






<https://doi.org/10.21320/1818-474X-2026-2-56-74>

Contribution of *AGTR1* rs275651 genetic polymorphism and immune system cells to survival of patients after haemorrhagic stroke: a prospective cohort study

Вклад генетического полиморфизма *AGTR1* rs275651 и клеток иммунной системы в выживаемость пациентов после перенесенного геморрагического инсульта: проспективное когортное исследование

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Abstract

Реферат

INTRODUCTION: Severe brain damage may result in prolonged or chronic critical illness (PCCI) representing a special clinical patient's model. Predicting early the high risk of poor outcome of PCCI should help for in-time use of personalized treatment modalities. Immunological and genetic markers may exhibit potentially high prognostic potential may exhibit. **OBJECTIVE:** To determine the contribution of the *AGTR1* (angiotensin II receptor type 1) rs275651 regulatory 5'-region polymorphism, the content of immune system cells and their neutrophil to lymphocyte ratio (NLR) to the outcome of PCCI in post-hemorrhagic stroke patients. **MATERIALS AND METHODS:** The study included 192 patients with hemorrhagic stroke in PCCI. 107 patients were admitted to the hospital with nosocomial pneumonia from other hospitals. Age was 59 (49; 67) years, Sequential Organ Failure Assessment score on the day of hospitalization was 3 (1; 4). Women constituted 43 % of the cohort. **RESULTS:** Neutrophil to lymphocyte ratio (NLR) higher than 4 on the fifth day of hospitalization predicted an unfavourable outcome ($p = 0.0001$; logrank test; Odds Ratio (OR) 6.7; 95% Confidence Interval (CI) 2.6–17.0; $n = 153$). Subgrouping the patients showed that the NLR value as determined on the fifth day of hospitalization predicted outcome only for patients admitted without pneumonia. For patients admitted with pneumonia, genetic variants of the angiotensin II receptor gene — *AGTR1* were predictive for outcome: minor allele *AGTR1* rs275651 A showed poor outcome of PCCI on the first day of hospitalisation ($p = 0.037$; logrank test; OR 2.6; 95% CI 0.9–7.5; $n = 107$). For patients admitted without pneumonia no effect of *AGTR1* rs275651 genotype

АКТУАЛЬНОСТЬ: Тяжелые повреждения мозга с исходом в продленное или хроническое критическое состояние (ПХКС) формируют особую клиническую модель пациента. Раннее прогнозирование риска неблагоприятного исхода ПХКС может иметь клиническое значение для принятия врачом решения о выборе персонализированных методов лечения. Ранее было показано, что генетические и иммунологические маркеры обладают высоким прогностическим потенциалом у пациентов с последствиями тяжелых повреждений головного мозга, вызванных разными причинами. **ЦЕЛЬ ИССЛЕДОВАНИЯ:** Определить вклад полиморфизма регуляторной 5'-области *AGTR1* (angiotensin II receptor type 1) rs275651, содержания клеток иммунной системы и их соотношения в исходе ПХКС у пациентов, перенесших геморрагический инсульт. **МАТЕРИАЛЫ И МЕТОДЫ:** В исследование включили 192 пациента с последствиями геморрагического инсульта, находившихся в ПХКС. В лечебное учреждение с нозокомиальной пневмонией поступили 107 из них. Возраст — 59 (49; 67) лет, оценка по шкале Sequential Organ Failure Assessment (SOFA) в день госпитализации — 3 (1; 4), женщины составили 43 % когорты. **РЕЗУЛЬТАТЫ:** Величина отношения нейтрофилов к лимфоцитам (ОНЛ) выше 4 на пятый день госпитализации прогнозировала неблагоприятный исход ($p = 0,0001$; логранговый критерий; отношение шансов (ОШ) 6,7; 95%-й интервал [95% ДИ] 2,6–17,0; $n = 153$), но при раздельном по подгруппам анализе было выявлено, что ОНЛ на пятый день госпитализации прогнозирует исход только

revealed ($p = 0.76$; $n = 85$). **CONCLUSIONS:** In post-hemorrhagic stroke patients in PCCI, the increased NLR value (> 4) on the fifth day of hospitalization predicts outcome of PCCI in patients admitted without pneumonia. For patients admitted with pneumonia, the genetic marker, minor allele A of *AGTR1* rs275651, associates with an unfavourable outcome.

KEYWORDS: critical illness, hemorrhagic stroke, polymorphism genetic, receptor angiotensin type 1, lymphocyte count, neutrophils

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✉ *For citation:* Chumachenko A.G., Vyazmina M.D., Kalov A.R., Petrova M.V., Pisarev V.M. Contribution of AGTR1 rs275651 genetic polymorphism and immune system cells to survival of patients after haemorrhagic stroke: a prospective cohort study. *Annals of Critical Care*. 2026; 2:56–74. <https://doi.org/10.21320/1818-474X-2026-2-56-74>

📅 *Received:* 02.09.2025

📅 *Accepted:* 15.02.2026

для подгруппы пациентов, поступивших без пневмонии. Для подгруппы пациентов, поступивших с пневмонией, прогностической информативностью обладали аллельные варианты гена рецептора ангиотензина II — *AGTR1*. В подгруппе пациентов, поступивших с пневмонией, обнаружена ассоциация наличия минорного аллеля *AGTR1* rs275651 A с неблагоприятным исходом ПХКС ($p = 0,037$; логранговый критерий; ОШ 2,6; 95% ДИ 0,9–7,5; $n = 107$). Среди пациентов в ПХКС с последствиями геморрагического инсульта, поступивших без пневмонии, различия в выживаемости в зависимости от генотипа *AGTR1* rs275651 не обнаружили ($p = 0,76$; $n = 85$). **ВЫВОДЫ:** Для пациентов в ПХКС, поступивших с последствиями геморрагического инсульта и без пневмонии, повышение значения ОНЛ выше 4 на пятый день госпитализации прогнозирует летальный исход. При наличии пневмонии в день госпитализации минорный аллель A *AGTR1* rs275651 являлся предиктором неблагоприятного исхода ПХКС.

КЛЮЧЕВЫЕ СЛОВА: критическое состояние, геморрагический инсульт, генетический полиморфизм, рецептор ангиотензина 1-го типа, количество лимфоцитов, нейтрофилы

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✉ *Для цитирования:* Чумаченко А.Г., Вязьмина М.Д., Калов А.Р., Петрова М.В., Писарев В.М. Вклад генетического полиморфизма AGTR1 rs275651 и клеток иммунной системы в выживаемость пациентов после перенесенного геморрагического инсульта: проспективное когортное исследование. *Вестник интенсивной терапии им. А.И. Салтанова*. 2026; 2:56–74. <https://doi.org/10.21320/1818-474X-2026-2-56-74>

📅 *Поступила:* 02.09.2025

📅 *Принята к печати:* 15.02.2026

DOI: 10.21320/1818-474X-2026-2-56-74

Introduction

Currently, there is no consensus on the definition of chronic critical illness [1]. Some authors refer to this condition as a prolonged critical illness, while others propose introducing the latter term to characterize a separate, in-

termediate state that still requires life-support measures to maintain organ function due to organ failure. However, greater stability or regression of the pathological symptoms of multiple organ failure indicate a high probability of recovery [2]. Until clear definitions accepted by the professional community are established, it seems logical to use

a working term that unites these possibly different conditions — prolonged and/or chronic critical illness (PCCI). In this case, despite the different understanding of the patient population meeting the definitions of chronic or prolonged critical illness, it can be said with certainty that the number of PCCI patients has doubled in recent decades and may double over the next decade, and the overall one-year survival rate of patients with PCCIs ranges from 40 to 50 % [3].

Severe brain damage resulting from trauma, stroke, intoxication, or prolonged hypoxic conditions leading to cerebral hemorrhagic stroke (CHS) creates a unique clinical profile for patients. These patients often survive the acute phase of the disease, ultimately resulting in a vegetative state or a state of low consciousness, and require specific approaches to long-term intensive and rehabilitative treatment [1]. Advances in resuscitation enable the survival of patients even after severe brain injury [4].

The presence of comorbid conditions and their sequential development during PCCI as a result of alterations in the central nervous system and neurohumoral regulation create a vicious cycle that hinders stabilization and restoration of cerebral function [3, 5].

Severe brain injury is often accompanied by the development of arterial hypotension, which may be caused by decreased systemic vascular resistance due to damage within the diencephalic region, increasing brain herniation, and the development of adrenal insufficiency. Another cause of hypotension is a drop in cardiac output due to decreased myocardial contractility or hypovolemia, which occurs as a result of bleeding, dehydration therapy, type II diabetes and hyperthermia. Hypovolemia initiates centralization of blood circulation, which subsequently leads to a number of adverse consequences, such as impaired capillary circulation, organ and tissue ischemia, tissue edema, and multiple organ failure [6].

The clinical heterogeneity of PCCI, including its severity and risk of adverse outcomes, significantly complicates the selection of optimal treatment in a personalized intensive care setting, which requires readiness for the timely use of high-tech life support methods. Predicting the high risk of severe and fatal PCCI cases can significantly facilitate the adoption of an appropriate treatment strategy.

The search for informative biomarkers to stratify high-risk patient groups remains a challenge. Such biomarkers, available early in a patient's stay in the intensive care unit (ICU), would help physicians select optimal, more personalized treatment options. Timely identification of patient groups requiring different treatment approaches may represent an approach to reduce PCCI mortality. On the other hand, identifying pathogenetically significant prognostic biomarkers will help elucidate the mechanisms underlying the development of critical conditions and associated molecular targets, impact on which could reduce mortality in life-threatening critical conditions. In intensive care medicine worldwide, angiotensin II is a second- or third-line

vasopressor for the treatment of shock; presumably, its use may be more effective if considering the genetic polymorphism of its receptor.

Since pneumonia (Pn) significantly contributes to PCCI patient's mortality, we selected two potential markers for our study that are related to key components of the cardiovascular and immune systems contributed to Pn pathogenesis. The selection was based on a vision the neutrophil-to-lymphocyte ratio (NLR) as an integral indicator reflecting the imbalance between innate (neutrophils) and adaptive (lymphocytes) immunity systems, while polymorphism of the angiotensin II receptor gene determined differences in the control of vascular wall health and immune cell motility.

Molecular and cellular markers are firmly established as prognostic biomarkers for various diseases, helping to plan and organize personalized treatment in advance [7, 8]. Single-nucleotide polymorphisms (SNPs), which determine the population distribution of gene variants that differentially contribute to PCCI pathogenesis or comorbidity, may serve as promising sources of such biomarkers.

The study of gene polymorphisms in critical illness facilitates the early identification of the most vulnerable patients predisposed to severe critical illness due to infectious complications [9]. One promising genetic biomarker for the early prediction of severe progression and outcome of chronic hepatitis C is the angiotensin II receptor gene, a vasopressor hormone with pleiotropic effects that determines the regulation of blood pressure, cardiac function, and the activation of immune cells [10].

Angiotensin II acts through angiotensin II receptor type 1 (*AGTR1*) and angiotensin II receptor type 2, which mediate its cardiovascular effects [11]. However, the pleiotropic effect of angiotensin II on both the cardiovascular system and immune cells is realized through interaction with *AGTR1*, stimulating neutrophils, phagocytosis and NETosis, migration and invasion of immune cells [12–14]. Salnikova L.E. and co-authors established an association of *AGTR1* rs5186 with nosocomial pneumonia [15]. Another single nucleotide polymorphism, *AGTR1* rs275651, is associated with the development of angina pectoris, pulmonary edema in high-altitude conditions, and hypertension [16]. This polymorphism within the part of the most common haplotype I TTAA in the promoter region of the gene: T (rs275651) – T (rs275652) – A (rs422858) – A (rs275653) has been shown to be associated with increased gene promoter activity and the development of hypertension in the Caucasian population [17].

Previously, we demonstrated the role of the *AGTR1* rs275651 genetic polymorphism in the outcome and course of sepsis [18, 19]. However, the potential informative value of this polymorphism for predicting the outcome of CHS and its association with immune system markers remained unclear.

Objective

The aim of the study was to determine the contribution of the *AGTR1* rs275651 regulatory region polymorphism, immune cell counts, and their ratios to the outcome in patients with CHS.

Materials and methods

Study design

We conducted a prospective, single-center cohort study with subgroup analysis (patients admitted with and without pneumonia). The study was approved by the Ethics Committee of the V.A. Negovskiy Research Institute of General Resuscitation, Federal Scientific and Clinical Center of Pneumonia and Respiratory Care, Protocol No. B 2.2.18 dated December 20, 2018. The study was conducted in accordance with the Declaration of Helsinki (2013); Article 21 of the Constitution of the Russian Federation; the Fundamentals of the Legislation of the Russian Federation on the Protection of Citizens' Health, and orders and instructions of the Ministry of Health of the Russian Federation. Patients were enrolled in the study between July 2019 and August 2022. A key feature of the study design was that the study did not involve additional invasive interventions for the patient. Residual biomaterial (blood) collected as a part of routine clinical monitoring was used for analysis. Thus, biomaterial intended for disposal after standard laboratory testing was retrospectively used for research purposes. This approach minimizes additional risk to the patient. For patients with acute neurological deficits precluding independent decision-making, informed consent was obtained from their legal representatives. Importantly, the legal representative was the person listed in the accompanying medical documentation as the contact for hospitalization and treatment matters, not one chosen by the researchers. This ensured objectivity and compliance with clinical practice. If such a representative was unavailable or unavailable, patient inclusion was decided by an independent medical board consisting of the attending physician, the head of the intensive care unit, and the research center coordinator.

According to our preliminary data, the mortality rate of patients admitted to this Center due to CHS was approximately 14%, and this was used to calculate the sample size. The formula used for its calculation was:

$$n = (t_2 * P * Q) / \Delta^2,$$

where t is the critical value of the Student's t -test (at a significance level of 0.05, it is 1.96), Δ is the maximum permissible error (5 %), p is the proportion of cases in which the studied characteristic is present (86), Q is the proportion of cases in which the studied characteristic is not present (14).

The number of patients (n) was 185. Taking into account possible losses during the study (4–5 %), the sample

size was increased accordingly. The study included 192 patients with CHS and its consequences, admitted to our hospital and requiring an intensive care in the ICU. Of these, 107 were admitted to the hospital with nosocomial pneumonia that developed at another hospital, and 85 patients were without pneumonia on admittance.

Patients were admitted to the Federal Scientific and Clinical Center of Intensive Care Medicine and Rehabilitology from other hospitals. The median time from case to hospitalization was 26 days (18;46) (Me (Q1;Q3)). The time from case to hospitalization varied from 1 day to 262 days. Ninety-seven percent of patients in our sample survived the acute phase of the disease (the first three days of illness), 48 percent were in the acute phase (28 days).

General inclusion criteria for the study (Figure 1):

- no cancer or polymerase chain reaction (PCR)-verified Coronavirus Disease 2019 (COVID-19);
- hospitalization due to complications of hemorrhagic stroke;
- age 18 years or older;
- written informed consent from the patient or their legal representative to participate in the study.
- Exclusion criteria included:
 - refusal of the patient and/or their legal representatives to participate in follow-up;
 - diagnosis of cancer or COVID-19 during treatment.

Reference population for verifying the distribution of AGTR1 rs275651 genotype frequencies

Anonymized, conditionally healthy donors from the donor center at the Federal Scientific and Clinical Center for Pediatric Hematology and Immunology (Moscow) ($n = 154$) were used as a reference group to check the compliance of the genotype distribution with the Hardy-Weinberg law. They had medical permission to take blood from them, implying the absence of comorbidities in the form of cardiovascular, oncological, endocrinological, infectious diseases, as well as nervous diseases, COVID-19 and AIDS, who gave informed consent for depersonalized participation in scientific research, aged 18 to 60 years, living in Moscow or the Moscow region, of mixed (with a predominance of Slavic) ethnicity, typical for the Moscow population. The exclusion criterion was the presence of antibodies against hepatitis B and C viruses.

Patients in the study cohort were treated according to clinical protocols and clinical guidelines. When infectious complications were detected, the principles of the Antibacterial Therapy Stewardship Strategy were followed for antibiotic prescribing, accompanied by microbiological monitoring. Glucocorticosteroids were prescribed using a personalized approach, strictly adhering to established clinical indications and protocols. Since patients were admitted from other healthcare facilities, accompanying medical records from the other healthcare facility from which the

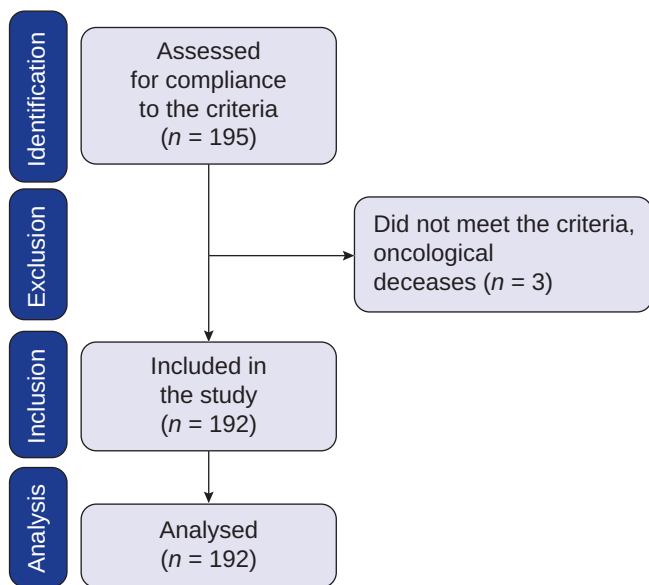


Fig. 1. Study flow chart

patient was transferred were reviewed when prescribing treatment. However, the inadequacy of such information in many cases hindered a comprehensive analysis of drug therapy, including antibiotic therapy and glucocorticosteroids, administered prior to admission. In turn, the incompleteness of such information hindered the elucidation of the relationship between the treatment being undertaken and the levels of key immune defense mechanisms—lymphocytes and neutrophils — in predicting outcome. On the other hand, the lack of information in the accompanying medical documentation on nutritional support of patients, as well as the variety of personalized and adequate nutritional support provided at our hospital in accordance with the targeted correction of the nutritional protocol according to indications, limited the formulation of the objectives in this study.

Data analysis

Allelic variants of *AGTR1* rs275651 were identified using tetraprimer polymerase chain reaction, followed by electrophoretic separation and identification of stained products in the gel. The following primers were selected and synthesized at Evrogen LLC (Russia) using the Primer-BLAST program (<https://www.ncbi.nlm.nih.gov/tools/primer-blast/>):

- 1for 5’-GGACATGCTACCCAAGTTGC-3’;
- 2for 5’-CCAAAAATCAATTAATGTTA-3’;
- 1rev 5’-GCAATTGGCATATCCATCAC-3’;
- 2rev 5’-GTCACCCTACTCACCTATCA-3’.

The Shapiro-Wilk test was used to assess the normal distribution of quantitative parameters. Normally distributed variables were described using mean values (M) and standard deviations (SD), and 95 % confidence intervals (95% CI). Non-normally distributed quantitative

data were described using median (Me) and interquartile range (IQR). Groups with normally distributed variables, provided that variances were equal, were compared using Student’s t-test. If non-normally distributed, the Mann-Whitney U-test was used. Categorical data were described as absolute values and percentages, and analyzed using four-field contingency tables and χ^2 test with Yates’s correction for sample continuity, or Fisher’s exact method. The odds ratio with a 95% confidence interval (OR; 95% CI) was used as a quantitative measure of effect when comparing relative variables. For survival analysis, the Kaplan-Meier log-rank test was performed. Results are presented as hazard ratios (HR) with 95% confidence intervals. Differences were considered significant at $P < 0.05$. Statistical analysis was performed using MedCalc version 11.6 (MedCalc Software, Belgium) and SigmaStat version 3.5 (BitWork Technologies, USA).

Assessment scales and laboratory parameters

Upon admission, the Sequential Organ Failure Assessment (SOFA), Cumulative Illness Rating Scale (CIRS), and Glasgow Coma Scale (GCS) scores were assessed (Table 1). Blood tests were performed using a UniCel DxH 800 Coulter automated hematology analyzer (Beckman Coulter, USA).

Results

Patient characteristics

Data on the patients who participated in the study are presented in Table 1.

We included data on the NIH on days 1 and 5 of hospitalization to determine patients’ response to treatment. As a result of treatment, the NIH decreased from day 1 to day 5 of hospitalization ($p = 0.006$, Wilcoxon signed-rank test). No differences were found between patients with different *AGTR1* rs275651 genotypes in age, gender, CIRS ($p = 0.71$), SOFA ($p = 0.20$), and GCS ($p = 0.16$) scores at admission. The NIH on day 5 of hospitalization was lower in patients with the minor AT and AA *AGTR1* rs275651 genotypes ($p = 0.036$). Survivors and nonsurvivors differed in age ($p = 0.001$), CIRS ($p < 0.001$), SOFA ($p = 0.004$), and GCS ($p = 0.027$) scores, NLR and neutrophil count at admission, NLR and neutrophil count on day 5, and length of hospitalization.

The mortality rate for the entire sample ($n = 192$) was 13 %. The mortality rate in the subgroup of patients admitted with pneumonia ($n = 107$) was 16 %. In 39 % of patients admitted without pneumonia ($n = 85$), it developed during hospitalization, and in patients who developed pneumonia during hospitalization, the mortality rate was 19 %. For patients admitted without pneumonia and with no pneumonia developed, the mortality rate was 2 %.

Table 1. Characteristics of patients included in the study

Parameters	All patients	Carriers of <i>AGTR1</i> rs275651 TT genotype	Carriers of <i>AGTR1</i> rs275651 TA, AA genotypes	<i>p</i> *	Survived	Deceased	<i>p</i> **
Age, years	59 (49; 67)	59 (50; 69)	58 (46; 65)	0.26	58 (47; 65)	67 (57; 73)	0.001
Women, <i>n</i> (%)	83 (43 %)	54 (41 %)	29 (48 %)	0.27	69 (41 %)	14 (56 %)	0.20
SOFA scores (upon admittance)	3 (1; 4)	3 (2; 4)	3 (1; 4)	0.20	2 (1; 4)	3 (3; 5)	0.004
CIRS scores (upon admittance)	15 (11; 18)	15 (12; 18)	15 (10; 18)	0.71	14 (11; 18)	18 (15; 20)	< 0.001
GCS scores (on admittance)	13 (10; 15)	12 (9; 15)	14 (10; 15)	0.16	13 (10; 15)	11 (7; 13)	0.027
Neutrophiles, $\times 10^9/L$ (upon admittance)	6.2 (4.5; 8.2)	6.2 (4.6; 8.5)	5.9 (4.3; 7.2)	0.31	5.9 (4.2; 8.1)	7.1 (4.9; 9.4)	0.11
Lymphocytes, $\times 10^9/L$ (upon admittance)	1.4 (1.0; 1.8)	1.3 (0.9; 1.8)	1.4 (1.1; 1.9)	0.23	1.4 (1; 1.8)	1.3 (0.8; 1.7)	0.18
Neutrophil-to-lymphocyte Ratio, NLR (upon admittance)	4.4 (2.7; 7.5)	4.7 (2.7; 8.7)	3.9 (2.7; 7.1)	0.20	4.3 (2.6; 7.2)	6.2 (3.5; 9.6)	0.037
Neutrophiles, $\times 10^9/L$ (day 5 after hospitalization)	5.4 (4.1; 8.3)	5.8 (4.2; 8.7)	4.9 (3.9; 6.4)	0.052	5.3 (3.9; 8.1)	7.2 (5.1; 12.6)	0.039
Lymphocytes, $\times 10^9/L$ (day 5 after hospitalization)	1.5 (1.2; 1.9)	1.4 (1.1; 1.8)	1.7 (1.3; 2.1)	0.057	1.6 (1.2; 1.9)	1.4 (0.9; 1.7)	0.22
Neutrophil-to-lymphocyte Ratio, NLR (day 5 after hospitalization)	3.7 (2.5; 6.5)	3.9 (2.6; 7.1)	3.4 (2.1; 5.2)	0.036	3.5 (2.5; 5.9)	6.3 (4.2; 9.9)	0.008
Longevity of hospitalization, days	49 (28; 64)	49 (29; 64)	44 (24; 65)	0.37	49 (29; 65)	24 (9; 49)	0.001
Disease longevity prior to secondary hospitalization, days (from case to hospitalization), days	26 (18; 46)	25 (17; 42)	29 (21; 52)	0.084	26 (18; 45)	29 (20; 53)	0.61
Lethality, lethal cases (%)	25 (13 %)	14 (11 %)	11 (19 %)	0.16			

Note: CIRS — Cumulative Illness Rating Scale; SOFA — Sequential Organ Failure Assessment; NLR — the ratio of the absolute content of neutrophils to the absolute content of lymphocytes per unit volume of blood; GCS — Glasgow Coma Scale.

* Between patients with *AGTR1* rs275651 TT genotype and *AGTR1* rs275651 TA, AA genotypes.

** Between surviving and deceased patients.

Age, SOFA, CIRS, and GCS scores, immune cell counts, immune cell ratios, and time points are presented as median (IQR). The number of women and mortality are presented in absolute values and percentages. *P*-values less than 0.05 are shown in bold.

Correlation analysis

The results of the correlation analysis of demographic variables, assessment scales, and cellular parameters for patients in our cohort are presented in Table 2.

Lymphocyte and neutrophil counts and their ratio on the first and fifth days of hospitalization correlated with SOFA and GCS scores (Table 2). CIRS scores correlated with NLR on the first and fifth days and with lymphocyte count on the fifth day. Age, SOFA, CIRS, and GCS scores, neutrophil count on the fifth day of hospitalization, and NLR on the first and fifth days of hospitalization correlated with outcome.

The patient's cohort was divided into two groups based on their *AGTR1* genotype. Tables 3 and 4 include data from the analysis of patients with the *AGTR1* rs275651 TT genotype and A allele carriers (AA and AT genotypes), respectively.

As shown in Table 3, for patients carrying the *AGTR1* rs275651 TT genotype, correlations with outcome were maintained for SOFA, CIRS, GCS, and neutrophil counts on day 1 and day 5 of hospitalization, as well as for the neutrophil count on day 5, as for all patients in our sample. Furthermore, lymphocyte counts on days 1 and 5 of hospitalization were associated with outcome. NLR values on

Table 2. Correlation of demographic variables, assessment scales and cellular parameters (all patients)

Parameters	Age	Gender	SOFA	CIRS	GCS	Lymphocytes, day 1	Neutrophiles, day 1	NLR, day 1	Lymphocytes, day 5	Neutrophiles, day 5	NLR, day 5
Age	—	0.037 0.15	0.000 0.33	0.000 0.30	0.000 -0.29	0.003 -0.23	0.25 0.10	0.005 0.21	0.002 -0.25	0.25 0.10	0.0096 0.21
Gender	0.037 0.15	—	0.041 0.15	0.08 0.13	0.01 -0.19	0.0497 -0.15	0.54 0.05	0.08 0.13	0.37 -0.07	0.47 0.06	0.10 0.13
SOFA	0.000 0.33	0.041 0.15	—	0.000 0.34	0.000 -0.72	0.000 -0.25	0.000 0.28	0.000 0.37	0.000 -0.29	0.000 0.28	0.000 0.32
CIRS	0.000 0.30	0.08 0.13	0.000 0.34	—	0.000 -0.28	0.03 -0.17	0.25 0.10	0.016 0.18	0.046 -0.16	0.25 0.10	0.034 0.17
GCS	0.000 -0.29	0.01 -0.19	0.000 -0.72	0.000 -0.28	—	0.000 0.31	0.000 -0.35	0.000 -0.45	0.000 0.28	0.011 -0.20	0.000 -0.32
Neutrophiles, day 1	0.25 0.10	0.54 0.05	0.000 0.28	0.25 0.10	0.000 -0.35	0.035 -0.16	—	—	0.21 -0.10	—	—
Neutrophiles, day 5	0.25 0.10	0.47 0.06	0.027 0.18	0.25 0.10	0.011 -0.20	0.17 -0.11	—	—	0.28 -0.10	—	—
Outcome	0.002 0.22	0.17 0.10	0.003 0.21	0.001 0.23	0.024 -0.16	0.19 -0.10	0.11 0.12	0.037 0.16	0.22 -0.10	0.038 0.17	0.0075 0.22

Note: CIRS — Cumulative Illness Rating Scale; SOFA — Sequential Organ Failure Assessment; GCS — Glasgow Coma Scale. In each column the upper value corresponds to the *p*-values, and the lower value corresponds to the *r* values. *P*-values less than 0.05 are shown in bold.

Table 3. Linear regression data of demographics, assessment scales on the first day of hospitalisation, and cellular parameters for patients with AGTR1 rs275651 TT genotype

Parameters	Age	Gender	SOFA	CIRS	GCS	Lymphocytes, day 1	Neutrophiles, day 1	NLR, day 1	Lymphocytes, day 5	Neutrophiles, day 5	NLR, day 5
Age	—	0.037 0.15	0.000 0.33	0.000 0.30	0.000 -0.29	0.003 -0.23	0.25 0.10	0.005 0.21	0.002 -0.25	0.25 0.10	0.0096 0.21
Gender	0.037 0.15	—	0.041 0.15	0.08 0.13	0.01 -0.19	0.0497 -0.15	0.54 0.05	0.08 0.13	0.37 -0.07	0.47 0.06	0.10 0.13
SOFA	0.000 0.33	0.041 0.15	—	0.000 0.34	0.000 -0.72	0.000 -0.25	0.000 0.28	0.000 0.37	0.000 -0.29	0.000 0.28	0.000 0.32
CIRS	0.000 0.30	0.08 0.13	0.000 0.34	—	0.000 -0.28	0.03 -0.17	0.25 0.10	0.016 0.18	0.046 -0.16	0.25 0.10	0.034 0.17
GCS	0.000 -0.29	0.01 -0.19	0.000 -0.72	0.000 -0.28	—	0.000 0.31	0.000 -0.35	0.000 -0.45	0.000 0.28	0.011 -0.20	0.000 -0.32
Neutrophiles, day 1	0.25 0.10	0.54 0.05	0.000 0.28	0.25 0.10	0.000 -0.35	0.035 -0.16	—	—	0.21 -0.10	—	—
Neutrophiles, day 5	0.25 0.10	0.47 0.06	0.027 0.18	0.25 0.10	0.011 -0.20	0.17 -0.11	—	—	0.28 -0.10	—	—
Outcome	0.002 0.22	0.17 0.10	0.003 0.21	0.001 0.23	0.024 -0.16	0.19 -0.10	0.11 0.12	0.037 0.16	0.22 -0.10	0.038 0.17	0.0075 0.22

Note: CIRS — Cumulative Illness Rating Scale; SOFA — Sequential Organ Failure Assessment; GCS — Glasgow Coma Scale. In each column the upper value corresponds to the *p*-values, and the lower value corresponds to the *r* values. *P*-values less than 0.05 are shown in bold.

days 1 and 5 of hospitalization correlated with SOFA, CIRS, and GCS scores, as for patients in the entire sample.

The data presented in Table 4 demonstrate that for patients carrying the minor *AGTR1* rs1058427 A allele, only age correlates with the outcome.

The values of SOFA, CIRS, GCS, NLR, neutrophils count and lymphocytes count were not associated with outcome. NLR values on the first day of hospitalization correlated with the SOFA and GCS scores, as was the case for all patients in our sample (Table 4).

Association of immune cell counts with outcome

The NLR value on the first day of hospitalization did not predict outcome ($p = 0.15$, log-rank test). No difference in survival was found based on neutrophil ($p = 0.16$) or lymphocyte ($p = 0.25$) counts during the same period.

Only on the fifth day of hospitalization a significant association between NLR value and outcome had been revealed. An NLR value more than 4 on the fifth day of hospitalization predicted an unfavorable outcome ($p = 0.0001$, log-rank test, OR = 6.7, 95% CI: 2.6–17.0, $n = 153$, Figure 2, A).

An insignificant trend toward an association between neutrophil counts greater than $5.5 \times 10^9/L$ and an unfavorable prognosis was found ($p = 0.093$, $n = 153$, Figure 2, B). The lymphocyte count on the fifth day of hospitalization was not associated with the outcome of patients with consequences of the CHS.

Half of the patients in our cohort were admitted with pneumonia. Mortality in this subgroup of patients was twice as high as in the subgroup of patients admitted without pneumonia. When separating the subgroups of patients admitted with and without pneumonia, we found that the NLR on the fifth day of hospitalization was significantly associated with outcome only for the proportion of patients admitted without pneumonia ($p = 0.0001$, OR = Inf, $n = 71$, Figure 3, D). NLR values on the first (Figure 3, A) and fifth days of hospitalization (Figure 3, B) for patients admitted with pneumonia did not predict outcome.

Thus, cellular immunological markers, easily detectable by clinical laboratory blood tests, were informative only for patients admitted to the hospital without clinical or tomographic signs of pneumonia. The search for candidate predictors of outcome after CHS was expanded by examining the gene polymorphism of the angiotensin II receptor gene *AGTR1*.

Genetic polymorphism *AGTR1* rs27565 and outcome

First, we conducted a comparative study of the genetic variability of our cohort of patients and conditionally healthy donors from the Moscow population. The distribution of patient genotypes was: *AGTR1* rs275651 TT — 69 %, TA — 28 %, AA — 3 %, which corresponded to the Hardy-Weinberg law ($p = 0.79$, $\chi^2 = 0.07$; $n = 192$), and did not dif-

fer, according to our data, from the distribution in the group of conditionally healthy donors of the Moscow population (TT — 76 %, TA — 22 %, AA — 2 %, $p = 0.672$; $n = 141$). Subgroups of patients admitted without pneumonia and with pneumonia also did not differ in *AGTR1* genotypes frequencies between themselves and conditionally healthy donors (Figure 4).

Analysis of the contribution of the *AGTR1* rs275651 genetic polymorphism to the outcome of hemorrhagic stroke sequelae revealed no differences between the subgroups of patients with alternative *AGTR1* genotypes (TA + AA vs TT, $p = 0.12$, $n = 192$, Figure 5, A).

In the subgroup of patients admitted with pneumonia, an association was found between the presence of the minor *AGTR1* rs275651 A allele and an unfavourable outcome ($p = 0.037$, log-rank test, OR = 2.6, 95% CI: 0.9–7.5, $n = 107$, Figure 5, B). Among patients with sequelae of CHS admitted without pneumonia no difference in survival depending on the *AGTR1* rs275651 genotype was found ($p = 0.76$, $n = 85$, Figure 5, C).

In a subgroup of patients with a NLR value greater than 4 on the first day of hospitalization, an association with improved survival was found in patients with the *AGTR1* rs275651 TT major genotype ($p = 0.0335$, log-rank test, HR = 2.8, 95% CI: 0.9–8.4, $n = 96$). Mortality among carriers of the minor A allele with a OLR value greater than 4 on the first day of hospitalization was 31 %, compared with 11 % for patients with the TT major genotype.

Thus, in patients with CHS sequelae admitted with pneumonia and elevated OLR values the genetic marker — the *AGTR1* rs275651 minor A allele — is associated with an unfavorable outcome.

The results of multiple linear regression confirm the relationship between the outcome of patients in the two study groups (with/without pneumonia) and genotype and NLR values, as well as the role of one of demographic confounders, the age (Table 5).

As it is seen from Table 5, only for patients admitted with pneumonia, there is a statistically significant association of adverse outcome with the *AGTR1* genetic marker and age, whereas for patients admitted without pneumonia, only the NLR values were informative on day 5 of hospitalization for outcome prediction.

Discussion

The results revealed that the minor genetic variant *AGTR1* rs275651 determined an increased risk of death in post-CHS patients. We have previously shown that the minor A allele (genotypes TA, AA) of *AGTR1* rs275651 has associated with an unfavorable outcome of sepsis in patients with comorbidities [9, 18]. There is an evidence that the minor A allele carriers exhibit reduced expression of the *AGTR1* receptor [17], and the patients with allele A *AGTR1*

Table 4. Linear regression analysis of demographics, assessment scales on the first day of hospitalisation, and cellular parameters for patients with AGTR1 rs275651 AT, AA genotypes

Parameters	Age	Gender	SOFA	CIRS	GCS	Lymphocytes, day 1	Neutrophiles, day 1	NLR, day 1	Lymphocytes, day 5	Neutrophiles, day 5	NLR, day 5
Age	—	0.037 0.15	0.000 0.33	0.000 0.30	0.000 -0.29	0.003 -0.23	0.25 0.10	0.005 0.21	0.002 -0.25	0.25 0.10	0.0096 0.21
Gender	0.037 0.15	—	0.041 0.15	0.08 0.13	0.01 -0.19	0.0497 -0.15	0.54 0.05	0.08 0.13	0.37 -0.07	0.47 0.06	0.10 0.13
SOFA	0.000 0.33	0.041 0.15	—	0.000 0.34	0.000 -0.72	0.000 -0.25	0.000 0.28	0.000 0.37	0.000 -0.29	0.000 0.28	0.000 0.32
CIRS	0.000 0.30	0.08 0.13	0.000 0.34	—	0.000 -0.28	0.03 -0.17	0.25 0.10	0.016 0.18	0.046 -0.16	0.25 0.10	0.034 0.17
GCS	0.000 -0.29	0.01 -0.19	0.000 -0.72	0.000 -0.28	—	0.000 0.31	0.000 -0.35	0.000 -0.45	0.000 0.28	0.011 -0.20	0.000 -0.32
Neutrophiles, day 1	0.25 0.10	0.54 0.05	0.000 0.28	0.25 0.10	0.000 -0.35	0.035 -0.16	—	—	0.21 -0.10	—	—
Neutrophiles, day 5	0.25 0.10	0.47 0.06	0.027 0.18	0.25 0.10	0.011 -0.20	0.17 -0.11	—	—	0.28 -0.10	—	=
Outcome	0.002 0.22	0.17 0.10	0.003 0.21	0.001 0.23	0.024 -0.16	0.19 -0.10	0.11 0.12	0.037 0.16	0.22 -0.10	0.038 0.17	0.0075 0.22

Note: CIRS — Cumulative Illness Rating Scale; SOFA — Sequential Organ Failure Assessment; GCS — Glasgow Coma Scale.

In each column the upper value corresponds to the *p*-values, and the lower value corresponds to the *r* values. *P*-values less than 0.05 are shown in bold.

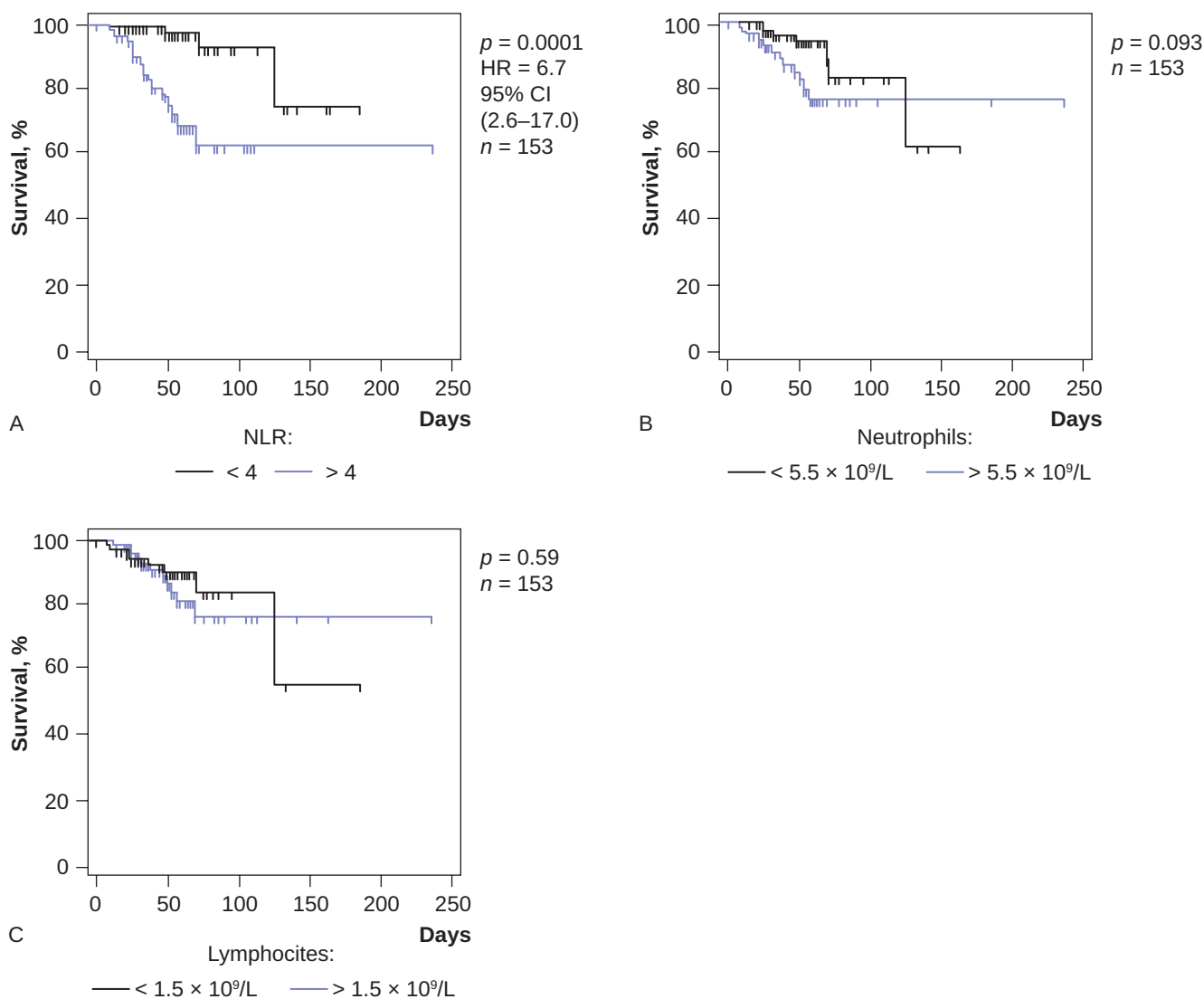


Fig. 2. Survival of patients after haemorrhagic stroke depending on immune cells values on the fifth day of hospitalization:

A — neutrophil to lymphocyte ratio (NLR); B — neutrophil count; C — number of lymphocyte count

Note: 95% CI — 95% confidence interval; HR — hazard ratio.

rs275651 themselves respond better to treatment of arterial hypertension with peridopril [20].

Pneumonia is one of the most common complications of stroke, with an incidence of 5–26 %. The development of pneumonia increases the risk of an unfavorable outcome by approximately 3 times compared to patients without pneumonia [21]. Risk factors for pneumonia in patients with hemorrhagic stroke include a GCS score values below 13, placement of a nasogastric tube, and a length of stay in the intensive care unit (ICU) exceeding 10 days [21, 22]. Stroke-associated pneumonia is often caused by aspiration. Hospitalized patients with neurological damage have a weakened swallowing reflex, making them susceptible to aspiration [23].

One complication of pneumonia is a decreased blood pressure [24], which reduces tissue perfusion and leads to

multiple organ failure. Decreased blood pressure in pneumonia worsens its prognosis. The CURB-65 (confusion, urea, respiratory rate, blood pressure) scale predicts the outcome of nosocomial pneumonia. One of the unfavorable markers on this scale is a decrease in systolic pressure below 90 mm Hg or diastolic pressure below 60 mm Hg [25]. This may explain the improved survival in pneumonia patients with the *AGTRI* rs275651 TT genotype, which is associated with the increased expression of the angiotensin II receptor and reduced risk of hypotension [17]. We have previously shown that this genetic variant of *AGTRI* gene is beneficial in sepsis, commonly associated with a life-threatening blood pressure dysregulation [18, 19].

It should be noted that despite the frequent development of multiple organ failure in CHS, no association between high SOFA score values and adverse outcomes was

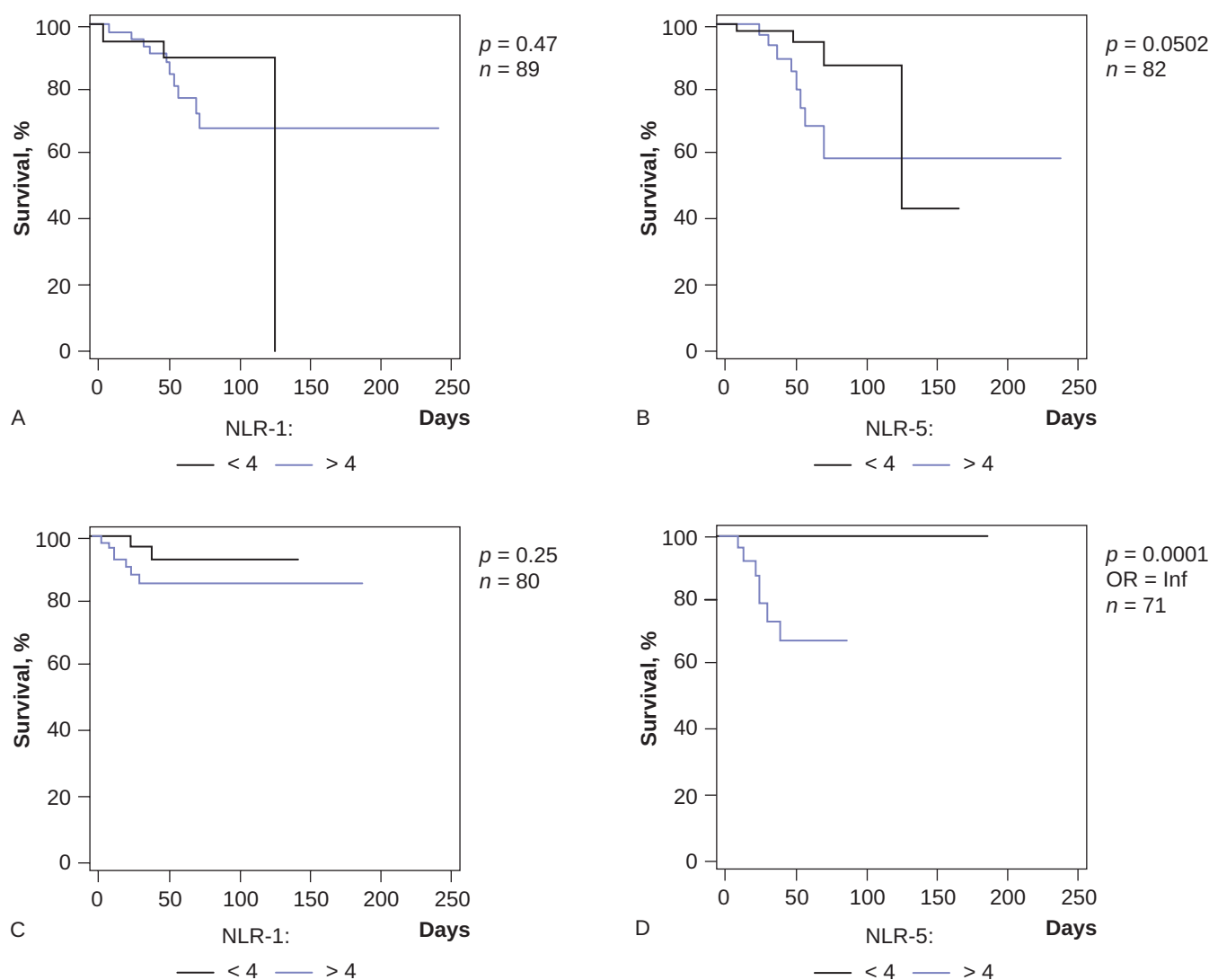


Fig. 3. Neutrophil to lymphocyte ratio (NLR) and outcome of haemorrhagic stroke consequences outcome:

A, B — patients admitted with pneumonia (NLR on the first day of hospitalization); C, D — patients admitted without pneumonia (NLR on the fifth day of hospitalization)

Note: OR — odds ratio.

found in a group of patients with CHS that was heterogeneous in disease onset [46]. Our data confirm this information.

Hypotension in ICU patients leads to organ damage and is associated with adverse outcomes [26]. The main risks of hypotension include target organ damage due to hypoperfusion, particularly renal and myocardial damage. Because hypotension impairs tissue perfusion, some organ damage can be prevented by maintaining appropriate blood pressure [27]. In several studies, the addition of angiotensin II to catecholamine therapy increased mean arterial pressure in patients with vasoplegic shock, allowing for a reduction in catecholamine dosage [28].

Angiotensin II is a highly effective vasopressor used for hypotension in patients with sepsis, particularly in septic shock, to stabilize blood pressure and reduce catecholamine

requirements. Administration of angiotensin II in refractory septic shock effectively increased blood pressure and reduced norepinephrine requirements. It was logical to assume that in sepsis (and especially in septic shock), patients with a genotype associated with increased expression of the angiotensin II receptor, TT *AGTR1* (-777 T>A) rs275651, would have a higher survival rate [18].

A study examining the association of *AGTR1* promoter methylation with the risk of hypertension showed that hypomethylation of the CpG1 region in the *AGTR1* promoter was associated with the risk of hypertension, with CpG1 methylation levels being lower in men than in women. These results suggest that hypomethylation activates *AGTR1* gene transcription, leading to its higher expression and, ultimately, plays a crucial role in the onset and development of hypertension [29].

Table 5. Results of multiple linear regression of the relationship between outcome and age, gender, *AGTR1* rs275651 genotype and NLR on the fifth day of hospitalization

Subgroups	Parameters	<i>p</i>	<i>r</i>
Admitted with pneumonia	Age	0.0282	0.2116
	Gender	0.4043	—
	<i>AGTR1</i>	0.0188	0.2166
Admitted with no pneumonia	Age	0.1421	—
	Gender	0.5762	—
	NLR, day 5	0.0410	0.2814

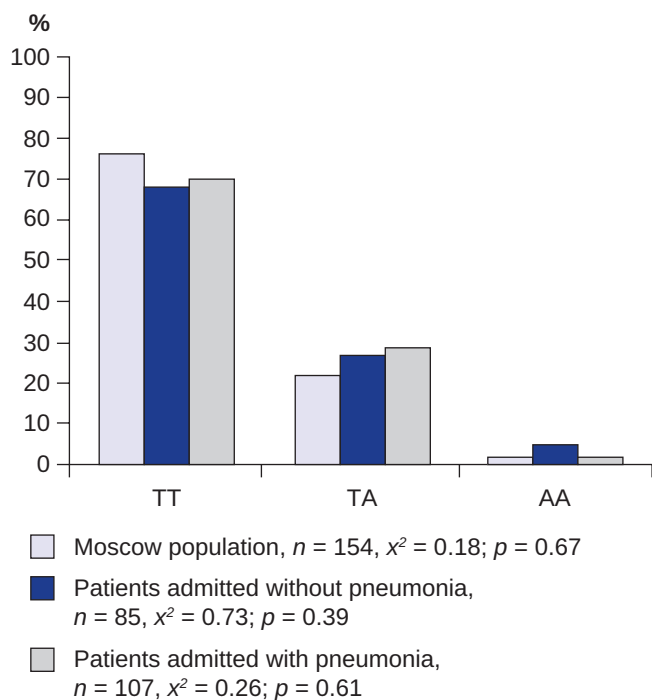


Fig. 4. *AGTR1* rs275651 genotype frequencies among patients after haemorrhagic stroke, and apparently healthy donors

AGTR1 influences the migration of immune cells. High *AGTR1* expression is associated with antitumor immunological activity determined by significant infiltration of B cells, myeloid dendritic cells, monocytes and low infiltration of myeloid immunosuppressive cells in lung adenocarcinoma, which is associated with a good prognosis [30]. An inverse correlation between the expression of *AGTR1* and Programmed cell death protein (PD-1), which prevents the activation of T lymphocytes, has been shown for gastric cancer [31]. In aortic valve stenosis, *AGTR* expression positively correlated with the activation of Natural Killer cells (NK cells) [32]. In our sample, the values of NLR, lymphocytes, and neutrophils counts correlated with the outcome only for patients with the major *AGTR1* rs1058427 TT genotype. A possible explanation for the presence or absence of

such an association may be the influence of *AGTR1* on the immune system.

AGTR1 regulates neutrophil and chemokine responses [14]. Incubation of neutrophils with angiotensin II followed by treatment of cells with bovine sperm as a model of corpuscular antigen showed that angiotensin stimulates the formation of extracellular traps and phagocytosis of sperm by neutrophils in vitro. This stimulatory effect of angiotensin II was abolished by the *AGTR1* antagonist losartan [12]. It is possible that the influence of *AGTR1* on neutrophils can explain the difference in NLR values in patients with different *AGTR1* rs275651 genotypes.

NLR value often serves as an informative biomarker of the systemic inflammatory response, recommended for use in assessing the severity of the condition and prognosing the outcome in many diseases: cerebrovascular accidents [33]; cardiovascular diseases [34]; bacterial, fungal infections and sepsis; community-acquired pneumonia; COVID-19 infection [35]; metabolic syndrome [36]; rheumatoid arthritis [37]; various types of cancer [38, 39]; decompensated liver cirrhosis [40]; severe trauma [41]. Easily calculated NLR values represent an informative hematological prognostic biomarker that is readily available and convenient for use in clinical practice [39–45].

Due to the existing specific evidence base, NLR has long been used to predict the course of various pathological conditions. However, its usefulness as a biomarker for the prognosis of post-CHS PCCI course was unknown. We studied the prognostic value of NLR for this particular category of patients for the first time. In our study, we demonstrated for the first time that the value of the NLR on day 5 of hospitalization predicted the outcome of PCCI following CHS. Lymphopenia and high NLR values are well-recognized as unfavorable prognostic markers of the progressive course of pneumonia, including COVID-19-associated pneumonia. Conversely, low NLR values, corresponding to reduced neutrophil concentrations and increased lymphocyte counts, were associated with a better pneumonia prognosis [44, 45].

Neutrophils release numerous proteolytic enzymes, such as elastase, acid phosphatase, and myeloperoxidase, which have a destructive effect on organs and tissues.

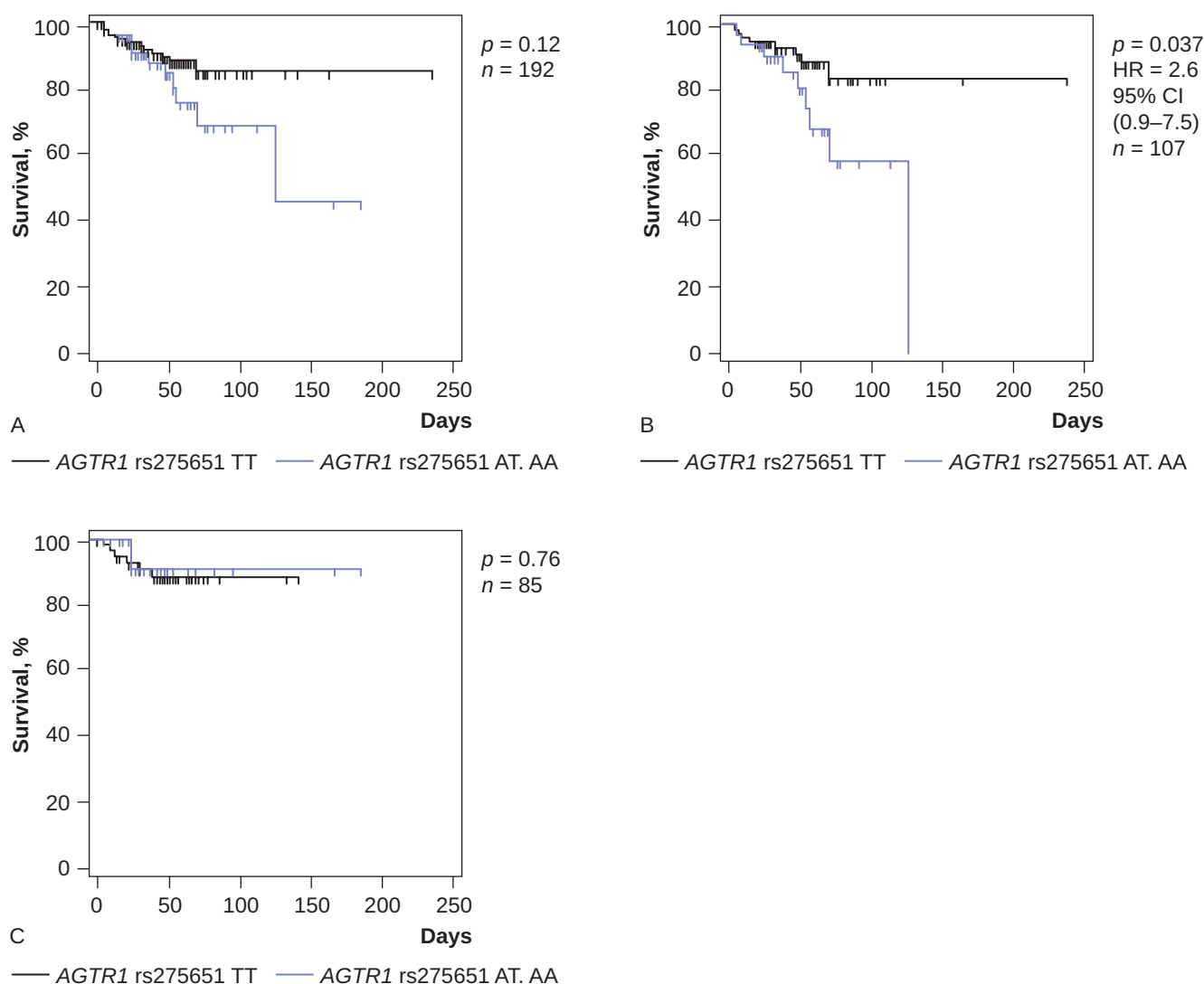


Fig. 5. Survival of patients with consequences of haemorrhagic stroke depending on the *AGTR1* rs275651 genotype:

A — all patients; B — patients admitted with pneumonia; C — patients admitted without pneumonia

Note: 95% CI — 95% confidence interval; HR — hazard ratio.

Combined with the release of cytokines, including granulocyte-macrophage colony-stimulating factor, as well as bacterial lipopolysaccharides and free radicals generating during the inflammatory process, this leads to a prolongation of neutrophil circulation and survival, which causes increased vascular endothelial damage.

On the other hand, lymphocytes exert an immunomodulatory effect by inducing the expression of tissue inhibitor of metalloproteinase-1. Activation of the hypothalamic-pituitary-adrenal axis during stress causes increased secretion of cortisol by the adrenal glands. This hormone induces lymphocyte apoptosis and, consequently, lymphocytopenia. Other causes of lymphopenia may include increased tumor growth factor concentrations [38], as well as depletion of adaptive immune cells during hyperstimulation.

It is known that the use of corticosteroids, certain antibiotics, and malnutrition can play a significant role

in lymphopenia. However, a recent study showed that in a heterogeneous in disease onset group of patients with CHS and its consequences requiring continued ICU treatment, the association between the risk of malnutrition (as determined by the prognostic nutrition index, PNI) and outcome was insignificant [46]. The simultaneous increase in neutrophil concentration due to “urgent” hematopoiesis in the bone marrow and lymphopenia make the informativity of elevated NLR values quite persistent. This explains the revealed prognostic significance of this relative biomarker. In our cohort, the NLR value on the first day of hospitalization was associated with outcome ($p = 0.034$, $r = 0.20$, linear regression), but did not have significant predictive value ($p = 0.15$, log-rank test). Only during further development of PCCI and concomitant treatment — on the fifth day of hospitalization — the altered NLR value had become highly informative in pre-

dicting outcome ($p = 0.0001$, log-rank test, HR = 6.7, 95% CI: 2.6–17.0).

Thus, our study revealed a relatively high value of the immunological indicator NLR and polymorphic variants of the *AGTR1* gene as predictors of post-CHS PCCI outcome depending on the presence or absence of pneumonia at hospitalization.

Study limitations

A limitation of our study is its lack of external validity (the study was conducted at a single center), which may necessitate confirmation of the results at other clinical institutions. However, achieving sufficient power for the PCCI cohort at another medical institution is challenging.

Another limitation is the high heterogeneity of patients by disease onset time. This is due to the specific characteristics of our institution, which admits patients with life-sustaining needs arising at various stages of CHS and its sequelae, primarily patients in PCCI. In our cohort, more than half of the patients were in PCCI. The high level of heterogeneity at the time of inclusion into the study after the stroke diagnosis may have influenced the lack of signif-

icance of the association between immune system markers in one of the subgroups. Nevertheless, significant predictive value of the genetic marker *AGTR1* was found for the outcome. Insufficient information on concomitant therapy (corticosteroids, antibiotics, vasopressors) and malnutrition during the previous stage of treatment, as well as the limited power of the study, which was adequate only for the stated objectives, prevented us from addressing other objectives (the contribution of concomitant treatment and possible malnutrition to the survival of patients with CHS and its sequelae).

Conclusion

The neutrophil-to-lymphocyte ratio on the fifth day of hospitalization predicted the outcome of chronic critical illness following hemorrhagic stroke in patients admitted without pneumonia. The presence of the minor A allele of *AGTR1* rs275651 was associated with an unfavorable outcome only in patients with sequelae of hemorrhagic stroke admitted with pneumonia.

Disclosure. The authors declare no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. This study was approved by the local Ethical Committee of V.A. Negovskiy Research Institute of general Reanimatology Federal Research and Clinical

Center of Intensive Care Medicine and Rehabilitology (reference number: B 2.2.18. 20.12.2018).

Funding source. This study was supported by funding from the Ministry of Science and High Education of Russian Federation.

Data Availability Statement. Data confirming conclusions of the study are available on a reasonable request from corresponding author.

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