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Pre- and Postoperative Urea Levels in Open Heart Surgery: An Inflammatory Biomarker for Predicting Mortality Risk

Urea Levels and Mortality in Open Heart Surgery

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Abstract: **Objective:** This study aimed to evaluate the predictive role of both preoperative and postoperative urea levels in estimating mortality risk for patients undergoing open-heart surgery. Although the prognostic value of urea levels remains underutilized in clinical practice, this study emphasizes its potential significance in risk stratification.

Methods: In this retrospective analysis, data from patients who had undergone open-heart surgery were reviewed, focusing on the relationship between their preoperative and postoperative urea levels and mortality outcomes. The data were analyzed statistically, employing multivariate analyses to determine the impact of urea levels on mortality risk.

Results: The analysis demonstrated that each unit increase in postoperative urea level correlated with a 5% increase in mortality risk. These findings reveal a compelling association between elevated urea levels and mortality, supporting the prognostic significance of urea as a biomarker. Additionally, higher preoperative urea levels were associated with lower survival rates, particularly among high-risk patients.

Conclusions: Our findings suggest that both preoperative and postoperative urea levels are critical determinants of mortality risk following open-heart surgery. Routine monitoring of these biomarkers could improve postoperative outcomes, particularly in high-risk patient groups. This study underscores the value of incorporating urea levels into standard perioperative assessment protocols to enhance patient survival rates.

Keywords: Open-heart surgery, Urea levels, Mortality risk, Biomarkers, Prognostic factors, Risk stratification

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Abbreviations and acronyms:

AKI: Acute Kidney Injury

CPB: Cardiopulmonary Bypass

EF: Ejection Fraction

HT: Hypertension

DM: Diabetes Mellitus

OR: Odds Ratio

CI: Confidence Interval

CRP: C-Reactive Protein

INTRODUCTION

Open-heart surgery remains a primary approach in managing severe cardiovascular conditions. Procedures involving cardiac surgery, particularly those utilizing cardiopulmonary bypass (CPB), are associated with substantial systemic inflammation and hemodynamic variability, both of which profoundly affect postoperative outcomes (1). These procedures expose patients to marked metabolic stress and hemodynamic instability, elevating the risk of severe complications (1-3). Specifically, the fluctuations in hemodynamics and inflammatory responses during CPB elevate the risk of acute kidney injury (AKI) in vulnerable patients, correlating with increased mortality rates (4,5). These adverse effects emphasize the importance of early identification of at-risk patients to enable customized perioperative care and reduce complications. Beyond its role as a marker of renal function, urea levels also reflect systemic inflammatory responses, which play a critical role in the pathophysiology of postoperative complications. This dual nature of urea underscores its importance as a biomarker not only for kidney health but also for broader systemic stress indicators. Routine protocols, especially in preoperative risk assessments, have limited utilization of biomarkers. Considering the unique role of urea levels in assessing both renal function and systemic inflammation, it is anticipated to fill this gap. The use of urea monitoring as a potential tool for early identification of high-risk patients can significantly enhance perioperative care. In the literature, the study by Liaño and Pascual reports that high preoperative urea levels increase mortality risk. Similarly, Refaat et al. emphasize that perioperative urea monitoring strongly correlates with organ dysfunction and mortality. These findings align with our study, which underscores the prognostic importance of preoperative and postoperative urea levels.

Inflammatory responses during CPB have been linked to an increased risk of AKI and subsequent mortality in patients with impaired renal function (14,16). Such complications are often exacerbated by factors like systemic inflammation and hypoxia, leading to compromised kidney function, with urea levels emerging as a key biomarker in this progression (6-8). Studies indicate that urea levels are not solely indicators of kidney function but are also reflective of systemic inflammation and tissue hypoxia (9). Urea has been established as a significant predictor of mortality, given its association with both renal impairment and the systemic inflammatory response (7,8). Martin et al. noted that elevated urea levels post-cardiovascular surgery are linked with increased mortality, particularly in cases involving renal failure and tissue hypoxia (2). Our findings similarly show that each unit increase in postoperative urea levels corresponds to a 5% rise in mortality risk, affirming the prognostic value of urea within our patient cohort. Elevated urea levels also correlate with cardiovascular complications such as heart failure and cerebrovascular events, in addition to renal dysfunction (10,11). These associations suggest that beyond kidney function, overall inflammatory and immune responses critically influence postoperative mortality risk (12-14).

Preoperative assessment of renal function is crucial for reducing mortality, particularly among high-risk patients. Research indicates that patients with high preoperative urea levels have lower survival rates following surgery (15,16). AKI has been recognized as a factor that heightens postoperative complication risks, with patients with chronic kidney disease facing an even higher likelihood of surgical complications (17,18). Evaluating urea levels in the preoperative period is increasingly regarded as a valuable predictor for enhancing postoperative survival (19-21). Additionally, the long-term impact of AKI may raise the likelihood of end-stage renal disease (ESRD) postoperatively, potentially resulting in sustained kidney dysfunction (22-23) Early identification and intervention for high-risk patients could significantly reduce postoperative mortality, highlighting the importance of robust predictive markers.

METHODS

This retrospective, observational cohort study was carried out at the Mersin University Medical Faculty Training and Research Hospital, a tertiary academic center with specialization in cardiovascular surgery. The study population included consecutive patients who underwent coronary artery bypass grafting (CABG) from January 1, 2022, to August 1, 2023.

Data Collection

Study Design: A nested case-control design within the cohort was utilized to enhance statistical power. Assuming an odds ratio (OR) of 1.5 for elevated urea levels and other mortality-associated factors, and with a confidence interval width set at 25%, the sample size required was determined to be 445 patients. Among these, deceased patients were matched at a 1:4 ratio with surviving patients.

Data Collection: Patient demographic data, laboratory test results, operative duration, left ventricular ejection fraction (EF), and multi-vessel disease presence were collected. Venous blood samples were taken upon admission and postoperatively on a daily basis in EDTA-containing vacuum tubes. Complete blood counts (CBC) were recorded at multiple time points, with specific focus on urea levels, white blood cell (WBC) count, hemoglobin level, and platelet count, all analyzed via an automated blood cell analyzer.

Data Analysis

-Variable Adjustments: To strengthen mortality prediction accuracy, adjustments were made for key demographic variables, including age, gender, and the presence of comorbidities.

Statistical Analysis: Multivariate analysis was employed to control for confounding variables, enhancing the reliability of identified mortality predictors. Continuous data were expressed as means and standard deviations or medians with ranges, while categorical data were presented as frequencies and percentages. For group comparisons, Student's t-test was applied for continuous variables (e.g., age, EF, biochemical measurements), and paired t-tests were used for repeated measures. Chi-square tests assessed relationships between mortality and categorical variables such as gender, diabetes mellitus (DM), and hypertension (HT). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for variables associated with mortality, including age, gender, EF, DM, HT, and biochemical markers. Statistical significance was defined as $p<0.05$.

Software: Data analyses were conducted using IBM SPSS 21 and MedCalc statistical software. Parametric tests were used for continuous variables without normality testing, based on the Central Limit Theorem.

Data Availability Statement

Datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

Ethical approval for the study was obtained from the Mersin University Ethics Committee with the decision numbered 2024/472 and dated 22/05/2024.

Declaration of Helsinki

The study and the writing of the article were prepared in accordance with the Declaration of Helsinki.

İnformed Written Consent

Informed written consent was obtained in the surgical consent form before the subjects were included in the study.

RESULTS

A total of 446 diagnosed patients were included in the study. The basic characteristics and clinical data are presented in Table 1.

Table 1. Distribution of Socio-Demographic Characteristics in Patients Undergoing Open Heart Vascular Surgery (n=446)		
Characteristic	**Mean±SD**	**Median(Min-Mak)**
Age (year)*	64.7±9.8	66(26-85)
	Count (n)	**Percentage (%)**
Gender**		
Male	312	70
Female	134	30
DM**		
No	192	43
Yes	254	57
HT**		
No	280	62,8
Yes	166	37,2
Mortality**		
Alive	350	78,5
Exitus	96	21,5
	(x̄ ±SS)	**Median (Min-Maks.)**
EF*	52.64±7.09	55(29-65)
PREOP		
Creatinine(mg/dL)*	0.96±0.57	0.88(0.44-9.75)
Ure (mg/dL)*	38.91±15.65	35.6(16.85-114.85)
NEU(103mcL)*	5.58±1.34	5.02(1.01-14.95)
LYM(103mcL)*	2.02±0.78	1.94(0.32-5.79)
PLT(103mcL)*	238.03±63.03	233(79-519)
CRP(mg/L)*	23.54±18.78	8.89(0.43-413.27)
Albumin(mg/L)*	37.75±3.94	38.32(24.15-46.4)

*Student's t-test, **Chi-Square test ($p<0.05$ significance), Paired t-test, p-value: Student's t-test was used for continuous variables, paired t-test for repeated measures, and Chi-Square test for categorical variables. (SD: Standard Deviation, EF: Ejection Fraction, DM: Diabetes Mellitus, HT: Hypertension, CRP: C-Reactive Protein, PLT: Platelets, NEU: Neutrophils, LYM: Lymphocytes.)

This study examined the socio-demographic and clinical characteristics of a total of 446 patients undergoing open heart vascular surgery. These data provide a comprehensive foundation for assessing the impact of biochemical factors on patient outcomes and identifying high-risk individuals for targeted interventions.

The age range of the patients varied from 26 to 85 years, with a mean age of 64.7 ± 9.8 years and a median age of 66 years. This indicates that the majority of the study population falls within the middle-aged and older age groups. Regarding gender, 70% of the patients were male, and 30% were female. This suggests that the majority of patients undergoing heart surgery were male.

Diabetes mellitus (DM) was present in 57% of the patients, indicating a significant portion of the population with this condition, which is known to increase the risk of complications. Hypertension (HT) was found in 37.2% of the patients, which is a known risk factor for cardiovascular diseases and can influence surgical outcomes.

Mortality occurred in 21.5% of the patients, underscoring the importance of assessing preoperative risk factors for better surgical planning and management. The mortality rate was adjusted for the study by matching deceased patients to surviving patients at a 1:4 ratio. This matching approach aimed to enhance the statistical analysis and provide more accurate comparisons between the groups.

The left ventricular ejection fraction (EF) ranged from 29% to 65%, with a mean EF of 52.64 ± 7.09%, suggesting a wide range of cardiac function within the population. Lower EF values may indicate higher surgical risk.

Biochemical measurements were also taken into account. The mean creatinine level was 0.96 ± 0.57 mg/dL, which is within normal limits but can still be indicative of renal function. The mean urea level was 38.91 ± 15.65 mg/dL, with a maximum value of 114.85 mg/dL. Urea levels, which reflect renal function and systemic inflammation, are important biomarkers to consider in assessing postoperative risk. Other biochemical parameters, including neutrophils (NEU), lymphocytes (LYM), platelets (PLT), C-reactive protein (CRP), and albumin levels, were also measured and could provide valuable insights into the inflammatory status and nutritional condition of patients, both of which are important for postoperative recovery and survival.

This study highlights the significant influence of preoperative risk factors on open heart vascular surgery outcomes. Conditions such as diabetes mellitus and hypertension were common among the patients and strongly associated with poorer surgical results. The findings emphasize the critical role of evaluating left ventricular ejection fraction (EF) and urea levels. Lower EF and elevated urea levels, which indicate both renal dysfunction and systemic inflammation, were key indicators of increased surgical risk. These results reinforce the importance of monitoring these biomarkers to better manage high-risk patients and improve postoperative outcomes.

Table 2. Assessment of Differences and Associations in Socio-Demographic and Biochemical Measurements According to Mortality Status (n=446)

		Alive (n=350)	Exitus (n=96)	
Features		**Mean±SD**	**Mean±SD**	**p-value*/*** **
Age (year)		63.88±9.52	64.64±12.72	0.52
EF		53.12±6.56	50.26±9.01	**0.01**
Pre-Creatinine(mg/dL)		0.94±0.54	1.1±0.35	0.21
Post-Creatinine(mg/dL)		0.99±0.56	1.35±0.57	**<0.0001**
p value**		**0.002**	**<0.0001**	
Pre-Ure (mg/dL)		38.37±16.96	42.71±13.81	**0.02**
Post-Ure (mg/dL)		36.86±13.71	53.01±23.18	**<0.0001**
p value**		**<0.0001**	**<0.0001**	
Pre-NEU(103mcL)		5.56±2.41	5.66±2.66	0.74
Post- NEU(103mcL)		10.03±3.87	12.76±5.18	**<0.0001**
p value**		**<0.0001**	**<0.0001**	
Pre-LYM(103mcL)		2.03±0.68	2.14±1.21	0.43
Post-LYM(103mcL)		1.13±0.48	1.53±1.02	**0.02**
p value**		**<0.0001**	**<0.0001**	
Pre-PLT(103mcL)		237.11±69.32	232.74±75.95	0.6
Post-PLT(103mcL)		156.68±48.83	138.81±71.83	0.06

Table 2. Assessment of Differences and Associations in Socio-Demographic and Biochemical Measurements According to Mortality Status (n=446)

		Alive (n=350)	**Exitus (n=96)**	
p value**		**<0.0001**	**<0.0001**	
Pre-CRP(mg/L)		19.06±17.11	26.99±22.39	0.36
Post-CRP(mg/L)		149.32±57.51	134.71±53.34	0.24
p value**		**<0.0001**	**<0.0001**	
Pre-Albumin(mg/L)		38.17±3.47	35.36±5.59	**0.003**
Post-Albumin(mg/L)		28.65±12.55	23.84±4.32	**0.02**
p value**		**<0.0001**	**<0.0001**	
		n(%)	**n(%)**	
Gender	Male	254(72.6)	58(60.4)	**0.02*****
	Female	96(27.4)	38(39.6)	
DM+		218(62.3)	36(37.5)	**<0.0001*****
HT+		136(38.9)	30(31.3)	0.17***

*Student's t-test, **Paired t-test, ***Chi-Square test ($p<0.05$ significance), p-value: Student's t-test was used for continuous variables, paired t-test for repeated measures, and Chi-Square test for categorical variables. Statistical significance was considered at $p < 0.05$. The values marked in bold in the table indicate statistically significant results. (EF: Ejection Fraction, DM: Diabetes Mellitus, HT: Hypertension, CRP: C-Reactive Protein, PLT: Platelets, NEU: Neutrophils, LYM: Lymphocytes)

In this study, the relationships between mortality and various socio-demographic and biochemical factors were assessed. Age did not show a significant difference between survivors and deceased patients, with no statistical significance observed ($p>0.05$). This suggests that age alone may not be a reliable predictor of mortality in this population. However, ejection fraction (EF) was significantly lower in deceased patients, with a mean EF of 50.26 ± 9.01 compared to 53.12 ± 6.56 in survivors ($p<0.05$), highlighting the importance of cardiac function in determining surgical outcomes.

Preoperative and postoperative creatinine levels did not exhibit a strong association with mortality. While the preoperative creatinine difference was not significant ($p>0.05$), the postoperative creatinine levels were significantly higher in deceased patients ($p<0.0001$), suggesting that renal dysfunction after surgery is a key factor in mortality risk.

Urea levels, both preoperative and postoperative, showed significant differences between the two groups. Preoperative urea levels were higher in deceased patients, and postoperative urea levels were significantly elevated in the deceased group ($p<0.0001$). This indicates that urea, a marker of renal function and systemic inflammation, is a strong predictor of postoperative complications and mortality.

Neutrophil and lymphocyte counts were also significantly different between survivors and deceased patients. Postoperative neutrophil and lymphocyte levels were significantly higher in those who did not survive, further supporting the role of inflammation in influencing surgical outcomes.

No significant difference was found in platelet count between the groups, and postoperative C-reactive protein (CRP) levels were not significantly associated with mortality, suggesting that while these markers may reflect inflammation, they are not as strong indicators of mortality risk as other biomarkers like urea, neutrophils, and lymphocytes. Lastly, albumin levels showed a significant difference, with lower postoperative albumin levels observed in deceased patients, indicating its potential role as a marker for nutritional status and overall health. These findings emphasize the importance of monitoring multiple biochemical parameters to assess the risk of postoperative complications and mortality.

The analysis of socio-demographic and biochemical parameters reveals significant associations between mortality and select clinical indicators. While age and hypertension showed no significant correlation with mortality, factors such as lower ejection fraction (EF), male gender, and absence of diabetes mellitus (DM) were significantly linked to higher mortality rates. Furthermore, postoperative assessments indicated pronounced differences in key biochemical markers, with elevated creatinine, urea, neutrophil, and lymphocyte levels, alongside reduced albumin, being notably higher in patients who did not survive. These findings suggest that postoperative renal function and inflammatory responses are critical in predicting mortality outcomes. Interestingly, the absence of significant variation in postoperative CRP and platelet levels underscores the value of focusing on specific biomarkers to optimize postoperative monitoring and risk stratification.

Logistic regression analysis was performed to evaluate the effects on mortality. Statistical significance was considered at $p < 0.05$. The values marked in bold in the table indicate statistically significant results. (CI: Confidance Interval, EF: Ejection Fraction, DM: Diabetes Mellitus, HT: Hypertension)

Table 3: Assessment of the Association Between Mortality and Age, Gender, and Chronic Disease Status(n=446)

Variables	Odds ratio	95% CI	p-value
Age	1.1	0.98-1.03	0.52
Ejection Fraction (EF)	0.95	0.92-0.98	**0.003**
Gender (Risk: Male)	1.73	1.08-2.78	**0.02**
Diabetes Mellitus (DM) (Risk: Present)	2.75	1.73-4.39	**<0.0001**
Hypertension (HT) (Risk: Present)	1.39	0.86-2.26	0.17

In this study, several factors were evaluated for their association with mortality following open heart surgery. Age did not show a significant relationship with mortality, as the odds ratio of 1.1 (95% CI: 0.98-1.03) and the p-value of 0.52 indicate that age alone does not significantly affect the risk of death. However, ejection fraction (EF) was significantly associated with mortality. Each 1-unit increase in EF reduced the risk of death by 0.95 times (95% CI: 0.92-0.98, $p<0.05$), emphasizing the role of cardiac function in predicting postoperative outcomes. Gender was another significant factor, with male patients showing a 1.73 times higher risk of mortality compared to females (95% CI: 1.08-2.78, $p<0.05$). This suggests that male gender is linked to a higher likelihood of adverse outcomes. Diabetes mellitus (DM) had a strong impact on mortality risk, with diabetic patients having a 2.75 times higher risk of death (95% CI: 1.73-4.39, $p<0.05$). This reinforces the known association between diabetes and increased postoperative complications. On the other hand, hypertension (HT) did not show a significant association with mortality, as its odds ratio of 1.39 (95% CI: 0.86-2.26) and p-value of 0.17 indicate no meaningful impact on mortality risk in this patient cohort.

Logistic regression analysis identified significant associations between mortality and key factors, with ejection fraction (EF), gender, and the presence of diabetes mellitus (DM) emerging as influential predictors. Specifically, each one-unit increase in

EF was associated with a 0.95-fold reduction in mortality risk, highlighting the protective effect of higher EF values. Male patients demonstrated a 1.73-fold higher risk of mortality compared to females, while the presence of DM was associated with a 2.75-fold increase in mortality risk. Notably, age and hypertension did not show significant associations with mortality, underscoring EF, gender, and DM status as primary predictors of postoperative survival.

Table 4: Assessment of the Association Between Preoperative Biochemical Parameters and Mortality(n=446)

Variables	Odds ratio	95% CI	p-value
Pre-Creatinine(mg/dL)	1.13	0.85-1.51	0.41
Pre-Ure (mg/dL)	**1.02**	**1.001-1.03**	**0.03**
Pre-NEU(103mcL)	1.02	0.93-1.11	0.74
Pre-LYM(103mcL)	1.16	0.89-1.52	0.28
Pre-PLT(103mcL)	0.99	0.98-1.01	0.6
Pre-CRP(mg/L)	1.01	0.99-1.001	0.19
Pre-Albumin(mg/L)	-0.84	0.78-0.92	**<0.0001**

Logistic regression analysis was performed to evaluate the effect of preoperative biochemical parameters on mortality. Statistical significance was considered at $p < 0.05$. The values marked in bold in the table indicate statistically significant results. (CI:Confidence Interval, DNI: Delta Neutrophil Index, CRP: C-Reactive Protein, NEU: Neutrophils, LYM: Lymphocytes, PLT: Platelets, EF: Ejection Fraction)

In this study, the association between preoperative biochemical parameters and mortality following open heart surgery was assessed. Preoperative creatinine levels did not show a significant association with mortality (p>0.05), suggesting that creatinine alone may not be a strong predictor of surgical outcomes. Similarly, preoperative neutrophil (NEU), lymphocyte (LYM), platelet (PLT), and C-reactive protein (CRP) levels did not demonstrate significant associations with mortality, as their p-values were above the threshold of 0.05 (p>0.05). These findings imply that these markers may not be as relevant for predicting mortality in this context.

However, preoperative urea levels showed a significant association with mortality (p<0.05). Specifically, each 1-unit increase in preoperative urea levels was found to increase the risk of death by 1.02 times (95% Confidence Interval: 1.001-1.03). This suggests that elevated urea levels, reflecting renal function and systemic stress, could serve as an important predictor of poor postoperative outcomes.

Furthermore, preoperative albumin levels were also significantly associated with mortality (p<0.05). A 1-unit increase in albumin was found to reduce the risk of death by 0.84 times (95% Confidence Interval: 0.78-0.92), highlighting albumin's potential as a protective factor. Lower preoperative albumin levels may indicate poor nutritional status and overall health, which are critical for recovery after surgery.

These findings underline the importance of monitoring specific biochemical parameters, such as urea and albumin, before surgery to better assess patient risk and guide management strategies.

The analysis of preoperative biochemical parameters identified urea and albumin levels as significant predictors of mortality. Specifically, each 1 mg/dL increase in preoperative urea was associated with a 1.02-fold increase in mortality risk, underscoring its prognostic importance. In contrast, higher albumin levels demonstrated a protective effect, with each 1 mg/dL increase in albumin reducing mortality risk by 0.84-fold. Other preoperative factors, including creatinine, neutrophils, lymphocytes, platelets, and CRP, did not exhibit significant associations with mortality. These findings highlight the value of evaluating urea and albumin levels preoperatively to improve mortality risk stratification.

Table 5: Assessment of the Association Between Postoperative Biochemical Parameters and Mortality(n=446)			
Variables	**Odds ratio**	**95% CI**	**p-value**
Post-Creatinine(mg/dL)	2.65	1.5-4.55	**<0.0001**
Post-Ure (mg/dL)	**1.05**	**1.03-1.07**	**<0.0001**
Post- NEU(103mcL)	1.14	1.08-1.21	**<0.0001**
Post-LYM(103mcL)	1.85	1.29-2.64	**0.001**
Post-PLT(103mcL)	0.98	0.97-0.99	**0.02**
Post-CRP(mg/L)	0.99	0.98-1.01	0.25
Post-Albumin(mg/L)	-0.67	0.59-0.76	**<0.0001**

Logistic regression analysis was performed to evaluate the effect of postoperative biochemical parameters on mortality. Statistical significance was considered at $p < 0.05$. The values marked in bold in the table indicate statistically significant results. (CI:confidence interval, DNI: Delta Neutrophil Index, CRP: C-Reactive Protein, NEU: Neutrophils, LYM: Lymphocytes, PLT: Platelets, EF: Ejection Fraction)

In this study, the relationship between postoperative biochemical parameters and mortality was assessed, revealing several key findings. Postoperative creatinine levels were strongly associated with mortality. For each 1-unit increase in postoperative creatinine, the risk of death increased by 2.65 times (95% CI: 1.5-4.55, p<0.0001), highlighting the importance of renal function in predicting postoperative survival. Similarly, postoperative urea levels were also significantly associated with mortality, with each 1-unit increase in urea raising the risk of death by 1.05 times (95% CI: 1.03-1.07, p<0.0001). This reinforces the role of urea as a critical marker for both kidney function and systemic inflammation. Postoperative neutrophils (NEU) were another important factor, with a 1-unit increase in neutrophil levels correlating with a 1.14 times higher risk of death (95% CI: 1.08-1.21, p<0.0001). This finding supports the idea that postoperative inflammation, as reflected by neutrophil levels, plays a significant role in mortality risk. Postoperative lymphocytes (LYM) were also associated with mortality, with a 1-unit increase increasing the risk of death by 1.85 times (95% CI: 1.29-2.64, p=0.001), further indicating the importance of the immune response in predicting outcomes.

On the other hand, postoperative platelet levels (PLT) showed an inverse relationship with mortality. For each 1-unit increase in platelet count, the risk of death decreased by 0.98 times (95% CI: 0.97-0.99, p=0.02), suggesting that platelet levels might act as a protective factor in the postoperative period. Postoperative albumin levels were also found to be a significant predictor, with each 1-unit increase in albumin decreasing the risk of death by 0.67 times (95% CI: 0.59-0.76, p<0.0001). This highlights albumin as an important marker for nutritional status and overall health, where lower levels are associated with higher mortality risk.

These findings underscore the critical role of monitoring various postoperative biochemical markers, particularly creatinine, urea, neutrophils, lymphocytes, platelets, and albumin, in predicting patient outcomes and guiding postoperative care.

Postoperative biochemical parameters revealed strong associations with mortality, with elevated creatinine, urea, neutrophil, and lymphocyte levels significantly increasing mortality risk. Specifically, a 1 mg/dL rise in creatinine correlated with a 2.65-fold increase in mortality risk, highlighting the critical role of renal dysfunction. Elevated urea and neutrophil levels were also strongly associated with mortality, with each 1-unit increase in urea and neutrophil count raising mortality risk by 1.05 and 1.14 times, respectively. In contrast, higher postoperative albumin and platelet counts demonstrated protective effects, with each 1-unit increase in albumin reducing mortality risk by 0.67-fold. These findings underscore the importance of renal, inflammatory, and nutritional markers in postoperative risk stratification.

DISCUSSION

This study corroborates existing literature by affirming the critical role of perioperative urea levels as predictors of mortality in open-heart surgery. Our findings support the argument for integrating urea monitoring into standard protocols to improve postoperative care by facilitating timely, targeted interventions for high-risk patients. Implementing routine urea monitoring can be seamlessly integrated into existing workflows by incorporating regular biochemical assessments during perioperative evaluations. Training healthcare personnel to interpret urea levels in conjunction with other markers can streamline the identification of high-risk patients and ensure timely interventions. Developing standardized guidelines for urea monitoring, including threshold levels for intervention, will further enhance its utility in clinical practice. For example, in intensive care units (ICUs), daily urea level monitoring could be paired with protocols to adjust fluid management and medication dosages based on identified risk thresholds. High urea levels could trigger multidisciplinary discussions to optimize renal function and minimize systemic stress, reducing the likelihood of complications such as acute kidney injury (AKI). This approach not only improves patient outcomes but also ensures efficient use of ICU resources by prioritizing care for high-risk individuals. Incorporating urea levels into routine monitoring protocols not only aids in assessing renal function but also provides a dynamic measure of the inflammatory milieu. Such integration could facilitate targeted anti-inflammatory interventions in patients with elevated perioperative urea levels, thereby mitigating the risk of systemic complications. Postoperative surveillance of renal biomarkers, especially urea and creatinine, provides valuable insight into patient risk stratification and can guide postoperative care aimed at reducing mortality (18,19). Our findings further support the hypothesis that elevated urea levels may serve as a surrogate marker for systemic inflammation. This association highlights the potential for urea to act as an integrative biomarker, capturing both renal dysfunction and inflammatory stress, particularly in the context of perioperative management. Previous studies indicate that each unit increase in postoperative urea levels may raise mortality risk by 5%, underscoring the link between kidney function and tissue hypoxia (2,9). In agreement with these findings, our study observed a significant correlation between elevated postoperative urea levels and increased mortality, further establishing urea as a sensitive marker of renal and systemic stress responses. The literature consistently shows that postoperative urea elevations are associated not only with renal dysfunction but also with systemic inflammation and hypoxia (4,10,12).

Preoperative urea levels have also been documented as effective predictors of mortality (6,13,14). Research by Liaño and Pascual indicates that high preoperative urea levels increase the risk of postoperative mortality (6). A finding our study supports, as lower survival rates were similarly observed in patients with elevated preoperative urea. Elevated urea has been linked to a higher risk of cardiovascular and renal complications, particularly among elderly patients (16). The long-term complications following acute kidney injury (AKI) can worsen outcomes in high-risk populations, emphasizing the necessity of close monitoring (17,18,21).

Zarbock et al. have underscored the relationship between sepsis-induced AKI and inflammation, highlighting its association with postoperative mortality (22). This link between inflammation and renal function underlines the predictive power of AKI for long-term outcomes and stresses the need for early intervention (22,24). Other studies on AKI prognosis suggest that early diagnosis is crucial to improving postoperative survival (23). Coca et al.'s systematic review further recommends vigilant monitoring for patients at high risk of adverse health outcomes and mortality post-AKI (18,19).

Research by Refaat et al. also points to a connection between high postoperative urea, organ dysfunction, and mortality (7). Our findings reinforce this association, showing a significant link between elevated postoperative urea levels and increased mortality within our study population. Wang et al. have reported that elevated urea levels are tied to systemic stress and trigger an inflammatory response (8). Such systemic stress markers, like increased urea, correlate with poor surgical outcomes, underscoring the importance of urea as a marker in postoperative evaluations (10,16). Collectively, these findings suggest that postoperative urea monitoring may play a crucial role in reducing mortality risk (15,20). This study's emphasis on renal function as a predictor of mortality indicates a potential gap in current clinical practices, advocating for a more integrated approach to patient monitoring. Implementing routine urea monitoring could not only enhance individual outcomes but also support a more personalized approach to perioperative management.

In conclusion, this study's observation that preoperative and postoperative urea levels are strong predictors of mortality aligns with existing literature. Routine monitoring of urea following cardiovascular surgery represents a valuable strategy in reducing mortality risk (13,23,24).

CONCLUSIONS

This study demonstrates that preoperative and postoperative urea levels are strong predictors of mortality following open-heart surgery. Particularly in the postoperative period, elevated urea levels reflect not only compromised renal function but also the metabolic stress associated with increased systemic inflammation and hypoperfusion. Our findings indicate that each unit increase in postoperative urea levels raises mortality risk by 5%, underscoring the influence of urea on cardiovascular stability beyond its role in renal function. This insight could inform the development of guidelines incorporating urea levels into postoperative monitoring, supporting a more personalized approach to patient care.

Additionally, our results, which suggest that preoperative urea levels may serve as a significant prognostic marker for mortality, underscore the importance of enhanced management of high-risk patients during the preoperative phase. These findings highlight the value of monitoring urea levels in strategies aimed at reducing postoperative complications. The dual role of urea as both a renal and inflammatory biomarker reinforces its utility in perioperative care. Future research should further elucidate its inflammatory pathways to optimize its application in predicting and managing postoperative complications. Overall, this study provides valuable insights into the incorporation of urea as a key biomarker in clinical decision-making, with its use emerging as a crucial tool for improving postoperative survival, especially in high-risk patient populations.

Limitations of the Study

Despite the comprehensive nature of this study, its retrospective design and single-center data collection limit the generalizability of the findings. The observational nature also restricts causal inferences and subgroup analyses for specific patient populations, such as those with varying levels of renal impairment or distinct surgical complexities. Future research should focus on large-scale, multicenter studies to validate these findings and ensure broader applicability across diverse patient populations. Prospective designs incorporating real-time urea monitoring protocols could further refine its prognostic utility and facilitate the development of universally accepted perioperative guidelines.

KEY POİNTS

What is known about the topic?

Urea levels are well-established indicators of kidney function and have been associated with systemic inflammation and hypoxia, especially in patients undergoing cardiac surgery. Elevated urea levels, both preoperatively and postoperatively, have been linked to an increased risk of adverse outcomes, including mortality, particularly in patients with compromised renal function. However, in clinical practice, the use of urea as a routine biomarker for mortality risk assessment in cardiac surgery remains underutilized. Current literature suggests that additional research could further clarify urea's predictive value and support its integration into perioperative management protocols for high-risk populations.

What does this study add?

This study underscores the importance of preoperative and postoperative urea levels as accessible and predictive biomarkers of mortality in open-heart surgery patients. By demonstrating that each unit increase in postoperative urea levels correlates with a 5% increase in mortality risk, the study emphasizes urea's prognostic value beyond kidney function. This research contributes a practical, cost-effective approach to mortality risk stratification, especially for resource-limited settings, and lays the groundwork for incorporating routine urea monitoring into perioperative care protocols. The findings provide a robust foundation for future, larger-scale studies aimed at validating urea levels as a key component of personalized perioperative management strategies, potentially improving outcomes in high-risk cardiac surgery patients.

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CONFLİCT OF INTEREST STATEMENT

We have no conflict of interest.

STATEMENT ON THE USE OF ARTİFİCİAL INTELLİGENCE

No artificial intelligence application was used.

FİNANCİNG

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Evaluation of machine learning methods in medicine: real data application

Running title: machine learning methods in medicine

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Abstract: **Objective:** One of the aims of a health study is to identify risk factors associated with the disease or to obtain predictive models for classification such as healthy / diseased. When the aim of a health study is classification, machine learning methods are widely used. Some of these methods; Logistic Regression, Decision Tree, Random Forest, Support Vector Machine and Naive Bayes. The aim of this study was to evaluate the performance of the machine learning such as Logistic Regression, Decision Tree, Random Forest, Support Vector Machine and Naive Bayes, for different sample size, prevalence and determination coefficient in real data sets.

Method: The data were randomly split into 70% training and 30% test set, and Logistic Regression, Decision Tree, Random Forest, Support Vector Machine and Naive Bayes were applied to the training set. The performance measure (Accuracy, Area Under Curve and Adjusted F Measure) of the methods evaluated on the test set were saved. This procedure was repeated 1000 times.These procedures were performed in the R 3.5 1.

Results: When all variables in the data are categorical, and determination coefficient is low with a moderate sample size, the Naive Bayes method exhibited higher performance. When all variables in the data are continuous, and determination coefficient is moderate with a low sample size, support vector machines method demonstrated superior performance. In cases where the dataset has a high number of categorical variables and a high determination coefficient, the Naive Bayes method outperformed others. The Random Forest method showed higher performance when determination coefficient is high, and the sample size is moderate.

Conclusion: This study provides valuable insights for researchers dealing with classification problems, guiding them to choose the most effective machine learning based on the characteristics of the datasets.

Keywords: Binary Logistic Regression, Random Forest, Support Vector Machine, Naive Bayes, Decision Tree, Real Data Sets

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INTRODUCTION

Classification is a type of problem in machine learning (ML) that is commonly addressed using methods such as Random forest (RF) and Support vector machines (SVM) in areas like marketing, telecommunications, and medicine.[1]

Among the ML models mentioned above, Logistic regression (LR) is one of the fundamental methods in classifying binary (alive/dead, patient/control) groups. Although LR is widely used, the use of other ML models has become widespread recently. Some of these methods are Decision Tree (DT), Artificial Neural Networks, K-nearest neighbor, Ensemble Methods (Bagging, Boosting and RF), Naive Bayes, SVM[2].

As in many other areas, decisions play an important role in medicine, especially in medical diagnostic processes. Since conceptual simple decision-making models that are capable of ML models should be considered for performing such tasks, DT is a very proper candidate.[3] The DT is potent ML model that has been used successfully in many medical studies as it provides easily understandable graphical classification rules.[3] However, in the RF, which is one of the commonly used ensemble learning methods, each tree is built based on recursive partitioning, and the prediction is made on the average of an ensemble of trees rather than of a single tree.[4]

The NB is simple probabilistic ML model based on Bayes' theorem with the assumption of independence between variables.[5]

The SVM is a ML model based on the statistical learning theory developed by Vapnik.[6] SVM and LR use both linear and non-linear data to separate the two groups, but SVM classifies non-linear data better than logistic regression because it uses kernel functions. LR generates the linear decision boundary through logit transformation. SVM finds the linear hyperplane that provides the maximum margin. Therefore, SVM is more optimal than logistic regression as the margin is maximized.

The most commonly used performance criteria for evaluation of ML models in the literature are Accuracy (ACC), Area Under Curve (AUC) and Adjusted F Measure (AGF).

The aim of this study was to evaluate the performance of the ML models such as LR, DT, RF, SVM and NB, for different sample size (n), prevalence (prev) and determination coefficient (R^2) in real data sets.

METHOD

Binary Logistic Regression

Regression methods have become an integral component of any data analysis concerned with describing the relationship between a response variable and one or more explanatory variables. Generally, logistic regression model is the case where the outcome variable is discrete by taking two or more possible values. The difference between an LR model and a linear regression model is that the outcome variable in LR is binary or dichotomous.[7] LR can be used for classification as well as for determining significant risk factors.

2.2. Decision Tree

DT is a non-parametric used for classification.[8] It consists of four parts, which are the decision node, the root node, leaf node, and branches.[9] In this structure, decision nodes represent the splitting measure on explanatory variables, leaf nodes represent a class label, and the root node represents the starting variable of the tree. Branches connect the nodes.

2.3. Random Forest

Breiman (1999) proposed RF, which combines the Random Subspace algorithm with the Bootstrap method.[11] Each DT was constructed from a set obtained from the starting training set using a bootstrap.[12] Ho (1998) has written many papers on "the random subspace" method, which does a random selection of a subset of features to use to grow each tree[13] .

2.4. Naive Bayes

NB is based on the assumption that the variables are conditionally independent[14]. This assumption is called class conditional independence. This assumption is made to simplify the computations involved, hence is called "naive". Despite this unrealistic assumption, the resulting classifier known as naive Bayes is remarkably successful in practice, often competing with much more sophisticated techniques.[15]

2.5. Support Vector Machine

SVM is an ML model based on the statistical learning theory developed by Vapnik (1998). SVM aims to find a maximal margin hyperplane to separate classes. The kernel function is used to map data to a higher dimensional space for learning non-linearly separable functions. The accuracy of the SVM largely depends on the properly chosen kernel and its parameters.[16]

The kernel function can be linear, radial, and polynomial functions. The Radial basis function is affected by the kernel width (γ) and the regularization (C) parameters; therefore, determination of the best pairs of parameters for the study was carried out.[17] The tune parameters for RF and SVM were automatically selected using the Caret package. Analyses were performed using R 3.5.1.

Real Data Study

ML models are tested on data sets from the UCI machine learning repository, including Breast Cancer[18], Breast (Breast Cancer coimbra)[19], Indian diabet pima [20], diabet[21], heart[22], Chronic kidney disease (CKD)[23]. The data were randomly split into 70% training and 30% test set, and the performance criteria of the methods in the test set were recorded. This procedure was repeated 1000 times. These procedures were performed in the R 3.5 1.

Performance Measures

In literature, performance evaluation of ML models is usually based on one performance measure. However, using these criteria, the performance of the methods is evaluated separately. in this evaluation, different evaluations can be made according to each performance criterion. for example, the method with the best performance for accuracy may have the worst performance according to the sensitivity value. In this case, it becomes difficult to determine which method performs better. To overcome this situation, ACC, AUC and AGF are evaluated together in this study.

The standard F measure has some limitations, especially in classification problems with class imbalance or significant differences between classes. The F-measure is defined as the harmonic mean of precision and recall and is often used to evaluate classification models. However, in some cases this metric may not provide sufficiently meaningful results. These tend to over-emphasize the majority class in imbalanced datasets. For example, in a dataset with 95% negative instances and 5% positive instances, a model that correctly classifies only the negative class may still have a high F-measure value, which may misrepresent the performance of the model. Therefore, the adjusted F-measure is used.

This evaluation is the mean performance measures were calculated for each ML model and ordered from largest to smallest and scored from 5 to 1. By summing the scores on each performance measure a final score was obtained. Table 1 shows how the ACC, AUC and AGF performance measures are calculated.

Table 1. Basic 2x2 Count Table			
Disease	**Test results**		
	Positive (*T=1*)	Negative (*T=0*)	Total
Present (D=1)	(True Positive)	(False Negative)	
Absent (D=0)	(False Positive)	(True Negative)	
Total			N

Sn(Recall) =P(T=1|D=1) = $s_1 \,/\, n_1$ Sp =P(T=0|D=0) = $r_o \,/\, n_0$

PPV(Precision) =P(D=1|T=1) = $s_1 \,/\, m_1$ NPV =P(D=1|T=1) = $s_1 \,/\, m_1$

ACC= (s_1+r_0)/N

$F_2 = 5 * \frac{Sn * precision}{(4 * Sn) + precision}$ Inv $F_{0.5} = \frac{5}{4} * \frac{Sn * Precision}{(0.25 * Sn) + Precision}$ AGF=$\sqrt{F_2 * \text{Inv}F_{0.5}}$

RESULTS

The performance criteria of the ML models were evaluated using real data sets. The performance scores and properties of the real data sets are given in Table 2.

Table 2 Properties and performance scores of ML models											
	Properties of data sets						**Performance scores**				
Datasets	Prev	R^2	n	NV	#Cat	#Cont	LR	DT	RF	SVM	NB
Breast cancer	0.3	0.3	277	9	9	0	3	8	12	7	**15**
Breast cancer coimbra	0.6	0.4	116	9	0	9	5	6	12	**13**	9
Chronic kidney disease	0.3	0.8	158	24	13	11	3	6	13	9	**15**
Heart	0.3	0.6	299	12	5	7	3	11	**15**	8	8

NV: Number of variables, Cat: Number of Categorical variables, Cont: Number of Continuous variables

In scenarios where Prev=0.3, R2= (0.3, 0.8) and n= (158, 277), NB method has higher performance than other methods. In scenarios where the number of categorical variables in the data is high, the NB method has higher performance.In the scenario where prev=0.3, R2= 0.6 and n=299, RF method has higher performance than other methods, while in the scenario where prev=0.6, R2= 0.4 and n=116, RF and SVM methods have similar and higher performance than other methods. In scenarios where R2 is medium and high and the number of continuous variables in the data is high, RF method has higher performance.

DISCUSSION

Machine learning methods are used to classify diseased and healthy individuals in health studies. Correctly classifying diseased and healthy individuals is of great importance for early diagnosis of diseases and determining treatments for these diagnoses. There are many papers in literature investigating the performance of classification methods, but it is not clear which method performs better under which conditions. Given this situation, our aim in this paper is to evaluate the performance of classification methods on real data sets with n, prev and (R^2). Performance evaluation of ML models is based on one real data set, mostly two- or three-ML models were compaired based on one or two and rarely three performance criteria. In this study, the performance of five ML models was evaluated based on ACC, AUC and AGF under real data sets. In this context, when all variables in the data were categorical, R^2 was low, and the sample size was moderate, the NB method demonstrated superior performance. When all variables in the data were continuous, and R^2 was moderate, and the sample size was low SVM method exhibited higher performance. When the number of categorical variables in the data was high, and R^2 was high, the NB method outperformed others. The RF method showed higher performance when R^2 was high, and the sample size was moderate to high.

Arasakumar et al. compared LR, DT, and RF on the breast cancer dataset and they observed that RF method shows better performance, which is consistent with our data[24].

Gokiladevi et al. compared SVM, RF, LR and DT on the chronic kidney disease dataset and observed that the performance of RF method shows better performance. This result is compatible with our real data[25].

Yu et al. compared DT, NB, RF and SVM according to the accuracy criteria, on breast cancer dataset and did not observe any significant difference[26].

Limitations of the study

More datasets can be used for comparisons, and different ML models can also be applied.

CONCLUSION

In conclusion, the performances of the data sets differ according to the structure of the data sets (n, r^2 and prev, continuous and categorical). Therefore, evaluating the data sets according to the characteristics of the data sets will enable us to make more accurate comments. We hope that this study helps any researcher confronted with classification problems to select the best performing two- or three-ML models based on the characteristics of the data set.

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