conditions.

A comparative analysis of recipient hospitalization rates based on the total MRCI score was also conducted (Fig. 2).

Table 3

General characteristics of recipients (n = 607)

Indicators	Values
Age, years	47.84 ± 11.83
Men, n (%)	526 (86.66%)
Women, n (%)	81 (13.34 %)
BMI, kg/m^2	26.87 ± 4.78
Pre-transplant diagnosis	
ICM , n (%)	237 (39.04%)
DCM, n (%)	334 (55.02%)
HCM, n (%)	7 (1.15%)
Others, n (%)	29 (4.77%)
Pre-transplant UNOS status	
1A, n (%)	150 (2.47%)
1B, n (%)	214 (35.26%)
2, n (%)	243 (40.03%)
Donor details	
Age, years	42.25 ± 11.6
Male, n (%)	470 (77.43%)
Female, n (%)	137 (22.57%)

Note: BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

Table 4

Number of medications taken by recipients after heart transplantation at different follow-up periods

Value	At the time of discharge after HT (n = 607)	At year 1 post-HT (n = 604)	At year 3 post-HT (n = 595)	At year 5 post-HT (n = 571)
Total number of drugs	8.9 ± 2.7	6.8 ± 4.2	8.8 ± 4.3	9.2 ± 4.2
Group 1 drugs	2.9 ± 0.2	2.5 ± 0.4	2.1 ± 0.2	2.1 ± 0.3
Group 2 drugs	4.8 ± 1.2	3.0 ± 1.3	2.7 ± 1.6	2.8 ± 1.4
Group 3 drugs	1.2 ± 1.3	1.3 ± 2.5	4.0 ± 2.5	4.3 ± 2.5

Table 5

MRCI score of the three drug groups for all recipients included in the study (n = 607)

Drug group	Value
Drug group 1	14.02 ± 2.51
Drug group 2	13.76 ± 4.58
Drug group 3	20.93 ± 10.42

Table 6

General characteristics of recipients, depending on administration of medication

Indicator	Group 1 (use of 5 to 8 drugs), n = 312	Group 2 (use of ≥9 drugs), n = 295	P
Age, years	46.09 ± 12.31	49.68 ± 10.99	0.02
Male, n (%)	270 (86.54%)	256 (86.78%)	0.93
Female, n (%)	42 (13.46%)	39 (13.22%)	
BMI, kg/m²	**23.07 ± 4.51**	**28.12 ± 4.93**	**0.027**
Level of education			
Secondary general education	37 (11.86%)	31 (10.51%)	0.82
Secondary vocational education	143 (45.83%)	145 (49.15%)	
Higher education	132 (42.31%)	119 (40.34%)	
Pre-transplant diagnosis			
ICM, n (%)	103 (33.01%)	134 (45.42%)	0.69
DCM, n (%)	186 (59.62%)	148 (50.17%)	
HCM, n (%)	3 (0.96%)	4 (1.36%)	
Others, n (%)	20 (6.41%)	9 (3.05%)	
Co-existing diseases			
Diabetes mellitus	**57 (18.2%)**	**102 (34.5%)**	**0.002**
Other endocrinological diseases (except diabetes mellitus)	132 (42.3%)	188 (63.7%)	0.415
Cerebrovascular diseases	119 (38.1%)	118 (40.0%)	0.639
Lung diseases	62 (19.8%)	58 (19.6%)	0.948
Gastrointestinal diseases	254 (81.4%)	286 (96.9%)	0.936
Dyslipidemia	**205 (65.7%)**	**265 (89.9%)**	**0.001**
Osteoporosis	113 (36.2%)	197 (66.7%)	0.174
Gout	60 (19.2%)	107 (36.2%)	0.172
Arterial hypertension	**239 (76.6%)**	**274 (92.8%)**	**0.039**
Rheumatic diseases	18 (5.7%)	25 (8.4%)	0.194
Kidney diseases	207 (66.3%)	255 (86.4%)	0.640
Total MRCI score			
Drug group 1	15.2 ± 4.98	13.71 ± 2.05	
Drug group 2	12.48 ± 3.16	15.38 ± 5.42	
Drug group 3	11.45 ± 5.48	29.4 ± 9.94	
Total MRCI score	39.13 ± 13.62	58.49 ± 17.41	

Note: BMI, body mass index; ICM, ischemic cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy.

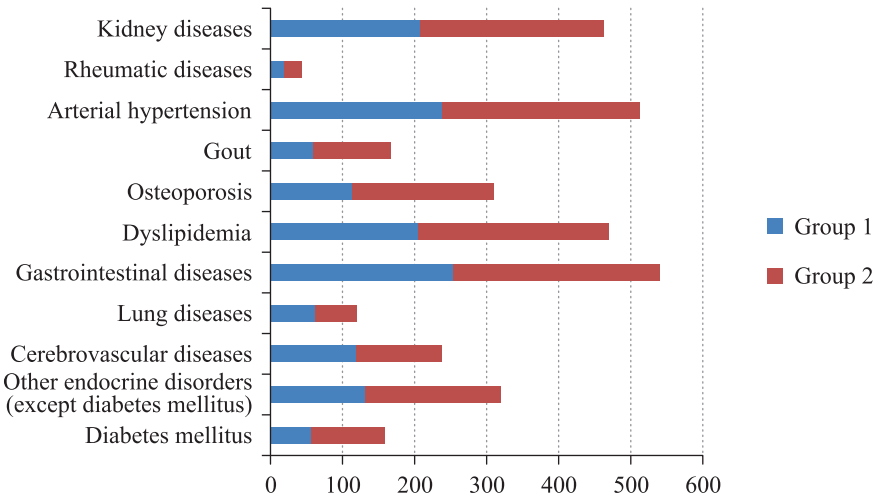

Fig. 1. Concomitant diseases of recipients depending on the number of drugs used

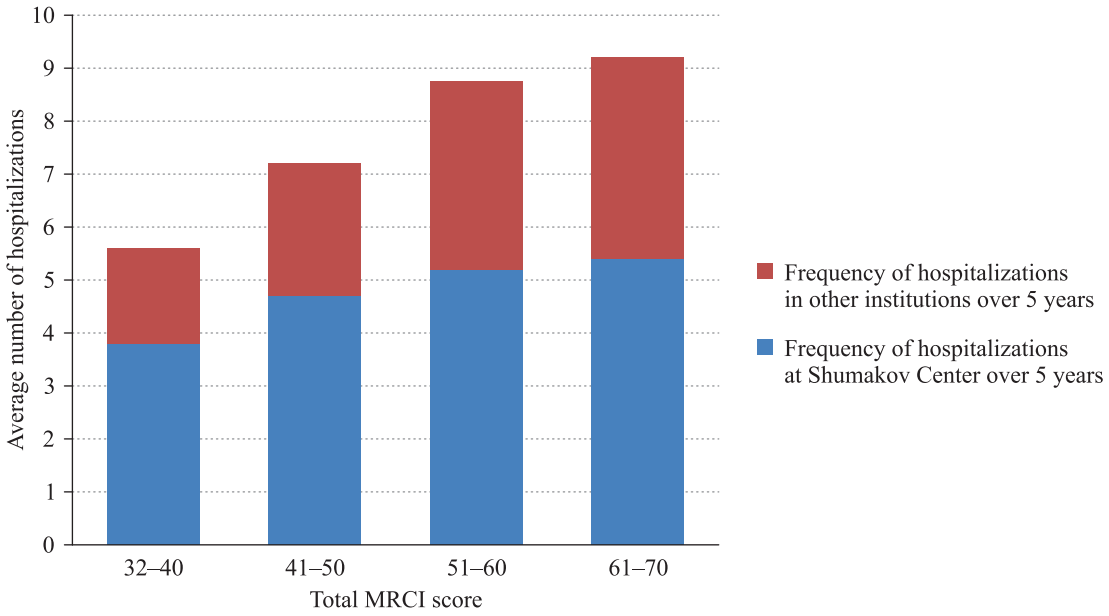

Fig. 2. Frequency of hospitalization of recipients depending on the total MRCI score

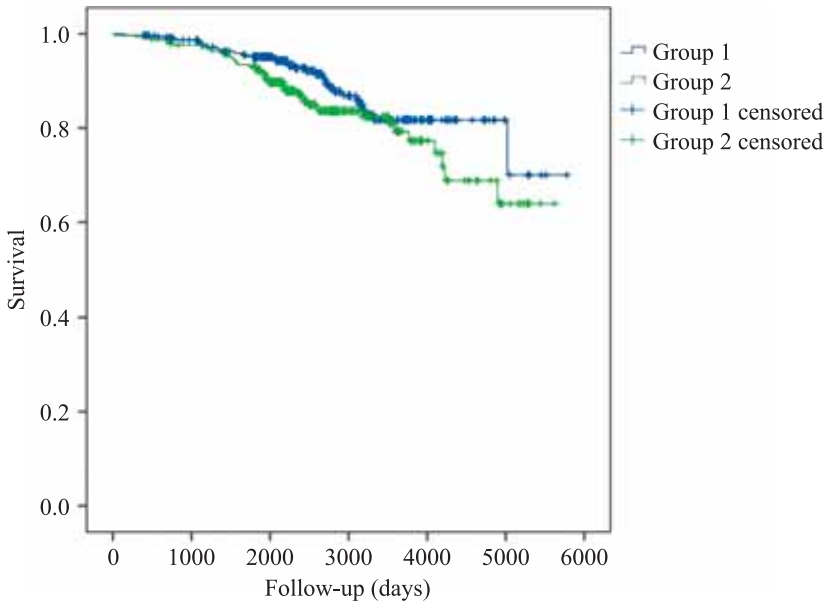

Fig. 3. Survival curves of recipients depending on the number of drugs used

The analysis demonstrated a significant correlation between total MRCI score and hospitalization rate. Patients classified under high-risk polypharmacy required inpatient treatment more frequently, both at Shumakov Center and in other medical facilities ($p < 0.05$).

Despite the observed difference in hospitalization rates, comparative survival analysis using Kaplan–Meier curves revealed no statistically significant difference in overall survival between recipients with polypharmacy and those with high-risk polypharmacy (Fig. 3).

DISCUSSION

The results of this study demonstrated that in the long-term post-HT period, recipients received an average of 5 to 15 medications. The MRCI score showed a clear correlation with the number of comorbidities and the presence of complications associated with immunosuppressive therapy, thereby linking MRCI to hospitalization rate. This is the first study to evaluate the impact of MRCI on long-term follow-up outcomes in HT recipients. To date, only a limited number of international studies have addressed the application of MRCI in this specific patient population. Our findings may become the basis for future research on this topic.

On average, each recipient was diagnosed with four comorbidities (requiring 5 to 15 medications) in the post-transplant period, each necessitating ongoing pharmacologic management. The presence of multiple comorbidi-

ties, coupled with lifelong immunosuppressive therapy, constitutes a significant risk factor for polypharmacy [12]. As the number of comorbid conditions increases, the demand for a broader scope of pharmacotherapy rises.

This study quantitatively analyzed drug therapy in HT recipients using the MRCI score. In a Spanish study, the reported average MRCI score was 42 [14], whereas in our cohort the mean score was 49. This difference may be attributed to a more detailed comparative analysis of the therapeutic components, particularly the contribution of immunosuppressive therapy and medications used to manage comorbid conditions.

When evaluating MRCI components, notably high scores were associated with the frequency of taking medications and additional instructions across the three main drug groups. These findings emphasize the necessity of a deeper examination of therapeutic regimens in HT recipients, particularly to enhance adherence to therapy.

When compared with MRCI scores in non-transplanted populations, the treatment burden in HT recipients is significantly higher. For instance, in a study conducted by Suzanne et al. [9], patients with mental illness undergoing long-term pharmacotherapy exhibited MRCI scores ranging from 6.21 to 25, considerably lower than those observed in our HT cohort.

Kamila et al. [15] also reported elevated MRCI scores in recipients following liver and kidney transplantation. Their study highlighted that MRCI not only quantifies pharmacologic load but also serves as a valuable analytical tool for evaluating the appropriateness and complexity of prescribed regimens in liver and kidney transplant recipients.

In our study, recipients classified within the high-risk polypharmacy group were notably older and had a greater burden of comorbidities, which accounted for the increased MRCI scores, particularly due to the use of medications aimed at managing comorbid conditions. In this group, no significant differences in survival outcomes were observed when compared to recipients with lower MRCI scores. This finding underscores the personalized approach employed by the multidisciplinary team at Shumakov Center, as well as the strong adherence of HT recipients to their therapeutic regimens.

Our results are consistent with those of Colavecchia et al. [16], who demonstrated a positive correlation between higher MRCI scores and increased hospitalization rates across various clinical scenarios. Similarly, our analysis showed that recipients with elevated MRCI scores had higher rates of inpatient treatment.

Evaluating the prescribed drug therapy through calculation of the MRCI score offers physicians an additional tool to identify patients who require more intensive monitoring during prescription and therapy adjustment. This approach can help reduce the risk of complications associated with multi-drug treatment regimens. Given that HT recipients must take a large number of life-saving drugs, cardiologists at the consultative and diagnostic department of Shumakov Center should prioritize regular assessment of pharmacotherapy in order to enhance adherence and minimize complications.

CONCLUSIONS

HT recipients in the long-term postoperative period are required to take a broad spectrum of medications, including immunosuppressive and adjuvant therapies. Consequently, it is essential for specialists overseeing these patients to closely monitor pharmacotherapy in order to evaluate potential drug interactions and promote adherence to prescribed regimens. Regular revision of dosages and treatment plans by the attending physician serves as a predictor of favorable long-term, event-free survival. In contrast, low adherence and therapeutic inertia are associated with reduced quality of life, increased hospitalization rates, and a higher risk of adverse events. Importantly, our study showed that with proper outpatient follow-up, there were no significant differences in survival between patients with polypharmacy and those with high-risk polypharmacy.

The authors declare no conflict of interest.

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