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# Use of blood parameters for the prediction of mortality in patients with below-knee amputation

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**Abstract.** The present retrospective study aimed to investigate the value of blood parameters in predicting mortality in patients with below-knee amputation (BKA). A total of 178 patients with BKA were included in the present study. The patients were divided into two groups, namely the exitus group (n=136; 76.4%) and the survivors group (n=42; 23.6%). Patients in the exitus group were further divided into three subgroups: i) Those who experienced mortality in <1 month (n=55; 40.4%); ii) those who experienced mortality between 1-12 months (n=48; 35.3%); and iii) those who experienced mortality in >12 months after surgery (n=33; 24.3%). Binary logistic regression and a generalized linear model were used for relational analysis, and a receiver operator characteristic curve was used for diagnostic tests. It was found that the parameters of age (B=0.061; P=0.01), eosinophil-to-lymphocyte ratio (ELR) (B=-2.861; P<0.05), C-reactive protein (CRP)/albumin ratio (B=0.027; P<0.01) and mean platelet volume (MPV)/lymphocyte ratio (B=0.310; P<0.01) had a significant effect on mortality at the multivariate level. Moreover, regression coefficients showed that the effect of age, CRP/albumin and MPV/lymphocyte ratios on mortality were positive, whereas the effect of the ELR was negative. The mortality predictive values of age [area under the curve (AUC)=0.681; P=0.01], ELR (AUC=0.630; P=0.01), CRP/albumin ratio (AUC=0.746; P=0.01) and MPV/lymphocyte ratio (AUC=0.676; P<0.01) were also found to be statistically significant. For the 27.51 CRP/albumin cut-off value, the sensitivity was found to be 80.1%, whereas the specificity was 54.8%. For the 36.93 CRP/albumin cut-off value, the sensitivity was 71.3%, and the specificity was 73.8%. Furthermore, MPV (B=-0.37; P<0.01) and hemoglobin/red-blood-cell distribution width (RDW) ratio (B=5.20; P<0.01) were found to have a significant effect on the time to death at the multivariate level. The parameters MPV (AUC=0.648; P<0.01) and hemoglobin/RDW (AUC=0.673; P=0.01) had predictive value in terms of the time to death. The predictive value for MPV was found to be 64.8%, whereas that for the hemoglobin/RDW ratio was 67.3%. For the 0.54 cut-off value for hemoglobin/RDW, the sensitivity was 74.5%, and the specificity was 11.1%. By contrast, for the 0.84 cut-off value for the hemoglobin/RDW ratio, the sensitivity was 10.9% and the specificity was 81.5%. In conclusion, the CRP/albumin ratio was identified as a significant mortality parameter, whereas the hemoglobin/RDW ratio was a significant time to death predictor, according to the results of the present analysis. These results may guide clinical practices and further research in terms of predicting mortality in patients with BKA.

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## Introduction

Lower-extremity diseases are common, often presenting a health-threatening problem that may lead to knee amputation. The estimated global frequency in adults, primarily those over 40 years old, was 9.7% (95% CI, 7.1-12.4), with women having a greater prevalence (10.2%) than men (8.8%) (1-3). Despite the therapeutic advances that have been made in this field, limb salvage still carries a high risk of functional restrictions, and is associated with pain for patients, which may eventually force a late amputation. Increased hospital admissions, higher costs, longer hospital stays, anxiety and depression have all been linked to late amputation (4-7). Below-knee amputation (BKA) is a rare form of surgery among patients who are subjected to total knee arthroplasty. For BKA, no set rules, indications or contraindications exist; decisions are made on a case-by-case basis according to expert opinions. Every patient is assessed for limb-sparing surgery before any amputations are performed, as in the case of other types of amputation. High-grade sarcoma of the lower limbs that is widespread and infiltrative provides typical grounds for BKA (8). The main benefit of BKA is that the knee joint is preserved, at least in cases where it remains functional and has <15% flexion contracture. In contrast to above-knee amputations, BKA enables improved prospects of recovery and ambulation (9). If the contralateral knee develops symptomatic osteoarthritis after BKA, the prosthesis can be adjusted to unload the affected compartment in addition to standard conservative therapy (10). Transmetatarsal amputation (TMA) may appear to be the best option among below-knee patients, since it is both quick and technically easy to perform, preserves lower extremity length, causes low levels of blood loss, improves energy conservation and is attractive to patients from a cosmetic standpoint. One drawback of TMA, however, is that it may conceivably result in a requirement for further revision surgeries, including more severe amputations, when compared with BKAs (11).

Especially with regard to studies analyzing the mortality and morbidity of patients after surgery, those that evaluate the ratios of blood values are currently increasing in importance. Ratios, such as the neutrophile-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio, are used in an increasing number of studies, and results on their predictive values are being published. The general common goal of these studies is to identify the ratios between blood values for specific diseases that provide information about the mortality and morbidity of patients (12-14).

Although the number of treatment options and the opportunities for selecting BKA have increased, BKA remains an important health problem in terms of mortality (1-7). Conditions for selecting BKA include standardized prosthetic care after trauma (4), the possibility for more effective treatment if the cause of amputation is a chronic disease, such as diabetic foot (5), and more dangerous situations, such as vasopressor-dependent sepsis (6). The mortality rate following BKA is 13-40% in the first year, 35-65% in the third year and 39-80% in the fifth year after amputation (2). Better knowledge of the indicators of mortality in the clinic, and especially the predictive values of blood parameters that are easily and routinely checked, can guide clinical practice and studies to predict and prevent mortality. Therefore, determining indicators of mortality according to the blood parameters may contribute to reducing mortality in patients with BKA.

Although studies have been performed on the ratios of post-surgical hemogram and blood values, at present, a small number of studies have evaluated the predictive value of these ratios on mortality and survival following BKA surgery (1-7). Therefore, the aim of the present retrospective study was to investigate the predictive value of blood parameters on the mortality rates of patients with BKA. The main research objective was to obtain information on clinical decision-making and treatment processes through making mortality predictions based on blood parameters in patients with BKA.

## Patients and methods

*Patients*. This single-center, cross-sectional, retrospective study included a total of 178 patients with BKA who were hospitalized and operated on in the Orthopedics and Traumatology Clinic in Kütahya Health Sciences University Hospital (Kütahya, Turkey) between December 2016 and December 2022. In G*power 3.1.9.2 (G*Power Team), power analysis was performed for 0.50 effect size, 95% confidence inverval and 0.05 significance level. T critical was found to be 1.6802300 and minimum patient number was found to be 45 patient files. The patients were divided into two groups, namely, the exitus group (n=136; 76.4%) and the survivors group (n=42; 23.6%). Patients in the exitus group were divided further into three subgroups: i) Those who experienced mortality in <1 month (n=55; 40.4%); ii) those who experienced mortality between 1-12 months (n=48; 35.3%); and iii) those who experienced mortality in >12 months after surgery (n=33; 24.3%). The present study was approved by the Non-Invasive Clinical Research Ethics Committee of Kütahya Health Sciences University (approval no. E-41997688-050.99-74729).

Data on demographic characteristics, the number of surgeries performed, postoperative mortality status and blood parameters were obtained from the patients' files and the hospital automation system. All data must have been present for inclusion in the study. The blood parameters and ratios of patients were evaluated at both the univariate and multivariate levels.

Since the study was retrospective, different risk factors for mortality, epicrisis information and information about which indication was followed in which center were not clear. For this reason, indication-linked mortalities that were directly reported as criteria in the study were excluded as BKA surgery criteria. Patients with diabetic foot-related BKA were excluded. The study was conducted in a public hospital where doctors may change, patients often change addresses, epicrises may not be complete, and certain patients may change institutions to benefit from private health services. This makes it difficult to follow up the patients in terms of risk factors for mortality.

*Statistical analysis*. Nominal data are presented as n (%), whereas measurement data are presented as the mean ± SD. $\chi^2$ or Fisher's exact test was used to analyze differences between categorical variables. Missing values were excluded. The Kolmogorov-Smirnov test was used to assess the normality of measurement data. According to the normality test results, non-parametric tests were used for statistical analysis, as the measurement parameters did not conform to the standard normal distribution. Therefore, Mann-Whitney U test was used to compare two groups, and Kruskal-Wallis followed by Dunn's post hoc test was used for pairwise comparisons between multiple groups. Binary logistic regression and the generalized linear model (ordinal logit) were used for linearization deviations of nonparametric data (15,16), and the parameters with significant differences between the mortality groups/subgroups were included in these analyses. Receiver operating characteristic (ROC) curve analysis was used, and in order to understand mortality rates, the cut-off values used were selected to achieve the highest sensitivity in the ROC analysis (17). Kaplan-Meier curve analysis was used for survival analysis over time. As this was a retrospective study that depended on the research design, Cox regression analysis was not performed. SPSS version 25.0 (IBM Corp.) was used. P<0.05 was considered to indicate a statistically significant difference.

## Results

*Sex and age distributions of patients*. The mean age of the survivors was 68.64±9.58 years (range, 52-90 years), whereas that of the patients in the exitus group was 74.91±0.01 years (range, 52-95 years). Of the survivor and exitus groups of patients, 31.0 and 40.4% were female, respectively. The baseline characteristics and results of the analysis between the survivors and exitus groups of patients are shown in Table I.

*Clinical parameters and difference analysis results*. The mean values of lymphocytes, monocytes, eosinophil-to-lymphocyte ratio (ELR), platelets (PLT), albumin, eosinophils and the hemoglobin/red-blood-cell distribution width (RDW) were found to be significantly higher in the survivors group compared with those in the exitus groups (P<0.05). By contrast, the mean values of patient age, neutrophils, mean platelet volume (MPV), C-reactive protein (CRP), NLR, eosinophil-to-monocyte ratio (EMR), CRP/albumin and MPV/lymphocyte ratios were significantly higher in the exitus group (P<0.05) (Table I). In the present study, the distribution of hypertension, cardiovascular events, diabetes mellitus and other chronic comorbidities (such as asthma and artery diseases) was found to be <5% in both groups, and the distributions of both groups were similar in terms of these comorbidities (Table I).

*Logistic regression analysis*. The binary logistic regression analysis results are shown in Table II. Since the single parameters among the significant parameters in Table I were also included in the ratios, the ratios were used in the regression analysis. For example, while the difference in neutrophils, lymphocytes and NLR was significant between the survivors and exitus groups, only NLR was used in the regression analysis, as it takes into account both neutrophils and lymphocytes, and therefore the proportional value was taken to avoid cointegration. Age, NLR, hemoglobin/RDW, and CRP/albumin and MPV/lymphocyte ratios were significant at univariate level. The results obtained showed that the exact age (B=0.061; P=0.01), ELR (B=-2.861; P=0.03), and the CRP/albumin (B=0.027; P<0.01) and MPV/lymphocyte (B=0.310; P<0.01) ratios had a significant effect on mortality at the multivariate level. Moreover, regression coefficients showed that the effects of the exact age, CRP/albumin and MPV/lymphocyte ratios were positive, whereas that of the ELR were negative (Table II).

The ROC analysis results showed that the predictive value of age on mortality [area under the curve (AUC)=0.681; P=0.01], ELR (AUC=0.630; P=0.01), CRP/albumin (AUC=0.746; P=0.01) and MPV/lymphocyte (AUC=0.676; P<0.01) ratios were statistically significant. Although all factors were found to have significant predictive value, the CRP/albumin ratio had the highest AUC value and a predictive value of ~74.6%. For the 27.51 CRP/albumin cut-off value, the sensitivity was found to be 80.1%, whereas the specificity was 54.8%. By contrast, for the 36.93 CRP/albumin cut-off value, the sensitivity was 71.3%, and the specificity was 73.8% (Fig. 1).

The baseline characteristics and results of the analysis among the time-to-death subgroups are shown in Table III. The parameter female-to-male sex ratio was significantly different between groups. The parameters RDW discharge, MPV and CRP/albumin ratio were significantly higher in the <1 month mortality subgroup (P<0.05) compared with those in the 1-12-month mortality and >12 month mortality subgroups. By contrast, age was found to be significantly higher in the 1-12-month mortality subgroup (P<0.05) compared with that in the <1 month mortality and >12 month mortality subgroups. Finally, albumin, hemoglobin and the hemoglobin/RDW ratio were significantly higher in the >12-month mortality subgroup (P<0.05) compared with those in the <1 month mortality and 1-12-month mortality subgroups (Table III).

A generalized linear model (ordinal logit) was used to associate the time to death with the factors that showed significant differences among subgroups, and the results of this analysis are presented in Table IV. MPV and hemoglobin/RDW were significant at univariate level. The results showed that MPV (B=-0.37; P=0.005) and the hemoglobin/RDW ratio (B=5.20; P<0.001) had a significant effect on the time to death (Table IV).

MPV (AUC=0.648; P=0.01) and the hemoglobin/RDW ratio (AUC=0.673; P=0.01) were found to have predictive value in terms of the time to death. The predictive value for MPV was 64.8%, whereas that for the hemoglobin/RDW ratio was 67.3%. For the 0.54 cut-off value for hemoglobin/RDW, the sensitivity was 74.5%, and the specificity was 11.1%. In addition, for the 0.84 cut-off value for hemoglobin/RDW, the sensitivity was found to be 10.9%, and the specificity was 81.5% (Fig. 2).

Finally, the results obtained from the Kaplan-Meier analysis showed that the mean survival time for patients with BKA was 23.616 months, with a 95% confidence interval of 18.620-28.612 months (Fig. 3).

## Discussion

Predicting mortality in patients with BKA will be able to guide future studies examining the underlying causes of mortality in these patients, and also enable further research in assessing patients who have a high probability of mortality. In addition, the ability to make effective predictions based on routinely measured blood parameters should contribute to improving both clinical practice and the treatment process. Motivated by these aims, the predictive value of blood parameters on mortality in patients with BKA was investigated in the present study. During the time period evaluated in the current study, 136 out of 178 patients died, whereas 42 patients survived.

Although BKA surgery enables superior recovery and ambulation (9), BKA that is performed early following trauma may increase the risk of post-amputation revision surgery (4). In spite of the possibility of revision surgery and the uncertainty in deciding to perform BKA surgery as part of a general procedure, BKA does have certain advantages for specific BKA patients compared with other types of lower-extremity surgery (18-20). However, the risk of mortality following BKA and the predictive factors associated with mortality after BKA need to be well-understood in order to both increase the success of the method and save patient lives.

Mortality following a lower-extremity surgical procedure and amputation presents a major problem that must be evaluated with prognostic and risk factors, such as age and sex (21-26). Norvell and Czerniecki (27) reported that age, white blood cell count, alcohol usage, revascularization, kidney failure, diabetes and the ankle-brachial index are risk factors associated with mortality following amputation. In another study, Mustapha *et al* (28) reported that revascularization and amputation techniques are associated with BKA risk factors and mortality following limb ischemia. Ordaz *et al* (11) reported that TMA provides higher ambulation rates compared with

Table I. Baseline characteristics and results of the analysis between the survivors and exitus groups.

| | Group | | | | |
|---|---|---|---|---|---|
| | Survivors (n=42) | | Exitus (n=136) | | |
| Parameter | Mean ± SD | Range | Mean ± SD | Range | P-value |
| Age, years | 68.64±9.58 | 52-90 | 74.911±0.01 | 52-95 | <0.001[a] |
| Sex | | | | | |
| Female | 13 (31.0) | | 55 (40.4) | | 0.178[b] |
| Male | 29 (69.0) | | 81 (59.6) | | |
| RDW initial, n | 15.49±2.15 | 12.4-22.4 | 15.97±2.36 | 11.5-24.8 | 0.201[a] |
| Neutrophils, n (x10$^9$/l) | 9.24±5.64 | 2.30-30.55 | 11.50±6.13 | 1.10-36.18 | 0.014[a] |
| Lymphocytes, n (x10$^9$/l) | 1.71±0.74 | 0.75-3.50 | 1.35±0.61 | 0.21-3.19 | 0.008[a] |
| RDW discharge | 15.45±1.85 | 12.2-20.8 | 16.06±2.26 | 12.3-26.4 | 0.150[a] |
| RDW difference | 0.05±1.31 | -3-7 | -0.09±1.03 | -4-4 | 0.768[a] |
| Monocytes, n (x10$^9$/l) | 0.73±0.26 | 0.31-1.57 | 0.59±0.31 | 0.01-1.40 | 0.004[a] |
| Eosinophill, n (x10$^9$/l) | 0.22±0.22 | 0.01-1.30 | 0.16±0.37 | 0.01-3.70 | 0.000[a] |
| PLT, g/l | 355.36±151.65 | 157-756 | 249.38±147.42 | 16-1259 | 0.000[a] |
| MPV, g/l | 8.73±1.21 | 6.1-11.3 | 9.40±1.43 | 5.4-13.2 | 0.005[a] |
| Albumin, g/l | 2.74±0.43 | 2-4 | 2.45±0.46 | 2-4 | <0.001[a] |
| Hemoglobin, g/l | 13.05±14.15 | 8-102 | 10.45±1.64 | 7-16 | 0.073[a] |
| CRP, mg/dl | 77.48±55.24 | 3-262 | 143.83±97.87 | 1-502 | <0.001[a] |
| NLR | 6.81±6.13 | 1.63-33.67 | 11.28±10.22 | 1.00-61.24 | 0.001[a] |
| ELR | 0.16±0.16 | 0-1 | 0.15±0.37 | 0-4 | 0.011[a] |
| MLR | 0.52±0.32 | 0-1 | 0.56±0.51 | 0-4 | 0.696[a] |
| PLR | 245.58±143.10 | 56-627 | 230.39±186.18 | 15-1114 | 0.227[a] |
| EMR | 0.32±0.32 | 0-2 | 1.42±10.40 | 0-116 | 0.040[a] |
| Hemoglobin/RDW | 0.81±0.61 | 0-5 | 0.67±0.14 | 0-1 | 0.037[a] |
| CRP/albumin | 30.10±24.16 | 1-105 | 62.78±46.76 | 0-245 | 0.000[a] |
| MPV/lymphocyte | 6.08±2.66 | 3-12 | 8.76±5.48 | 3-42 | 0.001[a] |
| HT | 2 (4.3) | | 2 (1.5) | | 0.272[b] |
| DM | 1 (2.2) | | 2 (1.5) | | 0.592[b] |
| CVE | 2 (4.3) | | 1 (0.8) | | 0.163[b] |

Nominal data are presented as n (%), whereas measurement data are presented as the mean ± SD. P-values were determined using [a]Mann-Whitney U test or [b]Fisher's exact test. ELR, eosinophil-to-lymphocyte ratio; MPV, mean platelet volume; RDW, red-blood-cell distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; CRP, C-reactive protein; MLR, monocyte-to-lymphocyte ratio; EMR, eosinophil-to-monocyte ratio; HT, hypertension; DM, diabetes mellitus; CVE, cardiovascular event.

BKA with low BKA risk factors. Finally, Bui *et al* (4) reported that the stage at which BKA is performed (early vs. late) may be a risk factor for mortality.

In the present study, the mean values of lymphocytes, monocytes, eosinophils, PLT, albumin, ELR and the hemoglobin/RDW ratio were significantly higher in the survivors group compared with in the exitus group, whereas the mean values for the exact age, number of neutrophils, MPV, CRP, NLR and EMR were significantly higher in the exitus group. It could be argued that the general blood parameters would be expected to be more healthy and in accepted ranges, and the patients' age would be expected to be higher in the mortality group. Therefore, the health-associated parameters would be likely to be worse in patients who lose their life. Blood ratios, such as the NLR and EMR, may be of predictive value for assessing mortality in patients with BKA. The results obtained in the present study were consistent with the findings of Ordaz *et al* (11), Norvell and Czerniecki (27), and Mustapha *et al* (28) in showing that blood parameters may help to predict mortality in patients with BKA. In our previous study, systemic immune inflammation index and prognostic nutritional index were associated with mortality in patients with BKA and diabetic foot. In the present study, patients with diabetic foot-related BKA were excluded (29). The agreement between the results obtained in the present study and those reported in previous studies may contribute to clinical practice, especially in terms of assessing mortality risk and subsequently including this risk in the treatment process. The development of metabolic disorders in more elderly patients and patients following amputation may also have an impact on these findings, as the the lifestyles would be similar.

Table II. Binary logistic regression analysis results.

| | Univariate analysis | | | Multivariate analysis | | | | | 95% CI for exponential (B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | OR | SE | P-value | OR | SE | Wald | P-value | Exponential (B) | Lower | Upper |
| Age | 0.065 | 0.019 | 0.001 | 0.061 | 0.022 | 7.652 | 0.006 | 1.062 | 1.018 | 1.109 |
| NLR | 0.087 | 0034 | 0.009 | -0.067 | 0.047 | 2.058 | 0.151 | 0.935 | 0.853 | 1.025 |
| ELR | -0.039 | 0.515 | 0.940 | -2.861 | 1.331 | 4.623 | 0.032 | 0.057 | 0.004 | 0.776 |
| EMR | 0.059 | 0.132 | 0.654 | 0.474 | 0.721 | 0.431 | 0.511 | 1.606 | 0.391 | 6.606 |
| Hemoglobin/RDW | -2.481 | 1.219 | 0.042 | -1.336 | 1.178 | 1.287 | 0.257 | 0.263 | 0.026 | 2.646 |
| CRP/albumin | 0.029 | 0.007 | <0.001 | 0.027 | 0.008 | 10.911 | 0.001 | 1.027 | 1.011 | 1.044 |
| MPV/lymphocyte | 0.207 | 0.464 | 0.002 | 0.310 | 0.104 | 8.944 | 0.003 | 1.363 | 1.113 | 1.670 |
| Regression constant | | | | -4.788 | 1.864 | 6.600 | 0.010 | 0.008 | | |

CI, confidence interval; SE, standard error; ELR, eosinophil-to-lymphocyte ratio; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; EMR, eosinophil-to-monocyte ratio; RDW, red-blood-cell distribution width.

Table III. Baseline characteristics and results of the analysis between the time of death subgroups.

| | Subgroup | | | | |
|---|---|---|---|---|---|
| Parameter | <1 month (n=55) | 1-12 months (n=48) | >12 months (n=33) | P-value | Post hoc analysis results |
| Age, years | 75.02±10.14 | 77.77±9.42 | 70.58±9.29 | 0.006[a] | II-III (0.003) |
| Sex | | | | | |
| Female | 32 (58.2) | 18 (37.5) | 5 (15.2) | <0.001[b] | |
| Male | 23 (41.8) | 30 (62.5) | 28 (84.8) | | |
| RDW initial, n | 16.51±2.47 | 15.70±2.35 | 15.48±2.09 | 0.068[a] | |
| Neutrophils, n (x10$^9$/l) | 13.05±6.75 | 10.08±4.31 | 10.96±6.84 | 0.061[a] | |
| Lymphocytes, n (x10$^9$/l) | 1.37±0.61 | 1.33±0.66 | 1.36±0.55 | 0.853[a] | |
| RDW discharge | 16.65±2.38 | 15.70±2.06 | 15.62±2.19 | 0.026[a] | I-II (0.009) |
| RDW difference | -0.14±1.26 | 0.00±0.82 | -0.14±0.90 | 0.984[a] | |
| Monocytes, n (x10$^9$/l) | 0.60±0.37 | 0.57±0.26 | 0.60±0.28 | 0.727[a] | |
| Eosinophils, n (x10$^9$/l) | 0.17±0.28 | 0.12±0.13 | 0.20±0.63 | 0.964[a] | |
| PLT, g/l | 233.45±177.61 | 274.90±133.86 | 238.79±103.00 | 0.125[a] | |
| MPV, g/l | 9.87±1.50 | 9.05±1.30 | 9.14±1.32 | 0.014[a] | I-II (0.011) |
| Albumin, g/l | 2.30±0.37 | 2.40±0.43 | 2.76±0.52 | <0.001[a] | I-III (0.000); II-III (0.005) |
| Hemoglobin, g/l | 10.01±1.71 | 10.49±1.26 | 11.15±1.81 | 0.005[a] | I-III (0.015) |
| CRP | 159.05±97.72 | 136.51±88.07 | 129.11±110.46 | 0.181[a] | |
| NLR | 12.19±10.56 | 10.37±9.60 | 11.09±10.69 | 0.451[a] | |
| ELR | 0.15±0.29 | 0.11±0.13 | 0.21±0.65 | 0.888[a] | |
| MLR | 0.55±0.47 | 0.53±0.39 | 0.62±0.72 | 0.940[a] | |
| PLR | 211.06±188.85 | 255.00±182.49 | 226.82±188.62 | 0.256[a] | |
| EMR | 2.47±15.62 | 0.27±0.34 | 1.32±6.41 | 0.947[a] | |
| Hemoglobin/RDW | 0.62±0.14 | 0.68±0.12 | 0.73±0.15 | 0.001[a] | I-III (0.003) |
| CRP/albumin | 70.69±44.50 | 60.80±43.75 | 52.47±53.36 | 0.046[a] | I-III (0.028) |
| MPV/lymphocyte | 8.58±3.86 | 8.89±5.71 | 8.85±7.30 | 0.564[a] | |

Nominal data are presented as n (%), whereas measurement data are presented as the mean ± SD. P-values were determined using [a]Kruskal Wallis or [b]$\chi^2$ test. Dunn's post hoc test was used for the comparisons between groups after a significant Kruskal-Wallis test, and the corresponding P-value is shown in brackets. I, <1 month subgroup; II, 1-12 months subgroup; III, >12 months subgroup; ELR, eosinophil-to-lymphocyte ratio; MPV, mean platelet volume; RDW, red-blood-cell distribution width; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PLT, platelet; CRP, C-reactive protein; MLR, monocyte-to-lymphocyte ratio; EMR, eosinophil-to-monocyte ratio.

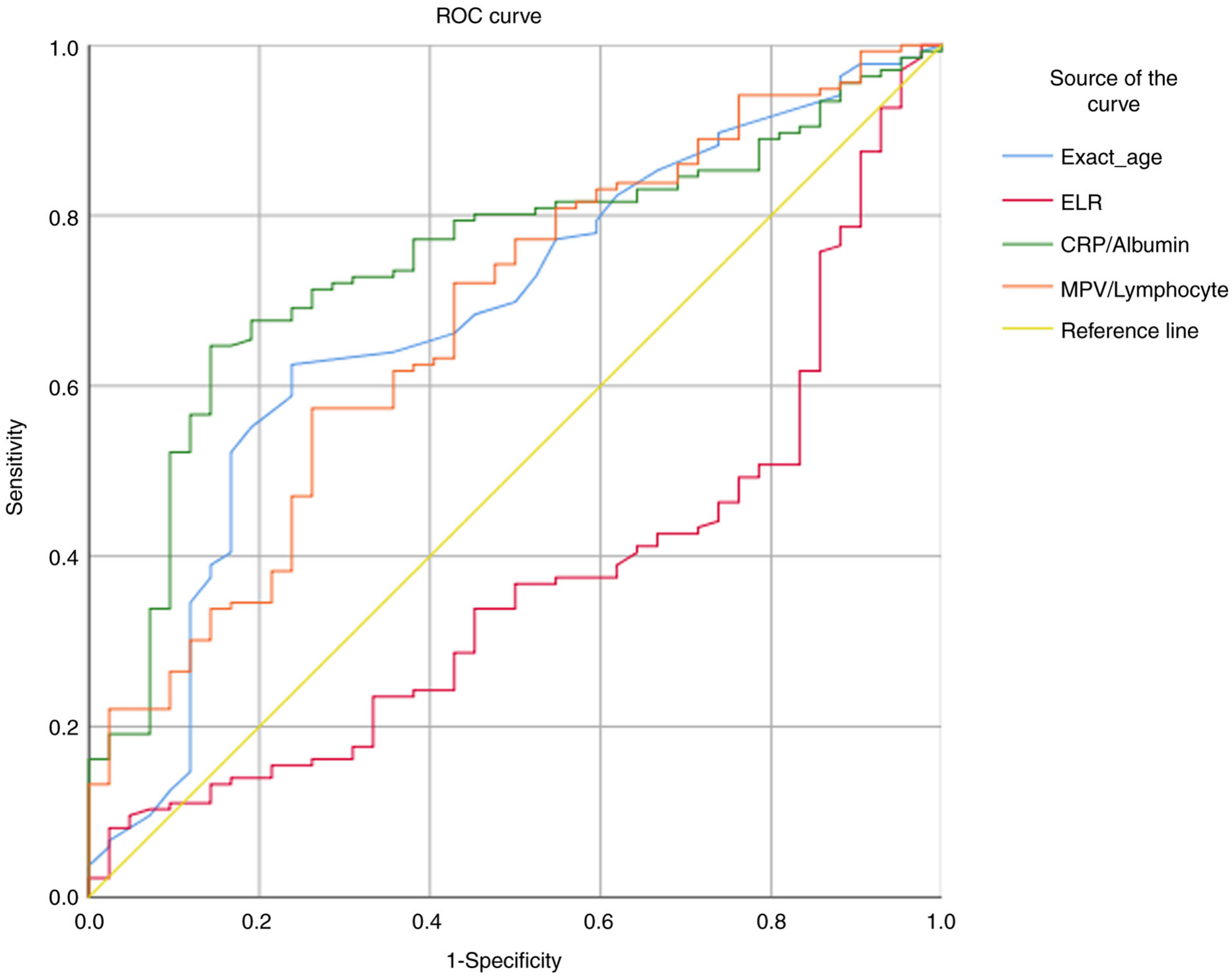


Figure 1. ROC analysis results for mortality and risk factors. ROC, receiver operating characteristic; ELR, eosinophil-to-lymphocyte ratio; CRP, C-reactive protein; MPV, mean platelet volume.

The multivariate regression analysis results showed that age (B=0.061), ELR (B=-2.861), and the CRP/albumin (B=0.027) and MPV/lymphocyte (B=0.310) ratios had a significant effect on mortality at the multivariate level. According to the regression coefficient, the most effective parameter was ELR (OR, -2.861), followed by exact age (OR, 0.061) and CRP/albumin (OR, 0.027). The effect of exact age may be associated with the presence of chronic diseases and comorbidities in older patients. However, the effects of ELR and CRP/albumin are also important factors that should be evaluated further.

According to the results of the time-to-death subgroup analysis, the female sex ratio differed among groups and the parameters RDW discharge, MPV and CRP/albumin were significantly higher in the <1-month mortality group compared with the >12 months groups. Age was found to be significantly higher in the 1-12-month mortality group, whereas albumin, hemoglobin and the hemoglobin/RDW ratio were significantly higher in the >12-month mortality group compared with the <1 month group. The multivariate analysis results revealed that MPV (B=-0.37) and the hemoglobin/RDW ratio (B=5.20) had a significant effect on the time to death. For the <1-month mortality group, the predictive value for MPV was 64.8%, and that for hemoglobin/RDW was 67.3% for prediction of <1 month mortality. Moreover, the predictive values for the exact age (AUC=0.681), ELR (AUC=0.630), and the CRP/albumin (AUC=0.746) and MPV/lymphocyte (AUC=0.676) ratios were statistically significant in terms of mortality. Taken together, these results showed that ELR, CRP/albumin and MPV/lymphocyte may be used for the prediction of mortality in patients with BKA. Age may not be used for the prediction of mortality due to cointegration. However, the survival predictive parameter, hemoglobin/RDW, was not a predictive parameter for mortality. This could be used to predict time-to-death for <1 month mortality. In this case, a patient having a high mortality risk due to CRP/albumin may be further evaluated for survival by analyzing the hemoglobin/RDW ratio.

The present study has a certain number of limitations. Although a good sample size was reached in accordance with the power analysis results of the current study, the number of patients was still small, and BKA-associated mortality has only recently started to be investigated. Furthermore, the fact that the present study was single-center was another important limitation. It would be beneficial to expand the study in the future with larger samples and multicenter studies. Another limitation of the present study is that it was retrospective. Patients having risk factors for mortality, such as post-traumatic, tumor-related, vessel-related or infections, will

Table IV. Generalized linear model (ordinal logit) for the time of death.

| | Univariate analysis | | | Multivariate analysis | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 95% CI | | Hypothesis test | | |
| Parameter | B | SE | P-value | B | SE | Lower | Upper | Wald $\chi^2$ | df | P-value |
| [Mortality, <1 month][a] | | | | -1.920 | 1.520 | -4.910 | 1.060 | 1.590 | 1 | 0.207 |
| [Mortality, 1-12 months][a] | | | | 0.080 | 1.520 | -2.890 | 3.060 | 0.010 | 1 | 0.956 |
| MPV | -0.322 | 0.118 | 0.006 | -0.370 | 0.130 | -0.623 | -0.110 | 7.960 | 1 | 0.005 |
| Hemoglobin/RDW | 4.604 | 1.229 | <0.001 | 5.200 | 1.320 | 2.61 | 7.780 | 15.480 | 1 | <0.001 |
| CRP/albumin | -0.007 | 0.004 | 0.066 | -0.010 | 0.010 | -0.015 | 0.010 | 2.120 | 1 | 0.145 |

[a]Threshold, grouped as <1 month (n=55), 1-12 months (n=48) and >12 months (n=33) (not applicable for univariate analysis). The >12 months group was the reference category. CI, confidence interval; SE, standard error; MPV, mean platelet volume; RDW, red-blood-cell distribution width; CRP, C-reactive protein; df, degrees of freedom.

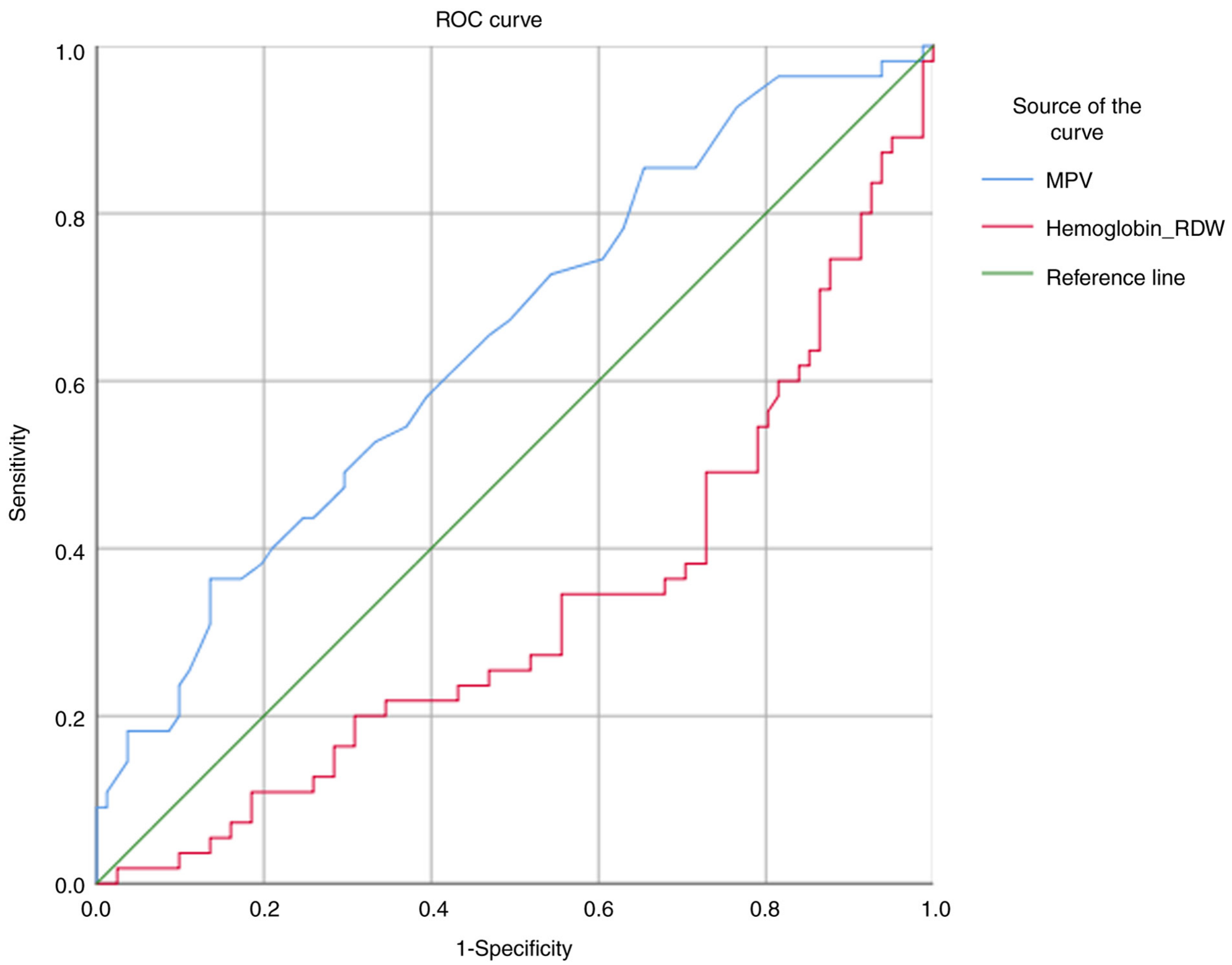


Figure 2. ROC analysis results for the time of death. ROC, receiver operating characteristic; MPV, mean platelet volume; RDW, red-blood-cell distribution width.

generally select private hospitals or clinics for treatment. When the indication becomes life-threatening or when there is organ amputation, financial resources of public hospitals are strained and services are sought from private health institutions. For the aforementioned reasons, the lack of data on the association of different indications with survival is a potential limitation of the current study. This limitation points to the need for data integration in public hospitals, and between the healthcare

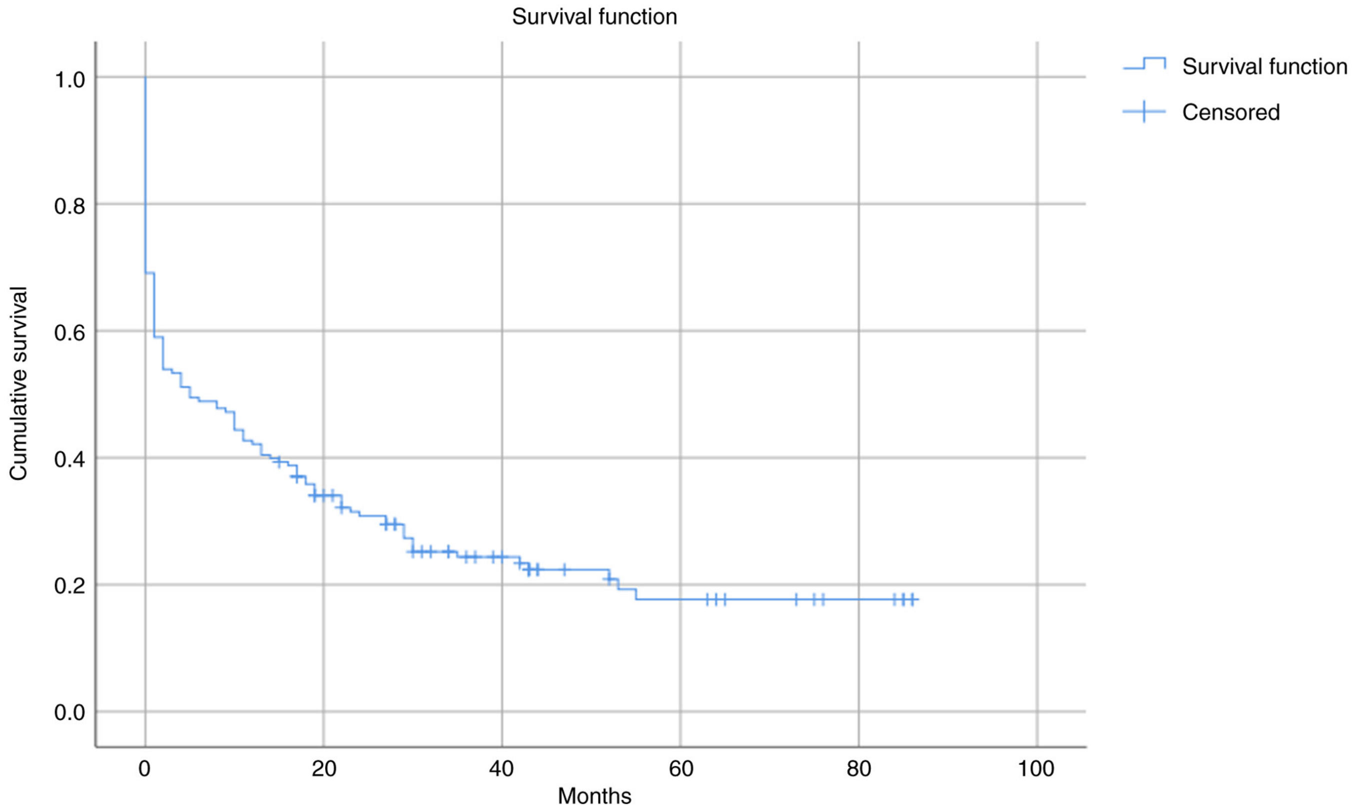


Figure 3. Kaplan-Meier curve analysis for mortality following below-knee amputation.

system and patient tracking systems in private hospitals. Due to the limited prevalence and incidence of BKA, prospective studies would require a long time to be completed, during which both the populations and the technologies are likely to change. Therefore, the present study was designed as a retrospective study. As a result, analyses were made only of the parameters available in the patient files. In the future, further parameters, such as other comorbidities, genetic predisposition or social factors, should also be included. Furthermore, although the present study has provided important results based on the analyzed group of patients and will be useful in terms of guiding clinical practice, further research is required to generalize these results. The aforementioned limitations prevent the present findings from being generalized; however, they still provide a basis for further research.

The most important contribution of the present study to the field is that, although previous studies have analyzed patients with different types of amputation, such as TMA, ipsilateral re-amputation and critical limb ischemia, there have been limited studies investigating BKA-associated mortality in patients with BKA with no indication (11,27-29). Furthermore, the results of the present study have suggested that the predictive value of different parameters on mortality in patients with BKA is high. In this regard, the present study may be considered a pioneering study in the field and offer a pragmatic approach for clinical applications. Another important contribution that has been made by the present study is that it has examined more than one blood value ratio, thereby allowing comparisons to be made between them as predictive values. Therefore, the results of the present study suggest that using more than one ratio in the same model proportional to their coefficients will provide the most effective results.

In clinical practice, previous studies have drawn attention to patients with a high probability of mortality following BKA (1-7). If an improved understanding of routinely monitored blood parameters is achieved, it may be possible to monitor individual patients more closely according to their risk of mortality, including performing further tests during follow-up and monitoring other conditions that may cause mortality.

In conclusion, assessing ELR, CRP/albumin and MPV/lymphocyte factors in patients with BKA may provide a better understanding of postoperative mortality. In this context, however, there is a need for more extensive studies to be performed, and other demographic and comorbidity values should be included in these further analyses. It is hoped that improved clinical outcomes will be achieved against postoperative mortality in the future.

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**Availability of data and materials**

The data generated in the present study are included in the figures and/or tables of this article.

## Authors' contributions

Data collection was performed by TCD. Statistical analysis was performed by TCD and MK. AOÜ, SY, SA and FK conducted the literature search, writing of the article and confirm the authenticity of all the raw data. TCD, AOÜ, SY, SA, MK and FK analyzed the results and contributed to the final manuscript. The original draft was written by TCD, AOÜ, SY, SA and FK. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

The present study was approved by the Non-Invasive Clinical Research Ethics Committee of Kütahya Health Sciences University (approval no. E-41997688-050.99-74729; Kütahya, Turkey). According to the research design and ethics approval, patient consent was not required for this retrospective study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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