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Seroprevalence of Japanese Encephalitis Virus, and Immunogenicity of the Vero-Cell Culture-Derived Vaccine in Hematopoietic Stem Cell Transplantation Recipients

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ABSTRACT

Background: Revaccination against Japanese encephalitis virus (JEV) in adult hematopoietic stem cell transplantation (HSCT) recipients is not recommended because of insufficient data regarding its efficacy and immunogenicity. Therefore, we aimed to evaluate JEV seropositivity in adult HSCT recipients and explored the seroconversion rate in pediatric HSCT recipients after vaccination against JEV.
Methods: This prospective study was conducted at the National Cancer Center, Goyang, Korea. Adult HSCT recipients (n = 103) were enrolled who visited the outpatient clinic. Additionally, pediatric recipients (< 19 years old; n = 11) who received JEV vaccination were enrolled. We collected serum samples from these participants and healthy healthcare workers (n = 50) for comparison. The JEV seropositivity rates and anti-JEV antibody titers were evaluated using the plaque reduction neutralization test.
Results: The JEV seropositivity rates were significantly lower in adult HSCT recipients than in healthy healthcare workers (55% vs. 92%, $P < 0.001$). In addition, only one out of nine pediatric recipients tested seropositive before JEV vaccination. However, six out of seven were seropositive after two doses of vaccination. Furthermore, all three recipients who completed the three-dose vaccination schedule turned seropositive. No significant seropositivity-related factors were identified in the multivariate analysis.
Conclusion: The low anti-JEV antibody seropositivity rate in Korean adult HSCT recipients indicates an increased vulnerability to this virus. Our findings provide a theoretical basis for the potential establishment of appropriate prevention strategies targeting this high-risk group.

Keywords: Seroprevalance; Immunogenecity; Japanese Encephalitis Virus; Japanese Encephalitis Vaccine; Hematopoietic Stem Cell Transplantation

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Disclosures

The authors have no conflicts of interest to declare.

Author Contributions

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INTRODUCTION

The Japanese Encephalitis Virus (JEV), a flavivirus transmitted by mosquitoes, is the most common cause of viral encephalitis in Asia and the western Pacific region.[1] Although most JEV infections are mild or asymptomatic, approximately one in 250 infections result in severe clinical illness.[2] These severe infections can rapidly progress to encephalitis, with an estimated case fatality rate of 20–30%.[3-5] Furthermore, 30–50% of survivors experience long-term neurological effects, including intellectual and physical disabilities.[6,7]

The incidence of Japanese encephalitis (JE) in South Korea has markedly decreased from thousands of cases to fewer than five cases per year since the 1980s, owing to the implementation of universal JEV vaccination programs in children.[2,8-10] However, JE re-emerged in 2010, with 26 cases reported. In addition, the number of confirmed cases peaked at 40 in 2015.[10,11] Recent JE cases predominantly affect unvaccinated adults aged 40 years or older, indicating a shift in age distribution from children to older adults.[11-17]

Despite the high prevalence and severity of JE in endemic countries such as South Korea, current international guidelines do not include recommendations for JE vaccination, owing to insufficient evidence regarding safety and immunogenicity. However, the recent increase in JE infections among adults in endemic countries,[8,12-16] along with the potential decline in immunity against various vaccine-preventable diseases (VPDs) after hematopoietic stem cell transplantation (HSCT), necessitate further evaluation of the risk of JEV in adult recipients of HSCT in Korea.[15,16] Therefore, in the present study, we aimed to investigate the baseline seroprevalence of JE virus in adult HSCT recipients in Korea. Additionally, we explored the factors influencing the seroprevalence of JEV. Finally, we sought to evaluate the immunogenicity of the JEV vaccine from pediatric HSCT recipients.

METHODS

Study design and participants

This prospective study was conducted at the National Cancer Center in Goyang, Korea, between August 2017 and November 2018. Recipients of allogeneic or autologous HSCT who visited the outpatient clinic and underwent routine blood tests were enrolled to the study. Residual serum samples were collected and stored at −80°C for subsequent analyses. Participant data, including demographics, clinical history, and HSCT-related information, were also collected. To compare the immunogenicity of transplantation recipients with that of healthy adults, serum samples were obtained from immunocompetent healthcare workers (HCWs) at Yonsei University Severance Hospital, Seoul, Korea.

Two separate analyses were conducted based on the age of the participants. The first analysis focused on adult recipients of HSCT (aged 19 years and older) who did not receive the JE vaccination routinely after transplantation. We aimed to evaluate the baseline seroprevalence of JEV in adults post-HSCT. The second analysis focused on pediatric recipients (< 19 years of age) who received the JE vaccination after transplantation. This analysis assessed the immunogenicity of a primary series of post-transplantation JE vaccinations.

The exclusion criteria were as follows: 1) recipients < 6 months post-HSCT, 2) those with moderate (Grade 2) or higher acute or chronic graft-versus-host disease (GVHD) at the time

of enrollment in case of allogeneic HSCT, 3) those with an acute febrile illness on the day of the blood test, 4) those with evidence of underlying disease relapse or progression, and 5) those who had received corticosteroids at ≥ 1 mg/kg/day, or equivalent immunosuppressive agents, for at least 14 days within 28 days before sample collection.

JE vaccination dosage and schedule

In accordance with the general principles in international immunization guidelines for immunocompromised individuals, JE vaccination in pediatric recipients started at least 6 months after transplantation in the absence of disease relapse, and with no or minimal use of immunosuppressive agents.[18] The cell-cultured, inactivated JE vaccine (Beijing-Handai strain, 0.4 and 0.7 mL/vial; Boryung Biopharma Co. Ltd, Seoul, Korea) was used in this study. The primary series consisted of three doses administered subcutaneously or intramuscularly at 0, 1 (minimum interval of 1 week), and 13 (minimum interval of 6 months) months. Residual blood samples were collected before vaccination and no earlier than two weeks after vaccination. Residual samples were only collected if a blood draw for clinical care was scheduled during the pre-vaccination period and at least two weeks post-vaccination.

JEV and neutralization assay

The JEV culture, amplification, and plaque reduction neutralization test (PRNT) was performed at the Institute for Immunology and Immunological Disease, Yonsei University College of Medicine (Seoul, Korea).[19] The JEV NCCP 41304 (genotype III) used for PRNT was provided by the Korea National Institute of Health (GenBank No. FJ938224).[20] The BHK-21 (Cl-13) cell line (Korean Cell Line Bank, Seoul, Korea) was used to seed a monolayer of 4×10^5 cells in 6-well tissue culture plates (Falcon, San Jose, CA, USA) one day before infection. Heat-inactivated serum samples were diluted, mixed with an equal volume of JEV (1,000 PFU/mL), and incubated at 37°C for 1 hour. The serum-virus mixtures were inoculated onto duplicate 6-well plates of confluent BHK-21 cells and incubated at 37°C for 1 hour, with gentle rocking every 15 minutes. Next, the mixtures were removed and the cells overlaid with 2X minimum essential medium (MEM, Gibco, Grand Island, NY, USA) containing 2% fetal bovine serum and 1.5% low-melting agarose (Sigma-Aldrich, St. Louis, MO, USA). The plates were then incubated at 37°C with 5% CO_2 for 4 days and fixed with 10% formaldehyde (Sigma-Aldrich) for 30 minutes. After careful removal of the agarose plugs, the monolayers were stained with 1% crystal violet (Sigma-Aldrich), and the plaques were counted.

The neutralizing antibody titer was defined as the reciprocal of the serum dilution that resulted in a 50% reduction in plaque formation ($PRNT_{50}$) relative to the plaque number of diluted JEV in the absence of antiserum,[19,21] and the geometric mean titer (GMT) was calculated to assess the immunogenicity of the JEV vaccine, with seropositivity and GMT serving as indirect indicators. Seroconversion was defined as either reaching a titer considered seroprotective (≥ 1:10) among participants with a baseline titer of < 1:10 or achieving at least a 4-fold rise in titer among participants with a baseline titer ≥ 1:10.

Statistical analysis

Continuous variables are presented as the mean or median with standard deviations (SDs), or ranges. categorical variables are presented as frequencies (percentages). The Mann-Whitney *U* test was used to compare continuous variables between groups, whereas the chi-square test was used for categorical variables. Logistic regression was used to determine factors associated with JE seroprevalence. Multivariate analysis was adjusted for factors such as sex, age at transplantation, time from transplantation to blood sampling, underlying disease, type

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and intensity of chemotherapy, and GVHD. Separate analyses were conducted for allogeneic (allo-HSCT) and autologous (auto-HSCT) HSCT, owing to their distinct characteristics. Differences with *P* values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS software version 27.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10 (GraphPad Software, Boston, MA, USA).

Ethics statement

All participants and/or their parents provided written informed consent. The study protocol (no. NCC2017-0176) was approved by the Institutional Review Board (IRB) of the National Cancer Center. The protocol of comparative study at Yonsei University Severance Hospital (IRB No. 4-2021-1717) was approved by the IRB of Yonsei University Severance Hospital.

RESULTS

Study participants

This study enrolled 103 adult participants. Of these, three participants were lost to follow-up; thus, 100 participants were considered for the present study (**Fig. 1**). The average age of the adult participants was 50 years (SD, 14 years), and 47% were women. The average duration from transplantation to study enrollment was 42 months (SD, 34 months). In total, 51 and 49 adult participants underwent allo-HSCT and auto-HSCT, respectively. The most common

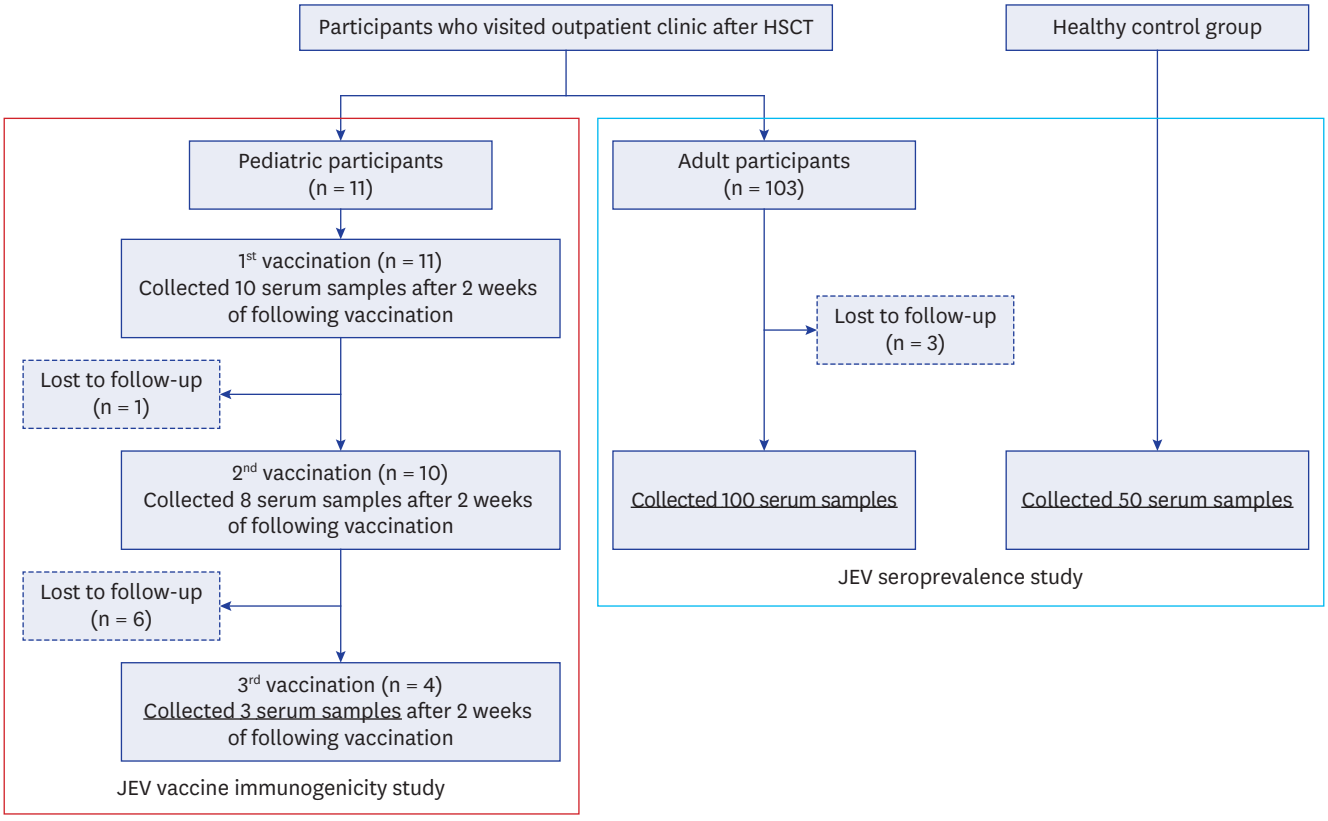

Fig. 1. Study design and participant demographics. Study participants who visited outpatient clinic after HSCT at National Cancer Center (South Korea) from August 2017 to November 2018. Healthcare workers at Severance Hospital as volunteers in the healthy control group.
HSCT = hematopoietic stem cell transplantation, JEV = Japanese encephalitis virus.

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underlying disease was multiple myeloma (30%), followed by acute myeloid leukemia (AML; 22%), lymphoma (21%), and acute lymphocytic leukemia (ALL; 11%). Other characteristics are described according to HSCT type in **Table 1**. A total of 50 HCWs (median age, 46.0 years; 86.0% female) were included as healthy controls.

Table 1. Comparison of characteristics between adult recipients of allogeneic and autologous HSCT

Characteristics	Total (N = 100)	Allogeneic (n = 51)	Autologous (n = 49)	*P* value
Sex, female	47	26 (51.0)	21 (42.9)	0.662
Age at HSCT, yr (mean)	46.4	42.3 ± 14.6	50.5 ± 12.3	0.003
Age at the time of enrollment, yr (mean)	49.8	46.0 ± 14.4	53.6 ± 12.2	0.006
Months from HSCT to blood sampling (mean)	42.2	46.2 ± 35.7	38.1 ± 32.8	0.236
Underlying diseases				< 0.001
ALL	11	11 (21.6)	0 (0.0)	
AML	22	21 (41.2)	1 (2.0)	
Lymphoma	21	6 (11.8)	15 (30.6)	
MM	30	1 (2.0)	29 (59.2)	
Others[a]	16	12 (23.5)	4 (8.2)	
Number of HSCT				0.205
1	90	44 (86.3)	46 (93.9)	
2	10	7 (13.7)	3 (6.1)	
Donor type				NA
MUD	24	24 (47.1)		
MRD	15	15 (29.4)		
MMRD	9	9 (17.6)		
MMUD	3	3 (5.9)		
Stem cell source				0.025
Bone marrow	5	5 (9.8)	0 (0.0)	
Peripheral blood	95	46 (90.2)	49 (100.0)	
Stem cell dose (CD34 cells × 10^6/kg) (mean)	5.1	5.5 ± 2.7	4.7 ± 2.5	0.128
Conditioning regimen				< 0.001
Mel-based	31	9 (17.6)	22 (44.9)	
Bu-based	26	17 (33.3)	9 (18.4)	
Cy-based	21	19 (37.3)	2 (4.1)	
BuCy-based	14	5 (9.8)	9 (18.4)	
BuMel-based	7	0 (0.0)	7 (14.3)	
Fludarabine	1	1 (2.0)	0 (0.0)	
Intensity of conditioning				NA
Myeloablative	24	24 (47.1)		
Reduced	27	27 (52.9)		
Use of TBI	37	37 (75.5)		NA
Use of ATG	36	36 (70.6)		NA
Positive in pre-HSCT CMV IgG (recipient)	100	51 (100.0)	49 (100.0)	NA
Positive in pre-HSCT VZV IgG (recipient)	90	47 (92.2)	43 (87.8)	0.727
Neutrophil engraftment days	23	12.0 ± 2.0	11.0 ± 2.0	0.001
History of acute GVHD (max.)				NA
None	15	15 (29.4)		
Grade 1–2	25	25 (49.0)		
Grade 3–4	11	11 (21.6)		
History of chronic GVHD (max.)				NA
None	20	20 (39.2)		
Localized	19	19 (37.3)		
Extensive	12	12 (23.5)		
Months from the last IVIG to sample collection (mean)	33.9	37.6 ± 36.0	30.1 ± 33.6	0.286
IVIG within 6 mon of sample collection	12	4 (7.8)	8 (16.3)	0.192

Values are presented as number (%) or mean ± standard deviation.
HSCT = hematopoietic stem cell transplantation, ALL = acute lymphoid leukemia, AML = acute myeloid leukemia, MM = multiple myeloma, MUD = matched unrelated donor, NA = not applicable, MRD = matched related donor, MMRD = mismatched related donor, MMUD = mismatched unrelated donor, Mel = melphalan, Bu = busulfan, Cy = cyclophosphamide, TBI = total body irradiation, ATG = anti-thymocyte globulin, CMV = cytomegalovirus, VZV = varicella-zoster virus, GVHD = graft-versus-host disease, IVIG = intravenous immunoglobulin.
[a]Includes myelodysplastic syndrome (n = 8), germ cell tumor (n = 2), severe aplastic anemia (n = 2), medulloblastoma (n = 1), Ewing sarcoma (n = 1), chronic myeloid leukemia (n = 1), and blastic plasmacytoid dendritic cell neoplasm (n = 1).

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Only three of the 11 pediatric participants completed sample collection before and after the primary series of JEV vaccinations, owing to limitations in study duration (**Fig. 1**). The median age was 11 years (range, 4–18 years), and there were three female participants. The average duration from transplant to study enrollment was 22.8 months (range, 11.4–69.3 months). Eight (72.7%) pediatric participants received auto-HSCT. Additional details are provided in **Supplementary Table 1**.

Seropositive rate of JEV after transplantation

The seropositivity rate for JEV was significantly lower in adult recipients of HSCT (54.5%) than in HCWs (92%) ($P < 0.001$) (**Fig. 2A**). Similarly, the GMT of JEV-neutralizing antibodies in adult recipients of HSCT (10.97) was significantly lower than that in HCWs (15.69) ($P = 0.001$, Mann-Whitney *U* test) (**Fig. 2B**). When the analysis was confined to seropositive participants, no significant difference was observed in the GMT between the two groups (17.0 in HCWs vs. 20.1 in adult recipients of HSCT; $P = 0.317$).

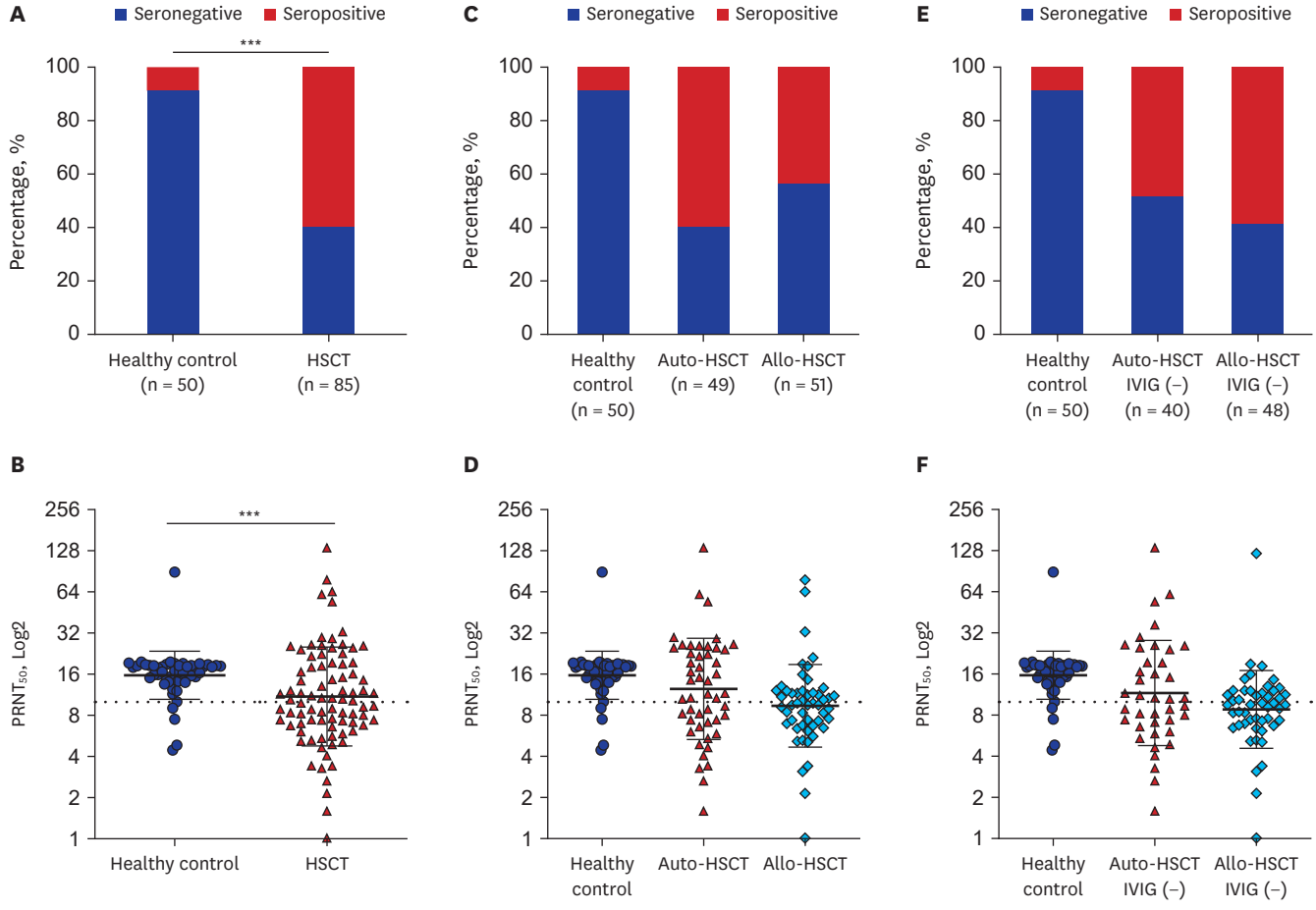

Fig. 2. Comparative analysis of seropositivity rates and protective anti-JEV antibody titers. (**A**) Comparison of the seropositive rates and $PRNT_{50}$ values between post-HSCT patients and healthy controls. (**B**) Comparison of the geometric mean titer of JEV-neutralizing antibody titers in adult HSCT recipients and healthy controls, as determined using the Mann-Whitney *U* test. (**C**, **D**) Comparison between healthy adult controls and the auto- and allo-HSCT groups. This comparison is also presented after the exclusion of patients who received IVIG within six months of blood sample collection (**E**, **F**).
HSCT = hematopoietic stem cell transplantation, PRNT = plaque reduction neutralization test, IVIG = intravenous immunoglobulin, JEV = Japanese encephalitis virus.
***$P < 0.001$.

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The seropositivity rate in recipients of allo-HSCT (45.1%) was lower than that in recipients of auto-HSCT (59.2%); however, this difference was not statistically significant ($P = 0.227$, χ^2 test) (**Fig. 2C**). Similarly, no significant difference was observed in the GMT between the two HSCT groups (12.5 in recipients of auto-HSCT vs. 9.4 in recipients of allo-HSCT; $P = 0.066$) (**Fig. 2D**).

A subgroup analysis was performed to account for potential false-positives due to intravenous immunoglobulin (IVIG), excluding 12 recipients who received IVIG within 6 months of sample collection. After exclusion, the overall seropositivity rate decreased from 54.5% to 45.5%; however, this decrease was not statistically significant ($P = 0.470$) (**Fig. 2E**). The seropositivity rate for allo-HSCT (41.7%) was lower than that for auto-HSCT (52.5%); however, the difference was not statistically significant ($P = 0.424$, χ^2 test). The GMT of the auto-HSCT group (11.62) was higher than that of the allo-HSCT group (8.82); however, the difference was not statistically significant ($P = 0.205$) (**Fig. 2F**). Comparison of the neutralizing antibody titer only in seropositive cases (20 each in the allo- and auto-HSCT groups) revealed that the GMT in auto-HSCT recipients (19.4) was significantly higher than that in allo-HSCT recipients (12.1) ($P = 0.007$).

Factors associated with JEV seropositivity

After excluding 12 participants who had received IVIG within six months of blood sampling, logistic regression analysis was performed by dividing the participants into recipients of allo- and auto-HSCT. In recipients of allo-HSCT, the underlying disease of AML was associated with a higher likelihood of seronegativity than ALL (hazard ratio [HR], 5.63; 95% confidence interval [CI], 1.05–30.13; $P = 0.044$) in the univariable analysis. However, multivariable analysis revealed no significant difference between these groups (HR, 6.36; 95% CI, 0.98–41.17; $P = 0.052$) (**Table 2**). Additionally, the analysis of data belonging to recipients of auto-HSCT revealed no factors that significantly influenced JE seropositivity.

Table 2. Risk factors for Japanese encephalitis virus seronegativity in adult recipients of HSCT

Variables	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Recipients of allogeneic HSCT (n = 47)						
Sex						
Female (ref) vs. male	0.81	0.25–2.64	0.730	1.11	0.26–4.80	0.893
Age at HSCT, older	1.01	0.97–1.06	0.568	1.00	0.74–1.34	0.971
Months from HSCT to blood sampling, longer	1.00	0.995–1.01	0.481	1.02	0.75–1.37	0.913
Underlying diseases						
ALL (ref)	NA					0.349
AML	5.63	1.05–30.13	0.044	6.36	0.98–41.17	0.052
Lymphoma	1.00	0.11–8.95	1.000	1.19	0.08–17.08	0.899
MM	2.4×10^9	0, ∞	1.000	2.5×10^9	0, ∞	1.000
Others[a]	2.10	0.38–11.59	0.395	2.53	0.35–18.27	0.359
Donor type						
Matched (ref) vs. mismatched	0.33	0.09–1.27	0.105			
Stem cell source						
BM (ref) vs. PB	1.08	0.16–7.20	0.934			
Stem cell dose (CD34 cells × 10^6/kg), higher	1.08	0.16–7.20	0.943			
Intensity of conditioning						
MA (ref) vs. RI	0.86	0.26–2.79	0.798	0.86	0.13–5.79	0.878
Conditioning regimen						
Bu-based (ref)	NA					
BuCy-based	2.22	0.19–25.72	0.523			

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Table 2. (Continued) Risk factors for Japanese encephalitis virus seronegativity in adult recipients of HSCT

Variables	Univariable			Multivariable		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Cy-based	0.87	0.21–3.71	0.854			
Mel-based	0.56	0.11–2.90	0.486			
Use of TBI	0.75	0.19–2.97	0.682			
Use of ATG	0.47	0.12–1.79	0.266			
Neutrophil engraftment days	0.95	0.72–1.24	0.691			
History of acute GVHD (max.)						
0–2 (ref) vs. 3–4	0.42	0.11–1.65	0.212	0.34	0.05–2.16	0.252
History of chronic GVHD (max.)						
None or localized (ref) vs. extensive	0.68	0.17–2.66	0.578	1.70	0.23–12.41	0.602
Status of underlying disease at blood sampling						
CR (ref)	NA					NA
PR	1.80	0.17–18.91	0.624	0.54	0.03–9.51	0.674
PD	0.30	0.03–3.60	0.342	1.61	0.10–26.45	0.741
Months from the last IVIG to blood sampling, longer	1.00	0.99–1.01	0.412			
Autologous HSCT participants (n = 41)						
Sex						
Female (ref) vs. male	1.11	0.33–3.80	0.867	0.76	0.12–4.93	0.775
Age at HSCT, older	0.97	0.92–1.02	0.206	0.96	0.88–1.06	0.422
Months from HSCT to blood sampling, longer	1.00	0.99–1.01	0.924	1.01	0.99–1.02	0.406
Underlying diseases						
Lymphoma (ref)						NA
MM	0.48	0.12–1.93	0.299	0.29	0.02–4.28	0.370
Others[a]	2.14	0.17–27.10	0.556	0.26	0.003–27.06	0.573
Conditioning regimen						
Bu-based (ref)						0.439
BuCy-based	0.25	0.02–3.8	0.317	0.07	0.002–2.42	0.140
BuMel-based	0.25	0.02–3.8	0.317	0.59	0.02–17.29	0.759
Cy-based	4.0×10^8	0, ∞	0.999	6.6×10^7	0, ∞	0.999
Mel-based	0.14	0.01–1.51	0.106	0.10	0.01–1.69	0.109
Status of underlying disease at blood sampling						
CR (ref)						NA
PR	3.86	0.36–41.20	0.264	7.50	0.62–90.87	0.113
PD	1.93	0.28–13.16	0.503	6.83	0.31–151.40	0.224
Months from the last IVIG to blood sampling, longer	1.00	0.99–1.01	0.868			

HSCT = hematopoietic stem cell transplantation, HR = hazard ratio, CI = confidence interval, ALL = acute lymphoid leukemia, AML = acute myeloid leukemia, MM = multiple myeloma, BM = bone marrow, PB = peripheral blood, MA = myeloablative, RI = reduced intensity, Bu = busulfan, Cy = cyclophosphamide, Mel = melphalan, TBI = total body irradiation, ATG = anti-thymocyte globulin, GVHD = graft-versus-host disease, CR = complete remission, NA = not applicable, PR = partial remission, PD = progressive disease, IVIG = intravenous immunoglobulin.

[a]Includes myelodysplastic syndrome (n = 8), germ cell tumor (n = 2), severe aplastic anemia (n = 2), medulloblastoma (n = 1), Ewing sarcoma (n = 1), chronic myeloid leukemia (n = 1), and blastic plasmacytoid dendritic cell neoplasm (n = 1).

Immunogenicity of JE vaccine in pediatric recipients of HSCT

Of the nine pediatric recipients from whom pre-vaccination residual samples were available, only one (11.1%) was seropositive for JEV. Following the first dose of JEV vaccine, 4 of 7 patients (57.1%) achieved seropositivity. After two shots of JE vaccination, six of seven pediatric recipients of HSCT (85.7%) were seropositive. Additionally, pediatric recipients (n = 3) who completed the primary three-dose vaccination series showed 100% seroconversion, with high titers ranging from 651 to 1,347 (**Fig. 3**). Detailed characteristics of the pediatric participants are described in **Supplementary Table 1**.

DISCUSSION

To the best of our knowledge, this is the most comprehensive examination of JEV seroprevalence among adult recipients of HSCT in South Korea, a JE-endemic country.

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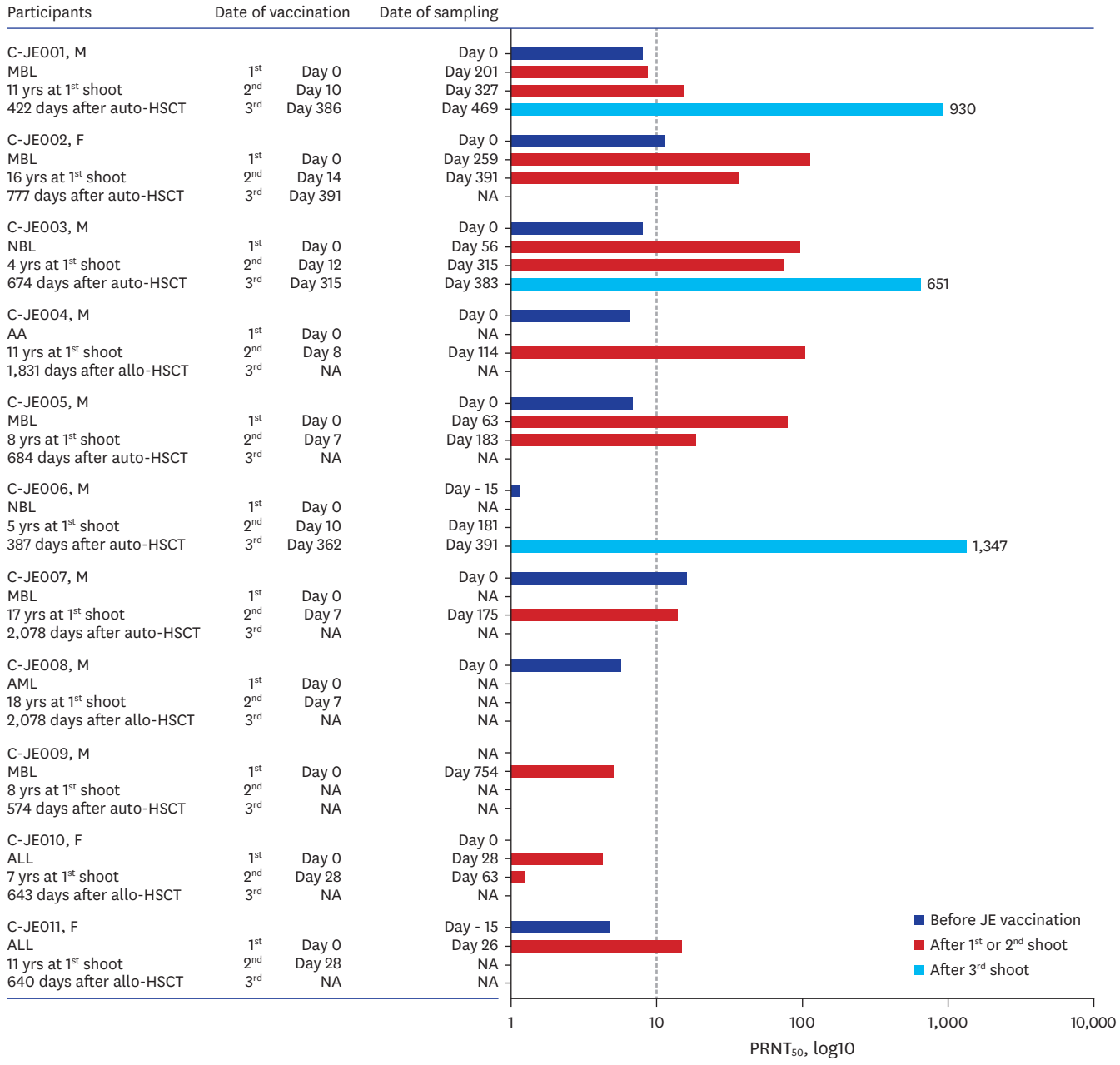

Fig. 3. Response to JE vaccination in pediatric patients post-HSCT. Characteristics and corresponding protective anti-JEV antibody titers of pediatric patients who received the JEV vaccine after HSCT. The $PRNT_{50}$ values are depicted as a bar graph, and the $PRNT_{50}$ value after the third shot is presented.
JE = Japanese encephalitis, MBL = monoclonal B-cell lymphocytosis, HSCT = hematopoietic stem cell transplantation, NA = not applicable, NBL = neuroblastoma, AA = aplastic anemia, AML = acute myeloid leukemia, ALL = acute lymphocytic leukemia, JEV = Japanese encephalitis virus, PRNT = plaque reduction neutralization test.

Our findings revealed a significantly lower JEV seropositivity rate in adult recipients of both auto- and allo-HSCT than in the general adult population. Despite limited data on vaccine immunogenicity against JEV in pediatric recipients of HSCT, the results suggest that JE vaccination after HSCT could be an effective preventive measure for these patients.

The low seropositivity rate (46–55%) in adult recipients of HSCT in South Korea is concerning. As demonstrated in our healthy control group, JEV seropositivity in the

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general adult population (92%) in South Korea is considerably high. Lee et al.[22] reported a JEV seropositivity rate of 98.1% and 98.3% in 30–69-year-old and > 50-year-old individuals, respectively. Remarkably, about 12 out of 945 samples (2.2%) were JEV IgM-positive, as measured by the enzyme-linked immunosorbent assay, which suggests a recent infection. However, JEV IgM positivity may also occur following recent vaccination, and this possibility cannot be excluded. As fewer than ten JE cases are reported annually in South Korea, it can be inferred that asymptomatic to mild infections still occur in the Korean community.[22] These individuals have sufficiently formed protective immunity against JEV, as indicated by neutralizing antibody positivity and prevention of progression to severe disease. Thus, our findings suggest that adult recipients of HSCT seronegative for JEV in South Korea are at risk of severe JE infection after transplantation.

Although the sample size was small (n = 3), the 100% seroconversion rate observed in pediatric recipients after the primary series of vaccinations suggests that JE vaccination after transplantation could be an effective preventive measure in adults, similar to other VPDs. Although only three pediatric patients were included, their 100% seroconversion suggests that the JEV Vero cell-derived vaccine may elicit effective immune responses in HSCT recipients. However, due to differences in immune reconstitution between children and adults, and the small sample size, these findings should be interpreted with caution and needs further study in a larger pediatric cohort. Assawawiroonhakarn et al.[23] also reported a high seroconversion rate (86.4%) following a primary series of JE vaccinations (three doses) with the Vero-cell JEV-inactivated vaccine in pediatric and young adult recipients of HSCT (< 25 years old) in Thailand, another country endemic for JE. However, the antibody titer in these recipients of HSCT remained lower than that in healthy children. Therefore, the duration of vaccine-induced immunity needs to be monitored in future studies.

The Korean Society of Infectious Diseases (KSID) emphasizes post-transplant vaccination for influenza, pneumococcus, tetanus-diphtheria-pertussis, hepatitis A and B, *Haemophilus influenza* type B, and meningococcal infections in adult recipients of HSCT.[19,24] However, the KSID only recommends vaccination against JE in rice field and pig farm workers or nearby inhabitants, adults without evidence of immunity, those who have moved from non-endemic areas for long-term residence, international travelers, and JEV laboratory workers. The KSID does not recommend re-vaccination for recipients of HSCT because of the lack of data on this population. Paradoxically, while most recommendations for vaccinations against various VPDs in adult recipients of HSCT in domestic guidelines are based on international epidemiological and vaccine studies, there is no recommendation for JE despite consistent reports of JE cases in Korea. This indicates that domestic recipients of HSCT may not receive adequate protection. Therefore, our findings can serve as baseline data to establish recommendations for these populations. However, whether the appropriate number of vaccine doses for adult recipients of HSCT is two or three remains debatable; this needs to be addressed in future prospective studies.[23]

Our study had a few limitations. First, because neutralization assays were performed based on residual samples, many blood samples were not collected within the optimal timeframe before and after JE vaccination to compare immunogenicity. Additionally, due to the short study duration, only three patients completed blood sample collection after the third dose, making it difficult to statistically assess the immunogenicity of the JE vaccine after transplantation. Nonetheless, all three pediatric recipients showed high anti-JEV antibody titers and seroconversion between Days 29 and 83 after the third dose, suggesting that

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JE vaccination after transplantation was effective. Second, although our study demonstrated low baseline seroprevalence in adult recipients and an effective vaccine response in pediatric recipients of HSCT, it did not directly represent the robust immunogenicity of the JE vaccine in the adult recipients. Lastly, this study is the lack of pre-HSCT antibody data, which may influence post-transplant seropositivity. Therefore, a follow-up prospective study is required to evaluate the immunogenicity of JE vaccines in adult recipients of HSCT. Finally, the neutralizing antibody test used in our study was based on genotype 3, which is the most prevalent genotype in South Korea. However, we did not assess the cross-immunogenicity against genotypes 4 and 5, which have recently been reported in Australia, India, and China.[3,25,26]

Despite these limitations, this study is significant as it represents the largest-scale research evaluating the seropositivity rate of JEV in adult recipients of HSCT in South Korea, a JE-endemic country in the Western Pacific region. Our data indicated a substantially low rate of JEV seropositivity among Korean adult recipients of HSCT, indicating a high susceptibility to this virus after transplantation. Therefore, it is crucial to consider appropriate preventive measures for this population, such as revaccination with the JE vaccine, a strategy already implemented in pediatric recipients of HSCT.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Characteristics of pediatric HSCT recipients

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