TITLE:

Intention-to-treat survival analysis of HCV/HIV co-infected liver transplant: Is it the waiting list?

AUTHORS

Juan J. Araiz
M. Trinidad Serrano
Francisco A. García-Gil
Elena M. Lacruz
Sara Lorente
José I. Sánchez
Miguel A. Suarez

J. J. Araiz
Transplant Procurement Management, University Hospital Lozano Blesa
Intensive Care Unit, University Hospital Lozano Blesa
Department of Medicine, University of Zaragoza
Avda San Juan Bosco, 50009 Zaragoza, Spain
M. T. Serrano
Department of Gastroenterology, Liver Unit, University Hospital Lozano Blesa
Avda San Juan Bosco, 50009 Zaragoza, Spain
Department of Medicine, University of Zaragoza
Domingo Miral s/n, 50009 Zaragoza, Spain
IIS Aragón, Spain
A. Garcıa-Gil
Department of Surgery, Hepatic Surgery Unit, University Hospital Lozano Blesa
Department of Surgery, University of Zaragoza
Domingo Miral s/n, 50009 Zaragoza, Spain
IIS Aragón, Spain
S. Lorente
Department of Gastroenterology, Liver Unit, University Hospital Lozano Blesa
Avda San Juan Bosco, 50009 Zaragoza, Spain
IIS Aragón, Spain
E. Lacruz, J.I. Sanchez[1], M.A. Suarez[2]

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as an 'Accepted Article', doi: 10.1002/lt.24474

Intensive Care Unit, University Hospital Lozano Blesa
[1] Transplant Coordinator of the Autonomous Community of Aragon, Spain
[2] Department of Medicine, University of Zaragoza
Avda San Juan Bosco, 50009 Zaragoza, Spain

KEY WORDS: Liver transplant, survival, VIH, waiting list, intention-to-treat analysis

ABBREVIATIONS:

AIDS, Acquired immunodeficiency syndrome; cART, combined antiretroviral treatment; CI, Confidence interval; CVA, Cerebrovascular accident; DDG, Died with disfunctioning graft; DFG, Died with functioning graft; DRI, donor risk index; FFP, fresh frozen plasma; HBV, Hepatitis B Virus; HCC, Hepatocellular Carcinoma; HCV, Hepatitis C Virus; HIV, Human Immunodeficiency Virus; HR; Hazard ratio; ICU, Intensive Care Unit; ITTA, Intention-to-treat analysis; LT, Liver Transplant; MELD, Model for End-Stage Liver Disease; NA, not applicable; NRTI Nucleoside Reverse Transcriptase Inhibitor. NNRTI Non Nucleoside Reverse Transcriptase Inhibitor; NS, not significant; PI Protease Inhibitor; RBCs, red blood cells; RFA, Radiofrequency Ablation; SSD, Statistically significant differences; UNOS, United Network for Organ Sharing; TACE, Transarterial chemoembolization; UW, University of Wisconsin;

CONFLICT OF INTERES:

None of the authors has any conflict of interest related to this article

CORRESPONDING AUTHOR:

J.J. Araiz
Transplant Procurement Management
Intensive Care Unit
University Hospital Lozano Blesa
Avda. San Juan Bosco 15,
50009 Zaragoza, Spain.
Tel.: +34 976 55 64 00; fax: +34 976 76 57 75
e-mail: jjaraiz@unizar.es

ABSTRACT

In HIV/HCV co-infected patients, the accelerated severity of liver disease, associated comorbidities, and mortality on the waiting list could change the possibility and results of liver transplantation (LT). Intention-to-treat survival analysis (ITTA) can accurately estimate the applicability and efficacy of LT. The primary objective of this study was to compare the survival of patients with HCV with and without HIV infection. We analysed a cohort of 199 patients with HCV infection enrolled for LT between 1998 and 2015; 17 were also infected with HIV. The patients with HCV/HIV co-infection had higher mortality on the waiting list than those with HCV monoinfection (35.3% vs. 4.6%; P<0.001). ITTA at 1, 3, and 5 years was 75%, 64%, and 57% for HCV monoinfection and 52%, 47%, and 39% for HCV/HIV co-infection, respectively (Wilcoxon test P<0.05). The ITTA at 1, 3, 6, and 12 months and was 96%, 91%, 87%, and 75% for HCV monoinfection and 76%, 70%, 64%, and 52% for HCV/HIV co-infection, respectively (Logrank P<0.05, Wilcoxon test P<0.01). A Cox regression analysis was carried out including all variables with predictive value in the univariate analysis, showing that only donor age > 70 years (HR = 3.12, P<0.05), UNOS 1 status (HR = 10.1, P<0.01), MELD (HR = 1.13, P<0.001), and HIV co-infection (HR = 2.65, P<0.05) had independent negative predictive value for survival. ***Conclusion*** Our study indicates that HIV co-infection is a factor in mortality prior to transplantation and associated with higher mortality on the waiting list.

INTRODUCTION

According to the Spanish Liver Transplant Registry, 36% of orthotopic liver transplants (OLT) carried out in our country correspond to patients infected with hepatitis C virus (HCV) (1). In these patients, the infection can be associated with different comorbidities, including hepatocellular carcinoma (HCC), co-infection with hepatitis B virus (HBV), and co-infection with human immunodeficiency virus (HIV), among others.

Until a few years ago, HIV infection was an absolute contraindication for any type of transplant due to the vital prognosis of these patients and the fear that transplant-associated immunosuppression could accelerate the progression of the disease or increase the risk of opportunistic infections. Since the introduction of highly active combined antiretroviral treatment (cART) (1) in 1996, the situation of HIV-infected patients has changed radically, with dramatically reduced morbidity due to opportunistic processes and reduced overall mortality of patients with AIDS (2). This, in turn, has resulted in sufficient time for chronic processes to evolve to terminal failure (hepatic, renal, cardiac), the only possible approach for which is transplantation (3).

The Spanish OLT in HIV-Infected Patients Working Group has published several papers with transplant results and associated prognostic factors in HCV/HIV co-infected liver transplant recipients (4,5). However, these works do not consider that the accelerated severity of hepatopathy, associated comorbidities, and mortality on the waiting list can change the possibility and results of treating patients. Therefore, in these situations, intention-to-treat survival analysis (ITTA) can accurately estimate the applicability and efficacy of liver transplantation. The primary objective of this study was to compare the intention-to-treat survival of patients with advanced hepatopathy caused by HCV monoinfection and HCV/HIV co-infection.

PATIENTS and METHODS

Patients and study design

This is a retrospective study using a prospectively collected database. All patients HCV-positive and enlisted for primary non-paediatric orthotopic liver transplantation (OLT) after 2004 (starting date of the HIV-HCV co-infected LT programme) were included in the study (N=199). The design of the study is shown in Figure 1. The monitoring start date was the

date when the patient was included on the waiting list. The main variable of the study was the intention-to-treat survival; thus, the death of the patient was considered to be the event. The patients were monitored by the electronic Health Record of the Regional Community of Aragon and of the hospital itself until they died, censoring the last documented day when they were alive. The basal characteristics, evolution on the waiting list, reasons for exclusion from the list, and their subsequent evolution were analysed for each patient.

Transplant criteria

HIV-infected patients had to fulfil the following criteria according to their infection status (6): no AIDS-defining events except tuberculosis, oesophageal candidiasis, or *Pneumocystis jiroveci* pneumonia; CD4 T cell count >100 cells/μL; and an undetectable plasma HIV-RNA viral load (or suppressible with cART). Former intravenous drug users had to have abstained from heroin or cocaine use for more than 2 years. The minimum period of abstinence for alcohol was 6 months.

In regards to liver disease, the criteria for accepting HIV-infected patients for transplantation were the same as those followed in Spain for HIV-negative patients: a minimum Child-Turcotte-Pugh score of 7 for patients with cirrhosis, and one tumour <5 cm or two to three tumours <3 cm in the absence of hepatic macrovascular tumour invasion and extrahepatic metastases in patients with HCC.

Donor procurement and characteristics

All donors were brain death donors. Donor liver recovery was performed using conventional multiorgan procurement techniques. The aorta and portal vein were perfused with preservation solution cooled to 4ºC by gravity in situ and on the back table through the portal vein. University of Wisconsin solution and Celsior solution were used indiscriminately. Total perfusion volumes were 4, 2, and 1 L for Celsior solution and 3, 2, and 1 L for University of Wisconsin solution. After recovery, the grafts were kept in conventional bags containing the same solution at 4ºC until transplantation.

The following donor variables were analysed and compared in both groups: age, sex, cause of death, number of days in the ICU, donor allocation, and graft steatosis. The donor risk index, a score derived from donor variables that helps estimate the influence of donor characteristics on the patient and graft outcome after transplantation, was also calculated according to the criteria described by Feng et al. (7).

Technical aspects

OLT was performed with preservation of the retrohepatic vena cava (piggyback technique) and without veno-venous bypass. The graft was washed systematically before reperfusion of the portal vein with 1200 mL of cold Ringers lactate. An arterial anastomosis was carried out between the graft celiac trunk or its branches and the common recipient hepatic artery or its branches. Protocol wedge liver biopsies were obtained prior to graft perfusion, during procurement, and immediately before closing the recipient laparotomy. The standard technique for biliary anastomosis was choledocho–choledocho anastomosis. Split liver transplantations were not performed in this population.

Post-transplant management

Induction immunosuppression consisted of standard dual therapy with cyclosporine or tacrolimus and steroids. Some patients received monoclonal antibodies (basiliximab), and some patients with impaired renal function received mycophenolate mofetil. Cytomegalovirus (CMV) prophylaxis with gancyclovir was given in the following circumstances: positive donor status and negative recipient, retransplantation, or the use of monoclonal antibodies.

cART was administered until the day of surgery and resumed when the patient was stable and oral intake reintroduced. Antiretroviral drugs were administered according to national guidelines (8). HIV-infected recipients received the same immunosuppressive regimens as HIV-negative patients according to local protocols.

Diagnosis, strategies, and protocols

The definitions of HIV, HCV, and HBV infection and AIDS-defining events were based on standard criteria (9). Strategies for local prioritisation were based on model of end-stage liver disease (MELD) allocation. Patients on the waiting list were monitored and treated every 2-3 months or earlier depending on their clinical situation. Patients with HCC and lesions > 3 cm or multinodularity underwent radiofrequency (RF) and/or chemoembolisation (TACE) while on the waiting list depending on individual characteristics. Patients could be removed from the list due to repeated improvement. Diagnosis of acute rejection was always based on histopathological features following the Banff schema (10). Doppler ultrasonography was performed within the first 48 hours after liver transplantation and in the 7 to 10 days following transplantation. If the findings were equivocal or indicated that an abnormality may be present, an angiographic study was prescribed. The severity of recurrent hepatitis C was routinely determined using the Scheuer index (11) at the end of the first year after liver transplantation.

Study endpoints

The monitoring start date was the date when the patient was included on the waiting list. The primary endpoint of the study was the overall survival from the time of listing (ITTA, including dropouts), and the patient's death was considered to be the event. The secondary endpoint was overall survival after transplantation (including only liver transplant recipients).

Statistical analysis

The HCV monoinfection and HCV/HIV co-infection groups were compared according to patient characteristics, evolution on the waiting list, operative and postoperative outcomes, and long-term outcomes. Continuous variables were compared using the Student t-test and categorical variables using the chi-square test for associations. Continuous variables are presented as the mean and standard deviation.

Overall survival was calculated using the Kaplan-Meier method; differences between subgroups were compared using the log-rank test and Wilcoxon test. To identify predictors of mortality, a multivariate Cox proportional hazards model was performed. Significant variables in a univariate analysis were included in a multivariate analysis.

Significance was defined as a P value < 0.05. All statistical analyses were performed in IBM® SPSS® Statistics version 22.0 (©Copyright IBM Corporation 1989 to 2013, Chicago, IL, USA).

RESULTS

Patient characteristics

From the launch of our liver transplant programme in December 1998 to June 2015, a total of 567 patients were included for primary OLT, including 199 with HCV infection that were included in this study. The characteristics of these patients are presented in Table 1. The subgroup of patients with HCV/HIV co-infection included on the waiting list (since 2004) were compared to the patients with HCV monoinfection who were on the list (ratio 1:10.7) and the patients with HCV monoinfection who were included in the same time period (ratio 1:7.6).

Of all analysed variables, a lower average age (45.6 years vs. 55.0 or 54.9 years; P<0.001) and a different distribution of HCV genotypes (P<0.01) were recorded in the group of patients with HCV/HIV co-infection. The other variables showed no significant differences.

Evolution on the waiting list

The evolution of the patients on the list included in the study is presented in Table 2. First, the patients with HCV/HIV co-infection had higher mortality on the waiting list than HCV monoinfection patients (35.3% vs. 4.9% or 4.6%, respectively; P<0.001), so the percentage of transplant recipients was lower among patients with HCV-HIV co-infection (52.9% vs. 83.5% or 82.3%; P<0.01). Regarding mortality on the waiting list, the patients on the list who died, did so in less time on average than the transplanted patients on the list. The causes of death of co-infected patients were liver disease decompensation (n=2), spontaneous bacterial peritonitis (n=2), urinary origin sepsis (n=1), and respiratory distress syndrome after pneumonia (n=1).

No significant differences were recorded regarding the number of patients excluded from the list and the reasons for exclusion. The most common cause was contraindication because of HCC progression. The overall mortality according to ITTA was higher in the group with HCV/HIV co-infection than HCV monoinfection patients (58.8% vs. 44.5% or 36.2%, respectively), but there were no significant differences between the groups.

Characteristics and outcomes of transplantation

The characteristics of the transplants carried out and their outcomes are presented in Tables 3 and 4. The group with HCV/HIV co-infection was compared only to the total HCV monoinfection group. No differences were detected among the donors in any of the variables studied or in the case of peritransplant variables concerning surgery and the donor-recipient correlation (Table 3). A higher percentage of retransplantation was found among patients with HCV/HIV co-infection than patients with HCV monoinfection (33.3% vs. 11.2%). However, the overall mortality was lower among the patients with co-infection (33.3% vs. 44.1%). Neither of these two variables reached significance.

In the group with HCV monoinfection, one-third of the patients who died did so because of graft dysfunction, and 9 of them died on the waiting list for retransplantation. In the co-infected group, two patients died because of graft HCV reinfection and one because of pneumonia with sepsis and multiorgan failure.

The post-transplantation Kaplan-Meier survival curves for the HCV monoinfected and HCV/HIV co-infected patients, regarding both the patient and the graft, indicated no significant differences in these groups. The graft survival was 74% vs. 66% at 1 year, 62% vs. 55% at 3 years, and 53% vs. 44% at 5 years. The patient survival was 78% vs. 88% at 1 year, 68% vs. 77% at 3 years, and 59% vs. 64% at 5 years.

Intention-to-treat survival analysis

Regarding the ITTA, Figure 2 presents the global survival curve. The survival at 1, 3, and 5 years was 75%, 64%, and 57% for patients with HCV monoinfection and 52%, 47%, and 39% for patients with HCV/HIV co-infection, respectively. The mortality in the group of patients with HCV/HIV co-infection was significantly higher (Wilcoxon test $P<0.05$) in the first few months and stabilised after a year. Therefore, we divided the survival curve into two parts: short-term (less than 1 year) and long-term (more than 1 year). The curve for short-term survival (Figure 3) clearly indicated a significantly higher mortality (Logrank $P<0.05$, Wilcoxon test $P<0.01$) in the group of patients with HCV/HIV co-infection. This rate was more accentuated in the first few months and stabilised after the third month. The survival at 1, 3, 6, and 12 months was 96%, 91%, 87%, and 75% for patients with HCV monoinfection and 76%, 70%, 64%, and 52% for patients with HCV/HIV co-infection, respectively.

COX regression analysis

A proportional Cox regression analysis was carried out in order to identify predictors of short-term survival (<1 year) in patients with HCV infection. All variables related to donor and recipient, represented in Tables 1 and 3, were included in the univariate analysis. The significant variables were then included in the multivariate analysis (Table 5). Of all the parameters analysed, only donor age > 70 years (HR = 2.51, $P<0.05$), UNOS 1 status (HR = 8.93, $P<0.001$) and UNOS 2 status (HR = 3.65, $P<0.05$), MELD (HR = 1.12, $P<0.001$), and HIV co-infection (HR = 2.95, $P<0.01$) had a negative predictive value for survival, whereas less time on the waiting list (HR = 0.98, $P<0.05$), isosexuality between donor and recipient (HR = 0.39, $P<0.05$), and donor normonatremia (HR = 0.96, $P<0.05$) had a positive predictive value (Table 5). Of all the variables with predictive value in the univariate analysis, only donor age > 70 years (HR = 3.12, $P<0.05$), UNOS 1 status (HR = 10.1, $P<0.01$), MELD (HR = 1.13, $P<0.001$), and HIV co-infection (HR = 2.65, $P<0.05$) had an independent negative predictive value for survival (Table 5).

DISCUSSION

Several studies have concluded that OLT is an effective procedure in HCV/HIV co-infected liver recipients with short-term survival similar to that observed in patients with HCV monoinfection and lower but acceptable long-term survival (12,13). In HCV/HIV co-infected liver transplant candidates the problem gets worse long before the transplantation, as life expectancy is shorter after liver disease becomes decompensated than in patients who are not infected (14,15). In one study, patients infected with HIV and suffering from an end-stage liver disease Child-Pugh A had an average survival of 26 months; if the patient was at the stage of advanced Child-Pugh (B or C) survival was 10 and 14 months, respectively (14). Another study detected very low survival in patients infected with HIV after the first episode of hepatic decompensation (15).

Pineda et al. (16) have shown that the evolution of cirrhosis after the first decompensation in patients co-infected with HIV and HCV is much worse than in HCV monoinfected patients; survival was 54% vs. 74% at 1 year, 40% vs. 61% at 2 years, and 25% vs. 44% at 5 years, respectively. Other groups have reported similar data (17,18). On the other hand, patients co-infected with HCV and HIV have lower access to liver transplantation compared to patients with HCV monoinfection (14,19). Moreover, Subramanian et al. (19) reported a higher mortality rate (14.4% vs. 10.5%, $P>0.05$) for co-infected patients on the waiting list compared to monoinfected patients. In addition, a significantly lower proportion of HIV-positive transplant candidates than HIV-negative patients underwent liver transplantation during the study period.

In this group of patients, ITTA allows transplantation to be considered not only a complicated surgery, but also a complex process that involves a sequence of different procedures (i.e., patient selection, evolution on the waiting list, allocation of organs, transplant results), more accurately estimating the applicability and efficacy of liver transplantation in these patients. A Spanish multicentre study (4) indicated the need for intention-to-treat analysis, which could not be carried out because of a lack of information on patients who did not receive a transplant.

Vibert et al. (21) published an ITTA of liver transplantation in HCC patients, analysing the impact of HIV infection. They found a higher dropout rate among HIV patients and worsened results of liver transplantation for HCC on an intent-to-treat basis. To the best of our knowledge, our study is the first to perform an ITTA in HCV/HIV co-infected liver recipients. Patients with HCV/HIV co-infection had significant differences from patients

with HCV monoinfection; the age of the former was significantly lower and genotype 1 more prevalent in the group of patients with monoinfection. These events were also recorded in the Spanish multicentre study (4). This genotype is associated with higher HCV recurrence after transplantation and higher incidence of evolution to fibrosis and cirrhosis (22).

The evolution on the waiting list is not widely discussed in the literature. Our analysis showed that mortality on the waiting list was clearly higher in the HCV/HIV co-infected patients (35.3% vs. 4.6%; P<0.001). Importantly, this mortality was not associated with a longer permanence on the list. In 2013 in Spain, according to the report of the National Transplant Organisation (23), mortality of adults on the waiting list for liver transplantation was 5.5%; there are no data for different pathologies. The only communication we found on ITTA made no reference to mortality on the list but indicated that the percentage of patients on the list who were excluded or died was significantly higher in the group with HCV/HIV co-infection (53% vs. 6%) (24).

In regards to the post-transplantation results, though the differences were not significant, the group of co-infected patients had a higher rate of graft loss because of HCV reinfection than monoinfected patients (22.2% vs. 11.2%). These data were also confirmed by other authors who relate the graft loss to the need for further immunosuppression in these patients, which results in premature HCV reactivation and faster evolution to fibrosis (12,13). In the study carried out by Miro et al. (4), the short-term post-transplant survival was similar, but after 5 years it was significantly worse, though acceptable. In our study, the overall post-transplant survival was similar in both groups.

The short-term ITTA indicated higher mortality in the first few months, which was related to higher mortality on the waiting list for the group of patients with HCV/HIV co-infection and stabilised after the third month. In the only communication on an ITTA in patients with HCV/HIV co-infection mentioned above (24), the probability of survival in these patients was significantly lower than the rest (0.68, 0.45, and 0.30 vs. 0.91, 0.85, and 0.79 at 6, 12, and 24 months, respectively).

Finally, with respect to the prognostic factors for short-term survival (<1 year) in patients with HCV infection, donor age > 70 years, UNOS status 1 and 2, MELD, and HIV co-infection had a negative predictive value, whereas less time on the list, isosexuality between donor and recipient, and donor normonatremia had positive predictive value. Of all the variables with predictive value in the univariate analysis, only donor age > 70 years, UNOS

status 1, MELD, and HIV co-infection had an independent negative predictive value for survival. HIV co-infection has been reported to be an independent factor for mortality after transplantation in patients with HCV infection (4). Our study indicates that, in addition to being a risk factor after transplantation, HIC co-infection is also a factor for mortality prior to transplantation and associated with higher mortality on the waiting list.

With regard to donor age, this factor is becoming increasingly well known to affect graft survival, along with many other factors. The age cut-offs proposed in the literature range from 50 to 70 years. We found significant differences in patients >70 years old. Notably, the larger the sample size the higher the probability of finding the differences caused by the age factor and the cut-off probably lower. Our sample is small and may only detect cases in which age plays an important role, coinciding with a higher cut-off.

The main limitation of our study is the small number of HCV/HIV co-infected patients. Therefore, more prospective studies are needed to confirm these observations and more accurately determine the risk factors and need for pre-transplant assessment and different policies in this group of patients.

In conclusion, liver transplantation is a possible treatment for patients with HCV/HIV co-infection and end-stage liver disease, but these patients have lower short-term survival (less than 1 year), mainly related to higher mortality on the waiting list. Receptor-dependent factors with worse independent predictive value for short-term survival in patients with HCV infection were: UNOS 1 status at enrolment on the list, MELD, and HIV co-infection.

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FIGURE LEGENDS

Figure 1. Flowchart describing the patients included in the study.

Figure 2. Global Survival by Intention-to-treat analysis for HCV monoinfection compared to HCV/HIV co- infection.

Figure 3. Short-term survival (< 1 year) by Intention-to-treat analysis for HCV monoinfection compared to HCV/HIV co-infection.

Table 1. Main Characteristics of the Cohort

	All cases	HCV Monoinfection		HCV/HIV Coinfection	*P*value*
		All cases	Since 2004	Since 2004	
N	**199**	**182**	**130**	**17**	
Age (years)[1]	54.2 + 8.7	55.0 + 8.6	54.9 + 8.6	45.6 + 3.2	< 0.001
Sex: Male *(vs female)*[2]	153 (76.9)	139 (76.4)	103 (79.2)	14 (82.4)	0.95
Blood Type[2]:					0.42
O	83 (41.7)	77 (43.3)	58 (44.6)	6 (35.2)	
A	92 (46.2)	84 (46.2)	54 (41.5)	8 (47.0)	
B	18 (9.0)	15 (8.2)	14 (10.7)	3 (17.6)	
AB	6 (3.1)	6 (3.3)	4 (3.0)	-	
MELD score[1]	15.5 + 5.8	15.2 + 5.2	15.2 + 5.2	17.9 + 9.6	0.63
Child-Pugh class[2]					0.29
A	43 (21.6)	38 (20.3)	32 (24.4)	5 (31.2)	
B	77 (38.7)	74 (41.2)	50 (38.5)	3 (12.5)	
C	79 (39.7)	70 (38.3)	48 (37.0)	9 (56.2)	
UNOS status[2]					0.08
ICU admission	13 (6.6)	10 (5.6)	6 (4.4)	3 (15.3)	
Hospital admission	34 (17.1)	29 (15.6)	19 (15.0)	5 (30.7)	
With continuous care	98 (49.2)	90 (49.3)	59 (45.1)	8 (46.1)	
At home	54 (27.1)	53 (29.3)	46 (35.3)	1 (7.6)	
Comorbidities:					
Ex-alcholism[2]	28 (14.1)	27 (14.8)	17 (13.1)	1 (5.9)	0.36
HCC[2]	68 (34.2)	64 (35.2)	50 (38.5)	4 (23.5)	0.48
Number of Nodules[2]					0.67
1 nodule<3 cm	20 (29.4)	20 (31.3)	16 (32.0)	-	
1 nodule>3 cm	19 (27.9)	17 (26.5)	14 (28.0)	2 (50)	
Multinodular	29 (42.7)	27 (42.2)	20 (40.0)	2 (50)	
Tumour diameter[1]					0.23
1 nodule	33.4 + 12.2	32.6 + 12.2	32.0 + 11.9	44.5 + 7.7	
$Multinodular_{(max)}$	25.0 + 4.9	25.7 + 4.9	26.3 + 4.7	30.0 + 0	
Treatment prior to OLT[2]					0.82
TACE	12 (70.6)	11 (73.3)	11 (73.3)	1 (50.0)	
RFA	4 (23.5)	3 (20.0)	3 (20.0)	1 (50.0)	
TACE and RFA	1 (5.9)	1 (6.7)	1 (6.7)	-	
HBV coinfection[2]	3 (1.5)	2 (1.1)	1 (0.8)	1 (5.9)	0.06
HCV Infection:					
HCV Genotype[2]					< 0.01
1	149 (74.9)	141 (77.5)	104 (80.0)	8 (47.1)	
2	1 (0.5)	-	-	1 (5.9)	
3	21 (10.6)	18 (9.9)	17 (13.0)	3 (17.6)	
4	11 (5.5)	7 (3.8)	5 (3.9)	4 (23.5)	
Others	17 (8.5)	16 (8.8)	4 (3.1)	1 (5.9)	
Plasma HCV RNA viral load (UE^6/mL)[1]	9.9 + 3.8	9.8 + 4.4	9.8 + 4.4	10.5 + 17.9	0.49
Negative plasma HCV RNA viral load before LT[2]	10 (5.0)	9 (4.9)	7 (5.4)	0	NA
HIV Infection:**					
$CD4^+$ Cell count[1]				220 + 164	NA
$CD8^+$ Cell count[1]				369 + 280	NA
CD4 / CD8[1]				0.57 + 0.13	NA
Plasma HIV RNA viral load < 200 copies/mL[2]				10 (58.8)	NA
Type of cART[2]					NA
NRTI based				5 (29.4)	
NNRTI based				5 (29.4)	
PI based				7 (41.2)	

HCV *Hepatitis C Virus;* ***HIV*** *Hepatitis Inmunodeficiency Virus;* ***MELD*** *Model for End-stage Liver Disease;* ***UNOS*** *United Network for Organ Sharing;* ***HCC*** *Hepatocellular Carcinoma;* ***TACE*** *Transarterial Chemoembolisation;* ***RFA*** *Radiofrequency Ablation;* ***HBV*** *Hepatitis B Virus;* cART combined Antiretroviral Treatment; NRTI Nucleoside Reverse Transcriptase Inhibitor; NNRTI Non Nucleoside Reverse Transcriptase Inhibitor; PI Protease Inhibitor.

[1] *The data are presented as mean and standard deviation.* [2] *The data are presented as n (%).*

**** P-value.*** *HCV/HIV Coinfection versus HCV Monoinfection (the same for both groups)**; NA:** not applicable.*
***** HIV infection (data at listing):*** Absolute number (cells/μL), Patient Plasma HIV-RNA below 200 copies/mL.

Table 2. Intention-to-treat evolution of the patients included in the study

	All cases	HCV Monoinfection		HCV/HIV Coinfection	*P*Value*
		All cases	Since 2004	Since 2004	
N	**199**	**182**	**130**	**17**	
Dropped on list[2]	**14 (7.0)**	**12 (6.6)**	**8 (6.2)**	**2 (11.8)**	**0.09**
Time at list[1]	122.0 + 78.3	117.0 + 80.5	104.3 + 42.8	152.0 + 79.1	0.82
Causes to drop out[2]					0.46
Contraindication	8 (57.1)	7 (58.3)	5 (62.5)	1 (50)	
Time at list[1]	78.8 + 38.4	76.4 + 40.8	88.0 + 29.0	96	NA
Improvement	6 (42.9)	5 (41.7)	3 (37.5)	1 (50)	
Time at list[1]	179.5 + 83.3	173.8 + 91.9	152.7 + 53.2	208	NA
Evolution[2]					0.43
Death	6 (42.9)	5 (41.7)	3 (37.5)	1 (50)	
Alive	8 (57.1)	7 (58.3)	5 (62.5)	1 (50)	
Dead on waiting list[2]	**15 (7.5)**	**9 (4.9)**	**6 (4.6)**	**6 (35.3)**	**< 0.001**
Time at list[1]	30.4 + 27.1	31.0 + 7.4	36.6 + 10.4	29.5 + 14.5	0.91
Causes of dead[2]					0.06
Liver Complications	9 (60.0)	7 (77.7)	5 (83.3)	2 (33.3)	
Infections	5 (33.3)	2 (22.2)	1 (16.6)	3 (50.0)	
Others	1 (6.66)	-	-	1 (16.6)	
LT[2]	**161 (80.9)**	**152 (83.5)**	**107 (82.3)**	**9 (52.9)**	**< 0.01**
Time at list[1]	72.9 + 74.2	72.7 + 74.2	92.5 + 80.1	74.8 + 65.5	0.53
Evolution[2]					0.93
Death	71 (44.1)	68 (44.7)	39 (36.4)	3 (33.3)	
Alive	90 (55.9)	84 (55.3)	68 (63.6)	6 (66.7)	
Global ITTA[2]					**0.07**
Dead	**91 (45.7)**	**81 (44.5)**	**47 (36.2)**	**10 (58.8)**	
Alive**	**108 (54.3)**	**101 (55.5)**	**83 (63.8)**	**7 (41.2)**	

HCV *Hepatitis C Virus;* ***HIV*** *Hepatitis Inmunodeficiency Virus;* ***LT*** *Liver Transplantation;* ***ITTA*** *Intention-To-Treat Survival Analysis.*
[1]*The data are presented as mean and standard deviation.* [2]*The data are presented as n (%).*
*** P-value.** *HCV/HIV Coinfection versus HCV Monoinfection (the same for both groups);* ***NS*** *not significant;* ***NA:*** *not applicable.*
** *Included 9 HCV Monoinfection Patients on Waiting list for OLT*

Table 3. Characteristics of liver transplants

	All cases	HCV Monoinfection	HCV/HIV Coinfection	*P* Value*
N	**161**	**152**	**9**	
Matching Donor Variables:				
Age (years)[1]	49.4 ± 16.9 (11-82)	49.4 ± 17.1 (11-82)	48.3 ± 13.3 (28-71)	0.73
Sex Male *(vs female)*[2]	98 (60.9)	95 (62.5)	3 (33.3)	0.06
Days in ICU[1]	2.9 ± 2.1 (1-16)	2.9 ± 2.4 (1-16)	2.3 ± 3.6 (1-14)	0.82
Cause of donor brain death[2]				0.49
CVA	103 (64.0)	97 (63.9)	6 (66.7)	
Head Trauma	42 (26.1)	41 (26.9)	1 (11.1)	
Others	16 (9.9)	14 (9.2)	2 (22.2)	
Donor Allocation[2]				0.08
Local	112 (69.6)	107 (70.4)	5 (55.6)	
Regional	5 (3.1)	5 (3.3)	-	
National	44 (27.3)	40 (26.3)	4 (44.4)	
Steatosis[2]				
Mild < 30	15 (9.9)	14 (9.2)	1 (11.1)	0.61
Donor Risk Index:				0.71
Median	1.48	1.48	1.52	
Interquartile range	1.24 – 1.76	1.24 – 1.76	1.26 – 1.78	
Matching Recipient Variables:				
Age (years)[1]	55 ± 8 (35-68)	55 ± 8 (35-68)	46 ± 3 (41-51)	< 0.01
Sex Male*(vs female)*[2]	125 (77.6)	117 (76.9)	8 (88.9)	0.52
HCC[2]	56 (34.8)	53 (34.9)	3 (33.3)	0.67
Peritransplant Variables:				
Elective *(vs urgent)*[2]	158 (98.1)	149 (98.0)	9 (100)	0.89
Correlation *(donor vs recipient)*[2]				
Blood Type				0.74
Isogroup	159 (98.8)	150 (98.7)	9 (100)	
Compatible	2 (1.2)	2 (1.3)	-	
Isosexuality	92 (57.1)	88 (57.9)	4 (44.4)	0.62
Technique:				
Preservation solution (UW)[2]	97 (60.2)	91 (59.9)	6 (66.7)	0.34
Cold ischemia time[1] (min)	375 ± 114 (188-720)	374 ± 115 (188-720)	397 ± 94 (310-515)	0.65
Surgery time[1] (min)	325 ± 64 (180-520)	324 ± 63 (180-520)	354 ± 93 (205-620)	0.37
Intraoperative infusion of blood products:				
RBCs[1] (units)	4.1 ± 3.9 (0-20)	4.1 ± 3.9 (0-20)	4.5 ± 4.0 (1-10)	0.98
FFP[1] (units)	4.1 ± 3.1 (0-15)	4.1 ± 3.1 (0-15)	2.5 ± 2.1 (1-4)	0.12
Platelets[1] (Nº pool)	1.7 ± 2.3 (0-10)	1.1 ± 2.3 (0-10)	-	NA
Intraoperative Events				
S. Postreperfusion[2]	23 (14.3)	22 (14.5)	1 (11.1)	0.52
Intraoperative mortality	0	0	0	NA

HCV *Hepatitis C Virus;* ***HIV*** *Hepatitis Inmunodeficiency Virus;* ***ICU*** *Intensive Care Unit;* ***CVA*** *Cerebrovascular Accident;;* ***UW*** *University of Wisconsin;* ***RBCs*** *red blood cells;* ***FFP*** *fresh frozen plasma;*

Allocation: Local *in the city;* ***Regional*** *<200 km;* ***National*** *>200 km.*

[1]*The data are presented as mean and standard deviation (range).* [2]*The data are presented as n (%).*

**** P-value.*** *HCV/HIV Coinfection versus HCV Monoinfection (the same for both groups);* ***NA:*** *not applicable.*

Table 4. Results of liver transplants

	HCV Monoinfection	HCV/HIV Coinfection	*P* Value*
N	**152**	**9**	
Posttransplant variables:			
Primary dysfunction[3]	1	0	NA
Complications[3]:			
Acute Rejection	15	0	NA
Vascular	2	2	0.53
Biliary	8	1	0.72
cART and HIV-1 viral load:			
Time to re-start[1] (days)		9 (5-20)	NA
Type[3]			NA
NRTI-based		2	
NNRTI-based		3	
PI-based		4	
Undetectable HIV viral load[3]		8	NA
Days in ICU[1]	5 (4-8)	5 (4-6)	0.58
Days on floor[1]	13 (10-17)	10 (9-18)	0.73
Days in hospital/total[1]	18 (15-23)	18 (13-22)	0.41
Retransplant[2]:	**17 (11.2)**	**3 (33.3)**	**0.06**
Reasons[3]:			NA
Primary dysfunction	1	0	
Liver recurrence	8	0[b]	
Chronic rejection	3	0	
Vascular complications	0	2	
Biliary complications	5	1	
Kaplan-Meier Graft Survival[4]:			0.63
At 1 year	74 (67-81)	66 (36-88)	
At 3 years	62 (53-70)	55 (23-81)	
At 5 years	53 (44-62)	44 (13-72)	
Patient Survival:			
Monitoring period (days):			0.71
Mean + Standard deviation	1804 + 1687	1878 + 1224	
Range	10 - 6042	279 - 3996	
Median	1272	1194	
Interquartile range	302 - 4507	1110 - 2861	
Global Death[2]	67 (44.1)	3 (33.3)	0.16
FunctionGraft[3]			0.35
DDG	23[a]	2[b]	
DFG	44	1	
Kaplan-Meier Patient Survival[4]:			0.47
At 1 year	78 (71-84)	88 (64-98)	
At 3 years	68 (60-76)	77 (45-94)	
At 5 years	59 (50-68)	64 (32-87)	

HCV *Hepatitis C Virus;* ***HIV*** *Hepatitis Inmunodeficiency Virus;;* ***ICU*** *Intensive Care Unit;* ***DDG*** *Died with Disfunctioning Graft;* ***DFG*** *Died with Functioning Graft.*

[1]*The data are presented as median (Interquartile Range).* [2]*The data are presented as n (%),*[3]*The data are presented as n.* [4]*The data are presented as % (95% CI)*

**** P-value.*** *HCV/HIV Coinfection versus HCV Monoinfection (the same for both groups);* ***NA:*** *not applicable.*

[a] *9 patients died on the waiting list for retransplantation.*

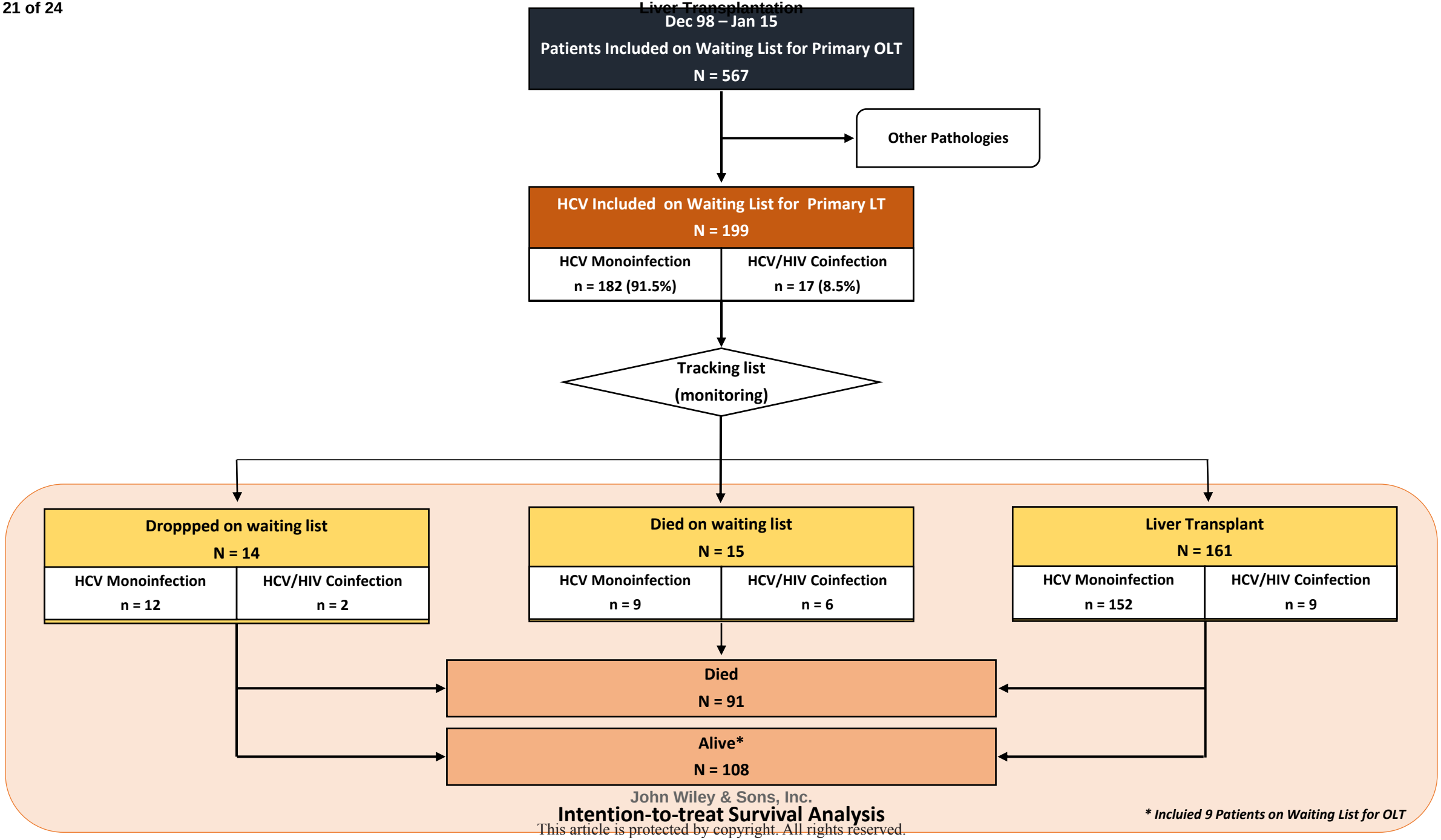
[b] *2 patients died with severe liver recurrence HCV.*

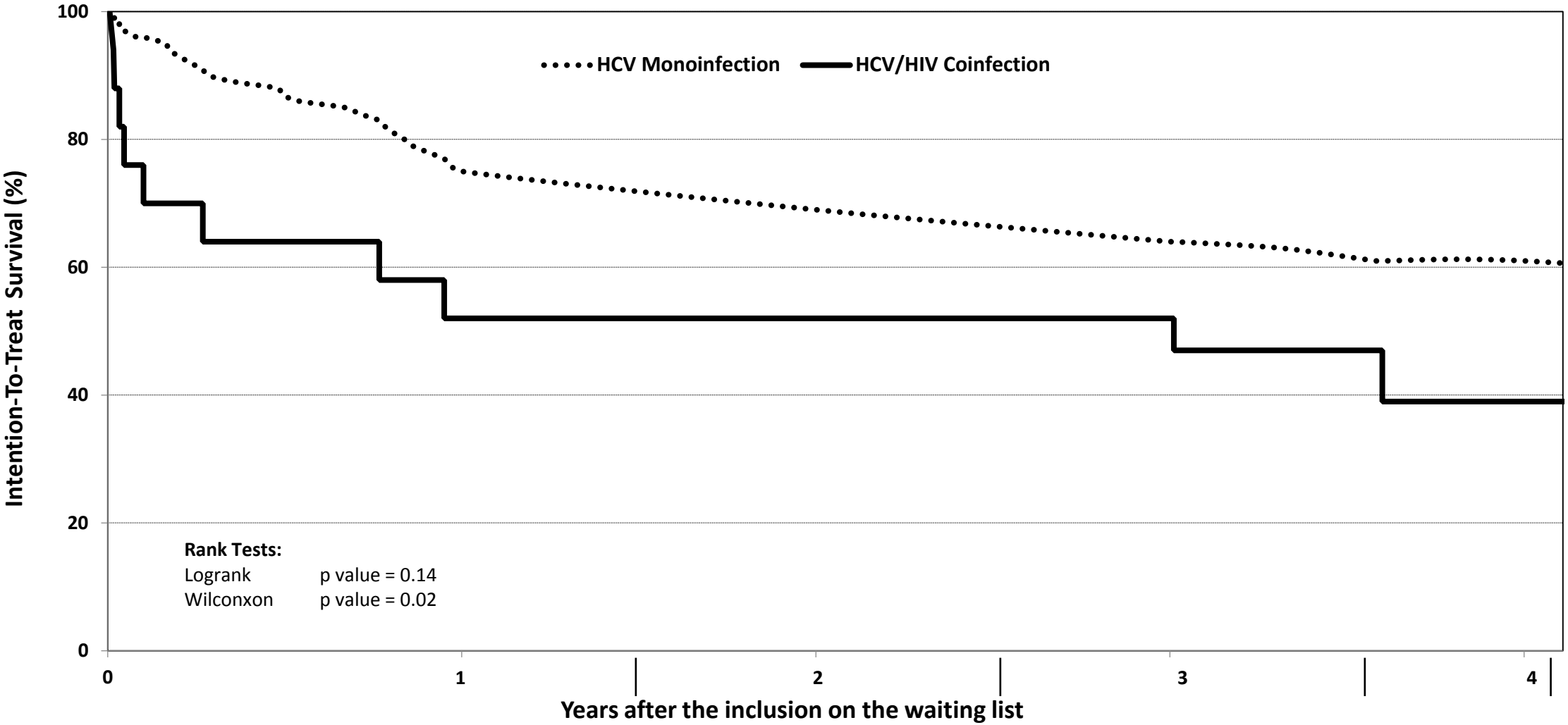
Table 5. Univariate and Multivariate Cox Regression of Possible Predictive Factors for Overall Intention-To-Treat Survival at 1 year in HCV Liver Recipients.

	Univariate Regression			Multivariate Regression		
Parameter	HR	95% CI	*P* Value	HR	95% CI	*P*Value
Donor Age $_{(>70)}$	2.51	1.04 – 6.07	0.04	**3.12**	**1.02 - 3.52**	**0.046**
Sodium $_{(<145)}$	0.96	0.92 - 0.99	0.04			
Isosexuality	0.39	0.15 - 0.97	0.04			
Time on List	0.98	0.97 - 0.99	0.02			
UNOS admission:						
1. ICU	8.93	2.60 - 30.62	< 0.001	**10.10**	**2.50 - 41.35**	**< 0.01**
2. Hospital	3.65	1.09 - 12.12	0.04			
MELD score	1.12	1.05 - 1.19	< 0.001	**1.13**	**1.05 - 1.20**	**< 0.001**
HIV Coinfection	2.95	1.35 - 6.39	< 0.01	**2.65**	**1.96 - 7.28**	**0.049**

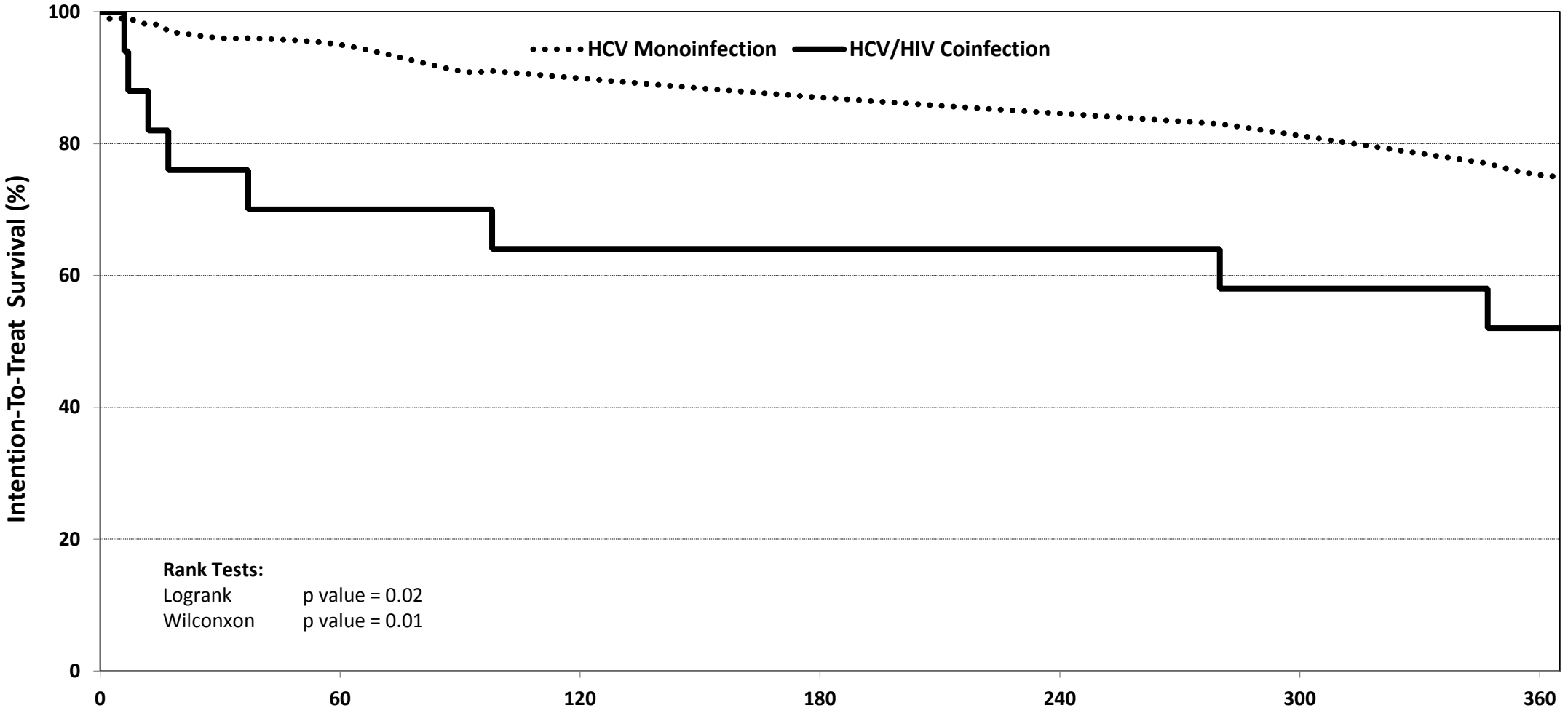
CI *Confidence Interval;* ***UNOS*** *United Network for Organ Sharing;* ***ICU*** *Intensive Care Unit;* ***MELD*** *Model for End-stage Liver Disease;* ***HCV/HIV*** *Hepatitis C Virus and Hepatitis Inmunodeficiency Virus.*

Variables significantly associated with survival ITT are highlighted in bold print





Patients at risk					
HCV Mono	182	123	100	88	78
HCV/HIV Co	17	9	9	8	5



Patients at risk							
HCV Mono	182	174	159	151	145	134	123
HCV/HIV Co	17	12	11	11	11	10	9

Supplement Table. Characteristics of HCV/HIV Coinfected Patients (*ordered by date on the waiting list)*

Baseline Characteristics on waiting list										Cause of Drop-out List *(cause dead)*	Time on waiting list *(days)*	Transplant Characteristics						ITTA	
												Donor			Receptor				
Case	Date on waiting list	Age	Sex	Primary Indication LT	Genotype	HCV viral load	CD4 cell Count	HIV viral load	Type of cART *(-based)*			Age	Sex	Cause of brain death	Type of cART *(-based)*	HIV viral load	Cause Retransplant	Survival	Days Follow-up
1	14/05/04	39	Female	Cirrhosis	1	4,42E5	480	50	NRTI-	EX *(infection)*	6							Dead	6
2	24/06/04	41	Male	Cirrhosis	2	5,00E5	149	970	NNRTI-	LT	28	28	Female	Head Trauma	NNRTI-	130	Vascular	Live	4024
3	15/04/05	47	Male	Cirrhosis	4	5,14E5	184	60	NRTI-	EX *(others)*	12							Dead	12
4	05/05/06	43	Male	Cirrhosis + HCC[(a)]	1	1,96E6	122	40	PI-	LT	37	57	Male	CVA	PI-	< 20		Live	3344
5	22/06/06	35	Female	Cirrhosis	other	6,73E5	105	740	PI-	IM	208							Live	3296
6	16/01/07	43	Male	Cirrhosis	4	4,47E6	127	450	PI-	EX *(liver)*	7							Dead	7
7	03/07/07	47	Male	Cirrhosis + HCC	3	5,24E7	485	40	PI-	LT	207	46	Female	CVA	PI-	< 20		Live	2920
8	13/07/07	46	Female	Cirrhosis	1	2,10E7	180	40	NRTI-	LT	132	58	Female	CVA	NRTI-	< 20		Dead[(c)]	1314
9	26/03/08	50	Male	Cirrhosis	1	6,41E5	124	980	PI-	EX *(infection)*	37							Dead	37
10	03/07/08	44	Male	Cirrhosis	1	4,80E7	166	40	NRTI-	LT	33	40	Male	Anoxia	NRTI-	< 20		Dead[(c)]	1099
11	12/06/09	48	Male	Cirrhosis + HCC	1	5,40E6	226	520	NRTI-	DC	96							Dead	347
12	20/10/09	49	Male	Cirrhosis + HCC	4	3,80E7	126	40	PI-	LT	39	40	Male	CVA	PI-	< 20		Live	2080
13	06/04/11	47	Male	Cirrhosis	1	4,30E5	673	40	NNRTI-	EX *(infection)*	17							Dead	17
14	02/12/11	47	Male	Cirrhosis	1	2,50E1	120	40	PI-	LT	113	71	Female	CVA	PI-	< 20		Live	1307
15	09/03/12	51	Male	Cirrhosis	3	3,10E3	170	40	NNRTI-	LT	84	57	Female	CVA	NNRTI-	< 20	Vascular	Live	1209
16	11/02/14	44	Male	Cirrhosis	4	3,62E5	110	840	NNRTI-	LT	1	38	Female	Anoxia	NNRTI-	< 20	Biliary	Dead	280
17	30/07/14	45	Male	Cirrhosis[(b)]	3	3,47E6	197	27800	NNRTI-	EX *(liver)*	98							Dead	98

(a) VHB Coinfection; **(b)** Hepatorenal Transplant; **(c)** Dead with Disfunctioning Graft (several liver recurrence HCV)
Cause of drop-oup at list: **EX**: Exitus waiting list; **LT**: Liver Transplant; **DC**: Definitive Contraindication; **IM**: Improvement
cART (combined antiretroviral treatment): **NRTI:** Nucleotido Reverse Transcriptase Inhibitor; **NNRTI:** No Nucleotido Reverse Transcriptase Inhibitor; **PI:** Protease Inhibitor
ITTA: Intention-to-treat Analysis