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Predicting Tree-Year Clinical Outcomes Using the Baseline and Trajectories of Serum Albumin in Patients on Peritoneal Dialysis

Mehri Khoshhali,[1] Iraj Kazemi,[2] Sayed Mohsen Hosseini,[3,*] and Shiva Seirafian[4]

[1]Student Research Center, and Department of Epidemiology and Biostatistics, School of Health, Isfahan University of Medical Sciences, Isfahan, Iran
[2]Department of Statistics, University of Isfahan, Isfahan, Iran
[3]Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
[4]Isfahan Kidney Diseases Research Center, Al-Zahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

[*]*Corresponding author*: Sayed Mohsen Hosseini, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran. Tel: +98-3137923251, Fax: +98-3136682509, E-mail: hosseini@hlth.mui.ac.ir

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Abstract

Background: The change and trend in serum albumin levels after initiation of peritoneal dialysis may be a crucial determinant for clinical outcomes.
Objectives: The current study aimed at determining the association between the trajectory of serum albumin and the 3-year clinical outcomes using a novel approach joint modeling longitudinal and survival data. Furthermore, the current study was performed to compare the impact of baseline and trajectory serum albumin on predictability of 3-year outcomes.
Methods: The current retrospective longitudinal study reviewed all of the available files of the patients undergoing continuous ambulatory peritoneal dialysis (CAPD) in Al-Zahra hospital, Isfahan, Iran, from May 2005 to March 2015. A total of 183 patients with at least 3 years follow-up were selected for the study. The independent variables of interest were baseline and the trajectories of serum albumin, age, gender, history of previous hemodialysis (HD), body mass index (BMI), baseline serum creatinine, and comorbidity including cardiovascular disease and diabetes. The outcomes of interest were death from all causes, transfer to HD and transplantation during the first 3 years of CAPD.
Results: The patient and technique survival rates at 36 months were 71% and 77%, respectively. C-indexes (prediction errors) of mortality, transfer to HD, and transplantation for joint modeling with trajectories of serum albumin were higher (lower) than those of the Cox regression with baseline albumin. Hazard ratios of mortality, transfer to HD, and transplantation for trajectories of serum albumin were 0.409, 0.273, and 3.394, respectively.
Conclusions: The current study indicated that the predictability of 3-year clinical outcomes using trajectories of serum albumin was higher than those of the baseline. According to the findings of the current study, it seems that controlling serum albumin over time in patients undergoing CAPD, particularly the ones with the history of diabetes and HD, can help to prevent or modify the clinical outcomes during the PD period.

Keywords: Longitudinal Studies, Iran, Serum Albumin, Survival Analysis, Peritoneal Dialysis

1. Background

Peritoneal dialysis (PD) is a widely accepted renal replacement therapy for end-stage renal disease (ESRD) (1). In 2008, the number of patients undergoing PD was estimated 197 000 patients with ESRD, or 11% of the global population undergoing dialysis. Bothe in the developing and developed countries, the number of patients per million population treated with PD increased over the last decade (2). In Iran, a developing country in the Middle East, hemodialysis (HD) and renal transplantation are the most common renal replacement therapy modalities (3). At this time, continuous ambulatory peritoneal dialysis (CAPD) modality was used much more than automated PD in Iran. According to the Iran Dialysis Center report of 2001, approximately 1% of the patients with ESRD were treated with CAPD; this figure increased to approximately 3.5% (6.8% of total patients undergoing dialysis) in 2006 (3).

Nutritional indices, such as serum albumin level, are significant predictors of the outcomes of the patients undergoing PD (4-8). In patients undergoing PD, the baseline serum albumin levels are closely associated with cardiovascular mortality (9, 10), PD technique survival (11), and peritonitis rate (12-14). Previous studies showed that serum albumin levels reflect conditions including inflammation (15), dialysis adequacy, residual renal function (4, 16), and volume status (17) in patients undergoing PD (12).

Predicting clinical outcomes in patients undergoing PD based on serum albumin is a challenge. The majority of previous studies examined the effect of the baseline serum albumin on the survival of patients undergoing PD using the Cox proportional hazards model (4, 11, 13, 14). Although

serum albumin trajectory may provide more information about the risk of adverse outcomes on dialysis than single measures, few studies examined the effect of trajectories of long-term serum albumin (ie, increasing, stable, or decreasing) on the outcomes of patients undergoing PD (12, 18, 19).

To the authors' best knowledge; there was no study on evaluation of the effect of trajectories of serum albumin on clinical outcomes in patients undergoing PD using a complex powerful statistical method of joint modeling of longitudinal and survival data. Therefore, the current study aimed at determining the relationship between the trajectory of serum albumin control over time and the 3-year clinical outcomes, including mortality, transfer to HD, and transplantation using the novel approach of joint modeling among patients undergoing CAPD in Isfahan, Iran.

2. Objectives

The current study utilized the approach to joint modeling of longitudinal and survival data to determine the relationship between the trajectory of serum albumin and the 3-year clinical outcomes in patients undergoing CAPD. This approach also revealed predictors of serum albumin and clinical outcomes in the current study. The current study mainly aimed at comparing the impact of baseline and trajectory serum albumin on predictability of 3-year outcomes for the patients undergoing CAPD.

3. Methods

3.1. Study Participants and Outcomes

The current retrospective cohort reviewed all of the available files of patients undergoing CAPD in the peritoneal dialysis center of Al-Zahra hospital affiliated to Isfahan University of Medical Sciences, Isfahan, Iran, from May 2005 to March 2015. A total of 300 patients received CAPD therapy for more than 3 months. Among them, patients' files with incomplete records and follow-up less than 3 years were excluded. Totally, 183 patients were included in the study. During the treatment period of PD, patients were evaluated approximately every 3 months by nephrologists and nurses at the PD clinic. Data were collected by the medical records review.

The Regional Bioethics Committee of Isfahan University of Medical Sciences approved the study (code number 394537; issue date 01 November, 2015).

The outcomes of interest were all-cause mortality, transfer to HD, and transplantation during the first 3 years undergoing CAPD. Patients were censored at 3 years if they did not develop any of the 3 events. Patients lost to follow-up within the first 3 years of PD were censored at the last information date. Data were also collected on baseline serum albumin and the trajectories of serum albumin during the time that corresponded to the visiting times (approximately every 3 months) for each patient during the first 3 years of PD, age at PD initiation, gender, history of HD, body mass index (BMI), baseline serum creatinine level, and comorbidity including cardiovascular disease (CVD) and diabetes mellitus. Patients were classified as CVD patients if coronary heart disease, heart failure, atherosclerotic heart disease, cerebrovascular accident/transient ischemic attack, and peripheral vascular disease were listed among the comorbidities.

3.2. Statistical Analysis

Results were presented as mean $\pm$ standard deviation (SD) for quantitative variables and were summarized by number (percentage) for qualitative variables. The median and interquartile range of serum albumin concentrations over time were examined using the box plot. The schematic diagram of analysis procedure is denoted in Figure 1. The associations among unadjusted and adjusted baseline serum albumin with the 3-year outcomes were examined using the univariate and multiple Cox regression models, respectively. Joint modeling of longitudinal and survival data (20, 21) was applied to examine the association between unadjusted and adjusted trajectories of serum albumin, and that of the 3-year outcomes. Baseline and trajectories of serum albumin were adjusted for age, gender, previous HD, BMI, baseline serum creatinine level and comorbidities of cardiovascular disease and diabetes mellitus. Furthermore, the relationship among the trajectories of serum albumin and the above-mentioned covariates of adjustment as well as time on CAPD was indicated using the joint modeling.

To evaluate the predictability of 3-year clinical outcomes using trajectories of serum albumin and baseline serum albumin, the data set was split randomly into 2 parts, the training set including a sample of 122 and the test set including a sample of 61. The developed models from the training data were used to predict the 3-year outcomes for each patient in the test data set. Discrimination of the model was assessed using concordance index (C-index), that gives a quantitative assessment of the model's predictive ability (20, 22). Also, the integrated prediction error (IPE) (20, 23) was used to estimate the absolute deviation between the predicted and observed survival rate at the end of 36 months.

All statistical analyses were performed using Packages of JM (24) and survAUC (25) that run within the open-

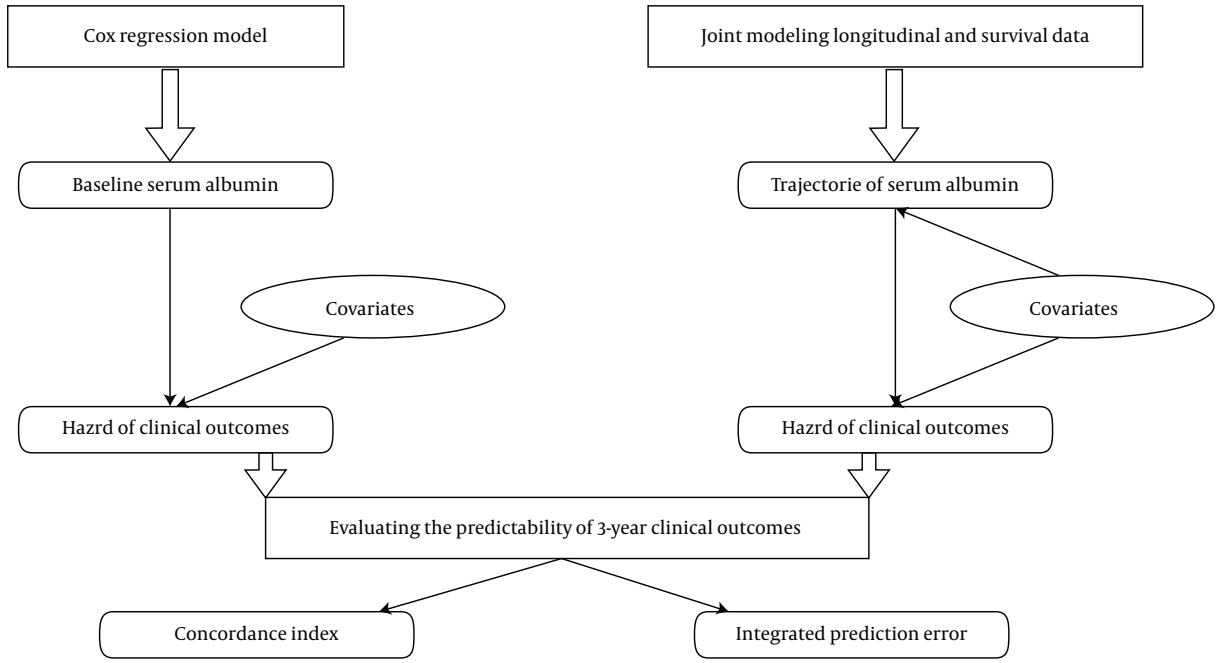

Figure 1. The Schematic Diagram of the Analysis Procedure in the Study

source R computing environment. A $P < 0.05$ was considered as level of significance.

4. Results

The current study comprised 183 patients undergoing CAPD followed over a 3-year period. The mean age of the patients was 54.13 years and 50.3% of them were male. Table 1 denotes the baseline characteristics of the patients, including demographics, clinical variables, and reported comorbidities. Figure 2 shows serum albumin levels decrease over time. Overall, after 3 years follow-up of the patients, 18% transferred to HD, 13.1% underwent transplantation, 21.9% died and the other patients were still under PD (censored, 54%) at the end of the follow-up. The majority of deaths were due to CVD and the main causes of transfer to HD were peritonitis (44.4%), catheter malfunction (24.2%), dialysis inadequacy (21.6%), and miscellaneous reasons unrelated to PD (9.8%). The Kaplan-Meier survival plots of 3 outcomes for the patients undergoing CAPD during the first 3 years are displayed in Figure 3; the patients had better survival from the outcome of mortality during the first 2 years of the follow-up. The patient and technique survival rates at 36 months were 71% and 77%, respectively.

Table 2 shows unadjusted and adjusted effects of baseline and trajectory for serum albumin on 3-year outcomes of patients. Hazard ratios of mortality and transfer to HD

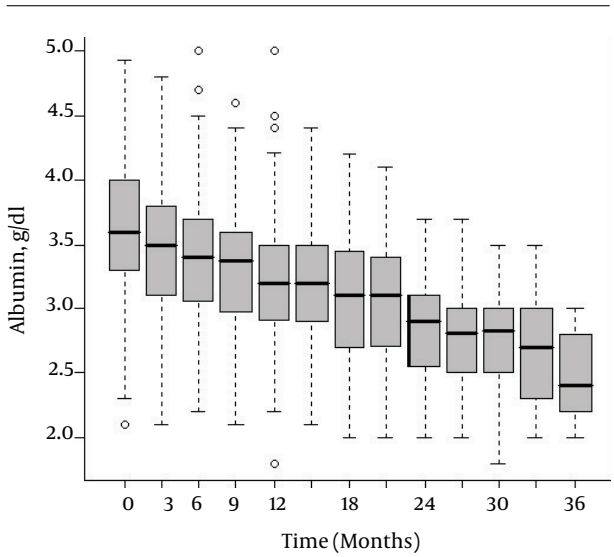

Figure 2. Box Plot Serum Albumin Over Time

for adjusted baseline serum albumin (0.648, and 0.515, respectively) were higher than those of the adjusted trajectory (0.409 and 0.273, respectively). The current study findings demonstrated that every 0.1-unit reduction in serum albumin over time was associated with 8.95% increased hazard for mortality, 12.97% increased hazard transfer to

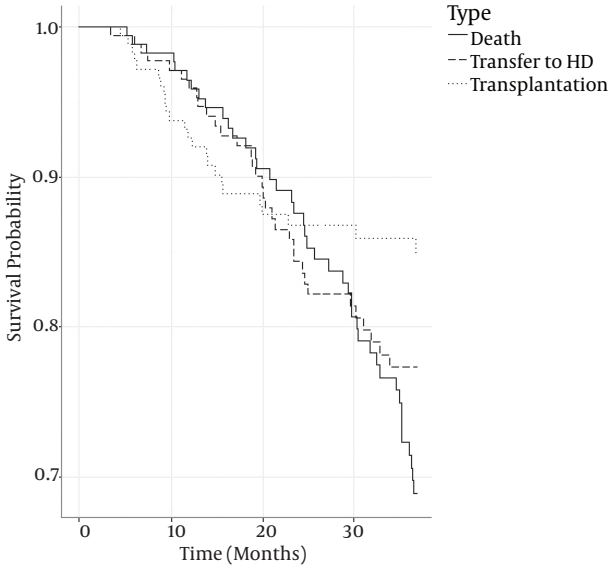

Figure 3. The Kaplan-Meier Survival Plots of the 3-Year Outcomes for the Patients on Continuous Ambulatory Peritoneal Dialysis

Table 1. Baseline Characteristics of the Patients Undergoing CAPD in the Study

Variables	Mean ± SD or N (%)[a]
Demographics variables	
Age at PD initiation (year)	54.13 ± 17.30
Gender (male)	92 (50.3%)
Clinical variables	
Serum albumin (g/dL)	3.65 ± 0.53
BMI (kg/m^2)	24.40 ± 4.72
Serum creatinine (mg/dL)	6.13 ± 2.83
Previous HD	54 (29.5%)
Comorbidity	
Cardiovascular disease	45 (24.5%)
Diabetes mellitus	73(39.9%)

Abbreviations: BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis.
[a]Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as number (%).

HD, and 12.2% decreased hazard for transplantation based on adjusted models with trajectories of serum albumin. Table 3 denotes the predictability of 3-year clinical outcomes using baseline and trajectory serum albumin (adjusted and unadjusted) for the patients undergoing CAPD based on the 2 criteria of C-index and IPE. Accordingly, adjusted models with trajectory serum albumin for each 3 outcomes had the highest C-index and lowest IPE. That is, the predictability of 3-year clinical outcomes using trajectories of serum albumin was higher than that of its baseline. The presented results in Table 4 show that lower BMI, longer time on CAPD, diabetes mellitus, and previous HD were significantly associated with low serum albumin over time ($P < 0.05$).

5. Discussion

The current retrospective cohort study revealed an important relationship between the trajectories of serum albumin and the 3-year outcomes (mortality, transfer to HD, and transplantation) using a novel approach of joint modeling of longitudinal and survival data among patients undergoing CAPD. Furthermore, the predictability of the 3-year outcomes using baseline and trajectory serum albumin was compared. Based on the criteria of C-index and IPE, adjusted model with trajectory serum albumin was the best model for each of the 3 outcomes. This is most likely explained by the fact that to compute these criteria, joint modeling used the available longitudinal information of serum albumin up to a time point of interest while the Cox regression used only the values of baseline.

Although other studies also found the association between the changes in serum albumin level over time and outcomes of patients undergoing PD, the powerful statistical models were not used to analyze these changes. A study by Jones et al., showed the effect of the changes in mean serum albumin between the first and second 6 months on survival of the patients undergoing CAPD as well as technique using the Cox regression model adjusted by age and presence or absence of a systemic disease (18). Chiu et al., by a 15-year follow-up study, identified that difference between peak with initial albumin after PD adjusted age, preexisting diabetes, CVD, BMI, and initial albumin could affect patients' survival rate using a Cox regression model (12). Mehrotra et al., evaluated the effect of change in serum albumin level on outcomes of the patients undergoing PD; changes in serum albumin level was calculated as the difference between the 6-month value from the time of entry into the cohort and the baseline value (19). In general, longitudinal information of serum albumin is actually collected intermittently and with error at a set of few time points for each patient. Therefore, to measure the effect of this covariate on the risk for an event, joint modeling estimated the true and the unobserved value of the trajectories of serum albumin at each time point approximated by the linear mixed model (20, 21, 26, 27).

At the present time, it is well established that early kidney transplantation is associated with optimal outcomes in the survival of patient and graft (28). The study by Molnar et al., showed that lower serum albumin before trans-

Table 2. Comparison Between Baseline and Trajectories of Serum Albumin to Predict the Three-year Clinical Outcomes in the Patients Undergoing CAPD

Outcomes\Criteria	Serum Albumin	C-Index		IPE	
		Unadjusted	Adjusted[a]	Unadjusted	Adjusted
All-cause mortality	Baseline	0.611	0.491	0.308	0.289
	Trajectory	0.729	0.822	0.093	0.088
Transfer to HD	Baseline	0.492	0.406	0.323	0.338
	Trajectory	0.611	0.656	0.060	0.060
Transplant	Baseline	0.476	0.546	0.341	0.288
	Trajectory	0.5028	0.7691	0.033	0.033

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; IPE, integrated prediction error.
[a]Models adjusted for age, gender, history of hemodialysis, body mass index, baseline serum creatinine level and comorbidities of cardiovascular disease and diabetes mellitus.

Table 3. Association Between the Baseline and Trajectories Serum Albumin and Clinical Outcomes in Patients Undergoing CAPD

Outcomes	Serum Albumin	Unadjusted				Adjusted[a]			
		Estimate	SE	P Value	HR	Estimate	SE	P Value	HR
All-cause mortality	Baseline	-0.574	0.563	0.150	0.563	-0.434	0.648	0.154	0.648
	Trajectory	-1.269	0.423	0.003	0.281	-0.895	0.433	0.039	0.409
Transfer to HD	Baseline	-0.635	0.320	0.047	0.530	-0.664	0.327	0.042	0.515
	Trajectory	-1.150	0.464	0.013	0.317	-1.297	0.483	0.007	0.273
Transplantation	Baseline	1.054	0.649	0.104	2.868	0.490	0.358	0.170	1.633
	Trajectory	0.995	0.586	0.090	2.705	1.222	0.575	0.033	3.394

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; HR, hazards ratio; SE, standard error.
[a]Models adjusted for age, gender, history of hemodialysis, body mass index, baseline serum creatinine level and comorbidities of cardiovascular disease and diabetes mellitus.

Table 4. Effect of Time on CAPD, Demographic, and Clinical Variables on Trajectories of Serum Albumin Using the Joint Modeling

Variables	Estimate	SE	P Value
Time on CAPD (month)	-0.010	0.001	< 0.0001
Age (year)	-0.002	0.002	0.290
Gender (male)	0.027	0.062	0.657
BMI (kg/m^2)	0.011	0.005	0.040
Serum creatinine (mg/dL)	0.010	0.007	0.146
Previous HD	-0.190	0.066	0.004
Diabetes mellitus	-0.113	0.066	0.090
Cardiovascular disease	-0.057	0.072	0.430

Abbreviations: BMI, body mass index; CAPD, continuous ambulatory peritoneal dialysis; HD, hemodialysis; SE, standard error.

plantation was associated with higher delayed graft function risk and increased all-cause and cardiovascular mortality and graft loss (29). In the current study, the majority of patients were transplanted in the first year after CAPD, and also an increase in serum albumin over time was associated with the increased risk of transplant loss. It may be explained by the serum albumin decline during time; therefore, in the early months, patients in the current study had a high amount of serum albumin. Another explanation might be that the transplant-waitlisted patients undergoing CAPD improved their nutritional status.

The current study found that a decrease in serum albumin level over time was associated with an increased hazard of transfer to HD in the patients undergoing CAPD. This is most likely explained by the fact that in the current study, the main cause of transfer to HD was peritonitis, and several other studies previously showed an association between serum albumin levels and subsequent risk of peritonitis (1, 13, 30-33).

The current study also showed that the increase of serum albumin over time was significantly associated with mortality in patients undergoing CAPD, which was consistent with the findings of previous studies (12, 19, 34). Although low serum albumin is often related with severe clinical disease states, the epidemiological association to mortality is intrinsically based on the low serum albumin and poor outcomes (35).

The serum albumin at the start of dialysis may be influenced by pre-existing morbidity. The early prediction

that patients with low albumin had the greatest risk of failure on CAPD might allow the development of strategies to intervene prior to treatment failure (18). The results of the current study statistically demonstrated that the predictability of 3-year outcomes using trajectories of serum albumin were higher than baseline albumin in the patients undergoing CAPD. To the authors best knowledge, there was no study on the comparison of predictability for these models.

Using the stepwise multiple regression model, Blake et al., showed that diabetes, lower body weight, and shorter time on CAPD were powerful predictors for low serum albumin (36). In general, the approach to joint modeling of longitudinal and survival data indicated the association between a time-dependent marker and survival time and determined predictors of the time-dependent marker. Using joint modeling, the current study findings indicated that diabetes and lower BMI were also associated with low serum albumin over time, but serum albumin decreased over time in the patients. This contrast might be explained by differences in the study design, health status of patients, and the history of comorbidities not considered to them. The current study also showed that the patients who transferred from HD to CAPD, on average, had lower serum albumin than the ones starting with CAPD, which was similar to the findings of the study by Nessim et al. (37).

There were some limitations on the current study. First, the study was carried out on the patients of a single center, and therefore, it may include a center-specific effect. On the other hand, it can also be an advantage that the data originated from one dialysis care provider that had uniform patient management practices; all laboratory measurements were performed in one facility. Hence, measurement variability was minimized (38). Second, the current study was a time-dependent analysis based on a 3-year period of the cohort, rather than complete longitudinal follow-up over many years; therefore, it may not apply to long-term survival of individuals. Nonetheless, the narrow time window of the current study guaranteed that confounding by changes in practice or technology was minimal (38). Third, the current study did not examine mortality by cause as the majority of deaths were from CVD; therefore, the study regarded all-cause mortality.

A major strength of the current study was the use of joint modeling of longitudinal and survival data to examine the effect of serum albumin over time on the 3-year outcomes while controlling the demographic and clinical characteristics. In principle, time-varying covariates can be added to the time-dependent Cox model. However, this requires to continuously measuring all time-varying covariates without measurement error, which is the only possibility in the special cases. An important advantage of joint modeling is its ability to handle irregularly and imperfectly measured time-varying covariates correctly (20, 21).

5.1. Conclusions

The findings of the current study showed that controlling serum albumin over time in the patients undergoing CAPD, particularly the ones with a history of diabetes and HD, can help to prevent or modify the clinical outcomes during the PD period.

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Footnotes

Authors' Contribution: Study design and data collection: Mehri Khoshhali, Shiva Seirafian, and Sayed Mohsen Hosseini; statistical analysis and interpretation of data: Mehri Khoshhali, Iraj Kazemi, Sayed Mohsen Hosseini, and Shiva Seirafian; drafting of the manuscript and revision: Mehri Khoshhali, Iraj Kazemi, Sayed Mohsen Hosseini, and Shiva Seirafian.

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