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# Clinical Efficacy of Pretransplant Vaccination for Preventing Herpes Zoster After Living Donor Liver Transplantation in Recipients Age 50 Years and Older

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Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
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**Background:** There have been no reports concerning the efficacy of pretransplant herpes zoster (HZ) vaccination following living donor liver transplantation (LDLT).

**Material/Methods:** From January 2013 to May 2016, 24 patients age 50 years and older received vaccination of HZ prior to transplantation and underwent LDLT at a single institution. We compared this to the 1-year HZ incidence of unvaccinated recipients (N=180) who underwent LDLT in the same time period.





**Results:** For general characteristics, the MELD scores ( $p<0.001$ ) and CTP grades ( $p=0.007$ ) of the vaccinated group were significantly lower than those of the unvaccinated group. In Kaplan-Meier analysis, the 1-year HZ incidence rates of the vaccinated and unvaccinated groups were 2 (8.7%) and 16 (9.9%) cases, respectively ( $p=0.883$ ). In the subgroup aged 50–59 years, 2 vaccinated recipients had HZ after LDLT. However, in the subgroup aged 60 years and older, no vaccinated recipients had HZ after LDLT. Multivariate analysis showed the independent risk factor for HZ after LDLT was use of mycophenolate mofetil (MMF; hazard ratio [HR]=3.00;  $p=0.041$ ).

**Conclusions:** The efficacy of pretransplant vaccination for preventing HZ was not apparent in our study. A large prospective study is needed to determine the indications for pretransplant HZ vaccination according to age group and to evaluate the efficacy of HZ vaccination after LDLT.

**MeSH Keywords:** Herpes Zoster • Liver Transplantation • Vaccination

**Abbreviations:** **ACIP** – Advisory Committee on Immunization Practices; **CNI** – calcineurin inhibitor; **CMV** – cytomegalovirus; **CTP** – Child-Turcotte-Pugh; **DM** – diabetes mellitus; **FDA** – The Food and Drug Administration; **HBV** – hepatitis B virus; **HCC** – hepatocellular carcinoma; **HTN** – hypertension; **HZ** – herpes zoster; **MELD** – model for end-stage liver disease; **MMF** – mycophenolate mofetil; **MRL** – modified right lobe; **LDLT** – living donor liver transplantation; **LT** – liver transplantation; **VZV** – varicella zoster virus

**Full-text PDF:** <https://www.annalsoftransplantation.com/abstract/index/idArt/914213>

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## Background

Herpes zoster (HZ) is the clinical feature of reactivated varicella zoster virus (VZV). The annual incidence of HZ in the general people is 1.5–3.0 cases per 1000 persons [1], and this incidence of HZ may be higher in post-transplant immunosuppressed recipients [2]. HZ vaccine (Zostavax®, Merck & Co., Inc.) was approved in 2006 for prophylaxis of HZ among adults over age 60 [3], and was approved by the Food and Drug Administration (FDA) in March 2011 among adults age 50–59 years. Although several studies have reported the incidence of HZ following liver transplantation (LT) [4,5], no data are accessible on the effectiveness of the HZ vaccine in LT recipients receiving immunosuppressant treatment following vaccination. Therefore, we performed a comparative study to evaluate the incidence of HZ among LT recipients with or without vaccination prior to living donor liver transplantation (LDLT). We assessed the efficacy of pretransplant HZ vaccination by performing multivariable analysis for assessment of independent risk factors of HZ after LT.

## Material and Methods

### Patients and study design

We collected data from 204 adults age 50 years and older who underwent LDLT at a single center from January 2013 to May 2016. Since this study was a historical prospective study, those patients who were not followed for at least 1 year due to mortality (N=17) or who underwent retransplantation (N=2) were excluded. According to vaccine implementation prior to LDLT, recipients were divided into the vaccinated group (N=24) and the unvaccinated group (N=180) and were followed for the incidence of HZ within 1 year of LDLT. This study received Institutional Review Board (No. 2017-05-177) approval.

HZ vaccination was performed when the following 3 indications were satisfied: age 50 years or above; more than 4 weeks remaining in the patient's schedule for LDLT; and patients who chose to get the vaccine had to pay for it themselves. Most LDLT candidates rejected vaccination due to costs or personal preference. HZ was considered as the clinical expression of a cutaneous vesicular eruption in accordance with a dermatome. Diagnosed HZ was treated by intravenous acyclovir or oral famciclovir for 2 weeks. We reviewed the medical records to investigate the location, extension, and treatment of HZ.

To induce immunosuppression, two 20-mg doses of basiliximab (Simulect®) were administered intravenously within 2 h after reperfusion and again on day 4 post-transplantation. Tacrolimus, mycophenolate mofetil (MMF), and steroids were administered for the initial maintenance of immunosuppression.

Tacrolimus and MMF were set to trough levels of 5–10 µg/ml and 1–3 µg/ml, respectively.

The following general characteristics of vaccinated and unvaccinated recipients were obtained: age, sex, etiology, type of liver failure, hepatocellular carcinoma (HCC), Model for End-stage Liver Disease (MELD) score, hepatorenal syndrome, diabetes mellitus (DM), hypertension (HTN), type of calcineurin inhibitor (CNI), and cytomegalovirus (CMV) status before LT.

### Statistical methods

The incidence rate of HZ in the 2 groups was assessed by Kaplan-Meier analysis. Categorical data are described as numbers and percentages. Continuous data are presented as the mean (±SD). Statistical analysis was conducted using Fisher's exact test for categorical values and Mann-Whitney test for continuous values. Univariate and multivariate analysis for factors affecting HZ incidence after LDLT were conducted using a Cox proportional hazard model. A p value below 0.05 was regarded as statistically significant. Data were analyzed using the Statistical Package for Social Science for Windows™ 22.0 (SPSS Inc., Chicago, IL).

## Results

Table 1 shows baseline characteristics among the vaccinated and unvaccinated groups. All patients were seropositive for CMV and VZV IgG. The principal diagnosis in the vaccinated and unvaccinated groups (69.6% vs. 71%, respectively) was hepatitis B virus (HBV). No patient showed acute liver failure in the vaccinated group. CTP grades and MELD scores in the unvaccinated group were remarkably higher than in the vaccinated group ( $p=0.007$  and  $p<0.001$ , respectively). Other factors did not show differences between the 2 groups. As shown in Table 2, HZ within 1 year of LDLT occurred in 18 recipients (8.8%) out of a total of 204 patients. In the Kaplan-Meier analysis, the 1-year cumulative incidence of HZ for the vaccinated and unvaccinated groups was 8.3% and 8.9%, respectively ( $p=0.839$ , Figure 1A). HZ eruption for the majority (66.7%) was located in the trunk. No patients developed a disseminated case of HZ. Only 1 patient (in the unvaccinated group) had a recurrence of HZ. The incidence of HZ according to age stratification (e.g., patients age 50–59 years or those age 60 years and older) was not different between the 2 groups (Figure 1B, 1C). However, there was no occurrence of HZ in the subgroup aged 60 years and older in the vaccinated group. As shown in Table 3, there was no significant factor for HZ occurrence after LDLT in univariate analysis for variables affecting the HZ incidence, including HZ vaccination prior LDLT. Multivariate analysis showed the independent risk factor for HZ following LDLT was use of mycophenolate mofetil (MMF; hazard ratio [HR]=3.00;  $p=0.041$ ).

**Table 1.** Baseline characteristics of zoster-vaccinated and unvaccinated groups.

Characteristics	Vaccinated group (N=24)	Unvaccinated group (N=180)	p-Value
Age, years	57.4±5.4	57.8±5.4	0.694
Sex, Male: Female, %	21 (87.5%): 3 (12.5%)	140 (77.8%): 40 (22.2%)	0.307
VZV seronegative, n, %	0 (0%)	0 (0%)	N/A
CMV seronegative, n, %	0 (0%)	0 (0%)	N/A
Diagnosis, n, %			0.632*
HBV	16 (66.7%)	126 (70.0%)	
HCV	1 (4.2%)	8 (4.4%)	
Alcohol	5 (20.8%)	23 (12.8%)	
Cryptogenic	1 (4.2%)	5 (2.8%)	
Other	1 (4.2%)	18 (10.0%)	
HCC, n, %	20 (83.3%)	119 (66.1%)	0.105
Liver failure, acute: chronic, %	0 (0%): 24 (100%)	17 (9.4%): 163 (90.6%)	0.230*
CTP grade, A: B: C, %	16 (66.7%): 8 (33.3%): 0 (0%)	74 (41.1%): 57 (31.7%): 49 (27.2%)	0.007
MELD score	10.5±3.9	15.5±10.0	<0.001
DM, n, %	6 (25.0%)	45 (25.0%)	1.000
Hepatorenal syndrome, n, %	1 (4.2%)	13 (7.2%)	1.000*
Immunosuppression at the endpoint**			
CNI type, n, %			0.664*
None	1 (4.2%)	11 (6.1%)	
Tacrolimus	22 (91.6%)	165 (91.7%)	
Cyclosporine	1 (4.2%)	4 (2.2%)	
Tacrolimus drug level (µg/ml)	9.7±25.1	6.5±10.2	0.550
MMF, n, %	18 (75.0%)	133 (73.9%)	1.000

\* Fisher exact test; \*\* The endpoint was defined as one year after LDLT in recipients without HZ or the time of HZ diagnosis in recipients with HZ.

## Discussion

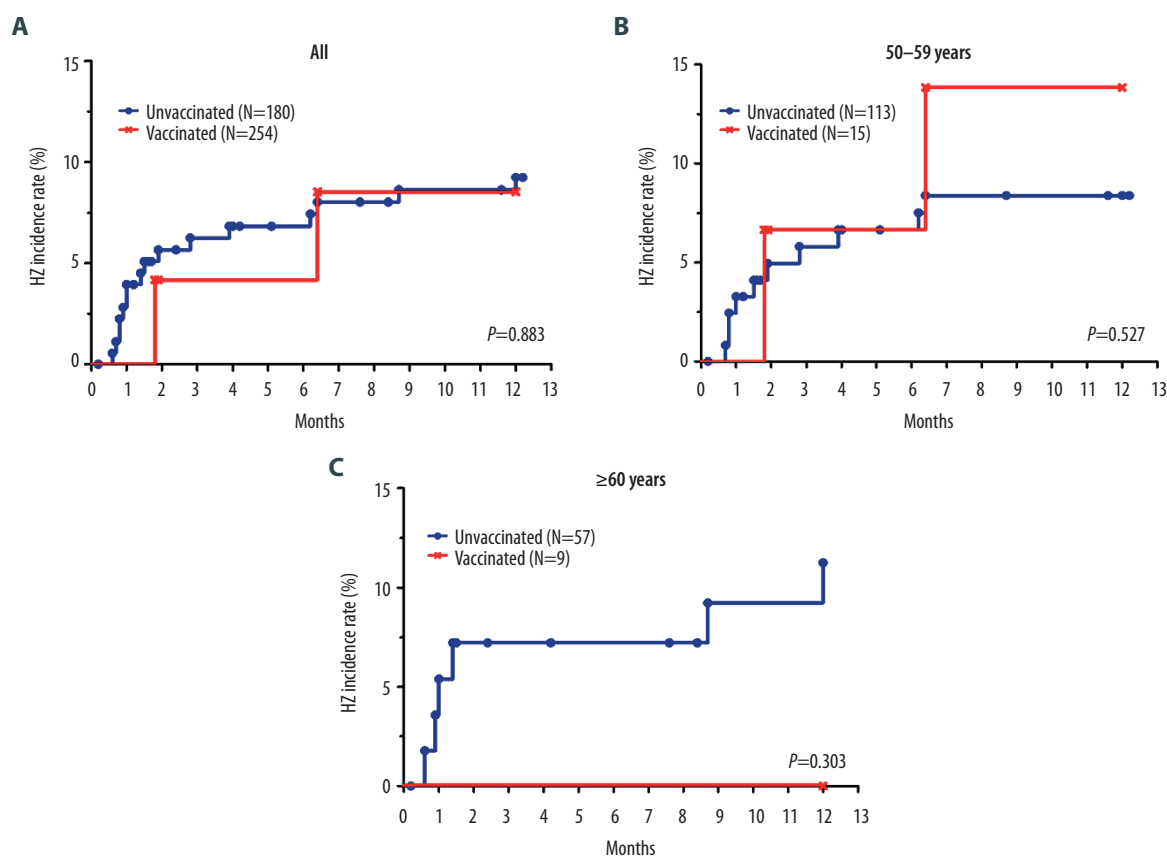
The burden of HZ increases with age, with large increases occurring after age 50 years. The HZ vaccine (Zostavax®, Merck & Co., Inc.) was first approved in 2006 and suggested by the Advisory Committee on Immunization Practices (ACIP) in 2008 for prevention of HZ and its complications among adults aged ≥60 years [3]. Despite approval of the FDA, in 2011 the ACIP withdrew its recommendation of the vaccine in adults age 50–59 years due to limited evidence on the long-term safety of Zostavax® [6]. As a result, the current ACIP recommendation regarding the HZ vaccine is to use it routinely for adults age ≥60 years [7]. However, there is no evidence regarding the efficacy of the HZ vaccine in LT recipients who become

immunosuppressed subsequent to vaccination. We performed a historical prospective study to investigate the 1-year incidence of HZ for vaccinated and unvaccinated groups during the same period to compare the efficacy of Zostavax®.

The 1-year incidence rate of HZ in recipients age 50 years and older was 8.8%, which is remarkably higher than in previous reports of recipients of all ages as target subjects [4,5]. The main finding of our study was that there was no significant difference in the post-transplant HZ incidence between the vaccinated and unvaccinated groups. In recipients age 60 years and older, the 1-year incidence rate for the unvaccinated subjects was 11.2%, but there was no incidence of HZ in recipients receiving pretransplant vaccination. A large prospective study

**Table 2.** Characteristics related to HZ between the vaccinated and unvaccinated groups.

Characteristics	Vaccinated group (N=24)		Unvaccinated group (N=180)		p-Value
HZ occurrence, n,%	2	(8.3%)	16	(8.9%)	1.000*
Median time from LT to HZ occurrence, days (range)	44	(17–54)	123	(54–191)	0.726
Extension, one dermatome,%	2	(100%)	16	(100%)	N/A
Location of HZ					1.000*
Trunk	2	(100%)	10	(62.5%)	
Buttock	0	(0%)	3	(18.8%)	
Face	0	(0%)	1	(6.3%)	
Lower extremity	0	(0%)	2	(12.5%)	
Recurrence, n,%	0	(0%)	1	(6.3%)	1.000*
Antiviral therapy, n,%					0.137*
Acyclovir (intravenous)	0	(0%)	11	(68.8%)	
Famciclovir (oral)	2	(100%)	5	(31.3%)	



**Figure 1.** The cumulative incidence rate of HZ for vaccinated and unvaccinated groups: in all patients (A), patients age 50–59 (B), and patients age 60 years and older (C).

**Table 3.** Univariate and multivariate cox analysis for risk factors affecting HZ incidence in LDLT recipients aged 50 years and older.

Variable	HZ occurrence		Univariate			Multivariate		
	No (n=186)	Yes (n=18)	HR	95% CI	p-value	HR	95% CI	p-value
Age ≥60 years	60 (32.3%)	6 (33.3%)	1.050	0.394–2.799	0.922	1.147	0.413–3.187	0.793
Female gender	41 (22.0%)	2 (11.1%)	0.451	0.104–1.964	0.289	2.762	0.566–13.481	0.209
MELD score ≤20	151 (81.2%)	14 (77.8%)	0.815	0.268–2.476	0.718	1.410	0.286–6.955	0.673
CTP grade C	44 (23.7%)	5 (27.8%)	1.218	0.434–3.417	0.708	0.555	0.118–2.616	0.457
Chronic liver failure	170 (91.4%)	17 (94.4%)	0.638	0.085–4.797	0.663	0.311	0.029–3.363	0.336
With HCC	126 (67.7%)	13 (72.2%)	1.225	0.437–3.435	0.700	0.776	0.234–2.577	0.679
ABO incompatible	41 (22.0%)	3 (16.7%)	0.698	0.202–2.410	0.569	1.250	0.345–4.527	0.734
Donor age ≥50 years	26 (14.0%)	1 (5.6%)	0.378	0.050–2.839	0.344	2.654	0.344–20.469	0.349
GRWR <0.8%	21 (11.3%)	1 (5.6%)	0.476	0.063–3.578	0.471	1.889	0.248–14.369	0.539
MMF	143 (76.9%)	11 (61.1%)	0.491	0.190–1.268	0.142	3.000	1.043–8.625	0.041
No HZ vaccination	164 (88.2%)	16 (88.9%)	1.090	0.251–4.739	0.909	0.877	0.191–4.028	0.866

is necessary to determine the indications for pretransplant HZ vaccination according to age group and to validate the statistical significance of our results on the efficacy of Zostavax®.

At our institution, use of Zostavax® was approved in 2013 and was applied to LDLT candidates age ≥50 years who wished to receive the vaccine. Because the HZ vaccine is an attenuated live virus, and a time interval of more than 4 weeks between vaccination and LT is needed, it is difficult to vaccinate LT recipients presenting acute liver failure. This is the reason that the vaccinated group included only a small number of LDLT patients and did not contain patients with acute liver failure.

Although disease severity (based on CTP grades and MELD scores) in the vaccinated group was lower than in the unvaccinated group, there was no significant difference in HZ incidence between 2 groups. Since it is known that lower MELD scores increase the risk of viral infection after LT [8], this difference in disease severity could have biased the study results. Therefore, it was necessary to identify antibody titers or assay for cell-mediated immunity to compare the efficacy of vaccination between the vaccinated and the unvaccinated groups.

There are several limitations to our study. Data was collected retrospectively. VZV-specific serology was not performed to evaluate the effectiveness of the zoster vaccine. The occurrence of HZ was merely investigated by a medical records review based on patients who were diagnosed with typical cutaneous eruption of HZ and treated by antiviral agents. Thus, we did not know how many cases were actually HZ. In the absence of medical records, HZ complications such as postherpetic neuralgia were not assessed. Finally, long-term outcomes regarding HZ and pretransplant vaccination were not available due to the recent use of Zostavax® at our institution.

## Conclusions

The post-LT efficacy of Zostavax® was not demonstrated in our small preliminary report. However, follow-up may be necessary to check the efficacy of Zostavax® in patients age 60 years and older. To establish an indication for the pretransplant use of HZ vaccination in LT recipients, as well as the efficacy of zoster vaccination, a large prospective study is needed.

## Conflicts of interest

None.

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