

# Hepatitis C Virus Infection Can Affect Lymphoproliferative Disorders Only as a Cofactor for Epstein-Barr Virus in Liver Transplant Recipients: PTLD.Int Survey

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## Abstract

**Objectives:** Hepatitis C virus infection has a 10.5% frequency in liver transplant posttransplant lymphoproliferative disorders. Studies have suggested that hepatitis C virus infection plays a role in developing posttransplant lymphoproliferative disorders. Pooling data of posttransplant lymphoproliferative disorders developing in liver recipients from the literature, we analyzed and compared characteristics, behavior, and prognoses of posttransplant lymphoproliferative disorders arising in hepatitis C virus-positive versus negative liver graft recipients.

**Materials and Methods:** We conducted a search for the available data through PubMed and Google Scholar for reports of posttransplant lymphoproliferative disorders and hepatitis C virus infection in liver transplant recipients. Overall, 29 studies were found and their data are included in the analyses.

**Results:** Overall, data of 212 liver transplant patients were included. Sixty-three percent were male. No difference was found between hepatitis C virus-positive liver transplant patients with posttransplant lymphoproliferative disorders compared to their hepatitis C virus-negative counterparts regarding sex, time from transplant to lymphoma development, lymphoma cell type, remission, mortality rate, multiorgan involvement, disseminated posttransplant lymphoproliferative disorders, and histopathologic evaluations ( $P > .1$  for all). Hepatitis C virus-positive liver transplant recipients representing posttransplant

lymphoproliferative disorders who were concomitantly positive for Epstein-Barr virus were significantly more likely to develop lymphomas in the early posttransplant period (26 [67%] vs 16 [40%];  $P = .024$ ) and to complicate liver (19 [63%] vs 8 [30%];  $P = .017$ ) than hepatitis C virus-/Epstein-Barr virus+ patients.

**Conclusions:** Hepatitis C virus infection alone has no significant effect on lymphoproliferative disorders after liver transplant; but when combined with Epstein-Barr virus infection, it represents some significant different presentations of the disease. However, no survival effect was found for hepatitis C virus with or without simultaneous Epstein-Barr virus infection, in the posttransplant lymphoproliferative disorders setting. Future prospective studies are needed for confirming our results.

**Key words:** Posttransplant lymphoproliferative disorders, PTLD, Liver transplant, EBV, Hepatitis C virus

## Introduction

The term *posttransplant lymphoproliferative disorder* (PTLD) is a well-known complication of organ transplants comprising a wide spectrum of clinically relevant lymphatic disorders ranging from plasmacytic hyperplasia to malignant monoclonal non-Hodgkin lymphoma. This entity was first reported by Penn and associates<sup>1</sup> in 1969, in a patient who had undergone living-related kidney transplant. Since then, several reports have been published indicating a high incidence of PTLD among recipients of all types of organs, including the liver. The reported incidence of PTLD in organ transplanted patients is 1% to 20%<sup>2-4</sup> with an incidence rate of 2% to 4% in adult liver allograft recipients.<sup>5-7</sup> It is shown that the rate of PTLD development has unequivocal associations with the

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type of organ transplanted, the intensity of the immunosuppression, underlying disease, age, and the occurrence of viral infections, particularly Epstein-Barr virus (EBV).<sup>8-10</sup> It also has been suggested that hepatitis C virus (HCV) and/or *cytomegalovirus*, as cofactors of EBV infection, may increase the risk of PTLD.<sup>11-12</sup>

Hepatitis C virus has been associated with several extrahepatic manifestations, most of which are through immunologic pathways.<sup>13</sup> There are overwhelming data indicating a powerful association between HCV infection and essential mixed cryoglobulinemia, which is generally considered as a low-grade non-Hodgkin lymphoma.<sup>14-17</sup> Hepatitis C virus-specific antibodies have been found in up to 98% of mixed cryoglobulinemia patients.<sup>18</sup> It also has been demonstrated that HCV can induce clonal proliferation of B lymphocytes and has been shown to be involved in the pathogenesis of B-cell lymphoproliferation.<sup>19, 20</sup>

Hepatitis C virus has a 10.5% frequency in liver transplant PTLD patients.<sup>8</sup> Evidence suggests that HCV infection plays a significant role in development of PTLD, and reports indicate that the incidence of PTLD in HCV-positive liver graft recipients is higher than that in HCV-negative patients.<sup>21</sup> Most of the available data on the above-mentioned issues are based on case reports and small series. In fact, such cases are only included in bigger series and have not received enough attention. Moreover, there is no mention about any specificity associated with HCV-induced PTLD, including histopathological features, any priorities in organ involvement, and rates of disseminated disease, remissions, and survival. Pooling data of HCV-positive PTLD liver recipients from the existing literature, we sought to analyze and compare characteristics, behavior, and prognosis of PTLD arising in HCV-positive versus negative liver graft recipients.

## Materials and Methods

### Approach to the study

We conducted a comprehensive search for the available data through PubMed and Google Scholar for reports of PTLD and HCV infection in liver transplant (LT) recipients. Search terms used were "lymphoproliferative disorders + transplantation + liver + hepatitis C virus," "lymphoproliferative disorders + transplantation + liver + HCV," "PTLD +

liver + hepatitis C virus," and "PTLD + liver + HCV." In some cases, we were unable to obtain the full text of the articles, e-mails were sent to the corresponding authors requesting the article file. Of the full texts obtained, we included studies in which data on each patient was presented separately. Hepatitis C virus-negative PTLD LT controls also were included for comparisons. For inclusion of controls, we only used cases for which HCV negativity was definitely reported, and cases with no presented data on HCV serology / polymerase chain reaction (PCR) analyses were excluded. A standard questionnaire was developed to collect data from different published studies. The time between transplant and PTLD onset was defined as the period between the engraftment and the first signs of PTLD or diagnosis, depending on the study's approach.

### Study population

Twenty-nine international published studies<sup>8, 22-49</sup> met our criteria (Table 1). A total of 212 cases of PTLD LT patients were included in the analysis; of whom 68

**Table 1.** List of the included studies and their share in case and control groups.

Study	No. of included patients (%)	No. of HCV positive (%) controls (%)	No. of HCV negative
1 Avolio et al. <sup>22</sup>	5 (2.4)	2 (2.9)	3 (2.1)
2 Duvoux et al. <sup>23</sup>	16 (7.5)	5 (7.4)	11 (7.6)
3 Capello et al. <sup>24</sup>	14 (6.6)	8 (11.8)	6 (4.2)
4 Norin et al. <sup>25</sup>	12 (5.7)	1 (1.5)	11 (7.6)
5 He'Zode et al. <sup>26</sup>	6 (2.8)	4 (5.9)	2 (1.4)
6 Buadi et al. <sup>27</sup>	4 (1.9)	2 (2.9)	2 (1.4)
7 Zimmermann et al. <sup>28</sup>	11 (5.2)	1 (1.5)	10 (6.9)
8 Lorenzini et al. <sup>29</sup>	4 (1.9)	1 (1.5)	3 (2.1)
9 Timurağaoğlu et al. <sup>30</sup>	1 (0.5)	0	1 (0.7)
10 Ziarkiewicz-Wróblewska et al. <sup>31</sup>	4 (1.9)	1 (1.5)	3 (2.1)
11 Mucha et al. <sup>8</sup>	2 (0.9)	1 (1.5)	1 (0.7)
12 Niedobitek et al. <sup>32</sup>	4 (1.9)	1 (1.5)	3 (2.1)
13 Dean et al. <sup>33</sup>	23 (10.8)	7 (10.3)	16 (11.1)
14 Baron et al. <sup>34</sup>	14 (6.6)	1 (1.5)	13 (9)
15 Ben-Ari et al. <sup>35</sup>	7 (3.3)	2 (2.9)	5 (3.5)
16 Koh et al. <sup>36</sup>	10 (4.7)	1 (1.5)	9 (6.3)
17 Baccarania et al. <sup>37</sup>	9 (4.2)	7 (10.3)	2 (1.4)
18 Bianchi et al. <sup>38</sup>	1 (0.5)	0	1 (0.7)
19 Burra et al. <sup>39</sup>	2 (0.9)	1 (1.5)	1 (0.7)
20 Lemoine et al. <sup>40</sup>	21 (9.9)	6 (8.8)	15 (10.4)
21 Cano et al. <sup>41</sup>	3 (1.4)	3 (4.4)	0
22 Dhillon et al. <sup>42</sup>	19 (9.0)	5 (7.4)	14 (9.7)
23 Sun et al. <sup>43</sup>	1 (0.5)	1 (1.5)	0
24 Pham et al. <sup>44</sup>	1 (0.5)	1 (1.5)	0
25 Nagarsheth et al. <sup>45</sup>	1 (0.5)	0	1 (0.7)
26 Hsi et al. <sup>46</sup>	2 (0.9)	1 (1.5)	1 (0.7)
27 Kogan-Liberman et al. <sup>47</sup>	2 (0.9)	0	2 (1.4)
28 Aseni et al. <sup>48</sup>	9 (4.2)	4 (5.9)	5 (3.5)
29 McCormack et al. <sup>49</sup>	4 (1.9)	1 (1.5)	3 (2.1)
<b>Total</b>	<b>212 (100)</b>	<b>68 (100)</b>	<b>144 (100)</b>

(32%) were HCV-positive PTLT, and the remaining 144 patients (68%) developed HCV-negative PTLT. Epstein-Barr virus was documented in 145 patients (68%), of whom, 112 (77%) were reported positive.

Because methodologies differed among the published studies, not all our measures were available for all patients. We recorded disseminated PTLT when it was reported by the study authors, or if at least 3 different organs were involved by the PTLT (different lymph node areas were excluded from the analysis owing to the lack of knowledge on how to categorize; unless they were concomitant with other organ involvements; or other authors specifically presented them as having disseminated disease). According to the above-mentioned, disseminated disease was reported for 28 patients (23%; 91 missing data). Multiorgan involvement, defined as *involvement of more than 1 organ* (the second organ could be a lymphatic region), was available in 49 patients (38%; 84 missing data).

At PTLT LT onset, all patients were under immunosuppressive regimens consisting of varying combinations of azathioprine, prednisone, cyclosporine, mycophenolate mofetil, ATG/ALG, and OKT3. A rather uniform approach was used to manage most of the included PTLT LT. On diagnosis of PTLT, the first step in almost all reports was to decrease or discontinue immunosuppressive therapy; various regimens of chemotherapy with or without surgical interventions also were used for some patients.

### Response to treatment

We defined response to treatment as *any favorable change both in PTLT measures as well as the patient's clinical condition*. Data on response to treatment was reported for 75 patients (35%), of whom 68 (91%) responded to treatment. To create a common standard across the studies, we defined a remission episode as *when a patient was alive 24 months after PTLT onset* (because all reported cases meeting this criterion had at least 1 confirmed remission episode) and as *no remission when a patient died within the first month after PTLT onset* (because there were no patients dying in the first posttransplant month that were reported to have any remission episodes). According to these criteria, data on remission were available for 99 patients (47%), of whom 86 (87%) had at least 1 response to treatment, irrespective of their future disease course. Data on mortality were available for

160 patients (75.5%), of whom 67 died (42%). We defined death owing to PTLT LT *when the authors stated it, when death was within 6 months after onset, or death was reported to be owing to PTLT LT treatment complications*. Death beyond this time was not labeled as PTLT-free mortality, unless it was defined by authors. Based on these criteria, 33 patients (49% of reported deaths, 24% of patients for whom mortality data was reported) died owing to PTLT.

### Statistical Analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 13.0, IBM Corporation, Armonk, New York, USA). Statistical comparisons between patient subgroups were performed using chi-square and Fisher exact tests for proportions, and the *t* test for continuous data. Survival analysis was done with life tables, Kaplan-Meier method and log-rank test. A *P* value of .05 was taken as the threshold for significance.

### Results

Overall, 212 cases of PTLT LT were found. There were 113 male (63%) and 66 female patients (31%) (33 missing data). Mean age at transplant was  $45.3 \pm 15.7$  years. The mean interval between transplant and the onset of PTLT LT was  $31.8 \pm 36.3$  months, and the mean follow-up after onset of PTLT was  $24.0 \pm 29.0$  months.

Characteristics of PTLT LT patients with and without HCV infection are summarized in Table 2. A chi-square test showed that HCV positive-PTLT LT patients were comparable to HCV-negative PTLT LT in sex ( $P = .19$ ), time from transplant to PTLT LT development ( $P = .633$ ), lymphoma cell type ( $P = .17$ ), remission ( $P = 1.0$ ), mortality rate ( $P = 1.0$ ), multiorgan involvement (based on our definition;  $P = .23$ ), and disseminated PTLT (based on our definition;  $P = .35$ ). Histopathologic evaluations also were not significantly different between the 2 groups ( $P = .11$ ). Hepatitis C virus-positive PTLT LT patients were significantly younger at the time of transplant ( $P = .002$ ).

Table 3 compares HCV-positive versus-negative LT recipients respecting organ involvement by PTLT. No differences were seen regarding priorities in organ involvements for the 2 patient groups. At the last follow-up, 68 patients (42% of reported; 51 missing data) died. Using death by any cause as the

**Table 2.** Characteristics of the included PTLT LT patients regarding HCV test results.

Variables	Study groups		P value	Available data
	HCV+	HCV-		
Age (y)	50.1 ± 11.2	43.4 ± 16.9	.002	193
Sex (male) (%)	42 (70)	71 (59.7)	.19	179
Time to PTLT development (mo)	33.8 ± 36.4	30.9 ± 36.3	.63	181
Early onset PTLT (vs late)	29 (46.8)	80 (57.6)	.17	201
Time from diagnosis to death (mo; dead patients included only)	8.6 ± 14.3	17.2 ± 25.6	.14	49
Multiorgan involvement (%)*	11(29.7)	38 (41.8)	.23	128
Disseminated PTLT (%) *	6 (16.7)	22 (25.9)	.35	121
Lymphoma cell type B cell (%)	43 (100)	81 (93)	.18	130
Clonality (%)	12 (80)	30 (69.8)	.52	58
Morphology			.29	137
Early lesion				
(Plasmacytic hyperplasia)	2 (4.5)	4 (4.3)		
Polymorphic				
B cell lymphoma	17 (38.6)	22 (23.7)		
Monomorphic PTLT	25 (56.8)	66 (71)		
Hodgkin lymphoma	0	1 (1.1)		
EBV status (%)	36 (78.3)	76 (76.8)	1.0	145
Mortality rate (%)	24 (42.1)	44 (42.3)	1.0	161
Remission episode (%)**	19 (86.4)	49 (92.5)	.41	75
Remission episode (%)*	27 (87.1)	59 (86.8)	1.0	99
Use of induction therapy (%)	15 (50)	40 (48.2)	1.0	113

\*according to the criteria defined in the methods section

\*\*author reported

Abbreviations: EBV, Epstein-Barr virus; PTLT, posttransplant lymphoproliferative disorder

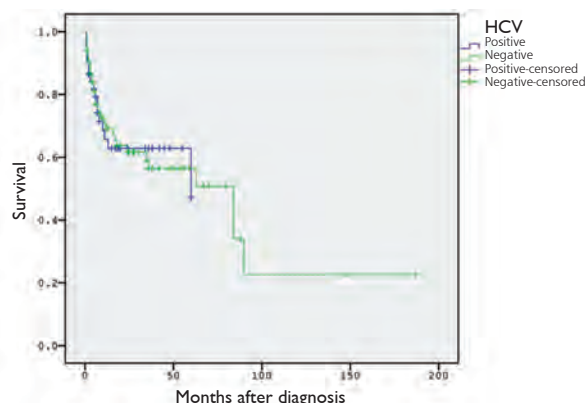
**Table 3.** Frequency of involved organs in PTLT LT patients with respect to their HCV test results.

Involved organs	HCV infection		P value	Available data
	HCV+	HCV-		
Orbital	0	1 (1.5)	1.0	102
Skeleton	1 (2.9)	2 (2.9)	1.0	104
Skin	0	1 (1.5)	1.0	102
Genitalia	0	2 (2.9)	0.55	102
CNS	1 (2.9)	3 (4.4)	1.0	102
Spleen	5 (15.2)	9 (13)	0.77	102
Colon	3 (9.4)	3 (4.5)	0.38	99
Stomach	0	3 (4.5)	0.55	99
Small intestine	1 (3)	7 (10.6)	0.26	99
Renal involvement	1 (3)	1(1.5)	0.55	101
Liver involvement	26 (57.8)	60 (59.7)	0.86	146
Respiratory system	3 (9.7)	13 (22)	0.24	90
Bone marrow	3 (8.6)	16 (22.9)	0.11	105

Abbreviations: CNS, central nervous system; HCV, hepatitis C virus

outcome, log-rank test did not show any difference between the 2 groups in survival ( $P = .96$ ; Figure 1). Nor was any difference seen between the 2 groups when death only owing to PTLT (based on our definition) was used as the outcome ( $P = .58$ ). One- and 5-year survival rates for HCV-positive PTLT LT patients were 65% and 62%, compared to 70% and 56% for HCV-negative PTLT LT patients.

In an attempt to find out whether a coinfection of HCV and EBV has any effect on PTLT, we

**Figure 1.** Survival curves of HCV-positive and -negative PTLT LT patients (Outcome: death irrespective of the reason)

Abbreviations: HCV, hepatitis C virus; PTLT, posttransplant lymphoproliferative disorder

introduced 2 patient groups according to their HCV and EBV test results: (1) EBV positive and HCV positive (HCV+/EBV+), and (2) EBV positive and HCV negative (HCV-/EBV+). Group 1 was significantly more likely to develop PTLT in the early posttransplant period (26 [67%] vs 16 [40%];  $P = .024$ ); moreover, HCV+/EBV+ PTLT LT patients were significantly more likely to complicate liver (19 [63%] vs 8 [30%];  $P = .017$ ) than HCV-/EBV+ patients. Other study parameters were comparable between the 2 groups (data not shown).

## Discussion

Posttransplant lymphoproliferative disorders comprise a spectrum of significant lymphatic disorders that induce a wide range of morbidity and mortality to organ transplant recipients; it has emerged as a serious complication that needs a huge amount of attention on exploring predictive and interfering factors. The incidence, features, and prognosis of PTLT varies between different transplant patients owing to several parameters including the transplanted organ, immunosuppression intensity, the use of antibody induction, and viral infections, most notably, EBV infection.<sup>50</sup>

In a nontransplant setting, hepatophil viruses are shown to have stimulating roles in inducing lymphoproliferative disorders. Several reports have suggested an exceeding prevalence of HCV<sup>51-53</sup> or of hepatitis B virus<sup>54, 55</sup> infection in patients with non-Hodgkin lymphomas. Hepatitis C virus can induce clonal expansion of B lymphocytes and has been involved in the pathogenesis of B-cell



lymphoproliferative disorders.<sup>19, 20</sup> It has been demonstrated that HCV nonstructural proteins (NS3 and HCV core protein) can induce cell transformation in nude mice, and that HCV core protein is capable of effecting cellular proto-oncogenesis regulation and stimulating B-cell secreting cryoglobulin, which potentially can result in clonal expansion and lymphoma.<sup>56-58</sup> Hepatitis C virus RNA or proteins also have been found in epithelial cells of parotid lymphoma, and in bone marrow and lymph nodes of patients with B-cell non-Hodgkin lymphomas.<sup>59, 60</sup> Other studies have demonstrated that HCV replicates blood cells including B-lymphocytes and CD34+ hematopoietic progenitor cells.<sup>16, 59, 61</sup> Other evidence for a potential association between HCV infection and lymphoma is provided by observations suggesting regression of monoclonal B-cell expansion in patients with lymphoproliferative disorders after clearance of HCV following  $\alpha$ -interferon treatment.<sup>62-64</sup>

In this era of transplant, it is also believed that chronic HCV infection may lead to the development of PTLD by stimulating lymphoid tissue and clonal B cells proliferation.<sup>10</sup> One reason for this risk enhancement is reportedly the immunosuppressive treatment in these patients, owing to preventing rejection episodes that can lead to activation of chronic infections including HCV. In this study of international data, we pooled the existing data from HCV-infected PTLD LT to find any potential associations between HCV infection in PTLD patients and disease features, behavior, and prognosis. The unexpected finding of this study is that we found no significant difference between HCV-positive and -negative PTLD LT patients.

Because our study deals with the largest patient population in the current literature, we think that this finding is not only due to the limited number of included patients, but the methodology of our study, which reviews and gathers data from different reports, despite some disadvantages, can be used precisely in several cases. For example, if HCV infection could have a provocative role for development of PTLD, at least we should expect a shorter time from transplant to PTLD in HCV-positive PTLD LT patients compared to HCV-negative controls, as we can observe it in EBV-positive setting.<sup>65, 66</sup> Moreover, no disparities also were found in the behavior of the PTLD between HCV-positive and -negative liver recipients

including remission rates and survival rates. This finding suggests that even if HCV has any role in the development of the PTLD, its role is not significant.

It also has been suggested that some viruses, including HCV, can act as cofactors of EBV infection, and may increase the risk of PTLD.<sup>11, 12</sup> Because we have not found any associations between HCV infection and PTLD, we tried to find out whether a coinfection of HCV and EBV can be different from that in only HCV-infected patients.

At first, we introduced 4 patient groups according to their HCV and EBV test results. We found that patients with EBV-positive tests had a significantly shorter time to PTLD development. To censor the effect of EBV infection, we recategorized our patients to 2 groups: (1) EBV-positive and HCV-positive, and (2) EBV-positive and HCV-negative. New categorization showed that HCV-positive PTLD patients with a simultaneous positive result for EBV were significantly more likely to develop PTLD in the early posttransplant period; moreover, HCV+/EBV+ PTLD LT patients were significantly more likely to complicate liver than HCV-/EBV+ patients. These findings confirm previous studies' findings in which authors have speculated HCV as a predictor for PTLD only as a cofactor for EBV infection.

Potential criticisms may arise over our study. First, our study population was gathered from different reports with inconsistent approaches. We also believe that this is the unique major limitation for this study leading to substantial missing data for some of study variables and thus, decreasing the power of our analyses. This limitation was most prominent for special data that are not typically included in reports on PTLD patients.

Another limitation owing to the inconsistencies available between the included studies was that results of different studies were not presented in the same way. For example, report of any response to treatment was presented very dissimilar in different studies; while in 1 study, partial and complete remission was used to translate the results; in another, only "response to treatment" was used, and in some others, no specific terminology was used. So, we ought to invent new methods to cumulate the existing data for analysis.

We conclude that, HCV infection alone has no significant effect on lymphoproliferative disorders after LT; but when it is combined with EBV infection, it represents some significant different presentations

of the disease. However, no survival effect was found for HCV with or without simultaneous EBV infection, in the PTLD setting. Future prospective studies are warranted to confirm our findings.

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