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Prediction of recurrence-free survival in patients with renal cell carcinoma and tumor thrombosis of the renal and inferior vena cava of levels I–II using an extended Cox model and machine learning methods

Musabek K. Mirzabekov[1], Nikolai D. Tikhonskii[2], Mikhail I. Shkolnik[1], Oleg A. Bogomolov[1], Nina V. Trukhacheva[2]

[1]Russian Scientific Center for Radiology and Surgical Technologies named after Academician A.M. Granov (Saint Petersburg, Russian Federation)
[2]Altai State Medical University (Barnaul, Russian Federation)

Abstract

Aim – to compare the predictive accuracy of Cox regression and machine learning (ML) methods regarding recurrence-free survival in patients with locally advanced renal cell carcinoma after radical treatment. Additionally, to investigate an extended Cox model in which the risk function is formed using a neural network approximator (DeepSurv).

Material and methods. This study conducted a retrospective analysis of data from patients diagnosed with renal cell carcinoma who underwent radical nephrectomy with thrombectomy from the renal and inferior vena cava between 2007 and 2024 at the Federal State Budgetary Institution "RSC for Radiology and Surgical Technologies named after Academician A.M. Granov". The study included 100 patients (54 men and 46 women). The median age was 61.5 years (IQR: 59.7–63). Of the total observations, disease progression was recorded in 41 cases, while in the remaining 59 cases, the data were censored. The models were evaluated based on the concordance index (C-index) and interpreted using SHAP analysis.

Results. The DeepSurv neural network model demonstrated higher predictive accuracy on the test dataset compared to the classical Cox model (C-index: 0.8056 vs. 0.7917, respectively). This indicates a superior ability of DeepSurv to rank patients by individual risk of disease progression. Using SHAP analysis, the key predictors contributing most significantly to the prognosis were identified: tumor size, ISUP grade, level of tumor thrombosis, and histological tumor type. The DeepSurv model enabled the capture of complex nonlinear interactions between features, thereby improving both the interpretability and clinical applicability of the results.

Conclusion. The obtained data confirm the feasibility of using machine learning methods for personalized prognosis and optimization of monitoring strategies in patients with RCC.

Keywords: recurrence-free survival, renal cell carcinoma, tumor thrombosis, Cox model, DeepSurv, machine learning, SHAP, prognosis, oncourology.
Conflict of interest: nothing to disclose.

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Information about authors
Musabek K. Mirzabekov – postgraduate student.
ORCID: 0009-0003-8365-7672
E-mail: musabek.mirzabekoff@yandex.ru
Nikolai D. Tikhonskii – lecturer at the Department of Physics and Informatics.
ORCID: 0009-0001-3077-1776
E-mail: wirelessm8@mail.ru
Mikhail I. Shkolnik – MD, Dr. Sci. (Medicine), chief researcher, Professor.
ORCID: 0000-0003-0589-7999
E-mail: shkolnik_phd@mail.ru
Oleg A. Bogomolov – MD, Cand. Sci. (Medicine), senior researcher, Associate professor.
ORCID: 0000-0002-5860-9076
E-mail: urologbogomolov@gmail.com
***Nina V. Trukhacheva** – Cand. Sci. (Pedagogics), Associate professor of the Department of Physics and Informatics.
ORCID: 0000-0002-7894-4779
E-mail: tn10@mail.ru
Corresponding Author

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Прогнозирование безрецидивной выживаемости больных с почечно-клеточным раком и опухолевым тромбозом почечной и нижней полой вены I–II уровней с использованием расширенной модели Кокса и методов машинного обучения

М.К. Мирзабеков[1], Н.Д. Тихонский[2], М.И. Школьник[1], О.А. Богомолов[1], Н.В. Трухачева[2]

[1]ФГБУ «Российский научный центр радиологии и хирургических технологий имени академика А.М. Гранова» Минздрава России (Санкт-Петербург, Российская Федерация)
[2]ФГБОУ ВО «Алтайский государственный медицинский университет» Минздрава России (Барнаул, Российская Федерация)

Аннотация

Цель – сравнить прогностическую точность регрессии Кокса и методов машинного обучения (ML) в отношении безрецидивной выживаемости пациентов с местно-распространенным почечно-клеточным раком после радикального лечения, а также исследовать расширенную модель Кокса, в которой функция риска формируется с использованием нейросетевого аппроксиматора (DeepSurv).

Материал и методы. В данном исследовании был проведен ретроспективный анализ данных пациентов с диагнозом «почечно-клеточный рак», перенесших радикальную нефрэктомию с тромбэктомией из почечной и нижней полой вены в период с 2007 по 2024 годы в ФГБУ «РНЦРХТ им. акад. А.М. Гранова». В исследование включены 100 пациентов (54 мужчины и 46 женщин). Медианный возраст составил 61,5 года (IQR: 59,7–63). Из общего числа наблюдений в 41 случае было зафиксировано прогрессирование заболевания, в остальных 59 случаях данные были цензурированные. Оценка моделей проводилась на основе индекса конкордации (C-index) и интерпретировалась с использованием SHAP-анализа.

Результаты. Нейросетевая модель DeepSurv продемонстрировала более высокую прогностическую точность на тестовой выборке по сравнению с классической моделью Кокса (C-index: 0,8056 против 0,7917 соответственно). Это свидетельствует о лучшей способности модели DeepSurv ранжировать пациентов по индивидуальному риску прогрессирования. С помощью SHAP-анализа установлены ключевые предикторы, вносящие наибольший вклад в прогноз: размер опухоли, степень злокачественности (ISUP-грейд), уровень опухолевого тромбоза и морфологический тип опухоли. Модель DeepSurv позволила учесть сложные нелинейные взаимодействия между признаками, что повысило интерпретируемость и клиническую применимость результатов.

Заключение. Полученные данные подтверждают целесообразность применения методов машинного обучения для персонализированного прогноза и оптимизации тактики наблюдения у больных с почечно-клеточным раком.

Ключевые слова: безрецидивная выживаемость, почечно-клеточный рак, опухолевый тромбоз, модель Кокса, DeepSurv, машинное обучение, SHAP, прогноз, онкоурология.

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Сведения об авторах
Мирзабеков М.К. – аспирант.
ORCID: 0009-0003-8365-7672
E-mail: musabek.mirzabekoff@yandex.ru
Тихонский Н.Д. – преподаватель кафедры физики и информатики.
ORCID: 0009-0001-3077-1776
E-mail: wirelessm8@mail.ru
Школьник М.И. – д-р мед. наук, главный научный сотрудник, профессор.
ORCID: 0000-0003-0589-7999
E-mail: shkolnik_phd@mail.ru
Богомолов О.А. – канд. мед. наук, старший научный сотрудник, доцент.
ORCID: 0000-0002-5860-9076
E-mail: urologbogomolov@gmail.com
***Трухачева Нина Васильевна** – канд. пед. наук. доцент кафедры физики и информатики.
ORCID: 0000-0002-7894-4779
E-mail: tn10@mail.ru
Автор для переписки

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INTRODUCTION

Prediction of recurrence-free survival in patients with renal cell carcinoma after radical surgery is an important task of urologic oncology. The accuracy of assessment of individual progression risk determines both the scheme of post-surgery supervision and the need for adjuvant therapy.

Traditionally, medical studies use the Cox proportionate risk model based on the supposition of linear impact of covariates on the risk function logarithm is used to analyze the time to event:

$$h(t|X) = h_0(t) \cdot e^{\sum b_i X_i} \quad (1)$$

where $h_0(t)$ –base risk function; $\sum b_i X_i$ – linear combination of predictors [1].

At the same time, the classic Cox model has several limitations, especially in the context of complex biomedical data. The main limitation is the suggestion of linearity and additivity of covariate influence on the risk function logarithm. This restricts its capability to model nonlinear or interacting effects, which is critically important for the analysis of heterogeneous oncological populations, e.g. patients with tumor thrombosis of the venous system.

The development of machine learning methods opened the possibility of flexible approximation of the dependence of the risk function from predictors without the need of strict prerequisites of its form [2-4]. Specifically, the DeepSurv neural network architecture is an extension of the Cox model, in which the linear prediction index ir replaced with the output of the multilayer neural network:

$$h(t) = h_0(t)\, e^{g(w_j, x_i)} \quad (2)$$

where $h_0(t)$ is the base risk function; $g(w_j, X_i)$ – result of the work of the neural network on predictors X_i and weighted coefficients w_j. Such a model retains the interpretable structure of the risk function, but demonstrates a significantly higher flexibility in accounting for nonlinear and highly dimensional correlations between the variables.

The use of DeepSurv allows for identification of implicit dependencies, unevident for the classic Cox regression, especially with complex clinical and morphological interactions in place. The question of interpretability remains a highly important aspect as well. This study additionally uses the SHAP method (SHapley Additive exPlanations) that allows for a quantitative assessment of contribution of each feature to the predicted risk [5].

It is thus possible to compare the traditional linear Cox model and its neural network extension using a single clinical sampling. This will allow evaluation of the potential of machine learning methods in the survival prediction tasks, and study the possibilities of interpretation of results in a clinically significant context.

AIM

To compare the predictive accuracy of Cox regression and machine learning (ML) methods regarding recurrence-free survival in patients with locally advanced renal cell carcinoma after radical treatment, and to investigate an extended Cox model in which the risk function is formed using a neural network approximator (DeepSurv).

MATERIAL AND METHODS

This study included a retrospective analysis of records of patients diagnosed with renal cell carcinoma who had undergone radical nephrectomy with thrombectomy from the renal vein and the lower hollow vein in the period from 2007 to 2024 at the Federal State Budgetary Institution "RSC for Radiology and Surgical Technologies named after Acad. A.M. Granov". The study included 100 patients (54 men and 46 women). The median age was 61.5 years (IQR: 59.7–63). Of the total observations, disease progression was recorded in 41 cases, while in the remaining 59 cases, the data were censored.

Exclusion criteria were level III–IV tumor thrombosis (Mayo classification), severe intraoperative complications that required access conversion, and lack of morphological verification of the tumor. The patients in which no progression had been recorded by the end of the study, were regarded as censored cases.

The statistical analysis comprised three successive stages. The primary analysis included an assessment of recurrence-free survival with the Kaplan-Meier method and the log-rank test to compare subgroups. Besides, a set of single-factor Cox regression models was constructed, which enabled a preliminary assessment of significance of clinical and morphological predictors [1].

On the stage of multivariate analysis, the classic Cox model of proportionate risks was developed. It included the clinically significant predictors, and those predictors that had $p < 0.1$ following the outcomes of the univariate analysis. The statistical significance of the factors was assessed with the Wald test, and the analysis was performed with the use of MedCalc and Statistica software suites.

On the final stage, two survival models were built and compared: the classis linear Cox model and the DeepSurv neural network [6]. The two models were trained only on predictors that proved statistically significant in the multivariate analysis ($p < 0.05$). DeepSurv is executed as a neural network approximating the risk function.

In order to assess the quality of the Cox linear model the following were used: Overall Model Fit, Likelihood Ratio Test, and the Wald test. To compare the Cox linear model and the DeepSurv model on the final stage, the concordance index (C-index) was used that measured the model's capability of properly ranking the patients by risk of progression [7]. To interpret the results of the DeepSurv model, the SHAP method was used that enabled a quantitative assessment of contribution made by each predictor to the individual prognosis and the identification of the most valuable risk predictors in the context of the neural network model [5].

RESULTS

On the first stage, the univariate analysis of predictors was performed using the Cox proportionate regression. The following were considered significant factors associated with decrease of time to progression: ISUP degree of malignity ($p = 0.0058$), tumor size ($p < 0.0001$), lymphatic node involvement ($p = 0.0070$), venous invasion ($p = 0.0074$), anemia status ($p = 0.0003$), thrombocytosis ($p = 0.0008$), Charlson comorbidity index ($p = 0.0105$), disease stage ($p < 0.0001$), and the level of tumor thrombosis (level 1: $p = 0.0016$; level 2: $p < 0.0001$). Some variables, such as age and arterial hypertension, did not demonstrate significant influence and were excluded from subsequent analysis (**Table 1**).

Predictors	P (value)
Hemoglobin	0.5087
Age	0.3034
Grade (ISUP)	0.0058
Tumor size, cm	<0.0001
Lymph nodes: indicator 2	0.0070
Level 1	0.0016
Level 2	<0.0001
Venous wall invasion: indicator 2	0.0074
Anemia (Hb <120): indicator 2	0.0003
Thrombocytosis (PLT>400): indicator 2	0.0008
Charlson (index) score	0.0105
Stage	<0.0001
Body mass index	0.1047
LDH_N (lactate dehydrogenase)	0.0520

Table 1. *Results of the Cox Univariate Model*
Таблица 1. *Результаты однофакторной модели Кокса*

On the second stage, the multivariate Cox model was constructed that included the predictors with clinical significance and $p < 0.1$ as per outcomes of the univariate analysis. The resulting model was statistically significant ($\chi^2 = 70.686$, $p < 0.0001$). The following covariates retained their impact on the decrease of recurrent-free survival: ISUP grade ($p = 0.0472$), morphological tumor type ($p = 0.0195$), tumor size ($p = 0.0031$), and the level of tumor thrombosis (level 1: $p = 0.0236$; level 2: $p = 0.0406$) (**Table 2**). Some variables were losing significance, likely due to multicollinearity and probable nonlinear interactions between parameters [8].

To compare the prediction accuracy of survival models, the entire sampling was randomly divided 80:20 into the training ($n = 80$) and testing ($n = 20$) subsamples. Based on the training subsample, both models were built: the classis linear Cox model and the neural network DeepSurv model. Both models were trained on the same subset of predictors chosen as statistically significant following the outcomes of the multivariate analysis ($p < 0.05$), which ensured the correct matching of their prognostic capabilities. In the process of training of the model, steps were taken to control overfitting.

The comparative analysis of prognostic accuracy of survival models is shown in **Table 3**.

Covariate	B	SE	Wald	P	Exp(b)
Charlson index, score	0.118	0.182	0.425	0.514	1.126
ISUP grade	0.3586	0.1807	3.9378	0.0472	1.431
Anemia (Hb<120)	0.6395	0.4694	1.8564	0.1730	1.8956
Body mass index	0.1468	0.09001	2.6593	0.1029	1.15810
Venous wall invasion	0.7418	0.7065	1.1023	0.2938	2.0996
LDH_N (lactate dehydrogenase)	0.3413	0.5506	0.3842	0.5354	1.4067
Lymph nodes	0.5176	0.5597	0.8553	0.3561	1.6781
Morphology	1.3723	0.5874	5.4572	0.0195	3.9445
Tumor size, cm	0.4665	0.1576	8.7603	0.0031	1.5943
Thrombocytosis, PLT_400	0.6035	0.5325	1.2845	0.2571	1.8284
Level_1	1.0505	0.4642	5.1223	0.0236	2.8591
Level_2	1.3413	0.6549	4.1943	0.0406	3.8239

Table 2. *Coefficients and Standard Errors in the Multivariate Model*
Таблица 2. *Коэффициенты и стандартные ошибки в многофакторной модели*

	C_index (training)	C_index (testing)
Cox linear model	0.8500	0.7917
DeepsurvK	0.8537	0.8056

Table 3. *Comparison of the Results of the Cox Linear Model and DeepSurvK*

Таблица 3. *Сравнение результатов построения линейной модели Кокса и DeepSurvK*

The Cox linear model demonstrated a high concordance index on the training sample (C-index = 0.8500) and a moderate decrease on the testing sample (C-index = 0.7917), which meets the expected degree of generalizing capability of linear models. The DeepSurv neural network model showed a similar level of prediction on the training sample (C-index = 0.8537), while showing a higher accuracy on the testing sample (C-index = 0.8056).

Significance of features in the DeepSurv model was visualized with the SHAP method [9]. The respective graph shows a distribution of SHAP-values for each included feature. The higher the absolute SHAP value, the greater the contribution of this feature to the resulting prediction of the risk. The color scale shows the significance of the feature in a specific patient, from low (blue) to high (red). The features are organized by the degree of their influence on the model (**Fig. 1**).

In the course of our study, we confirmed the applicability of the neural network extension of the Cox model (DeepSurv) for survival analysis and compared it with the classic model using a clinical sampling of patients with renal cell carcinoma and thrombosis of veins. Both approaches demonstrated high prediction accuracy (C-index ~0.80), notably, DeepSurv showed a slightly better result on the testing sample (0.8056 vs. 0.7917 in the Cox model). The increase matches the literature data: modern deep neural networks may be similar or even surpass the classic Cox regression in prediction accuracy when analyzing survivability [6, 10]. In particular, a large multicenter study involving 2139 patients with non-metastatic renal cell carcinoma performed by S.-S. Byun *et al.* (2021) showed that DeepSurv is better at predicting recurrence-free and specific survival that the Cox model (e.g., C-index for recurrence-free survival is 0.802 vs. 0.794) [11].

The major advantage of DeepSurv is the absence of the strict prerequisite of linear influence of covariates on the log-risk inherent in the Cox model [6]. The classic Cox regression describes the logarithm of the base risk as the sum of products

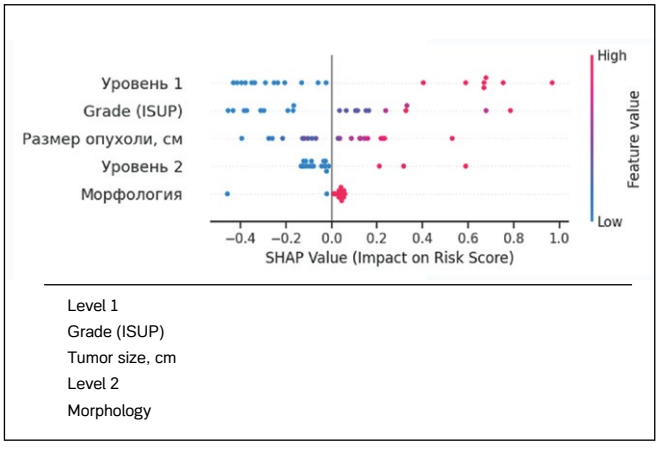

Figure 1. *Results of predictor analysis using the SHAP method.*

Рисунок 1. *Результат анализа предикторов методом SHAP.*

of coefficients multiplied by predictor values, which simplifies interpretation but limits the capability of identifying nonlinear effects and interactions between features. In our multivariate analysis, this was manifested in the following: some variables significant in a univariate analysis (e.g., anemia, thrombocytosis) lost significance on simultaneous inclusion in the model likely due to multicollinearity and overlapping information between related factors. Indeed, high correlation of predictors is known to result in an unstable assessment of coefficients in the Cox regression and their complicated interpretation [12]. The neural network approach of DeepSurv, conversely, is capable of flexible approximation of the connection between the features and survival without the prerequisite of additive nonlinearity. The multilayer network may identify underlying nonlinear dependencies not accessible to the classic model thereby taking into account the multifactor interactions (e.g., mutual influence of correlated clinical and morphological features). Furthermore, implementation of methods of regularization and decrease of feature dimensions improves the stability of deep models towards noise and data multicollinearity [6].

Interpretability remains a significant issue of implementation of deep learning methods into clinical practice. We solved this problem by using SHAP, a contemporary approach facilitating quantitative assessment of the contribution of each feature to the prediction of the model [13]. The results of the SHAP-analysis (Fig. 1) show that the greatest influence on the progression risk in the DeepSurv model came from the tumor size, degree of malignity (ISUP grade), level of tumor thrombosis and histological subtype of the tumor. These features are plotted in the top part of the graph and are characterized with the greatest scattering of the SHAP-values. Contribution of factors agrees with clinical concepts: the larger size of the tumor was associated with the increased risk of recurrence (red dots on the right of the graph), which reflects the higher tumor burden and the aggressiveness of the disease. Higher degrees of malignity (ISUP 3–4) also significantly increased the predicted risk; this fact matches the well-known predictive significance of the degree of nuclear atypia of the renal carcinoma, in which the badly differentiated tumors have worse outcomes [11]. The presence of level II tumor thrombus (with proliferation to the inferior vena cava) resulted in a significant increase of progression risk as compared to levels 0 and I. This coincides with literature data, according to which the tumor invasion of the venous system per se, especially with the involvement of the inferior vena cava, is an independent adverse prediction factor for patients with renal cell carcinoma.

In is noteworthy that according to SHAP-analysis the influence of level I thrombosis was even more pronounced than that of level II. This may reflect the statistical peculiarities of the specific sample: in this study, there were significantly less patients with level II (n=16), which might have resulted in the decrease of stability of assessments in the training of the DeepSurv model. Besides, tumors with level II thrombosis could be combined, in individual cases, with less aggressive morphological characteristics (e.g., smaller size or lower ISUP grade), which the neural network could have considered in a cumulative way and partially compensate the total risk.

According to H. Park *et al.* (2019), the presence of the venous thrombus in the renal cell carcinoma (RCC) is associated with almost two-fold risk of progression (HR ~1.9) [14]. In our study, the higher level of thrombosis decreased the recurrence-free survival in a similar way. Finally, the neural network identified the significance of the histological type of the tumor: while the non-clear cell forms (papillary, chromophobe, and other forms) are usually associated with a negative outcome of the RCC with venous thrombosis, in our model the clear-cell histotype showed some increase of the risk, even though the SHAP scattering was narrow.

A possible explanation of the observed increase of the risk in the clear-cell RCC could be that this histotype prevailed in the studied sample, whereas the rare forms (papillary, chromophobe, medullar) were represented only by a small sample. This decreases the statistical capacity for the assessment of their influence and may result in a lowered assessment of risk associated with them. Besides, clear cell tumors may be combined with other adverse characteristics, namely, larger size, high ISUP grade, extended venous thrombosis, which, in aggregate, increased the predicted progression risk. Finally, the deep learning model DeepSurv, capable of considering the nonlinear interactions between variables, was able to identify the characteristic combinations of features, more typical of the clear-cell type, and to interpret them as an integral prognostic marker augmenting the contribution from this histotype.

In our study, the benefit of DeepSurv over the classic approach in the concordance metrics was rather modest (difference of ~0.01–0.02), which may be explained by a limited size of sample (n=100) and the fact that the key risk drivers for this group of patients are identified quite well by the linear model. At the same time, even a minor increase in accuracy assisted by the neural network may be clinically significant in boundary cases (e.g., in stratification into groups of high or low risk); what is most important, DeepSurv became a tool for a deeper understanding of structure of patient data. On the other hand, the downsides of deep learning include a more complicated learning process requiring selection of hyper-parameters and, quite often, large arrays of data for a reliable generalization. Besides, the "black box" of the neural networks makes it difficult to provide a direct explanation why some patient of the other received a certain prognosis. We demonstrated that this problem may be solved with SHAP methods. This allowed to make the model conventionally interpretable, making it close in terms of information value to the Cox regression known to medical professionals.

The obtained results have practical implications for clinical practice. The ability to stratify risk in patients with renal cell carcinoma and tumor thrombosis in a more accurate way may help optimize treatment strategies and follow-up care. Firstly, identification of patients with extremely high risk of progression after surgical treatment may facilitate addressing the question of adjunctive therapy. The present-day standard for localized RCC with thrombus remains the radical nephrectomy with thrombectomy [15]. At the same time, five-year survival in this group varies greatly (from ~23% to 70% depending on the tumor volume, level of thrombosis, and accompanying factors) [15]. Currently, there is no universally accepted single criterion to identify which patients from this heterogeneous group would truly benefit from adjuvant therapy, such as postoperative immunotherapy, to improve clinical outcomes [16]. It follows from our data that a combined model based on DeepSurv may serve as the basis for such a prognostic tool. Individual risk prognosis calculated by a neural network with consideration of a set of clinical and morphological features may potentially serve as the integral criterion that is used to select the patients for additional interventions. For instance, a patient with a large-sized tumor, high ISUP grade and level II thrombus will be identified as having a model-predicted high risk of early progression, this warrants both the intensified surveillance and the consideration of adjuvant systemic therapy through multidisciplinary team discussion. Secondly, such models will assist in informing the patients and planning the follow-up care. Conventional prognostic schemes (TNM-staging, gradation type factors, involvement of lymphatic nodes, etc.) do not consider many nuances, therefore, patients of one group (e.g., stage pT3a N0) may have different outcomes [11]. The use of a ML-model aggregating the data on tumor morphology, biomarkers and thrombus volume, will enable compilation of a more personalized schedule of clinical examinations: some of the low-risk patients will avoid redundant visits and check-ups, whereas the high-risk group should be given more attention. Thirdly, the use of stratification algorithms at the stage of planning of examinations and treatment will facilitate a more justified comparison of various methods. Specifically, in the context of choosing surgical access (laparoscopy vs. laparotomy) our analysis confirmed comparability of oncological outcomes, if the risk factors are spread in the same fashion. In the future, the DeepSurv type models may be used to rank patients according to their prognostic index even before the operation: this will assist correct comparison of new methods of treatment thereby obtaining higher quality data for evidence-based medicine. A promising approach involves integrating clinical variables with molecular and radiological tumor characteristics (genomic markers, CT/MRI data) within a unified neural network model [16-18]. Existing examples demonstrate how combining radiomics with DeepSurv algorithms improves prognostic accuracy and therapy selection in lung cancer [16]; similarly, adopting such comprehensive models in renal cell carcinoma could significantly enhance risk stratification precision.

CONCLUSION

The neural network Cox model DeepSurv confirmed its methodological viability in the task of predicting recurrence-free survival in patients with renal cell carcinoma and thrombosis of the vein. It allowed consideration of nonlinear links of predictors and provided a higher (if marginally) prognostic rating. The use of the SHAP methods provided interpretation of the model in terms of conventional clinical categories making the results fit for practical use. These findings demonstrate the potential for broader implementation of the DeepSurv approach in oncourology, including patient selection for adjuvant therapies, development of personalized surveillance protocols, and treatment strategy decisions based on integrated prognostic indices. This aligns with the global trend of incorporating artificial intelligence in medicine to enhance prognostic accuracy and treatment personalization [5].

ADDITIONAL INFORMATION	ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ
Ethical Approval Statement. Extract from the protocol of the LEC No. 03-11/021 dated 11/19/2021.	***Этическая экспертиза.*** Выписка из протокола ЛЭК №03-11/021 от 19.11.2021 г.
Study funding. The study was the authors' initiative without external funding.	***Источник финансирования.*** Работа выполнена по инициативе авторов без привлечения финансирования.
Conflict of interest. The authors declare that there are no obvious or potential conflicts of interest associated with the content of this article.	***Конфликт интересов.*** Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с содержанием настоящей статьи.
Contribution of individual authors. Mirzabekov M.K.: concept development, statistical analysis, writing of the text. Bogomolov O.A., Shkolnik M.I.: editing and approval of the text. Trukhacheva N.V., Tikhonskii N.D.: concept development, statistical analysis, preparation of graphs and editing of the text. The authors gave their final approval of the manuscript for submission, and agreed to be accountable for all aspects of the work, implying proper study and resolution of issues related to the accuracy or integrity of any part of the work.	***Участие авторов.*** Мирзабеков М.К. – разработка концепции, проведение статистического анализа, написание текста. Богомолов О.А., Школьник М.И. – редактирование и утверждение текста. Трухачева Н.В., Тихонский Н.Д. – разработка концепции, проведение статистического анализа, подготовка графиков и редактирование текста. 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 или добросовестностью любой части работы.

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