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Effect of Lipid Abnormality on CKD Progression from Moderate to Severe Stage: Application of Flexible Parametric Proportional-Hazards and Proportional-Odds Models

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Abstract

Background: Lipid disorders are a well-documented risk factor for chronic kidney disease (CKD), but the impact of lipid abnormalities in the progression of the disease remains mixed.
Objectives: The current study aimed to extend the existing knowledge about the effect of lipid disorders in disease progression from moderate to severe stage using Flexible parametric survival models.
Methods: This retrospective cohort study included 308 moderate CKD patients who received the nephrologist follow-up visits at the nephrology clinic, Ilam (Iran), from 2012 to 2019. The survival time was determined based on the time medically diagnosed with moderate stages (GFR = 59 - 55 mL/min per 1.73 m^2) to the time of progression to the severe stage (GFR = 29 - 25 mL/min per 1.73 m^2) hazard using flexible parametric survival models.
Results: In univariate analysis, high levels of TG, LDL, and cholesterol were important risk factors which affect the CKD progression. The hazard of patients with TG > 200 mg/dL was 1.69 times higher than patients with desirable TG levels (P = 0.09). Moreover, for patients with LDL > 160 mg/dL, the hazard was 2.12 times higher than patients with desirable LDL levels (P = 0.01). The hazard of patients with total cholesterol levels > 240 mg/dL was 2.10 times higher than patients with desirable cholesterol levels (P = 0.003). The adjusted model was shown to better fit the PH model. Cholesterol levels > 240 mg/dL remains a significant risk factor for CKD progression (P = 0.03).
Conclusions: Effective treatment programs should pay closer attention to screening and treatment of hyperlipidemia in patients diagnosed with moderate CKD.

Keywords: Lipid Disorders, Iran, Flexible Parametric Model, Proportional Hazards Model, Proportional Odds Model

1. Background

Chronic kidney disease (CKD) is a worldwide public health problem that imposes a significant financial burden on healthcare systems. CKD is broadly defined as a renal impairment that results in an estimated glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2 persisting for more than 3 months. It has 5 stages: stage 1 with a normal or high GFR (GFR > 90 mL/min/1.73 m^2), stage 2 or mild CKD (GFR = 60 - 89 mL/min/1.73 m^2), Stage 3 or moderate CKD (GFR = 30 - 59 mL/min/1.73 m^2), stage 4 or severe CKD (GFR = 15 - 29 mL/min/1.73 m^2), and stage 5 or end-stage CKD (GFR < 15 mL/min/1.73 m^2) (1). GFR is estimated using the modification of diet in renal disease (MDRD) formula as following (2).

GFR = 186 × (SCr) - 1.154 × (Age) - 0.203 × (0.742 if female) × (1.210 if African - American).

CKD is a worldwide public health problem that its incidence and prevalence are rising. Nearly 10% of the global population is affected by CKD (3). Mainly due to the dramatic increases in atherosclerosis and type 2 diabetes (4). The overall prevalence of CKD in the Iranian general population is 15.1%, which is much higher than the average

global prevalence of CKD (5). CKD is a progressive condition that can lead to significant mortality and morbidity and is commonly asymptomatic in the early stages. Thus, the overall prevalence of the disease is likely to be higher than expected (5).

CKD has several risk factors that may contribute to both structural and functional damages. Epidemiologic studies have reported several independent risk factors for the progression of CKD, including diabetes, hypertension, cardiovascular disease (CVD), and aging. A growing body of evidence indicates that CKD tends to be diagnosed in the presence of one or more comorbidities (6, 7). The burden of comorbidities and the costs of caring for patients with CKD are enormous. Slowing the progression of CKD is, therefore, a major public health problem. There is an urgent need for more studies with the aim of early CKD identification, screening, monitoring, and treatment.

Estimates on the prevalence of lipid disorders in CKD patients range from 0% to 60%, of hypertension ranging from 60% to 95%, of diabetes of 40%, and cigarette smoking ranging from 30% to 60% (8). Lipid disorders are common complications of the progression of kidney disease. Various studies suggested a role for lipid disorders in the development and progression of CKD. In population-based studies, higher levels of triglyceride, LDL, and lower levels of HDL are associated with an increased risk of progressive CKD (6-11).

Lipid disorders are a well-documented risk factor for CKD, but the impact of lipid abnormalities in the development and progression of the disease is not clear yet. This might be due to the application of different statistical methods, which may have led to misleading conclusions (12). The main purpose of this study was to evaluate the effect of lipid disorders in CKD progression from the moderate to the severe stage using flexible parametric survival models. A wide variety of statistical methods can be effectively used for survival analysis. Two primary methods to estimate the true underlying survival curve are the parametric and Cox semi-parametric regression models, although these models have limitations. In the Cox model, the proportional hazard assumption (PH) must be held. On occasions, this assumption is breached, therefore, estimates derived from the Cox model will lead to incorrect results and noisy estimates of hazard and survival functions (13). Parametric models typically provide smooth estimates and reduce the chance of artifacts of the hazard and survival functions (14). But these models may not fit the data well enough (15). To the best of our knowledge, Flexible parametric survival models have not been used to explore the effect of lipid disorders in CKD progression. In these models, the hazard function is flexible and goes in a different direction with time and fits the data well enough. In fact, these models adapt themselves to increase or decrees hazards in many real-life datasets (16, 17).

2. Objectives

In this study, covariates' effects were evaluated based on proportional-hazards or proportional-odds scales. The main purpose of the current study was to find out whether lipid disorders are independently associated with the progression of CKD from moderate to severe stage, adjusted for other covariates.

3. Methods

3.1. Research Setting

This study was conducted in a single-centered nephrology clinic located within an academic teaching hospital in the city of Ilam (Iran). The hospital has a daily outpatient nephrology clinic that, on average, serves 15 patients. This clinic is currently the only leading medical service available to Ilamain patients with CKD.

3.2. Research Design and Participants

This retrospective cohort study investigated 308 moderate CKD patients who received the nephrologist follow-up visits at the nephrology clinic, Ilam (Iran), from 2012 to 2019. The time of stage 3 CKD diagnosis is an important factor in this survival analysis. The inclusion criterion was the diagnosis of stage 3 CKD (GFR = 59 - 55 mL/min per 1.73 m^2) as recorded on the medical record of the patient. Patients with the following properties were excluded: having a GFR < 55 mL/min per 1.73 m^2, having acute kidney stones, having acute kidney injuries, and having acute kidney disorders. Besides, patients were excluded if the time of diagnosis of stage 3 CKD was not available, or had systematic diseases at the time of diagnosis or were unable to provide written informed consent, and cases that experienced rapid progression from stage 3 CKD to end-stage renal disease (ESRD) during the data collection process were also excluded.

The survival time of the patients was determined using the time medically diagnosed with moderate stages with GFR = 59 - 55 mL/min per 1.73 m^2 to the time of progression to the severe stage with GFR = 29 - 25 mL/min per 1.73 m^2. We performed interval censoring in the calculation of GFR (a difference of minimum 4 points in GFR values was considered as clinically relevant moderate CKD diagnosis). An average of almost 2 medical visits every month was made to each patient. Laboratory data were recorded during each visit. In this study, we had multiple outcome variables. The sample mean of covariate and categories of the covariate was computed.

3.3. Measurements

3.3.1. Laboratory Measures

For the blood tests, 5 cc of fasting venous blood was taken after an overnight fasting period. Whole blood levels of fasting blood sugar (FBS), hemoglobin, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and phosphate were measured.

Lipid profile depends on the level of kidney function and the degree of proteinuria. The lipid abnormalities in patients without nephritic syndrome and non-dialysis dependent CKD is characterized to be undesirable if be as follows: total cholesterol > 240 mg/dL, LDL > 130 mg/dL, HDL < 35 mg/dL, and TG > 200 mg/dL (18).

3.3.2. Urinary Analysis

24-hour urinary protein excretion was measured at each visit during the study period.

3.3.3. Clinical Measures

Blood pressure was measured after subjects were in a quiet, seated position for 5 minutes with a cuff placed on their dominant arm at the same vertical height as the heart. Both systolic and diastolic blood pressure were recorded separately.

3.3.4. Socio-Demographic and Medical History

The following socio-demographic variables were recorded: age, gender, smoking status, family history of CKD, CVD, history of receiving statin, and Gemfibrozil.

3.4. Statistical Analysis

All data were analyzed using Stata version 12 (STATA Corporation, College Station, TX). The Hazard ratio, odds ratio, and 95% confidence intervals were reported. A P value of < 0.05 was considered as statistically significant, with two-tailed values. Values are expressed as mean $\pm$ SE for continuous variables or N (%) for categorical variables. We incorporated a cubic spline function to approximate complex hazard function in the analysis of the time to event data. The effect of lipid abnormalities on CKD progression was evaluated using Flexible parametric survival models. Models were fitted using two various scales: proportional hazards (PH), and proportional odds (PO) with a 2 to 5 degree of freedom (1 and 4 knots). The Knots or cut points, placed at symmetric centiles of the predictor distribution (17). Based on the degree of freedom and the lowest level of AIC, a fitted PO or PH model was selected for analysis. Data were better fitted by the PH model (df = 5) in multivariate analysis. All of the measured variables, except for LDL (because of its close collinearity to cholesterol: correlation coefficient 0.75), were entered into the multivariate-adjusted analysis model.

4. Results

4.1. Participant's Disposition

This retrospective cohort study was conducted on 308 patients with moderate CKD who received the nephrologist follow-up visits at the nephrology clinic in Ilam (Iran) from 2012 to 2019. During the follow-up period, 182 patients reached the severe stages of the CKD. Nearly 92% of the study participants completed the study. The main reason for the loss to follow-up was migration to out of the study catchment area and the consequent loss of contact.

4.2. Characteristics of the Study Participants

The mean age of participants was 54.8 $\pm$ 0.9 years, and more than half of them were male (55.8%). The majority of participants had a history of hypertension (92.2%), followed by diabetes mellitus (47.2%), CVD (36%), and family history of CKD (8.1%). More than three-quarters of the patients had no history of smoking (87%). Participants were characterized by high levels of cholesterol (196.6 $\pm$ 5.3) and triglyceride 216.7 $\pm$ 10. The average systolic and diastolic blood pressure of participants was 145.5 mmHg $\pm$ 1.5 and 86 mmHg $\pm$ 0.9, respectively. Less than half of study participants (46.2%) had a history of using statin and 14.5% Gemfibrozil to control their hypercholesterolemia and hypertriglyceridemia, respectively.

The exposure of interests were CKD progression and time-varying lipid profile levels. The CKD stages were treated as a categorical variable and divided into 2 categories: failure (those who progressed to severe CKD stage); and non-failure (those who had moderate CKD stage). There were significant differences concerning the LDL, TG, and Cholesterol levels between failure and non-failure groups.

According to the flexible model and Kaplan-Meier curves, the median survival time was 33 months (Figures 1 and 2). We observed an increasing trend in the shape of hazard function across CKD stages 3-4, which suggests that hazard function increases with the progression of CKD stages (Figure 3). Participants in the failure group were younger (mean age: 54.2 $\pm$ 1.1) compared to the non-failure group (mean age of 55.7 $\pm$ 1.3). Participants in the failure group had a high prevalence of hypertension and diabetes compared to the non-failure group. The failure group had high levels of TG, Cholesterol, LDL, FBS, Phosphate, 24-hour urinary protein excretion, and lower HDL compared with the non-failure group.

4.3. Application of Flexible Parametric Survival Models

The proportion hazards assumption in the Cox model was confirmed by a graphical check using a Kaplan-Meier

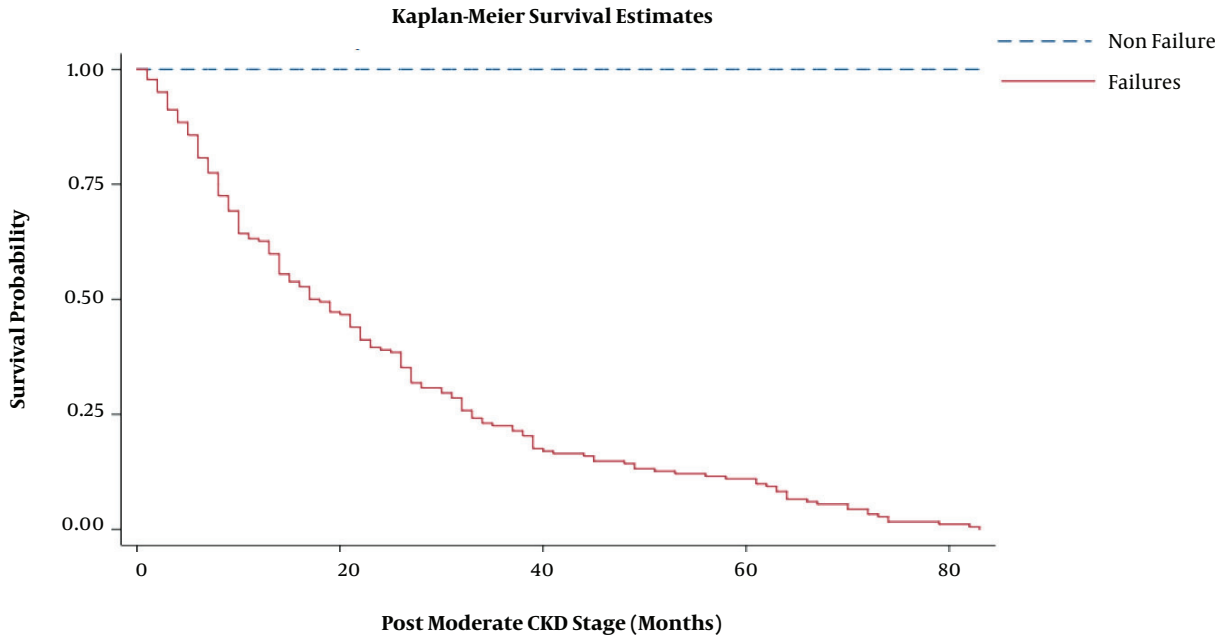

Figure 1. Kaplan-Meir estimated median of survival time for transition from moderate to severe CKD.

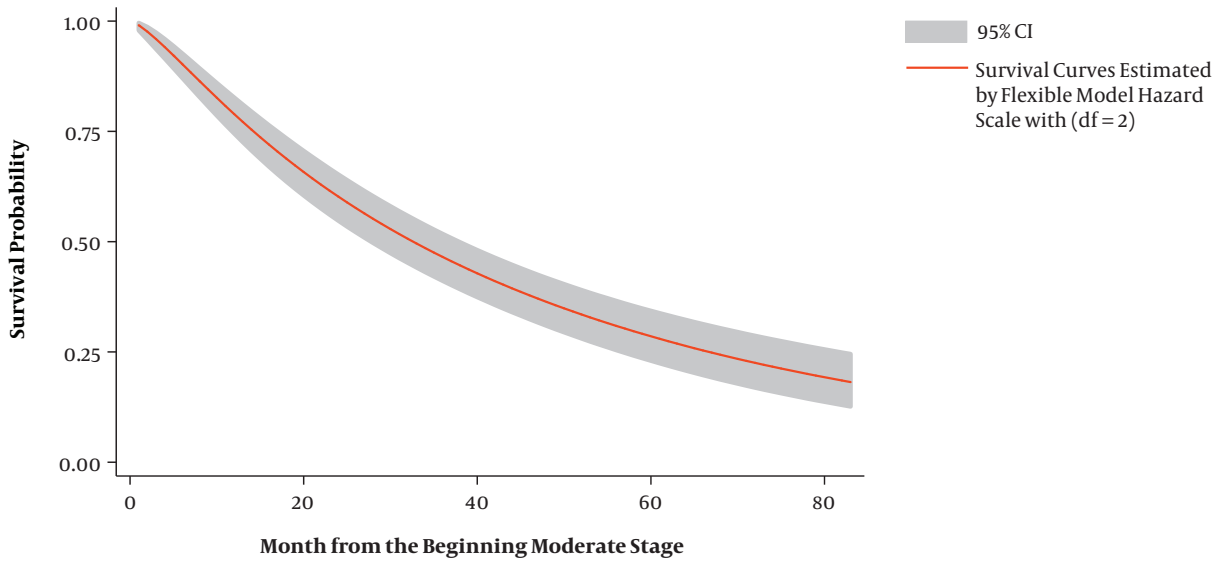

Figure 2. Survival probability, with pointwise 95% CIs, estimated by a flexible parametric survival model.

plot. All covariates, except cholesterol and TG, hold the PH assumption. Data did not satisfy the underlying assumptions required for the Cox PH model, which is why we used flexible parametric survival models as an alternative survival model. Flexible parametric survival models were applied with a 3 degree of freedom cubic splines for the baseline covariates selected for the final models to capture the shape of the underlying hazard function. The minimum Akaike Information Criteria (AIC) was used to select the best model.

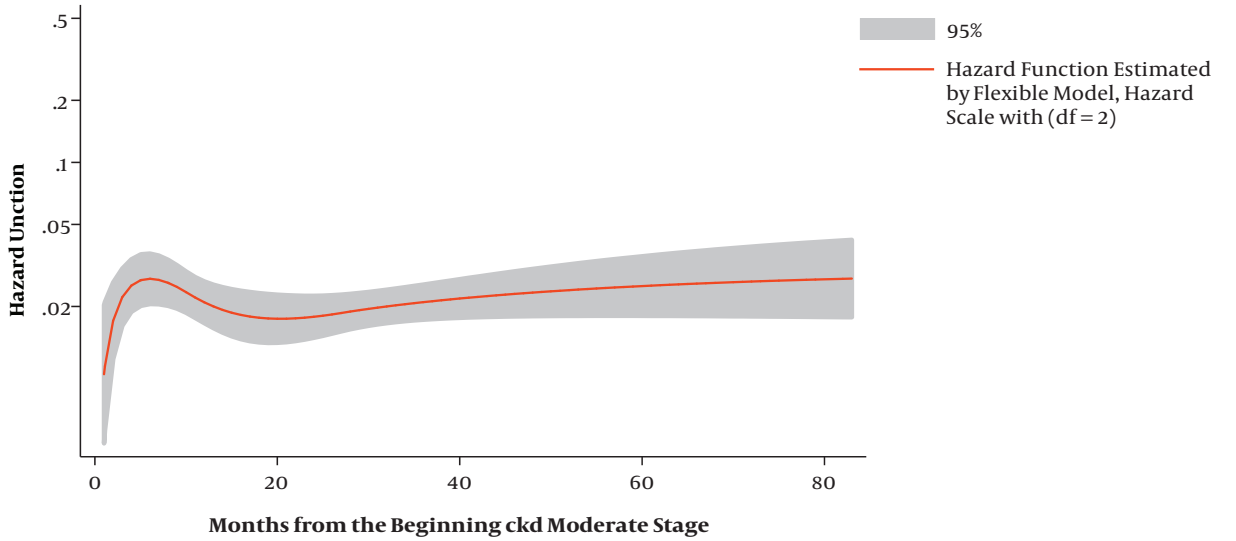

Figure 3. Hazard functions estimated, with point wise 95% CIs, estimated by a flexible parametric survival model.

4.4. Prognostic Factors for CKD Progression, Univariate Analysis

The AIC analysis indicated that the PO model (AIC = 784.2, df = 3) provided better fits to the data when excluding covariates. The proportional hazard is a more appropriate scale for total cholesterol and LDL effects than proportional odds (Table 2). High levels of cholesterol (> 240 mg/dL) and LDL (≥ 160 mg/dL) were found to be a risk factor for transition from moderate to severe CKD. The hazard for patients with total cholesterol levels > 240 mg/dL was 2.10 times higher for patients with desirable cholesterol levels. The PO model revealed a significant association between TG and progression of CKD to severe stage. Patients with TG levels 200 - 400 mg/dL had a hazard 1.69 times higher for the patients with desirable TG levels (odds Ratio = 1.69 (95% CI, 0.92 - 3.00, P = 0.09). The analysis did not reveal a significant association between HDL levels and the progression of CKD to the severe stage. This variable was fitted in the PO model (Table 2).

4.5. Prognostic Factors for CKD Progression, Multivariate Analysis

Variables with a P value of less than 0.05 in the univariate analysis were included in the multivariate model. A multivariate model adjusted for gender, smoking status, hemoglobin level, 24-hour urinary protein excretion, and systolic and diastolic blood pressure was performed. PH model has the lowest AIC, which was estimated to fit the data set (AIC of -147.1, df = 5). CKD patients with high cholesterol level (i.e. > 240 mg/dL) had an adjusted hazard ratio of 3.1 (95% CI, 1.12 - 8.15, P = 0.03) compared to those who had desirable cholesterol levels. Hence, a cholesterol level > 240 mg/dL is a significant risk factor for CKD progression (Table 3).

5. Discussion

In this paper, we evaluated the effect of Lipid disorders on CKD progression from moderate to severe stage, using Flexible parametric PH and PO models. Lipid disorders are important modifiable risk factors for CKD progression. Recent epidemiologic data suggested that both the incidence and prevalence of lipid abnormalities in CKD patients are increasing worldwide. To date, many studies have reported an association between lipid disorders and risk of CKD progression, but the findings often show mixed results and do not provide a clear, conclusive result (2, 19-26). These differences can be attributed to various characteristics of the study population, sample size, follow-up duration, prescribed medications, and applied methodological approaches. Augmentation reports in the literature indicate that all patients with CKD are at increased risk of developing CVD regardless of their underlying risk factors. Lipid disorders are the leading risk factor for CVD in CKD patients. More importantly, CVD remains the leading cause of death in CKD patients (27). The survival time of patients was estimated using the time medically diagnosed with moderate stages (i.e., GFR = 59 - 55 mL/min per 1.73 m^2) to the time of progression to the severe stage (GFR= 29 - 15 mL/min per 1.73 m^2).

The median survival time was 33 months. During the follow-up period, half of the patients progressed to the

Table 1. Baseline Characteristics of the Total Cohort Sample, Non-Failures, and failures, Who Subsequently Developed a Severe CKD and P Value for Cox PH Model[a]

Variables	Total Cohort (N = 308)	Non-Failures (Moderate CKD Stage) (N = 126)	Failures (Severe CKD Stage) (N = 182)
Age (years)	54.8 ± 0.9	55.7 ± 1.3	54.2 ± 1.1
Gender			
Male (%)	55.8	63.5	50.5
Female (%)	44.2	36.5	49.5
Family history of CKD (%)	8.1	6.5	9.5
CVD (%)	36	40	33.5
Hypertension (%)	92.2	89	94.5
Diabetes mellitus (%)	47.2	44.8	49
Diastolic blood pressure (mean ± SE)	86 ± 0.9	82.6 ± 1.2	88.3 ± 1.3
Systolic blood pressure (mean ± SE)	145.5 ± 1.5	138 ± 1.8	151 ± 2.2
Laboratory data			
Hemoglobin (g/dL) (mean ± SE)	12.6 ± 0.1	13.5 ± 0.15	11.9 ± 0.17
Phosphate (mg/dL) (mean ± SE)	3.97 ± 0.05	3.8 ± 0.08	4.1 ± 0.06
FBS (mg/dL) (mean ± SE)	126.6 ± 3.2	119.1 ± 3.9	131.7 ± 4.6
24-hour urinary protein (mg) (mean ± SE)	960.9 ± 85.3	572.8 ± 66.6	1320.8 ± 144
Total cholesterol (mg/dL) (mean ± SE)	196.6 ± 5.3	187.3 ± 7.1	205.3 ± 7.6
HDL-cholesterol (mg/dL) (mean ± SE)	48.6 ± 1.2	49.5 ± 1.5	47.3 ± 1.8
LDL-cholesterol (mg/dL) (mean ± SE)	102.1 ± 1.9	99.6 ± 2.5	103.8 ± 2.6
Triglyceride (mg/dL) (mean ± SE)	216.7 ± 10	201.5 ± 14.7	233.8 ± 13.2
Smoking status			
Non-smoker (%)	87.01	88.46	86.27
Ex-smoker (%)	4.76	6.41	3.92
Smoker (%)	8.23	5.13	9.8
Medication Prescription			
Statin (%)	46.2	47.9	44.9
Fibrate (%)	14.5	10.5	18.8

Abbreviations: Failures, patients who are still in the moderate stage, and have not progressed to the severe CKD stage; non-failures, patients who have progressed to the severe stage of CKD; Ex-smoker, quit smoking

[a]Cox PH model was used to compare the hazard of CKD progression for continuous and desecrate variables.

severe stage. In univariate analysis, cholesterol (> 240 mg/dL), LDL (> 160 mg/dL), and TG (> 200 mg/dL) were found to be significant risk factors for CKD progression.

In the ARIC study, elevated baseline creatinine was associated with increased TG levels and decreased HDL levels (9). Epidemiological studies have reported that the incidence of CKD is associated with increased TG as well as decreased HDL levels (25).

As reported in the MDRD study, lower HDL levels were independently associated with the CKD progression and decline in GFR (6). In contrast, our analysis did not reveal any significant difference between HDL levels and CKD progression. It can be attributed to the issue that most of the participants of the current study had desirable HDL levels (> 35 mg/dL). The previous study reported that individuals with HDL < 30 mg/dL had a 10% - 20% higher risk of CKD progression compared with individuals with desirable HDL levels (28).

The atherosclerosis risk in community study (ARIC) showed that high triglyceride levels were associated with an increased risk for progression of kidney disease (9). In contrast to the results of previous studies, we did not find a significant association between TG levels and CKD progression in the adjusted PH model. A possible explanation could be that participants of the current study had borderline TG levels (216.7 ± 10) at baseline. Moreover, almost a

Table 2. Discrimination Among Proportional Hazards and Proportional Odds Models, Using Akaike Information Criteria (AIC) (N = 308)[a]

Model No.	Variables Name	The Goodness of Fit Criteria	Proportional Hazards (PH)				Proportional Odds (PO)				Best Model
			d.f. = 2	d.f. = 3	d.f. = 4	d.f. = 5	d.f. = 2	d.f. = 3	d.f. = 4	d.f. = 5	
1	Without covariate	AIC	786.2	785	787.1	789.1	788.9	784.2	786.1	787.5	PO (d.f.=3)
2	Total cholesterol	AIC	411.1	412.1	414	415.2	414.3	414.6	416.4	417.7	PH (d.f.=2)
3	HDL-cholesterol	AIC	787.1	786	788	790	789.4	784.8	786.7	788.2	PO (d.f.=3)
4	LDL-cholesterol	AIC	781.6	780.1	782.2	784.1	786.2	781.1	783.1	784.6	PH (d.f.=3)
5[b]	Triglyceride	AIC	383.7	384.3	385.7	385.9	384.1	382.7	383.9	381.8	PO (d.f.=5)
6[c]	HB, FBS, smoking, TG, Total cholesterol, sex, phosphate, systolic blood pressure, diastolic blood pressure, and 24-hour urinary protein	AIC	148.1	149.5	148.8	147.1	150.6	152.1	151.4	150.1	PH (d.f.=5)

Abbreviation: d.f., degrees of freedom (specifies the df for the restricted cubic spline function used for the baseline hazard rate).
[a] AIC = -2LL+2P, where p is the number of parameters in the model,
[b] Model number 5 is the best-fitted model
[c] Adjusted Model

Table 3. Unadjusted Univariate Analysis Using Proportional Hazards and Proportional Odds Models for Lipids Profile (the First Category is Considered as a Reference Group).

Variables	Non-Failure (%)	Failure (%)	Exp β (95% CI)	P Value	Best Model
LDL-cholesterol level (mg/dL)					PH (d.f. = 3)
Desirable (< 130)	89.68	80.11	1	-	
Moderate risk (130 - 159)	7.94	11.60	1.22 (0.76 - 1.94)	0.39	
High risk (> 160)	2.38	8.29	2.1 (1.18 - 3.42)	0.01[a]	
Triglyceride level (mg/dL)					PO (d.f. = 5)
Desirable (< 200)	60	40	1	-	
Moderate risk (200 - 400)	33.68	51.76	1.69 (0.92 - 3.09)	0.09[a]	
High risk (> 400)	6.32	8.24	1.53 (0.51 - 4.67)	0.45	
HDL-cholesterol level (mg/dL)					PO (d.f. = 3)
Desirable (> 35)	89	85.2	1	-	
Low (< 35)	11	14.8	1.72 (0.69 - 4.31)	0.25	
Total cholesterol level (mg/dL)					PH (d.f. = 2)
Desirable (< 200)	67.8	47.3	1	-	
Moderate risk (200 - 240)	19.6	23.7	1.23 (0.74 - 2.10)	0.43	
High risk (> 240)	12.6	29	2.10 (1.29 - 3.36)	0.003[a]	

Abbreviations: PH, proportional hazards; PO, proportional odds; failure, patients who were progressed to the severe stage of CKD; non-failure, have not progressed to the severe CKD stage; Best model, the model with lowest AIC; d.f.; degrees of freedom (specify the df for the restricted cubic spline function used for the baseline hazard rate); HR, hazard ratio; exp β, for models on the scale (hazard) this gives hazard ratios and on the scale (odds) this gives odds ratios for non-time-dependent effects
[a] Significant

fifth of participants (14.5%) were using Gemfibrozil to control hypertriglyceridemia. Probably the protective effect of anti-hypertriglyceridemia agents had masked the true effects of TG on CKD progression.

Based on the results of the adjusted PH model, total cholesterol (> 240 mg/dL) was significantly associated

Table 4. Adjusted Multivariate Analysis Using Proportional Hazards (d.f. = 5) Model for Lipids Profile (the First Category is Considered as a Reference Group).

Variables	HR (95% CI)	SE	P Value
Total cholesterol (mg/dL)			
Desirable (< 200)	1	-	-
Moderate risk (200 - 240)	1.59 (0.58 - 4.39)	0.82	0.37
High risk (> 240)	3.1 (1.12 - 8.15)	1.51	0.03[a]
Triglyceride (mg/dL)			
Desirable (< 200)	1	-	-
Moderate risk (200 - 400)	1.03 (0.46 - 2.33)	0.43	0.93
High risk (> 400)	1.18 (0.22 - 6.32)	1.01	0.85

Abbreviations: HR, hazard ratio; Best model, the model with lowest AIC; d.f.; degrees of freedom (specify the df for the restricted cubic spline function used for the baseline hazard rate); adjusted model, adjusted for HB, FBS, smoking, phosphate, systolic blood pressure, diastolic blood pressure, and 24-hour urinary protein, sex
[a]Significant

with CKD progression from moderate to the severe stage. Our findings appear to be well supported by other studies (23, 29-31). Whereas, an analysis of data from the CRIC study indicated no significant association between cholesterol or LDL and CKD progression (50% reduction of GFR). In the current study, the univariate analysis showed a significant association in LDL levels between failure and non-failure groups. When performing multivariate-adjusted analysis, LDL was excluded from analysis because of its close collinearity to cholesterol. In the present study, most of the participants had desirable LDL levels (i.e., < 130 mg/dL). Several lines of evidence indicated that LDL levels are often in normal ranges or have decreased somehow. This could be because the LDL level is not a good predictive of CVD's risk in CKD patients (32). PH and PO flexible survival models with a restricted cubic spline were used to evaluate the effect of lipid abnormalities on CKD progression. The PH model was better fitted in the current study. The presence of lipid abnormalities increases the hazard of CKD progression from moderate to severe stage.

A strong point of this study lies in the opportunity to conduct a flexible parametric survival analysis, which allowed us to draw a clearer conclusion about the effect of lipid abnormalities on CKD progression. This study, therefore, provides additional support for the link between lipid abnormalities and CKD progression.

Analytical results of the current study can be used as practical guidelines when designing and developing a standard preventive program for CKD patients. Screening for the early detection and treatment of lipid abnormalities has an important role in preventing or delaying CKD progression and its consequent complications. Effective treatment programs should pay closer attention to screening and treatment of lipid abnormalities in CKD patients. There is still a huge gap in the evidence to support the benefits of Anti-hyperlipidemia treatment in delaying the progression of the CKD (33, 34), and further studies should be conducted to develop more effective treatment options. In short, the treatment of lipid disorders in CKD patients may have a great role in slowing the disease progression.

The main limitation of the current study was selecting participants from a single centered hospital-based clinic in Ilam city. The second limitation was the small sample size and short follow-up duration. Besides, due to limitations in access to eligible patients, participants were selected using the convenient sampling technique, which may limit the generalizability of the findings. This issue should particularly be addressed in future studies. We cannot deduce that lipid abnormalities play an important role in disease initiation rather than disease progression. Given the small sample size and hospital-based sampling technique, the results should be interpreted with caution. In this respect, it would be advantageous to have results of high quality, longer-term community-based studies with a larger sample size.

5.1. Conclusion

Based on the findings, total cholesterol level > 240 mg/dL is an important risk factor for the CKD progression from moderate to severe stage. Careful monitoring of cholesterol levels is an important strategy in patients with moderate CKD stage. Effective treatment programs should pay closer attention to screening and treatment of hypercholesteremia in patients diagnosed with moderate CKD.

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Footnotes

Authors' Contribution: A.A.M drafted the manuscript, and all authors contributed substantially to its revision.

Conflict of Interests: None.

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