Hcv Seroconversion after Kidney Transplantation

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Abstract: Background: Overall survival after solid organ transplantation has significantly increased over the last several years. The prevalence of anti – HCV antibody positivity in kidney transplant recipients is estimated to be between 6 % and 46 %. **Patients and Methods:** Eighty kidney transplanted patients were divided into two groups: HCV – ve Group A (40 patients) and HCV + ve Group B (40 patients). Nine patients out of 40 (22.5 %) of Group A were seroconverted (from HCV – ve to HCV + ve), and constituted Group C. The remaining persistent HCV – ve patients of Group A (31 patients) constituted Group A[1]. We didn`t have any seroconversion from HCV + ve to HCV –ve. All patients were subjected to clinical examination and for all patients the following was done: serum creatinine, blood urea, AST, ALT. HCV antibody ELISA (third generation) was done before and post – transplantation. **Results:** Group B patients was slightly older than Group A, in a borderline significant way. There was no significant difference between Group A[1], Group B, and Group C as regards age. There was no significant difference as gender distribution between Group A[1], Group B, and Group C. Group B had longer duration of HD before transplantation than Group A ($P < 0.001$). Group B and Group C had longer duration of HD before transplantation than Group A[1] ($P < 0.001$) Group A had much less percent of patients (22.6 %) who received blood transfusion before transplantation, than Group B (62.5%) & Group A[1] had much less percent of patients (19.3 %) who received blood transfusion after transplantation, than Group C (44.44 %). HD after transplantation was much less in Group A[1] (12.9 %) than Group C (44.4 %). **Conclusion:** HD before and after transplantation, blood transfusion before and after transplantation, acute rejection therapy and graft infection transmission, are still the main causes of seroconversion (from HCV –ve to HCV + ve) after kidney transplantation.

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1.Introduction

In 1988, Choo *et al.* (1989), were able to clone and express in *Eschericha coli* the main agent of the parenterally – transmitted HNANB (Hepatitis non – A non – B), now called hepatitis C virus (HCV) Kuo *et al.* (1989), developed a specific serological assay for circulating antibodies to HCV.

Kidney transplantation is renal replacement modality of choice for ESRD and is associated with lower mortality and improved quality of life compared with chronic dialysis treatment (Tonelli *et al.*, 2011).

Hepatitis virus infections, mainly hepatitis B virus and hepatitis C virus (HCV) infections still constitute a major problem because they are common in allograft recipients and are a significant cause of morbidity and mortality after transplantation. (Delladetsima *et al.*, 2006; Vallet - Pichard *et al.*, 2011).

HCV Ab seroconversion is relatively rare after kidney transplantation in general whether from positive to negative, or the opposite. Although Egypt is one of the countries in the world having high prevalence of HCV infection among dialysis patients, if not the highest, yet the literature is poor in studies relevant to this issue in our country.

The prevalence of anti – HCV antibodies among kidney recipients living in different countries varies between 2.6 % to 80 %. HCV seems to be the most important cause of chronic liver disease in kidney recipients. (Moghaddam *et al.*, 2008).

The prevalence of HCV infection may be underestimated according to antibody assay alone, and HCV RNA testing, to confirm infection in anti – HCV antibody positive patients is performed inconsistently (Terrault and Adey, 2007).

2. Patients and Methods

Eighty kidney transplantation patients were included in this study. All patients have been investigated at the renal transplantation outpatient clinic of Nasr City Insurance Hospital, Cairo, Egypt.

At first Patients were divided into two groups: Group A included 40 Kidney transplanted patients who were HCV antibody – negative by ELISA, at time of transplantation.

Group B included 40 Kidney transplanted patients who were HCV antibody – positive by ELISA, at time of transplantation. Nine patients

derived from Group A constituted Group C (who were found to be seroconverted from negative to positive to HCV at time of our study) and the remainder of Group A patients who persisted as HCV negative (31) patients constituted Group A [1], and in our study we didn t have any seroconverted patients from positive to negative.

All patients who were subjected to dialysis therapy, have undergone conventional hemodialysis sessions for 4 hours 3 times weekly, using polysulfone dialysers (low flux) and bicarbonate dialysate.

We excluded from our study patients having other hepatotropic viruses co – infection, patients having ALT level more than twice normal, patients having advanced post - transplant liver cirrhosis or post – transplant liver cell failure. An informed consent was obtained from participants in the study.

Methods

All patients were subjected to full clinical examination and to the following laboratory investigations: serum creatinine, blood urea, liver enzymes (ALT, AST) complete blood count. All previous investigations were done by routine laboratory methods used in Nasr City Insurance Hospital laboratories, Ministry of Health, Cairo, Egypt.

HCV antibody by ELISA (third generation) for all patients before transplantation and post – transplantation after variable periods.

PCR for HCV RNA were done to ten patients who were selected randomly from each group to demonstrate the relevance of antibody assay in relation to PCR. Extraction and Isolation of viral RNA from the samples were done by the QIA symphony SP using QIAEGEN assay technology.

Statistical Methodology

Statistical analysis was performed using Statistical Package for Social Sciences, Version 17.0 (SPSS, Inc., Chicago, III., USA) for Windows. Continuous variables were analyzed as mean values $\pm$ standard deviation (SD) or median (range) as appropriate. Percentages were calculated for categorical data. For categorical variables, differences were analyzed with X^2 (chi – square) test and Fischer s exact test when appropriate. Differences among continuous variables with normal distribution were analyzed by Student s T – test; for continuous variables without normal distribution, we used non – parametric tests and differences were analyzed by the Mann – Whitney U – test. Differences among the three groups (sero – negative, sero – positive and sero – converted group) were analyzed with Kruskal Wallis test (non - parametric analogue for ANOVA) and Bonferroni post hoc test to adjust for multiplicity. Correlations were determined by using Pearson s test. *P* value ≤ 0.05 was considered statistically significant and < 0.001 was considered as highly significant. *P* value >0.05 to < 0.1 is considered borderline significant.

3.Results

Table (1): Comparison between Group A (HCV – ve, 40 patients) and Group B (HCV + ve, 40 patients) as regards age (years).

	Groups	*Mean*	*Std. Deviation*	*P value*
Age	Group A	41.5	12.2	0.088
	Group B	46.4	12.8	

Student t- test

There was a borderline statistically significant difference between group A and group B as regard age.

Table (2): Comparison between Group A (HCV – ve, 40 patients) and Group B (HCV + ve, 40 patients) as regards gender distribution.

	Groups	*Male*	*Female*	*P value*
Gender	Group A	28	12	0.056
	Group B	35	5	

Chi – square test

Males constituted 70 % (28 / 40) of HCV – ve Group A and 87.5 % (35 / 40) of HCV + ve Group B. Females constituted 30 % (12 / 40) of HCV – ve Group A and 12.5 % (5 / 40) of HCV + ve Group B. There was a borderline significant difference in gender distribution between Group A and Group B.

Table (3): Comparison between Group A (HCV – ve, 40 patients) and Group B (HCV + ve, 40 patients) as regard dialysis therapy before transplantation.

	Group	*On dialysis*	*Not on dialysis*	*precent*	*P value*
Dialysis	Group A	35	5	87.5	0.055
	Group B	40	0	100	

Fischer exact test

In HCV –ve group A, 35 patients (87.5%) were on dialysis therapy before transplantation, while in HCV + ve group B, 40 patients (100%) who were on dialysis therapy before transplantation.

There was a borderline significant difference between HCV – ve Group A and HCV + ve Group B as regards number of patients receiving dialysis therapy before transplantation.

Table(4): Comparison between Group A (HCV - ve, 40 patients) & Group B (HCV + ve, 40 patients) as regards the duration of dialysis therapy before transplantation (years).

	Groups	*Median*	*Range*	*P value*
Duration of dialysis	Group A	2	0.3-10	<0.001
	Group B	4	1-12	

Chi – square test

There was a highly significant difference between HCV – ve Group A and HCV + ve Group B as regards duration of dialysis therapy before transplantation.

As regards graft donors of HCV – ve Group A (40 patients), 11 donors out of 40 (27. 5 %) were recipient relatives, while 29 donors out of 40 (72.5 %) were not recipient relatives. In HCV + ve Group B (40 patients), also 11 donors out of 40 (27.5 %) were recipient relatives, while 29 donors out of 40 (72. 5 %) were not recipient relatives. There was no significant difference between the two groups as regards donors being related or not to recipients (P = 1.000).

In persistent HCV - ve Group A^1 (31 patients), 10 donors out of 31 (32.3 %) were recipient relatives and 21 donors out of 31 (67.7 %) were not recipient relatives. The percent of recipient related and non – related donors in HCV + ve Group B is as stated before (27.5 % and 72.5 % respectively). In seroconverted Group C (9 patients), 1 donor out of 9 (11.1 %) were recipient relatives and 8 donors out of 9 (88.9 %) were not recipient relatives. There was no significant difference between the three groups as regards percentage of recipient – related and non – related donors (P= 0.457), as performed by Chi – Square test

In the eighty kidney transplanted patients in our study, 79 donors out of 80 were HCV – ve by antibody detection by ELISA 3rd generation, Only one donor was HCV + ve by antibody assay and his recipient was also positive (included in HCV + ve Group B).

All the eighty transplanted patients in our study, had a mean transplantation duration of 2.0116 $\pm$ 0.004 years (24.139 $\pm$ 0.04 months).

The HCV - ve Group A^1 (31 patients) had a mean transplantation duration of 2.0082 $\pm$ 0.0002 years (24.098 $\pm$ 0.0024 months).

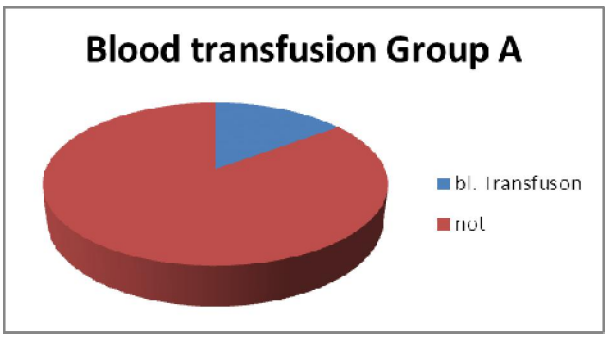
The HCV + ve Group B (40 patients) had a mean transplantation duration of 2.022 $\pm$ 0.015 years (24.264 $\pm$ 0.18 months).

The seroconverted Group C (9 patients) had a mean transplantation duration of 2.0077 $\pm$ 0.00003 years (24.092 $\pm$ 0.00036 months).

There was no statistically significant difference as regards duration of transplantation between HCV – ve Group A^1 (31 patients), HCV + ve Group B (40 patients), and the seroconverted Group C (9 patients).

In our study, 14 patients out of 80 (17.5 %), had experienced acute rejection as follows:

4 patients out of 31 (12.9 %) in HCV -ve Group A^1 and they have responded to pulse steroids. 6 patients out of 40 (15 %) in HCV + ve Group B, and 5 patients out of these 6 patients have responded to pulse steroids, while the 6th has responded to pulse steroids and ATG. 4 patients out of 9 (44.44 %) in seroconverted Group C have experienced acute rejection and 3 patients out of these 4 patients have responded to pulse steroids, while the fourth has responded to pulse steroids and ATG.



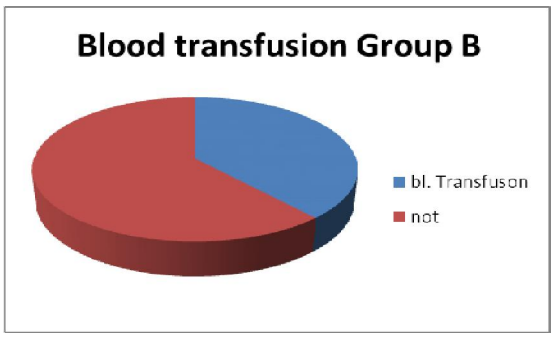
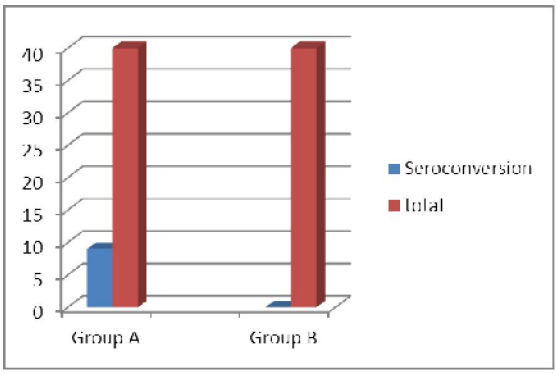


Figure (1): Comparison of blood transfusion before transplantation in HCV – ve Group A (40 patients) and HCV + ve Group B (40 patients).

In HCV – ve Group A, there was 7 patients out of 40 had a history of blood transfusion before transplantation (22.6 %), while there was 25 patients out of 40 in HCV + ve Group B having a history of blood transfusion before blood transplantation (62.5 %). There was a highly significant difference between the two groups as regards blood transfusion before transplantation (P =0.001).



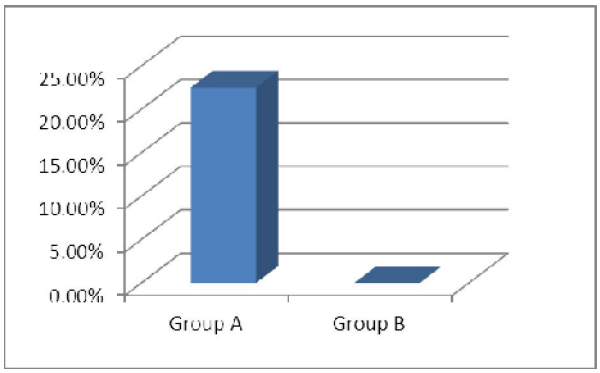


Figure (2): the rate of HCV seroconversion after transplantation in group A (HCV – ve, 40 patients) & group B (HCV + ve, 40 patients) as detected by HCV antibodies (ELISA 3rd generation).

HCV seroconversion after transplantation was found in 9 patients out of 40 in group A (22.5%), these 9 patients constituted group C, and there was no seroconversion in group B.

• PCR for HCV RNA was done to ten patients who were selected randomly from each group to demonstrate the relevance of antibody assay in relation to PCR and the results were identical to antibody assay by ELISA 3rd generation.

Table (5): Comparison between Group A (HCV – ve, 40 patients) and group B (HCV + ve, 40 patients) as regards serum creatinine (mg/dl), blood urea (mg / dl), AST (U/L), ALT (U/L) and serum albumin (gm / dl) in group A and group B.

	Group A			Group B			
	Median	Min	Max	Median	Min	Max	P value
S.Creat.	1.2	0.6	5.3	1.4	0.5	4	0.078
Urea	44	22	106	47	18	174	0.261
AST	18	10	122	22	12	102	0.051
ALT	21	3	158	31	11	154	0.004
Albumin	4	3.1	5.1	4	2.7	4.5	0.028

Mann Whitney test

Study showed borderline significant difference between HCV – ve Group A (40 patients) and HCV + ve Group B (40 patients) as regards serum AST level and serum creatinine, while it showed significant difference between the two groups as regards serum albumin, and a highly significant difference as serum ALT level.

Table (6): Comparison of age & gender between Group A[1] (persistent HCV – ve, 31 patients) & Group B (HCV + ve, 40 patients) & Group C (seroconverted, 9 patients).

	Group A[1] Group B		Group C		
Factors	**Negative**	**Positive**	**Seroconverted**	**Test**	***P* value**
	n=31	**n=40**	**n=9**	**value**	
Age (yrs)					
Mean ±SD	40.7±12.5	46.4±12.8	44.2±12.0	f=1.757	0.180
Range	15-56	16-65	24-62		
Gender					
Male	21(70.0)	35(87.5)	6(66.7)	χ^2=3.948	0.139
Female	9(30.0)	5(12.5)	3(33.3)		

Age by Fischer exact test, Gender by Chi-square.
There was no statistically significant difference between the three groups (A[1], B, & C) as regard age and gender.

Table (7): Comparison of the dialysis therapy beforetransplantation in Group A[1] (persistent HCV – ve,31 patients), group B (HCV + ve, 40 patients) & group C (seroconverted, 9 patients).

	Group	On dialysis	Not on dialysis	percent	P value
Dialysis	Group A[1] (31)	26	5	86.7	0.032
	Group B (40)	40	0	100	
	Group C (9)	9	0	100	

Fischer exact test

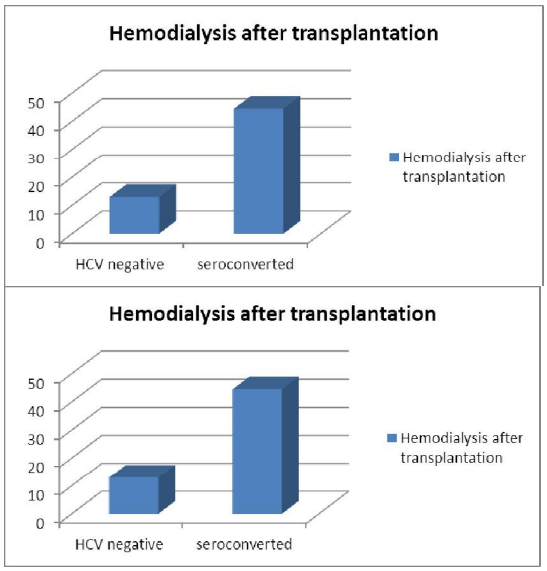
Study showed a statistically significant difference as regard undergoing dialysis therapy before transplantation between the 3 groups.

Table (8): Comparison of the dialysis therapy duration before transplantation in Group A[1] (persistent HCV – ve, 31 patients), group B (HCV +ve, 40 patients) & group C (seroconverted, 9 patients).

	Groups	***Median***	***Range***	***P value***
Duration of dialysis	Group A[1]	2	0.3-6	<0.001
	Group B	4	1-12	
	Group C	3	1-10	

Chi – square test

There was a highly statistically significant difference as regard duration of dialysis therapy before transplantation between the three groups.



Figre (3): Comparison of hemodialysis therapy after transplantation between Group A[1] (persistent HCV – ve, 31 patients) & group C (seroconverted, 9 patients).

The incidence of hemodialysis therapy after transplantation in our study in HCV – ve group A[1] patients who were still HCV negative was 4 patients out of 31 (12.9%) while it was 4 patients out of 9 (44.4%) in group C (the seroconverted group).

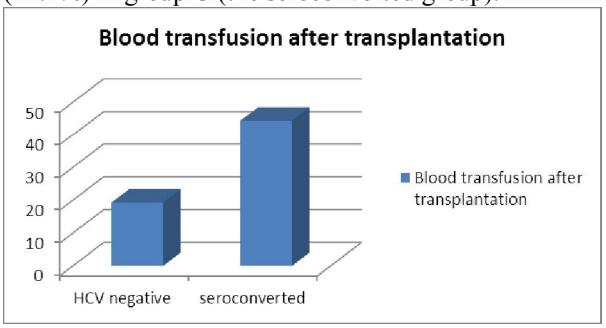


Figure (4): Comparison in blood transfusion after transplantation between Group A[1] (persistent HCV – ve, 31 patients) & group C (seroconverted, 9 patients).

The incidence of blood transfusion after transplantation in our study in HCV – ve group A[1] patients who were still HCV negative was 6 patients

out of 31 (19.3%), while it was 4 patients out of 9(44.4%) in group C (the seroconverted group).

Table (9): The frequency of different immunosuppressive drugs between the 3 groups (HCV – ve Group A[1] [31 patients], HCV +ve Group B [40 patients], and seroconverted Group C [9 patients]).

	Group A[1] N (%)31	Group B N(%)40	Group C N(%)9	Total N(%)80
Cyclosporin	29(93.5%)	31(77.5)	8(88.9%)	68(85%)
Tacrolimus	2(6.5)	9(22.5%)	1(11.1%)	12(15%)
MMF	24(77.4%)	23(57.5%)	6(66.7%)	53(66.3%)
Azathioprine	7(22.6%)	17(42.5%)	3(33.3%)	27(33.7%)

All the patients are receiving immunosuppressive protocol low dose corticosteroids, low dose calcinurin inhibitors CNI (either cyclosporine or tacrolimus) and antiproliferative drugs (either MMF or azathioprine).

68 patients (85%) are on cyclosporine 29 patients out of 31 in persistent HCV-ve group A[1] (93.5%), 31 patients out of 40 in HCV + ve group B (77.5%) & 8 patients out of 9 in group C (88.9%)} while 12 patients out of the 80 patients (15 %) of our study are on tacrolimus {2 patients out of 31 in persistent HCV – ve group A[1] (6.5%), 9 patients out of 40 in HCV + ve group B (22.5%)& 1 patient out of 9 in seroconverted group C (11.1%)}.

In our study, 53 patients out of 80 (66.3%) are on MMF{24 patients out of 31 in persistent HCV –ve group A[1] (77.4%), 23 patients out of 40 in HCV + ve group B (57.5%)& 6 patients out of 9 in seroconverted group C (66.7%)} while 27 patients out of 80 (33.7%) are on azathioprine {7 patients out of 31 in persistent HCV –ve group A[1] (22.6%),17 patients out of 40 in HCV +ve group B (42.5%)& 3 patients out of 9 in seroconverted group C (33.7%)}.

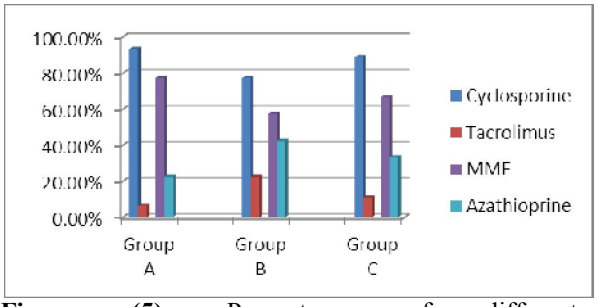


Figure (5): Percentages of different immunosuppressive drugs received between the 3 groups (Group A [1] [31 patients] Group B [40 patients], and Group C [9 patients]).

Table (10): Comparison between Group A[1] (persistent HCV – ve, 31 patients), Group B (HCV + ve, 40 patients), and Group C (seroconverted, 9 patients) as regards serum creatinine (mg / dl), blood urea (mg / dl), AST level in serum (U / L), ALT level in serum (U / L), and serum albumin (gm / dl).

	Negative(group A[1])			Positive(group B)			Seroconverted(group C)			
	Median	Min	Max	Median	Mini	Max	Median	Min	Max	p value
S.**Creat**.	1.2	0.6	3	1.4	0.5	4	1.4	0.7	5.3	0.145
Urea	45	22	97	47	18	174	42	25	106	0.519
AST	18	10	42	22	12	102	36	15	122	<0.001
ALT	17	3	62	31	11	154	51	12	158	<0.001
Albumin	4.2	3.1	5.1	4	2.7	4.5	3.9	3.2	4.3	0.003

Kruskels Wallis test

There was statistically significant difference as regard AST, ALT, and serum albumin between the 3 groups.

Table (11): Comparison between the 3 groups as regard AST (Group A[1] [31 patients], Group B [40 patients], and Group C [9 seroconverted]).

AST	Negative(group A[1])	Positive (group B)
Positive (group B)	0.010	
Seroconverted (group C)	0.011	0.064

There was a statistically significant difference between HCV – ve Group A[1] and each of HCV + ve Group B and seroconverted Group C as regards AST. There was a borderline significant difference between HCV + ve Group B and seroconverted Group C as regards AST.

Table (12): Comparison between the 3 groups as regard ALT (Group A^1 [31 patients], Group B [40 patients], and Group C [9 patients]).

ALT	Negative (group A^1)	Positive (group B)
Positive (group B)	<0.001	
seroconverted (group C)	<0.001	0.361

Study showed a statistically significant difference as regards ALT between HCV - ve group A^1 & each of HCV + ve Group B and seroconverted Group C.

Table (13): Comparison between the 3 groups as regard Serum Albumin (Group A^1 [31 patients], Group B [40 patients], and Group C [9 patients]).

Albumin	Negative (group A^1)	Positive (group B)
Positive (group B)	0.003	
Seroconverted (group C)	0.007	0.517

There was a statistically significant difference as regards Serum Albumin between HCV – ve group A^1 & each of HCV + ve Group B and seroconverted Group C.

There was a positive correlation between blood urea and serum creatinine ($P < 0.001$) and between AST & ALT ($P < 0.001$), in all the eighty transplanted patients (HCV – ve and HCV + ve).We also found a significant inverse correlation between Serum Albumin and each of Serum creatinine ($P < 0.001$), blood urea ($P < 0.001$), serum AST ($P = 0.032$), and serum ALT ($P = 0.005$), in the eighty kidney transplanted patients.

There was a direct correlation between urea and s. creatinine ($P = 0.000$) and between AST & ALT ($P = 0.000$), in HCV – ve Group A (40 Patients).We also found an inverse relationship between Albumin and each of S.creatinine ($P = 0.002$),blood urea ($P = 0.013$) &serum ALT($P = 0.039$).

There was a direct correlation between urea & s. creatinine ($P = 0.000$) and between AST & ALT ($P = 0.000$), in HCV + ve Group B (40 Patients).We also found an inverse relationship between Albumin & each of serum creatinine ($P = 0.026$) and blood urea ($P = 0.018$).

We couldn t do correlation of different laboratory parameters in seroconverted Group C (9 patients), due to the small number of patients included in this group.

4.Discussion

Solid organ transplantation is the best treatment for end – stage organ failure. Tremendous progress has been made in the transplantation setting over the last two decades, mainly related to improvement of surgical techniques, immunosuppressive regimens and diagnosis and treatment of infections (Cervera et al., 2011; Vallet – Pichard et al., 2011)

HCV infection is more frequent in renal transplant recipients and dialysis patients than in the general population and a significant impact on the survival of these patients (Chan et al.,[1993]; Roth [1995]; Periera and Levey, [1997]; Jadoul et al., [1998]; Furusyo et al., [2001]; Jain and Nijhawan, [2008]; Kliem et al., 2008; Vallet - Pichard et al., 2011).

HCV infection in renal transplant recipients is associated with a significant reduction in patient and graft survival (Legendre et al., 1998; Mathurin et al., 1999; Breitenfeldt et al., 2002; Kahraman et al., 2011; Vallet – Pichard et al., 2011) There is a consensus that all kidney transplant candidates should be tested for HCV infection and HCV must be screened in all kidney allograft donors (KDIGO, 2009).

In kidney transplant recipients, the priorities of treatment include renal function and immune – suppression, rather than potential hepatitis – related liver problems. (Roth, 1995; Vallet – Pichard et al., 2011)

HCV + ve Group B[40 patients] were older than HCV -ve Group A [40 patients], in a borderline significant way.This may be because older patients usually spends a longer time on hemodialysis, being exposed to HCV infection.

We didn t find in our study any significant difference between persistent HCV – ve patients (Group A^1) [31 patients], HCV + ve patients (Group B) [40 patients] and seroconverted patients (Group C)[9 patients], as regards age. This means that age didn`t play any role in seroconversion event.

Both HCV – ve Group A and HCV + ve Group B, were constituted mainly of males, with males number being higher in Group B than Group A, and females number being higher in Group A than Group B in a borderline significant way ($P = 0.056$).

Gender distribution didn t show any significant difference between the three Groups: persistent HCV – ve Group A^1, HCV + ve Group B, and seroconverted Group C. Gender didn t play a role in seroconversion in our study.

Baur *et al.,* 1991; and Esteban *et al.* 1989, found that anti – HCV prevalence was not related to age or sex of the patients.

HCV + ve Group B had a higher percentage of patients (100 %) who had undergone hemodialysis therapy before transplantation, in a borderline significant way, when compared to HCV – ve Group A (87,5 %), ($P = 0.055$).

HCV + ve Group B (100 %) and seroconverted Group C (100 %) had significantly higher percentages of patients that had been subjected to hemodialysis therapy before transplantation, as compared to persistent HCV –ve Group A^1 (86.7 %), ($P = 0.032$).

Inspite of Universal hygiene rules, HCV contamination persists in the dialysis setting, with a current incidence of 0 – 2.4 % per year depending on the center, mainly via nosocomial transmission (Thompson *et al.*, 2009).

Compliance with Universal Hygiene Rules has eliminated nosocomial transmission of HCV.(Jadoul *et al.*, 1998).

Transmission of HCV infection by dialysis equipment per se is today anecdotal.(Allander *et al.*, 1994).

Inter – human transmission (possibly hand – born by personel) or transmission by contaminated medication vials are the main routes of contamination in hemodialysis centers. (Vallet - Pichard *et al.*, 2011; Carbone *et al.*, 2013). HCV + ve Group B had a significantly longer duration of dialysis before transplantation (4 years), than HCV – ve Group A (2 years), ($P < 0.001$).

Duration of dialysis before transplantation was much longer in HCV + ve Group B (4 years) and in seroconverted Group C (3 years), than persistent HCV – ve Group A^1 (2 years), ($P < 0.001$).

Risk factors of developing HCV infection after transplantation included (I) the number of previous graft (s), (ii) the time (duration) of dialysis, and (iii) the number of blood units tansfused. These factors are those usually found (Baur et al., 1991; Macreen et al., 1993; Chan et al., 1993; Romero et al., 2008; Vallet - Pichard et al., 2011)

In our study, we didn t have any previous graft in our patients.

HCV – ve Group A had much less patients with a history of blood transfusion before transplantation (22.6 %), when compared to HCV +ve Group B (62.5 %).

Persistent HCV – ve Group A^1 had much patients (19.3 %) who had been subjected to bood transfusion after transplantation, when compared to seroconverted Group C patients (44.44 %).

Alter *et al.*, 1982; and Baur *et al.*, 1991, reported an odds ratio of 14 for acquisition of post – transfusion non – A, non – B hepatitis

(hepatitis C virus now) infection after blood transfusion.

Transfusion of more than 5 blood units is associated with a 4.1 times higher risk for post – transfusion non – A, non –B hepatitis infection than transfusion up to 5 blood units ($P = 0.002$).(Baur *et al.*, 1991.

Colombo *et al.*, 1987, found a statistically significant raised incidence of post – transfusion non – A, non – B hepatitis at higher transfusion volumes (6.7 blood units versus 9.6 blood units).

This is in contrast to studies where post – transfusion hepatitis non-A,non-B was not influenced (Koziol *et al.*, 1986; Sugg *et al.*, 1988), or increased progressively (Seeff *et al.*, 1977;Hernandez *et al.*, 1983) with the number of blood units transfused.

Transplantation duration in our study was nearly the same (about 2 years) in all groups included in the study, which means that it didn`t play a role in seroconversion process.

In our study seroconversion rate was 22.5 % (9 patients out of 40) in initially HCV – ve Group A.

Immunosuppressed renal transplant recipients show a high prevalence of HCV infection, ranging from 10 % to 50 % in various studies (Justa *et al.,* 2010; Morales *et al.,* 2002); from 6 to 64 % (Legendre *et al.,* 1998; and Sabry, 2010); from 2.6 to 66 % (Moghaddam *et al.,* 2008) depending on geographic areas.

Studies from Japan, Poland, Sweden, Spain, USA, Germany, France, Turkey, Italy, and Korea have reported a prevalence of 13 %, 50 %, 3 %, 13 %, 5.2 %, 13.1 %, 25 %, 18 %, 20 %, and 2.6 % respectively. (Fabrizi *et al.,* 1996; Kliem *et al.,* 1996; Durlik *et al.,* 1998; Legendre *et al.,* 1998; Tokumoto *et al.,* 1998; Brauchfeld *et al.,* 2004; Huang *et al.,* 2004; Melon *et al.,* 2005; Manga Shahin *et al.,* 2006; Terrault and Adey, 2007).

The prevalence of HBV and HCV infections has markedly decreased in patients who are candidates for transplantation since the introduction of screening, hygiene, and prevention measures, including systematic screening of blood and organ donations, use of erythropoietin, and compliance with universal hygiene rules (Jadoul *et al.,* 1998; Vallet – Pichard *et al.,* 2011).

The anti – HCV prevalence among patients after kidney transplantation was 10 %.(Baur et al., 1991).A slight elevation due to nosocomial infections during frequent medical examinations may be possible (Baur et al., 1991; Jadoul et al., 1998).

In one retrospective single center study in France, Rostaing et al., (1997), 11 % were found to be HCV infected after transplantation by transplant procedure (graft or blood transfusion).

Hepatitis C virus transmission through organ transplantation has been well described (Periera et al.,

1991; Tugwell et al., 2005; Ison et al., 2011;Marvin et al., 2011).

Another rare cause that may transmit HCV to kidney transplant recipients, is the donor having been probably in the window period

(8 to 10 weeks of infection before the development of detectable anti – HCV). (Bush et al., 2000; Kleinman et al., 2009). In addition, studies have included donors with negative viral serologic tests, but behavioural and clinical risk factors suggesting greater likelihood of undetected infection.(Reese et al., 2009; Ison et al., 2009; Duan et al., 2010; Reese et al., 2011).

Zou et al., (2004), reported an analysis that estimated the probability of undetected viremia with HCV in antibody - negative donors to be 1 in 42000 donors, while Ellingson et al., (2011), reported that the incidence of undetected HCV infection by serologic screening for anti – HCV antibody varies from 1 in 5000 for normal – risk patients to 1 in 1000 for patients at high risk.

Public Health Service recently drafted guidelines recommending testing of all organ donors with NAT for HCV regardless of risk status. (Draft PHS guideline, 2011).

HCV was transmitted when a transplant facility inadvertently used a blood vessel conduit from an HCV – positive donor in a seronegative recipient. (Humar et al., 2011).

Transmission of HCV to renal transplant recipients is higher wth slush perfusion of the kidney compared to pulsatile perfusion preservstion. (Zucker et al., 1994; Papafragkakis et al., 2011).

Persistent HCV – ve Group A^1 had the least percent of patients (12.9 %), who had been subjected to acute rejection. HCV + ve Group B had a higher percent of patients (15 %) who had been subjected to acute rejection, while seroconverted Group C had the highest percent (44.44 %) of acute rejection. Whether acute rejection with its treatment protocols is in favour of seroconversion or not, needs further study to decide it.

Different immunosuppressive drugs were used with different doses according to different protocols in the 3 groups (persistent HCV – ve Group A^1, HCV + ve Group B, and seroconverted Group C).Cyclosporine and Mycophenolate Moftile are used in smaller percent of patients in HCV + ve Group B (77.5 % and 57.5 %, respectively) and in seoconverted Group C (88.9 % and 66.7 %, respectively), than in persistent HCV – ve Group A^1 (93.5 % and 77.4 %, respectively). Both Cyclosporine and Mycophenolate Moftile don t seem to favour seroconversion in our study.

Immunosuppressive therapies for the prevention of graft rejection after transplantation, enhance the risk of infections and modify their natural history. (Vallet – Pichard et al., 2011).

Tacrolimus and Azathioprine had higher percent of patients using them in HCV + ve Group B (22.5 % and 42.5 %, respectively) and in seroconverted Group C (11.1 % and 33.3 %, respectively), when compared to persistent HCV – ve Group A^1 (6.5 % and 22.6 %, respectively). Further studies are needed to state whether Tacrolimus and Azathioprine are in favour or not of seroconversion to HCV + ve state among kidney transplanted patients, being HCV – ve at time of transplantation.

Watashi et al., (2003),have reported that in vitro studies have suggested that cyclosporine may have an inherent anti – HCV activity, inhibiting viral replication. This agrees with our results, especially in persistent HCV –ve Group A^1.

Berenguer et al., (2010), found no differences in terms of virological response, between patients receiving a Cyclosporin – or a Tacrolimus - based immune suppression.

Kahraman et al. [2011], in their study, have reported that lower acute rejection rates were observed in patients receiving Tacrolimus as compared to Cyclosporine, (This was not the case in our study).

In a large study, using data from the Scientific Registry of Transplant Recipients (SRTR) involving more than 75,000 kidney transplant recipients (including 3,708 HCV – infected patients), the use of Tacrolimus or Cyclosporine was not associated with any survival benefit in HCV – infected patients (Luan et al., 2008; Berenguer et al., 2007).

In the study by Luan et al., 2008, the use of MMF among HCV – infected patients was associated with a 33 % lower risk of mortality.

Persistent HCV – ve Group A^1 had much less percent (12.9 %) of hemodialysis therapy after transplantation than seroconverted Group C (44.44 %).

Baur et al., 1991, reported that patients after kidney graft rejection had a history of high – dose immunosuppressive therapy, underwent more invasive diagnostic procedures, and may have spent a longer time on hemodialysis. This poses a high risk for nosocomial HCV infection.

Baur et al., (1991), and Zeldis et al., (1990), stated that the effect of graft rejection therapy seems to predominate.

As regards laboratory parameters, HCV + ve Group B had a significantly higher ALT ($P = 0.004$) and significantly lower serum albumin ($P = 0.028$) than HCV – ve Group A, and this was quite expected due to chronic hepatitis C state.

AST and serum creatinine were higher in HCV + ve Group B than HCV – ve Group A, in a

borderline significant way (P = 0.051 and P = 0.078, respectively), this may show the effect of chronic HCV infection on liver enzymes and kidney function.

AST and ALT were significantly higher in HCV + ve Group B than persistent HCV – ve Group A^1 ($P = 0.01$ and $P < 0.001$, respectively).

Also, AST and ALT were significantly higher in seroconverted Group C than persistent HCV – ve Group A^1 ($P = 0.011$ and $P < 0.001$, respectively).

AST was higher in seroconverted Group C than HCV + ve Group B, in a borderline way (P = 0.064). This means that liver enzymes were more affected by hepatitis C infection in those patients who were seroconverted after transplantation than those who were HCV + ve from the start, at the time of transplantation.

Serum Albumin was significantly higher in persistent HCV – ve Grroup A^1 as compared to HCV + ve Group B ($P = 0.003$).Serum Albumin was significantly higher in persistent HCV – ve Group A^1 as compared to seroconverted Group C ($P = 0.007$).This shows the better preserved liver function in persistent HCV – ve group as compared to HCV + ve group and seroconverted group, inspite of the use of immunosuppressive drugs which could affect liver function on the long run.

Roth et al.,(2011), reported that despite many years of immunosuppression, liver histology remained stable (or even improved) in the majority of rebiopsied transplanted patients.

Vallet - pilchard et al., (2011), reported that sustained suppression of necro – inflammation may result in regression of cirrhosis, which in turn may lead to decreased disease – related morbidity.

Conclusion

Hemodialysis, blood transfusion, and multiple grafts are not the only factors contributing to HCV infection after renal transplantation.Organ, tissue, and nosocomial transmission have to be avoided.

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