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**RESEARCH**

# Predictors of 30-day mortality in patients with an international normalized ratio of 4.5 - 10 due to warfarin-related overanticoagulation: a retrospective cohort study

## Varfarin ilişkili aşırı antikoagülasyona bağlı olarak international normalized ratio değeri 4.5 - 10 arasında olan hastalarda 30 günlük mortalitenin prediktörlerinin belirlenmesi: retrospektif kohort çalışması.

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**Abstract**

**Purpose:** Although it has been shown that vitamin K administration does not benefit patients with INR levels between 4.5 to 10, there are studies in the literature showing that some complications including the risk of bleeding in these patients increase significantly. For this reason, it is crucial to select high-risk patients who present with elevated INR to apply closer follow-up and monitoring. The primary objective of our study is to define the predictors for 30-day mortality of the patients with an INR between 4.5 to 10 due to warfarin-related overanticoagulation. The secondary objective of our study is to derive a regression model which can predict mortality in 30 days and to compare the performance of this model with the National Early Warning Score-2(NEWS-2).

**Materials and Methods:** We included patients older than 18 years old, admitted between the dates 01.01.2016 - 01.01.2022 who are using warfarin as medication and with an INR between 4.5 – 10 in our study. We excluded patients with trauma, major bleeding on admission or patients with missing data. For the regression model, backward-wald stepwise method was utilized. We used the Hosmer-Lemeshow test for the goodness of fit. For the overall performance of the model, we evaluated the Nagelkerke R Square, and the Reciever Operating Characteristics test. DeLong test was used to compare the area under the curves (AUC).

**Results:** A total of 263 patients were examined in the statistical analysis. Mean arterial pressure, SpO2, pulse rate, and age were the independent predictors of 30-day mortality. The model have classified 81.4% of the patients correctly. The AUC of the regression model was 0.848

**Öz**

**Amaç:** K vitamini uygulamasının international normalized ratio(INR) değeri 4.5 ila 10 arasında olan hastalara fayda sağlamadığı gösterilmiş olmasına rağmen, literatür bu hasta grubunda kanama dahil olmak üzere bazı komplikasyonların önemli ölçüde arttığını göstermektedir. Bu nedenle, INR düzeyi artmış hastalarda yüksek risk taşıyan hastaların belirlenmesi ve daha yakın takip ve izlem altına alınması önemlidir. Çalışmamızın birincil amacı, varfarin ilişkili aşırı antikoagülasyon nedeniyle INR değeri 4.5 - 10 arasında olan hastaların 30 günlük mortalite prediktörlerini belirlemektir. Çalışmamızın ikincil amacı, 30 gün içindeki mortaliteyi öngören bir regresyon modeli oluşturmak ve bu modelin performansını National Early Warning Score-2 (NEWS-2) ile karşılaştırmaktır.

**Gereç ve Yöntem:** Çalışmamıza, 01.01.2016 - 01.01.2022 tarihleri arasında hastaneye başvuran, 18 yaşından büyük, warfarin kullanan ve INR değeri 4.5 ila 10 arasında olan hastalar dahil edildi. Travma ile başvuran, başvuru esnasında majör kanaması olan veya veri eksiği olan hastalar çalışmamızdan dışlandı. Regresyon modeli için, backward-Wald stepwise yöntemi kullanıldı. Modelin fitliği Hosmer-Lemeshow ile test edildi. Modelin genel performansı Nagelkerke R Square ile değerlendirildi ve Reciever Operating Characteristics testi uygulandı. Eğri altında kalan alanların (AUC) karşılaştırması için DeLong testi kullanıldı.

**Bulgular:** İstatistiksel analizde toplam 263 hasta dahil edildi. Ortalama arteriyel basınç, $SpO_2$, nabız ve yaş, 30 günlük mortalitenin bağımsız prediktörleri olarak bulundu. Model, hastaların %81.4'ünü doğru şekilde sınıflandırdı. Regresyon modelinin AUC değeri 0.848 0.799 - 0.898)

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(0.799 to 0.898). The sensitivity of the model as a tool for mortality prediction was 94.1%, specificity 66.5%, and accuracy 71.9%. The AUC of the NEWS-2 score for 30-day mortality was calculated as 0.782 (95%CI = 0.715 to 0.849). The difference between the AUCs of our model and the NEWS-2 score was statistically significant.

**Conclusion:** Mean arterial pressure, SpO2, heart rate, and age were the independent predictors for the 30-day mortality of patients with an INR between 4.5 to 10 due to overanticoagulation because of warfarin medication. The regression model we derived showed good overall discrimination and performed significantly better than NEWS-2 score.

**Keywords:**. Warfarin, supratherapeutic INR, overanticoagulation, vitamin-K, predictors of mortality.

olarak hesaplandı. Mortalite tahminindeki tanısal performansı incelendiğinde duyarlılığı %94.1, özgüllüğü %66.5 ve doğruluğu %71.9 olarak hesaplandı. 30 günlük mortalite için NEWS-2 skorunun AUC değeri 0.782(95% CI = 0.715 - 0.849) olarak hesaplandı. Modelimizin ve NEWS-2 skoru arasındaki AUC farkı istatistiksel olarak anlamlı bulundu.

**Sonuç:** Ortalama arteriyel basınç, $SpO_2$, nabız ve yaş, varfarin kullanımına bağlı olarak INR değeri 4.5-10 arasında olan hastalarda 30 günlük mortalite için bağımsız prediktörler olduğu saptandı. Elde ettiğimiz regresyon modeli genel olarak iyi bir sınıflama sağladı ve NEWS-2 skorundan anlamlı şekilde daha iyi performans gösterdi.

**Anahtar kelimeler**: Varfarin, yüksek INR, aşırı antikoagülasyon, K vitamini, mortalite prediktörleri

## INTRODUCTION

An important side effect of vitamin K antagonists is an elevated international normalized ratio (INR). The desired target range for most conditions is an INR between 2 to 3, and INR values lower than 2 are linked to a higher risk of thromboembolism, while values exceeding 4 are shown to be associated with an elevated likelihood of bleeding[1]. The most frequent reasons for overanticoagulation are deficiencies in INR monitoring and irregularities in the use of medication[2]. There are various algorithms for the treatment of elevated INR due to the use of oral anticoagulants (OACs). According to the American Society of Hematology guidelines for the management of venous thromboembolism published in 2018, it is recommended that patients with major bleeding and elevated INR be given prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP) with vitamin K. The same guideline recommends that OACs be discontinued for only 1-2 days and no additional medication, including vitamin K, should be given to patients with an elevated INR between 4.5 and 10 [3].

The literature have demonstrated a significant increase in complications, including bleeding risk, in patients with elevated INR compared to those within acceptable INR levels[4-5]. Although the administration of vitamin K in patients with elevated INR has been shown to effectively lower the INR level to the desired range in various studies, its positive impact on bleeding and mortality remains contradictory in patients with INR between 4.5 and 10 [1,6,7]. This indicates that patients require interventions beyond mere INR control. Identifying high-risk patients within this group who present with an elevated INR is crucial, necessitating the implementation of closer follow-up and monitoring instead of administering vitamin K. The National Early Warning Score-2 (NEWS-2) can be utilized for this purpose, but to our knowledge, there are no studies examining the performance of this scoring system in this specific patient group[8].

We aimed to contribute to the existing literature by identifying specific predictors of 30-day mortality in patients with warfarin-related overanticoagulation. It is worth noting that the majority of studies in this field have primarily focused on identifying predictors of adverse outcomes in patients with an INR above 10, while patients with elevated but lower INR levels are often overlooked. Therefore, our study addresses this gap in the literature by specifically investigating the predictors of mortality in patients with an INR between 4.5 and 10. Additionally, the proposal of a regression model with superior predictive performance compared to the NEWS-2 score can assist clinicians in decision-making as a tool for predicting mortality in this patient population.

The primary objective of our study is to identify predictors of 30-day mortality in patients with an INR between 4.5 and 10 due to warfarin-related overanticoagulation. Our secondary objective is to develop a regression model that can predict mortality within 30 days and compare its performance to the NEWS-2 score.

## MATERIALS AND METHODS

### Study setting

This retrospective cohort study was conducted in the emergency medicine department (ED) of a tertiary training and research hospital, following approval from the Umraniye Training and Research Hospital

Review Board (Approval Date: 27.05.2022, Approval Number: E-54132726-000-12317). The ED where the study took place handles approximately 600,000 admissions annually, and healthcare services are provided by emergency medicine residents, who work under the supervision of emergency medicine specialists. Patient information within the emergency department is documented in an electronic database. Patient follow-up and treatment are carried out using this electronic record system, with access to these records granted upon approval from the ethics committee.

## Study protocol

In the department of emergency medicine where the study was conducted, patient management for those presenting with an elevated INR was based on the guideline provided by the American College of Chest Physicians[9]. According to the guideline, for patients with an INR between 4.5 and 10, the recommended treatment is the discontinuation of warfarin, and the routine use of vitamin K is not routinely employed. In our ED, patients with an isolated high INR within this range are typically managed as outpatients and are not routinely hospitalized. However, due to the retrospective design of the study, no interventions were made concerning physician management of the patients. As a result, there was a protocol breach in the management of some patients. The elevated INR levels in these patients were due to warfarin overdose.

International normalized ratio is calculated accoring to the following forumla: $INR = (patient's\ PT / mean\ normal\ PT)^{ISI}$ where the mean normal prothrombin time (PT) is the average PT of healthy individuals, and International Sensitivity Index (ISI) is the sensitivity of the thromboplastin reagent utilized in our laboratory to detect changes in the clotting factors.

The calculation of the National Early Warning Score-2 was performed according to the study published in 2017 which is conducted by the Royal College of Physicians[8].

## Sample

Patients older than 18 years, who were admitted to the ED between the dates of January 1, 2016, and January 1, 2022, and were using warfarin as medication, with an INR between 4.5 and 10, were included in this retrospective study. The INR values were measured using standard laboratory methods. Patients who presented with major bleeding upon admission, those with trauma, and those with missing data were excluded from the study. Additionally, patients who received vitamin K in addition to warfarin discontinuation were excluded due to a protocol breach.

Since our study was designed as a logistic regression study, we followed Green's suggestion for sample size calculation, using the formula 50 + 8 x (number of variables)[10]. For the univariate analysis, we planned to analyze the effect of 17 variables on the outcome. Hence, we calculated the sample size for our study as 50 + 8 x 17 = 186 to ensure that our study would not be underpowered, even if all variables were included in the regression analysis. Considering a 10% margin of error, a minimum of 205 patients were required for the study.

After collecting the data, it was observed that the number of events (30-day mortality) was 51. In the literature, it has been discussed that the number of events per predicted variable (EPV) can be relaxed up to 5-9, particularly for model studies focusing on sensitivity[11]. Based on this, we calculated that including 7 predictors in the final regression model would be appropriate to avoid an increased risk of overfitting.

## Statistical analysis

For the statistical analysis, SPSS (*IBM Corp. Released 2019 IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.*) program was utilized. Shapiro Wilk test was chosen for the test of normality. Given the non-normal distribution of all continuous data, countinuous data were expressed as median (25% - 75% quartiles), and pairwise group comparisons were performed using the Mann-Whitney U test. Categorical variables were presented as frequency (%) and were compared using the Chi-Square test. In cases where the expected cell counts were low, Fisher's Exact test was employed.

For the development of the regression model, we included all variables initially and utilized the backward-wald stepwise method to iteratively select the most significant predictors and refine the model. This rigorous approach allowed us to arrive at the final, best performing model. The assumption of multicollinearity was assessed for the final model. To evaluate the goodness of fit, we employed the Hosmer & Lemeshow test. For assessing the overall performance of our model, we utilized the

Nagelkerke R Square. Subsequently, the predicted probabilities for each patient were computed, and the Receiver Operating Characteristics (ROC) test was employed to calculate the area under the curve (AUC) as a measure of the model's performance. To compare the AUCs, we utilized the DeLong test.

For internal validation, we employed the random split validation method. The dataset was randomly divided into a derivation set and a validation set, with an 80/20 ratio. The model's performance was compared between the training and validation sets, and the results were summarized. The level of statistical significance was set at $p < 0.05$.

## Outcome measures

The primary outcome of our study was to identify predictors of 30-day mortality in patients with an INR between 4.5 and 10 due to warfarin-related overanticoagulation. The secondary objective was to develop a regression model capable of predicting mortality within 30 days and to compare the performance of this model with the NEWS-2 score.

## RESULTS

A total of 371 patients who met the inclusion criteria between January 1, 2016, and January 1, 2022, were included in our study. Among them, 86 patients were excluded due to missing data, 8 patients due to major bleeding upon presentation, and 14 patients due to the administration of vitamin K in the treatment despite the absence of major bleeding. In total, 263 patients were included in the final analysis (figure-1).

The median age was 73 (64 to 81) years and 160 (60.8%) of the patients were female. The median INR was 5.5 (4.8 to 6.5). Seven (2.7%) of the patients died within the first 24 hours after admission, and 51 (19.4%) in the first 30 days. Descriptives of the study population were summarized in Table-1.

When the univariate analysis was conducted, it is found that systolic blood pressure (sBP), diastolic blood pressure (dBP), mean arterial pressure (mAP), saturation of peripheral oxygen ($SpO_2$), and Glasgow Coma Scale (GCS) were significantly lower in the 30-day mortality group ($p<0.001$, $p=0.001$, $p<0.001$, $p<0.001$, $p<0.001$ respectively). Conversely, the pulse rate was significantly higher in the 30-day mortality group ($p=0.006$). There was no statistically significant difference between the 30-day mortality groups in terms of sex, age and INR ($p=0.19$, $p=0.085$, $p=0.176$, respectively). Chronic renal failure was also significantly higher in the 30-day mortality group ($p=0.001$) (Table-1).

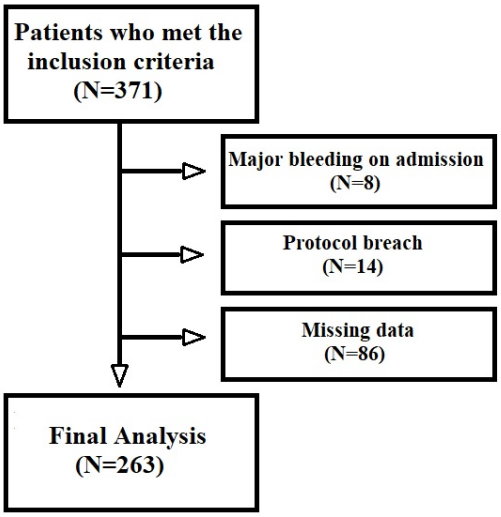


**Figure 1. Patient flow chart.**

Two hundred and sixty-three patients were included in the model, and the backward-Wald stepwise method was utilized. In the final model, there was no strong correlation between the predictors. The assumption of multicollinearity and goodness of fit were met (Hosmer-Lemeshow $p=0.250$). Our regression model could explain 34.8% of the total variance (Nagelkerke R Square = 0.348) and could classify 81.4% of the patients correctly. Mean arterial pressure, age, saturation of peripheral oxygen ($SpO_2$), and pulse rate were the independent predictors of 30-day mortality (Table-2).

There were only two outliers in the model (patient 11 and patient 46), but the influence of each of the outlier patient was negligible (cook distances = 0.12522 and 0.10054 respectively), so they were not excluded from the model.

The area under the curve (AUC) of our regression model was found to be 0.848 (95% confidence interval: 0.799 to 0.898, $p < 0.001$) (Figure-2). The sensitivity of the model, as a tool for predicting mortality, was calculated as 94.1%, with a specificity of 66.5% and an overall accuracy of 71.9%. (Table-3).

**Table 1. Basic descriptives and the univariate analysis of the 30-day mortality groups.**

| Median (25% - 75% quartiles) / N (%) | Total Population | 30-Day Mortality (-) | 30-Day Mortality (+) | p |
|---|---|---|---|---|
| Age (years) | 73 (64 to 81) | 72 (63 to 81) | 76 (66 to 82) | 0.085 |
| Sex (male) | 103 (39.2) | 79 (37.3) | 24 (47.1) | 0.198 |
| INR | 5.5 (4.8 to 6.5) | 5.4 (4.8 to 6.5) | 5.7 (4.9 to 6.7) | 0.176 |
| sBP (mmHg) | 127 (110 to 141) | 130 (118 to 142) | 110 (94 to 135) | **<0.001** |
| dBP (mmHg) | 74 (62 to 80) | 75 (65 to 80) | 66 (50 to 80) | **0.001** |
| mAP (mmHg) | 93 (80 to 101) | 93 (83 to 103) | 80 (67 to 96) | **<0.001** |
| Pulse Rate (bps) | 85 (76 to 100) | 84 (76 to 98) | 93 (80 to 110) | **0.006** |
| $SpO_2$ (%) | 95 (92 to 98) | 95 (93 to 98) | 92 (80 to 96) | **<0.001** |
| Glasgow Coma Scale | 15 (15 to 15) | 15 (15 to 15) | 15 (14 to 15) | **<0.001** |
| Diabetes Mellitus | 93 (35.4) | 69 (32.5) | 24 (47.1) | 0.052 |
| Hypertension | 196 (74.5) | 162 (76.4) | 34 (66.7) | 0.151 |
| Coronary Artery Disease | 111 (42.2) | 86 (40.6) | 25 (49) | 0.272 |
| Chronic Renal Failure | 36 (13.7) | 22 (10.4) | 14 (27.5) | **0.001** |
| History of Ischemic Stroke | 84 (31.9) | 62 (29.2) | 22 (43.1) | 0.056 |
| Atrial Fibrillation | 151 (54.7) | 122 (57.5) | 29 (56.9) | 0.929 |
| Valve Replacement | 63 (24) | 56 (26.4) | 7 (13.7) | 0.057 |
| Alzheimer's | 19 (7.2) | 13 (6.1) | 6 (11.8) | 0.138* |
| Indication for warfarin medication** | | NA | NA | NA |
| Atrial fibrillation | 151 (54.7) | NA | NA | NA |
| Ischemic stroke | 84 (31.9) | NA | NA | NA |
| Valve replacement | 63 (24) | NA | NA | NA |
| | | | | |
| NEWS-2 Score | 3 (1 to 6) | 2 (0 to 5) | 6 (3 to 10) | **<0.001** |
| 24-Hour Mortality | 7 (2.7) | NA | NA | NA |
| 30-Day Mortality | 51 (19.4) | NA | NA | NA |

* Fisher's Exact Test was used. ** Some patients have more than one indication for Warfarin medication. dBP: Diastolic Blood Pressure, INR: International Normalized Ratio, mAP: Mean arterial pressure, SpO2: Saturation of peripheral oxygen, sBP: Systolic Blood Pressure.

**Table 2. Beta coefficients and Wald statistics of the predictors in the final regression model.**

| | B Coefficients | Wald Statistic | p Value | OR (95% CI) |
|---|---|---|---|---|
| Mean arterial pressure | -0.053 | 19.331 | **<0.001** | 0.948 (0.926 to 0.971) |
| $SpO_2$ | -0.092 | 15.032 | **<0.001** | 0.912 (0.870 to 0.955) |
| Pulse rate | 0.020 | 7.114 | **0.008** | 1.021 (1.005 to 1.036) |
| Age (years) | 0.038 | 4.605 | **0.032** | 1.039 (1.003 to 1.076) |
| Gender (male=1, female=0) | 0.693 | 3.118 | 0.077 | 1.999 (0.927 to 4.314) |
| Hypertension (present=1) | -0.757 | 3.474 | 0.062 | 0.469 (0.212 to 1.040) |
| Chronic renal failure (present=1) | 0.754 | 2.849 | 0.091 | 2.125 (0.886 to 5.098) |
| Intercept (Constant) | 7.481 | 5.907 | **0.015** | NA |
| Regression function (RF) = 7.481 + (Mean Arterial Pressure x -0.053) + ($SpO_2$ x -0.092) + (Pulse rate x 0.020) + (Age x 0.038) + (Gender x 0.693) + (Hypertension x -0.757) + (Chronic renal failure x 0.754). | | | | |

SpO2: Saturation of peripheral oxygen

**Table 3. Diagnostic test performance of the regression model for the optimal cut-off value (RF*=0.1193).**

| | Result | 95% CI |
|---|---|---|
| AUC | 0.848 | 0.799 to 0.898 |
| Sensitivity | 94.1% | 83.8 to 98.8 |
| Specificity | 66.5% | 59.7 to 72.8 |
| PLR | 2.8 | 2.4 to 3.4 |
| NLR | 0.1 | 0 to 0.3 |
| PPV | 40.3% | 35.6 to 45.3 |
| NPV | 97.9% | 94 to 99.3 |
| Accuracy | 71.9% | 66 to 77.2 |

*RF: Regression Function. PLR: Positive likelihood ratio, PPV: Positive predictive value, NLR: Negative likelihood ratio, NPV: Negative predictive value,

The AUC of the NEWS-2 score for 30-day mortality was calculated as 0.782 (95%CI = 0.715 to 0.849) (figure-2). When compared, the difference between the AUCs of our model and the NEWS-2 score was statistically significant (AUC difference= 0.066, 95%CI= 0.009 to 0.123, p= 0.024).

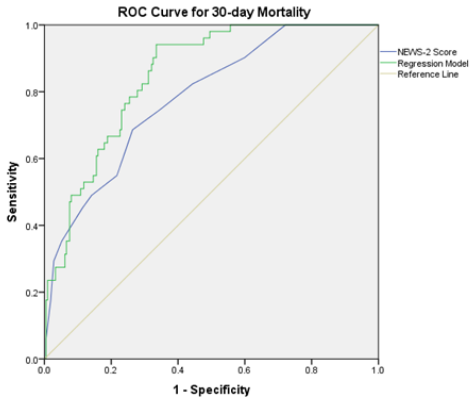


**Figure 2. Receiver Operating Characteristics Curve of the final regression model for 30-day mortality.**

For the internal validation of our model, we utilized the random split validation method, randomly dividing the dataset into training and validation sets with an 80/20 ratio. The AUC of the training model was calculated as 0.823 (95% CI = 0.762 to 0.883). When applying this model to the validation dataset, it demonstrated excellent performance (AUC = 926 (95% CI = 0.852 to 1)).

## DISCUSSION

In this retrospective cohort study, our objective was to identify the predictors of 30-day mortality in patients with an INR between 4.5 to 10, resulting from overanticoagulation due to warfarin medication. This specific group of patients is known to have an increased risk of complications, such as bleeding. However, the factors that are most strongly associated with mortality in these patients have not been clearly established[12]. Hence, determining the predictors for 30-day mortality in this patient population can assist clinicians in prioritizing high-risk individuals for closer monitoring and appropriate interventions.

Our analysis identified several independent predictors for 30-day mortality, including mean arterial pressure (mAP), oxygen saturation ($SpO_2$), age, and heart rate. These parameters have also been identified as predictors of mortality in various patient populations in previous studies[13]. Notably, mAP has been recognized as an important predictor of mortality in critically ill patients and has been incorporated into predictive models such as the Acute Physiology and Chronic Health Evaluation - II score[14]. Likewise, decreased $SpO_2$ has been found to be a predictor of mortality in patients with respiratory distress, and elevated heart rate has been associated with mortality in different clinical settings[15]. Additionally, the association between increased age and 30-day mortality aligns with the well-established understanding that age is a significant risk factor for adverse outcomes[14].

In the evaluation of critically ill patients, various arterial pressure measurements have been reported as significant indicators of outcome in numerous studies[8,16-20]. While the value of mean arterial pressure in predicting adverse outcomes has been demonstrated, there is no consensus regarding its superiority over systolic blood pressure[21]. However, due to the limitation on the number of predictors that can be included in the logistic regression analysis, we aimed to incorporate information from both

variables by combining systolic and diastolic blood pressure parameters into a single variable. Thus, mean arterial pressure was utilized as a combined predictor in the model. In our logistic regression analysis, it was observed that mean arterial pressure contributed the most to the model.

Interestingly, in the univariable analysis, we did not observe a significant difference in terms of INR levels between the groups with 30-day mortality. We speculate that this could be attributed to the fact that the INR levels in our studied patient population were not at a level that would lead to fatal complications. Also, there are some studies arguing that the INR level is over-interpreted in terms of predicting adverse outcomes in patients medicated with warfarin[22].

One interesting aspect of our study is the identification of mAP, $SpO_2$, age, and heart rate as predictors of mortality specifically in patients with an INR between 4.5 to 10 due to warfarin-related overanticoagulation. This finding suggests that these patients may possess unique physiological characteristics that render them more susceptible to mortality when considering these particular clinical factors. While the immediate response for these patients might involve the administration of vitamin K, it has been demonstrated that vitamin K treatment does not significantly impact mortality in this specific patient population[9]. Consequently, it would not be advisable to provide additional treatment to this selected group of patients. Instead, close monitoring of vital signs and risk stratification based on mAP, $SpO_2$, age, and heart rate can assist healthcare providers in identifying high-risk patients who require enhanced attention and intervention. Further research is warranted to gain a deeper understanding of the underlying mechanisms contributing to the association between these parameters and mortality in this patient population.

In addition to identifying predictors of 30-day mortality, our objective was to propose a regression model capable of predicting mortality in patients presenting to the emergency department with supratherapeutic INR levels between 4.5 and 10. We aimed to compare the performance of our model with that of the NEWS-2 score. Our developed model demonstrated effective prediction of 30-day mortality in this patient group. The internal validation process yielded consistent results, indicating the absence of significant overfitting or generalizability issues. The model exhibited favorable discrimination overall, with high sensitivity for the optimal cut-off value determined. Therefore, we believe that our model holds potential as a screening tool for patients with supratherapeutic INR levels. Furthermore, the superior performance of our model compared to the NEWS-2 score, which is one of the most up-to-date risk screening tools, suggests that our model may serve as a promising scoring system in this specific patient population.

Some of the variables used in our model overlap with those included in the NEWS-2 score[8]. It is well-known that physiological measurements such as arterial blood pressure, pulse rate, and oxygen saturation play significant roles in many scoring systems[16-19]. However, recent publications on scoring systems have emphasized the importance of selecting predictors from multiple categories, including demographic characteristics, comorbid diseases, imaging, and laboratory results, instead of relying solely on physiological measurements[23]. With this in mind, we conducted an analysis of our stepwise regression model using various potential predictors, including demographic characteristics, comorbid diseases, physiological measurement results, and laboratory findings. This comprehensive approach aims to enhance the accuracy and robustness of our model.

There are several limitations to our study. Firstly, the retrospective design and the utilization of data from a single center may introduce potential biases and limit the generalizability of our findings. Additionally, the necessity to exclude a substantial number of cases could have resulted in selection bias. Due to the limited number of cases, we opted for split validation instead of k-fold cross-validation for internal validation of the model. Although our training and validation results exhibited consistency, the use of k-fold cross-validation would have provided more reliable assessment of generalizability and mitigated the risk of overfitting.

In conclusion, the study identified mAP, $SpO_2$, heart rate, and age as independent predictors for 30-day mortality in patients with an INR of 4.5 to 10 due to warfarin-related overanticoagulation. These findings suggest that close monitoring of vital signs and age-based risk stratification can assist clinicians in identifying high-risk patients who require closer attention and intervention. Furthermore, the study proposed a regression model for predicting mortality in this patient group and compared its performance to that of the NEWS-2 scoring system, revealing the

potential of the new model as a promising screening tool. However, it is important to consider the study's limitations, such as its retrospective design and single-center setting. Further research is warranted to enhance our understanding of the underlying mechanisms that contribute to the association between these predictors and mortality in this specific patient population.

**Author Contributions:** Concept/Design : MMİ; Data acquisition: MMİ; Data analysis and interpretation: MMİ; Drafting manuscript: MMİ; Critical revision of manuscript: MMİ; Final approval and accountability: MMİ; Technical or material support: MMİ; Supervision: MMİ; Securing funding (if available): n/a.
**Ethical Approval:** This study was conducted after the review board approval (*XXX* Review Board, date: 27.05.2022, approval number: E-54132726-000-12317) and was carried out in accordance with the principles of the Declaration of Helsinki.
**Peer-review:** Externally peer-reviewed.
**Conflict of Interest:** Authors declared no conflict of interest.
**Financial Disclosure:** No financial support was taken.
**Acknowledgement:** This study was designed as a retrospective study and no informed consent was obtained from the participants.

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