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Identification of Significant Prognostic Factors of Dialysis Population

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Abstract

Chronic Kidney Disease (CKD) is becoming a dreaded disease by increasing at alarming rate every year, worldwide. Globally, incidence of treated End Stage Renal Disease (ESRD) is rising at annual growth rate of 8% and one of ten individuals has any stage of Chronic Kidney Disease. The annual mortality rate in hemodialysis patients fluctuates within 10% to 25% globally and it is a critical health issue of Pakistan. In this study, combined Prognostic influence of demographic and biochemical variables was investigated to determine the best and worst prognosis for survival of dialysis receiving patients. Variety of Survival methods, Non-parametric and Semi-parametric techniques on the questionnaire based collected data has been employed in this research. Significant Prognostic factors were derived by fitting a Cox model in both Univariate and Multivariate Analysis. After checking the Adequacy of Fitted Cox model, the prediction model has been obtained with interactions of Prognostic factors at low, medium and high levels. Hazard Ratios confirmed the overall survival benefit at high level of serum albumin, high hemoglobin, low or medium inter-dialytic weight gain and low or medium potassium simultaneous reduces Hazard Rate by 99.34%. Combined effect of low level of serum albumin and hemoglobin, high level of inter-dialytic weight gain and potassium proved as more hazardous for concerned population. Complete set of interactions of main Prognostic factors has been presented that would become more beneficial to provide insight to clinicians for better survival of dialysis population.

Keywords

Chronic kidney disease, End stage renal disease, Hazard ratio, Dialysis therapy, Inter-dialytic weight gain

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1. Introduction

The Chronic Kidney Disease (CKD) has turn into a common disorder and there is growing number of CKD patients with worldwide rising prevalence. Researchers documented the high prevalence of CKD in European, Australian and Asian studies (Chadban et al., 2003; Chen et al., 2005; De Zeeuw et al., 2005 and Hallan et al., 2006). Coresh et al. (2007) reported thatthe number of End Stage Kidney failure patients maintained on Renal Replacement Therapy either by dialysis or transplantation has raised a lot in USA from 209,000 in 1991 to 472,000 in 2004. CKD is a burden because of Renal Replacement Therapy demands as well as for overall population health.At the moment world widely, CKD is at the 12^{th} topmost cause of mortality and 17^{th} topmost cause of disability (Codreanu et al., 2006). All over the world, incidence of treated ESRD (annual counts of new patients/million population) is continuously increasing at annual growth rate of 8% while population growth rate is 1.3% (Schieppati and Remuzzi, 2005). The increasing number of patients of treated ESRD is connected with the "globally aging, multi-morbid population, the growing admission of the young population of patients in developing countries and the higher life-expectancy of currently treated ESRD patients" (Lysaght, 2002).

Pakistan is a developing country which does not have such policies to cure End Stage Renal Disease due to lack of technical, human and economic resources. Jafar (2006) reported that out of every three Pakistanis; one is suffering from any stage of kidney disease. Effective policies to prevent the progression of Chronic Renal Disease in developing countries have faced more challenges in implementations (Barsoum, 2006). In Pakistan Chronic Renal failure has emerged as a crucial medical, social and economic problem for the people suffering from this disease. CKD preventive programs including management and control of main prevalent risk factors of diabetes and hypertension are relatively nonexistent. Unawareness of common people or poor symptomatic medical practice leads Chronic Kidney Disease towards End Stage Renal Disease and consequently patients have to bear the costly Renal Replacement Therapy. According to the Dialysis Registry of Pakistan (2008) 6351 patients in 175 Centres are being dialyzed in Pakistan (Naqvi, 2009).

Hemodialysis (HD) is the mainstay of Renal Replacement Therapy all over the world. In spite of the use of some other methods, above 1.7 million patients are treated with HD in about 28, 500 dialysis units globally. The HD population was estimated to grow to 2.0 million in 2010 (Floege et al., 2010). In economically

privileged patients of CKD, only 10% can meet the expenses of dialysis. insufficient dialysis, infections and malnutrition are the major causes of high mortality among CKD patients globally (Barsoum, 2006).

In spite of significant advances in dialysis technology, the annual death rate in HD patients fluctuates within 10% to 25% globally, might be a result of demographic, geographic, cultural, economic and genetic factors differences (Floege et al., 2010). High prevalence of CKD and costly treatment of dialysis therapy made Chronic Kidney Disease a critical health issue of Pakistan. The growing Burdon of Chronic Kidney Disease patients need dialysis, and still their poor Survival Rateare signs of importance of statistical inferential research in the field of nephrology. Thus importance is evident of identifying the significant Prognostic factors for the better survival of this vital public health problem of those patients who somehow made it possible to access the costly dialysis sessions as Renal Replacement Therapy. Up till now, physicians have done few descriptive researches related to causes of kidney failure and quality of life of dialysis patients, but there is rare chance of any documented statistical inferential work, regarding exploration of Prognostic factors, done by statisticians in Pakistan. The intent of the present study is to clarify Prognostic factors for adverse outcomes while accounting for the time varying covariates by usingSurvival techniques. In this research, variety of Survival methods Non-parametric and Semi-parametric techniques applied on the questionnaire based collected data. The Proportional Hazard model is establishedas the standard approach for Regression Analysis of survival time in various applied settings.Significant Prognostic factors derived by fitting a Cox model in both Univariate and MultivariateAnalysis. After assessing the adequacy of fitted Cox model the prediction model has been obtained with interactions of Prognostic factors at low, medium and high levels. Complete set of interactions of marginalPrognostic factors has been presented that would be more beneficial to provide insight to clinicians for better survival of dialysis population.

2. Patients and methods

2.1 Study population: For this research work the focused area was Punjab and population consisted of all patients, undergoing dialysis, admitted in all hospitals of Punjab, province of Pakistan. Target population consisted of all the patients of dialysis, admitted in the dialysis units of 2 divisions of Punjab, during the clinical study time of five years.

2.2 Outcome of interest and sample size: Outcome variable of interest is survival time until an event occurs. In Cohort studies one can either, fix study time or the number of events. Sample size depends on the availability of data that how many individuals are included in the study during the fixed time period. For this research, the total study time was fixed to be 5 years and data was collected retrospectively. In order to obtain reliable estimates of Survival and Hazard functions and their standard errors at each time interval, a feasible sample size of dialysis patients was taken from public sector hospitals of 2 divisions of Punjab province. Dialysis patients of 25 districts of Punjab out of 36, and combined 12 districts of Khyber Pakhtunkhwa (KPK), Northern areas and Azad Kashmir were covered by the dialysis units of hospitals of Rawalpindi and Lahore divisions of Punjab. These two divisions (Rawalpindi and Lahore) have well equipped tertiary care centres in comparison with other divisions of Punjab, easily accessible to nearby remote areas with trained staff and equipment to treat dialysis patients. That is why even patients from other cities prefer to come here weekly (once or twice) to attend dialysis sessions instead of undergoing treatment in newly established medical units in nearby districts due to lack of up to mark staff and equipment. For these reasons hospitals of these two divisions for data collection was covered. Various researchers such as (Abbott et al., 2004; Chandna et al., 1999; From et al., 2008; Herzog et al., 2005; Holland and Lam, 2000 and Pastan et al., 2002) have used hospital based data from dialysis units of Chronic Kidney Disease patients by fixed time period of study.

2.3 Retrospective / Historical Cohort study: Generally, study design comprises of two types; studies wherein subjects are kept under observation and studies where the outcomes of an intervention (treatment) are observed. The type of study design where the subjects are scrutinized is described as observational studies. Cohort study is a "forward-looking" (starting from a risk factor to an outcome) observational study where a cluster of patients are followed longitudinally over a period of time. In medical studies the patients of Cohort are chosen by some significant distinctiveness supposed of being a sign of a disease or health consequence. Numerous Cohort studies are also carried out by using previous particulars saved in records and annals. Validity of these studies is frequently dependent on medical records and memory. Several investigators such as, (Abbott et al., 2004; Chandna et al., 1999; From et al., 2008; Herzog et al., 2005; Holland and Lam, 2000; Huang et al.,2006; Pastan et al., 2002 and Slinin et al., 2005) named this type of study a Historical Cohortstudy or Retrospective Cohortstudy, due to the reason that information from previous studies is utilized in these studies and the events become apparent earlier than at the beginning of study. However in

the Historical Cohortstudy the tendency of the query is further survival time, from a probable ground or risk factor to the outcome (Dawson and Trapp, 2004).

2.4 Data inclusion criteria: All patients with Chronic Renal failure who are treated with maintenance hemodialysis at the various dialysis centers of Punjab, and have been on Hemodialysis for at least 3 months were eligible for inclusion in the present study. The Analysis was performed upon only those patients who survived for at least 90 days after undergoing hemodialysis. This study is a Retrospective follow-up study and the clinical patients were followed through the medical charts until death or 30th December 2012, whichever came earlier.

2.5 Potential Prognostic factors: Values of the studied clinical variables such as, hemoglobin, serum phosphate, serum potassium, serum albumin, serum creatinine, inter-dialytic fluid weight gain for each patient were updated every 3rd month in order to minimize the measurement variability and reduce bulk of data (Kalantar-Zadeh et al., 2009).Collected data included age, gender, date of start of dialysis, age at start of dialysis, and duration of dialysis at entry of study/months, collected by reviewing the medical records. Laboratory and clinical data included serum albumin, pre dialysis creatinine, pre dialysis urea, serum potassium, serum phosphate, hemoglobin, inter-dialytic weight gain, post dialysis weight. Also, the type of dialysis membrane, duration of dialysis hours per session and frequency of dialysis were incorporated in the dialysis prescription data. Variables, covariates and Prognostic factors are interchangeably used in this document.

3. Statistical methods

Descriptive Analysis of Prognostic factors is based on Kaplan Meier Survival functions (1958) and related computations that provide insight for demographic and clinical covariates. Continuous Prognostic factors were analysed by Cox (1975)Regression and Categorical Prognostic factors were explored by performing the Kaplan Meier and the log-rank methods for Univariate Analysis.

The Cox (1975) Proportional Hazards model or Cox Regression is a renowned Regression technique and extensively applied approach to analyze the time to event data, and to study the impact of numerous risk factors on survival concurrently. Cox (1972) proposed this approach by using an expression he referred as partial Likelihood function that means, model depends only on the parameter of interest. Cox (1972) made the supposition that yielded parameter Estimators from Partial Likelihood function hold the same Distributional properties as that of Maximum Likelihood Estimators. Foremost characteristics of

Cox (1975) modeling consists of, measure of association by the relative risk, refusal parametric assumptions, the utilization of the Partial Likelihood function, obtaining of Survival function estimates and deriving effects of numerous covariates (Collett, 2003 and Hosmer et al., 2008). Another aspect of Cox (1975) Regression is, it does not have to go for the density function of a Parametric Distribution, which implies that Cox's (1972) Semi-parametric modeling has no need for assumptions to be made about the Parametric Distribution of the survival times, which confirms that technique is obviously more robust and flexible. Instead of Parametric assumptions, the researchers have required to only confirm the assumption that the Hazards are proportional over time and the Hazard Ratio remains constant over time. The Proportional Hazards assumptions support the fact that the Hazard functions are multiplicatively related, that is the effect of a unit increase in a covariate is multiplicative with respect to the Hazard Rate. The probability of the endpoint, whatever death or recurrence of disease, is described in terms of hazard. The implementation of this modeling technique is referred by CoxProportional Hazards model, Cox Regression model,Proportional Hazards model and Semi-parametric Hazard model. Hence, Semi-parametric Regression models have fully Parametric Regression structure with unspecified time dependence (Hosmer et al., 2008).

Model based inferences completely rely on the fitted statistical model. After completion of steps of fitting the model, the adequacy and validation of that model should be assessed as an essential part of modeling process as well as careful development of model. Cox (1975) Proportional Hazard model is most extensively performed popular procedure for conducting Analysis of time to event data in clinical research. Visual inspection of data would not be informative due to several explanatory variables, and the scenario has become more complicated due to the presence of censoring and the use of the Partial Maximum Likelihood function for Proportional Hazard models. As for as, presence of censored survival times make it slightly more complex to identify features of model adequacy than analogous methods employed in Linear Regression modeling (Collett, 2003 and Wilson, 2013). Residual based diagnostics generally applied to check the adequacy of fitted Cox (1975) Model. All statistical Analysis was performed by using STATA 12 and SPSS statistical package version 17.

4. Results and discussion

4.1 Patients characteristics: To acquire the graphical display of Distribution of survival time, Histogram was plotted along with survival time and frequencies in

Figure 1. The pattern shows unimodality with positive Skewness. High peaks show the majority of events (death) occurring in starting 20 months of the total follow up time. Maximum number of deaths occurred at 3rd month after initiation of dialysis treatment.

The overall survivor function for the 5 years of survival time by using Kaplan Meier Survival Estimates is presented in Figure 2. In dialysis therapy, patient survival is undeniably the most important question. From Non-parametric Survival curve the sample median survival time for the target population is estimated approximately 11 months.

Graphs of Kaplan Meier Survival Estimates are plotted for different categorical covariates with their levels, to have understanding about their survival pattern, and proportionality. The upper survival curve shows long survival time for that particular level while the lower curve shows short survival time for corresponding level.

Comparison of the both gender groups, using Kaplan Meier Estimates is provided by a graph of Survival function. The plot of the survival probabilities is referred to as a step function. Horizontal lines show the probability of survival stay at the same point in time period, and long horizontal lines show no change in survival probability for a long period. The graph shows that the Survivor function for the females group lies above the males from 5th month of follow up to onward. This difference indicates that Females group has better survival at those follow-up times. Though, in the first 5 months of follow-up, the two Survival functions are closer together, but thereafter relatively spread apart. This widening gap suggests that the survival of females group improved later during follow-up than that of beginning point. From plot of Survival function, median survival time for female is 15 months while for male is 10 months.

Among all categories of age at start of dialysis, 2 categories “age greater than 50” and “age 40-49” exposed short survival time than other age categories. Frequency of dialysis “once” a week has shorter survival time and thrice dialysis sessions per week showed increase in survival time. It is logical that patients with no exposure of incidence of hepatitis would achieve more survival time among rest of categories but it is important finding that patients with B+ hepatitis had lower survival in comparison to C+ hepatitis. “No” hospital acquired hepatitis gave higher survival as well as both other categories B+ and C+ showed almost same survival time. “None” co-morbidity had advantage of survival for patients under dialysis and patients with “Cardio vascular diseases” had less chances of survival

as compare to other categories. Dialysis duration of greater than 24 months at entry of study revealed higher survival time for patients as compared to less than 6 months, 7 – 12 months and 13 -24 months. It shows more rapid decline of survival on the beginning of survival therapy and improvement in condition of patients later on as duration on being dialysis increased with no worsening effect of survival on increased duration of dialysis. Some major "causes of kidney failures" are summarized in one variable and it is notable that "drug induced (including Hikmatand peers prescriptions)" patients have lowest chances of survival than rest of causes upsetting the functions of kidney.

Graphical representation of Product Limit Estimate established that survival time is varying within the levels of factors. A statistical test would be useful to confirm whether Survival curves are statistically differing with each other or just due to by chance variation. Log Rank test (Nathan, 1966) is a Non-parametric test and can be used to compareSurvival curves.It is a formal method for testing hypotheses about survival, in two or more groups. By Log Rank test of categorical variables, incidence of hepatitis and gender, age at start of dialysis, frequency of dialysis, hospital acquired hepatitis, co-morbidity, causes of dialysis and dialysis duration differ significantly within their categories. It is indication of significant fluctuation of survival time among levels of categorical variables.

4.2 Univariate Analysis: Cox (1975) Regression model is used to determine the impact of potential covariates on survival time of patients by Univariate Analysis primarily given in Table 1.Univariate Analysis depicts that all variables have significant effect on survival time of patients after being dialyzed except age at start of dialysis (category 2), frequency of dialysis, incidence of hepatitis, causes of ESRD (except drug induced), Co-morbidities and serum urea. Female gender group expressed more chances of survival over male group. Younger group of patients showed greater survival than, older age patients and those who delayed to switch over to dialysis therapy. Those patients who dialysed thrice a week showed more Survival Rates as compared to those undergoing dialysis twice a week. Instead of exposure to hepatitis, hospital acquired hepatitis proved to be more hazardous for survival of patients for both B+ and C+ hepatitis. Greater dialysis duration (months) has also shown better survival than initial months of therapy. Increase in inter-dialytic weight gain, urea, potassium and phosphate cause decrease in survival time and high rate of early death, whereas increase in hemoglobin and serum albumin would reflect in increased survival.

Ours were the same findings from Univariate Analysis of each variable in relation to survival time (in years) alike with Descriptive Analysis and Kaplan Meier Survival Analysis. Univariate Analysis provided the understanding of association of survival time and each of the covariate under consideration. Simultaneous study of variables through Multivariate Analysis would clarify the consequences of significant variables that have influenced survival. Cox (1975) Proportional Hazard Regression Analysis is performed for Multivariable model building.

4.3 Assessment of adequacy of fitted Cox model: As for concern of Proportional Hazards (PH) Regression model, there are two important assumptions that need the satisfaction to allow one to trust on the statistical inferences and predictions of established model. The first assumption is called PH assumption that is, the ratio of the Hazard function for two individuals with different explanatory variables, does not differ with time, in other terms, the Hazard Ratio remains constant over time. The second assumption is about the relationship between log cumulative hazard and a continuous predictor variable (covariate), should be linear (Collett, 2003; Hosmer et al., 2008 and Wilson, 2013). Residual based diagnostics are particularly used for Cox (1975) model. Residuals are the central part of evaluation of model adequacy in all settings of Regression models. The values of residuals are calculated for each individual in the data set. Several residuals have been proposed related to Cox Regression model for evaluating specific aspect of model adequacy.

4.3.1 Test of proportionality assumption of Proportional Hazard model: Schoenfeld residuals are generally applied to discover departures from the Proportional Hazards assumption. If there exists a pattern in the plot of residuals versus survival time, then Proportional Hazard assumption will be questionable. Tests and graphical display for Proportional Hazards based on the scaled Schoenfeld residuals were proposed by Schoenfeld (1982). He proposed the initial set of residuals to check the fitted Proportional Hazard model. Grambsch and Therneau (1994) proposed that scaling the Schoenfeld residuals by an Estimator of its variance provides a residual having superior diagnostic power in comparison of unscaled residuals. As Schoenfeld residuals are based on the effects of the covariates that are supposed to be independent of time, consequently plot of these residuals opposed to time is a visually assessing method to see the effect of the covariates varying over the follow-up span. Number of procedures are found in literature to check the Proportionality assumption but Grambsch and Thernue (1994) and simulations by Ng'andu (1997) suggested an easily employed test and associated graphical representation which is a useful evaluation of this

vital assumption (Collett, 2003 and Hosmer et al., 2008). The result of test is summarized in Table 2.

The null hypothesis tests whether the Log-Hazard Ratio remains constant over time. Accordingly rejection of null hypothesis indicates deviations from the Proportional Hazard assumption. It's obvious that global 12 degrees of freedom test = 0.1868 is not significant. There is no evidence of violation of Proportional Hazard assumption. Moreover, the covariate specific test provides the details of proportionality of each covariate so that there is no chance to miss out non-proportionality of any covariate summarized in Figure 3-7. Even though the graphical method of assessment of the validity of assumption is subjective approach, still it is a supportive tool. Graphical assessment of violation of PH assumption yield the same information like statistical test, implying that PH assumption has not been violated. Appropriateness of Cox (1975) Proportional Hazard model for current data is confirmed by both test and graphical method.

4.3.2 Test of linearity assumption of Proportional Hazard model: The Martingale residuals have been recommended as promising diagnostics for the correct functional form (Therneau et al., 1990). Nonlinearity is actually incorrectly specified functional form in the Parametric part of the model and a probable difficulty in Cox (1975) Regression as it is in linear and generalized linear models. The martingale residuals are plotted versus each covariate to detect nonlinearity and functional form of that covariate. Generally the resulting graph seems to be very noisy and to ease the interpretation a *loess* or *lowess* smoothed line proposed by Cleveland (1979) has been superimposed to the plot and the form of the smoothed line indicates an Estimate of the functional form of the covariate in the model. If the smoothed line is reasonably linear, then the chosen scale considered appropriately linear in the Log-Hazard. If considerably departure of smoothed line from a linear trend exists, then the shape can give idea to correct the scale of covariate in the model (Hosmer et al., 2008 and Wilson, 2013). Nearly flat and horizontal *Lowess* smoothing line is considered sufficient for the fulfillment of linearity assumption.

Smoothed Residual Plots for Linearity of covariates are given in Figure 8-12. Martingale residuals are useful in assessing the functional form of a covariate to be included into Cox(1975) model. The smoothing lines appear in all figures almost log linear for each covariate, supporting the inclusion of untransformed version of covariates into Cox model.

4.3.3 Influential diagnostics of Cox Proportional Hazard model: Identification of unusual impact of particular observations, on inferences based on fitted model, needs to be assessed. These kinds of observations are referred as influential observations. There is approach of *delta-betas* for assessment of these suspicious observations. First the model estimated with full data set, then after omitting the effect of i^{th} observation, model is refitted to assess the effect on estimates by comparing the original measures of that full data set. Cain and Lange (1984) presented an approximation based on scale residuals. Plots of *delta-betas* for each covariate would provide better description of those observations which have substantial impact on Parameter Estimates for any particular covariate. Moreover, Plots of *delta-betas* versus rank order of survival time can present the information which has concern about influence (Collett, 2003).

From Figure 13-17 of the *Df beta*, Plots it can be identified that the observations maybe, are the influential values. We can see these observations are far away from most of the other observations and these points need particular attention. From all graphs, no influential observation is found which exceeds cut-off criterion. By examining theses values in more detail, none of the observations appeared as terribly influential individual, even though they are large values compared with others. Observation of ID 565 stands out away from all other points shown in the graphical presentation. It contains high values explained in descriptive statistics. After removal of the ID 565 the ID 620, 37 and 796 appeared as influential observations in graphs of *Df beta*. That's happened due to widening of the gap of vertical lines that some other observations appeared as influential observations. In fact these observations are not influential observations, might be shown as, due to unusual or unexpected survival behavior. For instance, in spite of better survival condition based upon clinical and laboratory tests suddenly death occurred for that patient or in reasonably bad condition prolonged life of patient, might be the reason of lying far away of these observations. It is common behavior in survival data and didn't cause much concern. Even though the removal of these kinds of observations especially in survival data is not considered a good practice, we obtained the Cox model's standard errors for the sake of comparison of with and without influential observations. The resulting differences were very small, that had no practical importance, and consequently those suspicious observations were retained in the data set.

4.3.4 Multicollinearity: Multicollinearity is also verified through method of Variance Inflation Factor (VIF). None of VIF value goes above 10, so we can conclude that no severe multicollinearity was present there between covariates.

4.3.5 Goodness of fit of final Cox Model: Goodness of Fit of Cox(1975) model is verified by the Cox-Snell (1968) residuals. The Nelson Aalen cumulative Hazard function was graphed with the calculated Cox-Snell variable, so that Hazard function to the diagonal line can be compare. If Hazard function follows the 45 degree line, then it approximately has an Exponential Distribution with a Hazard Rate of one and that model is considered appropriately fit to data. In Figure18 it could be seen that Cox model does not fit the data too badly.

4.4 Multivariate Analysis: Approach of purposeful selection of covariates to a Proportional Hazard model has been followed to search out a set of statistically and clinically significant covariates. At earliest step of fitting a Multivariable model all covariates were included, that appeared significant in the Univariate Analysis as well as those variables that have clinical importance nevertheless of their significance (Hosmer et al., 2008). Except urea, causes of ESRD and incidence of hepatitis all other variables are included in the model at this step. Results of this Multivariable model are summarized in the Table 3.

By performing Multivariate analysis, age at start of dialysis, frequency of dialysis, hospital acquired hepatitis and co-morbidities are clearly not significant and are dropped from the model step by step based on their significance level.

Hence current age, weight gain, potassium, hemoglobin, serum albumin and dialysis duration were potential candidates for being included in main effect model given in Table 6. In recent years, researchers gave attention to these clinical covariates in their studies as important Prognostic factors. Hatakeyama et al. (2013) had evaluated prognosis in Japanese hemodialysis patients aged ≥80 years. In his study, large differences of survival time also clarify the picture as low risk group had 63 months, while other groups had 23-24 months survival time. They concluded that theold age is no more considered as contraindication for initiation of hemodialysis therapy. Hatakeyama et al. (2013) findings are in line with the previous several reports by (Faller et al., 2013; Joly et al., 2003; Neves et al., 1994; Rohrich et al., 1998; Schaefer and Rohrich, 1999 and Vandelli et al., 1996) had studied indications and survival behavior of maintenance dialysis in elderly patients. Hemodialysis therapy in elder age group is now considered an established reality from recent decade. Earlier outcomes of different studies lead towards conflicting conclusions. Vandelli et al. (1996) stated that by maintenance on dialysis therapy, patients would be able to avoid the death from uraemia, but Survival Rate for such patients is substantially low in comparison to general population. The mean expected life time would remain only 9.3 years for those

who started dialysis at age of 40, and 4.3 years for those who started at age 59, compared with those of 37.4 and 20.4 years for general population for the same age. Although Survival Rate of elder patients found in some studies less than the general population, Vandelli et al. (1996) concluded that old aged patients can attain improved Survival Rate and their quality of life can be improved by taking under consideration main determinants of survival like, cardiovascular diseases, nutritional status and adequacy of dialysis treatment. Joly et al. (2003) supported the outcomes of earlier studies in favor of initiation of dialysis treatment for elder patients, like younger patients. Although patient's individual refusal, late referral, social isolation, low functional capacity, and diabetes affect the survival of elder patients but it is established reality that majority of such patients experienced a extensively prolonger life. Contradictory concluding had been made by Munshi et al. (2001) by suggesting that very old aged patients on dialysis therapy contained poor prognosis might be because of late referral to Renal Replacement Therapy (RRT) as an emergency admission, possibly could be a significant predictor for poor prognosis of RRT, suggested by also (Byrne et al., 1994; Eadington,1996; Jungers et al., 1993 and Ratcliffe et al.,1984).

Naves et al. (2011)concluded on the basis of Multivariable-adjusted Hazard Ratio that low level of serum albumin was associated with increased mortality rate. Iseki et al. (1993) also presented the similar type of relationship for serum albumin as predictor variable and the impact on survival of chronic hemodialysis patients. He identified serum albumin as strong predictor of mortality among chronic hemodialysis patients and suggested that low level of serum albumin should be cautiously treated.

For inter-dialytic weight gain Kalantar-Zadeh et al. (2009) chose Cut-off level of 1.5 kg, supported by Rodriguez et al. (2005) who suggested an inter-dialytic fluid gain less than 1.5 to 2.0 kg as the most favorable target beneficial for survival of patients. Kalantar-Zadeh et al. (2009) concluded that higher Inter-dialytic weight gain proved to be related with higher risk of death. He categorized different subgroups of dialysis patients and on the basis of outcomes suggested that inter-dialytic weight gain >1.5 kg is associated with mortality and minimum inter-dialytic fluid retention <1.0 kg had a considerable survival benefit. Researcher proposed these findings on basis of 2-year period of the Cohort instead of a longitudinal follow-up of several years, this limitation of study may have the consideration. Kalantar-Zadeh et al. (2009) concluded results by using Univariateanalysis that elevated Inter Dialetic Weight Gain (IDWG) linked with better survival, but findings of MultivariateAnalysis no longer supported the earlier findings of Descriptive Analysis. Increase in Inter-dialytic weight gain

showed association with high risk of mortality. Kimmel et al. (2000) had also found similar type of relationship between Inter-dialytic weight gain and survival. Kimmel et al. (2000) conducted an observational longitudinal study to determine the relationship of IDWG and survival, with adjustments of several medical and dialytic risk factors. Assessment of the relative death risk of higher IDWG resulted in association of higher mortality risk with higher IWG (De-Nour and Czaczkes.,1972; Manley and Sweeney., 1986; Leggat et al., 1998 and Agashua et al., 1981) employed diverse ways for defining IDWG and the level of IDWG had been reported in different studies. Kimmel et al. (2000) adopted more precise method to measure IDWG with continuously updated dry weight.Percentage of IDWG for each day in thrice a week sessions over every month was computed and average of measurements for three-month period was calculated. None of the previous study had identified the relationship between IDWG and mortality among HD patients, adjusted for numerous medical risk factors. The effect of IDWG on survival was not obvious in preceding studies. Leggat et al. (1998) stated that HD patients with more than 5.7% IDWG had a 35% higher risk of mortality, in case of missing or shortening HD sessions risk of mortality would be higher. Koch et al. (1993) in a multicenter European study did not find and documented any association of IDWG and higher mortality risk in ESRD patients who had diabetes. Lopez et al. (2005) also explored the Prognostic effect of inter-dialytic weight gain and its consequences on nutritional status. Findings of Univariate Analysis suggested that excessive IDWG related with better nutritional status and higher percentage of IDWG may be predictor of better long term prognosis of patients. Lopez et al. (2005) concluded that, higher pre dialysis IDWG had negative aspect, even though beneficial impact of IDWG upon nutritional status and prognosis is more valuable and cannot be ignored.

Kovesdy et al. (2007) examined the association between predialysis serum potassium levels and mortality. Predialysis serum potassium between 4.6 to 5.3 mEq/L was reported to be associatedwith the higher survival of patients, while potassium <4.0 or >5.6 mEq/L resulted in association with increased mortality. After adjustments results remained consistent and did not show any difference for higher serum potassium >5.6 mEq/L on death risk, consistent with the results of Bleyer et al. (1999) and Bleyer et al. (2006).

Gilbertson et al. (2008) verified the associations between the degrees of hemoglobin level variability in hemodialysis patients receiving erythropoietin therapy. Levels of hemoglobin were calcified as low L= < 11 g/dl, intermediate I = 11 to 12.5 g/dl, and high H = >12.5 g/dl. Patients whose hemoglobin levels

were constantly placed within the target range of 11 to 12.5 g/dl had lowest chances of mortality. Also the longer time duration with a hemoglobin level < 11 g/dl, resulted in higher risk of death. Furthermore, the time duration of the low hemoglobin value within the 6 months period was strongly linked with higher mortality risk. Along with, patients experiencing the least numbers of months with hemoglobin levels below the recommended range of 11 to 12.5 g/dl had chances of lowest mortality risk. The results of current study elaborated that there is significant association between particular hemoglobin variability patterns and increased risk of death. Gilbertson et al. (2008) concluded that particular exposure measurement period to be precise, number of months with values of hemoglobin below the target range, instead of hemoglobin variability itself, probably be the primary driver of improved risk of mortality. Regidor et al. (2006) explored associations between baseline hemoglobin values and survival accounted longitudinal variations in clinical and laboratory measures of maintenance hemodialysis patients. Hemoglobin levels stable at 12 to 13 g/dl were shown to be associated with greatest survival and the lower range of the hemoglobin range (11 to 11.5 g/dl) suggested by Kidney Disease Quality Outcomes Initiative was found to be associated with a higher death risk compared with the 11.5- to 12-g/dl range. Additionally independent of baseline hemoglobin, rise or drop in hemoglobin with time was proved to be associated with increased or decreased death risk respectively. In spite of, in previous studies (Collins, 2002; Collins et al., 2000 and Locatelli et al., 1998 and Locatelli et al., 2004) had examined the associations between baseline hemoglobin levels and survival in patients of CKD, without bothering about the changes in hemoglobin levels over time. Ofsthun et al. (2003) reported the association of higher hemoglobin level more than the current Kidney Dialysis Outcomes Quality Initiative (K/DOQI) recommendations with increased risk of death. They examined both extremely low and high levels of hemoglobin to discover any negative effect for any case. Patients with hemoglobin< 9 g/dL showed the lowest proportion of patients surviving, and patients group with hemoglobin>13 g/dL showed the highest proportion of patients surviving over time. On basis of these results Ofsthun et al. (2003) established the findings that hemoglobin higher than the current recommended values is not associated with increased risk of death. Also Positive link between survival and high hemoglobin level reported by Collins et al. (2001), Ma et al. (1999) and Xia et al. (1999), supported the results of Ofsthun et al. (2003).

The final step of variable selection process is consideration of interaction terms in to the main effect model. To check the effects of interactions without prior knowledge of important interactions, the selection process started by forming a set of all plausible interactions, including all marginal variables and just one

interaction in the model at one time. After that resulting significant interactions at 5% level of significance were added simultaneously to the marginal effect model. Selected interaction terms for the final model were based on *p-values* of statistical significance. Most of the time with insertion of interaction term in the model, it is quite possible that any marginal effect variable of that interaction appears with an insignificant Wald test due to the reason that estimates of effect required the marginal effects and interaction effect simultaneously. Though insertion of interaction terms made model more difficult to interpret but on the other hand provides improved inferences, more realistic and informative model. Subsequent to evaluation of model diagnostics and assessment of overall goodness of fit model, it is referred to as final model. Results of the final model with significant predictors would be useful for prediction purpose presented in Table 5.

Comparison of the model with interaction, to the model without interactions can be made by Likelihood Ratio testwith assumption that models are nested.The significant *p-value* = 0.00 with 4 degree of freedom supported the rejection of null hypothesis that the two models fit the data equally well and concluding that the bigger model with interactions fits the data better than the smaller model which did not include the interactions.

Cox (1975) Proportional Hazard Regression technique was applied to explore the impact of fixed and time varying covariates on survival of dialysis patients. Current age, inter-dialytic weight gain, serum potassium, hemoglobin, serum albumin and duration of dialysis proved to be significant variables with respect to death. As Likelihood Ratio test referred the model without interactions to be incorrect Model. Since, it is pointless to interpret the non-informative modeland marginal effects of covariates which are already included in the interaction terms.

4.4.1 Interpretation of final model (prediction model) in terms of Hazard Ratios: Duration of dialysis in months is an only variable which in not included in interaction terms. For this variable all categories are significantly associated with risk of death. Dialysis duration time category 2 “13 – 24 months” has (1-34.4846=-33.4846) 33 times more chance of death of patients during this interval than interval of “greater than 24 months”. Dialysis duration time category 3 “7 – 12 months” has (1-929.6099=- 928.6099) 928 times more chance of death of patients during this interval than interval of “greater than 24 months”. While duration of “less than 6 months” exposed out with (1-13815.98=- 13814.98) 13814 times more chance of death of patients during this interval than interval of reference category “more than 24 months”.

In this model, 4 interaction terms of main variables were proved significant. Interaction of Age*ID weight gain showed .53% (1- .9946083= .0053917) chance of decrease in death risk with one percent increase in combined effect of age and ID weight gain from low range to high range. Similar trend can be seen for interaction of serum albumin*HB. One percent increase from low range to high range of combined effect of Serum albumin and HB has 21.32% (1-.7868289=.213171) chance of decrease in death risk for dialysis patients. Interaction of serum albumin and ID weight gain showed 24% (1-1.240298=.240298) increase in Hazard Risk. Moreover, simultaneous increase in combined effect of serum albumin and potassium have 8.78% (1-1.087844=.087844) more chance of death for the current dialysis population.

Here, marginal effect is an approximation of how much the survival time is expected to increase or decrease for a unit change in any covariate, by ignoring the effect of all other covariates. Occasionally, we are also interested in that how the variation in one covariate changes the effects of another covariate, or change in one covariate effects the results of another covariate, that is, the interaction effect. In statistical perspective, it can be described as deviation from conditional independence. For instance, we all know that exercise is always better than sedentary lifestyle for overall health as well as for weight reducing purpose, and in the same way diet selection is always better than unhealthy food. These are the established marginal effects, but diet selection and exercise coming together would be particularly more effective than either diet selection or exercise only.

To study possible interaction effects, it was assessed whether the different conditions for a covariate produce results that vary, depending on the conditions that were considered for a second covariate. Another way to find out is to check if the effect of a clinical covariate on disease risk differs among individuals with different levels of clinical covariate. We have to look forward for the combined effects of covariates, as there is more to consider than simply the marginal effect of each covariate. The effect of one independent covariate depends on the level of the other independent covariate and different levels of covariates yield different interaction effects leaving the marginal effects not interpretable individually.

In order to explain the interaction effects of covariates at different levels 3^5 factorial design was applied, in which the five independent covariates are crossed with one another with the intention that there are observations at every combination of levels of the five independent covariates. To obtain numerical value of different interaction combinations at low, medium and high level of five

variable's meaningful values were taken at random from their low, medium and high ranges.

4.4.2 Interaction effects of covariates at low, medium and high levels in Cox model: Following Table 6 and Table 7 represents only highest 10% and lowest 10% (respectively) of Hazard Ratios in ascending order to have an idea about the effects of covariates at different levels.

In this study, we inspected the joint Prognostic influence of demographic and biochemical variables, to ascertain the Prognostic information for best and worst survival of dialysis receiving patients. Significant interaction effects at low, medium and high levels of covariates made the picture clearer. Hazard Ratios explained some of the survival advantage (low Hazard Risk) at high level of albumin, medium or high hemoglobin, low or medium ID weight gain and low or medium potassium at the same time. Simultaneous effect of low level of serum albumin and hemoglobin, high level of ID weight gain and potassium proved to be more hazardous for concerned population.

Lowest Hazard Ratio 0.0066 explained (1-0.0066=0.9933) 99.34% reduction in Hazard Risk for the patient who achieved lower level of weight, lower level of potassium, higher level of hemoglobin and higher level of albumin with less age. Such a 99.34% lower Hazard Risk would be a best ever possible condition for current population under study. Possible worst condition of a patient under dialysis would be with highest Hazard Ratio (1-7.7496=6.7496) of 6.74 times more Hazard Risk with higher weight gain, higher potassium level, lower hemoglobin level and lower albumin level irrespective of age. On the whole at high level of serum albumin and hemoglobin, low level of ID Weight gain and potassium, all together, with three age group of patient (low, med, and high) demonstrated better survival condition and good prognosis for such patients, reducing Hazard Risk by (99.34%, 99.09%, 98.80% resp.)

Furthermore, it's noticeable that there are some specific conditions which breached the typical trend. At high level of serum albumin and hemoglobin, low level of potassium and lower age group and lower ID Weight gain, all together, reduced Hazard Rate by 99.34%, compared to those patients with transformation of level of low ID weight gain to medium ID weight gain showing reduction in Hazard Rate by 98.42%. Besides this high level of serum albumin and hemoglobin, low level of potassium and medium age group and medium ID weight gain showed 98.07% decreased Hazard Risk and joint effect of high level

of serum albumin and hemoglobin, low level of potassium and higher age group and medium ID weight gain showed 97.68% decreased Hazard Risk, which is slightly increased Hazard Risk as compared to low level of age group and ID weight gain. On the other hand its worth mentioning, with lower hemoglobin level and lower albumin level, higher potassium level and higher weight gain, there is increased Hazard Risk for older age groups (6.50 times) as compared to medium (6.61 times) and low age groups (6.74 times). These results suggested that increase in levels of weight gain will be more harmful than that of older age of patients, and will yield more increase in Hazard Risk.

To illustrate the mix effect of weight gain and albumin, we have particular situations in that, low age group, higher potassium, lower hemoglobin level and higher weight gain with rise in levels of albumin from low to medium level increased Hazard Risk 6.64 times and 5.56 times respectively. Moreover, low age group, lower potassium, higher hemoglobin level and higher albumin with rise in levels of weight gain from low to medium level represented reduction in Hazard Risk by 99.34% and 98.42% respectively. So that low reduction in Hazard Rate at higher level of weight gain showed harmful effects on survival of patients.

As reported earlier with high level of serum albumin, high level of hemoglobin, lower age group, lower ID weight gain and low level of potassium all together reduced Hazard Ratio by 99.34%. Keeping constant levels of other covariates and rise in levels of potassium up to medium and high level proposed decline in Hazard Risk by 98.80% and 98.12% respectively. It's clear that decline in Hazard Risk goes on decreasing further by increasing the levels of potassium. Similarly, at higher ID weight gain, low level of hemoglobin, any of three age groups, low level of serum albumin and higher level of potassium gave about 6 times greater Hazard Risk. In another case, with low level of hemoglobin, lower age group, higher ID weight gain and higher level of potassium with low and medium level of serum albumin revealed 6.74 times and 5.56 times increased Hazard Risk, respectively. Increase in Hazard Risk is low where albumin is at medium level instead of low, even in the company of the high potassium level, shows a slight benefit for survival of patients. On the whole, it comes out that shift towards high levels of potassium irrespective of albumin increased the Hazard Risk.

In the best possible combination of covariates high level of serum albumin, high level of hemoglobin, lower age group, lower ID weight gain and low level of potassium reduced Hazard Rate by 99.34%. In that condition by turning down the hemoglobin level from high to medium will decrease the reduction in Hazard Risk by 98.23% from 99.34%. In opposite situation, with low age group, higher weight

gain, higher potassium, lower hemoglobin level and with rise in levels of albumin from low to medium level increased Hazard Risk by 6.64 times and 5.56 times respectively. Therefore, it is understandable that increased levels of both albumin and hemoglobin resulted in lower Hazard Risk for the maintenance dialysis patients.

5. Conclusion

In this study, joint Prognostic influence of demographic and biochemical variables was studied, to determine the Prognostic information for best and worst survival of dialysis receiving patients. Combinations of significant interaction effects at low, medium and high levels of covariates made the picture clearer. Hazard Ratios clarified the overall survival advantage at high level of albumin, medium or high hemoglobin; low or medium inter-dialytic weight gain and low or medium potassium at the same time. Simultaneous effect of low level of serum albumin and hemoglobin, high level of inter-dialytic weight gain and potassium appeared as more hazardous for concerned population.

On the whole, at high level of serum albumin and hemoglobin, low level of inter-dialytic weight gain and potassium, simultaneously, with three age group of patient (low, med, and high) provided better survival condition and good prognosis for dialysis patients, reducing Hazard Risk by approximately 99.34%, 99.09%, and 98.80%, respectively. The results of detailed combinations of weight gain and age proposed that increase in levels of weight gain will be more harmful than that of older age of patients, and will be resulted of more increase in the Hazard Risk. Moreover, increased levels of both albumin and hemoglobin provided lower Hazard Risk for the maintenance dialysis patients. The best possible combination of covariates at high level of serum albumin, high level of hemoglobin, lower age group, lower inter-dialytic weight gain and low level of potassium decreased Hazard Rate by 99.34%.

6. Limitations of study and recommendations

a) Lack of availability of data was major limitation from all over the Punjab hospitals. Among 15 teaching hospitals of both divisions of Lahore and Rawalpindi, it was hardly possible to obtain data from just 7 teaching hospitals. Some, among rest of those refused to give the access to data files and others had no record keeping system of dialysis units.

b) The number of dialysis patients who were referred from other hospitals or who changed the dialysis units on their own choice and feasibility after the onset of their treatment, were dropped to avoid the problem of duplication of patients registered in two or more dialysis units, resulted in reduced sample size of patients than actual, because of being dropped from both dialysis units.
c) Records were not kept well and up to date even in Lahore and Rawalpindi division for those patients who came from faraway places and other cities for dialysis sessions. Either these patients had not available dialysis units in their own cities or they were not satisfied with the treatment, which was provided in their own city's dialysis units.
d) Cox Proportional Hazard model is Semi-parametric approach fitted in this study. Besides this full parametric approach should perform for identification of Prognostic factors and also for comparison purpose. As Parametric approaches have less standard errors and also applicable to handle all type of censoring and are accountable for time dependent covariates too. Parametric Regression models such as Accelerated Failure Time Regression models represents results in terms of time ratios instead of Hazard Ratios, possibly be easy to understand for clinical investigators.

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Table 1: Cox Proportional Hazard model for individual demographic variables and clinical variables

Factors/ Covariates	**ID**	**Level**	**B**	**S.E.**	**Sig.**	**Exp(B)**	**95% C.I. for Exp(B)**	
							Lower	**Upper**
Gender	gender	Male	-	-	-	-	-	-
		Female	-.1495	.0757	0.048	0.8610	0.7422	.9989
Current age	Current_ age	None	.0075	.0024	0.002	1.0076	1.0027	1.0125
Age at start of dialysis	Age_start_ dialysis	Less than 29 yr	-	-	-	-	-	-
		30- 39 yr	.0485	.1309	0.711	1.0497	.8122	1.3568

		40- 49 yr	.2917	.1124	0.009	1.3387	1.0740	1.6687
		Greater than 50 yr	.3132	.1022	0.002	1.3678	1.1193	1.6714
Frequency of dialysis	Freq-dial	once	-	-	-	-	-	-
		twice	.0440	.7082	0.950	1.0450	.2607	4.1881
		thrice	-.2726	.7163	0.704	0.7613	.18697	3.1001
Incidence of hepatitis	Incidence_ hepatitis	No	-	-	-	-	-	-
		C+	.0184	.1006	0.855	1.0185	.8362	1.2406
		B+	.2835	.1904	0.137	1.3278	.9141	1.9288
Hospital acquired hepatitis	Hospital_ acquired_ hepatitis	No	-	-	-	-	-	-
		C+	.6845	.0807	0.000	1.9829	1.6927	2.3229
		B+	.6395	.1120	0.000	1.8955	1.5216	2.3612
Causes of ESRF	Causes_ ESRF	Diabetes	-	-	-	-	-	-
		Hypertension	-.0353	.0884	0.689	.9652	.8116	1.1479
		Obstructive uropathy	.1509	.1080	0.162	1.1629	.9410	1.4372
		Congenital	.10007	.1611	0.535	1.1052	.8058	1.5158
		Drug induced	.4810	.1645	0.003	1.6177	1.1717	2.2336
		CRF	.3633	.2744	0.185	1.4381	.8399	2.4624
		Polycystic disease	-.1038	.3077	0.736	.9013	.4931	1.6475
		Any other	-.9513	.5039	0.059	.3862	.1438	1.0369
		None	-	-	-	-	-	-
		Tuberclosis	.1661	.3543	0.639	1.1807	.5895	2.3650
		HTN	-.1269	.1919	0.509	.8808	.60458	1.2832
		DM	.0323	.2069	0.876	1.0329	.6884	1.5496
		CLD	.5220	.2702	0.053	.59328	.3493	1.0076
		Cardio vascular disease	.0793	.2036	0.697	1.0825	.7263	1.6136
Inter-dialytic weight gain	Weight	None	.5401	.0308	0.000	1.7163	1.6155	1.8234
Serum urea	urea	None	.0001	.0007	0.869	1.0001	.9985	1.0016
Serum Creatinine	Creatinine	None	-.0306	.0119	0.010	.9697	.9472	.9928
Serum Potassium	Pota	None	.2358	.0222	0.000	1.2659	1.2118	1.3224
Serum Phosphate	Phosphate	None	.1788	.0140	0.000	1.1957	1.1633	1.2290
hemoglobin	HB	None	-.3235	.0171	0.000	.7235	.6996	.7482
Serum albumin	Alb	None	-.9307	.0493	0.000	.3942	.3578	.4343
Dialysis duration at	Dduration	Greater than 24 (months)	-	-	-	-	-	-

entry of study		13-24 months	3.1931	.5210	0.000	24.364	8.7741	67.656
		7-12 months	6.7637	.5635	0.000	865.91	286.94	2613.128
		Less than 6 (months)	9.693	.5828	0.000	16213.54	5172.81	50819.29

Table 2: Overall test of proportionality

Covariates	**Chi-square**	**d.f.**	**Sig.**
current_Age	0.84	1	0.3606
Weight_gain	0.35	1	0.5537
Potassium	0.03	1	0.8632
HB	1.21	1	0.2709
Serum_Albu	0.01	1	0.9252
1.dduration	-	1	-
2.dduration	0.11	1	0.7425
3.dduration	0.49	1	0.4817
4.dduration	1.10	1	0.2952
Age_weight	0.71	1	0.3990
Alb_weight	1.99	1	0.1583
Alb_pota	0.03	1	0.8535
Alb_HB	1.91	1	0.1665
global test	**16.10**	**12**	**0.1868**

Table 3: Cox Regression model for identification of Prognostic factors

Variables	B	S.E.	Z	Sig.	Exp.	95% CI for Exp.	
						Lower	Upper
Gender= male							
Gender= female	.0023	.0788	0.03	0.976	1.0023	.8587	1.1699
current_Age	.0145	.0062	2.33	0.020	1.0146	1.0023	1.0270
Age_start_dia= < 29 yr	-						
Age_start_dia=30- 39 yr	-.0264	.1492	-0.18	0.859	.9738	.7269	1.3046
Age_start_dia=40- 49 yr	-.2015	.1771	-1.14	0.255	.8174	.5776	1.1568
Age_start_dia= >50 yr	-.3799	.2497	-1.52	0.128	.6839	.4191	1.1158
freq_dia_weekly=once							
freq_dia_weekly=twice	-.6654	.7194	-0.92	0.355	.5140	.1254	2.1057
freq_dia_weekly=thrice	-.3727	.7241	-0.51	0.607	.6888	.1666	2.8476
Hospital_acqu_hepa=No							
Hospital_acqu_hepa= C+	-.0400	.0918	-0.44	0.663	.9607	.8024	1.1503
Hospital_acqu_hepa= B+	-.0113	.1200	-0.09	0.925	.9887	.7814	1.2509
Co_morbidities= None							
Co_mor=Tuberclosis	-.1151	.3600	-0.32	0.749	.8912	.4400	1.8049
Co_mor=HTN	.0626	.1955	0.32	0.749	1.0646	.7256	1.5618
Co_mor=DM	.2434	.2112	1.15	0.249	1.2755	.8430	1.9299
Co_mor=CLD	-.0786	.2775	-0.28	0.777	.9243	.5365	1.5924
Co_mor=Cardio vascular disease	.3131	.2082	1.50	0.133	1.3677	.9094	2.0569
Weight_gain	.1242	.0346	3.58	0.000	1.1323	1.0578	1.2120
Creatinine	-.0074	.0121	-0.61	0.541	.9926	.9692	1.0165
Potassium	.1080	.0216	4.99	0.000	1.1141	1.0678	1.1624
Phosphate	-.0023	.0174	-0.14	0.891	.9976	.9640	1.0323
HB	-.1686	.0241	-6.98	0.000	.8448	.8057	.8858
Serum_Albumin	-.3574	.0631	-5.66	0.000	.6994	.6180	.7916
Dduration> 24(months)							
Dduration=13-24 months	3.2542	.5825	5.59	0.000	25.8997	8.2689	81.122
Dduration=7-12 months	6.5721	.6202	10.60	0.000	714.9066	211.98	2411.0
Dduration= <6 months	9.2359	.6373	14.49	0.000	10259.37	2941.79	35779.

Table 4: Main effect Cox Regression model for identification of Prognostic factors

Variables	B	S.E.	Z	Sig.	Exp.	95% CI for Exp.	
						Lower	Upper
current_Age	.0054	.0024	2.21	0.027	1.0054	1.0006	1.0102
Weight_gain	.1081	.0327	3.30	0.001	1.1142	1.0448	1.1881
Potassium	.0916	.0206	4.44	0.000	1.0960	1.0525	1.1412
HB	-.1687	.0231	-7.30	0.000	.8447	.8072	.8838
Serum_Albumin	-.3371	.0617	-5.46	0.000	.7138	.6324	.8057
Dduration> 24 months	.	.	.	.	.	.	.
Dduration =13-24 months	3.2362	.5845	5.54	0.000	25.4385	8.0895	79.9950
Dduration =7-12 months	6.5597	.6224	10.54	0.000	706.0615	208.4677	2391.367
Dduration =< 6 months	9.1673	.6392	14.34	0.000	9579.463	2736.65	33532.28

Table 5: The final Cox Regression model for identification of Prognostic factors (prediction model)

Variables	B	S.E.	Z	Sig.	Exp.	95% CI for Exp.	
						Lower	Upper
current_Age	.0259	.0082	3.14	0.002	1.0263	1.0098	1.0430
Weight_gain	-.2541	.1459	-1.74	0.082	.7756	.5826	1.0324
Potassium	-.1241	.0970	-1.28	0.201	.8832	.7302	1.0682
HB	.5507	.0927	5.94	0.000	1.7344	1.4462	2.0801
Serum_Albumin	.2575	.4214	0.61	0.541	1.2938	.5664	2.9552
Dduration> 24 months	.	.	.	.	.	.	.
Dduration =13-24 months	3.5405	.6667	5.31	0.000	34.4846	9.3343	127.3998
Dduration =7-12 months	6.8347	.6998	9.77	0.000	929.6099	235.8261	3664.456
Dduration =< 6 months	9.5335	.7152	13.33	0.000	13815.98	3400.857	56127.4
Age_weight	-.0054	.0017	-3.04	0.002	.9946	.9911	.9980
Alb_weight	.2153	.0542	3.97	0.000	1.2402	1.1152	1.3793
Alb_pota	.0841	.0393	2.14	0.032	1.0878	1.0071	1.1749
Alb_HB	-.2397	.0333	-7.19	0.000	.7868	.7370	.8399

Table 6: Highest 10% of Hazard Ratios

Age	Weight	potassium	HB	Albumin	Σ(βx)	Hazard Ratios
60	5	6.5	12	2.9	1.5812	4.8610
60	5	5	9	3.5	1.5934	4.9207
60	5	3	9	2.9	1.5948	4.9274
45	5	6.5	12	2.9	1.5970	4.9386
45	5	5	9	3.5	1.6093	4.9993
45	5	3	9	2.9	1.6106	5.0061
29	5	6.5	12	2.9	1.6139	5.0227
29	5	5	9	3.5	1.6261	5.0844
29	5	3	9	2.9	1.6275	5.0913
60	1.2	5	9	2.9	1.6599	5.2590
45	2.5	6.5	9	2.9	1.7129	5.5452
60	2.5	5	9	2.9	1.7197	5.5833
60	5	5	9	2.9	1.8348	6.2644
60	1.2	6.5	9	2.9	1.8399	6.2964
60	5	6.5	9	3.5	1.8492	6.3552
45	5	5	9	2.9	1.8507	6.3643
45	5	6.5	9	3.5	1.8651	6.4567
29	5	5	9	2.9	1.8676	6.4727
29	5	6.5	9	3.5	1.8820	6.5666
60	2.5	6.5	9	2.9	1.8998	6.6848
60	5	6.5	9	2.9	2.0149	7.5001
45	5	6.5	9	2.9	2.0307	7.6198
29	5	6.5	9	2.9	2.0476	7.7496

Table 7: Lowest 10% of Hazard Ratios

Age	Weight	potassium	HB	Albumin	Σ(βx)	Hazard Ratios
29	1.2	3	13.5	5	-5.017	0.0066
45	1.2	3	13.5	5	-4.7056	0.0090
29	1.2	5	13.5	5	-4.4237	0.0119
60	1.2	3	13.5	5	-4.4132	0.0121
29	2.5	3	13.5	5	-4.1518	0.0157
45	1.2	5	13.5	5	-4.1119	0.0163
29	1.2	3	12	5	-4.0453	0.0175
29	1.2	6.5	13.5	5	-3.9784	0.0187
45	2.5	3	13.5	5	-3.9524	0.0192
60	1.2	5	13.5	5	-3.8196	0.0219
60	2.5	3	13.5	5	-3.7655	0.0231
45	1.2	3	12	5	-3.7335	0.0239
45	1.2	6.5	13.5	5	-3.6666	0.0255
29	2.5	5	13.5	5	-3.5581	0.0284
29	1.2	5	12	5	-3.4517	0.0316
60	1.2	3	12	5	-3.4412	0.0320

Age	Weight	potassium	HB	Albumin	Σ(βx)	Hazard Ratios
60	1.2	6.5	13.5	5	-3.3743	0.0342
45	2.5	5	13.5	5	-3.3587	0.0347
29	2.5	3	12	5	-3.1797	0.0415
60	2.5	5	13.5	5	-3.1718	0.0419
45	1.2	5	12	5	-3.1399	0.0432
29	2.5	6.5	13.5	5	-3.1128	0.0444
29	1.2	6.5	12	5	-3.0064	0.0494
45	2.5	3	12	5	-2.9804	0.0507

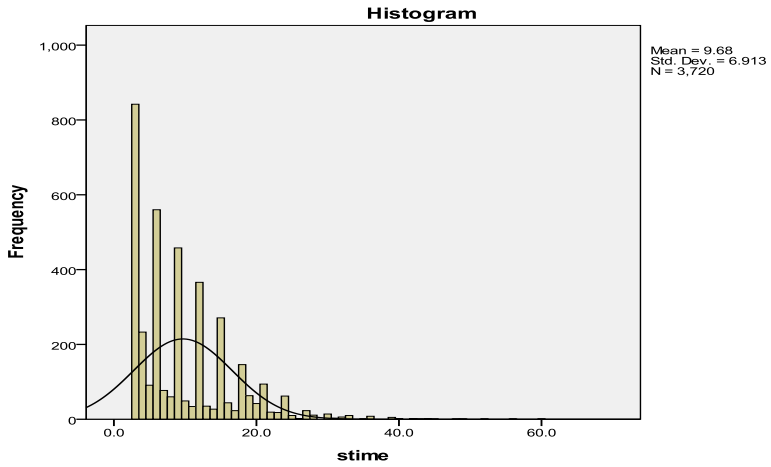

Figure 1: Histogram of survival time

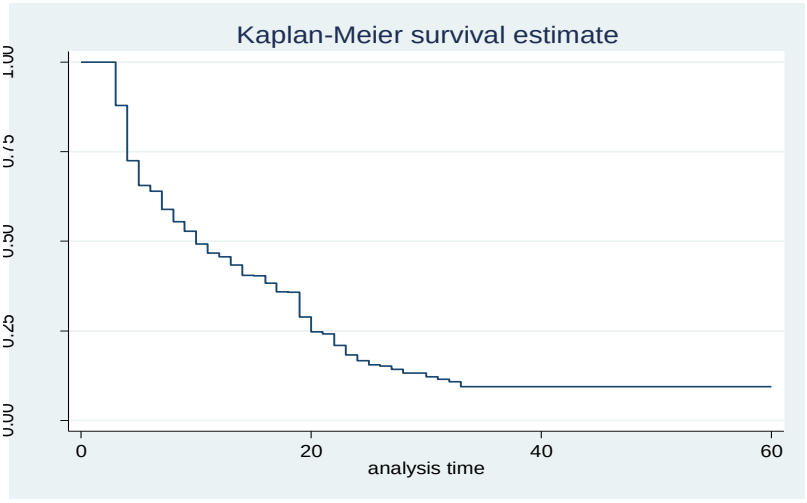

Figure 2: Kaplan Meier Survivor function for overall survival time of dialysis patients

Figure 3-7: Graphical assessment of PH assumptions

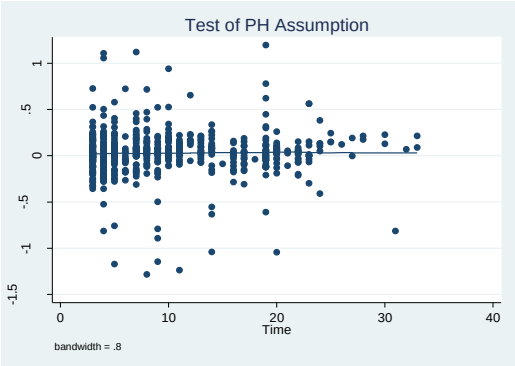

Figure 3: Scaled Schoenfeld residual plot for current age

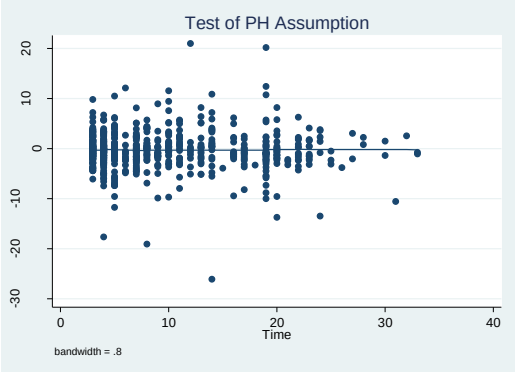

Figure 4: Scaled Schoenfeld residual plot for ID weight gain

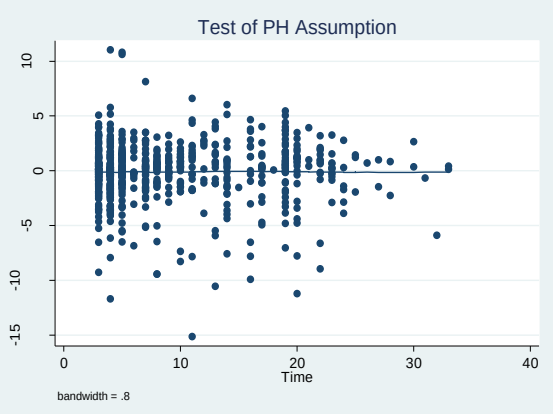

Figure 5: Scaled Schoenfeld residual plot for potassium

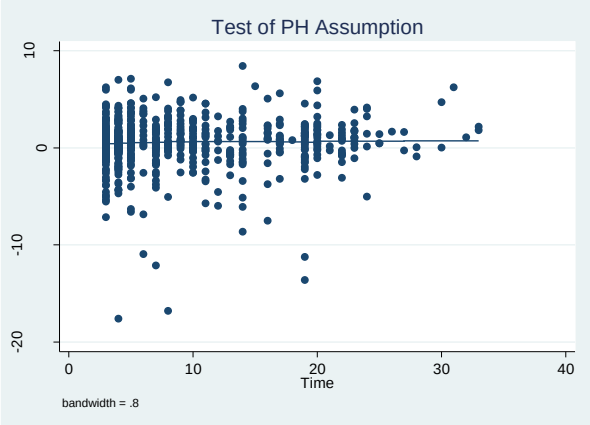

Figure 6: Scaled Schoenfeld residual plot for HB

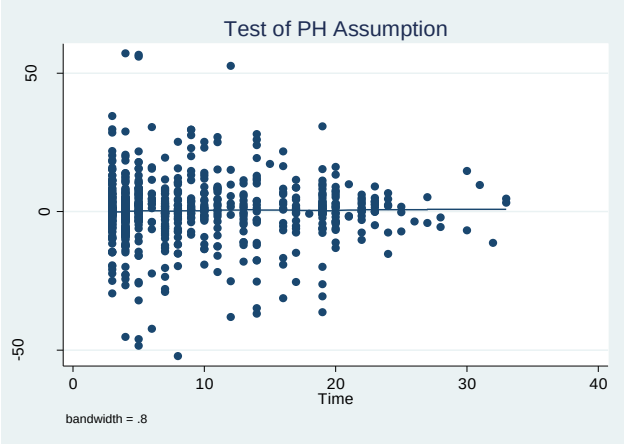

Figure 7: ScaledSchoenfeld residual plot for serum albumin

Figure 8-12: Smoothed residual plots for Linearity

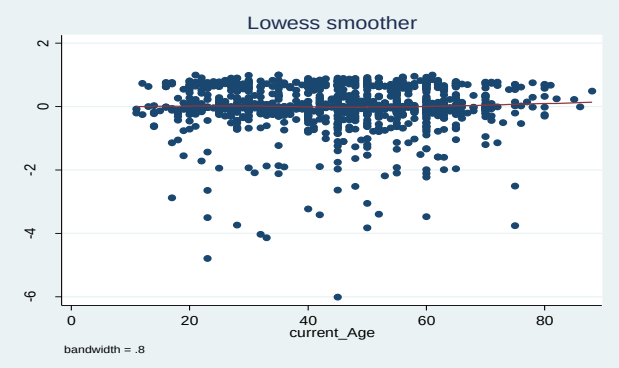

Figure 8: Smoothed Residual plot for current age

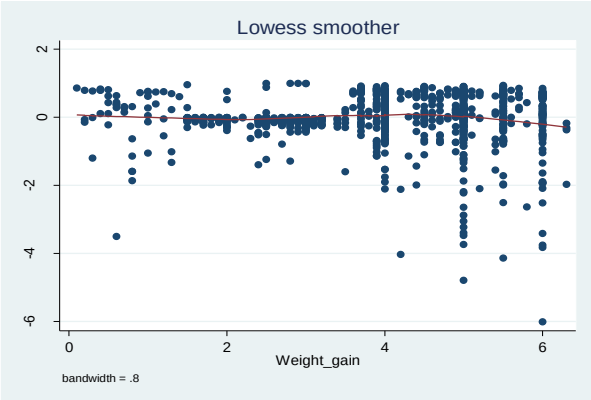

Figure 9: Smoothed Residual plot for weight gain

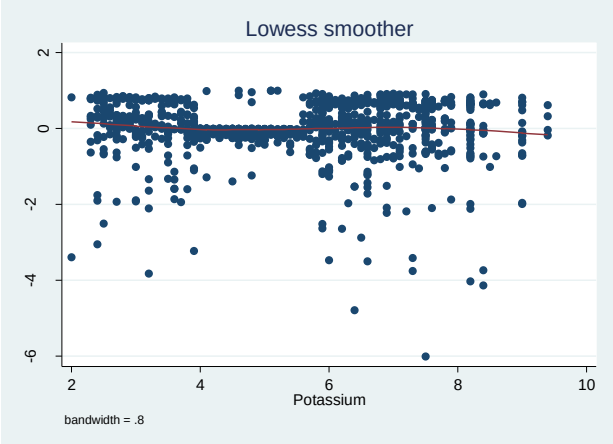

Figure 10: Smoothed Residual plot for potassium

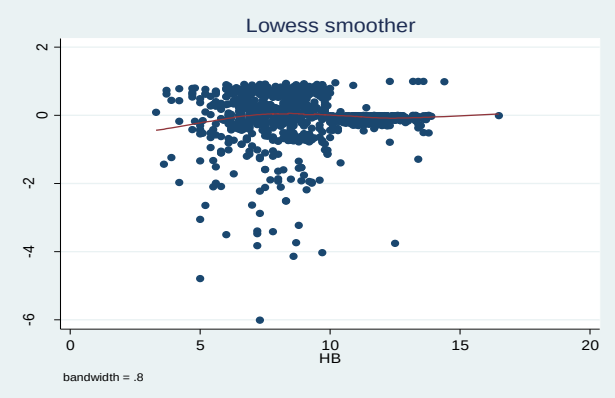

Figure 11: Smoothed Residual plot for HB

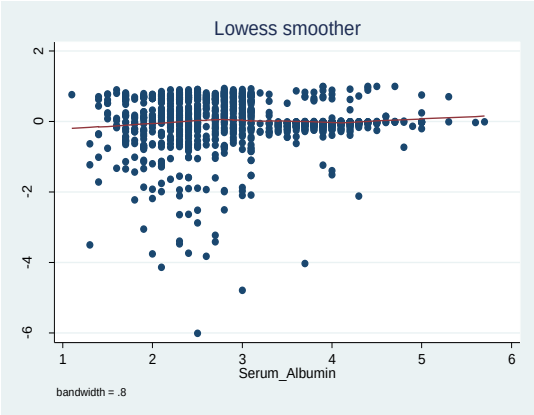

Figure 12: Smoothed Residual plot for serum albumin

Figure 13-17: Df beta plots for detection of outliers

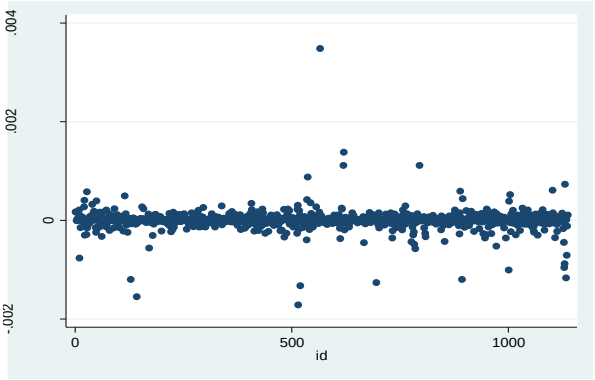

Figure 13: Df beta for current age vs case ID

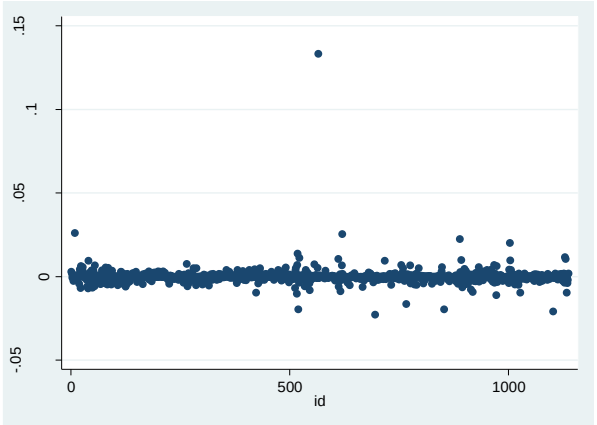

Figure 14: Df beta for weight gain vs case ID

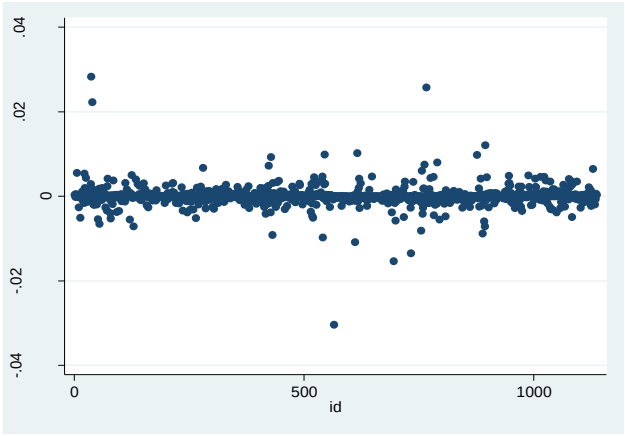

Figure 15: Dfbeta for potassium vs case ID

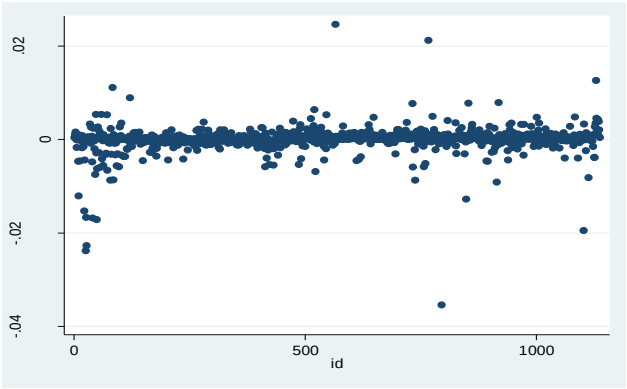

Figure 16: Dfbeta for HB vs case ID

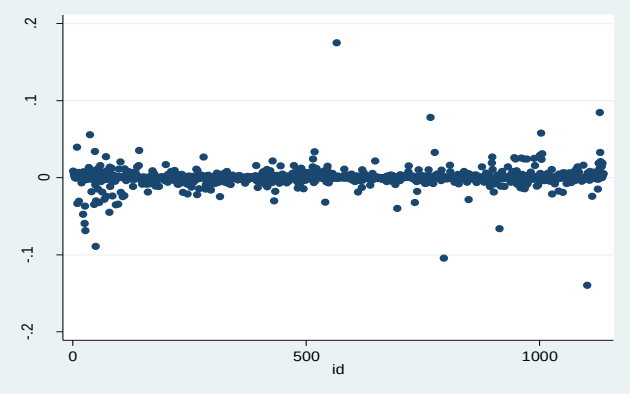

Figure 17: Dfbeta for serum albumin vs case ID

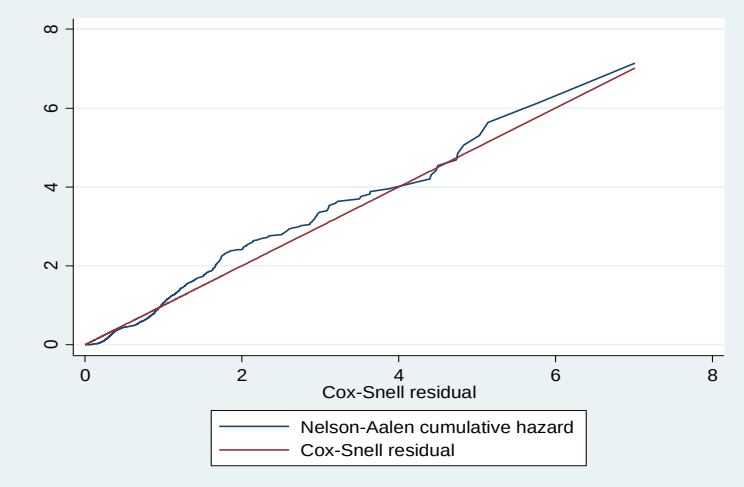

Figure 18: Graph of Goodness of Fit of final Cox model

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