Original Paper

Evaluation of the Performance of Biomarkers in Predicting Hemodialysis Patients Survival Using Time-Dependent ROC Curve

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Introduction. End-stage kidney disease (ESKD) is a growing global public health problem, and patients undergoing hemodialysis (HD) experience a high mortality rate despite advances in medical care. Identifying reliable prognostic biomarkers is therefore essential. Regression-based survival models are widely used in HD studies; however, while they estimate associations, they do not directly quantify the predictive accuracy of biomarkers. This study aimed to evaluate the predictive performance of selected baseline biomarkers for survival in HD patients using the time-dependent receiver operating characteristic (ROC) curve.
Methods. This retrospective cohort study included 2,192 ESKD patients undergoing maintenance HD in Fars province, Iran, between 2011 and 2020. Time-dependent area under the ROC curve (AUC) values were calculated to assess the prognostic performance of baseline biomarkers at 3, 12, 24, and 36 months after initiation of dialysis.
Results. Age, serum albumin, creatinine, and calcium showed relatively better predictive performance for survival. For age, the AUCs at 3, 12, 24, and 36 months were 64.2, 57.1, 57.1, and 58.8, respectively, while corresponding values for serum albumin were 67.5, 62.3, 61.4, and 59.8. Serum albumin and calcium demonstrated higher discrimination for early survival, whereas serum creatinine showed more stable predictive performance over the follow-up period. The combined risk score outperformed individual biomarkers, with AUCs of 71.2, 63.9, 63.5, and 64.1 at 3, 12, 24, and 36 months, respectively.
Conclusion. Time-dependent ROC analysis revealed time-varying prognostic performance of baseline biomarkers in HD patients and demonstrated improved discrimination when biomarkers were combined into a composite risk score.

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INTRODUCTION

End-stage kidney disease (ESKD) represents a significant and growing global public health challenge.[1] Epidemiological studies suggest that the incidence of chronic kidney disease is expected to increase worldwide over the coming decade.[1,2] Moreover, mortality rates are projected to rise substantially by 2030, particularly among individuals with glomerulonephritis, those aged over 40 years, and populations living in high- to middle-income countries.[3] Hemodialysis (HD), the most common and widely available treatment for patients with ESKD, is associated with a considerably high mortality rate despite substantial advances in dialysis technology and medical care.[4] Consequently, identifying and evaluating factors associated with mortality has become an important area of research in the management of ESKD patients. Various statistical approaches have been applied to investigate mortality-related risk factors in this population.[5] Regression-based methods, particularly the Cox proportional hazards model, are commonly used to analyze survival data. While these models are effective in estimating the strength of association between biomarkers and survival, they do not directly quantify the predictive accuracy of biomarkers.[6] The area under the receiver operating characteristic (ROC) curve (AUC) is widely used to summarize the predictive accuracy of biomarkers. However, conventional ROC analysis assumes a fixed disease status and does not account for time-to-event outcomes, which limits its applicability in survival studies where the outcome may occur at varying time points during follow-up.[7-9] Given the chronic nature of ESKD and the extended follow-up of patients receiving maintenance HD, patients may experience different clinical outcomes over time, such as kidney transplantation, changes in dialysis modality, or death. In this context, time-dependent ROC curve methods have been introduced to evaluate prognostic performance while accounting for the time-varying nature of survival outcomes.[9-13] These methods are particularly suitable for prognostic studies in which biomarkers are measured at baseline but outcomes may occur at any time during follow-up, including studies involving HD patients.

Compared with hazard ratios, the AUC provides a scale-independent and easily interpretable measure of prognostic accuracy, ranging from 0.5 to 1.0. Additionally, time-dependent AUC allows for the comparison of biomarkers with different measurement scales and enables the assessment of predictive performance at multiple time points throughout the follow-up period.[6] To the best of our knowledge, only a limited number of studies have applied time-dependent ROC curve methods to survival analysis in hemodialysis patients. Therefore, the present study aimed to evaluate the predictive performance of selected baseline biomarkers for survival in patients undergoing maintenance HD using time-dependent ROC analysis. We further assessed the stability of biomarker performance over time and examined whether combining significant biomarkers into a composite risk score could improve prognostic discrimination.

MATERIALS AND METHODS

Study-population

In this retrospective cohort study, data of all ESKD patients undergoing maintenance HD who survived three months after initiation of HD in centers affiliated with Shiraz University of Medical Sciences (SUMS), Fars Province, Iran, were used. The source of data was the SUMS Specific Diseases Affairs electronic database, [14] which included the information of patients undergoing maintenance HD from March 2011 to September 2020.

The present study was a multicenter study including 46 centers across Fars Province, Iran.

Patients older than 18 years were enrolled in this study. Those who transferred to centers outside the university, switched to peritoneal dialysis, underwent kidney transplantation or recovered were excluded. In addition, patients with more than five missing variables were excluded from the study. Nearly, the record of 4801 patients was available in this dataset.

Covariates

The following covariates were assessed in the analysis: sex, age (years), body mass index (BMI), adequacy of dialysis (Kt/V), serum albumin (Alb), serum creatinine (Cr), fasting blood sugar (FBS), mean corpuscular hemoglobin concentration (MCHC), serum phosphate concentration (Ph), serum uric acid concentration, serum calcium (Ca), serum sodium (Na), and blood urea nitrogen (BUN). All variables were extracted at baseline to predict death over the follow-up period. Other potential variables such as hemoglobin, lipid profile indices, and serum potassium were deleted due to a high missing rate. Instead of using serum calcium, we used the serum calcium concentration corrected by serum albumin by applying this formula: corrected calcium = total serum calcium+ 0.8×(4-serum albumin).[15]

The outcome was defined as the time interval from the first HD session to death as time event. Those who were alive and continued the dialysis to the end of study period were considered "censored".

Statistical methods

At first, the missing values were imputed 10 times by the MICE (Multiple Imputation by Chained Equations) package,[16] and then, Rubin´s Rules (RR) were applied to pool parameter estimates, such as coefficient, standard errors and AUC estimates.[17]

The time-dependent ROC analysis has been proposed to evaluate the accuracy of a biomarker to predict a clinical outcome in the future. This method considers the censoring of the outcome for survival time. The AUC values were estimated by using the Inverse Probability of Censoring Weighting (IPCW) method with marginal weight.[18-20] Ties in biomarker values were handled using the default mid-rank averaging method implemented in the timeROC package, and right-censored observations were weighted via inverse probability of censoring (IPCW) using the Kaplan–Meier estimator.[21]

To calculate the time-dependent AUC, we reversed the sign of a biomarker values if lower values of the marker were associated with higher risk of death. Then, we computed AUCs at follow-up time points of 3, 12, 24 and 36 months. The AUC value range is from 0.5 to 1 where 0.5 is poor discrimination (i.e., ability to diagnose patients with and without the condition based on the biomarker) and AUC value greater than 0.5 indicates good discrimination.

After that, the multivariable Cox proportional hazard model was employed to identify risk factors associated with death. Based on the coefficients of the main factors in 10 imputed data sets, a risk score for each patient was computed. The risk score was equal to the sum of regression coefficients × level of biomarkers. Then the risk score was averaged from each of the 10 imputed data sets using Rubin´s Rules. Finally, to evaluate the performance of the risk score in predicting survival, AUC was obtained by the time-dependent ROC curve.

Statistical analysis was conducted using SPSS 18.0, "MICE",[16] "time ROC"[21] and "survival" packages in the R 3.6.1 software. *P*-value < .05 was considered statistically significant.

RESULTS

Among the 2192 subjects who met the inclusion criteria, 1293 were male (59%). The mean age of the subjects was 62.1 ± 15.7 years (18-94 years) and the mean BMI was 23.3 ± 4.5. The minimum and maximum follow-up times were 6 and 1647 days, respectively, and the median follow-up time was 509 days, considering that 1340 (61.1%) patients did not experience the event of death. Table 1 presents baseline characteristics and laboratory values of the study subjects.

Maximum and minimum missing rates belong

Table 1. Patients' characteristics and laboratory values

Variable	Mean (SD)		
Demographics	**Total**	**Alive**	**death**
Sex (%)			
Male	1293 (59.0)	802 (62.0)	491 (38.0)
Female	899 (41.0)	538 (59.8)	361 (40.2)
Age (years)	62.1 (15.7)	59.9 (15.7)	65.5 (15.2)
Body Mass Index (BMI) (kg/m^2)	23.3 (4.5)	23.3 (4.5)	23.4 (4.5)
Dialysis Factors			
Adequacy of Dialysis (Kt/Vurea)	1.32 (0.47)	1.33 (0.49)	1.30 (0.43)
Laboratory Values			
Mean Corpuscular Hemoglobin Concentration (MCHC) (g/dl)	31.15 (1.96)	31.38 (3.02)	31.07 (3.10)
Blood Urea Nitrogen (BUN) (mg/dl)	53.97 (19.73)	54.22 (18.76)	53.47 (21.15)
Creatinine (mg/dl)	6.12 (2.70)	6.36 (3.56)	5.81 (2.60)
Sodium (meq/lit)	138.21 (6.67)	138.35 (6.53)	138.03 (6.89)
Calcium (mg/dl)	8.78 (0.99)	8.54 (0.99)	8.53 (0.99)
Phosphate (mg/dl)	4.82 (1.38)	4.99 (3.90)	4.72 (1.33)
Uric acid (mg/dl)	6.66 (8.50)	6.44 (7.75)	6.80 (9.59)
Albumin (g/dl)	3.70 (0.61)	3.81 (1.01)	3.58 (0.64)
Fasting Blood Sugar (FBS) (mg/dl)	131.98 (75.82)	131.18 (74.80)	133.01 (76.97)

to BMI and BUN variables with almost 39% and 1% missing rates, respectively. Missing data were imputed using the MICE method 10 times.

Time-dependent ROC curves

The time-dependent ROC curves were calculated for each biomarker for 10 imputed data sets. Table 2 presents the results. It was shown that variables of age, serum albumin, creatinine and calcium had relatively better performance to predict mortality compared to other biomarkers. The AUC at 3, 12, 24, and 36 months after the start of dialysis was 64.2, 57.1, 57.1, and 58.8 for age, and 67.5, 62.3, 61.4, and 59.8 for serum albumin, respectively. In the early period, after initiation of HD (i.e., at 3 months), age and serum albumin had greater ability to predict mortality.

The AUC for serum creatinine varied from 56.4 at t = 3 to 57.9 at t = 36 month. Serum creatinine was relatively a good prognostic biomarker to predict mortality, which was stable throughout the follow-up period. The AUC for the corrected serum calcium was from 57.2 at t = 3 to 53.8 at t = 36 month. Thus, the performance of serum calcium to predict mortality was similar over the follow-up period with a slightly more power in the early period.

Based on the above-mentioned results, as the time interval between the biomarker measurements to the survival time increases, the predictive ability of most of the biomarkers (evident by AUC) diminishes.

Cox regression

The backward stepwise method in the cox regression was applied for each of 10 imputed data sets, and then the coefficients and standard errors were combined using Rubin's rule. The results indicated that age ($P < .001$), serum albumin ($P < .001$), serum creatinine ($P = .040$) and MCHC ($P = .020$) were significant predictors of mortality.

As Table 3 shows, with increasing one year of the patient's age, the risk of death was significantly increased by approximately 2% (HR = 1.02, $P < .001$). However, with increasing one unit serum creatinine (HR = 0.97, $P = .040$), MCHC (HR = 0.96,

Table 2. The AUC (%) estimates using time-dependent ROC curve for each biomarker

Variables	Follow up time points (month)				Classic ROC
	3	12	24	36	
Age	64.2 (0.025*)	57.1 (0.016)	57.1 (0.015)	58.8 (0.018)	60.5 (0.004)
BMI**	51.8 (0.032)	51.8 (0.021)	51.6 (0.022)	51.0 (0.024)	50.0 (0.004)
Kt/v	50.6 (0.030)	50.3 (0.016)	50.3 (0.016)	48.5 (0.019)	52.3 (0.003)
MCHC	49.7 (0.027)	54.1 (0.015)	53.6 (0.016)	53.0 (0.019)	53.7 (0.003)
Corrected Ca	57.2 (0.029)	56.2 (0.015)	56.3 (0.016)	53.8 (0.019)	55.1 (0.004)
Uric acid	51.1 (0.027)	54.1 (0.015)	53.1 (0.016)	51.9 (0.019)	50.4 (0.004)
Alb	67.5 (0.030)	62.3 (0.016)	61.4 (0.016)	59.8 (0.019)	60.2 (0.003)
FBS	51.1 (0.027)	49.2 (0.016)	53.6 (0.015)	53.8 (0.018)	50.8 (0.004)
Cr	56.4 (0.028)	55.9 (0.016)	56.6 (0.015)	57.9 (0.018)	55.6 (0.003)
Na	55.5 (0.026)	52.2 (0.016)	53.3 (0.015)	53.1 (0.018)	52.5 (0.004)
Bun	51.1 (0.027)	54.1 (0.016)	53.1 (0.015)	51.9 (0.019)	52.7 (0.004)
Ph	50.2 (0.028)	51.4 (0.015)	52.7 (0.016)	53.6 (0.019)	53.6 (0.003)
Risk score	71.2 (0.026)	63.9 (0.015)	63.5 (0.015)	64.1 (0.018)	64.0 (0.012)

*standard error
**BMI: Body Mass Index; Kt/V: Adequacy of Dialysis; MCHC: Mean Corpuscular Hemoglobin Concentration; BUN: Blood Urea Nitrogen; Cr: Creatinine; Na: Sodium; Ca: Calcium; Ph: Phosphate; Alb: Albumin.

Table 3. The result of Backward Cox regression for the association of significant variables with mortality

Variables	Coefficient	HR*	*P*	95% Confidence Interval	
				Lower	Upper
Age	0.02	1.02	< .001	1.001	1.018
Cr**	-0.03	0.97	.040	0.943	0.999
MCHC	-0.04	0.96	.020	0.933	0.994
Alb	-0.50	0.61	< .001	0.537	0.705

*HR: Hazard Ratio
**MCHC: Mean Corpuscular Hemoglobin Concentration; Cr: Creatinine; Alb: Albumin.

P = .020) and serum albumin (HR = 0.61, *P* < .001), the risk of mortality was significantly decreased by approximately 3%, 4% and 39%, respectively.

Risk Score

A risk score was calculated for each of 10 imputed data sets based on the coefficients of significant biomarkers. Afterward, a single averaged risk score was achieved applying Rubin's rule as follows:

$$\text{Risk Score} = (0.02\times age) - (0.03\times cr) - (0.04\times mchc) - (0.50\times alb)$$

According to this score, the higher the score, the higher is the risk of mortality. In Figure 1 and Table 2, the area under the curve was obtained by the time-dependent ROC curve. Obviously, in the first year of follow-up, the AUC of the risk score had higher ability to predict mortality, particularly in the first three months. Afterward, the predictive ability of the calculated risk score was decreased and finally remained constant after one year. As Table 2 shows, in predicting mortality, the performance of the risk score obtained from the combination of biomarkers was superior to that calculated from individual biomarkers.

DISCUSSION

In the present study, we showed that while some biomarkers, such as MCHC, had significant impact on mortality by using conventional methods, i.e., cox regression, their ability to predict survival was unacceptable in the time-dependent ROC curve analysis. In addition, most of the baseline variables such as age, serum calcium and serum albumin did not have the same performance throughout the follow-up period, while had more power in predicting first year survival.

The time-dependent ROC curve analysis is a new tool to evaluate and compare the predictive power of biomarkers in populations with a long-term follow-up, particularly in conditions in which the disease status may change over time. Also, it assumes that if the time of biomarker measurement is closer to the prediction time, its discriminative ability increases.[9] Our study applied the time-dependent ROC curve method to evaluate the ability of a biomarker at baseline to predict mortality in HD patients over 3, 12, 24, and 36 months after starting dialysis. As it was shown in our study, the classic ROC curve was more consistent with the AUCs obtained from the time-dependent ROC curve of those patients that their survival time occurred at longer intervals to biomarkers measurement (Table 2). Therefore, due to long follow-up time of the patients in maintenance hemodialysis, the ability of classic ROC curve compared to time-dependent ROC curve is not valid since the survival time occurred in a long interval from biomarker measurement.

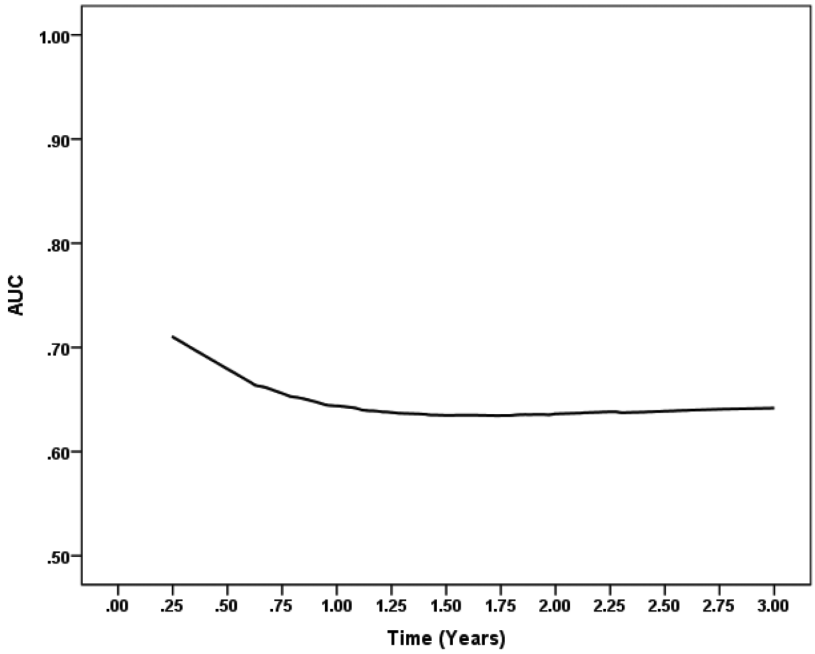

Figure 1. Areas under time-dependent ROC curves over time based on the risk score.

In patients undergoing maintenance HD, it is well known that mortality increases with age where patients under the age of 45 have better survival compared to older ones.[22-23] With the AUC of 64 in the first three months on maintenance HD, our study was able to show that age exhibits higher performance in predicting early than later survival, i.e., the AUC of 58 for the third year.

Among the present study variables, only serum creatinine had stable and relatively constant performance in predicting survival over the follow-up time. Although serum creatinine fluctuates following initiation of HD, mostly with a rise in level in early months on HD and due to a reduction in the residual renal function,[24] this study highlighted the survival impact of baseline serum creatinine and therefore the baseline nutritional status with the same strength over the following years of follow-up. Several studies have also showed that higher serum creatinine is linked to better survival not only in patients on maintenance HD but also in patients on peritoneal dialysis.[25-27] Since most prevalent HD patients have a very low residual renal function, this relationship reflects the effect of muscle mass and nutritional status on survival.[27-28]

In the present study, the serum albumin exhibits the highest performance in predicting survival compared to other study variables. Previous studies indicated that hypoalbuminemia, as an index of malnutrition and protein energy wasting, was associated with both decreased survival and increased hospitalization.[24,29] The higher performance of baseline albumin in the early period of starting HD in our study could be due to change of serum albumin later on maintenance HD owing to improvement in patients' nutritional and general health conditions. Goldwasser *et al.* in their study showed that serum albumin was increased in stable patients in the first half year on maintenance HD.[30] Therefore, the baseline serum albumin fails to predict survival in later years with the same power as on the earlier days of dialysis. Kalantar-Zadeh *et al.* also showed that time-varying hypoalbuminemia predicted mortality differently from the baseline measures of serum albumin, and a rise in serum albumin level over time was linked to improved survival regardless of the baseline serum albumin.[29]

As the result of the time-dependent ROC curve analysis, serum calcium was another biomarker that had a relatively good predictive ability. However, it was not a significant biomarker with the Cox regression analysis. Abnormal serum calcium has been found to be a predictor of mortality in many studies on maintenance HD population.[31-32] Contrary to many studies, which used uncorrected serum calcium, we used albumin-corrected serum calcium in the analysis of survival. Rivara *et al.* found that the association between serum calcium and risk of mortality was considerably affected by serum albumin.[33] However, there are some data demonstrating that the conventional correction formula is invalid in HD patients.[34] Our study also revealed that the ability of the baseline serum calcium to predict survival was slightly higher for the first year on HD than later; however, the difference is not significant.

Evaluation of the performance of biomarkers over the follow-up period and demonstration of the power of each biomarker to predict mortality with AUC are among the advantages of the present study. Improvement of the ability of prediction with calculating risk scores is another advantage of our study.

There are several limitations to our study that should be acknowledged. First, some clinically important variables, including hemoglobin, lipid profile indices, and serum potassium, were not included due to a high proportion of missing data. Second, several potential confounders—such as the underlying etiology of ESKD, comorbid conditions, and social determinants of health—were unavailable in the dataset, which may limit the clinical interpretability and generalizability of the findings. In addition, the cause of death was not recorded; therefore, all-cause mortality was considered as the event of interest, precluding cause-specific or competing-risk analyses.

Future studies may benefit from incorporating longitudinal biomarker measurements and applying advanced statistical approaches, such as landmark analysis or joint modeling, to provide a more comprehensive evaluation of dynamic biomarker trajectories and their prognostic value in hemodialysis patients.

CONCLUSION

In conclusion, this study demonstrated that time-dependent ROC analysis provides a flexible framework for evaluating the predictive performance of biomarkers for survival over time in hemodialysis patients, compared with conventional approaches. Among baseline biomarkers, serum albumin and calcium showed relatively better performance in predicting early survival, while serum creatinine exhibited more stable discrimination throughout follow-up. Although the discriminatory ability of individual biomarkers was modest, the risk score derived from the combination of significant predictors achieved improved performance, highlighting the advantage of multivariable risk stratification in this population.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was conducted according to the principles expressed at Shiraz University of Medical Sciences, and it was approved by the local Ethics Committee of Shiraz University of Medical Sciences by the code IR.SUMS.REC. 1397.742. Based on the approval of the Ethics Committee, all information was collected only by patients' code, and their identity was not disclosed. The patients' information was kept confidential.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

ZSH contributed to the study conception, implementation of the study, design, analysis, interpretation and critical was involved in drafting of the manuscript. SA contributed to data analysis and implementation of the study. SHE was involved in interpretation of data, drafting and revising the manuscript. KM involved in analysis. FN contributed to collection of data. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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