Prototypical Study Detecting the Outcome of Patients with CKD Stage 5 (ESRD) Treated Conservatively (PSCKD5C), at Sheffield Kidney Institute (SKI) over a Period of 5 Years

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Abstract

Very few studies have investigated and made decisions regarding RRT in elderly patients, and their conclusions are rather discordant [1,2,3,4,5,6,7,8,9,10]. Treatment option for ESRD (End Stage Renal Disease) is to decide not to have dialysis or transplantation and to manage such a condition medically with blood pressure control, dietary restrictions, and adjustment of medical regimen. This is known as conservative management. The increase in the ESRD (end stage renal disease), primarily due to the increasing of Diabetes and age of the population. It is a serious medical and economic public health problem throughout the world, and it has become a health concern both medically and economically [11].

Keywords: CKD5; (Chronic kidney disease stage 5). CKD5; (Chronic kidney disease stage 5 treated conservatively). COPD; (Chronic obstructive pulmonary disease). CI ; (Confidential interval). CVD; (Cerebrovascular disease). DM ; (Diabetes Mellitus). eGFR; (Estimated Glomerular filtration rate). ESRD ; (End stage renal disease). IHD ; (Ischemic Heart disease). KDOQI ; (Kidney Disease Outcomes Quality Initiatives). PVD ; (Peripheral Vascular Disease). RRT ; (Renal Replacement Therapy). RRT ; (Renal Replacement Therapy). SD ; (Standard deviation). SK ; (Sheffield Kidney Institute). t test ; (Student t-test). X² ; (Chi-square test).

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1. Introduction

Patients undergoing treatment for CKD 5 (Chronic kidney disease stage 5) represent a group with higher mortality compared with the general population, even when adjusted for age, race, sex, and co-morbid conditions and I focused on 84 patients (40 of them died) treated conservatively at SKI (Sheffield Kidney Institute), another 84 dialysis patients have also included in the study as a control group over 5 years duration. These patients are at increased risk for various life-threatening complications, including atherosclerotic disease, left ventricular hypertrophy, malnutrition, and infection. Clinicians should   have to make decision about RRT (Renal replacement therapy) versus Conservative therapy, and to study factors influencing the recommendation for palliative (non-dialysis) treatment in patients preferring not to dialyze.

2. Methods

 The statistical analysis expressed as numerical values and percentages for categorical variables and as a means (±SD) for continuous variables. Frequency and cross tables have been used and comparison between category 1 and category 2 were based on the X^2(Chi-square test) for categorical data and t test (Student t-test) for continuous data. Survival methods were computed using life-table method namely the Kaplan-Meier survival curves.

3. Results/Conclusion

(80 years) is the mean age of the patients treated conservatively compared with 70 years in Dialysis group. Improving quality of life, further intention towards medical managements and tracing the diseases that contribute to the decline in renal function might give rise to a better outcomes, the main survival time is around 2.7 years, the majority prefer conservative management rather than dialysis, 40% are progressors. Comorbidities affect the survival time of the Conservative as well as the Dialysis patients. Diabetes play a major role as a cause of renal failure and it is the most predictor variable for survival. High quality conservative care is a viable.

4. Material and Methods

Study site

The Sheffield Kidney Institute (SKI) was founded in 1990, bringing together all the clinical and research activities in the field of nephrology in the city of Sheffield within a purpose built 60-bed unit. The SKI is situated at the Northern General Hospital Campus of the Sheffield Teaching Hospital Foundation Trust, where it provides a regional service within Sheffield and its surroundings (mid-land) in nephrology for a population approaching 1.7 million. It corporate all acute and chronic nephrology services. *Patients* Between Jan. 2006, and Jun. 2010, 168 patients have been collected from computerized saved data to be studied to know the finding of their conservative management, 98 patients under conservative management, 14 of them excluded from the study as they were not fit the KDOQI (Kidney Disease Outcomes Quality Initiatives) diagnostic criteria of CKD 5 (eGFR< 15 ml/min/1.73 m²). So the actual number of patients treated conservatively was 84 patients (45

males and 39 females), 40 of them died earlier over the period. The remaining 84 patients (55 males and 29 females) on regular dialysis 17 of them have also died during the study. The Mean age for the conservative and dialysis patients was (80 years, standard deviation 7), (70 years, standard deviation 8) respectively. Patients who have been under conservative managements continued to benefit from regular follow-up in close cooperation with the family doctor, symptoms present in patients with ESRD and which are generally not well managed, including pruritus, nausea, constipation, fatigue, neuropathy, cramps, pain, anxiety, depression and psychological concerns over dependence. It should be obvious therefore that supportive care is not solely of use at the end of life, but should be an adjunct to the management of patients at all stages of their illness. Supportive care should be available to patients at the time of diagnosis. It does not simply mean conservative care in dialysis and does not mean any treatment. Patient who has been offered conservative or supportive management (rather than dialysis) must be on regular follow up [12]. Identification of factors influencing the conservative group and it's comparison with the dialysis one has influenced the therapeutic proposals and made the survival analysis taken into account effective factor for my study.

Data Organization:

The day of clinical and laboratory data collection and starting of study was defined as the first day of CKD 5 diagnosis at which the first value of eGFR(estimated glomerular filtration rate) was taken. Survival duration was measured as the number of years and months from the diagnosis until death or latest news. The dialysis category has been collected randomly over the same period of time (one patient for every 15 patients). Variables collected were: age(two groups,<70and >70/<80and>80 years), gender, ethnicity, time of diagnosis, Causes of ESRD, presence or absence of eight co morbid conditions (heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, chronic obstructive airway disease, dementia and cancer).

5. Statistical Analysis

The statistical results are expressed **as Numerical values and percentages for categorical variables** and as **a means (±SD) for continuous variables**. Comparison between category 1 and category 2 were based on the **X^2(Chi-square test)** for categorical data and t test **(Student t-test)** for continuous data. Survival curves from date of diagnosis of stage 5 CKD to last news (date at time of end point eGFR) were computed using life-table methods. I used **Kaplan-Meier survival curves** to compare survival in both categories in respect of (age, gender, ethnicity, heart failure, ischemic heart disease, cerebrovascular disease, peripheral vascular disease, diabetes, chronic obstructive airway disease, dementia and cancer).. **Kaplan-Meier survival method with log-rank test** has also been included in the analysis as it is useful for comparing survival curves in two or more groups. All data of the study has been collected from **SKI (PROTON) data base** which shows detailed programmed regular follow up in terms of exploring patients complaint, investigations, clinical examination, Doctors opinions and managements, part of the data collected from patients notes, there are missing data ignored from the statistical analysis which was performed using the SPSS 14.0 software package for PC computer. The practicing of all the above statistical analysis tests are the ideal components of this prototypical study **(PSCKD5C).** Performing such a study is intended for CKD5 as it carry a controverters in managements

between different institutes.

6. Results

Table 1: Comparison between conservative and dialysis statistical data

			Conservative	Dialysis
Age	Mean		80	70
	Std Deviation		7	8
Gender	female	Count	39	29
		Col %	46.4%	34.5%
	Male	Count	45	55
		Col %	53.6%	65.5%
Race	White	Count	55	74
		Col %	93.2%	91.4%
	Non White	Count	4	7
		Col %	6.8%	8.6%
Diabetes Mellitus	No	Count	62	58
		Col %	73.8%	82.9%
	Yes	Count	22	12
		Col %	26.2%	17.1%
Heart failure	No	Count	67	70
		Col %	79.8%	100.0%
	Yes	Count	17	
		Col %	20.2%	
I.H.D*	No	Count	59	46
		Col %	70.2%	65.7%
	Yes	Count	25	24
		Col %	29.8%	34.3%
C.V.D*	No	Count	69	64
		Col %	82.1%	91.4%
	Yes	Count	15	6
		Col %	17.9%	8.6%
P.V.D*	No	Count	67	57
		Col %	79.8%	81.4%
	Yes	Count	17	13
		Col %	20.2%	18.6%
COAD*	No	Count	69	59
		Col %	82.1%	84.3%
	Yes	Count	15	11
		Col %	17.9%	15.7%
Dementia	No	Count	78	70
		Col %	92.9%	100.0%
	Yes	Count	6	
		Col %	7.1%	
Cancer	No	Count	69	61
		Col %	82.1%	87.1%
	Yes	Count	15	9
		Col %	17.9%	12.9%

During the years of observation period, 168 patients with CKD (Chronic kidney disease) stage 5 and calculated eGFR (Estimated glomerular filtration rate) of <15ml/min/1.73m² was followed in SKI by using MDRD (Modification of diet in renal disease) formula. Demographic and medical characteristics included in this study that compares conservative with dialysis groups are shown on(*table 1. Table 2a, Table 2b*):

Frequency *IHD= (Ischemic heart disease). *CVD=(Cerebrovascular disease).

*PVD=(Peripheral vascular disease).*COPD=(Chronic obstructive pulmonary disease).

Table 2a: Age group 1:

Crosstab

			Group belonging to		Total
			conservative	dialysis	
Agegroups1	Less than 70 years	Count	7	40	47
		% within Agegroups1	14.9%	85.1%	100.0%
		% within Group belonging to	8.3%	47.6%	28.0%
	More than 70 years	Count	77	44	121
		% within Agegroups1	63.6%	36.4%	100.0%
		% within Group belonging to	91.7%	52.4%	72.0%
Total		Count	84	84	168
		% within Agegroups1	50.0%	50.0%	100.0%
		% within Group belonging to	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	32.170(b)	1	.0001	.0001	.0001	

Table 2b: Age group2:

Crosstab

			Group belonging to		Total
			conservative	dialysis	
Agegroups2	Less than 80 years	Count	35	74	109
		% within Agegroups2	32.1%	67.9%	100.0%
		% within Group belonging to	41.7%	88.1%	64.9%
	More than 80 years	Count	49	10	59
		% within Agegroups2	83.1%	16.9%	100.0%
		% within Group belonging to	58.3%	11.9%	35.1%
Total		Count	84	84	168
		% within Agegroups2	50.0%	50.0%	100.0%
		% within Group belonging to	100.0%	100.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)	Point Probability
Pearson Chi-Square	39.734(b)	1	.0001	.0001	.0001	

Furthermore, factors including a patient's spiritual beliefs and the extent of the patient's social support network are important predictors of quality of life [13]. So there is controversy whether to choose conservative option or dialysis, the economic pressure for conservative treatments may prove hard to resist. Patients have also the right to have the legal choice (e.g. Patient self discrimination act) to refuse or accept medically indicated treatment. Patient therefore require careful counseling about the most appropriate treatment option, such issues should involve senior nurses, renal counselors and social workers assessing the patients in terms of understanding of their illness, functional capacity and dependency, and their family and social support, and to provide the prognosis and treatment options. The option not to dialyze should be part of the discussion with the patient and supported by a plan to offer support to individual and family, including community agencies, this is not rationing dialysis but rational dialysis, i.e. limiting the use of dialysis therapy in circumstances that render them detrimental, for instance, Patients with co morbidities that could not tolerate dialysis. Here comes the role of conservative management which aims to improve quality of life and treat uraemic symptoms, while fully supporting the patient and answering all their questions [13]. On the other hand, it is the duty of physicians to identify the clinical fitness and any comorbid conditions through the clinical follow up and decide whether to

commence conservative management or not. In circumstances where there are discrepancy (patient refusal) between the doctor and the patient opinions in SKI, both sides must be taken into consideration and one decision is sorted out to be medically satisfactory after discussion, the patient must be willingly agreed and satisfied.

Reason for choice of Conservative managements:

All of the choices are joint decision between the patient and the doctor despite that most of the patients in SKI prefers the Conservative option rather than renal replacement therapy for a number of reasons mentioned below:

1. Frail and Comorbid patients.

2. Social reasons.

3. Quality of life.

4. Refuse RRT.

5. The demented patients the only option is Conservative.

6. Patients with sever disability (Rheumatoid arthritis) cold not tolerate prolonged hours under Dialysis.

Among the conservative group, 40% of Conservative patients considered to be progressors (their eGFR>1 ml/min/1.73m²) while 60% are non-progressors as their (eGFR <1 ml/min/1.73m²).Percentage change of renal function deterioration over the last 5 years among the (conservative group) is 20% fall per year as shown in figure 1 and table 3:
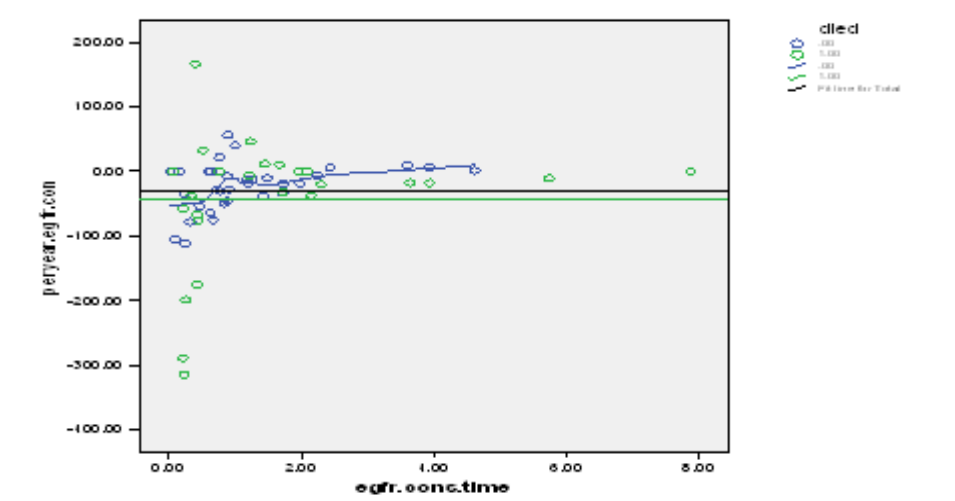
Figure 1

Table 3: The mean percentage change of eGFR (start or mean as baseline).

	Group belonging to	N	Mean	Std. Deviation	Std. Error Mean
percent progression (start as baseline)	conservative	78	-19.7835	34.23240	3.87606
percent progression (mean as baseline)	conservative	78	-30.0270	44.17960	5.00235

Table 4: Paired samples test.

	Paired Differences					t	df	Sig. (2-tailed)
Group	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
				Lower	Upper			
1	2.308	3.922	.444	1.423	3.192	5.196	77	.000
2	-7.465	10.793	1.164	-9.779	-5.151	-6.414	85	.000

Most of the patients submitted to conservative or dialysis measures underwent regular follow up at SKI out patient department for every 2, 4, 6 weeks or longer according to the patient clinical conditions, 40 patients were lost (died) over the period of study in the conservative group. Over this period, the mean survival time is 33.9 months (95% confidential interval, 25 to 42) and the median is 27.4 months (95% confidential interval, 22 to 32) in patients treated conservatively ($P = 0.0001$) .

Looking at the Kaplan-Meier survival curve shown below, figure 1. Generally, I found that dialysis patients live longer than conservative one (a round 7 years and more than 3 years respectively). There is a dramatic deterioration in renal function in the conservative group compared with a gradual decline in renal function in dialysis group.

50% survival is 3 years for the conservative patients while more than 7 years in the dialysis group (P value 0.001), after this period, most of the dialysis patients (a round 50%) still survive while most of the conservative patients have died already. That means the cumulative Hazard increases with time which is much more obvious with the Conservative patients, figure 3. Overall comparisons of statistical significance are shown in figure 7 and 8:
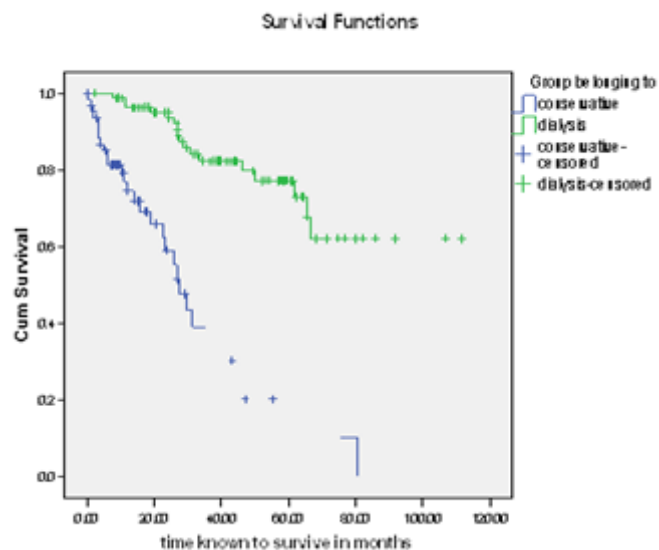
Figure 2: Kaplan-Meier survival curve Comparing the survival function between Conservative and Dialysis Patients.
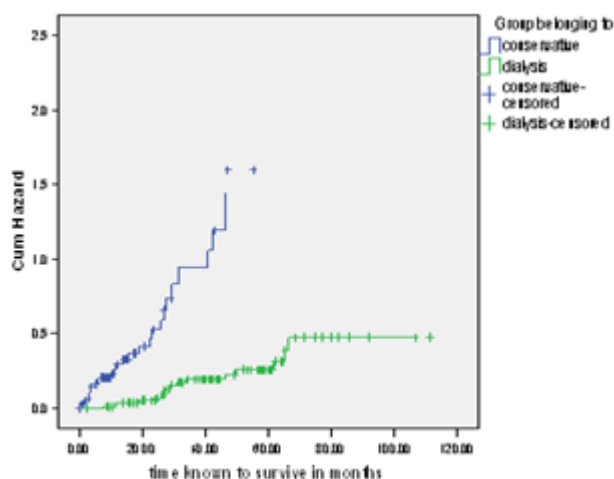

Figure 3: Kaplan-Meier survival curve comparing the cumulative Hazard between Conservative and Dialysis Patients

Table 4: Overall Statistical Comparisons between Conservative and Dialysis groups.Test the equality of survival distributions for the different levels of both groups.

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	41.391	1	.000

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Survival time function depends on many factors. For instance, the medical causes of CKD 5(Table 7), age of patients and the associated co morbidities that the patients had. It is obvious from the survival analysis of each comorbidity, the most statistical significant condition is Diabetes (P value=0.002), others are not significant.

Table 5: Causes of Renal Failure in the Conservative group:

Serial no.	Cause of Renal Failure	No.of Pt.	Percent
1	Renovascular disease	10	11.90%
2	Diabetes	18	21%
3	Obstructive Uropathy	10	11.90%
4	Malignancy/Myelomatosis	8	9.50%
5	Hypertension	14	16.60%
6	Renal Stones	6	7.10%
7	Others	18	21%
	Total	84	100%

Cause of death in the Conservative group:

There is no enough data demonstrating a clear cause of death in the Proton database, the patients notes as well as in the admission office of the Hospital as the majority of the patients had died out side Sheffield (Chesterfield, Rotherham, Doncaster and others).

The following are some causes of death

in the Conservative group I have found:

1. IHD, MI, Heart failure

2. Carcinoma liver.

3. Fracture nick of femur

4.Ruptured Aortic aneurysm.

5.Chronic renal failure and its sequalae

.6. Cardiovascular complication of Diabetes.

And those are the Causes

of death in the dialysis group:

1. Bronchopneumonia.

2. Peripheral vascular disease.

3. Valvular Heart disease.

4. Sever Heart disease.

5. Sepsis.

6. Cancer.
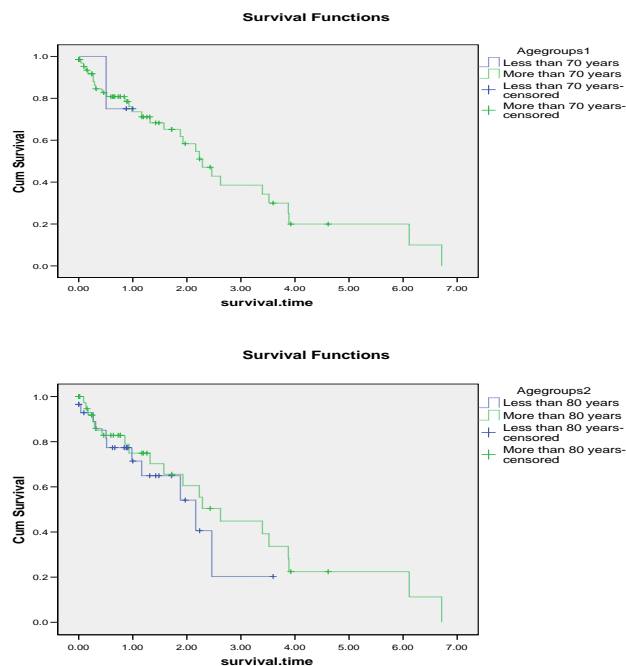
Figure 4: Survival functions of the conservative patients belonging to the age group 1 and 2:
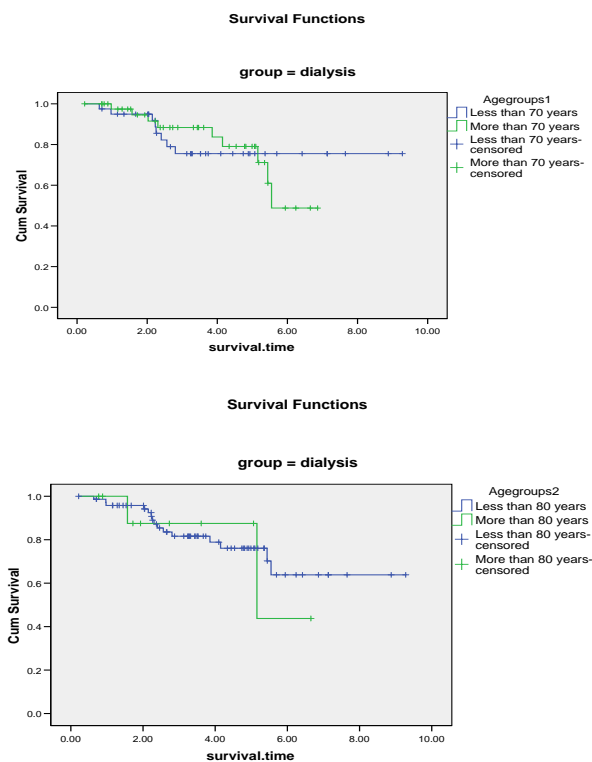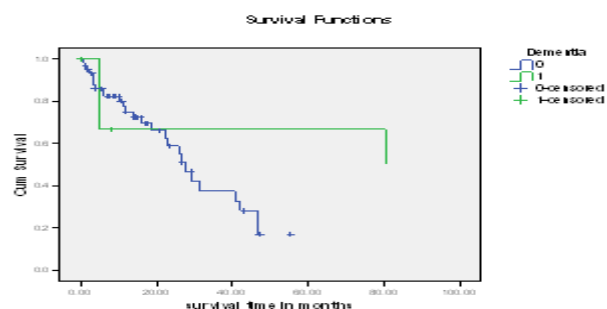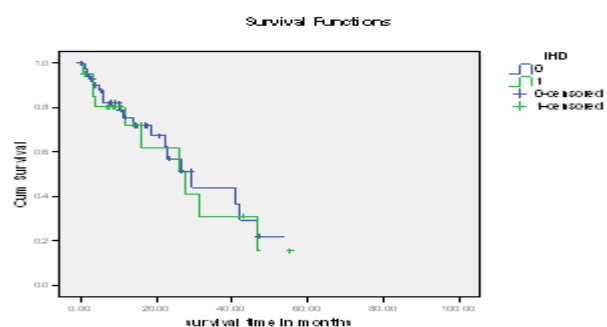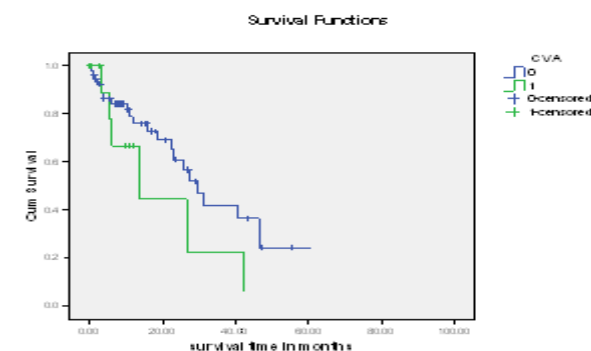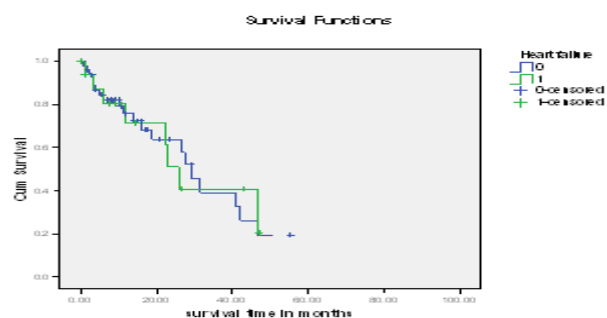

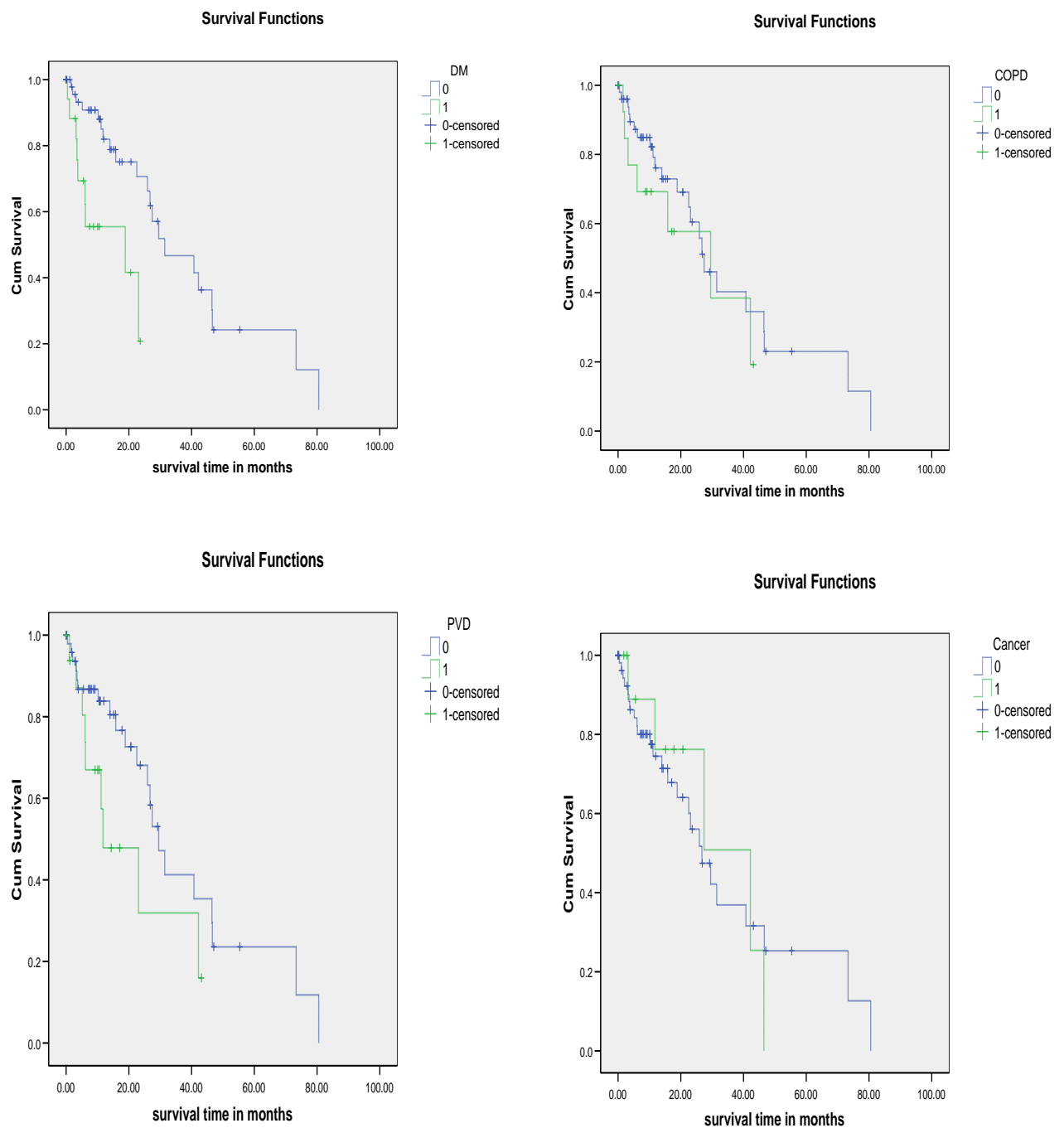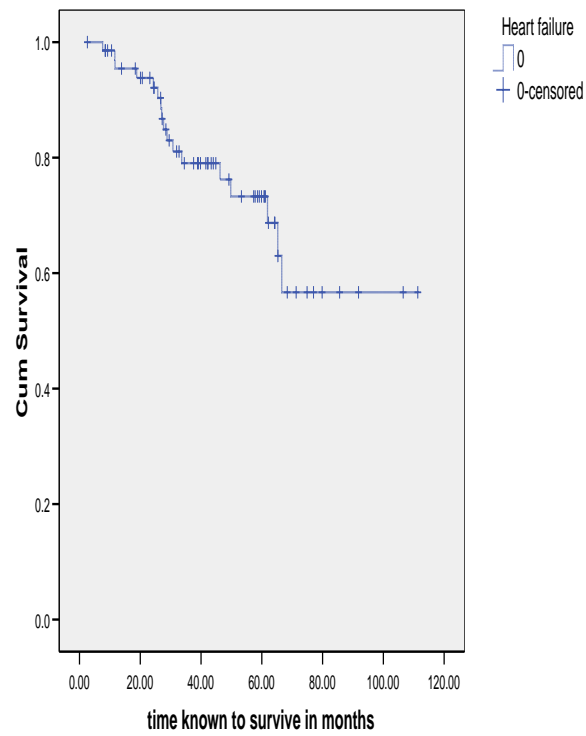**Figure 5:** Survival functions of the Dialysis patients belonging to the age group 1 and 2**Figure7:** survival The curves for each Comorbid condition in the conservative patients:

HF. P value=0.99, IHD. P value=0.79, CVA. P value=0.12, PVD. P value=0.08 DM. P value=0.002, COPD.

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P value=0.38, Dementia. P value=0.32, Cancer. P value=0.98

Figure 6: survival The curves for each Comorbid condition in the conservative patients:

HF. P value=0.99, IHD. P value=0.79, CVA. P value=0.12, PVD. P value=0.08
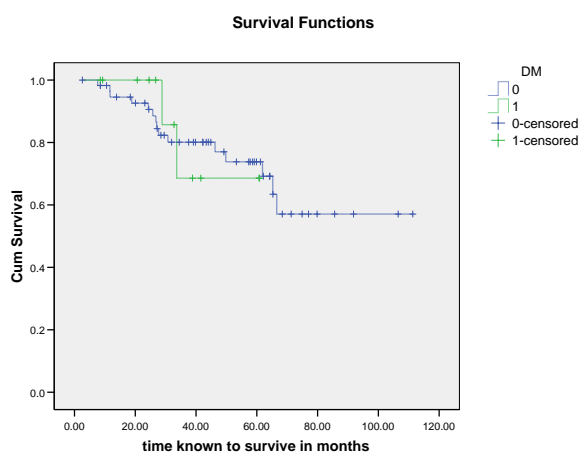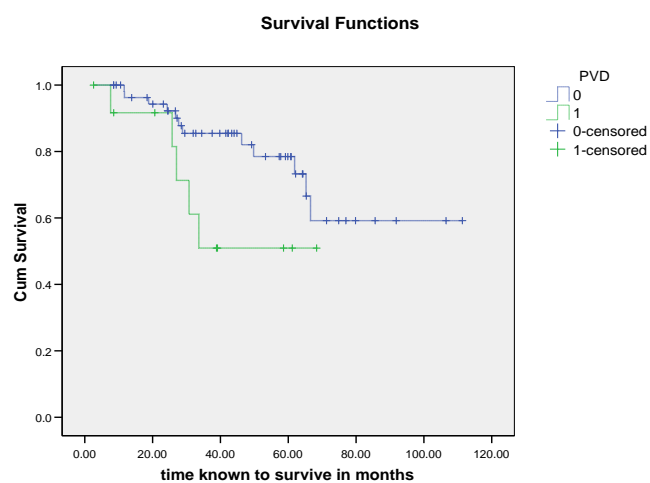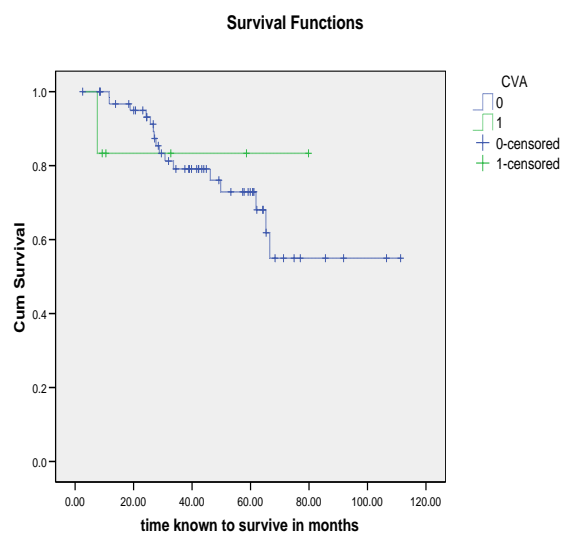
DM. P value=0.002, COPD. P value=0.38, Dementia. P value=0.32, Cancer. P value=0.98

Survival Function

Survival Functions

Survival Functions

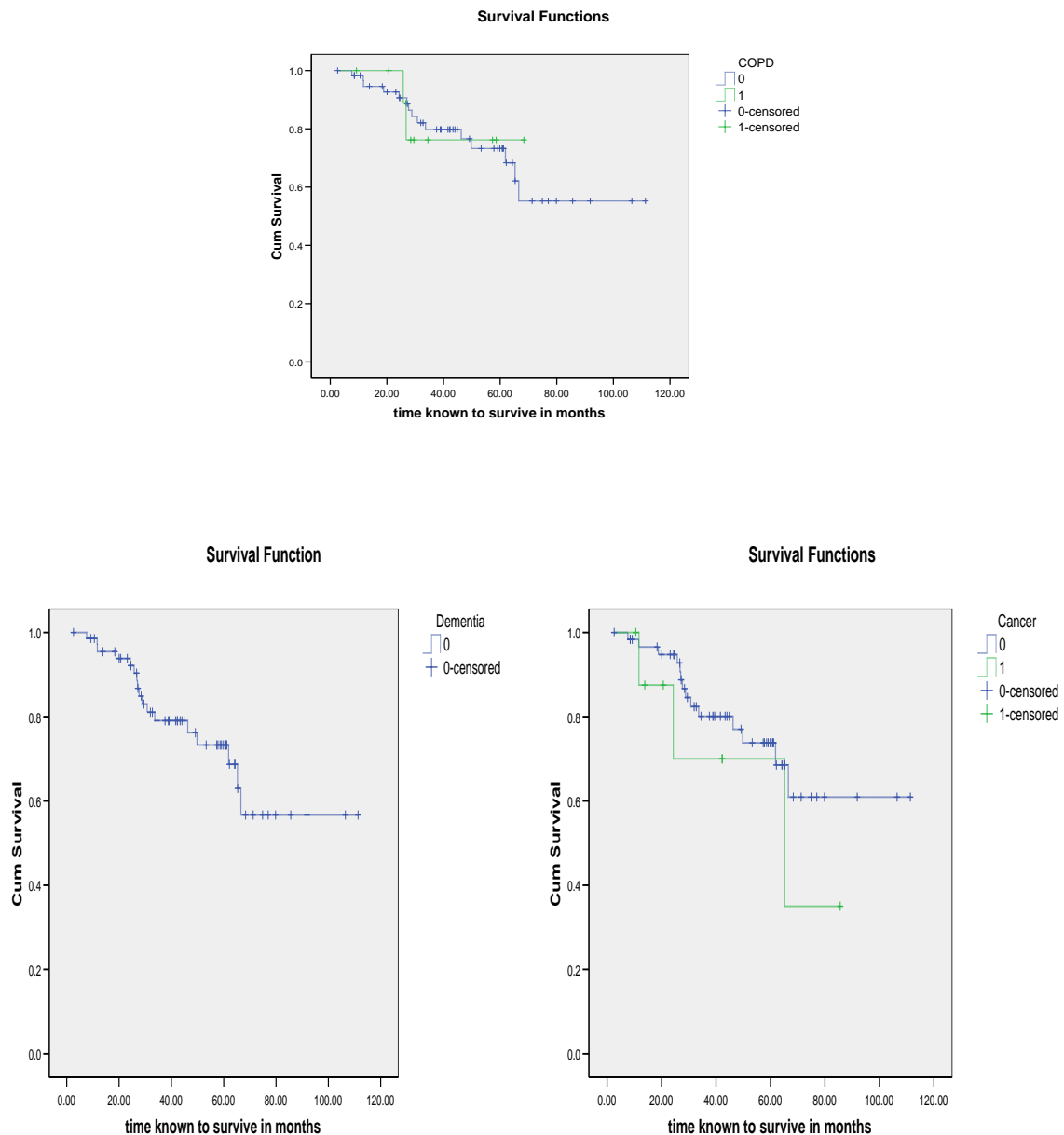**Survival Functions**

Survival Functions
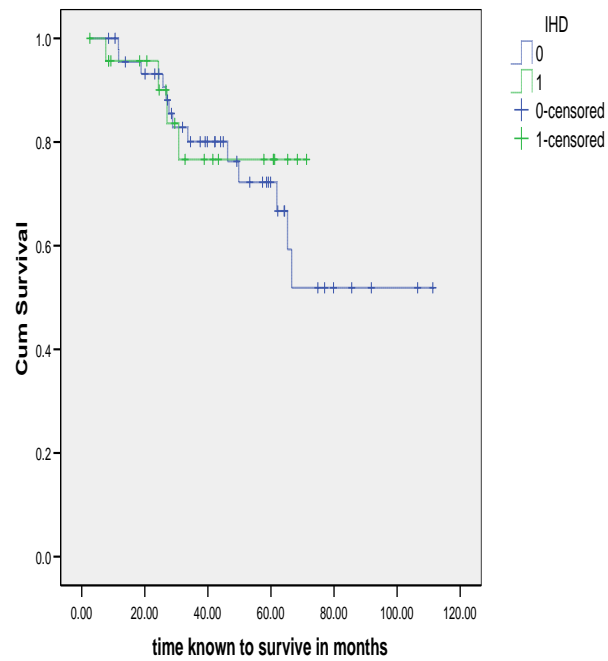
Figure 7: The survival curves for each Comorbid condition in the Dialysis patients:

IHD. P value=0.718, CVA. P value=0.913, PVD. P value=0.070

DM. P value=0.988, COPD. P value=0.913, , Cancer. P value=0.304.

It was clearly noted from the above survival analysis that, there was no much difference in the survival time of the Conservative patients aged >70 and those >80 compared with a longer survival time in case of Dialysis patients.

Analyzing the survival curves related to co morbidity in the Conservative group showed that co morbidity has a clear impact on survival which is most pronounced in Diabetes, here 50% of Conservative patients with no

diabetes survive 4 years compared with 2 years in those who have got diabetes(*P value=0.02*).

There is also a borderline statistical significance in those with CVD (P value= 0.08) as an impact of this co morbidity on survival (Figure: 3).

In the other hand, dialysis patients with comorbidity have shown a lesser survival time compared with those with no comorbidity especially noticed in patients with PVD (*P value 0.070*).

7. Discussion

No indication was given about patients with ESRD in terms not referred to a nephrology unit or were withheld from maintenance therapy, there is no formal barrier based on age for accepting older ESRD patients on a dialysis program in any Western country [1,2,7,9].

The mean age in the Conservative patients is 80 years compared to 70 years in the dialysis one, and they live shorter. The mean survival time in SKI is 33.9 months (95% confidential interval, 25 to 42) and the median is 27.4 months (95% confidential interval, 22 to 32) in patients treated conservatively (P =0.0001) which is 3 times more than Median survival 8.9 mo (95% CI, 4 to 10) of the conservative group (*P* < 0.0001) in Paris Necker University Hospital this which studied a smaller number of patients (37 Patients), the same Median survival in New Zealand.

The decision to dialyze or commence the Conservative approach has an impact on survival. Dialysis in such patients risks death caused by Conservative medical treatment [13] in the renal unit, Lister Hospital, Steven age, UK, in which the median survival after dialysis in these patients is 8.3 months was not significantly longer than beyond date of dialysis initiation in palliative treated patients 6.3 months.

One year survival is 80% in (SKI) compared with 71% in North Thames Dialysis Study. According to UK Renal Registry data 2015, Survival falls progressively with increasing age, 1 year after 90 days survival in 75-79 year olds is 74$\dot{/}$ compared with 57 $\dot{/}$ in those aged ≥ 85 years, and in New Zealand study is73.6% [14].

Most of the Conservative patients (38.4%) prefer Conservative treatment over Dialysis irrespective of the doctor opinion (32.9%), 40% having eGFR progression (Progressors) and the percentage change of their renal function is 20%.

The highest mortality in the Conservative group was caused by diabetes which is the highest percentage. In concordance with most of the similar studies. Diabetes play a major role as a cause of renal failure, and considered to be the most predictor factor for survival of the Conservative patients (the same as in Lister Hospital, Stevenage, UK). In SKI this followed by Cerebrovascular diseases as well which is defined as a damage to the blood vessels in the brain, resulting in a stroke. The blood vessels can become blocked because of fat deposits, or a wandering blood clot, blocking the flow of blood to a part of the brain. Sometimes, the blood vessels may leak, break, or burst, resulting in a hemorrhagic stroke. People with diabetes are at higher risk of cerebrovascular disease . Generally, The Mean survival time as well as one year survival is best achieved

in SKI.

8. Limitation of the study

1. We need further solutions.
2. Subgroups of patients do poorly on dialysis but we have not identified them yet and Conservative management outcomes have shown difference among many studies despite of being minor but it is going to be of great concern.
3. There is no randomized trial comparing dialysis versus conservative treatment as there are difficulties in data interpretation.
4. All studies are retrospective.
5. Difficulties in collecting data affects some results of the study.

9. Conclusion

As it has already been shown from **(PSCKD5C)** that;

1. Stage 5 (ESRD) increases the mortality.
2. Transplant/Dialysis prolongs survival but only in some patients.
3. Elderly patients with significant co-morbid disease may not benefit renal replacement therapy (RRT).
4. The mean age in the Conservative group is 80 years compared with 70 years in Dialysis group
5. The mean Survival time is 33.9 months.
6. Majority of the patients prefer Conservative Managements rather than dialysis.
7. 40% of patients on Conservative managements have progressive decline in their renal function.
8. More than 2 years survival time in Conservative group is 50% compared with 8 years in Dialysis group. (Function progressives)
9. Percentage change of the renal function over the last 5 years in (SKI) shows 20% decline per year in their renal function.
10. Diabetes is a major cause of renal failure and most predictor factor determines the survival time followed by Cerebrovascular disease and hence the total number of mortality increased in association with these comorbidity conditions.
11. We are certainly sure that this study is mythological, informative, practical as well as a prototypical one which can be performed in any area in the world as informative and for further assessment and management of CKD which will improve the disease outcomes even further. In the main time it gives a clue regarding the way and the success of such that particular kidney institute.
12. Performing such a study is intended for CKD5 as it carry a controverters in managements between different institutes.

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