Anemia and Hypoalbuminemia at Initiation of Hemodialysis as Risk Factor for Survival of Dialysis Patients

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ABSTRACT

Objective: To determine the survival of patients undergoing chronic maintenance hemodialysis by determining the relative risk (RR) of anemia and hypoalbuminemia at initiation of dialysis on survival.

Study Design: Cohort study.

Place and Duration of Study: Hemodialysis Unit of Shalamar Hospital, Lahore, from June 2003 to October 2006.

Methodology: This study was conducted on all patients of end stage renal disease who presented in Accident/Emergency Department of the hospital for the first time or received calls from other departments in getting dialysis. Patients with acute renal failure and those lost to follow-up were excluded from the study. At presentation, a history and examination was done and recorded. At the same time a blood sample was sent for routine hematological parameters (hemoglobin, total leucocyte count (TLC), biochemical (urea, creatinine, serum potassium and albumin) and viral markers (anti-HCV and HbsAg). Patients were followed up for outcomes. The outcomes of the study were continued dialysis, death and renal transplant. Kaplan-Meier and log Rank tests were used for determining survival. Relative risk was assessed on medical 9.2.

Results: One hundred and eighty five patients were studied including 99 (52.8%) males and 86 (47.2%) females. Major causes of renal failure were Diabetes mellitus in 125 (67.6%), chronic glomerulonephrotis in 31 (16.8%) and hypertension in 18 (9.7%). Most of the patients - 105 (60%) were euvoicmic. Sixty percent of patients had very high urea (> 200 mg/dl) and creatinine (> 8.0 mg/dl). The mortality of haemodialysis patients was seventy four percent per 100 patients per year, 62.24% being in the initial 6 months. One hundred and sixty four patients (91.1%) were anemic (hemoglobin < 11 gm/dl) and 124 (67%) were hypoalbuminemic (serum albumin < 4 gm/dl) on first presentation. Patients with group 1 have hemoglobin less than 11gm/dl (7.83 ± 1.51), group 2 had hemoglobin of equal to more than 11 gm/dl (11.56 ± 0.64) which was statistically significant (t = - 9.54, p= 0.000). The survival freedom in group 2 (Hb > 11 gm/dl) was higher than group 1 (Hb < 11 gm/dl) which is statistical significant (p = 0.023). On the basis of serum albumin (S.Alb), patients were divided into two groups i.e S.Alb less than 4 (3.15 ± 0.38 gm/dl) was group 1, and more than or equal to 4 (4.23 ± 0.28 gm/dl) was group 2, which were statistically significant (t = - 11.58, p < 0.001). The overall survival time was significantly shorter in group 1 patients than group 2 (p = 0.037). RR for low albumin was 1.27 and for low hemoglobin, it was 1.30.

Conclusion: Mortality of haemodialysis patients was seventy four percent per 100 patients per year. Amongst these 62.24% were in the initial 6 months. The mean survival time was 296 days. Patients with very low hemoglobin and albumin are at more risk for early deaths than patients with normal hemoglobin and albumin on first presentation for dialysis.

Key words: Anemia. Hypoalbuminemia. Nephrologist.
vascular diseases, inadequate dialysis i.e. Kt/V > 1.2/dialysis for thrice weekly dialysis, lower hemoglobin levels i.e. hemoglobin < 11 gm/dl, renal osteodystrophy, inflammation and hypertension. Several investigators reported that mortality rates for hemodialysis patients were greater during the first 90 days of dialysis therapy than at subsequent times. When kidney function deteriorates and GFR is less than 30 ml/minute, then erythropoitin secretion is decreased which leads to anemia. Anemia is very common in dialysis patients. Anemia of CKD is associated with several abnormalities like fatigue, shortness of breath, feeling cold, headache, deterioration in cardiac function, decreased cognition and mental activity. Anemia is related to reduced quality of life and increased morbidity and mortality of dialysis patients. Anemia correction by Erythropoietin Stimulating Agents (ESA’s) results in decreased cardiac output, stroke volume, heart rate, reduced myocardial ischemia and regression of left ventricular hypertrophy (LVH).

Wong et al. showed that patients with lower mean serum albumin levels on their first Kt/V method to assess adequacy of dialysis i.e. Kt/V < presentation for dialysis had an increased risk for early death. Serum albumin, serum protein, serum cholesterol and total leucocyte count are predictors of the nutritional status of dialysis patients. Low serum albumin is an important predictor of malnutrition which shows increased morbidity and mortality of dialysis patients. Serum albumin is used because of easy availability and a strong association with outcome, especially in ESRD patients. Patients who start dialysis at a very advanced stage (lower level of GFR) are more likely to have hypoalbuminemia because serum albumin is inversely proportional to GFR and directly proportional to hemoglobin level.

Anemia and malnutrition is quite common in our country and other developing countries, so this study was conducted to determine the survival of hemodialysis patients and its relationship with hemoglobin and albumin on their first presentation for dialysis.

**METHODOLOGY**

This study was conducted at the Hemodialysis Unit of Shalamar Hospital, Lahore, from June 2003 to October 2006. At presentation, a complete history of the patients was taken and a general physical and systemic examination was done and recorded. Patients of End Stage Renal Disease (ESRD) maintained on long term hemodialysis were included in the study. Patients lost to follow-up and those who never had regular dialysis were excluded from the study. Patients were put on bicarbonate dialysis through temporary access catheter until arteriovenous fistula/graft was mature for usage. Blood sample of each patient was drawn for hematological (hemoglobin and total leucocyte count (TLC)), biochemical (urea, creatinine, serum potassium and serum albumin) and viral markers (anti-HCV and HbsAg). Amongst all these parameters only serum albumin and hemoglobin was used for the determination of risk for the survival of dialysis patients. Patients were divided into two categories on the basis of hemoglobin. Patients in group 1 have hemoglobin less than 11 gm/dl (7.83 ± 1.51) and those in group 2 have hemoglobin equal to more than 11 gm/dl (11.56 ± 0.64). On the basis of S.Alb, patients were divided into two groups- group 1 with S.Alb less than 4 (3.15±0.38 gm/dl) and group 2 having S.Alb more than or equal to 4 (4.23 ± 0.28 gm/dl). Group 2 in hemoglobin and albumin was considered as a reference group according to Dialysis Outcome Quality Initiative (DOQI) guidelines. Patients were followed up for outcomes. The outcomes of this study were continued dialysis, death and renal transplant. Survival of the patients was analyzed by the Kaplan-Meier method and by comparing the estimated survival curves by the Log Rank test. A multivariate analysis was done using the proportional hazard regression model to detect possible prognostic variables associated with survival. All this analysis were done using the statistical package software SPSS 14.0 and relative risk (RR) was calculated by using Medcalc 9.2.

**RESULTS**

Two hundred and forty eight patients were registered for hemodialysis in the study period. Sixty three patients were excluded from the study because they were lost to follow-up. A majority of the patients were male 99 (53.5%) and their mean age was 51 ± 22.47 years, as shown in Table I. Causes of ESRD were diabetic nephropathy (n=125, 67.6%), hypertensive nephropathy (n=18, 9.7%), chronic glomerulonephritis (n=31, 16.8%), nephrolithiasis/obstructive nephropathy (n=7, 3.78%), unknown cause (n=3, 1.62%), and amyloidosis (n=1, 0.54%). Most of the patients were euvoelemic and hepatitis B and C were negative in a majority of the

<table>
<thead>
<tr>
<th>Date</th>
<th>Results (n)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>99 (53.5%)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>86 (46.5%)</td>
</tr>
<tr>
<td>Causes of ESRD</td>
<td>Diabetic nephropathy</td>
<td>125 (67.6%)</td>
</tr>
<tr>
<td></td>
<td>Hypertensive nephropathy</td>
<td>18 (9.7%)</td>
</tr>
<tr>
<td></td>
<td>Chronic glomerulonephritis</td>
<td>31 (16.8%)</td>
</tr>
<tr>
<td></td>
<td>Nephrolithiasis/obstructive nephropathy</td>
<td>7 (3.78%)</td>
</tr>
<tr>
<td></td>
<td>Unknown cause</td>
<td>3 (1.62%)</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
<td>1 (0.54%)</td>
</tr>
<tr>
<td>Volume overload</td>
<td>80 (37-40%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>Negative</td>
<td>182 (73.4%)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>66 (26.6%)</td>
</tr>
<tr>
<td>HbsAg</td>
<td>Negative</td>
<td>240 (86.8%)</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>8 (3.2%)</td>
</tr>
<tr>
<td>Outcome</td>
<td>Death</td>
<td>104 (56.2%)</td>
</tr>
<tr>
<td></td>
<td>Still on dialysis</td>
<td>71 (38.4%)</td>
</tr>
<tr>
<td></td>
<td>Renal transplant</td>
<td>10 (5.4%)</td>
</tr>
</tbody>
</table>
patients. All patients were getting twice weekly bicarbonate dialysis. Temporary access catheter was used in patients without permanent access and they were then switched to AV fistula when it was mature. Mean survival time was 296 ± 325 days ranging from 1 to 1400 and 55 days. Outcome of the patients is shown in Table I. Mean hemoglobin (Hb) was 8.22 ± 1.78 gm/dl and a majority of the patients 164 (88.64%) were anemic. A majority of the patients 124 (67%) were hypoalbuminemic also and mean serum albumin was 3.24 gm/dl. The statistical significance of the hematological and biochemical parameters is shown in Table II. Patients in group 1 had hemoglobin less than 11 gm/dl (7.83 ± 1.51), group 2 patients had hemoglobin equal to or more than 11 gm/dl (11.56 ± 0.64) which was statistically significant (t= - 9.54, p < 0.001). The survival freedom in group 2 (Hb > 11 gm/dl) was higher than group 1 (Hb < 11 gm/dl), which was statistically significant (p= 0.023) as shown in Figure 1. On the basis of S.Alb, patients were divided into two groups i.e. S.Alb less than 4 (3.15 ± 0.38 gm/dl) - group 1, and S.Alb more than or equal to 4 (4.23 ± 0.28 gm/dl) group 2, which were statistically significant (t= -11.58, p < 0.001). The overall survival time was significantly shorter in group 1 patients than group 2 (p= 0.037) as shown in Figure 2. Other factors like gender, serum urea, serum creatinine and TLC had no statistically significant effect on survival time. S.Alb of less than 4 gm/dl (RR=1.27) and Hb of less than 11 gm/dl at initiation of dialysis (RR=1.30) implied poor prognosis for survival.

Table II: Statistical significance of hemoglobin and serum albumin of hemodialysis patients on first presentation (n=185).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin group 1 (&lt; 10.9 gm/dl) to group 2 (&gt; 11 gm/dl = reference group)</td>
<td>1.30</td>
<td>1.07-2.13</td>
</tr>
<tr>
<td>S. Albumin group 1 (&lt; 3.9 gm/dl) to group 2 (&gt; 4 gm/dl = reference group)</td>
<td>1.27</td>
<td>1.21-2.26</td>
</tr>
</tbody>
</table>

Figure 1: Survival functions.

DISCUSSION

In this study, the mortality of dialysis patients was 74.4% per 100 patients per annum as compared to 6.6% in Japan, 15.6% in Europe, and 21.7% in the US. This high mortality is alarming for health authorities and renal physicians and there is need to do more extensive analysis in other centers. The high rate of mortality is much worse than in the general population and in patients with acute myocardial infarction (AMI) and stroke patients. The relative risk of death for AMI and stroke patients was 0.39 (0.33-0.46) and 0.40 (0.36-0.46) respectively, when death risk of dialysis patients was taken as reference (1.00). In this study, a majority of deaths (62.%) happened in the initial six months as are observed in other international studies. This high rate of mortality is due to late referral to nephrologists, unnecessary delay in the initiation of dialysis, malnutrition on presentation for dialysis leading to anemia and hypoalbuminemia, temporary access catheter as primary access for first dialysis and co-morbidities.

Anemia is an important predictor of morbidity and mortality in dialysis patients. In this study hemoglobin (> 11gm/dl) was normal in only 21 (11.35%) patients and the majority of the patients (164 - 88.64%) were anemic. A similar fact was observed by Anees et al. and Butt et al. when 7 (14%) patients were had normal hemoglobin. This degree of severity of anemia is not seen in any international report where usually serum hemoglobin is in the range of 11-12 gm/dl. A lower level of hemoglobin at the initiation of dialysis therapy may be caused by one and more factors like iron deficiency, lack of pre-dialysis erythropoietin therapy and inhibition of erythropoiesis by uremic factors. The absorption of oral iron is decreased in the presence of ESRD and it is unlikely that iron deficiency can be corrected solely by the administration of oral iron. In a developing country like Pakistan, the per capita income is 430 US Dollars.
Dialysis expenses are 400 US Dollars/month and if erythropoietin therapy is added, this further increases the amount of the finances required. In this study, severity of anemia at initiation of dialysis was directly related with mortality of these patients. The survival freedom in group 2 (Hb > 11 gm/dl) is higher than group 1 (Hb < 11 gm/dl) which was statistically significant. A similar observation was made in Thailand by Krairittichai.25 According to him, patients with hematocrit of 27%, 27-29.9%, 30-32.9% and 36% had mortality risk of 1.90%, (p < 0.01), 2.10%, 1.74% and 1.174% respectively. The same thing is observed by Portoles’ Morbidity and Mortality Anemia Renal (MAR) study.26 According to him, hospitalization and mortality rates during hemodialysis are related to anemia. The relative risk and confidence interval (CI) for hospitalization and death were 0.86 (0.81-0.91) and 0.82 (0.73-0.91) respectively, per 1gm/dl increase in initial Hb after adjustment for comorbidity, vintage, etiology, access type, albumin and kt/v. The probability of remaining free from hospitalization was 0.34 (0.27-0.41) for initial Hb < 10 gm/dl, 0.47 (0.41-0.53) for Hb 10.11 gm/dl, 0.54 (0.49-0.59) for Hb 11-12 gm/dl and 0.63 (0.59-0.67) for Hb > 12 gm/dl. The analysis for patients survival was 0.77 (0.71-0.83) for Hb < 10gm/dl vs. 0.82 (0.77-0.87) for Hb 10-11 vs. 0.89 for Hb 11-12 vs. 0.92 (0.90-0.94) for Hb > 12 gm/dl, p < 0.001.26

Serum albumin is very commonly used in the assessment of the nutritional status of dialysis patients and hyposalbuninemia predicts morbidity and mortality for these patients.28-29 K/DOQI Nutritional Guidelines recommend measurement of serum albumin as part of the routine assessment of nutritional status in maintenance dialysis patients. In this study, a majority of the patients 12 (67%) were hypoalbuminemic and their mean albumin was 3.24 gm/dl. The severity of hyposalbuninemia was directly related with increased mortality. Factors responsible for hyposalbuninemia may be unnecessary restriction in taking protein, metabolic acidosis, delayed gastric emptying, co-morbidities and underlying inflammation. The overall survival time was significantly shorter in group 1 (serum albumin < 11 gm/dl) patients than group 2 (serum albumin > 11 gm/dl) patients. The same fact was observed by Wong and Orlic et al.11,29 According to Orlic, mean serum albumin was 3.19 ± 0.59 gm/dl in patients with less than one year survival as compared to 4.18 ± 0.67gm/dl in patients with 5 years survival.30 According to Wong, multivariate analysis demonstrated that each -1 g/dl difference in serum albumin between patients was associated with a 54% higher risk of death [adjusted relative risk (aRR): 1.54%].11 This was independent of glomerular causes for their ESRD and other potential confounding variables.

Early referral to nephrologists, work up for anemia and its management including erythropoietin therapy intervention by a dietitian in pre-dialysis patients is recommended in view of the present findings. There is also a need to study other factors affecting the survival of dialysis patients.

This study is based upon data of a single centre and only two factors (hemoglobin and S.Alb) were studied in relation to survival of dialysis patients. These are limitations of this study.

**CONCLUSION**

Patients with advanced renal failure have a high mortality directly related with severity of anemia and hyposalbuninemia, particularly in the first 6 months.

**REFERENCES**


