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Original Article

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Risk Factors Affecting 5-Year Mortality in Incident Hemodialysis Patients in the Black Sea Region of Türkiye

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ABSTRACT

Objective: This study aimed to investigate the risk factors for all-cause mortality in incident hemodialysis patients during 5 years of the follow-up period.
Methods: The study was conducted with 163 incident hemodialysis patients in the Black Sea region of Turkey. The patients were followed up for up to 5 years. The Cox proportional hazards regression analysis was used to detect the independent risk factors that affect mortality.
Results: The median duration of follow-up was 50 (25-60) months. A total of 73 (44.8%) patients died during the 5 years of the follow-up period. The 5- year survival was 52%. Age ≥ 65 years [hazard ratio (95% CI): 1.917 (1.068-3.444); *P* = .029], use of a central venous catheter [hazard ratio (95% CI): 4.136 (2.338-7.319); *P* < .0001], serum albumin < 3.5 g/dL [hazard ratio (95% CI): 3.689 (1.876-7.257); *P* < .0001], corrected calcium < 8.4 mg/dL [hazard ratio (95% CI): 2.219 (1.132-4.351); *P* = .020], parathyroid hormone < 150 pg/mL [hazard ratio (95% CI): 2.243 (1.048-4.803); *P* = .037], uric acid > 7 mg/dL [hazard ratio (95% CI): 2.386 (1.154-4.933); *P* = .019], hemoglobin < 10 g/dL [hazard ratio (95% CI): 2.404 (1.280-4.515); *P* = .006], and transferrin saturation < 20% [hazard ratio (95% CI): 2.215 (1.102-4.453); *P* = .026] were identified as independent risk factors for mortality.
Conclusion: Advanced age, use of a central venous catheter, hypocalcemia, hypoalbuminemia, hyperuricemia, adynamic bone disease, hemoglobin < 10 g/dL, and transferrin saturation < 20% are associated with an increased all-cause mortality risk in incident hemodialysis patients.
Keywords: Central venous catheter, hemodialysis, hypoalbuminemia, mortality

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INTRODUCTION

Kidney failure with replacement therapy (KFRT) is a globally increasing problem. Hemodialysis is one of the treatment options for KFRT. Mortality has increased in chronic kidney disease (CKD) grade 5 dialysis patients compared to the general population. Cardiovascular disorders are the most frequent cause of mortality in CKD grade 5 dialysis patients. On the other hand, non-cardiovascular mortality causes, such as infection and malignancy, are common in dialysis patients.[1]

It is important to detect mortality-related risk factors in CKD grade 5 hemodialysis patients, and thereby measures can be taken to reduce morbidity and mortality.[2] Mortality-related risk factors in hemodialysis patients have been investigated in various studies. There are studies reporting that conventional cardiovascular risk factors, such as advanced age and diabetes mellitus (DM), are also valid for hemodialysis patients.[3,4] Furthermore, factors resulting from KFRT also affect mortality.[5] Anemia was found to be related to mortality.[6]

Chronic kidney disease–mineral bone disorder (CKD-MBD)-related hyperphosphatemia, hypercalcemia, and hyperparathyroidism were found to be related to all-cause mortality.[7] Malnutrition and chronic inflammation, hypoalbuminemia, low serum cholesterol, prealbumin, creatinine levels, and low body mass index were also defined to be risk factors for mortality.[3,8-11] Infection-related mortality rates are much higher compared to the general population.[12] Central venous catheters (CVC) are also among the most important factors of infection-related mortality in hemodialysis patients.[13,14]

The purpose of this study was to investigate the relationship between clinical factors including age, gender, diabetes, vascular access type, hemodialysis adequacy, as well as biochemical markers, including serum phosphorus, corrected calcium, parathyroid hormone (PTH), albumin, uric acid, C-reactive protein (CRP), transferrin saturation (TSAT), ferritin, and all-cause mortality in incident hemodialysis patients during the 5-year follow-up period. Most studies investigating the risk factors for mortality in hemodialysis patients were conducted with prevalent hemodialysis patients. Again, in most studies, the influence of the baseline laboratory data on mortality was investigated. In this study, we planned to explore the effects of various factors on mortality in incident hemodialysis patients. We also intended to search the influence of the time-averaged values of laboratory parameters on mortality.

METHODS

Patients

This study was carried out with 163 incident hemodialysis patients in 3 outpatient hemodialysis centers in the Middle Black Sea region of Turkey. All patients were diagnosed with CKD grade 5 treated by hemodialysis. Patients with acute kidney injury treated by hemodialysis were not included in this study. The CKD grade 5 patients who started hemodialysis replacement therapy between January 1, 2011, and January 1, 2016, were included in the study. The patients who came to one of these outpatient hemodialysis centers within 3 months of starting hemodialysis replacement therapy were included in the study. The patients who died within 90 days of starting hemodialysis replacement therapy were excluded from the study. The patients were followed up for up to 5 years. The data were analyzed retrospectively. The data of those patients who died during the follow-up went to another hemodialysis center, underwent kidney transplantation, or whose treatment was switched to peritoneal dialysis were evaluated during their follow-up. No patients developed coronavirus disease 2019 during the follow-up.

MAIN POINTS

- Mortality has increased in chronic kidney disease grade 5 dialysis patients. It is important to detect mortality-related risk factors in hemodialysis patients, and thereby measures can be taken to reduce morbidity and mortality.
- Age ≥ 65 years, use of a central venous catheter (CVC), serum albumin < 3.5 g/dL, corrected calcium < 8.4 mg/dL, parathyroid hormone < 150 pg/mL, uric acid > 7 mg/dL, hemoglobin < 10 g/dL, and transferrin saturation < 20% are the independent risk factors in incident hemodialysis patients for all-cause mortality.
- The most important factors affecting mortality are CVC use and hypoalbuminemia.

The age at the beginning of hemodialysis treatment, gender, and DM status of the patients were recorded. Patients who were using oral anti-diabetics or insulin were accepted as diabetic. The patients were separated into 3 groups according to the vascular access type as arteriovenous fistula (AVF), AVF-CVC, and CVC. Patients who started hemodialysis replacement therapy with AVF and continued with a fistula in their follow-ups constituted the AVF group, patients who started hemodialysis replacement therapy with an AVF and passed a CVC after AVF failed in their follow-ups constituted the AVF-CVC group, and patients who initiated hemodialysis replacement therapy with a CVC and used a catheter in their follow-ups constituted the CVC group. No patients had arteriovenous graft (AVG).

When carrying out the Cox proportional hazards regression analysis, the patients were separated into 2 groups according to age, serum albumin, hemoglobin, CRP, TSAT, and ferritin values. Most of the studies in the literature used cutoff values for age as 65 years and 3.5 g/dL for albumin.[8,15] We used the same cutoff values. We used the hemoglobin cutoff value of 10 g/dL as low hemoglobin values were related to mortality.[6] Transferrin saturation < 20% was associated with an increased risk of all-cause mortality.[16,17] We also used this value as the cutoff. The Kidney Disease: Improving Global Outcomes (KDIGO) anemia guideline recommends intravenous iron therapy when serum ferritin ≤ 500 ng/mL.[18] We also used a value of 500 ng/mL as the cutoff for serum ferritin. The association of serum uric acid, corrected calcium, phosphorus, and PTH levels with mortality is generally U-shaped.[7,19,20] Therefore, serum uric acid, corrected calcium, and phosphorus levels were divided into 3 groups. The PTH levels were separated into 4 groups, and their relationship with all-cause mortality was investigated. The Kidney Disease Outcomes Quality Initiative hemodialysis adequacy guideline recommends a minimum delivered single-pool Kt/V (spKt/V) value of 1.2 in patients receiving hemodialysis treatment three times per week.[21] However, the number of patients with spKt/V < 1.2 in our study was small. Therefore, we used 1.4 and 1.6 as cutoff levels for spKt/V.

The patients were treated following the KDIGO guidelines during their follow-up period. The patients were administered phosphate-binder therapy, calcimimetics, calcitriol or vitamin D analogs, intravenous iron, and erythropoiesis-stimu lating agents according to their clinical conditions. It was aimed to achieve treatment goals recommended in the KDIGO

guidelines.[18,22] However, some patients could not completely adhere to phosphate-lowering treatment.

The study was approved by the local Ethics Committee (Approval Date: June 10, 2021; Approval Number: 2021/294). Informed consent could not be obtained from all patients because it was a retrospective study. Some patients were not alive at the time of study data collection.

Laboratory Tests

During the follow-ups, blood tests were performed before hemodialysis. Corrected calcium, phosphorous, albumin, and hemoglobin values were measured each month, and PTH, uric acid, CRP, TSAT, and ferritin levels were measured every 3 months. The spKt/V urea was calculated each month.[23] The mean values of laboratory tests examined during the follow-up were taken. The time-averaged value of all laboratory measurements was used. For those patients who died during follow-up, switched to peritoneal dialysis, underwent kidney transplantation, or went to another hemodialysis center, the mean values of the laboratory tests during their follow-up were taken. Laboratory tests were performed at the same laboratory for all patients. Corrected calcium was calculated for the patients for hypoalbuminemia using the formula: "Corrected calcium, mg/dL = [(0.8 (×) (4−serum albumin, g/dL)] + measured calcium, mg/dL."

Statistical Analysis

Statistical Package for Social Sciences version 21.0 (IBM Corp., Armonk, NY, USA) was used during data analysis. The distribution of deceased and survived patients is given as numbers and percentages (Table 1). The time-averaged value of all laboratory measurements was used. The Kaplan–Meier test was used for the 1-, 3-, and, 5-year survival analyses. The Cox proportional hazards regression analysis was used to determine the independent risk factors affecting all-cause mortality. A multivariable-adjusted model was used in Cox regression analysis. Age, gender, vascular access type, DM status, serum albumin, corrected calcium, phosphorus, PTH, uric acid, hemoglobin, TSAT, ferritin, CRP, and spKt/V are the variables used in the multivariable-adjusted analysis. Receiver operating characteristic (ROC) curve analysis was done to determine the cutoff value for the value for age, serum albumin, hemoglobin, and TSAT, which were statistically significant variables of multivariable-adjusted analysis. *P*-values < .05 were accepted as statistically significant.

RESULTS

This study was conducted with 163 incident hemodialysis patients. There were 83 (50.9%) female and 80 (49.1%) male patients. The mean age of the patients was 63.9 ± 10.2 (34-84) years. The median follow-up was 50 (25-60) months. During the 5-year follow-up period, 73 (44.8%) patients died. Nine (5.5%) patients underwent kidney transplantation. Eight (4.9%) patients went to other hemodialysis centers. One (0.6%) patient underwent peritoneal dialysis. Sixty-one (37.4%) patients had

Table 1. Characteristics of Hemodialysis Patients Who Died and Survived

Variables	Deceased Patients (n = 73) n (%)	Survived Patients (n = 90) n (%)
Age (years)		
<65	28 (38.4)	56 (62.2)
≥65	45 (61.6)	34 (37.8)
Gender		
Female	33 (45.2)	50 (55.6)
Male	40 (54.8)	40 (44.4)
Diabetes mellitus		
No	39 (53.4)	63 (70)
Yes	34 (46.6)	27 (30)
Vascular access		
AVF	32 (43.8)	76 (84.4)
AVF-CVC	6 (8.2)	5 (5.6)
CVC	35 (47.9)	9 (10)
Corrected calcium, mg/dL		
<8.4	16 (21.9)	11 (12.2)
8.4-9.39	49 (67.1)	73 (81.1)
≥9.4	8 (11)	6 (6.7)
Phosphorus, mg/dL		
<4	14 (19.2)	7 (7.8)
4-5.49	46 (63)	63 (70)
≥5.5	13 (17.8)	20 (22.2)
PTH, pg/mL		
<150	17 (23.3)	5 (5.6)
150-299	32 (43.8)	33 (36.7)
300-499	19 (26)	42 (46.7)
≥500	5 (6.8)	10 (11.1)
Albumin, g/dL		
<3.5	22 (30.1)	1 (1.1)
≥3.5	51 (69.9)	89 (98.9)
Uric acid, mg/dL		
<5.5	25 (34.2)	24 (26.7)
5.5-7	34 (46.6)	52 (57.8)
>7	14 (19.2)	14 (15.6)
spKt/V urea		
<1.4	23 (31.5)	15 (16.7)
1.4-1.59	28 (38.4)	19 (21.1)
≥1.6	22 (30.1)	56 (62.2)
CRP, mg/L		
<10	22 (30.1)	37 (41.1)
≥10	51 (69.9)	53 (58.9)
Hemoglobin, g/dL		
<10	19 (26)	6 (7)
≥10	54 (74)	84 (93)
TSAT, %		
<20	17 (23.3)	9 (10)
≥20	56 (76.7)	81 (90)
Ferritin, ng/mL		
<500	34 (46.6)	48 (53.3)
≥500	39 (53.4)	42 (46.7)

AVF, arteriovenous fistula; CRP, C-reactive protein; CVC, central venous catheter; PTH, parathyroid hormone; TSAT, transferrin saturation.

DM. The 1-year survival was 91.8%, the 3-year survival was 68.8%, and the 5-year survival was 52%.

The data of the patients who died and survived during the 5-year follow-up period are presented in Table 1. The Cox proportional hazards regression analysis was used to identify the independent risk factors affecting the 5-year mortality risk. In the multivariable-adjusted analysis, a statistically significantly increased risk of all-cause mortality was found in patients with age ≥ 65 years, CVC use, corrected calcium < 8.4 mg/dL, PTH < 150 pg/mL, serum albumin < 3.5 g/dL, uric acid > 7 mg/dL, hemoglobin < 10 g/dL, and TSAT < 20% (Table 2).

The ROC curve analysis was done to determine the cutoff value for age, serum albumin, hemoglobin, and TSAT (Table 3). The ROC curve graphs are shown in Supplementary Figures 1–4.

DISCUSSION

In this study conducted with incident hemodialysis patients, the 5-year survival was 52%. Age ≥ 65 years, use of a CVC, serum albumin < 3.5 g/dL, corrected calcium < 8.4 mg/dL, PTH < 150 pg/mL, uric acid > 7 mg/dL, hemoglobin < 10 g/dL, and TSAT < 20% were detected as the independent risk factors for all-cause mortality. The most important factors affecting mortality were CVC use and hypoalbuminemia.

In this study, the all-cause mortality risk was higher in patients with CVC than those with AVF. Similar results were found in different studies.[24-26] Brown et al[25] followed up hemodialysis patients up to 58 months. The lowest mortality was found in patients with AVF. Mortality was lower in patients who switched to catheters after failed AVF than in patients with CVC since the beginning of hemodialysis. The highest mortality rate was found in patients using CVC since the beginning of hemodialysis treatment. The mortality rates of patients with CVC are higher than those with both AVF and AVG.[26] The AVFs have a lower risk of infection than AVG and CVC, have longer patency rates, a better quality of life, and lower all-cause mortality rates. The first choice of a vascular access type is AVF.[13] Infection is more common with the use of CVC. Moreover, adequate blood flow might not be achieved during hemodialysis, and solute clearance might remain low. All of these factors increase the all-cause mortality in patients with CVC.[13]

In most dialysis patients, the serum albumin level is usually normal. Hypoalbuminemia in hemodialysis patients is an important indicator of mortality and morbidity. In patients with protein-calorie malnutrition, albumin synthesis and serum albumin decrease. Albumin is also a negative acute-phase reactive protein. Even in the absence of malnutrition, the serum albumin level decreases in cases of inflammation.[27] In this study, the all-cause mortality risk was higher in patients with low time-averaged serum albumin levels. It has also been shown in multiple studies that serum albumin level is an important predictor of mortality in dialysis patients. However,

Table 2. Risk Factors for All-Cause Mortality in Incident Hemodialysis Patients—Multivariable-Adjusted Cox Proportional Hazards Regression Analysis

	HR	95% CI	*P*
Age (years)			
<65	Reference		
≥65	1.917	1.068-3.444	.029
Gender			
Female	Reference		
Male	1.166	0.584-2.331	.663
DM			
No	Reference		
Yes	1.451	0.834-2.524	.188
Vascular access			
AVF	Reference		
AVF-CVC	1.307	0.476-3.586	.604
CVC	4.136	2.338-7.319	<.0001
Corrected calcium, mg/dL			
<8.4	2.219	1.132-4.351	.020
8.4-9.39	Reference		
≥9.4	1.912	0.838-4.363	.124
Phosphorus, mg/dL			
<4	1.522	0.700-3.308	.289
4-5.49	Reference		
≥5.5	0.938	0.449-1.960	.864
PTH, pg/mL			
<150	2.243	1.048-4.803	.037
150-299	1.854	0.963-3.568	.065
300-499	Reference		
≥500	1.649	0.538-5.050	.381
Albumin, g/dL			
<3.5	3.689	1.876-7.257	<.0001
≥3.5	Reference		
Uric acid, mg/dL			
<5.5	1.323	0.671-2.608	.419
5.5-7	Reference		
>7	2.386	1.154-4.933	.019
spKt/V urea			
<1.4	1.684	0.881-3.221	.115
1.4-1.59	1.679	0.744-3.786	.212
≥1.6	Reference		
CRP, mg/L			
<10	Reference		
≥10	0.668	0.371-1.203	.179
Hemoglobin, g/dL			
<10	2.404	1.280-4.515	.006
≥10	Reference		
TSAT, %			
<20	2.215	1.102-4.453	.026
≥20	Reference		
Ferritin, ng/mL			
<500	Reference		
≥500	0.911	0.503-1.650	.758

Age, gender, vascular access type, DM status, serum albumin, corrected calcium, phosphorus, PTH, uric acid, hemoglobin, TSAT, ferritin, CRP, and spKt/V are the variables used in the multivariable-adjusted analysis.
AVF, arteriovenous fistula; CRP, C-reactive protein; CVC, central venous catheter; HR, hazard ratio; PTH, parathyroid hormone; TSAT, transferrin saturation.

Table 3. ROC Curve Analysis Results by Death Status

Risk Factors	Cutoff Value	AUC (95% CI)	*P*	Sensitivity (%)	Specificity (%)
Age (years)	63.5	0.668 (0.585-0.750)	<.0001	67	61
Serum albumin (g/dL)	3.60	0.677 (0.592-0.761)	<.0001	40	96
Hemoglobin (g/dL)	10.95	0.655 (0.570-0.740)	.001	60	69
TSAT (%)	30.78	0.599 (0.512-0.687)	.029	81	36

AUC, area under curve; ROC, receiver operating characteristic; TSAT, transferrin saturation.

in most of these studies, the relationship between serum albumin level at the beginning of the study and mortality was examined.[28,29] Different from these studies, Kalantar-Zadeh et al[30] showed that time-varying hypoalbuminemia predicts mortality. In a study conducted with peritoneal dialysis patients, a 2-year time-averaged albumin level of < 3.5 g/dL was associated with increased mortality.[31] In our study, we report that time-averaged hypoalbuminemia is a predictor of mortality in incident hemodialysis patients.

In our study, the all-cause mortality risk was increased in patients with time-averaged PTH of <150 pg/mL. A U-shaped relationship has often been found between PTH and all-cause mortality. In the study of Floege et al.[7] an increased risk of all-cause mortality was found when PTH was <150 and >300 pg/mL according to the time-dependent Cox analysis. Kalantar-Zadeh et al[32] followed up with their patients for 2 years. The lowest mortality was found when the PTH level was between 200 and 300 pg/mL. In a different study conducted in Japan, the prevalent hemodialysis patients were followed up for 3 years. In the baseline, time-dependent and time-averaged models, the mortality risk was highest when PTH > 300 pg/mL and ≤60 pg/mL.[20] The Japanese CKD-MBD guideline recommends a target intact PTH value between 60 and 240 pg/mL.[33] The KDIGO CKD-MBD guideline recommends that the target intact PTH value be maintained between 2 and 9 times the upper normal limit.[22] In our study, the risk of all-cause mortality increased in the patient group with PTH ≥ 500 pg/mL, but this increase was not statistically significant. Since the patients were treated for secondary hyperparathyroidism, the number of patients with high time-averaged PTH values was low. In addition, a long hemodialysis vintage is required for the development of secondary hyperparathyroidism in hemodialysis patients.[34,35] In our study, incident patients were followed up for up to 5 years. The mechanism between low PTH levels and mortality is not clear. With the suppression of PTH levels, low bone turnover disease and arterial calcification might develop. Cardiovascular calcification might cause increased mortality.[36] In addition, in dialysis patients, there might be insufficient protein intake due to phosphorus restriction, which might lead to a decrease in serum phosphorus, albumin and PTH levels. A low serum PTH level might be an indicator of malnutrition. Malnutrition causes increased mortality in dialysis patients.[37]

In our study, patients with age ≥ 65 years, corrected calcium < 8.4 mg/dL, uric acid > 7 mg/dL, hemoglobin < 10 g/dL, and TSAT < 20% had an elevated risk of all-cause mortality. We determined that advanced age at the commencement of hemodialysis was a risk factor for mortality. Advanced age is a risk factor for mortality in hemodialysis patients in many studies.[3,4,9,10,15] The relationship between serum calcium and mortality is generally U-shaped.[7,20] In our study, there was an increased risk of all-cause mortality in hypocalcemic patients. The hazard ratio also increased in hypercalcemia, but this increase was not statistically significant. Hypocalcemia was associated with an elevated risk of all-cause mortality, especially in incident hemodialysis patients.[38] Secondary hyperparathyroidism and calcium increase are more common in patients with long hemodialysis vintage.[35] The association of uric acid with mortality in hemodialysis patients is generally U-shaped.[19] In our study, the hazard ratio followed in U-shaped, but there was a statistically significant increased mortality risk only in hyperuricemia. Similar to our study, hemoglobin < 10 g/dL and TSAT < 20% were associated with an elevated risk of all-cause mortality in hemodialysis patients.[6,17]

In this study, the time-averaged CRP level was not a risk factor for mortality. In some studies, an increased CRP level in dialysis patients was a risk factor for mortality. However, in most of these studies, the CRP value at the beginning of the study was measured, and the patients were followed up.[39-41] Bazeley et al[41] stated in their study that CRP predicted 1-year mortality. Zimmermann et al[39] showed that the baseline CRP value predicted 2-year mortality. Although CRP is increased in some chronic inflammatory conditions, it is classically an acute-phase reactant.[42] In our study, we evaluated the CRP levels as time-averaged. Acute increases in CRP might better indicate mortality, so there might not be a relationship between time-averaged CRP level and mortality.

Our study has some limitations. The sample size of our study is small. Since our patients were treated following the KDIGO CKD-MBD guideline, the number of patients with PTH > 600 pg/mL was low. Our patients received phosphate-binder therapy, so the number of patients with high time-averaged serum phosphorus was low. Since we were working with incident hemodialysis patients, some of our patients started hemodialysis treatments twice per week and then received

hemodialysis treatment 3 times per week in the subsequent follow-ups. In addition, while calculating spKt/V, the residual native kidney function of the patients was not taken into account.

CONCLUSION

In conclusion, age ≥ 65 years, use of a CVC, serum albumin < 3.5 g/dL, corrected calcium < 8.4 mg/dL, PTH < 150 pg/mL, uric acid > 7 mg/dL, hemoglobin < 10 g/dL, and TSAT < 20% were detected as the independent risk factors for all-cause mortality in incident hemodialysis patients in the Black Sea region of Turkey. The most important factors affecting mortality are CVC use and hypoalbuminemia. Knowing the factors associated with mortality will help reduce morbidity and mortality in incident hemodialysis patients. Avoiding CVC, choosing AVF, might decrease mortality. The cause of hypoalbuminemia should be investigated in hemodialysis patients. If there are correctable causes of hypoalbuminemia, treating them might reduce mortality in incident hemodialysis patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Ondokuz Mayıs University (Date: June 10, 2021; Decision No: 2021/294).

Informed Consent: Since our study was a retrospective data review, we could not get informed consent from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – E.E.; Design – E.E., A.K., T.E.; Data Collection and/or Processing – E.E., A.K.; Analysis and/ or Interpretation – E.E., A.K., T.E.; Literature Search – E.E., A.K., T.E.; Writing – E.E.; Critical Revision – E.E., T.E.

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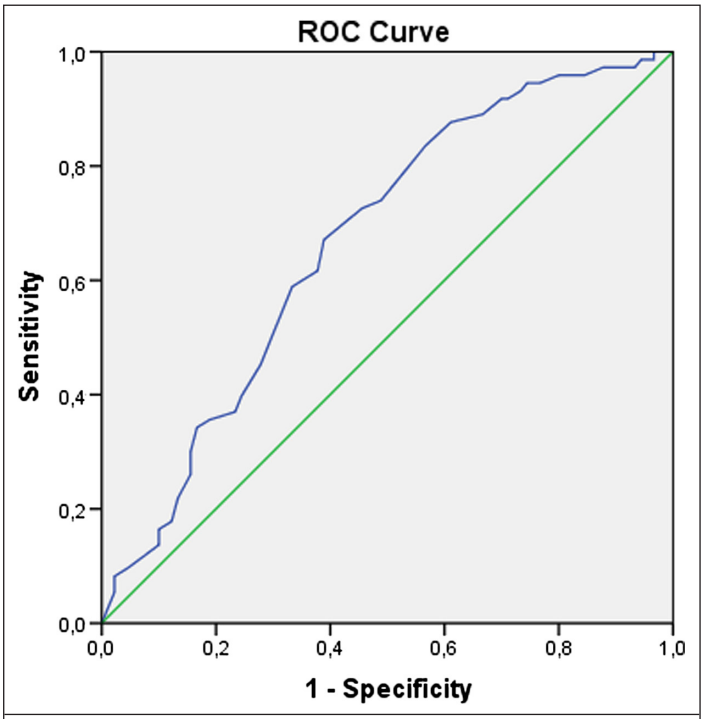
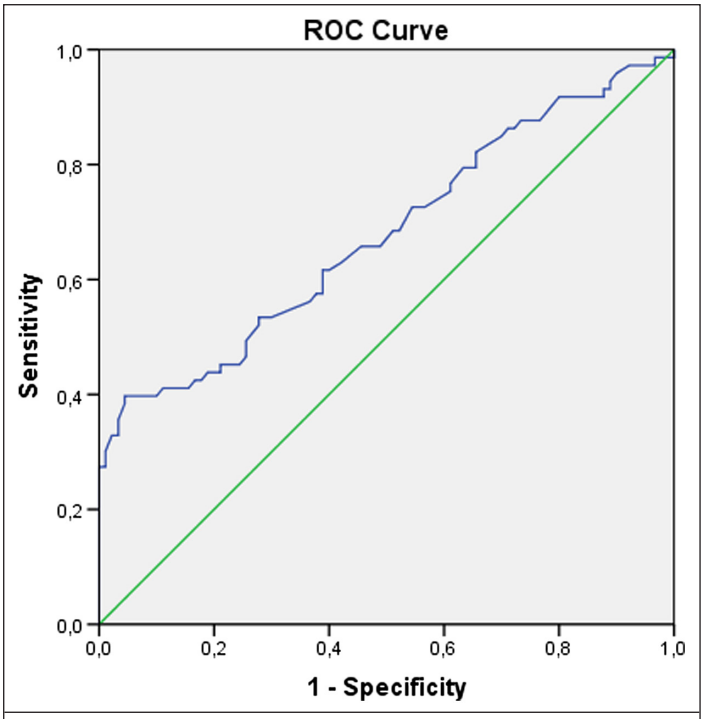
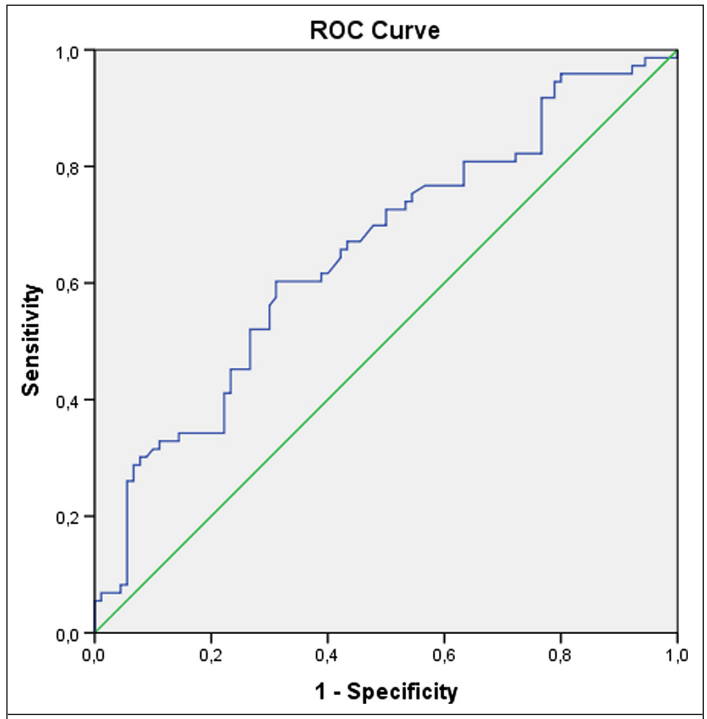


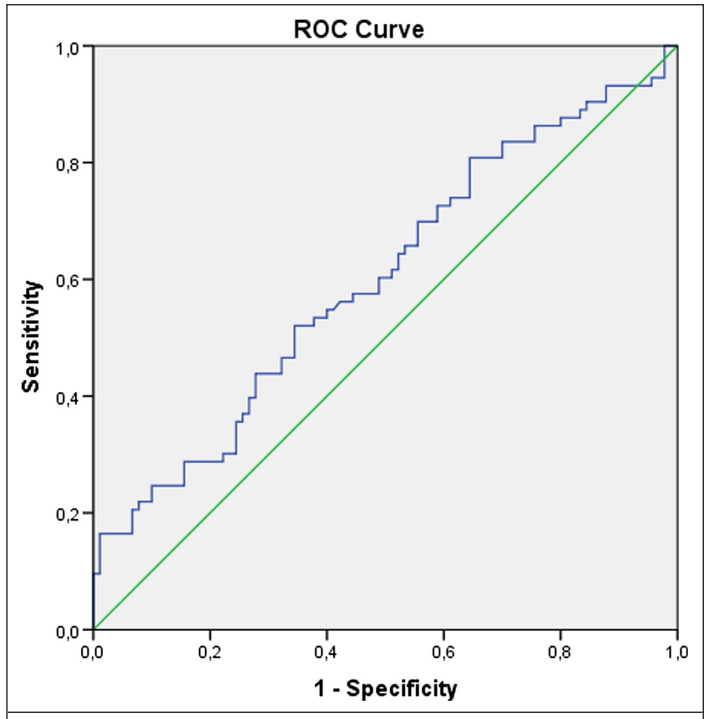
Supplementary Figure 1. Receiver operating characteristic curve analysis for age.



Supplementary Figure 2. Receiver operating characteristic curve analysis for serum albumin.



Supplementary Figure 3. Receiver operating characteristic curve analysis for hemoglobin.



Supplementary Figure 4. Receiver operating characteristic curve analysis for transferrin saturation.