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Geriatric factors affecting the safety of direct oral anticoagulants in atrial fibrillation patients aged 80 years and older: An observational prospective cohort study

Marina S. Cherniaeva,^{1,2,3} Anna O. Pavlova,² Polina A. Alferova,¹ Maria A. Rozhkova,⁴ Mikhail I. Trifonov,⁵ Tatyana V. Nikeeva,³ Larisa A. Egorova,² Olga M. Maslennikova,² Nikita V. Lomakin,^{1,6} Dmitry A. Sychev¹

¹ Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation, Barrikadnaya str., 2/1, bldg. 1, Moscow, 125993, Russia

² Central State Medical Academy, Administrative Directorate of the President of the Russian Federation, Marshala Timoshenko str., 19, bldg. 1a, Moscow, 121359, Russia

³ Hospital for War Veterans No. 2, Moscow City Health Department, Volgogradsky Ave., 168, Moscow, 109472, Russia

⁴ Federal Research and Clinical Center for Specialized Types of Medical Care and Medical Technologies, Federal Medical-Biological Agency, Orekhovyi Blvd., 28, Moscow, 115682, Russia

⁵ A Medelinic, 3rd Monetchikovskiy Ln., 16, bldg. 1, Moscow, 115054, Russia

⁶ Central Clinical Hospital with a Polyclinic, Administrative Directorate of the President of the Russian Federation, Marshala Timoshenko str., 15, Moscow, 121359, Russia

ABSTRACT

Background. Older age is associated with the presence of geriatric syndromes, whose effect on the safety of direct oral anticoagulants in atrial fibrillation patients is studied extensively. Scientific literature focuses on the prevention of major bleeding, while clinically relevant non-major bleeding occurs much more frequently and can have a significant impact on the patient's condition. **Objective.** To assess the potential of geriatric factors for predicting the risk of clinically relevant non-major bleeding on direct oral anticoagulants in nonvalvular atrial fibrillation patients aged 80 years and older. **Methods.** The article presents the results of an observational prospective cohort study that included 367 atrial fibrillation patients aged 80 years and older on direct oral anticoagulants. The study was conducted at a multi-specialty inpatient clinic in Moscow from January 2019 to December 2022 and reflected real clinical practice. The medical records were prospectively analyzed for the presence of clinically relevant non-major bleeding; the observation period lasted 12 months. The patients were divided into groups: the main group comprising patients with clinically relevant non-major bleeding ($n = 195$), with a median age of 84 [82; 87] years, and the control group consisting of patients without clinically relevant non-major bleeding ($n = 172$), with a median age of 84 [82; 88] years. The groups were comparable in terms of key bleeding risk factors. In order to identify geriatric risk factors, a comprehensive geriatric assessment was performed in four main domains: physical status; mental and emotional status; functional capacity; identification of social problems. Statistical data processing and visualization were performed in the R software environment, version 4.4.0 (R Foundation for Statistical Computing, Vienna, Austria). Differences were considered statistically significant at $p < 0.05$. **Results.** The performed analysis identified risk factors for clinically relevant non-major bleeding in all four domains of the comprehensive geriatric assessment: social (living in a family, number of household members, legal marriage, and church attendance); mental and emotional (Geriatric Depression Scale); physical and functional (balance tests, Lawton IADL scale, use of assistive devices, senile asthenia as per the *Age is No Barrier* questionnaire, SPRINT (Systolic Blood Pressure Intervention Trial) frailty index, $p < 0.05$). In the course of a multiple-factor analysis, a multiple-factor logistic regression model was created to predict clinically relevant non-major bleeding, and a prognostic nomogram was derived to estimate the probability of clinically relevant non-major bleeding (prognostic accuracy of 59.9%, sensitivity of 48.9%, and specificity of 72.4%). The predictors were as follows: number of household members, Barthel ADL score, Lawton IADL score, Timed Up and Go Test, and use of any assistive device. **Conclusion.** In the study, socially active, emotionally stable, mobile, and robust patients were shown to have a higher risk of developing clinically relevant non-major bleeding events. The authors identified geriatric factors that may serve as predictors of clinically relevant non-major bleeding on direct oral anticoagulants in atrial fibrillation patients aged over 80 years. Given the active AI implementation in clinical practice, the obtained data can be integrated into clinical decision support systems.

KEYWORDS: clinically relevant non-major bleeding, drug safety, direct oral anticoagulants, atrial fibrillation, old age, risk factors, geriatric syndromes, senile asthenia, frailty

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COMPLIANCE WITH ETHICAL STANDARDS: The study complies with the Declaration of Helsinki standards and was approved by the independent ethics committee (Minutes No. 1-L/19 as of February 5, 2019) of the Central State Medical Academy, Administrative Directorate of the President of the Russian Federation (Marshala Timoshenko str., 19, bldg. 1a, Moscow, Russia). All patients participating in this study signed a written voluntary informed consent.

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✉ **CORRESPONDING AUTHOR:** Marina S. Cherniaeva, Cand. Sci. (Med.), Assoc. Prof., Department of Clinical Pharmacology and Therapy named after Academician B.E. Votchal, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation; Assoc. Prof., Department of Internal and Preventive Medicine, Central State Medical Academy, Administrative Directorate of the President of the Russian Federation; geriatrician, Head of the Geriatric Department No. 5, Hospital for War Veterans No. 2, Moscow City Health Department. Address: Marshala Timoshenko str., 19, bldg. 1a, Moscow, 121359, Russia. E-mail: doctor@cherniaeva.ru

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Гериатрические факторы риска безопасности прямых оральных антикоагулянтов у пациентов с фибрилляцией предсердий 80 лет и старше: обсервационное когортное проспективное исследование

М.С. Черняева^{1,2,3✉}, А.О. Павлова², П.А. Алферова¹, М.А. Рожкова⁴, М.И. Трифонов⁵, Т.В. Никеева³, Л.А. Егорова², О.М. Масленникова², Н.В. Ломакин^{1,6}, Д.А. Сычев¹

¹ Федеральное государственное бюджетное образовательное учреждение дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации, ул. Баррикадная, д. 2/1, стр. 1, г. Москва, 125993, Россия

² Федеральное государственное бюджетное учреждение дополнительного профессионального образования «Центральная государственная медицинская академия» Управления делами Президента Российской Федерации, ул. Маршала Тимошенко, д. 19, стр. 1а, г. Москва, 121359, Россия

³ Государственное бюджетное учреждение здравоохранения города Москвы «Госпиталь для ветеранов войн № 2 Департамента здравоохранения города Москвы», пр-т Волгоградский, д. 168, г. Москва, 109472, Россия

⁴ Федеральное государственное бюджетное учреждение «Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий Федерального медико-биологического агентства», б-р Ореховый, д. 28, г. Москва, 115682, Россия

⁵ Общество с ограниченной ответственностью «А Медклиник», пер. 3-й Монетчиковский, д. 16, стр. 1, г. Москва, 115054, Россия

⁶ Федеральное государственное бюджетное учреждение «Центральная клиническая больница с поликлиникой» Управления делами Президента Российской Федерации, ул. Маршала Тимошенко, 15, г. Москва, 121359, Россия

АННОТАЦИЯ

Введение. Пожилой возраст коррелирует с наличием гериатрических синдромов, вклад которых в безопасность прямых оральных антикоагулянтов у пациентов с фибрилляцией предсердий активно изучается. В научной литературе основное внимание уделяется профилактике больших кровотечений, в то время как клинически значимые небольшие кровотечения возникают значительно чаще и могут оказывать существенное влияние на состояние больного. **Цель исследования** — оценить возможность гериатрических факторов прогнозировать риск развития клинически значимых небольших кровотечений на фоне приема прямых оральных антикоагулянтов у пациентов с неклапанной фибрилляцией предсердий в возрасте 80 лет и старше. **Методы.** В работе представлены результаты наблюдательного проспективного когортного исследования, включавшего 367 пациентов от 80 лет с фибрилляцией предсердий, получавших прямые оральные антикоагулянты. Исследование проводилось на базе многопрофильного стационара Москвы в период с января 2019 по декабрь 2022 года и отражало реальную клиническую практику. Проспективно проведена оценка медицинской документации на наличие клинически значимых небольших кровотечений, период наблюдения — 12 месяцев. Были сформированы группы: основная с клинически значимыми небольшими кровотечениями ($n = 195$), медиана возраста 84 [82; 87] года, и контрольная без клинически значимых небольших кровотечений ($n = 172$), медиана возраста — 84 [82; 88] года. Группы были сопоставимы по основным факторам риска кровотечений. Для определения гериатрических факторов риска выполнена комплексная гериатрическая оценка по четырем основным доменам: физического и психоэмоционального статуса, функциональных возможностей и выявления социальных проблем. Обработка статистических данных и их визуализация были выполнены в программной среде R, версия 4.4.0 (R Foundation for Statistical Computing, Вена, Австрия). Различия считали статистически

значимыми при $p < 0,05$. **Результаты.** В результате анализа были выявлены факторы риска клинически значимых небольших кровотечений из всех четырех доменов комплексной гериатрической оценки: социальный (проживание в семье, количество проживающих в семье, официальный брак, посещение церкви), психоэмоциональный (гериатрическая шкала депрессии), физический и функциональный (тесты на равновесие, шкала Лоутон, применение вспомогательных средств, старческая астения по опроснику «Возраст не помеха», индекс хрупкости по шкале SPRINT (Systolic Blood Pressure Intervention Trial) ($p < 0,05$)). В ходе многофакторного анализа была создана многофакторная логистическая регрессионная модель для прогнозирования клинически значимых небольших кровотечений и разработана прогностическая номограмма, позволяющая оценить вероятность развития клинически значимых небольших кровотечений (прогностическая точность 59,9%, чувствительность 48,9%, специфичность 72,4%). Предикторами явились количество проживающих в семье, индекс Бартел, индекс Лоутон, тест «Встань и иди» и использование любого вспомогательного средства. **Заключение.** В исследовании было показано, что социально активные, эмоционально устойчивые, мобильные и крепкие пациенты имеют более высокий риск развития клинически значимых небольших кровотечений. Выявлены гериатрические факторы, которые могут являться предикторами клинически значимых небольших кровотечений на фоне приема прямых оральных антикоагулянтов у пациентов с фибрилляцией предсердий старше 80 лет. С учетом активного внедрения технологий искусственного интеллекта в клиническую практику полученные данные могут быть интегрированы в системы поддержки врачебных решений.

КЛЮЧЕВЫЕ СЛОВА: клинически значимое небольшое кровотечение, безопасность лекарственных средств, прямые оральные антикоагулянты, фибрилляция предсердий, пожилой возраст, факторы риска, гериатрические синдромы, старческая астения, хрупкость

ДЛЯ ЦИТИРОВАНИЯ: Черняева М. С., Павлова А. О., Алферова П. А., Рожкова М. А., Трифионов М. И., Никеева Т. В., Егорова Л. А., Масленникова О. М., Ломакин Н. В., Сычев Д. А. Гериатрические факторы риска безопасности прямых оральных антикоагулянтов у пациентов с фибрилляцией предсердий 80 лет и старше: обсервационное когортное проспективное исследование. *Кубанский научный медицинский вестник*. 2025;32(3):15–35. <https://doi.org/10.25207/1608-6228-2025-32-3-15-35>

ИСТОЧНИКИ ФИНАНСИРОВАНИЯ: авторы заявляют об отсутствии спонсорской поддержки при проведении исследования.

КОНФЛИКТ ИНТЕРЕСОВ: авторы заявляют об отсутствии конфликта интересов.

ДЕКЛАРАЦИЯ О НАЛИЧИИ ДАННЫХ: данные, подтверждающие выводы этого исследования, можно получить у корреспондирующего автора по обоснованному запросу. Данные и статистические методы, представленные в статье, прошли статистическое рецензирование редактором журнала — сертифицированным специалистом по биостатистике.

СООТВЕТСТВИЕ ПРИНЦИПАМ ЭТИКИ: проведенное исследование соответствует стандартам Хельсинкской декларации, одобрено независимым этическим комитетом федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» Управления делами Президента Российской Федерации (ул. Маршала Тимошенко, д. 19, стр. 1 а, г. Москва, Россия), протокол № 1-Л/19 от 05.02.2019. Все лица, вошедшие в исследование, подписали письменное информированное добровольное согласие.

ВКЛАД АВТОРОВ: М. С. Черняева, А. О. Павлова, П. А. Алферова, М. А. Рожкова, М. И. Трифионов, Т. В. Никеева, Л. А. Егорова, О. М. Масленникова, Н. В. Ломакин, Д. А. Сычев — разработка концепции и дизайна исследования; М. С. Черняева, А. О. Павлова, П. А. Алферова, М. А. Рожкова, М. И. Трифионов, Т. В. Никеева, Л. А. Егорова, О. М. Масленникова, Н. В. Ломакин, Д. А. Сычев — сбор данных; М. С. Черняева, Л. А. Егорова, О. М. Масленникова, Н. В. Ломакин, Д. А. Сычев — анализ и интерпретация результатов; А. О. Павлова, П. А. Алферова, М. А. Рожкова, М. И. Трифионов, Т. В. Никеева — обзор литературы, проведение статистического анализа; М. С. Черняева, М. И. Трифионов, Л. А. Егорова, О. М. Масленникова — составление черновика рукописи и формирование его окончательного варианта; А. О. Павлова, П. А. Алферова, М. А. Рожкова, Т. В. Никеева, Н. В. Ломакин, Д. А. Сычев — критический пересмотр черновика рукописи с внесением ценного замечания интеллектуального содержания. Все авторы одобрили финальную версию статьи перед публикацией, выразили согласие нести ответственность за все аспекты работы, подразумевающую надлежащее изучение и решение вопросов, связанных с точностью и добросовестностью любой части работы.

✉ **КОРРЕСПОНДИРУЮЩИЙ АВТОР:** Черняева Марина Сергеевна, кандидат медицинских наук, доцент, доцент кафедры клинической фармакологии и терапии имени академика Б.Е. Вотчала федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации; доцент кафедры внутренних болезней и профилактической медицины федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» Управления делами Президента Российской Федерации; врач-гериатр, заведующий гериатрическим отделением № 5 государственного бюджетного учреждения здравоохранения города Москвы «Госпиталь для ветеранов войн № 2 Департамента здравоохранения города Москвы». Адрес: ул. Маршала Тимошенко, д. 19, стр. 1 а, г. Москва, 121359, Россия. E-mail: doctor@cherniaeva.ru

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INTRODUCTION

Atrial fibrillation (AF) is a common condition that occurs in 1–2% of the general population, with the number of AF patients increasing with age, from <0.5% at ages 40–50 to 5–15% at the age of 80. The number of AF patients is expected to nearly double in the next 50 years. This pathology is associated with a high risk of systemic thromboembolism and ischemic stroke, which can be prevented via treatment

with direct oral anticoagulants (DOACs) [1, 2]. However, their use may cause bleeding, especially in elderly patients due to a number of age-related changes in the body. In particular, decreased hepatic perfusion and reduced activity of some cytochrome P450 isoforms affect the pharmacokinetics of DOACs, while the age-related decrease in the number of functioning nephrons increases the elimination half-life of these drugs. The receptor sensitivity and distribution density

are modified, which directly affects the pharmacodynamic properties of DOACs¹ [3–5].

Old age is known to be associated with the presence of geriatric syndromes, which include chronic pain syndrome, urinary/fecal incontinence, high fall risk, cognitive impairments, dementia, decreased mobility, frailty, etc. Frailty constitutes a major geriatric syndrome causing a decrease in the physiological reserves of the body.²

In the 2020 clinical guidelines of the European Society of Cardiology (ESC) on AF diagnosis and treatment [6], the HAS-BLED scale (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio, elderly (> 65 years), drugs/alcohol concomitantly) assessed patient frailty, and risk factors for bleeding complications included certain geriatric syndromes, e.g., cognitive impairments or dementia and high fall risk. The ESC clinical guidelines for AF treatment revised in 2024 [2] abandon HAS-BLED bleeding risk assessment since systematic reviews and controlled trials in comparison groups showed highly inconsistent results and little prognostic value while focusing on the assessment and management of modifiable and potentially modifiable risk factors for bleeding, which include a high fall risk and cognitive impairments or dementia. The effect of frailty on the development of bleeding is mentioned neither in the 2024 EOC guidelines for AF treatment [2] nor in the clinical guidelines for the treatment of atrial fibrillation and flutter of the Russian Society of Cardiology [1].

Nevertheless, the results of studies in elderly AF patients receiving DOACs show that the risk of falls and frailty increase the risk of bleeding [7–11]. These studies primarily focus on major and intracranial bleeding, with clinically relevant non-major bleeding (CRNMB) not considered as a separate group. Nevertheless, the incidence of CRNMB is much higher than that of major bleeding, reaching 17.4% and increasing with age [12, 13]. This complication should not be underestimated, as it is a reason for DOAC discontinuation, which increases the risk of thromboembolism and, consequently, disability or a fatal outcome. In addition, CRNMB can lead to major bleeding or patient hospitalization and a medical intervention [12]. We found no information on the contribution of other geriatric syndromes to bleeding events in patients receiving DOACs.

Current studies, therefore, lack data on geriatric syndromes as predictors of CRNMB on DOACs. Furthermore, the mean age of patients in studies examining the relationship between geriatric syndromes and DOAC safety ranges from 75 to 78 years, while the number of patients aged over 80 years is rising worldwide with increasing life expectancy [14, 15]. This fact prompted the present study.

The present study aims to assess the potential of geriatric factors for predicting the risk of clinically relevant non-major bleeding on direct oral anticoagulants in nonvalvular atrial fibrillation patients aged 80 years and older.

METHODS

Study design

The observational prospective cohort study of actual clinical practice included 367 AF patients on DOACs aged ≥80 years who were treated at a multi-specialty inpatient clinic in Moscow from January 2019 to December 2022.

Study conditions

The study was conducted at the Department of Clinical Pharmacology and Therapy named after Academician B.E. Votchal, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation. The patients were included in the study from January 2019 to December 2022. After that, outpatient and inpatient medical records were prospectively analyzed to determine the incidence of CRNMB during DOAC therapy. The observation period lasted one year.

Eligibility criteria

Inclusion criteria

Nonvalvular atrial fibrillation patients of both sexes; aged 80 years or older at study entry; regular DOAC use for at least one year from the time of study entry; signed voluntary informed consent for participation in the study.

Exclusion criteria

Age of <80 years; clinically significant heart disease (including cardiogenic shock; recent, i.e., less than one month prior to the study, complicated myocardial infarction; third-degree atrioventricular block without artificial pacemaker; hypertrophic cardiomyopathy; severe aortic and mitral stenosis); significant liver diseases (including liver cirrhosis with ascites); patients receiving renal replacement therapy (long-term hemodialysis; peritoneal dialysis; history of kidney transplant); clinically significant immunologic disease; neurological diseases (including acute cerebrovascular disorders and transient ischemic attack less than three months prior to the study); surgical procedure (except for dental or cosmetic surgeries), injuries, and fractures within the previous three months; presence of clinically significant changes in laboratory parameters indicating undiagnosed disease and requiring further examination.

Removal criteria

Violation of the examination and treatment procedures by the patient; refusal of the patient to participate in the study and withdrawal of informed consent.

Description of eligibility criteria (diagnostic criteria)

The diagnosis of AF was made according to the criteria of clinical guidelines for the treatment of atrial fibrillation and flutter of the Russian Society of Cardiology [1]. In patients receiving DOACs, CRNMB was diagnosed using criteria developed by the International Society on Thrombosis and Haemostasis (ISTH) [12]. The list of interventions performed on patients is regulated by the order of the Ministry of Health of the Russian Federation of January 29, 2016 (Order No. 38n) “On Approval of the Geriatric Medical

¹ Sychev D.A., Tkacheva O.N., Kotovskaya Yu.V., Malaya I.P. *Pharmacotherapy in the aged and elderly*. Moscow: KONGRESSKHIM; 2024. (In Russ.)

² Ministry of Health of the Russian Federation. Russian Association of Gerontologists and Geriatricians. *Clinical Guidelines “Senile Frailty.”* 2024. Available: https://rgnkc.ru/images/metod_materials/%D0%9A%D0%A0613.pdf

Care Protocol” as amended on December 20, 2019 (Order No. 1067n).³

Selection of group members

The study cohort included 367 patients aged ≥ 80 years who were consecutively enrolled in the study, provided they met the inclusion criteria. At the end of the one-year observation, the patients were divided into two groups according to the data on CRNMB manifestation and recurrence: the main group included patients with CRNMB ($n = 195$), and the control group comprised patients without CRNMB ($n = 172$).

Target parameters in the study

Main parameters in the study

In order to identify geriatric factors affecting the development of CRNMB in patients on DOACs, patients underwent a comprehensive geriatric assessment, which included analysis in four main domains: physical status; mental and emotional status; functional capacity; identification of social problems.⁴

Additional parameters in the study

Additional parameters are not provided in this study.

Methods for measuring the target parameters

The study used the following validated charts, questionnaires, scales, tests, and estimated indices: a chart of comprehensive geriatric assessment,⁵ the *Age is No Barrier* questionnaire, self-assessment of quality of life and health status on the visual analogue scale (VAS), the Barthel Index for Activities of Daily Living (ADL) [16], the Lawton Instrumental Activities of Daily Living (Lawton IADL) Scale [17], Mini Nutritional Assessment [17, 18], Short Physical Performance Battery, Timed Up and Go Test, and single-leg stance test.⁶ Also, all patients underwent dynamometry to determine hand-grip strength; the criteria for low handgrip strength were established depending on sex and body mass index as per the clinical guidelines for frailty.²

The frailty index was calculated on the Rockwood scale [19] and on the scale used in the SPRINT (Systolic Blood Pressure Intervention Trial) study [20].

Mental and emotional status was assessed using the following tests, scales, and questionnaires⁷: Mini-Cog screening test, Mini-Mental State Examination, Montreal Cognitive Assessment Scale, Word List Recall, Digit Symbol Substitution Test, 10-word-list recall test, verbal fluency test (literal fluency/letters and category fluency/animals), Boston Naming Test, Functional Activities Questionnaire, Alzheimer’s Disease Assessment Scale-Cognitive, as well as Geriatric Depression Scale (GDS), GDS-15 (short form) and GDS-30 (long form).

Variables (predictors, confounders, and effect modifiers)

In the present study, factors affecting the final outcome were categorized as exclusion criteria, thus completely excluding the possibility of their presence in the examined patients.

Statistical procedures

Principles behind sample size determination

The sample size was not determined in advance.

Statistical methods

Statistical data analysis and visualization were performed in the R software environment, version 4.4.0 (R Foundation for Statistical Computing, Austria). Descriptive statistics are presented as absolute and relative frequencies for qualitative variables; as medians (Me) ($Q1$; $Q3$), for quantitative variables. Pearson’s χ^2 test and Fisher’s exact test were used to compare the groups in terms of categorical indicators (with a minimum expected number of observations < 5 in the cells of the contingency table). The Mann–Whitney test was used to compare the two groups in terms of quantitative and ordinal measures. Odds ratios (ORs) with the corresponding 95% confidence intervals (CIs) were used to assess the strength of quantitative and binary indicators with binary outcomes.

The stepwise selection of predictors for prognostic models was performed using the Akaike information criterion (AIC). The selected predictors were included in a multi-factor logistic regression model without interactions. The Nagelkerke pseudo- R^2 , Somers’ D_{xy} coefficient, and C-index (area under the curve, AUC) were estimated as model quality metrics, including metrics adjusted for potential overfitting using a non-parametric bootstrap ($B = 1000$). The multicollinearity of predictors was assessed using the variance inflation factor (VIF). The optimal threshold value of predicted probability was determined employing Youden’s index; the prognostic accuracy, sensitivity, specificity, and positive and negative predictive values were assessed with the corresponding 95% CI.

RESULTS

Sampling

Continuous sampling was conducted according to the inclusion/exclusion criteria. Upon inclusion in the study, all participants underwent a comprehensive geriatric assessment. CRNMB detection during DOAC therapy was based on a prospective study of outpatient and inpatient medical records. The observation period lasted one year. The patients were divided into groups according to the presence or absence of CRNMB. No group had any patients who refused to participate in the study.

³ Ministry of Health of the Russian Federation. Order No. 38n as of January 29, 2016 “On Approval of the Geriatric Medical Care Protocol (as amended on by the orders of the Ministry of Health of the Russian Federation No. 1067n as of December 20, 2019, No. 114n as of February 21, 2020, and No. 148n as of March 29, 2024)

⁴ Ministry of Health of the Russian Federation. Russian Association of Gerontologists and Geriatricians. *Clinical Guidelines “Senile Frailty.”* 2024. Available: https://rgnkc.ru/images/metod_materials/%D0%9A%D0%A0613.pdf

⁵ Russian Association of Gerontologists and Geriatricians. *Patient chart: comprehensive geriatric assessment.* Available: https://rgnkc.ru/images/metod_materials/Patient_card.pdf

⁶ Ministry of Health of the Russian Federation. Russian Association of Gerontologists and Geriatricians. *Clinical Guidelines “Senile Frailty.”* 2024. Available: https://rgnkc.ru/images/metod_materials/%D0%9A%D0%A0613.pdf

⁷ Ministry of Health of the Russian Federation. Russian Association of Gerontologists and Geriatricians. Russian Society of Psychiatrists. *Cognitive impairment in the aged and elderly.* 2020. Available: https://rgnkc.ru/images/metod_materials/KR_KR.pdf

Characteristics of the study sample (groups)

Nonvalvular AF patients ($n = 367$) were selected according to the inclusion and exclusion criteria (median age of 84 [82; 88] years). In order to prevent thromboembolism, all participants were receiving DOACs: rivaroxaban ($n = 238/367$, relative proportion of 64.9%), apixaban ($n = 95/367$, relative proportion of 25.9%), or dabigatran etexilate ($n = 34/367$, relative proportion of 9.2%). The main group included 195 patients with CRNMB (median age of 84 [82; 87] years), with women accounting for 66.7%. The control group consisted of 172 patients without CRNMB (median age of 84 [82; 88] years), with women accounting for 72.7%. No significant differences were found between the groups in terms of sex, age, risk of ischemic stroke on the CHA₂DS₂-VASc (Congestive heart failure; Hypertension; Age; Diabetes mellitus; Prior Stroke or TIA or Thromboembolism; Vascular disease; Age 65–74 years; Sex category) scale, risk of bleeding on the HAS-BLED scale, body mass index, and key bleeding risk factors according to the criteria of clinical guidelines for the treatment of atrial fibrillation and flutter of the Russian Society of Cardiology [1, 20].

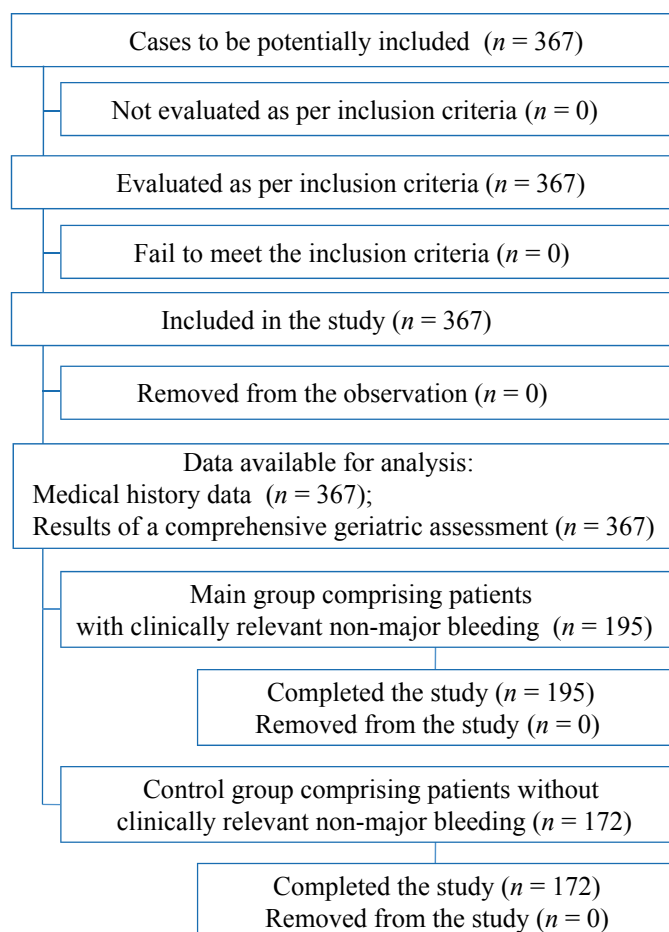


Fig. 1 Block diagram of the study design

Note: The block diagram was created by the authors (as per STROBE recommendations).

Рис. 1. Блок-схема дизайна исследования

Примечание: блок-схема выполнена авторами (согласно рекомендациям STROBE).

Main study results

Analysis of geriatric factors affecting the development of clinically relevant non-major bleeding

The social domain was assessed by studying 24 parameters, including the presence of a disability; the presence of a partner or spouse; the presence of children; marital status; social circle and social contacts; living conditions; financial capabilities; work activity; profession; education; religiosity; the need for outpatient, inpatient, routine, or emergency medical care; preferential provision of medicines. The patients with CRNMB exhibited higher social engagement as compared to the patients without CRNMB. For example, it was statistically significantly more common for the patients with CRNMB to live in a family ($p = 0.031$); living alone was statistically significantly associated with 1.65-time lower odds (95% CI: 1.08; 2.51) of having CRNMB as compared to living in a family ($p = 0.025$). As compared to the patients without CRNMB, the CRNMB patients had a statistically significantly higher number of household members ($p = 0.003$); on average, a one-person increase in the number of household members was statistically significantly associated with 1.22-time higher odds (95% CI: 1.03; 1.47) of having CRNMB ($p = 0.025$). It was statistically significantly more common for the patients with CRNMB to be married ($p = 0.014$) and attend church ($p = 0.046$); regular church attendance (mosque, synagogue, Buddhist temple, or place of worship) was found to be associated with 3.75-time higher odds (95% CI: 1.23; 11.5) of having CRNMB ($p = 0.025$) (Table 1).

The mental and emotional domain was analyzed using ten scales that cover cognitive functions and emotional state. As compared to the patients without CRNMB, the CRNMB patients were found to be more emotionally stable. For example, the patients with CRNMB had statistically significantly lower scores on the GDS-15 and GDS-30 scales ($p = 0.007$ and 0.027, respectively); on average, every 1-point increase in the GDS-15 scale score was associated with 1.08-time lower odds (95% CI: 1.02; 1.14) of having CRNMB ($p = 0.01$), and every 1-point increase in the GDS-30 scale score was associated with 1.04-time lower odds (95% CI: 1.00; 1.07) of having CRNMB ($p = 0.032$) (Table 2).

Thirteen parameters were analyzed to assess functional activity and physical health, which included screening for frailty; self-assessment of quality of life and health status; basic and instrumental activities; mobility; muscle strength; nutritional status; presence of the chronic pain syndrome, orthostatic hypotension, sensory deficits, and urinary and fecal incontinence; occurrence of falls; use of assistive devices. The results revealed that compared to the patients without CRNMB, the CRNMB patients were less likely to have frailty and use assistive devices, rated their quality of life and health status higher, were more active in performing activities of daily living, and were more mobile. For example, the patients with CRNMB exhibited better mood (OR = 0.65 (95% CI: 0.43; 0.99), $p = 0.043$), and it was statistically significantly more uncommon for them to have frailty according to the *Age is No Barrier* questionnaire ($p = 0.015$). As compared to the patients without CRNMB, the CRNMB patients had higher VAS

Table 1. Geriatric risk factors: social domain
Таблица 1. Гериатрические факторы риска: социальный домен

Parameter	All patients (<i>n</i> = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (<i>n</i> = 172)	present (<i>n</i> = 195)	
Disability, <i>n</i> (%)	304/359 (84.7%)	141/169 (83.4%)	163/190 (85.8%)	0.536
Class 1, <i>n</i> (%)	19/359 (5.3%)	9/169 (5.3%)	10/190 (5.3%)	0.999
Class 2, <i>n</i> (%)	223/359 (62.1%)	100/169 (59.2%)	123/190 (64.7%)	0.39
Class 3, <i>n</i> (%)	62/359 (17.3%)	32/169 (18.9%)	30/190 (15.8%)	0.495
Type of living arrangement				
independent living, <i>n</i> (%)	155/363 (42.7%)	84/171 (49.1%)	71/192 (37%)	0.034
with family, <i>n</i> (%)	206/363 (56.7%)	86/171 (50.3%)	120/192 (62.5%)	0.021
nursing home, <i>n</i> (%)	2/363 (0.6%)	1/171 (0.6%)	1/192 (0.5%)	0.728
Number of household members, persons, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	1 (1; 2)	1 (1; 2)	2 (1; 2)	0.003
Marital status				
married, <i>n</i> (%)	81/362 (22.4%)	31/171 (18.1%)	50/191 (26.2%)	0.103
widowed, <i>n</i> (%)	257/362 (71%)	130/171 (76%)	127/191 (66.5%)	0.039
divorced/separated, <i>n</i> (%)	18/362 (5%)	5/171 (2.9%)	13/191 (6.8%)	0.155
single, <i>n</i> (%)	4/362 (1.1%)	4/171 (2.3%)	0/191 (0%)	0.047
common law marriage, <i>n</i> (%)	2/362 (0.6%)	1/171 (0.6%)	1/191 (0.5%)	0.999
Presence of children, <i>n</i> (%)	334/364 (91.8%)	156/171 (91.2%)	178/193 (92.2%)	0.729
Number of children, persons, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	1 (1; 2)	1 (1; 2)	1 (1; 2)	0.645
Education				
no formal education, <i>n</i> (%)	2/362 (0.6%)	0/170 (0%)	2/192 (1%)	0.501
primary / incomplete primary education, <i>n</i> (%)	45/362 (12.4%)	24/170 (14.1%)	21/192 (10.9%)	0.442
secondary/incomplete secondary education, <i>n</i> (%)	70/362 (19.3%)	28/170 (16.5%)	42/192 (21.9%)	0.252
technical education, <i>n</i> (%)	98/362 (27.1%)	48/170 (28.2%)	50/192 (26%)	0.710
higher education / incomplete degree, <i>n</i> (%)	129/362 (35.6%)	61/170 (35.9%)	68/192 (35.4%)	0.993
higher education + academic degree, <i>n</i> (%)	18/362 (5%)	9/170 (5.3%)	9/192 (4.7%)	0.975
Medical house calls, cases, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	0 (0; 2)	1 (0; 2.8)	0 (0; 2)	0.118
Visits to the outpatient clinic, cases, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	4 (1; 10)	4 (1.0; 9.8)	4 (1.0; 10.5)	0.344
Ambulance calls, cases, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	1 (0; 3)	1 (0; 2)	1 (0; 3)	0.557
Total number of requests for medical attention, cases, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	8 (4; 14)	8 (4; 14)	8 (4; 14)	0.959
Number of hospitalizations, cases, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	1 (1; 2)	1 (1; 2)	1 (1; 2)	0.812
Reason for emergency hospitalization, <i>n</i> (%)	27/342 (7.9%)	10/161 (6.2%)	17/181 (9.4%)	0.276
Preferential provision of medicines, <i>n</i> (%)	241/348 (69.3%)	109/162 (67.3%)	132/186 (71%)	0.458
Still working, <i>n</i> (%)	8/361 (2.2%)	3/169 (1.8%)	5/192 (2.6%)	0.728

Table 1. Continued
Таблица 1. Продолжение

Parameter	All patients (<i>n</i> = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (<i>n</i> = 172)	present (<i>n</i> = 195)	
Age of retirement, years, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	60 (55; 69)	60 (55; 70)	60 (55; 68)	0.887
Financial capabilities				
low, <i>n</i> (%)	36/363 (9.9%)	18/170 (10.6%)	18/193 (9.3%)	0.825
medium, <i>n</i> (%)	324/363 (89.3%)	150/170 (88.2%)	174/193 (90.2%)	0.661
high, <i>n</i> (%)	3/363 (0.8%)	2/170 (1.2%)	1/193 (0.5%)	0.602
Religion/faith				
atheist, <i>n</i> (%)	39/362 (10.8%)	19/170 (11.2%)	20/192 (10.4%)	0.940
Eastern Orthodoxy, <i>n</i> (%)	268/362 (74%)	121/170 (71.2%)	147/192 (76.6%)	0.334
Islam, <i>n</i> (%)	10/362 (2.8%)	4/170 (2.4%)	6/192 (3.1%)	0.755
Christianity (except for Orthodoxy), <i>n</i> (%)	41/362 (11.3%)	23/170 (13.5%)	18/192 (9.4%)	0.275
other, <i>n</i> (%)	2/362 (0.6%)	2/170 (1.2%)	0/192 (0%)	0.219
refusal to respond, <i>n</i> (%)	2/362 (0.6%)	1/170 (0.6%)	1/192 (0.5%)	0.999
Frequency of church attendance				
never, <i>n</i> (%)	167/363 (46%)	80/170 (47.1%)	87/193 (45.1%)	0.796
sometimes, <i>n</i> (%)	176/363 (48.5%)	86/170 (50.6%)	90/193 (46.6%)	0.528
regularly, <i>n</i> (%)	20/363 (5.5%)	4/170 (2.4%)	16/193 (8.3%)	0.025
Frequency of guest visits to the patient's home				
not once, <i>n</i> (%)	97/364 (26.6%)	39/171 (22.8%)	58/193 (30.1%)	0.157
once or twice a year, <i>n</i> (%)	115/364 (31.6%)	57/171 (33.3%)	58/193 (30.1%)	0.557
once or twice a month, <i>n</i> (%)	102/364 (28%)	50/171 (29.2%)	52/193 (26.9%)	0.692
once or twice a week, <i>n</i> (%)	46/364 (12.6%)	24/171 (14%)	22/193 (11.4%)	0.54
every day, <i>n</i> (%)	4/364 (1.1%)	1/171 (0.6%)	3/193 (1.6%)	0.626
Frequency of the patient's visits to a friend or family member				
not once, <i>n</i> (%)	141/364 (38.7%)	66/171 (38.6%)	75/193 (38.9%)	0.999
once or twice a year, <i>n</i> (%)	121/364 (33.2%)	60/171 (35.1%)	61/193 (31.6%)	0.534
once or twice a month, <i>n</i> (%)	66/364 (18.1%)	31/171 (18.1%)	35/193 (18.1%)	0.999
once or twice a week, <i>n</i> (%)	33/364 (9.1%)	13/171 (7.6%)	20/193 (10.4%)	0.472
every day, <i>n</i> (%)	3/364 (0.8%)	1/171 (0.6%)	2/193 (1%)	0.999
Frequency of outings				
not once, <i>n</i> (%)	43/364 (11.8%)	20/171 (11.7%)	23/193 (11.9%)	0.999
once or twice a year, <i>n</i> (%)	21/364 (5.8%)	11/171 (6.4%)	10/193 (5.2%)	0.767

Table 1. Continued
Таблица 1. Продолжение

Parameter	All patients (n = 367)	Clinically relevant non-major bleeding		Level of statistical significance, p
		non-present (n = 172)	present (n = 195)	
once or twice a month, n (%)	29/364 (8%)	16/171 (9.4%)	13/193 (6.7%)	0.459
once or twice a week, n (%)	117/364 (32.1%)	56/171 (32.7%)	61/193 (31.6%)	0.881
every day, n (%)	154/364 (42.3%)	68/171 (39.8%)	86/193 (44.6%)	0.436
Internet use				
not once, n (%)	299/364 (82.1%)	139/171 (81.3%)	160/193 (82.9%)	0.865
once or twice a year, n (%)	9/364 (2.5%)	5/171 (2.9%)	4/193 (2.1%)	0.739
once or twice a month, n (%)	10/364 (2.7%)	5/171 (2.9%)	5/193 (2.6%)	0.999
once or twice a week, n (%)	17/364 (4.7%)	8/171 (4.7%)	9/193 (4.7%)	0.999
every day, n (%)	29/364 (8%)	14/171 (8.2%)	15/193 (7.8%)	0.999
Telephone and/or Internet communication				
not once, n (%)	23/364 (6.3%)	9/171 (5.3%)	14/193 (7.3%)	0.581
once or twice a year, n (%)	9/364 (2.5%)	2/171 (1.2%)	7/193 (3.6%)	0.182
once or twice a month, n (%)	15/364 (4.1%)	10/171 (5.8%)	5/193 (2.6%)	0.192
once or twice a week, n (%)	60/364 (16.5%)	36/171 (21.1%)	24/193 (12.4%)	0.037
every day, n (%)	257/364 (70.6%)	114/171 (66.7%)	143/193 (74.1%)	0.175

Notes: The table was compiled by the authors; p — the values were obtained by comparing the two groups using the Mann–Whitney test (for quantitative indicators), as well as Fisher's exact test and Pearson's χ^2 test (for categorical indicators); the table indicates the number of patients included in the analysis.

Примечания: таблица составлена авторами; p — значения получены при сравнении двух групп с использованием теста Манна — Уитни (для количественных показателей), а также точного теста Фишера и теста χ^2 Пирсона (для категориальных показателей); в таблице указано количество пациентов, которые были включены в анализ.

Table 2. Geriatric risk factors: mental and emotional status
Таблица 2. Гериатрические факторы риска: психоэмоциональный статус

Parameter	All patients (<i>n</i> = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (<i>n</i> = 172)	present (<i>n</i> = 195)	
Mini-Cog screening test				
• presence of cognitive impairment (score of 0–3), <i>n</i> (%)	217/367 (59.1%)	103/172 (59.9%)	114/195 (58.5%)	0.782
• no cognitive impairment (score of 4–5), <i>n</i> (%)	150/367 (40.9%)	69/172 (40.1%)	81/195 (41.5%)	0.782
Mini-mental State Examination				
• no cognitive impairment (score of 28–30), <i>n</i> (%)	88/351 (25.1%)	44/161 (27.3%)	44/190 (23.2%)	0.674
• pre-dementia cognitive impairment (score of 24–27), <i>n</i> (%)	136/351 (38.7%)	59/161 (36.6%)	77/190 (40.5%)	0.674
• mild dementia (score of 20–23), <i>n</i> (%)	96/351 (27.4%)	43/161 (26.7%)	53/190 (27.9%)	0.674
• moderate dementia (score of 11–19), <i>n</i> (%)	30/351 (8.5%)	14/161 (8.7%)	16/190 (8.4%)	0.674
• severe dementia (score of 0–10), <i>n</i> (%)	1/351 (0.3%)	1/161 (0.6%)	0/190 (0%)	0.674
Montreal Cognitive Assessment				
• no cognitive impairment (score of 26–30), <i>n</i> (%)	75/354 (21.2%)	36/164 (22%)	39/190 (20.5%)	0.744
• presence of cognitive impairment (score of 0–25), <i>n</i> (%)	279/354 (78.8%)	128/164 (78%)	151/190 (79.5%)	0.744
verbal fluency test: literal (VFT-L), points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	9 (6; 11)	9 (6; 11)	8.5 (6; 11)	0.805
13 or more points, <i>n</i> (%)	52/352 (14.8%)	23/162 (14.2%)	29/190 (15.3%)	0.779
verbal fluency test: category fluency (VFT-C), points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	12 (9; 15)	12 (8; 15)	12 (9; 15)	0.775
13 or more points, <i>n</i> (%)	151/352 (42.9%)	71/162 (43.8%)	80/190 (42.1%)	0.745
VFT-L/ VFT-C, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	0.8 (0.5; 1)	0.8 (0.6; 1)	0.8 (0.5; 0.9)	0.69
Boston Naming Test, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	34 (28; 37)	34 (29; 37)	33 (28; 37)	0.32
Literary cues, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	4 (1; 7)	4 (1; 7)	4 (1; 8)	0.313
Category cues, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	0 (0; 4)	0 (0; 3)	1 (0; 5)	0.114
Forward digit span test, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	8 (6; 10)	8 (6; 10)	8 (6; 10)	0.801
Maximum length of a sequence, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	5 (4; 6)	5 (4; 6)	5 (4; 6)	0.832
Digit Symbol Substitution Test, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	17 (10; 21)	17 (10; 21)	17 (11; 21)	0.702
10-word-list recall test: immediate recall, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	16 (12; 19)	16 (12; 19)	16 (13; 19)	0.786
10-word-list recall test: delayed recall, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	4 (2; 5)	4 (2; 5.3)	4 (2; 5)	0.541
10-word-list recall test: learning capacity, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	8 (6; 10)	9 (6; 10)	8 (6; 10)	0.473
Alzheimer’s Disease Assessment Scale-Cognitive, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	17.4 (11.6; 25.0)	18.2 (11.8; 25.6)	16.4 (11.3; 24.4)	0.505
Geriatric Depression Scale, GDS-15, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	5 (2; 8)	5 (3; 8)	4 (2; 7)	0.007

Table 2. Continued
Таблица 2. Продолжение

Parameter	All patients (<i>n</i> = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (<i>n</i> = 172)	present (<i>n</i> = 195)	
Geriatric Depression Scale, GDS-15				
normal (score of 0–4), <i>n</i> (%)	182/367 (49.6%)	70/172 (40.7%)	112/195 (57.4%)	0.001
• probable depression (score of 5–15), <i>n</i> (%)	185/367 (50.4%)	102/172 (59.3%)	83/195 (42.6%)	0.001
Geriatric Depression Scale, GDS-30, points, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)				
	11 (6; 16)	12 (7.0; 16.3)	10 (5.5; 15.0)	0.027
Geriatric Depression Scale, GDS-30				
• normal (score of 0–9), <i>n</i> (%)	153/351 (43.6%)	63/164 (38.4%)	90/187 (48.1%)	0.171
• mild depression (score of 10–19), <i>n</i> (%)	163/351 (46.4%)	82/164 (50%)	81/187 (43.3%)	0.171
• severe depression (score of 20–30), <i>n</i> (%)	35/351 (10%)	19/164 (11.6%)	16/187 (8.6%)	0.171

Notes: The table was compiled by the authors; *p* — the values were obtained by comparing the two groups using the Mann–Whitney test (for quantitative indicators), as well as the exact test; the table indicates the number of patients included in the analysis. Abbreviations: MMSE — Mini-mental State Examination; VFT-L — verbal fluency test (literal); VFT-C — verbal fluency test (category); WLT — 10-word-list recall test; GDS — Geriatric Depression Scale.

Примечания: таблица составлена авторами; *p* — значения получены при сравнении двух групп с использованием теста Манна — Уитни (для количественных показателей), а также точного теста; в таблице указано количество пациентов, которые были включены в анализ. Сокращения: MMSE — краткая шкала оценки психического статуса; VFT-L — тест вербальных ассоциаций: литеральные; VFT-C — тест вербальных ассоциаций: категориальные; WLT — тест запоминания 10 слов; GDS — гериатрическая шкала депрессии.

Table 3. Geriatric risk factors: functional and physical status
Таблица 3. Гериатрические факторы риска: функциональный и физический статус

Parameter	All patients (n = 367)	Clinically relevant non-major bleeding		Level of statistical significance, p
		non-present (n = 172)	present (n = 195)	
<i>Age is No Barrier</i> questionnaire (weight), n (%)	117/364 (32.1%)	60/171 (35.1%)	57/193 (29.5%)	0.257
<i>Age is No Barrier</i> questionnaire (deterioration of vision or hearing), n (%)	298/364 (81.9%)	144/171 (84.2%)	154/193 (79.8%)	0.275
<i>Age is No Barrier</i> questionnaire (fall-related injuries), n (%)	106/363 (29.2%)	47/170 (27.6%)	59/193 (30.6%)	0.541
<i>Age is No Barrier</i> questionnaire (mood), n (%)	186/364 (51.1%)	97/171 (56.7%)	89/193 (46.1%)	0.043
<i>Age is No Barrier</i> questionnaire (memory problem), n (%)	240/363 (66.1%)	111/170 (65.3%)	129/193 (66.8%)	0.756
<i>Age is No Barrier</i> questionnaire (urinary incontinence), n (%)	206/364 (56.6%)	97/171 (56.7%)	109/193 (56.5%)	0.962
<i>Age is No Barrier</i> questionnaire (walking difficulty), n (%)	218/364 (59.9%)	106/171 (62%)	112/193 (58%)	0.442
<i>Age is No Barrier</i> questionnaire, points, <i>Me (Q1; Q3)</i>	4 (3; 5)	4 (3; 5)	4 (2; 5)	0.245
<i>Age is No Barrier</i> questionnaire				
• fit (score of 0–2), n (%)	86/364 (23.6%)	29/171 (17%)	57/193 (29.5%)	0.008
• less fit (score of 3–4), n (%)	151/364 (41.5%)	80/171 (46.8%)	71/193 (36.8%)	0.063
• frail (score of 5–7), n (%)	127/364 (34.9%)	62/171 (36.3%)	65/193 (33.7%)	0.663
Self-assessment of quality of life on the visual analogue scale, points, <i>Me (Q1; Q3)</i>	6 (5; 8)	6 (4; 7.5)	6 (5; 8)	0.053
Self-assessment of health status on the visual analogue scale, points, <i>Me (Q1; Q3)</i>	5 (4; 6)	5 (4; 6)	5 (4; 7)	0.050
Barthel Index for Activities of Daily Living, points, <i>Me (Q1; Q3)</i>	90 (85; 95)	90 (80; 95)	90 (85; 95)	0.380
Barthel Index for Activities of Daily Living				
• total independence (score of 96–100), n (%)	67/364 (18.4%)	34/171 (19.9%)	33/193 (17.1%)	0.570
• slight dependence (score of 91–95), n (%)	80/364 (22%)	35/171 (20.5%)	45/193 (23.3%)	0.614
• moderate dependence (score of 61–90), n (%)	203/364 (55.8%)	94/171 (55%)	109/193 (56.5%)	0.893
• severe dependence (score of 21–60), n (%)	14/364 (3.8%)	8/171 (4.7%)	6/193 (3.1%)	0.608
• total dependence (score of 0–20), n (%)	0/364 (0%)	0/171 (0%)	0/193 (0%)	–
Lawton IADL scale, points, <i>Me (Q1; Q3)</i>	7 (5; 8)	6 (5; 7.5)	7 (5; 8)	0.004
Functional Activities Questionnaire, points, <i>Me (Q1; Q3)</i>	8 (4; 14)	9 (5; 15)	8 (3; 13)	0.106
Mini Nutritional Assessment, points, <i>Me (Q1; Q3)</i>	22 (19.5; 24)	22 (19.5; 24)	22.5 (20; 24.5)	0.117
Mini Nutritional Assessment				
• normal nutritional status (23.5–30 points), n (%)	121/350 (34.6%)	51/164 (31.1%)	70/186 (37.6%)	0.246
• at risk of malnutrition (17–23.5 points), n (%)	204/350 (58.3%)	102/164 (62.2%)	102/186 (54.8%)	0.215
• malnourished (less than 17 points), n (%)	25/350 (7.1%)	11/164 (6.7%)	14/186 (7.5%)	0.928
Short Physical Performance Battery, points, <i>Me (Q1; Q3)</i>	5 (3; 6)	4 (3; 6)	5 (3; 6)	0.999
Short Physical Performance Battery				
• fit (score of 10–12), n (%)	18/360 (5%)	5/169 (3%)	13/191 (6.8%)	0.155
• less fit (score of 8–9), n (%)	41/360 (11.4%)	19/169 (11.2%)	22/191 (11.5%)	>0.999
• frail (7 or less points), n (%)	301/360 (83.6%)	145/169 (85.8%)	156/191 (81.7%)	0.35
Tandem stance, seconds, <i>Me (Q1; Q3)</i>	2 (0; 6.5)	1 (0; 4.2)	2.3 (0; 8.5)	0.014

Table 3. Continued
Таблица 3. Продолжение

Parameter	All patients (n = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (n = 172)	present (n = 195)	
four-meter walk test, seconds, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	9 (6.7; 15.3)	9.5 (7.0; 15.3)	8.9 (6.3; 14.9)	0.27
walking speed, m/s, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	0.4 (0.3; 0.6)	0.4 (0.3; 0.6)	0.4 (0.3; 0.6)	0.552
five-time chair stand test, seconds, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	15.9 (0; 24.5)	17.7 (3.5; 26.3)	15.5 (0; 20.5)	0.045
Five-time chair stand test				
• unable to perform the test or over 60 s, <i>n</i> (%)	100/359 (27.9%)	47/169 (27.8%)	53/190 (27.9%)	0.999
• over 16.7 seconds, <i>n</i> (%)	168/359 (46.8%)	81/169 (47.9%)	87/190 (45.8%)	0.711
• 13.7–16.69 s, <i>n</i> (%)	48/359 (13.4%)	24/169 (14.2%)	24/190 (12.6%)	0.755
• 11.2–13.69 s, <i>n</i> (%)	27/359 (7.5%)	13/169 (7.7%)	14/190 (7.4%)	0.999
• 11.19 s or less, <i>n</i> (%)	16/359 (4.5%)	4/169 (2.4%)	12/190 (6.3%)	0.125
Timed Up and Go Test, seconds, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	16.1 (12.0; 21.4)	17.1 (12.9; 22.8)	15.3 (11.5; 20.4)	0.025
Timed Up and Go Test				
• normal (10 s or less), <i>n</i> (%)	59/348 (17%)	26/163 (16%)	33/185 (17.8%)	0.743
• intermediate (11–13 s), <i>n</i> (%)	289/348 (83%)	137/163 (84%)	152/185 (82.2%)	0.787
• gait and balance abnormalities (14 s and more), <i>n</i> (%)	0/348 (0%)	0/163 (0%)	0/185 (0%)	–
single-leg stance test, seconds, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	1.2 (0; 2.8)	1.0 (0; 2.6)	1.5 (0; 3)	0.321
Dynamometry: handgrip strength, kg, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	12.5 (9.0; 17.5)	12.5 (9.2; 17.3)	12.3 (9.0; 17.9)	0.869
handgrip strength (women), kg, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	10.5 (7.8; 13.3)	10.5 (8.0; 14.0)	10.3 (7.5; 13.0)	0.410
handgrip strength (men), kg, <i>Me</i> (<i>Q1</i> ; <i>Q3</i>)	19.8 (16.4; 22.6)	19.8 (17.6; 2.02)	19.3 (16.3; 23.3)	0.953
decrease in handgrip strength, <i>n</i> (%)	352/362 (97.2%)	166/170 (97.6%)	186/192 (96.9%)	0.755
decrease in handgrip strength (women), <i>n</i> (%)	243/250 (97.2%)	120/123 (97.6%)	123/127 (96.9%)	0.999
decrease in handgrip strength (men), <i>n</i> (%)	109/112 (97.3%)	46/47 (97.9%)	63/65 (96.9%)	0.999
orthostatic hypotension, <i>n</i> (%)	72/363 (19.8%)	34/171 (19.9%)	38/192 (19.8%)	0.983
Precursors of orthostatic hypotension, <i>n</i> (%)	199/356 (55.9%)	95/168 (56.5%)	104/188 (55.3%)	0.816
hearing impairment, <i>n</i> (%)	294/364 (80.8%)	136/171 (79.5%)	158/193 (81.9%)	0.573
visual deficit, <i>n</i> (%)	357/361 (98.9%)	169/170 (99.4%)	188/191 (98.4%)	0.625
chronic pain, <i>n</i> (%)	340/363 (93.7%)	161/170 (94.7%)	179/193 (92.7%)	0.444
urinary incontinence, <i>n</i> (%)	212/364 (58.2%)	97/171 (56.7%)	115/193 (59.6%)	0.581
difficult urination, <i>n</i> (%)	86/349 (24.6%)	42/163 (25.8%)	44/186 (23.7%)	0.648
nocturia, <i>n</i> (%)	316/351 (90%)	150/164 (91.5%)	166/187 (88.8%)	0.401
fecal incontinence, <i>n</i> (%)	37/362 (10.2%)	16/170 (9.4%)	21/192 (10.9%)	0.632
falls in the past year, <i>n</i> (%)	158/363 (43.5%)	70/171 (40.9%)	88/192 (45.8%)	0.347

Table 3. Continued
Таблица 3. Продолжение

Parameter	All patients (<i>n</i> = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (<i>n</i> = 172)	present (<i>n</i> = 195)	
Number of falls in the past year				
• no falls, <i>n</i> (%)	205/363 (56.5%)	101/171 (59.1%)	104/192 (54.2%)	0.351
• one fall, <i>n</i> (%)	66/363 (18.2%)	29/171 (17%)	37/192 (19.3%)	0.697
• two or more, <i>n</i> (%)	92/363 (25.3%)	41/171 (24%)	51/192 (26.6%)	0.696

Notes: The table was compiled by the authors; p — the values were obtained by comparing the two groups using the Mann–Whitney test (for quantitative indicators), as well as Fisher's exact test and Pearson's χ^2 test (for categorical indicators); the table indicates the number of patients included in the analysis.

Примечания: таблица составлена авторами; p — значения получены при сравнении двух групп с использованием теста Манна — Уитни (для количественных показателей), а также точного теста Фишера и теста χ^2 Пирсона (для категориальных показателей); в таблице указано количество пациентов, которые были включены в анализ.

Table 4. Geriatric risk factors: physical status (use of assistive devices)

Таблица 4. Гериятрические факторы риска: физический статус (использование вспомогательных средств)

Parameter	All patients (n = 367)	Clinically relevant non-major bleeding		Level of statistical significance, p
		non-present (n = 172)	present (n = 195)	
Use of glasses/lenses, n (%)	293/364 (80.5%)	142/171 (83%)	151/193 (78.2%)	0.248
Use of a hearing aid, n (%)	35/364 (9.6%)	19/171 (11.1%)	16/193 (8.3%)	0.362
Use of prosthetic denture, n (%)	268/364 (73.6%)	120/171 (70.2%)	148/193 (76.7%)	0.160
Use of a cane, n (%)	210/364 (57.7%)	103/171 (60.2%)	107/193 (55.4%)	0.356
Use of crutches, n (%)	10/364 (2.7%)	7/171 (4.1%)	3/193 (1.6%)	0.200
Use of a walker, n (%)	28/364 (7.7%)	17/171 (9.9%)	11/193 (5.7%)	0.130
Use of walking aids, n (%)	222/363 (61.2%)	109/171 (63.7%)	113/192 (58.9%)	0.340
Use of orthopedic footwear, n (%)	42/363 (11.6%)	19/170 (11.2%)	23/193 (11.9%)	0.826
Use of orthopedic insoles, n (%)	67/364 (18.4%)	28/171 (16.4%)	39/193 (20.2%)	0.346
Use of an orthopedic corset, n (%)	32/364 (8.8%)	16/171 (9.4%)	16/193 (8.3%)	0.720
Use of incontinence pads, n (%)	134/363 (36.9%)	68/170 (40%)	66/193 (34.2%)	0.253
Use of diapers or underpads, n (%)	37/364 (10.2%)	20/171 (11.7%)	17/193 (8.8%)	0.363
Number of assistive devices, pcs, Me (Q1; Q3)	3 (2; 4)	3 (2; 4)	3 (2; 4)	0.316
Use of any assistive device, n (%)	354/364 (97.3%)	170/171 (99.4%)	184/193 (95.3%)	0.022

Notes: The table was compiled by the authors; p — the values were obtained by comparing the two groups using the Mann–Whitney test (for quantitative indicators), as well as Fisher's exact test and Pearson's χ^2 test (for categorical indicators); the table indicates the number of patients included in the analysis.

Примечания: таблица составлена авторами; p — значения получены при сравнении двух групп с использованием теста Манна — Уитни (для количественных показателей), а также точного теста Фишера и теста χ^2 Пирсона (для категориальных показателей); в таблице указано количество пациентов, которые были включены в анализ.

scores measuring quality of life and health status ($p = 0.053$ and 0.05 , respectively); on average, every 1-point increase in the VAS quality of life score was associated with 1.09-time higher odds (95% CI: 0.99; 1.21) of having a bleeding event ($p = 0.084$); every 1-point increase in the health status score, 1.11-time higher odds (95% CI: 0.99; 1.26) ($p = 0.07$). The patients with CRNMB had statistically significantly higher Lawton IADL scores ($p = 0.004$); on average, every 1-point increase in the score was associated with 1.17-time higher odds (95% CI: 1.04; 1.32) of having CRNMB ($p = 0.008$). The presence of CRNMB was associated with a longer tandem stance time ($p = 0.014$); on average, for every one-second increase, the odds of having CRNMB increased by 1.05 times (95% CI: 1.01; 1.10) ($p = 0.013$). The CRNMB patients had statistically significantly lower scores on the 5-time chair stand test and Timed Up and Go Test as compared to patients without CRNMB ($p = 0.045$ and 0.025 , respectively); on average, every 10-point increase in scores on these scales was associated with 1.16-time (95% CI: 1.01; 1.34) ($p = 0.045$) and 1.23-time lower odds (95% CI: 1.02; 1.50) of having CRNMB ($p = 0.03$), respectively (Table 3).

The use of assistive devices was statistically significantly less common in the patients with CRNMB as compared to the patients without CRNMB ($p = 0.022$) (Table 4).

The frailty index was calculated using a deficit accumulation model, which involved the assessment of 46 deficits on the Rockwood scale [18] and 34 deficits on the scale used in the SPRINT study [19]. An analysis of frailty indices revealed that the CRNMB patients were less frail compared to the patients without CRNMB according to the frailty index used

in the SPRINT study. For example, a statistically significant association was found between the presence of CRNMB and lower SPRINT scores ($p = 0.005$); on average, every 0.1-point increase in the score was associated with a decrease in the odds of having CRNMB by 1.46 [1.14; 1.88] times ($p = 0.003$) (Table 5).

This study presents a systems approach to comprehensive geriatric assessment that relies on the analysis of four key domains: social functioning; mental and emotional status; physical health; functional capacity. The research design enables a comprehensive status analysis of elderly patients, taking the modern geriatric principles into account. The findings provide a holistic understanding of the relationships between different aspects of geriatric status, which is essential for the development of personalized approaches in geriatric practice.

Multi-factor analysis predicting the probability of clinically relevant non-major bleeding events

Table 6 presents a multi-factor model for predicting the probability of CRNMB, developed using a stepwise selection of predictors, with their exclusion according to the Akaike information criterion (AIC). The resulting model was characterized by a Nagelkerke pseudo- R^2 value of 0.1 (adjusted value of 0.05), a Somers' D_{xy} coefficient of 0.27 (adjusted value of 0.23), and an AUC of 0.64 [95% CI: 0.58; 0.69] (adjusted value of 0.61) (Figs 2, 3). The coefficients of the model were used to develop a prognostic nomogram to estimate the probability of CRNMB on DOACs (Fig. 4).

At a threshold predicted CRNMB probability of 55%, the resulting model was characterized by a prognostic accuracy of 59.9% [95% CI: 54.6; 65.1], a sensitivity of 48.9% [95% CI:

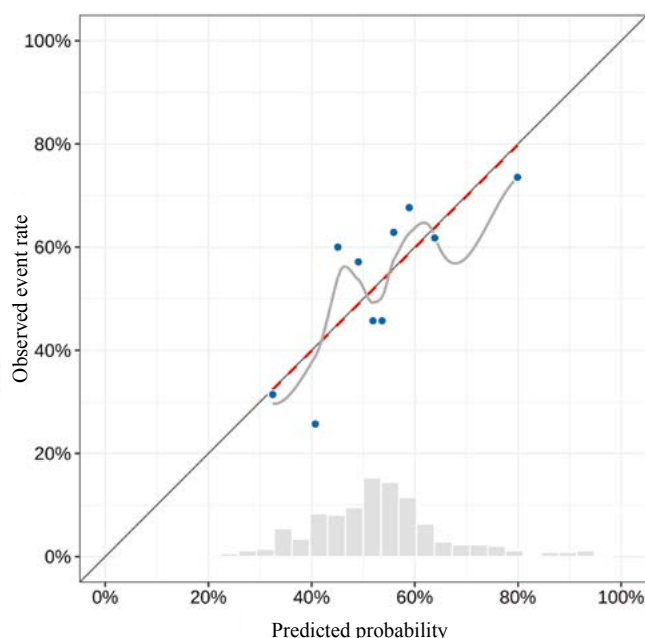


Fig. 2. Calibration curve for the predictions obtained using the model

Note: performed by the authors.

Рис 2. Калибровочная кривая для предсказаний, полученных с использованием модели

Примечание: рисунок выполнен авторами.

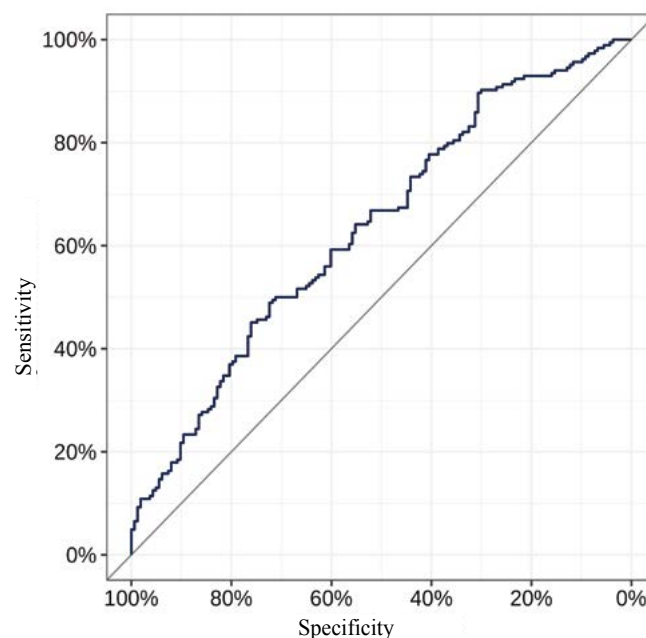


Fig. 3. ROC curve for the predictions obtained using the model

Note: performed by the authors.

Рис 3. ROC-кривая для предсказаний, полученных с использованием модели

Примечание: рисунок выполнен авторами.

Table 5. Geriatric risk factors: frailty indices
Таблица 5. Гериатрические факторы риска: индексы хрупкости

Parameter	All patients (n = 367)	Clinically relevant non-major bleeding		Level of statistical significance, <i>p</i>
		non-present (n = 172)	present (n = 195)	
Rockwood frailty index	0.36 (0.29; 0.44)	0.37 (0.31; 0.44)	0.35 (0.29; 0.43)	0.172
Frailty status on the Rockwood scale				
• fit (≤ 0.1)	0/367 (0%)	0/172 (0%)	0/195 (0%)	–
• less fit (0.11–0.20)	13/367 (3.5%)	6/172 (3.5%)	7/195 (3.6%)	0.999
• frail (≥ 0.21)	354/367 (96.5%)	166/172 (96.5%)	188/195 (96.4%)	0.999
• SPRINT frailty index	0.37 (0.31; 0.43)	0.39 (0.33; 0.44)	0.36 (0.31; 0.42)	0.005
Frailty status on the SPRINT scale				
• fit (≤ 0.1)	0/367 (0%)	0/172 (0%)	0/195 (0%)	–
• less fit (0.11–0.20)	5/367 (1.4%)	1/172 (0.6%)	4/195 (2.1%)	0.377
• frail (≥ 0.21)	362/367 (98.6%)	171/172 (99.4%)	191/195 (97.9%)	0.377

Notes: The table was compiled by the authors; *p* — the values were obtained by comparing the two groups using the Mann–Whitney test (for quantitative indicators), as well as Fisher’s exact test and Pearson’s χ^2 test (for categorical indicators). Abbreviations: SPRINT — Systolic Blood Pressure Intervention Trial.
Примечания: таблица составлена авторами; *p* — значения получены при сравнении двух групп с использованием теста Манна — Уитни (для количественных показателей), а также точного теста Фишера и теста χ^2 Пирсона (для категориальных показателей). Сокращения: SPRINT — шкала оценки индекса хрупкости.

Table 6. Coefficients in the resulting model for predicting the probability of clinically relevant non-major bleeding
Таблица 6. Коэффициенты в полученной модели прогнозирования вероятности клинически значимого небольшого кровотечения

Predictor	β (SE)	OR	95% CI	<i>p</i>	VIF
Intercept term	2.15 (1.62)	–	–	–	–
Number of household members	0.28 (0.1)	1.32	1.10; 1.62	0.005	1.06
Barthel ADL score	–0.02 (0.01)	0.98	0.96; 1.01	0.239	1.65
Lawton IADL score	0.21 (0.08)	1.24	1.06; 1.45	0.008	1.53
Timed Up and Go Test (seconds)	–0.01 (0.01)	0.99	0.96; 1.01	0.237	1.35
Use of any assistive device	–2.3 (1.08)	0.10	0.01; 0.57	0.033	1.02

Notes: The table was compiled by the authors; *p* — the values were obtained using the Wald test. Abbreviations: CI — confidence interval; OR — odds ratio; SE — standard error; VIF — variance inflation factor.
Примечания: таблица составлена авторами; *p* — значения получены с использованием теста Вальда. Сокращения: CI — доверительный интервал; OR — отношение шансов; SE — standard error, стандартная ошибка; VIF — variance inflation factor, фактор инфляции дисперсии.

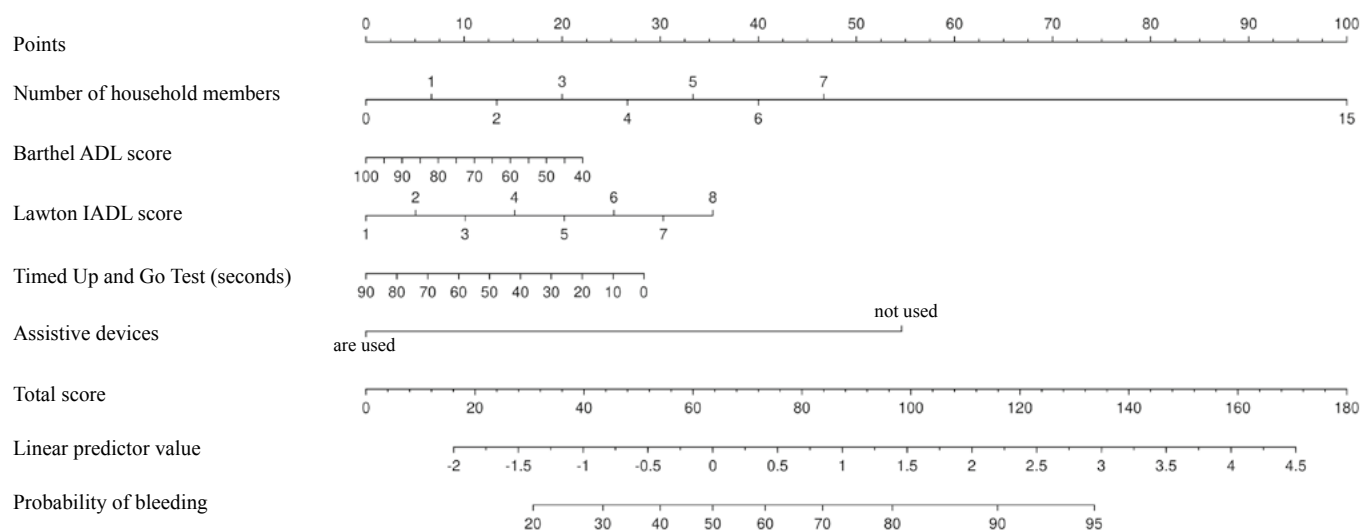


Fig. 4. Nomogram to predict the probability of clinically relevant non-major bleeding

Notes: performed by the authors; to estimate the probability of an event, it is necessary to determine the score corresponding to the value of the predictor by dropping the normal to the appropriate scale; then, it is necessary to find the total score and, by dropping the normal to the appropriate scale, estimate the linear predictor (log odds) and the probability of the event.

Рис. 4. Номограмма для прогнозирования вероятности развития клинически значимого небольшого кровотечения

Примечания: рисунок выполнен авторами; для оценки вероятности события необходимо определить балл, соответствующий значению предиктора, опустив нормаль на соответствующую шкалу, затем необходимо найти сумму баллов и, опустив нормаль на соответствующую шкалу, найти оценку значения линейного предиктора (логарифма шансов события) и вероятности события.

41.5; 56.4], and a specificity of 72.4% [95% CI: 64.9; 79.1], with a positive predictive value of 66.7% [95% CI: 58; 74.5] and a negative predictive value of 55.7% [95% CI: 48.7; 62.5].

Additional study results

No additional results were obtained during the study.

DISCUSSION

Summary of the main study result

The analysis of geriatric predictors of CRNMB on anticoagulants in AF patients aged ≥ 80 years identified significant factors in all four domains of comprehensive geriatric assessment: social; mental and emotional; physical; functional.

The performed multiple-factor regression analysis provided a means to develop a prognostic CRNMB risk model. The obtained coefficients were used to develop a prognostic nomogram to estimate the probability of CRNMB in patients receiving DOACs. Significant prognostic factors included the number of household members, Barthel ADL score, Lawton IADL score, Timed Up and Go Test, and use of assistive devices. The developed model was characterized by a prognostic accuracy of 59.9%, a sensitivity of 48.9%, and a specificity of 72.4%. The positive predictive value amounted to 66.7%; the negative predictive value, 55.7%.

Research limitations

The main limitations of the study include the small sample size and the associated lack of statistical power. Also, this observational study of real clinical practice does not provide a means to assess patient compliance with regard to DOAC therapy and the presence of CRNMB in frail patients (or patients with frailty); however, it reflects the actual health care practice.

Interpretation of the study results

In the social domain, the study showed that it was more common for the CRNMB patients to live in a large household and to attend church. High social engagement contributes to CRNMB detection: friends, coworkers, and relatives may notice the signs of CRNMB and pay more attention to them than the patients themselves, which makes the patient seek the help of specialists who can diagnose CRNMB.

The assessment of mental and emotional status showed that the patients with CRNMB were not prone to depression and had lower scores on the GDS-15 and GDS-30 scales. This can be attributed to the fact that depressed patients may be less likely to complain, including about CRNMB, and as a consequence, may not mention something relevant at a doctor's appointment [3].

The assessment of functional and physical status revealed that the patients with CRNMB were more active in performing their daily living activities (high Lawton IADL score), more mobile (according to balance tests, i.e., tandem stance, 5-time chair stand test, and Timed Up and Go Test), and it was less common for them to use assistive devices, which could lead to collisions and falls, resulting in CRNMB. In addition, it was less common for the CRNMB patients to have frailty according to the *Age is No Barrier* questionnaire, and they were less frail according to the frailty index used in the SPRINT study [19, 20].

Thus, the present study showed that the group of CRNMB patients included fewer frail patients and those in need of assistance since in actual clinical practice, patients with frailty are less likely to seek the help of specialists despite the pres-

ence of CRNMB. On the other hand, self-reliant patients are under less supervision, which may lead to injuries and the development of CRNMB.

The findings differ from the results of other studies [7–11]. For example, Brook et al. [7] presented a retrospective evaluation of 658 AF patients with a high fall risk assessed using the Northern Hospital modified STRATIFY tool [21, 22]. The overall median age of patients was 75 [31–96] years, which was comparable for all three DOACs (78 years for apixaban, 72 years for rivaroxaban, and 76 years for dabigatran etexilate), with an even distribution by sex. One of the study endpoints was clinically significant bleeding that scored three or more points on the 2010 ISTH (International Society of Thrombosis and Haemostasis) bleeding scale [23]. The analysis showed that a high fall risk constitutes a risk factor for clinically significant bleeding ($p = 0.032$).

The present study examined several parameters that determine the risk of falls: the Timed Up and Go Test, falls in the previous year, and fall-related injuries on the *Age is No barrier* scale. The study found that none of these parameters had a significant effect on the risk of developing CRNMB. The difference in results can be attributed to the study design, the difference in the age of the examined patients, and the older age of the patients (Me 84 [82; 88] years vs Me 75 [31; 96] years). Another reason is the difference in the criteria for the definition of bleeding: this study used the 2015 ISTH definition of CRNMB, whereas the article discussed above studied clinically significant bleeding according to the 2010 ISTH scale, which required medical intervention and the use of tranexamic acid, surgical hemostasis, transfusion, infusion of clotting factor concentrates and desmopressin, i.e., major bleeding as defined by the 2015 ISTH scale.

A number of studies examined the effect of frailty on the risk of bleeding. The retrospective study by Yamamoto et al. [8] included 240 AF patients (mean age of 76.1 ± 10.0 years) on DOACs, with women accounting for 42.9%. The patients were divided into frail (5–9 points) or fit (1–4 points) as per the 2005 Rockwood scale [24]. Frail patients accounted for 50% (mean age of 81.2 ± 7.8 years) of the total number of patients; women, 55.8%. The study endpoint was the cumulative incidence of major or symptomatic bleeding in a critical area or organ according to the definitions established by the 2005 ISTH [25]. The study results showed that the cumulative incidence of bleeding was significantly higher in the frail patient group as compared to the fit patients ($p < 0.001$).

In [9], Sogaard et al. present the results of an observational cohort study examining the safety of DOACs as compared to warfarin in frail AF patients. The study included 32,048 patients who had not previously taken anticoagulants. The median age of patients receiving a standard DOAC dose was 75 (69; 81) years. Patient frailty was defined using the hospital frailty risk score (HFRS) [26], with all patients categorized as having “moderate” (5–15 points) or “high” (>15 points) frailty risk. Moderate frailty risk was exhibited by 87.7% of patients (14,138/16,122) receiving a standard DOAC dose, with 12.3% of patients (1984/16,122) having a high risk of frailty. With moderate frailty risk, major bleeding developed

in 2.77% of patients (392/14,138) on a standard DOAC dose, and the relative risk of developing major bleeding on a standard DOAC dose amounted to 0.71 (95% CI 0.60–0.84). In the high frailty risk group, major bleeding developed in 3.53% (70/1984) of patients on a standard DOAC dose, and the relative risk for major bleeding was 0.62 (95% CI 0.41 to 0.92). A supporting analysis covering any bleeding events (including CRNMB and minor bleeding) leading to hospitalization showed comparable results. Although the incidence of major bleeding was slightly higher in the group of patients exhibiting high frailty risk than in the moderate frailty risk group, the relative risk of major bleeding was lower in the high frailty risk group.

The study by Candeloro et al. [10] reports on the association of frailty levels in AF patients with a higher risk of such adverse clinical events as clinically significant bleeding, including major bleeding and CRNMB. The patients were grouped as frail, pre-frail, and fit. Among the 236 patients included in the study (median age of 78 years, with women accounting for 44%), 156 (66%) patients had AF, and 80 (34%) patients had venous thromboembolism. Ninety-eight patients (41%) were frail, 115 patients (49%) were pre-frail, and 23 patients (10%) were fit. During a median observation period of 304 days, the incidence of clinically significant bleeding amounted to 20% in frail patients and 10% in pre-frail patients; no clinically significant bleeding occurred in fit patients.

In [11], Kim et al. present the results of a retrospective study on the effect of frailty on the relationship between DOACs (dabigatran, rivaroxaban, and apixaban) and major bleeding in AF patients as compared to warfarin. Frailty was determined using a deficit accumulation model (claims-based frailty index) [27]. The patients were divided into the following groups: fit at CFI < 0.15, pre-frail at CFI of 0.15–0.24, and frail at CFI ≥ 0.25 . The mean age of patients was 76.4 ± 7.1 years in the dabigatran-warfarin cohort, 76.8 ± 7.3 years in the rivaroxaban-warfarin cohort, and 77.3 ± 7.4 years in the apixaban-warfarin cohort. The results of this study are presented as cases per 1000 person-years. The study results showed that the incidence of major, gastrointestinal, and intracranial bleeding increased with increasing frailty.

Unlike the studies described above, the present study assessed the frailty of patients using several scales: *Age is No Barrier*, Short Physical Performance Battery, 2010 Rockwood frailty index, and the SPRINT scale. It was shown that frailty, defined by these parameters, had no significant effect on the risk of developing CRNMB; in addition, the CRNMB patients were more fit according to the SPRINT frailty index. The difference in results can also be attributed to the study design, the age of patients, the criteria for the definition of bleeding, and the method for measuring target parameters.

CONCLUSION

This study revealed that socially active, emotionally stable, mobile, and fit patients have a higher risk of developing CRNMB. Conversely, frail patients may be less likely to experience CRNMB. Also, a lower incidence of CRNMB was linked to reduced social activity, depression, need for assistance, and use of assistive devices. The study identified geri-

atric factors that may serve as predictors of CRNMB in AF patients aged over 80 years on DOACs, which were used to develop a prognostic nomogram that can be used to estimate the probability of CRNMB. Significant prognostic factors included the number of household members, Barthel ADL score, Lawton IADL score, Timed Up and Go Test, and use of assis-

tive devices. Given the active AI implementation in clinical practice, the obtained data can be integrated into clinical decision support systems. This would provide a means to assess the risk of developing CRNMB prior to its onset and select high-risk patients to continue work on the prevention of this adverse event.

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INFORMATION ABOUT THE AUTHORS

Marina S. Cherniaeva — Cand. Sci. (Med.), Assoc. Prof., Department of Clinical Pharmacology and Therapy named after Academician B.E. Votchal, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation; Assoc. Prof., Department of Internal and Preventive Medicine, Central State Medical Academy, Administrative Directorate of the President of the Russian Federation; geriatrician, Head of the Geriatric Department No. 5, Hospital for War Veterans No. 2, Moscow City Health Department.

<https://orcid.org/0000-0003-3091-7904>

Anna O. Pavlova — Assistant, Department of Internal and Preventive Medicine, Central State Medical Academy, Administrative Directorate of the President of the Russian Federation.

<https://orcid.org/0009-0008-4907-7144>

Polina A. Alferova — Assistant, Department of Clinical Pharmacology and Therapy named after Academician B.E. Votchal, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation.

<https://orcid.org/0009-0008-2524-8340>

Maria A. Rozhkova — primary care physician, Federal Research and Clinical Center for Specialized Types of Medical Care and Medical Technologies, Federal Medical-Biological Agency

<https://orcid.org/0009-0001-9329-7477>

Mikhail I. Trifonov — geriatrician, Head of the Department of Therapy, A Medclinic.

<https://orcid.org/0009-0005-5042-8288>

Tatyana V. Nikeeva — primary care physician, Consulting Department, Hospital for War Veterans No. 2, Moscow City Health Department.

<https://orcid.org/0009-0001-1928-6040>

Larisa A. Egorova — Dr. Sci. (Med.), Prof., Department of Internal and Preventive Medicine, Central State Medical Academy, Administrative Directorate of the President of the Russian Federation.

<https://orcid.org/0000-0001-9777-3832>

Olga M. Maslennikova — Dr. Sci. (Med.), Assoc. Prof., Head of the Department of Internal and Preventive Medicine, Central State Medical Academy, Administrative Directorate of the President of the Russian Federation.

<https://orcid.org/0000-0001-9599-7381>

Nikita V. Lomakin — Dr. Sci. (Med.), Assoc. Prof., Head of the Cardiology Department, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation; Head of the Cardiology Department No. 2, Central Clinical Hospital with a Polyclinic, Administrative Directorate of the President of the Russian Federation.

<https://orcid.org/0000-0001-8830-7231>

Dmitry A. Sychev — Dr. Sci. (Med.), Prof., Prof. of the Russian Academy of Sciences, Academician of the Russian Academy of Sciences, Head of the Department of Clinical Pharmacology and Therapy named after Academician B.E. Votchal, Russian Medical Academy of Continuous Professional Education, Ministry of Health of the Russian Federation.

<https://orcid.org/0000-0002-4496-3680>

СВЕДЕНИЯ ОБ АВТОРАХ

Черняева Марина Сергеевна ✉ — кандидат медицинских наук, доцент, доцент кафедры клинической фармакологии и терапии имени академика Б.Е. Вотчала федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации; доцент кафедры внутренних болезней и профилактической медицины федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» управления делами Президента Российской Федерации; врач-гериатр, заведующий гериатрическим отделением № 5 государственного бюджетного учреждения здравоохранения города Москвы «Госпиталь для ветеранов войн № 2 Департамента здравоохранения города Москвы».

<https://orcid.org/0000-0003-3091-7904>

Павлова Анна Олеговна — лаборант кафедры внутренних болезней и профилактической медицины федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» управления делами Президента Российской Федерации.

<https://orcid.org/0009-0008-4907-7144>

Алферова Полина Алексеевна — лаборант кафедры клинической фармакологии и терапии имени академика Б.Е. Вотчала федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации.

<https://orcid.org/0009-0008-2524-8340>

Рожкова Мария Александровна — врач-терапевт федерального государственного бюджетного учреждения «Федеральный научно-клинический центр специализированных видов медицинской помощи и медицинских технологий Федерального медико-биологического агентства».

<https://orcid.org/0009-0001-9329-7477>

Трифонов Михаил Игоревич — врач-гериатр, заведующий отделением терапии общества с ограниченной ответственностью «А Медклиник».

<https://orcid.org/0009-0005-5042-8288>

Никеева Татьяна Васильевна — врач-терапевт консультативного отделения государственного бюджетного учреждения здравоохранения города Москвы «Госпиталь для ветеранов войн № 2 Департамента здравоохранения города Москвы».

<https://orcid.org/0009-0001-1928-6040>

Егорова Лариса Александровна — доктор медицинских наук, профессор, профессор кафедры внутренних болезней и профилактической медицины федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» управления делами Президента Российской Федерации.

<https://orcid.org/0000-0001-9777-3832>

Масленикова Ольга Михайловна — доктор медицинских наук, доцент, заведующий кафедрой внутренних болезней и профилактической медицины федерального государственного бюджетного учреждения дополнительного профессионального образования «Центральная государственная медицинская академия» управления делами Президента Российской Федерации.

<https://orcid.org/0000-0001-9599-7381>

Ломакин Никита Валерьевич — доктор медицинских наук, доцент, заведующий кафедрой кардиологии федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации; заведующий кардиологическим отделением № 2 федерального государственного бюджетного учреждения «Центральная клиническая больница с поликлиникой» управления делами Президента Российской Федерации.

<https://orcid.org/0000-0001-8830-7231>

Сычев Дмитрий Алексеевич — доктор медицинских наук, профессор, профессор Российской академии наук, академик Российской академии наук, заведующий кафедрой клинической фармакологии и терапии имени академика Б.Е. Вотчала федерального государственного бюджетного образовательного учреждения дополнительного профессионального образования «Российская медицинская академия непрерывного профессионального образования» Министерства здравоохранения Российской Федерации.

<https://orcid.org/0000-0002-4496-3680>

✉ Corresponding author / Автор, ответственный за переписку