ISSN 2306-5559 (print)
ISSN 2410-938X (online)

www.vhk.kz

№2 (83) 2025

BULLETIN OF SURGERY IN KAZAKHSTAN

АЛМАТЫ /ALMATY

№1 (82) 2025
Издается с 2005 г.
ISSN 2306-5559 (print)
ISSN 2410-938X (online)

ҚАЗАҚСТАН ХИРУРГИЯ ХАБАРШЫСЫ
ВЕСТНИК ХИРУРГИИ КАЗАХСТАНА
BULLETIN OF SURGERY IN KAZAKHSTAN

әр тоқсанда шығып тұратын А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығының ғылыми-тәжірибелік журналы
ежеквартальный научно-практический журнал Национального научного центра хирургии им. А.Н. Сызганова
a quarterly scientific-practical journal of the«Syzganov National Scientific Center of Surgery»

Журнал ҚР ақпарат, мәдениет және спорт Министрлігінде тіркелген.
Журнал ҚР ҒБМ Ғылым және білім саласындағы бақылау комитеті ұсынған Ғылыми еңбектің негізгі нәтижелерін жариялау үшін ұсынатын ғылыми баспалар тізбесі енгізілген.
Тіркеу нөмірі 5564-Ж.
Журналдың иесі – «А.Н. Сызғанов атындағы Ұлттық ғылыми хирургия орталығы» АҚ.
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«Старков С.А.» ЖК
Көкшетау қ., Әуелбеков к., 98

Тапсырыс №634
Таралымы - 500 дана

ҚАЗПОЧТА жазылу индексі – 75327

Журнал зарегистрирован в Министерстве информации, культуры и спорта РК.
Журнал включен в перечень научных изданий, рекомендуемых Комитетом по контролю в сфере образования и науки МОН РК
Регистрационный номер: 5564-Ж.
Владелец журнала – АО «Национальный научный центр хирургии имени А.Н. Сызганова».
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Заказ 634
Тираж - 500 экз.

Подписной индекс КАЗПОЧТЫ – 75327

The journal is registered with the Ministry of Information, Culture and Sports of the Republic of Kazakhstan.
The journal is included in the list of scientific publications recommended by the Committee for Control of Education and Science, Ministry of Education and Science of Kazakhstan.
Registration number: 5564-Ж
The owner of the journal – «Syzganov National Scientific Center of Surgery» JSC
Editorial address:
62, Zheltoksan street, Almaty, 050004
tel. +7 (727) 2795306
http://vhk.kz, e-mail: dr.gismailova@gmail.com
Design and lead out:
«Starkov S.A.» SP
98 Auelbekov street, Kokshetau

Order №634
Edition - 500 copies

Subscript index of KAZPOST – 75327

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SURGERY

RESULTS OF THE ANALYSIS OF THE EFFICACY AND SAFETY OF LONG-TERM ANTICOAGULANT THERAPY IN KAZAKH NATIONALITY PATIENTS AFTER OPEN HEART VALVE SURGERY

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DOI: 10.35805/BSK2025II004
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recieved: 22.05.2025
accepted: 09.06.2025

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Conflict of interest:
The authors declare no potential conflict of interest requiring disclosure in this article.

Keywords:
open heart surgery, mechanical prosthesis, warfarin complications, pharmacogenetics.

Abstract

Background. Surgical replacement of heart valves with mechanical prostheses is a life-saving procedure for patients with valvular defects. Postoperative success depends heavily on the efficacy and safety of anticoagulant therapy. Warfarin remains the primary drug to prevent thrombotic complications in such patients. Despite its efficacy, warfarin requires individualized dosing, long-term monitoring, and careful bleeding risk assessment. It is a leading cause of serious adverse drug reactions, accounting for up to one-third of related hospitalizations and deaths. A pharmacogenetic approach is increasingly important in optimizing warfarin therapy. Gene polymorphisms affect warfarin metabolism and sensitivity, making the study of these factors particularly relevant in underrepresented populations, such as patients of Kazakh nationality. However, there is limited data on warfarin response in this group.

Materials and Methods. This is the first study of its kind among Kazakh patients. It includes 310 individuals who underwent mechanical heart valve replacement and received warfarin therapy between 2015 and 2020. The aim was to evaluate the association between genotype, warfarin dose, and complication rates.

Results. Patients showed variable coagulation responses, with INR fluctuations and both hemorrhagic and thrombotic complications documented. Risk factors for adverse outcomes were identified, underscoring the importance of individualized dosing and close monitoring.

Conclusions. This study highlights the need for genotype-based dose adjustment to improve the safety and effectiveness of warfarin therapy in Kazakh patients after mechanical valve replacement.

Introduction

Warfarin is a widely used anticoagulant that requires individualized dosing due to significant interindividual variability in metabolism and the risk of complications. Genetic factors influence sensitivity to warfarin and predisposition to hemorrhagic and thrombotic events. Warfarin is a leading cause of severe adverse drug reactions and is responsible for up to one-third of adverse drug reaction-related emergency hospitalizations and fatalities.[1] Patients require lower doses of warfarin to achieve a therapeutic level of anticoagulation, measured as an international normalized ratio (INR) of prothrombin time in the range of 2–3.[2] Many studies are criticized for their small

sample sizes, limited follow-up periods, and the use of surrogate endpoints (such as anticoagulation-related parameters) instead of clinically significant outcomes like bleeding or thrombosis.[3]

Therefore, we decided to analyze our results in two leading centers. In populations of different ethnic backgrounds, the response to warfarin may vary. However, to date, no analysis of the clinical efficacy and safety of warfarin have been conducted specifically among individuals of Kazakh nationality. This study focuses on evaluating the clinical experience of warfarin use in this population. A second phase of the research will involve investigating the genetic characteristics of the Kazakh population. Few studies have investigated the impact of the variant alleles on the incidence of clinical events, and most of them have been unpowered to show significant differences. It has been shown that the incidence of hemorrhagic events is higher among genetically sensitive individuals with the risk for major hemorrhages increasing up to 2–5 fold.[4] However, not all the studies have confirmed these associations.[5] The risk and prevalence of bleeding depend on the allele variant.[6] Although the data obtained from nationwide registries have been validated and recognized as high-quality, in this study the use of registry data did not pose limitations in assessing warfarin exposure and identifying outcomes.[7]

This is a retrospective, non-randomized study that includes all patients who have undergone valve replacement with a mechanical prosthesis. The findings of this study are expected to contribute to the development of more accurate, personalized anticoagulant therapy guidelines, thereby improving both the safety and efficacy of treatment.

Materials and Methods

This study included 310 patients of Kazakh nationality who received warfarin therapy following open-heart surgery with mechanical valve replacement between 2015 and 2020. The evaluation covered anthropometric data, the traditional Kazakh tribal classification ("Zhuz" and "Ru"), disease etiology, comorbid conditions, coagulation profile indicators (preoperative, postoperative, INR achievement, and at 6 months), and the frequency of complications.

A subgroup of patients with complications (n = 44) was further divided into those with minor and major complications. Due to the high thrombogenicity of mechanical heart valve prostheses, lifelong anticoagulant therapy with warfarin is required. In addition to the total duration of therapy, the quality of warfarin treatment can be assessed by measuring INR variability.

The main criteria for evaluating the efficacy and safety of treatment included:

1. Presence of thromboembolic complications (strokes, thrombosis).

2. Adverse effects of anticoagulant therapy (bleeding, hematomas).

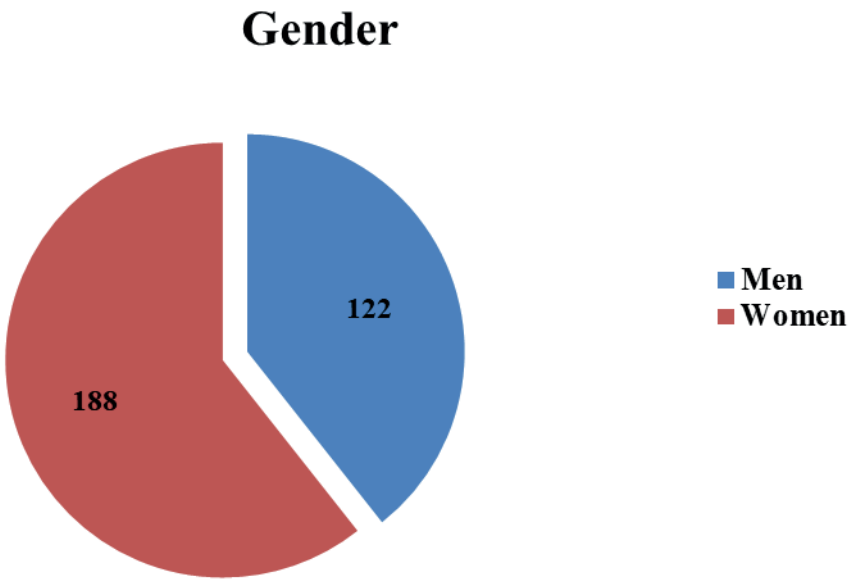


Figure 1. Gender Distribution of Patients.

For the analysis of the age category of patients in the study groups, statistics based on the calculation of the mean value, standard error, and standard deviation were used. In this study, a comparison of age characteristics between women and men was conducted to assess the potential impact of age differences on the analysis of diseases and treatment outcomes, (Fig. 1, tab. 1, 2)

Table 1.
Descriptive Statistics of Age

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q3	Max
Age	**310**	52.868	0.716	12.609	11	46	55	62	80

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Table 2.
Descriptive Statistics of Age

Variable	Groups	N	Mean	SE Mean	StDev	Min	Q1	Median	Q3	Max
Age	**Women**	1188	53.638	0.852	11.684	11	47	56	62	75
	Men	122	51.680	1.257	13.880	15	44.5	54	62	80

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Comparative Analysis: The average age of women is higher than that of men (53.64 vs. 51.68 years). The age variation (StDev) is higher in men, indicating a greater age difference within this group. The age group of women is more balanced, with smaller extremes (maximum age 75 years vs. 80 years in men), (Table 3)

Table 3.
The average age of patients in the group with complications

Variable	Group	N	Mean	SE Mean	StDev	Min	Q1	Median	Q3	Max
Age Complications	**1**	16	54.5	3.478	13.914	24	46	58	62	80
	2	28	50.5	1.800	9.524	28	43.75	52.5	57.75	68

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Analysis of Patient Distribution by BMI: Underweight (7 patients, 2.3%). Normal weight (126 patients, 41.3%). This is the largest group of patients, indicating that a significant portion of the study population has a normal weight.

Overweight (108 patients, 35.4%). A significant portion of patients falls into the category of pre-obesity, which is a risk factor for liver diseases, (Figure 2).

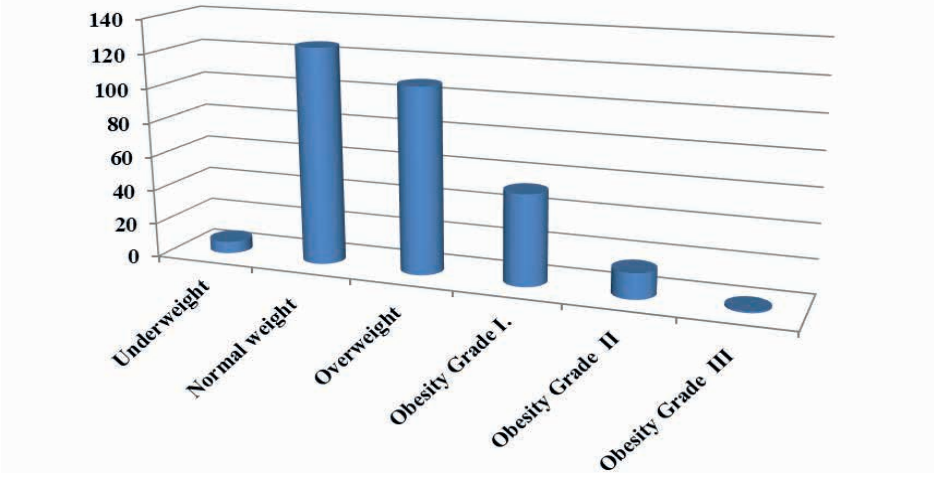
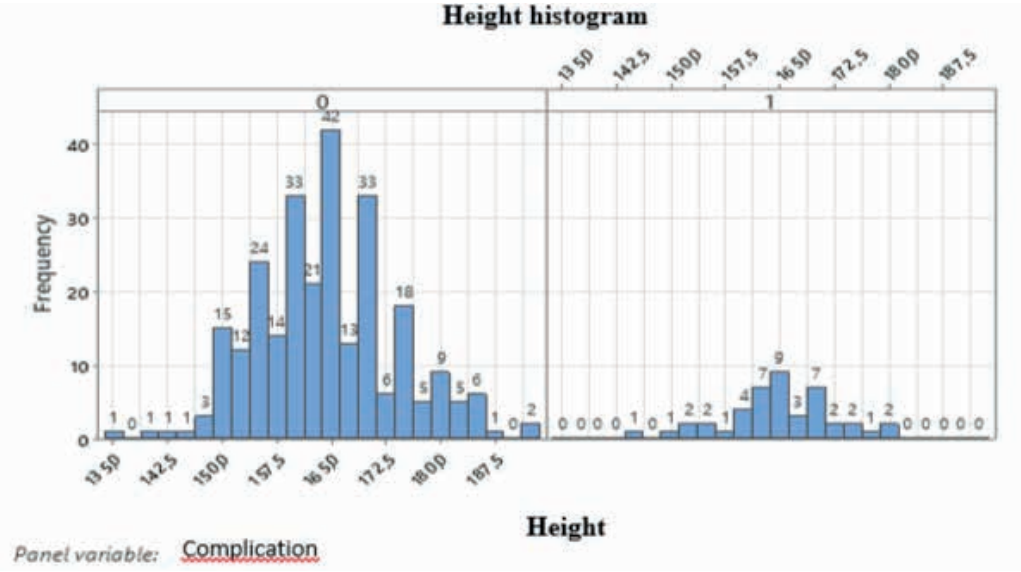


Figure 2.
Analysis of Patient Distribution by BMI

Figure 3.
Height of Patients



The study included 310 patients, distributed according to their primary diagnoses as follows: 201 patients were diagnosed with chronic rheumatic heart disease (RHD). 21 patients were found to have congenital heart defects (CHD). 77 patients were observed to have valve dysfunction (VD). 6 patients were diagnosed with acquired heart defects (AHD), (Figure 3).

Among the patients under study, the following comorbidities were observed: In the CRHD group (201 patients), the most common comorbid conditions included: hypertension (HT) of varying severity, type 2 diabetes mellitus (T2DM), arrhythmias of various types, and cardiac liver damage, (Table 4).

Table 4.
Comorbid Diagnoses of the Studied Patients

	RHD– 201	CHD-21	VD-77	AHD-6
Stage 3 Hypertension, Risk 4	2	1	5	
Stage 3 Hypertension, Risk 3		1		
Stage 2 Hypertension, Risk 3	4			
Type 2 Diabetes Mellitus (T2DM)	3	1	2	
Arrhythmia, Atrial Fibrillation (AF), Subclinical Hypothyroidism	1			
Chronic Kidney Disease (CKD) Stage 3, resulting in Heart Failure (HF) (eGFR 42 ml/min/1.73 m² by EPI)	1			
Cardiac Liver Damage with mild biochemical activity, with fibrosis stage F4 according to the Metavir scale	1			

Results

An analysis of warfarin use was conducted to assess its efficacy and safety. The study revealed changes in coagulation profile parameters, including the international normalized ratio (INR) and other blood clotting factors. Cases of complications, such as hemorrhagic or thrombotic events, associated with warfarin therapy, were documented. The obtained data allow for the evaluation of risk factors and the necessity of strict monitoring of the prescribed dosage to improve the safety and effectiveness of treatment, (Tables 5 and 6).

Table 5.
Average dose of warfarin in all patients

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
Warfarin dose	310	3.308	0.080	1.411	0.6	2.5	2.5	3.75	10
N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age									

Variable	Complication	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
Warfarin dose	0	266	3.308	0.087	1.421	0.6	2.5	2.5	3.75	10
	1	44	2.207	0.206	1.167	0.525	2.5	3.1	4.16	7.5

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Table 6.
Average dose of warfarin in the group with complications

Data Analysis:

Overall Sample (N = 310): The average warfarin dose is 3.31 mg, with doses ranging from 0.6 mg to 10 mg. The median is 2.5 mg, which coincides with the first quartile (Q1), indicating data concentration at the lower end of the range.

Group without Complications (N = 266): The average warfarin dose is also 3.31 mg, which is almost identical to the overall sample. Warfarin doses range from 0.6 mg to 10 mg, with similar quartiles and median. The standard deviation (1.42) is comparable to the overall sample.

Group with Complications (N = 44): The average warfarin dose is lower—2.2 mg. Doses range from 0.625 mg to 7.5 mg. The median (3.1 mg) is higher than in the group without complications (2.5 mg), and the third quartile (Q3) is also higher (4.16 mg vs. 3.75 mg), (Tables 7 and 8).

Key Findings: In the group with complications, the average warfarin dose is lower (2.2 mg) compared to the group without complications (3.31 mg), which may indicate insufficient anticoagulation. However, the median and upper quartile in the complications group are higher, suggesting a subgroup of patients receiving higher doses. Overall, the data show that in patients with complications, the warfarin dosage is less stable, which may be related to individual sensitivity to the drug or difficulties in adjusting the optimal dose (Figure 4).

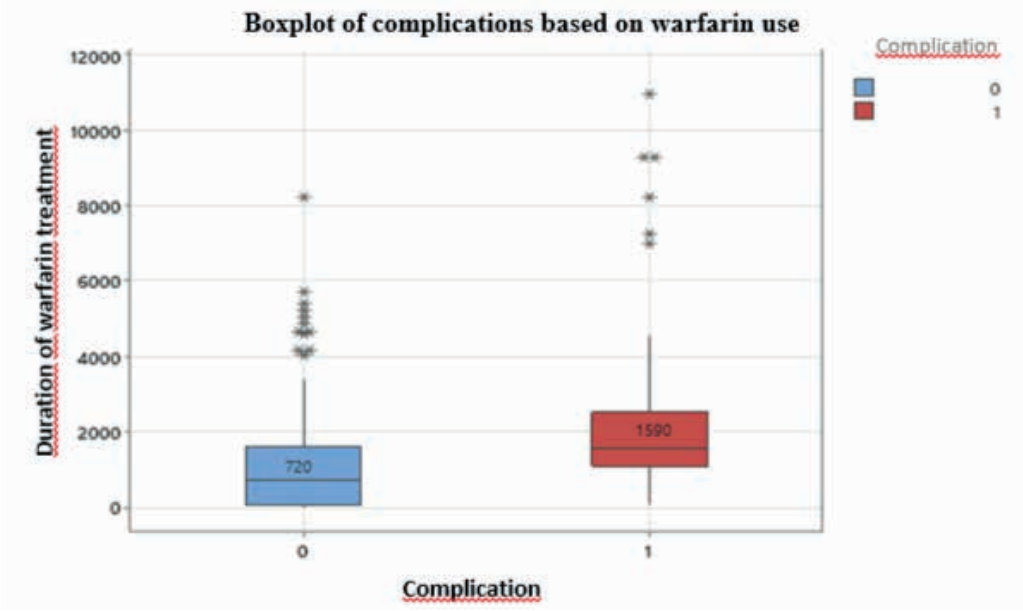


Figure 4.
Boxplot of complications based on warfarin use

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
Target INR dose	310	2.266	0.043	0.764	0.86	1.86	2.17	2.6	6.2

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Table 7.
Target dose of warfarin in groups

Table 8.
Target dose of warfarin in the group with complications

Variable	Compli-cation	N	Mean	SE Mean	St-Dev	Min	Q1	Medi-an	Q 3	Max
Target INR dose	0	266	2.282	0.047	0.775	0.86	1.86	2.2	2.603	6.2
	1	44	1.917	0.104	0.689	1.06	1.772	1.9	2.100	4.5
N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age										

Data Analysis. Overall Sample (N = 310): The mean INR (International Normalized Ratio) is 2.27. The values range from 0.86 to 6.2. The median is 2.17, with Q1 at 1.86 and Q3 at 2.6, indicating moderate skewness in the data, (Table 9).

Group Without Complications (N = 266): The mean INR is 2.28, slightly higher than in the overall sample. Values range from 0.86 to 6.2. The median is 2.2, also higher than in the overall sample. The standard deviation (0.775) indicates slightly greater variability compared to the group with complications.

Group with Complications (N = 44): The mean INR is lower—1.9. Values range from 1.06 to 4.5. The median is also lower—1.9, and Q3 is 2.1, which is lower than in the group without complications (2.6025). The standard deviation (0.689) is smaller, indicating a tighter distribution of data in this group.

Key Finding. Patients without complications have a higher mean INR (2.28) compared to the group with complications (1.9), indicating more stable coagulation control. In the group with complications, the INR has less variability and a more compact distribution, but the mean values are lower than the therapeutic range, which may indicate insufficient anticoagulation and an increased risk of thrombotic events. Overall, the data emphasize the importance of maintaining the INR within target ranges to reduce the likelihood of complications.

Table 9.
INR before and after surgery in groups

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
INR Before Surgery	310	1.261	0.100	1.759	0.8	0.99	1.065	1.2	30.9
INR After Surgery	310	2.524	0.188	3.304	0.86	1.8	2.15	2.6	41.49
N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age									

Data Analysis.

1) INR Before Surgery (N = 310): The mean INR is 1.26, which is close to the normal range for most patients. The minimum value is 0.8, and the maximum reaches 30.9, indicating outliers (unusually high values). The median is 1.065, closer to the lower boundary of the normal range. Q1 is 0.99, and Q3 is 1.2, with data showing a narrow range around the normal.

2) INR After Surgery (N = 310): The mean INR is significantly higher at 2.52, which corresponds to the expected increase in INR following surgery, such as due to anticoagulant therapy. The minimum value is 0.86, and the maximum is 41.49, also indicating the presence of outliers. The median is 2.15, closer to the target range for anticoagulation therapy. Q1 is 1.8, and Q3 is 2.6, showing a noticeable shift toward higher values.

Comparison of INR Before and After Surgery. After surgery, the mean INR significantly increased (from 1.26 to 2.52), which corresponds to the expected effect of anticoagulant therapy. Before surgery, the INR values were concentrated within the normal range, with minor deviations. After the procedure, the range of values expanded, as confirmed by the increase in the maximum INR (up to 41.49), likely due to outliers. The median INR after surgery (2.15) is closer to the target range for anticoagulation, and the interquartile range shifted to-

ward higher values. This indicates more pronounced variability in the coagulation status of patients after surgery.

Conclusions. The INR after surgery is significantly higher, indicating the influence of therapy or surgical intervention on coagulation. The pre-surgery data shows less dispersion, reflecting a more stable condition of patients before the procedure.

Table 10.
PTI before and after surgery in groups

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
PTI before surgery	309	88.055	1.276	22.427	1.5	76.25	90	101	189
PTI after surgery	310	45.824	1.152	20.292	2.33	35.95	44	51	248
N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age									

Data Analysis.

1) PTI Before Surgery (N = 309): Mean: 88.06%, which corresponds to normal levels of prothrombin index for most patients. Median: 90%, confirming that values concentrate in the upper normal range. Minimum value: 1.5%, and maximum value: 189% — a very wide range, indicating potential outliers. Q1: 76.25%, Q3: 101%, indicating a normal distribution of data around the median, (Table 10).

2) PTI After Surgery (N = 310): Mean: 45.82%, indicating a significant decrease in the prothrombin index post-surgery. Median: 44%, confirming the reduction in PTI for most patients. Minimum value: 2.33%, and maximum value: 248% — a very wide spread of data. Q1: 35.95%, Q3: 51%, indicating a significant decrease in values compared to pre-operative levels.

Comparison of PTI Before and After Surgery. After surgery, the mean prothrombin index (PTI) significantly decreased from 88.06% to 45.82%, reflecting the expected depression of the coagulation system due to anticoagulant therapy. The median also dropped (from 90% to 44%), confirming that most patients experienced a reduction in PTI. Before surgery, PTI values were within the normal range, with some outliers. After the procedure, the range expanded even further (from 2.33% to 248%), which could indicate individual patient responses to anticoagulant therapy. The interquartile range also decreased (Q1: 35.95%, Q3: 51%), which supports the overall reduction of PTI levels in most patients, (Figure 5 and 6).

In general, the data suggest a significant change in blood coagulation after surgery, which necessitates careful monitoring to prevent the risks of bleeding or thrombosis.

Key Conclusions. Post-surgery, there is a significant reduction in PTI, likely related to both the surgical intervention and anticoagulant therapy. The wide range of values after surgery (especially the maximum values) may indicate individual patient differences, which should be taken into account for future treatment and monitoring.

Wilcoxon Test Results. Statistic (W): 0.0 p-value: 3.61×10^{69}

Interpretation: The very low p-value (less than 0.05) indicates statistically significant differences between PTI values before and after surgery. This confirms that the reduction in PTI after surgery is not accidental but is linked to the surgical procedure and/or anticoagulant therapy.

Figure 5.
Individual Value Plot of PTI before Surgery

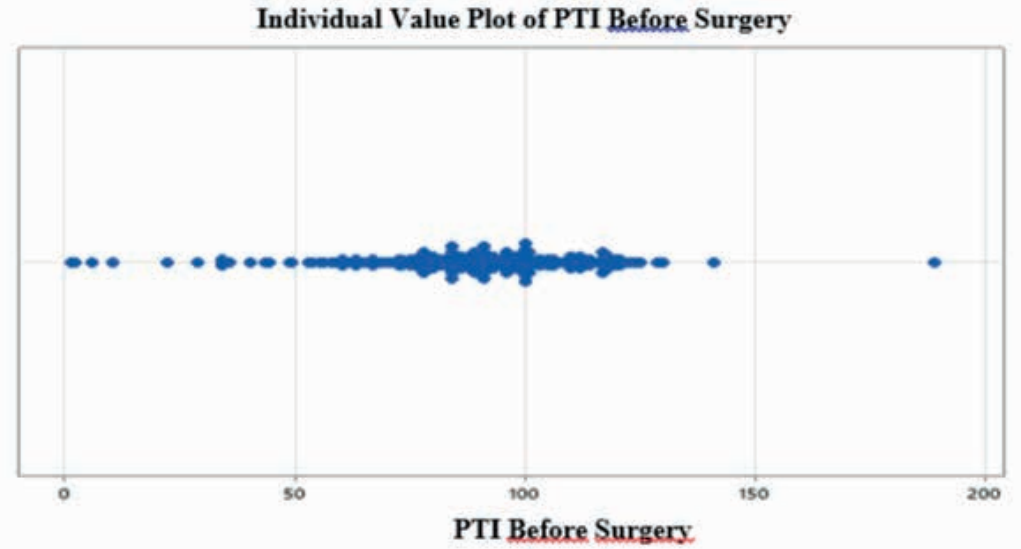


Figure 6.
Individual Value Plot of PTI after Surgery

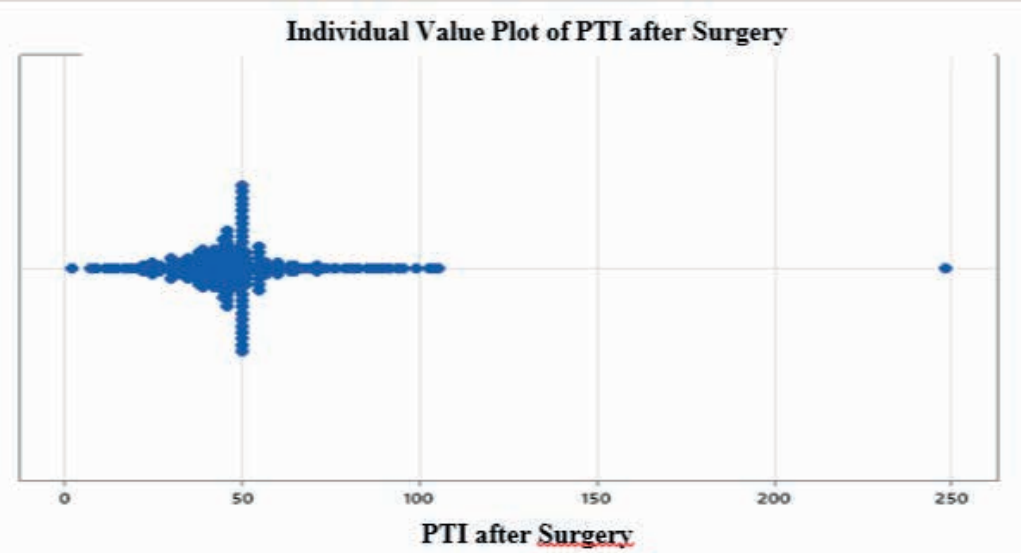


Table 11.
Number of days for standard treatment

Variable	Complication	N	Mean	SE Mean	St-Dev	Min	Q1	Median	Q 3	Max
Number of days for standard treatment	0	266	4.553	0.106	1.715	1	3	5	5	16
	1	44	4.75	0.382	2.535	2	3	5	5	18

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Data analysis. Number of days for standard treatment:

1. Group without complications (N = 266): Average: 4.55 days. Median: 5 days, indicating that the majority of patients completed treatment within 5 days. Standard deviation: 1.72 days, indicating moderate variability in the duration of treatment. Minimum value: 1 day, Maximum value: 16 days, this may suggest variability in outcomes.

2. Group with complications (N = 44): Average: 4.75 days, slightly higher than in the group without complications. Median: 5 days, similar to the group without complications. Standard deviation: 2.53 days, which is higher than in the group without complications, indicating greater variability in treatment duration. Minimum value: 2 days, Maximum value: 18 days.

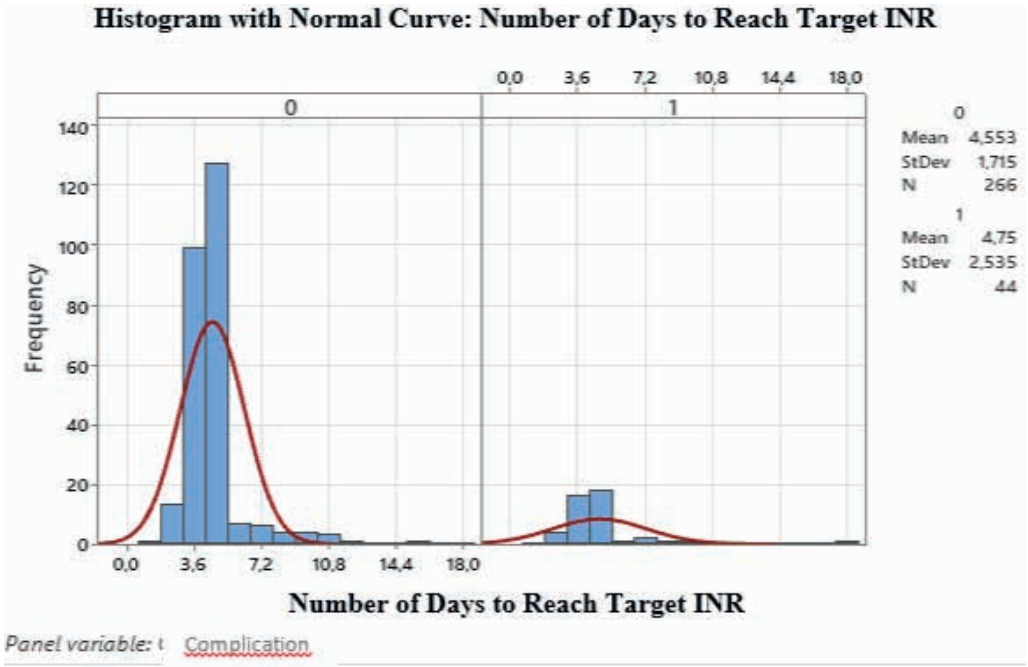


Figure 7.
Histogram with Normal Curve: Number of Days to Reach Target INR

Data analysis.

What the chart shows: X-axis — *Number of days to reach target INR.* Y-axis — *Frequency* (number of patients who reached the target INR in a given number of days)

The chart is split into two panels based on the presence of complications: 0 — without complications (n = 266). 1 — with complications (n = 44)

Interpretation: The average number of days to reach the target INR is similar between groups: Without complications: 4.55 days (StDev = 1.72). With complications: 4.75 days (StDev = 2.54), (Figure 7).

The group with complications shows greater variability (wider spread).The overlaid normal curve helps visualize how close the data are to a normal distribution in each group.

Conclusion. The time to reach target INR is similar between groups, but patients with complications show greater variability.

Table 12.
Number of hours for standard treatment

Variable	Complication	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
Number of hours for standard treatment	0	266	109.263	2.524	41.169	24	72	120	120	384
	1	44	114	9.171	60.831	48	72	120	120	432

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

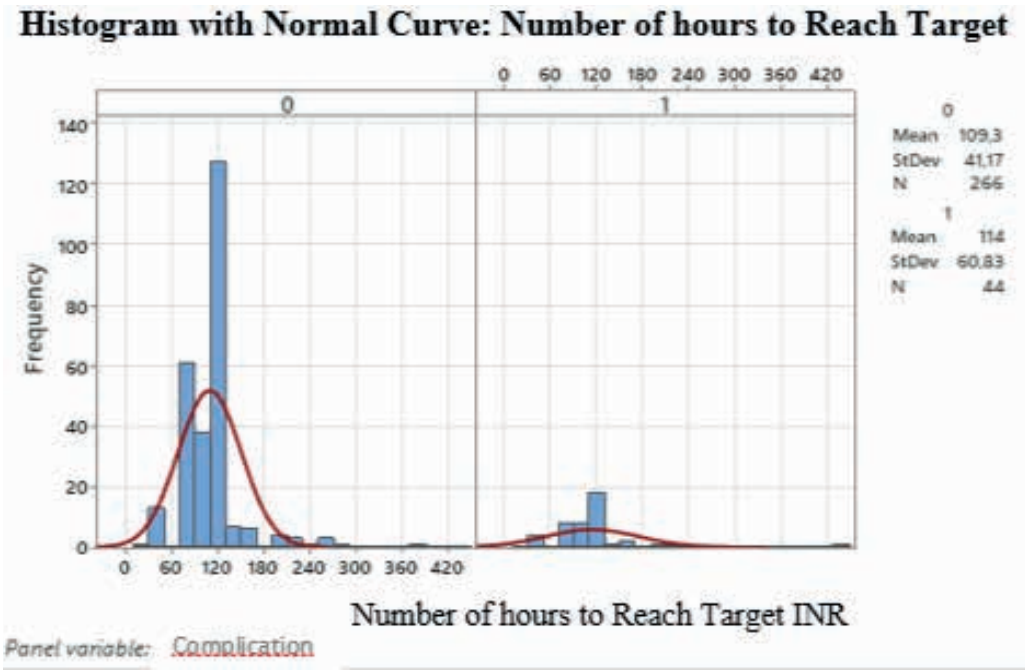
Number of hours for standard treatment:

1. Group without complications (N = 266): Mean value: 109.26 hours. Median: 120 hours, indicating that most patients completed treatment within 5 days (120 hours). Standard deviation: 41.17 hours, suggesting considerable variability in treatment duration. Minimum value: 24 hours, maximum: 384 hours, this could indicate deviations from standard treatment durations, (Table 12).

2. Group with complications (N = 44): Mean value: 114.00 hours, slightly higher than the group without complications. Median: 120 hours, the same as in the group without complications. Standard deviation: 60.83 hours, significantly higher than in the group without complications, indicating even greater variability in treatment duration. Minimum value: 48 hours, maximum: 432 hours.

Comparison. In the group with complications, the average treatment duration is slightly longer (4.75 days versus 4.55 days in the group without complications), but the median remains the same — 5 days. However, the standard deviation in the group with complications is higher, indicating greater variability in treatment duration. When analyzed in hours, a similar trend is observed: the average treatment time in the group with complications is higher (114 hours versus 109.26), and the spread of values is significantly wider, suggesting a more individualized approach to treating this group of patients. Overall, patients with complications require longer treatment, but the greater variability in the data points to possible individual factors affecting the duration of therapy, (Figure 8).

Figure 8.
Histogram with Normal Curve: Number of hours to Reach Target



Data analysis.

What the chart shows: X-axis— *Number of hours to reach target INR*. Y-axis — *Frequency* (number of patients who reached the target INR in a given number of hours).

The chart is split into two panels based on the presence of complications: 0 — without complications (n = 266). 1 — with complications (n = 44)

The average time to reach the target INR in patients without complications is approximately 109.4 hours (standard deviation 41.2), while in patients with complications it is about 114 hours (standard deviation 60.84). The difference between the groups in mean time to reach the target INR is negligible, indicating that the presence of complications does not significantly affect the speed of achieving the target INR in this sample, (Tables 13).

Therefore, it can be concluded that the time to reach the target INR is roughly the same for patients both with and without complications. Other factors may have a greater impact on the development of complications than the speed of reaching the target INR, (Figure 9).

Table 13.
Duration of warfarin intake in days

Variable	N	Mean	SE Mean	StDev	Min	Q1	Median	Q 3	Max
Duration in days	310	1275.32	90.723	1597.34	1	150	885	1717.5	10980

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

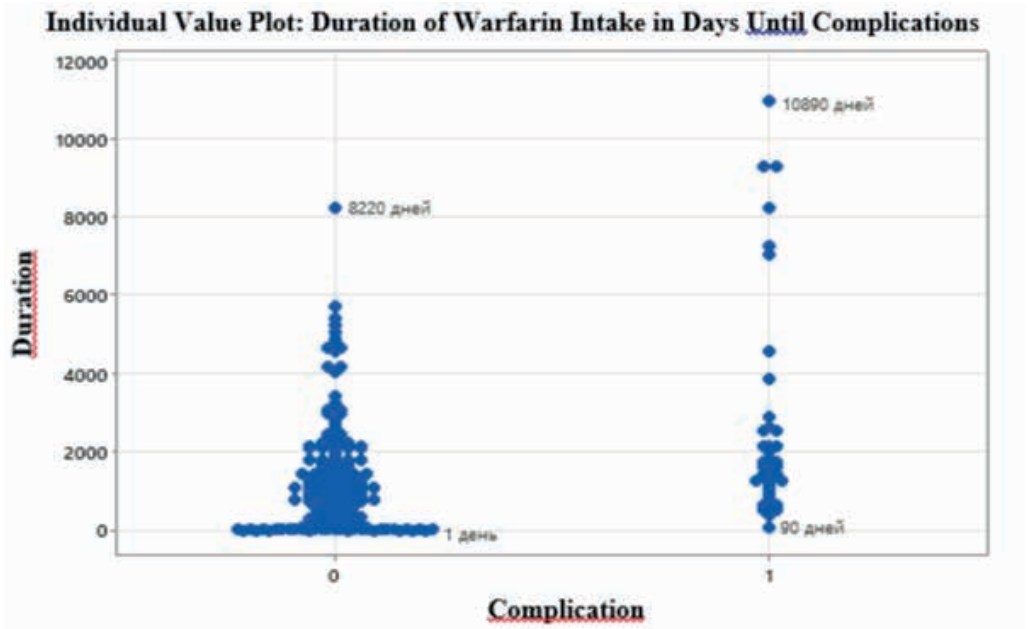


Figure 9.
Individual Value Plot: Duration of Warfarin Intake in Days Until Complications Occur

Intervention n =310	Complications		Total	Chi-squared	P value
	With	Without			
AV, n (%)	8 (12.7%)	55 (77.3%)	63 (20.3%)	13.4 [α]	0.0002*
AV, MV, n (%)	4 (10.2%)	35 (89.7%)	39 (12.6%)	14.2 [α]	0.0002*
MV, n (%)	32 (15.4%)	176 (84.6%)	208 (67.1%)	67.0 [α]	0.0001*
All, n (%)	44 (14.2%)	266 (85.8%)	310	104.7 [α]	0.0001*
α: The observed frequency distribution is significantly different from its expected frequency distribution; *Statistically significant difference P≤0.05					

Table 14.
Distribution of complications by surgery

Table Analysis.

1. Overall Complication Rate: A total of 310 surgeries were performed, with complications occurring in 44 cases (14.2%), (Tables 14).

2. Distribution by Surgery Type: The most frequently performed procedure was mitral valve replacement (208 out of 310, or 67.1% of all surgeries). This group also had the highest complication rate for this type of surgery — 15.4%.

The group that underwent aortic valve replacement accounted for 63 out of 310 (20.3% of all surgeries), with a complication rate of 12.7%. The combined aortic and mitral valve replacement was less common (39 out of 310, or 12.6% of all surgeries), and this group had the lowest complication rate — 10.2%.

Complications occurred in 14.2% of cases, highlighting the need for careful monitoring of risk factors. Mitral valve replacement was the most common surgery (67.1% of all cases) and had the highest complication rate (15.4%). Aortic valve replacement was less frequent (20.3%) with a 12.7% complication rate. Combined valve replacement occurred in 12.6% of cases and was associated with the lowest complication rate (10.2%). Thus, isolated mitral valve replacement is associated with the highest risk of complications, which may be due to hemodynamic complexities and the technical challenges of the procedure. The lowest complication rate was observed in combined valve replacement, which warrants further investigation, including patient selection and post-operative management, (Figure 10 and 11).

Etiological Factors: The diseases leading to surgery are caused by various pathological processes affecting the heart valves. One of the main causes is rheumatic heart disease — seen in 195 out of 310 patients (62.9%), which develops after rheumatic fever and results in fibrotic changes to the valve leaflets. Degenerative changes (age-related, atherosclerotic, calcific) are also significant, especially in elderly patients — observed in 87 out of 310 patients (28.1%), causing

thickening and reduced mobility of the valves. Other causes include congenital anomalies, such as bicuspid aortic valve — found in 28 out of 310 patients (9%). In some cases, the disease develops due to a combination of factors, requiring a comprehensive approach to diagnosis and treatment.

Summary. The condition is most commonly due to rheumatic and degenerative changes, though congenital anomalies or multifactorial causes also play a role. This highlights the importance of an individualized approach to patient care.

Complications. In 42 cases (95.5%), hemorrhagic complications were identified, and in 2 cases (4.5%), thrombotic complications occurred. Since the majority of cases involved hemorrhagic complications, patients were divided into two groups: 15 with minor complications (34.1%), 29 with major complications (65.9%)

Figure 10.
Venn diagram of complications

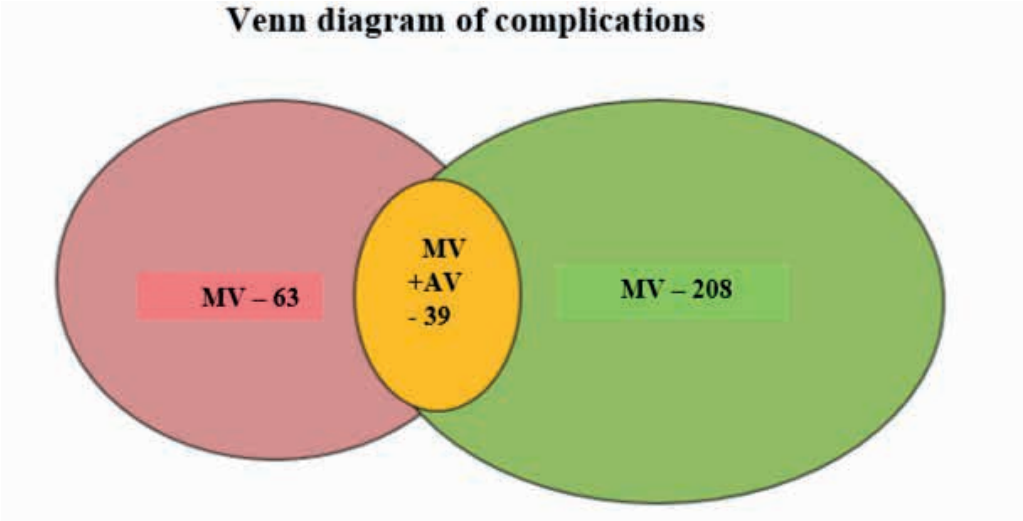


Figure 11.
Distribution of complications

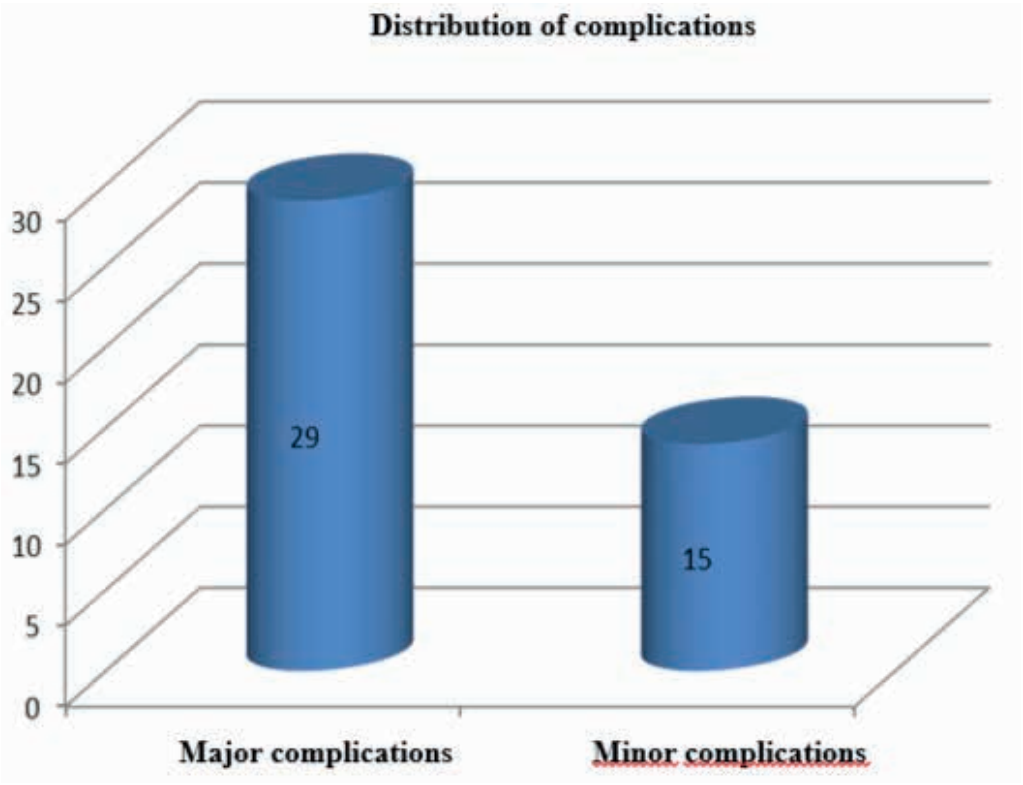


Table 15.
Association of complications with various factors

Source	DF	Adj SS	Adj MS	F-Value	P-Value
Regression	22	19.011	0.864	13.43	0.000
Height	1	0.002	0.002	0.03	0.863
Weight	1	0.016	0.016	0.25	0.616
Age	1	0.187	0.187	2.91	0.089
BMI (Body Mass Index)	1	0.138	0.138	2.15	0.144
Доза варфарина	1	0.001	0.001	0.01	0.926
INR target	1	0.016	0.016	0.25	0.620
Diagnosis	5	0.319	0.064	0.99	0.423
Gender	1	0.005	0.005	0.07	0.787
Comorbidities	8	18.353	2.294	35.65	0.000
Total	310	36.837			

Model and Explained Variance

- R-sq (51.61%) indicates that the included factors explain just over half (51.61%) of the variation in the dependent variable (complications). This means that approximately 48.39% is explained by other factors not included in the model.

- Adj R-sq (47.77%) is the adjusted R-squared, which accounts for the number of predictors in the model. It lowers the R-squared value if the included variables have little impact on the dependent variable. This adjustment is important for evaluating the true strength of the model (Table 15).

Impact of Factors on Complications. Let's review each variable from the model:

1) Gender: Coefficient for male sex: 0.1305 – meaning that men have a 0.1305 higher risk of complications compared to women (reference group). P-value = 0.056: Close to the threshold of statistical significance (0.05). This suggests the influence of sex is not definitively significant but deserves attention.

2) Age: Coefficient: -0.00241 – each additional year slightly decreases the risk of complications. P-value = 0.089: Not statistically significant (P > 0.05), but the effect is close to being meaningful.

3) Height and Weight: Height: Coefficient 0.00036, P = 0.863 Weight: Coefficient -0.000172, P = 0.616. Both have high P-values, indicating no significant effect on complications.

4) BMI (Body Mass Index): Coefficient: 0.00172, P = 0.507. The effect is not significant; no clear relationship was found. Warfarin Dose and INR (International Normalized Ratio): Warfarin Dose: Coefficient 0.0006, P = 0.926

5) INR: Coefficient 0.0010, P = 0.620. Neither variable shows a significant impact on the likelihood of complications.

6) Diagnoses: CRHD (Chronic Rheumatic Heart Disease): Coefficient 0.1305, P = 0.056 Similar effect to sex—just above the significance threshold. Other diagnoses showed insignificant coefficients (high P-values).

Gender and presence of chronic rheumatic heart disease (CRHD) show a weak association with complications, though not statistically significant (P ≈ 0.056), and therefore require further investigation. Age, height, weight, BMI, warfarin dose, and INR were not significantly associated with the likelihood of complications, suggesting no direct dependence of these parameters on adverse outcomes. Thus, the identified factors only partially explain the occurrence of complications. To improve the predictive power of the model, additional clinical and laboratory data should be incorporated, (Figure 12).

Figure 12.
Pareto chart of the Standardized Effects

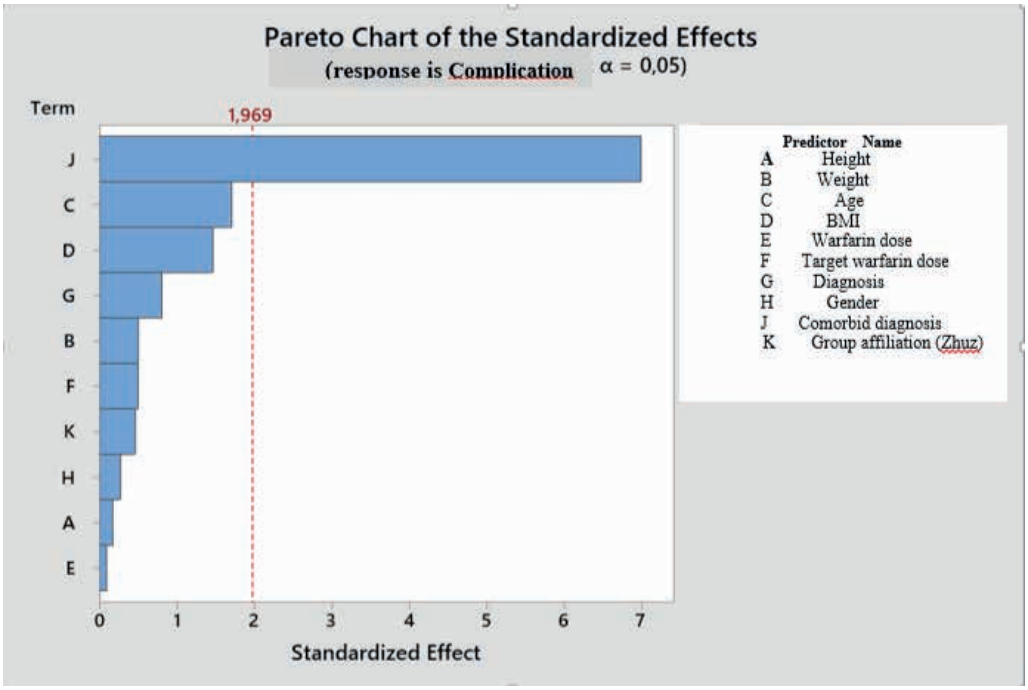
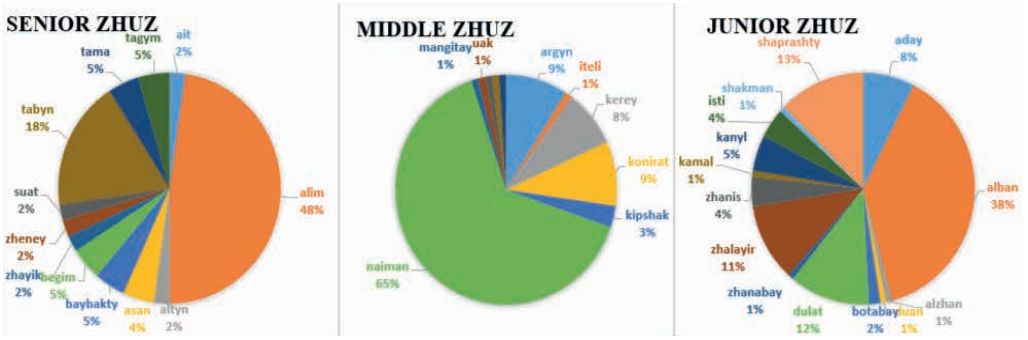


Figure 13.
Pareto chart of the Standardized Effects



Taking into account the division of Kazakhs into tribal groups, we analyzed the distribution of the patients according to their **"Zhuz"** (group), as well as by their specific **"Ru"** (tribe) / among the patients studied, 63 belonged to the Senior Zhuz, 101 to the Middle Zhuz, and 137 to the Junior Zhuz. The distribution by clans in Figure 13. The analysis shows that the majority of patients came from the Junior Zhuz, then Middle and Senior Zhuzes.

The next analysis focused on achieving target INR in the complication group

Table 16.
Association of complications with various factors

Variable	Complication	N	Mean	SE Mean	St-Dev	Min	Q1	Median	Q 3	Max
INR target	0	266	2.282	0.047	0.775	0.86	1.86	2.2	2.60	6.2
	1	44	1.917	0.104	0.689	1.06	1.772	1.9	2.1	4.5

N – Number of participants; Mean – Mean age; SE Mean – Standard error of the mean; StDev – Standard deviation; Min – Minimum age; Q1 – 1st quartile; Median – Median; Q3 – 3rd quartile; Max – Maximum age

Data Analysis. Group without complications (N = 266):

The average INR value is 2.28, slightly higher than in the total sample. Values range from 0.86 to 6.2. The median is 2.2, also higher than the overall median. The standard deviation is 0.775, indicating slightly greater variability compared to the complications group (Table 16).

1. Group with complications (N = 44):

The average INR is lower — 1.9. Values range from 1.06 to 4.5. The median is also 1.9, and the third quartile (Q3) is 2.1, which is lower than in the group

without complications (Q3 = 2.6025). The standard deviation is 0.689, indicating a narrower spread of values in this group.

Key Findings. In the group without complications, the average INR is higher (2.28) compared to the complication group (1.9), suggesting a possible association between lower INR levels and increased risk of complications. Moreover, the complication group shows a narrower INR range and lower standard deviation, indicating a tighter clustering of INR values. However, despite this consistency, INR levels tended to remain below the therapeutic target, potentially leading to insufficient anticoagulation. These findings emphasize the need for more rigorous monitoring of INR in postoperative patients to minimize the risk of complications, especially in those at higher risk of falling below the therapeutic range.

Discussion

Out of the 310 patients analyzed, 44 patients (14.2%) experienced various postoperative complications related to anticoagulant therapy. These complications included thromboembolic events as well as adverse effects associated with impaired blood coagulation.

Efficacy of Anticoagulant Therapy

- In the group receiving anticoagulant therapy for up to 6 months (100 patients), 12 thromboembolic events were observed, accounting for 12% of this group. All cases were related to thrombus formation in the area of the valve prosthesis or in major veins.
- In the group treated for 6 to 12 months (105 patients), the complication rate dropped to 5% (5 cases). These patients had a longer period to adapt to the medication, which contributed to a reduced risk of thrombosis.
- In the group receiving long-term therapy (more than 12 months, 95 patients), only 2 thromboembolic events were recorded, representing 2.1% of the group.

The duration of anticoagulant therapy directly affects the frequency of thromboembolic complications, with the lowest risk observed in patients undergoing long-term therapy (more than 12 months). However, this is not always feasible for all patients due to the increased risk of side effects such as bleeding.

Adverse Effects of Anticoagulant Therapy

In the group receiving anticoagulant therapy for up to 6 months, 8% (8 patients) experienced bleeding events of varying severity, including nasal bleeding and gastrointestinal hemorrhages. These side effects were most commonly observed in patients over 70 years of age. In the 6 to 12 months therapy group, adverse effects were observed in 6% of patients, most commonly presenting as mild bleeding episodes such as ecchymoses, hematomas, and minor nosebleeds that did not require discontinuation of therapy.In the long-term therapy group (more than 12 months), the incidence of adverse effects was the lowest at 4%. However, these patients required closer monitoring of international normalized ratio (INR) levels and careful dose adjustments.

Bleeding-related side effects are a critical aspect of long-term anticoagulant use. Older age, in particular, increases the likelihood of bleeding, necessitating more frequent monitoring and individualized dosing strategies.

Ethnic and Genetic Factors

One of the most notable aspects of this study is the impact of genetic and physiological characteristics in patients of Kazakh nationality on the efficacy and safety of anticoagulant therapy. Comparative analysis revealed that Kazakh patients tend to have specific metabolic responses to warfarin, likely due to increased activity of certain liver enzymes responsible for drug metabolism. As a result, dose adjustments were required in a significant number of cases, which was supported by more frequent episodes of subtherapeutic or supratherapeutic anticoagulation (elevated or low INR levels). Additionally, the analysis showed that patients with certain gene mutations related to blood clotting required longer and more consistent monitoring of their anticoagulant therapy.

The results of the study highlight the importance of an individualized approach to anticoagulant therapy in patients with valvular heart disease. Certain ethnic and genetic characteristics—such as warfarin metabolism in patients of Kazakh nationality—necessitate precise adjustment of dosage and treatment du-

ration to minimize the risk of thromboembolism and adverse effects.

Another key finding is that the duration of anticoagulant therapy should be based on a careful evaluation of risks and benefits. Long-term therapy (more than 12 months) may reduce the risk of thromboembolic events but increases the likelihood of bleeding and requires continuous monitoring. For most patients, a treatment duration of 6 to 12 months appears to be the optimal balance between efficacy and safety.

The duration of anticoagulant therapy in patients who have undergone heart valve surgery plays a critical role in preventing thromboembolic complications but also carries a risk of side effects. In patients of Kazakh nationality, genetic factors influencing anticoagulant metabolism must be considered, which may require individualized dose adjustments and more frequent monitoring. The best outcomes in terms of safety and effectiveness were observed with therapy lasting 6 to 12 months, although extended treatment may be necessary for some patients.

Limitations. This study has several limitations. It was conducted retrospectively and was based on data from two centers. Although the sample size was sufficient for analysis, it may not be large enough to draw definitive conclusions applicable to a broader population. Furthermore, the study included only Kazakh patients who underwent mechanical heart valve replacement, which limits the generalizability of the findings to other patient groups.

What's known? Warfarin remains the primary anticoagulant following valve replacement. The effectiveness of therapy depends on the duration of treatment, INR monitoring, and individual factors such as age and genetics. Adverse effects, particularly bleeding, are more common in elderly patients and those with inappropriate dosing.

What's new? For the first time in Kazakhstan, a study was conducted demonstrating that patients of Kazakh nationality have specific features in warfarin metabolism that require individualized dose adjustment. It was established that the optimal duration of therapy for most patients is between 6 and 12 months, providing the best balance between thrombosis prevention and bleeding risk.

Conclusion. The results of the study highlight the importance of an individualized approach to anticoagulant therapy in patients with valvular heart disease. Certain ethnic and genetic characteristics—such as warfarin metabolism in patients of Kazakh nationality—necessitate precise adjustment of dosage and treatment duration to minimize the risk of thromboembolism and adverse effects.

Acknowledgements. The authors would like to express their sincere gratitude to the scientific advisors for their invaluable guidance, support and expertise throughout the study. Their encouragement, insightful comments, and continuous support were essential for the successful completion of this work.

Author's contributions. Study concept: N.Zh., T.R.; Study design: N.Zh., M.E.; Data analysis: N.Zh, Y.D.; Drafting of manuscript: N.Zh, I.U.; Writing the text of the article: N.Zh, M.E., I.U., M.A.; Critical revision of the manuscript: S.G., P.M., B.G. All authors approved the final version of the manuscript.

Funding. This study was funded by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan ("Pharmacogenetics of Indirect Anticoagulants in Patients with Operated Heart Conditions" (AP19677439). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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