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Types and hospital manifestation of the "risk-treatment" paradox in non-ST-elevation acute coronary syndrome: the regional vascular centre experience

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Abstract

Background There is reason to believe that unfavorable outcomes of non-ST-elevation acute coronary syndrome (NSTE-ACS) is due to the "risk-treatment" paradox (RTP). However, the true prevalence, types and causes of RTP have not been studied, and data from previous studies have shown an equivocal effect of RTP on outcomes of NSTE-ACS.

Methods The retrospective analysis included 600 patients initially diagnosed with NSTE-ACS. Upon admission, all patients were re-stratified into four groups according to their risk of adverse ischemic events. RTP was defined as a mismatch between a patient's risk profile and the recommended invasive strategy.

Results RTP was present in 53.5% of the study population (321/600), with the highest frequency observed in the intermediate-risk group (74%) and the lowest in the high-risk group (28.5%). In the overall cohort, the presence of RTP ($n=321$) was not associated with a significant difference in in-hospital adverse cardiovascular events or length of stay compared to patients without RTP ($n=279$). After adjustment for RTP in each risk group, only the high-risk group showed an increase in adverse outcomes in the presence of RTP (5.4% mortality vs. 2.9% (OR 1.9 (95% CI 0.5–8.9), $p=0.037$) and a negative effect of RTP on the risk of recurrent myocardial ischemia (RMI) after 24 h (7.1% vs. 0.7%, OR 10.7 (95% CI 1.2–97.9), $p=0.01$).

Conclusions RTP in relation to the type of invasive strategy is common in patients with NSTE-ACS (53.5%). For high-risk patients, RTP worsened in-hospital outcome and influenced the risk of RMI after 24 h.

Clinical trial number This research is a retrospective observational study, which does not require mandatory registration as defined by the ICMJE.

Highlights

- The evidence base for invasive management strategies in NSTE-ACS is not perfect;
- Objective risk stratification is not fully implemented in practice;
- The "risk-treatment" paradox is typical for 53.5% of NSTE-ACS patients;
- The "risk-treatment" paradox worsens hospital outcomes only in high-risk patients.

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Keywords Non-ST-elevation acute coronary syndrome, "Risk-treatment" paradox, Risk stratification, Invasive coronary angiography

Introduction

Non-ST-elevation acute coronary syndrome (NSTE-ACS) is a heterogeneous disease with outcomes that remain unfavorable despite advanced treatment strategies [1, 2]. There is reason to believe that the slow decline in mortality, adverse outcomes, and ineffective translation of research developments into clinical practice may be caused by the "risk-treatment" paradox (RTP) observed in the NSTE-ACS cohort when there is a mismatch between the level of risk of adverse ischemic events and the treatment approaches used [3]. It has been reported that RTP most often implies that very high- and high-risk patients do not receive timely and/or appropriate pharmacoinvasive treatment [4]. RTP described in the literature is typically not associated with cases in which the most aggressive approaches are used to treat low-risk patients, namely an early routine invasive strategy and a more intensive pharmacological strategy. It is well established that a strategy of early invasive coronary evaluation does not improve the overall long-term prognosis in all NSTE-ACS patients, but it does improve outcomes in high-risk patients [5, 6]. As a result, a proportion of patients who don't require invasive testing may undergo invasive coronary angiography (ICA), exposing them to its associated risks [7]. The ever-improving method of ICA reduces the likelihood of perioperative complications; however, the risks of this procedure cannot be completely eliminated, given the invasive nature of the examination and the inevitable use of contrast agents. According to the latest data, the incidence of contrast-induced nephropathy (CIN)– the most common complication of ICA– ranges from 2 to 30% in groups with risk factors for kidney disease [8]. Another commonly identified complication is periprocedural myocardial injury (PMI), with a prevalence of up to 37% in patients with non-ST-elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention (PCI) [9].

While RTP is frequently discussed in the literature, its true prevalence in NSTE-ACS patients remains unknown. Furthermore, its main types and causes are not well characterized, and previous studies have reported inconsistent associations between RTP and clinical outcomes. For example, most studies have shown negative associations of RTP with in-hospital and long-term disease outcomes [10], while other data suggest that RTP does not adversely affect outcomes in NSTE-ACS patients [11]. It is important to note that the RTP studies almost exclusively used the GRACE calculator for risk stratification and largely ignored other patient characteristics that objectively increase the risk listed in clinical guidelines [10].

Objective

To study the sequence of risk stratification, types and incidence of RTP and its association with hospital outcomes in NSTE-ACS patients based on a retrospective analysis of clinical practice at the Regional Vascular Centre (RVC).

Materials and methods

This is a single-center retrospective observational study. The study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Research Institute of Cardiology, Tomsk National Research Medical Center, protocol No. 235 of 23-Nov-2022.

The analysis included 600 consecutive patients of both sexes who were admitted to the RVC between January 2019 and January 2021.

Study inclusion criteria

1) Patients with an initial diagnosis of NSTE-ACS, defined as acute clinical signs or symptoms of myocardial ischemia in the absence of persistent (> 20 min) ST-segment elevation in at least two contiguous ECG-leads or acute left bundle branch block.
2) Patients aged 18 years and older.
3) Provision of written informed consent for the processing of personal data, obtained from the patient or their legal representative at the time of hospital admission.

Study exclusion criteria

1) Patients with an initial diagnosis of acute coronary syndrome with persistent ST elevation.
2) Insufficient clinical and diagnostic data to permit meaningful assessment of the patient's condition and disease outcomes.
3) Absence of written informed consent for the processing of personal data signed by the patient or their legal representative.

To achieve the study objective, the criteria for different risk categories of NSTE-ACS were assessed in each patient by an independent expert. The criteria

recommended by the European Society of Cardiology (ESC) 2015 [12] and 2023 [13] and the Russian Society of Cardiology (RSC) 2020 [14] were used to define the risk group:

- Very high risk: (1) hemodynamic instability or cardiogenic shock; (2) ongoing or recurrent chest pain refractory to medical treatment; (3) life-threatening arrhythmias or circulatory arrest; (4) mechanical complications of myocardial infarction (MI); (5) acute heart failure; (6) recurrent dynamic ST-segment or T-wave changes.
- High risk: (1) elevation or decrease in high-sensitivity cardiac troponin (hs-cTn) blood concentrations consistent with the criteria for MI; (2) dynamic ST-segment or T-wave changes; (3) GRACE score > 140 points.
- Intermediate risk: (1) diabetes mellitus; (2) glomerular filtration rate < 60 ml/min/1.73 m2; (3) left ventricular ejection fraction < 40% or congestive heart failure; (4) early postinfarction angina; (5) recent PCI; (6) history of coronary artery bypass grafting (CABG); (7) GRACE score of 109–140 points.
- Low risk: absence of all of the above criteria.

The intermediate risk category is deliberately described as a separate category, taking into account retrospective data analysis and current RSC recommendations (2020). As we know, this category was excluded in the most recent update of the ESC guidelines for the management of acute coronary syndrome (2023).

In order to analyze and store clinical information, an electronic database in the form of a personalized summary table was created using Excel 2010 (Certificate of State Registration No. 2023622190 dated 03.07.2023) [15]. Each patient was assigned an individual number. The risk category was determined on the basis of the medical records at the time of admission. Re-stratification of patients was carried out independently the type of invasive strategy chosen during hospitalization.

At this stage of the study, RTP was defined as any situation where the risk of adverse ischemic events did not match the recommended type of invasive strategy (Fig. 1).

The type of invasive strategy (emergency, early, or delayed) was determined by the time between NSTE-ACS diagnosis and ICA performance, regardless of subsequent myocardial revascularization (by PCI or CABG) in the presence of appropriate indications. A selective invasive strategy involved either prior ischemia testing or the detection of obstructive coronary artery disease by means of coronary computed tomography angiography.

In the present study, RTP was analyzed solely in the context of invasive strategies. It should be noted that the study did not focus on a detailed analysis of the extent of conservative treatment. All patients received standard NSTE-ACS therapy upon admission, consistent with national guidelines, encompassing dual antiplatelet and lipid-lowering therapy, angiotensin-converting enzyme inhibitors, and beta-blockers (unless contraindicated). In cases of adverse outcomes, the specific medical treatments administered were further examined to provide a more granular description of inpatient management.

The primary endpoints of the study were inpatient adverse cardiovascular events and hospital outcomes. Adverse cardiovascular events included: acute cerebral circulation disorder (ACCD) (ischemic stroke, intracranial hemorrhage or transient ischemic attack); unplanned repeat revascularization; life-threatening cardiac arrhythmias (ventricular tachycardia, ventricular fibrillation, second- or third-degree atrioventricular block); evidence of recurrent myocardial ischemia (RMI) within 24 h of admission or thereafter. RMI was defined as a recurrence of anginal pain and/or dyspnea despite treatment.

Hospital outcomes were categorized as: improved condition followed by a discharge to outpatient care; deterioration due to decompensation of extracardiac pathology;

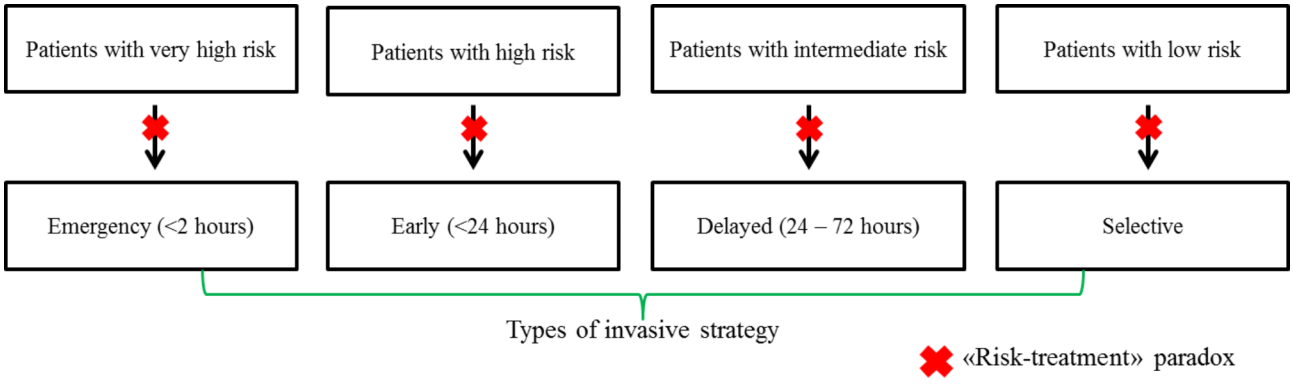

Fig. 1 "Risk-treatment" paradox situations

in-hospital mortality; stabilization without significant improvement.

Statistical analysis

Statistical analysis was performed using SPSS 23.0 (IBM SPSS Statistics, USA). The distribution of quantitative variables was assessed using the Shapiro-Wilk W test. Quantitative variables are presented as median and interquartile range (Q25-Q75). For qualitative variables, results were reported as absolute numbers (n) and percentages (%). Between-group comparisons of continuous variables in independent samples were performed using the Kraskell-Wallis test. Pairwise comparisons between two independent groups were performed using the non-parametric Mann-Whitney U test and Pearson's $\chi 2$ test or two-tailed Fisher's exact test (when expected frequencies were less than 5). Multiple comparisons between groups were performed using Bonferonni corrections. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using contingency Table (2×2 tables) to compare the incidence of different outcomes and adverse events. A value of $p^{<}0.05$ was considered statistically significant.

Results

The study population was stratified into four risk groups at hospital admission, reflecting their risk of adverse ischemic events: 34.7% were classified as very high risk ($n = 208$), 32.7% as high risk ($n = 196$), 18.0% as intermediate risk ($n = 108$), and 14.6% as low risk ($n = 88$). Patient enrollment is depicted in the flowchart presented in Fig. 2.

Detailed patient characteristics for each risk group are presented in Table 1.

The "risk-treatment" paradox in the context of the type of invasive strategies

Objective risk stratification and justification of the risk category in the medical history were documented for 285 patients (47.5%), most commonly in the high-risk group (112; 57.1%) (Table 2).

RTP was identified in 321 cases (53.5%) of all patients and was most characteristic of the intermediate-risk group (74%). The lowest number of RTP cases was found in high-risk patients (28.5%). Very high- and low-risk patients had a similar incidence of RTP at 62.5%. In the group of patients with reliable risk stratification, RTP was seen in 106 cases (37.2%), which is significantly less compared to the group without risk stratification: 215 cases of RTP (68.2%), $p < 0.001$.

In the low-risk group, 33 patients underwent selective invasive strategy. Ultimately, 14 of these patients were determined to have no indication for ICA, while the remaining 19 underwent ICA within 72 h due to evidence of myocardial ischemia by testing.

Analysis of the data identified four primary types of RTP: type 1– refusal of timely invasive intervention in high- and very high-risk patients; type 2– early invasive strategy in intermediate- and low-risk patients; type 3– routine ICA after 24–72 h without prior verification of myocardial ischemia and in the absence of its recurrence; type 4– exclusively conservative management tactics without additional diagnostic procedures.

ICA was performed during the index hospitalization in 493 patients (82.1%). ICA frequency was higher in patients without RTP (93.9% vs. 71.9%), $p < 0.001$. Refusal of ICA was observed in 107 patients (17.8%) and was most characteristic of the very high-risk group (19.7%). The primary reasons for foregoing ICA were: comorbid pathology (63 patients, 58.9%), previously known

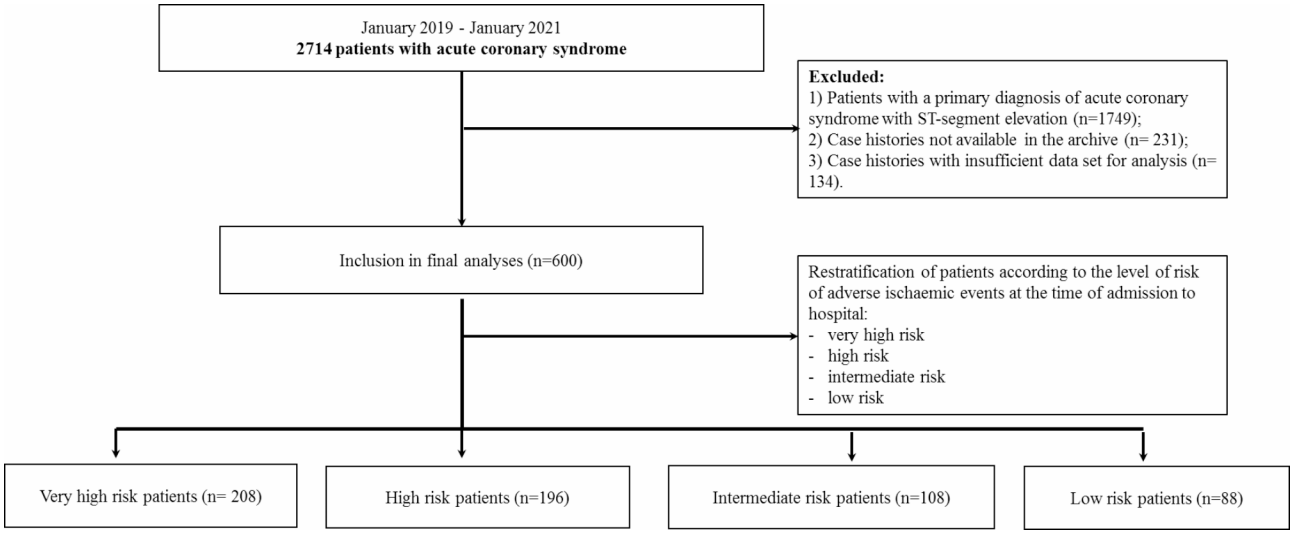

Fig. 2 Flowchart of patients enrolled

Table 1 General characteristics of patients by risk group for adverse ischemic events

Risk at admission	First group	Second group	Third group	Fourth group
Parameters, *n* (%)/ Me [Q25; Q75]	**Very high risk, *n* = 208**	**High risk, *n* = 196**	**Intermediate risk, *n* = 108**	**Low risk, *n* = 88**
Male	112 (53.8)	107 (54.6)	74 (68.5)	65 (73.9) [#]
Age (years)	69.5 [62; 79]	70 [61; 79]	63 [56; 69.8] [¶] [†]	60.5 [54.3; 65.8] [#] [*]
Number of bed days	9 [6; 12]	10 [7; 13]	8 [5.25; 11] [†]	8 [7; 11.8]
BMI, kg/m^2	28.9 [24.9; 33]	28 [24.9; 32.6]	28 [25.2; 32]	29.3 [25.1; 32]
GRACE, %	3.4 [1; 10]	3 [1; 6]	1 [0.6; 1] [¶] [†]	0.6 [0.4; 1] [#] [*]
CRUSADE, scores	10.1 [6.9; 19.5]	8.6 [5.6; 11.9] [§]	5.6 [4.5; 8.6] [¶] [†]	5.5 [3.3; 8.6] [#] [*]
Charlson comorbidity index, scores	6 [4; 8]	6 [4.3; 7]	4 [3; 7] [¶] [†]	4 [3; 5] [#] [*]
Hypertension, n (%)	201 (96.6)	187 (95.4)	97 (89.8)	80 (90.9)
Coronary artery disease history	146 (70.2)	115 (58.7)	71 (65.7)	41 (46.6) [#] [‖]
Postinfarction cardiosclerosis	108 (51.9)	78 (39.8) [§]	42 (38.8) [¶]	26 (29.5) [#] [*]
Prior ICA	76 (36.5)	57 (29.1)	54 (50) [†]	25 (28.4) [‖]
Prior PCI	58 (27.9)	30 (15.3) [§]	35 (32.4)	24 (27.3) [#]
Prior CABG	17 (8.2)	18 (9.3)	17 (15.7)	0 (0) [#] [*] [‖]
ACCD history	19 (9.1)	14 (7.1)	10 (9.3)	3 (3.4)
Diabetes mellitus type 2 history	61 (29.3)	39 (19.9)	19 (17.6)	0 (0) [#] [*] [‖]
GFR, ml/min/1.73 m^2 (at admission)	56.5 [39.3; 76.7]	62 [43.8; 79.8]	70.5 [58; 91.3] [¶] [†]	80.7 [64.3; 99.5] [#] [*]
Cholesterol, mmol/L	4.4 [3.6; 5.4]	4.5 [3.7; 5.3]	4.4 [3.6; 5.4]	4.5 [3.6; 5.4]
Atrial fibrillation	59 (28.4)	52 (26.7)	13 (12) [¶] [†]	8 (9.1) [#] [*]
Smoking	53 (28.3)	60 (32.9)	41 (41.4)	38 (46.3) [*]
Family history of cardiovascular disease	77 (39.9)	66 (33.7)	53 (49.1)	41 (46.6)
QTc, mc	426 [405.5; 451.5]	424 [406; 451]	416 [405.3; 434]	411.5 [401; 427.8] [#] [*]
Left ventricular ejection fraction (B-mode), %	57 [42; 63]	59 [50; 64]	61.5 [53; 65] [¶]	62 [58; 65] [#] [*]
Local contractility disorders	136 (66.9)	121 (62.4) [§]	40 (37.7) [¶] [†]	40 (45.5) [#] [*]
Multivessel coronary lesion	76 (43.7)	74 (44)	25 (27.5)	20 (26.7)

Note: Quantitative values are presented according to the law of normal distribution of values: median, interquartile range (Me [Q25; Q75]), qualitative values are presented with absolute values (n) and relative frequencies (%). Multiple comparisons between groups were performed using Bonferonni corrections. Abbreviation: BMI– body mass index, GRACE– Global Registry of Acute Coronary Events, CRUSADE– Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines, ICA– invasive coronary angiography, PCI– percutaneous coronary intervention, CABG– coronary artery bypass grafting, ACCD– acute cerebral circulation disorder, GFR– glomerular filtration rate, QTc– corrected QT interval. [§] $p < 0.05$ - difference between the first and the second group; [¶] $p < 0.05$ - difference between the first and the third group; [#] $p < 0.05$ - difference between the first and the fourth group; [†] $p < 0.05$ - difference between the second and the third group; [*] $p < 0.05$ - difference between the second and the fourth group; [‖] $p < 0.05$ - difference between the third and the fourth group

coronary anatomy (21 patients, 19.6%), lack of objective evidence of myocardial ischemia by stress testing as part of a selective invasive strategy (14 patients, 13%), and patient refusal (9 patients, 8.5%). Such patients received only optimal medical therapy.

In 264 patients (53.5%), ICA was performed for diagnostic purposes only, revealing the following coronary anatomy: (1) non-obstructive coronary artery disease (143; 54.2%); (2) multivessel coronary artery disease (84; 31.8%); (3) intact coronary arteries (32; 12.1%); (4) technical challenges that precluded PCI (5; 1.9%).

Of 195 patients diagnosed with multivessel coronary artery disease, single-stage PCI was the predominant revascularization strategy during the index hospitalization (102 patients, 52.3%), while only 9 patients (4.6%) underwent complete surgical revascularization by means of CABG (regardless of risk level). A delayed CABG (1–3 months post-discharge) was recommended for 18 patients (9.2%). The remaining 66 patients with multivessel disease were treated conservatively (66; 33.9%).

The frequency of PCI (stenting and/or balloon angioplasty) across different risk groups is summarized in Table 2.

Outcomes of index hospitalization

Following the index hospitalization, 551 of 600 patients (91,8%) were discharged with significant symptomatic

Table 2 Associations of the level of risk of adverse ischemic events with risk stratification, "risk-treatment" paradox, invasive strategy and mortality

Risk upon admission / parameters, *n* (%)	First group Very high risk, *n* = 208	Second group High risk, *n* = 196	Third group Intermediate risk, *n* = 108	Fourth group Low risk, *n* = 88
Implementation of objective risk stratification upon admission	107 (51.4)	112 (57.1)	32 (29.6) [¶] [†]	34 (38.6) [#] [*]
The "risk-treatment" paradox	130 (62.5)	56 (28.5) [§]	80 (74) [†]	55 (62.5) [*]
ICA	167 (80.2)	164 (83.7)	88 (81.5)	74 (84)
Emergency ICA (< 2 h)	78 (37.5)	26 (13.3) [§]	11 (10.2) [¶]	8 (9) [#]
Early ICA (2–24 h)	74 (35.5)	114 (58.1) [§]	47 (43.5)	39 (44.3)
Delayed ICA (24–72 h)	10 (4.8)	16 (8.2)	28 (25.9) [¶] [†]	8 (9)
ICA after 72 h	5 (2.4)	8 (4)	2 (1.8)	19 (21.5) [#] [*] [‖]
Stenting / balloon angioplasty	92 (44.2)	79 (40.3)	30 (27.7) [¶]	28 (31.8)
Conservative treatment without ICA only	41 (19.7)	32 (16.3)	20 (18.5)	14 (15.9)
Fatal outcome	33 (15.8)	7 (3.5) [§]	0 [¶] [†]	2 (2.3) [#] [‖]

Note: Qualitative values are presented with absolute values (n) and relative frequencies (%). Multiple comparisons between groups were performed using Bonferonni corrections. Abbreviation: ICA– invasive coronary angiography. [§] $p < 0.05$ - difference between the first and the second group; [¶] $p < 0.05$ - difference between the first and the third group; [#] $p < 0.05$ - difference between the first and the fourth group; [†] $p < 0.05$ - difference between the second and the third group; [*] $p < 0.05$ - difference between the second and the fourth group; [‖] $p < 0.05$ - difference between the third and the fourth group

Table 3 Adverse cardiovascular events during inpatient follow-up and hospital outcomes

Parameters	All patients with RTP (*n* = 321)	All patients without RTP (*n* = 279)	ORs (95% CIs)	*p*-value
Adverse cardiovascular events				
Acute cerebral circulation disorder	2; 0.6%	5; 1.8%	0.3 (95% CI 0.1–1.8)	0.65
Repeat unplanned revascularization	2; 0.6%	1; 0.4%	1.7 (95% CI 0.1–19.3)	0.74
Life-threatening cardiac rhythm disorder	4; 1.2%	5; 1.8%	0.7 (95% CI 0.2–2.6)	0.11
Evidence of recurrent myocardial ischemia in the first 24 h after admission	36; 11.2%	38; 13.6%	0.8 (95% CI 0.5–1.2)	0.32
Recurrent myocardial ischemia during admission later than day 1	17; 5.3%	10; 3.6%	1.5 (95% CI 0.7–3.3)	0.41
Hospital outcomes				
Improvement in condition, discharge to the outpatient stage	295; 91.9%	256; 91.7%	1.0 (95% CI 0.6–1.8)	0.94
Deterioration due to decompensation of extracardiac pathology and transfer to another hospital	1; 0.3%	1; 0.4%	1.7 (95% CI 0.2–19.3)	0.64
Fatal outcome	23; 7.2%	19; 6.8%	1.1 (95% CI 0.6-2.0)	0.86
Stabilization without significant improvement	2; 0.6%	3; 1.1%	0.6 (95% CI 0.1–3.5)	0.54

Note: Qualitative values are presented with absolute values (n) and relative frequencies (%). *P*-value is for x2 test and Fisher's exact test was used for small samples (categorical variables). Abbreviation: RTP– "risk-treatment" paradox

improvement and referred for ongoing outpatient management.

Adverse hospital outcomes (death or deterioration requiring transfer to another hospital) occurred in 44 patients (7.3%). Of these, 34 (75.5%) were classified as very high risk on admission. 5 patients (0.8%) were discharged without significant improvement. 13 patients who died (28.9%) received revascularization and optimal medical therapy (dual antiplatelet therapy, angiotensin-converting enzyme inhibitors, beta-blockers and high-dose statins). 5 patients (11.1%) underwent revascularization but did not receive optimal medical therapy. The remaining 27 deceased patients (60%) received medical therapy only. Of these, 14 (51.8%) underwent ICA that did not lead to revascularization. Adverse outcomes were observed in 23 patients (51.1%) with a final diagnosis of NSTEMI or unstable angina (without comorbidity or concomitant disease).

It should be noted that these figures do not fully characterize the RVC's in-hospital mortality rate for NSTE-ACS, as a number of patients were not included in the analysis for reasons previously described (Fig. 2).

Among all patients with ($n = 321$) and without ($n = 279$) RTP, no differences were found in the incidence of adverse cardiovascular events during hospital follow-up. Furthermore, RTP had no adverse effect on hospital outcomes when comparing these groups (Table 3).

Hospital outcomes and the incidence of adverse cardiovascular events within each individual risk group with regard to the presence of RTP were further analyzed (Table 4).

Among high-risk patients, we observed a statistically significant increase in adverse outcomes in the RTP group. Specifically, the incidence of fatal events was 5.4% in the RTP group compared to 2.9% in the group without RTP (OR 1.9, 95% CI 0.5–8.9, $p = 0.037$). In the RTP

Table 4 Adverse cardiovascular events and in-hospital outcomes by risk category and RTP

Risk upon admission / parameters	Very high risk, *n* = 208			High risk, *n* = 196			Intermediate risk, *n* = 108			Low risk, *n* = 88		
	RTP cases, *n* = 130	Cases without RTP, *n* = 78	*p*-value	RTP cases, *n* = 130, *n* = 56	Cases without RTP, *n* = 140	*p*-value	RTP cases, *n* = 80	Cases without RTP, *n* = 28	*p*-value	RTP case, *n* = 55	Cases without RTP, *n* = 33	*p*-value
Adverse cardiovascular events												
ACCD	-	1; 1.3%	0.62	1; 1.8%	1; 0.7%	0.63	1; 1.3%	-	0.32	-	3; 9.1%	0.4
Repeat unplanned revascularization	-	1; 1.3%	0.54	1; 1.8%	-	0.12	1; 1.3%	-	0.29	-	-	0.19
Life-threatening cardiac rhythm disorder	3; 2.3%	2; 2.6%	0.9	1; 1.8%	2; 1.4%	0.87	-	-	0.65	-	1; 3.0%	0.78
Evidence of recurrent myocardial ischemia in the first 24 h after admission	28; 21.5%	21; 26.9%	0.37	6; 10.7%	10; 7.1%	0.4	2; 2.5%	3; 10.7%	0.07	-	4; 12.1%	**0.001**
Recurrent myocardial ischemia during admission later than day 1	10; 7.7%	7; 8.9%	0.74	4; 7.1%	1; 0.7%	**0.01**	2; 2.5%	-	0.4	1; 1.8%	2; 6.1%	0.29
Hospital outcomes												
Improvement in condition, discharge to the outpatient stage	111; 85.4%	62; 79.5%	0.27	50; 89%	136; 97.1%	**0.04**	80; 100%	28; 100%	0.55	54; 98.2%	30; 90.9%	0.11
Deterioration due to decompensation of extracardiac pathology and transfer to another hospital	-	1; 1.3%	0.19	1; 1.8%	-	0.11	-	-		-	-	-
Fatal outcome	19; 14.6%	14; 17.9%	0.52	3; 5.4%	4; 2.9%	**0.037**	-	-		1; 1.8%	1; 3.0%	0.71
Stabilization without significant improvement	-	1; 1.3%	0.19	2; 3.6%	-	**0.02**	-	-		-	2; 6.1%	0.06
Number of bed-days	9 [6; 13]	8 [5.8; 12]	0.24	10 [8; 14]	10 [7; 13]	0.2	8 [5.3; 11.8]	8 [5.3; 10]	0.86	8 [7; 11]	8 [7; 12.5]	0.72

Note: Quantitative values are presented according to the law of normal distribution of values: median, interquartile range (Me [Q25; Q75]), qualitative values are presented with absolute values (n) and relative frequencies (%). *P*-value is for x^2 test and Fisher's exact test was used for small samples (categorical variables) and Kraskell-Wallis test (continuous variables). Abbreviation: RTP– "risk-treatment" paradox; ACCD– acute cerebral circulation disorder

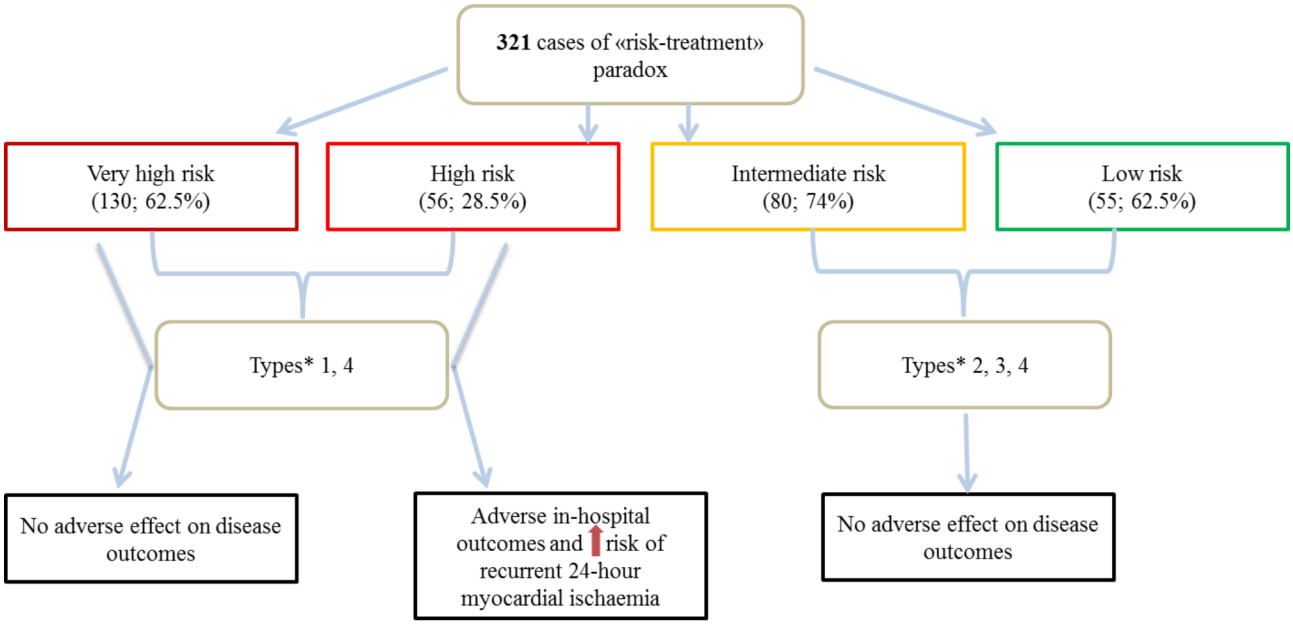

Fig. 3 Key findings from the current phase of the study
*Explanations given in the text

group, one additional patient was transferred to another hospital due to deterioration (1.8%, $p = 0.11$), and 2 (3.6%, $p = 0.02$) were discharged in the same condition. In contrast, among high-risk patients without RTP, no similar adverse outcomes were observed, with 136 patients (97.1%) discharged to the outpatient phase with improvement (OR 0.2 (95% CI 0.1–0.9), $p = 0.04$).

Separate comparisons of the very high-, intermediate-, and low-risk groups revealed no statistically significant impact of RTP on the incidence of in-hospital adverse events. Specifically, within the very high-risk group, where fatal outcomes were most common, the mortality rate was 17.9% in patients who underwent ICA within the guideline-recommended time frame of 2 h, compared to 14.6% in the RTP group (OR 0.8 (95% CI 0.4–1.7), $p = 0.52$).

No adverse hospital outcomes occurred in the intermediate-risk group, which had the highest number of RTP cases. Among low-risk patients, 2 deaths (2.3%) were recorded. One of these patients had type 4 RTP, with the underlying disease complicated by COVID-19. The other patient was not classified as an RTP case as a selective management strategy was chosen. However, while under observation and treatment in the hospital, this patient developed an ACCD, resulting in an adverse outcome.

Adverse cardiovascular events during hospital follow-up, including ACCD, repeat unplanned revascularization, and life-threatening cardiac rhythm disorders, occurred with similar frequency in patients with and without RTP across all analyzed risk groups. However, high-risk patients without timely ICA experienced a significantly higher rate of RMI after 24 h (7.1% vs. 0.7%; OR 10.7, 95% CI 1.2–97.9, $p = 0.01$). Furthermore, among low-risk patients managed with a selective invasive strategy, RMI was observed in the first 24 h in 12.1% of the cases ($p = 0.001$), prompting a change to an early ICA strategy. In the remaining risk groups, no significant differences in the development of RMI were observed, either during the first day of admission or subsequently. A comprehensive summary of the findings related to RTP is presented in Fig. 3.

There was no effect of RTP on various complications of ICA.

Discussion

This study is the first to look at all the clinical guideline criteria to determine the risk of adverse ischemic events and to assess RTP. Most previous studies on the practical application of risk stratification and RTP have mainly used the GRACE calculator as a scale-based risk assessment tool to stratify patients into risk groups for adverse ischemic events [10]. Other patient characteristics identified by clinical guidelines as objectively increasing the risk of adverse ischemic events have not been considered. At the same time, it is recognized that there is a lack of studies defining the isolated value of a GRACE risk score > 140 points in the era of hs-cTn availability. Indeed, recent evidence suggests that the 0/1 h algorithm using hs-cTn is far superior to the GRACE risk score for identifying patients with confirmed MI [16].

In our study, we purposefully stratified patients into risk groups according to clinical guideline criteria and to

assess the presence of RTP and associated hospital outcomes. RTP was analyzed both in terms of the underuse of necessary invasive strategy in very high- and high-risk patients and the early use of ICA in low-risk patients.

Previous studies generally indicate that deviations from current clinical guidelines and the resulting RTP are associated with worse outcomes in NSTE-ACS patients [10]. However, it is well known that the earliest possible invasive strategy (up to 2 h) is now recommended for very high-risk patients, although previous randomized clinical trials have predominantly excluded very high-risk patients [17] and the level of recommendation for emergency intervention is still IC [13, 14]. For high-risk patients, the use of an early invasive strategy has been downgraded to level IIaA according to the updated ESC guidelines (2023) [13]. This change was mainly influenced by the results of the largest meta-analysis to date [17], which included more than 10,000 patients. The meta-analysis showed that in all NSTE-ACS patients, early ICA reduces the risk of RMI and the length of hospital stay, but does not significantly affect all-cause mortality, MI and heart failure, or repeat revascularization. However, the trials in this meta-analysis included patients with significantly different inclusion criteria and coronary lesion patterns.

A key limitation in global studies and meta-analyses evaluating invasive strategies in NSTE-ACS is the following feature: ICA performed at the same time is often analyzed as a single group, whereas it should be taken into account that not all patients undergo a single-stage endovascular intervention [18]. This caveat also applies to our study, as we assessed the efficacy of different invasive strategies based on the time interval between NSTE-ACS diagnosis and arterial catheterization, without considering the need for or timing of subsequent PCI or CABG. Overall, our study shows that more than half of the patients did not undergo revascularization after ICA. In each individual risk group, revascularization rates did not reach 45%. The main reasons were: non-obstructive coronary atherosclerosis (more than half of all cases), severe multivessel coronary lesions, intact arteries and technical difficulties in performing PCI. While some studies focusing exclusively or mainly on NSTEMI patients report higher rates of single-stage PCI (60–65%) [19, 20], our lower revascularization rate likely reflects the inclusion of patients referred for CABG and those with unstable angina, where non-obstructive atherosclerosis was common. Furthermore, very high-risk patients in our cohort often did not have obstructive atherosclerosis.

As previously shown, guideline-recommended risk stratification is still poorly implemented in practice [21]. In our study, analysis of real-world clinical practice data showed that 52.5% of hospitalized patients with a primary diagnosis of NSTE-ACS were not risk stratified or were risk stratified using criteria other than those recommended by clinical guidelines.

Our study showed that RTP is characteristic of patients with NSTE-ACS in a real-world clinical practice setting (more than half of the cases analyzed). The findings on the incidence of RTP in the NSTE-ACS cohort are consistent with the FORCE-ACS registry [10]. However, most of the previously published data on RTP are mainly based on cases where very high- or high-risk patients did not undergo ICA at the required time [3, 21]. In our study, we defined RTP as any discrepancy between a patient's risk level for adverse ischemic events and the type of invasive strategies used, including the assumption that in low-risk patients, early invasive intervention cannot guarantee unconditional benefit and improved disease outcome.

RTP was found to occur both in patients with (37.2%) and without (62.8%) risk stratification. Therefore, the underlying cause of RTP can be attributed to inaccurate risk assessment due to the lack of risk stratification or the application of unregulated risk criteria. On the other hand, each type of RTP was characterized by individual causes relevant to the patient's condition and characteristics. Type 1 RTP was most commonly due to chronic kidney disease (CKD) and anemia, which prevented a necessary invasive strategy, and myocardial ischemia that had resolved at the time of the initial examination. The primary predictors of type 2 RTP in our study were the characteristic clinical trajectory of the disease observed in the prehospital setting and a previously documented history of coronary heart disease (CHD). In these cases, those factors prompted early or emergency invasive strategies, limiting the use of a selective approach appropriate for low-risk patients.

The highest number of RTP cases was observed in intermediate-risk patients. This may be because intermediate-risk criteria include recent revascularization or prior CABG, which, according to the 2020 RSC guidelines, warrant ICA within 24–72 h. In this study, a history of known CHD was one of the main causes of type 2 RTP, and such patients often underwent early or even emergency ICA. RTP was least characteristic of high-risk patients. The routine availability of hs-cTn assays, which facilitate risk stratification based on troponin elevation, has ensured that myocardial damage is recognized early and invasive strategies are implemented in a timely manner.

One of the aims of the study was to examine the effect of RTP on hospital outcomes and the incidence of adverse cardiovascular events during the index hospitalization. Most previous studies suggest an adverse effect of RTP on outcomes [21, 22]. However, there is evidence that RTP does not adversely affect outcomes and other events [11, 23]. In our study, the presence of RTP in the context of invasive strategies had a negative impact on hospital

outcomes only in high-risk patients and also increased their risk of RMI at 24 h. Among other risk groups, RTP did not adversely affect outcomes or the incidence of in-hospital adverse events.

The established high-risk criteria (dynamic hs-cTn corresponding to MI and dynamic ST-segment or T-wave changes) are specific enough to identify true cases of coronary lesions when early intervention is required. In the present study, we used these criteria in addition to the conventional GRACE score to identify high-risk patients. As a result, we found a worsening of hospital outcomes in this group when an early invasive strategy was not implemented (patients with RTP). Delayed CABG (more than 24 h) for multivessel coronary lesion may also be associated with worse outcomes in high-risk patients.

While the accepted criteria for very high risk are designed to identify critical myocardial ischemia, they lack high specificity. The very high-risk group is known to include a high proportion of elderly patients with significant comorbidity [23, 24]. Decompensated comorbidities can influence the presentation of very high-risk criteria. For example, hemodynamic instability, a criterion for very high risk in NSTE-ACS, can be caused by other conditions such as infectious diseases and manifestations of septic or mixed shock. These aspects may explain the high incidence of non-obstructive coronary artery lesions and the lack of efficacy of the emergency invasive strategy. In our study, RTP had no effect on outcomes in very high-risk patients. Our findings and the inadequate evidence base for the use of an emergency invasive strategy in very high-risk patients highlight the need for further studies. This will be an important step in understanding the causes of adverse outcomes in these patients and identifying optimal management strategies for this very high-risk group.

There was no association between RTP and disease outcomes in the intermediate- and low-risk groups. The tendency to perform routine ICA is often driven by a failure to adequately utilize a selective invasive strategy in low-risk patients. The updated ESC guidelines recommend routine ICA for patients with a working diagnosis of NSTE-ACS and a high index of suspicion for unstable angina [13], but the benefit of a routine invasive strategy in reducing the risk of adverse cardiovascular events has not been proven [25]. Current risks of ICA include bleeding (mainly with femoral artery access) [26] and CIN. In addition, early intervention in unstable plaque may lead to distal coronary embolization, development of a slow/no-reflow phenomenon, or complete occlusion of a previously patent coronary artery, resulting in an increased risk of acute MI (type 4a) [25]. According to a recently published study, patients with NSTEMI and PMI (with or without type 4a MI) had a 3-fold increased risk of all-cause mortality and an elevated risk of major adverse cardiovascular events during one-year follow-up compared to patients without periprocedural ischemic events [9]. Given these potential adverse effects of the invasive strategy in practice, we tracked cases with various ICA complications. Our study found no statistically significant association between RTP and ICA complications. Future studies with larger sample sizes may be needed to determine if a relationship exists.

It should be noted that the results of this study were obtained in a preliminary sample of patients. Further analysis is planned to confirm the results in a larger number of patients. In addition, a further phase of our study will examine the impact of RTP on disease outcomes in relation to the timing of different methods of myocardial revascularization in each of the risk groups.

Study limitations

First, the study is retrospective, which may introduce a degree of subjectivity into the analysis of the data when re-stratifying the risk of adverse ischemic events. Full verification of the scope and accuracy of the medical history data is not feasible.

Second, the study is single-center in nature, resulting in the potential influence of established diagnostic and treatment practices at this institution on patient management decisions.

Third, limitations of our study include the short follow-up period for patient outcomes and the small number of adverse cardiovascular events.

Finally, the current analysis did not explore the independent predictors of adverse outcomes or employ logistic regression modeling. To address these limitations, our ongoing study will investigate potential confounding variables and examine long-term clinical outcomes using comprehensive health information systems.

Conclusions

RTP in relation to the type of invasive strategy is common in patients with NSTE-ACS (53.5% of all cases) and is manifested by various discrepancies between the level of risk of adverse ischemic events and the invasive strategies used. For high-risk patients, RTP worsened in-hospital outcome and influenced the risk of RMI after 24 h. In the other risk groups, RTP did not worsen hospital outcomes or increase the development of adverse cardiovascular events during hospital follow-up.

Abbreviations

ACCD	Acute cerebral circulation disorder
CABG	Coronary artery bypass grafting
CHD	Coronary heart disease
CIN	Contrast–induced nephropathy
CKD	Chronic kidney disease
ECS	European Society of Cardiology
hs-cTn	high–sensitivity cardiac troponin
ICA	Invasive coronary angiography

MI	Myocardial infarction
NSTE-ACS	non–ST–elevation acute coronary syndrome
NSTEMI	Non–ST–elevation myocardial infarction
PCI	Percutaneous coronary intervention
PMI	Periprocedural myocardial injury
RMI	Recurrent myocardial ischemia
RSC	Russian Society of Cardiology
RTP	"Risk–treatment" paradox
RVC	Regional Vascular Centre

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Author contributions
A.N.: Study concept and design. Recruitment of patients, formation of the database. Statistical processing of data. Writing the article, editing. D.V.: Recruitment of patients, formation of the database. Statistical processing of data. Writing an article, editing. V.R.: Conceptualisation and design of the study. Editing of the article. Final approval of the manuscript.

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Data availability
Availability of data and materials: Data are stored in closed access in the form of a personalised electronic summary table created using Excel 2010 (Certificate of State Registration No. 2023622190 dated 03/07/2023). The datasets used and/or analysed in the current study are available from A. Nesova upon reasonable request.

Declarations

Ethics approval and consent to participate
This is a single-center retrospective observational study. The study was conducted in compliance with the principles of the Declaration of Helsinki and was approved by the Human Research Ethics Committee of the Research Institute of Cardiology, Tomsk National Research Medical Center, protocol No. 235 of 23-Nov-2022. All patients have signed consent to the processing of personal data.

Informed consent
Informed consent was obtained from all subjects involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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