



## Original Article

# Long-term Immunogenicity of the 13-valent Pneumococcal Conjugate Vaccine during Adjuvant Chemotherapy in Patients with Gastric and Colorectal Cancer: A 5-Year Follow-up of a Randomized Controlled Trial

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**Purpose** Current guidelines recommend vaccination at least 2 weeks before chemotherapy initiation to optimize the immune response despite limited evidence. Our previous study indicated no differences in short-term immune response for the 13-valent pneumococcal conjugate vaccine (PCV13) according to the vaccination timing. This study aims to investigate the long-term efficacy of PCV13 and clinical factors associated with the respective antibody response.

**Materials and Methods** Patients with gastric or colorectal cancer who received adjuvant chemotherapy were enrolled and divided into two groups: vaccinated 2 weeks before chemotherapy (arm A) and vaccinated concurrently with chemotherapy (arm B). Serum samples were collected before vaccination and in one month, 3 years, and 5 years. Immune responses were measured using enzyme-linked immunosorbent assay and multiplex opsonophagocytosis assay.

**Results** Including 63 patients, both groups showed an initial increase in the geometric mean titers of opsonophagocytic activity and the geometric mean concentrations of serotype-specific IgG levels after one month, followed by a decline at 3 and 5 years, particularly for serotypes 1, 14, 18C, and 19A. Despite the decline, global protection was maintained for 5 years, although global response decreased. The two arms did not show significant differences in immunogenicity nor in factors such as vaccination timing, age, cancer type, or chemotherapy regimen.

**Conclusion** Vaccination timing is not a significant factor for the immunogenicity of PCV13 in cancer patients undergoing adjuvant chemotherapy. Global protection against pneumococcal infection was sustained for > 5 years, and global response remained in over half of patients.

**Key words** Pneumococcal vaccines, Chemotherapy, Adjuvant, Stomach neoplasms, Colorectal neoplasms

## Introduction

Pneumonia accounts for nearly 10% of cancer patients' hospitalizations, with bacterial pneumonia significantly contributing to morbidity and mortality in this population [1]. In immunocompromised patients, the pathogens responsible for community-acquired pneumonia (CAP) are often detected at prevalences similar to those in immunocompetent individuals, with pneumococcus being the most common pathogen among cancer patients [2]. Furthermore, pneumococcal vaccination reduces pneumonia incidence, decreases hospitaliza-

tion, and improves clinical outcomes in cancer patients [3].

Current guidelines recommend pneumococcal vaccination for immunocompromised individuals, including cancer patients, to prevent pneumococcal infections. The Infectious Diseases Society of America developed clinical practice guidelines in 2013, advocating for pneumococcal vaccination in immunocompromised individuals, including cancer patients receiving chemotherapy [4]. Similarly, the U.S. Advisory Committee on Immunization Practice recommends pneumococcal conjugate vaccines for adults aged  $\geq 65$  years, as well as for individuals aged 6-64 years with altered immu-

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nocompetence [5]. Numerous oncology practice guidelines, including those from the National Comprehensive Cancer Network and the American Society of Clinical Oncology, have adopted these recommendations and suggest using the pneumococcal conjugate vaccine for pneumococcal vaccine-naïve newly diagnosed cancer patients [6,7]. However, the optimal timing for vaccination remains uncertain. Existing guidelines suggest vaccination before initiating chemotherapy to optimize an immune response. However, the evidence is primarily limited to patients with severe humoral immunity impairment, such as those with chronic lymphocytic leukemia receiving rituximab or Bruton Tyrosine Kinase inhibitors [7].

Previously, we investigated the impact of vaccination timing with the 13-valent pneumococcal conjugated vaccine (PCV13) in patients with colorectal and gastric cancer undergoing adjuvant chemotherapy [8]. Our initial study found that the interval between vaccination and chemotherapy did not significantly influence immunogenicity and antibody response [8]. However, the study only assessed short-term post-vaccination outcomes. A long-term follow-up was needed to identify the trend in antibody response and the potential need for revaccination after completing chemotherapy. Therefore, this follow-up study aims to further evaluate the long-term immunogenicity of PCV13 in these patients and identify factors associated with the respective antibody response.

## Materials and Methods

### 1. Patients and study design

Patients from the previous study who agreed to long-term follow-up and repeat blood sampling were enrolled in this follow-up study. All subjects had undergone curative resection for gastric or colorectal cancer and completed an adjuvant chemotherapy course. The PCV13 was administered to all patients who were divided into two groups: arm A received the vaccine 2 weeks before chemotherapy, and arm B received it on the first day of chemotherapy. Serum samples were collected at baseline and in one month, 3 years, and 5 years after vaccination. Additionally, data on the incidence of invasive pneumococcal infections or pneumonia were gathered through follow-up assessments.

### 2. Immunogenicity

As in the previous study, the serologic response was evaluated using a multiplex opsonophagocytosis assay (MOPA) for serotypes 5, 6B, 18C, and 19A, which were selected based on the nasopharyngeal carriage rate and invasive disease potential. The assay was conducted using follow-up sam-

ples. Geometric mean titers, fold increase of titers, the seroprotection rate (percentage of patients with post-vaccination opsonophagocytic activity [OPA] titer  $\geq 1:64$ ), and the seroconversion rate (percentage of patients with  $\geq 4$ -fold increase in OPA titers) were used to assess the immunogenicity.

Additionally, antibody responses to all 13 serotypes in PCV13 were measured using an enzyme-linked immunosorbent assay (ELISA). Global protection (IgG concentration  $\geq 1 \mu\text{g/mL}$  for at least five PCV13 tested serotypes) and global response (at least a two-fold increase, compared to the baseline, in specific IgG antibody levels for at least five PCV13 tested serotypes) were also used to evaluate the immune response to the vaccine [9-14].

### 3. Protocol of ELISA and MOPA

The MOPA assay was conducted to estimate the level of functional antibodies against four selected pneumococcal serotypes. The titer of OPA was defined as the serum dilution ratio that killed 50% of bacteria. A detailed MOPA assay protocol is posted online at <http://www.vaccine.uab.edu>. Briefly, frozen aliquots of *S. pneumoniae* (streptomycin-resistant-serotype 5, spectinomycin-resistant serotype 6B, optochin-resistant serotype 18C, and trimethoprim-resistant serotype 19A) were washed twice. Then, 10  $\mu\text{L}$  of the serially diluted serum and pneumococcal mixture were added to 96-well plates and incubated for 30 minutes with gentle shaking (700 rpm). Afterward, 40  $\mu\text{L}$  of HL60 cells ( $1 \times 10^7$  cells/mL) and 10  $\mu\text{L}$  of baby rabbit complement (Pel-Freez Biological) were added to each well. The plate was incubated in a 5%  $\text{CO}_2$  incubator at 37°C for 45 minutes with shaking (700 rpm) and transferred to ice for 20 minutes. Afterward, 10  $\mu\text{L}$  of the final reaction mixture was spotted on four different THY agar plates. Then, THY with 0.75% agar and 2,3,4-triphenyl tetrazolium chloride (TTC; Sigma-Aldrich) as an overlay agar containing one of the four antibiotics was added to each plate and incubated overnight at 37°C. Bacterial colonies were counted using the National Institute of Standards and Technology (NIST)-developed NIST's Integrated Colony Enumerator software.

Pneumococcal ELISA was performed to measure the polysaccharide serotype-specific IgG titers as previously described (<http://www.vaccine.uab.edu>). The immunoplates (SPL) were coated with 100  $\mu\text{L}$ /well of polysaccharide (5  $\mu\text{g/mL}$ , ATCC) in the phosphate-buffered saline (PBS) and incubated at 37°C for 5 hours. The coated plates were stored at 4°C overnight and washed 3 times with PBS containing 0.05% Tween 20 (PBS-T; Sigma-Aldrich). The sera were diluted using the adsorption solution by adding 5  $\mu\text{g/mL}$  of cell wall polysaccharide (Statens Serum Institut) and 22F capsular polysaccharide (ATCC) to PBS-T. The adsorbed sera were serially 2-fold diluted in PBS-T on the washed plates and

**Table 1.** Patients' characteristics (n=63)

Characteristic	Arm A (n=29)	Arm B (n=34)	p-value
<b>Age (yr)</b>	58.3 (33.2-69.6)	58.9 (29.1-78.9)	0.210
<b>Sex</b>			
Male (n=35)	14 (22.2)	21 (33.3)	0.283
Female (n=28)	15 (23.8)	13 (20.6)	
<b>ECOG PS</b>			
0 (n=15)	9 (14.3)	6 (9.5)	0.214
1 (n=48)	20 (31.7)	28 (44.4)	
<b>Stage</b>			
I (n=1)	0	1 (1.6)	> 0.99
II (n=21)	10 (15.9)	11 (17.5)	
III (n=39)	18 (28.6)	21 (33.3)	
IV (n=2)	1 (1.6)	1 (1.6)	
<b>Type of cancer</b>			
Colorectal cancer (n=52)	21 (33.3)	31 (49.2)	0.093
Gastric cancer (n=11)	8 (12.7)	3 (4.8)	
<b>Chemotherapeutic regimen</b>			
Fluoropyrimidine (n=15)			0.247
5-Fluorouracil	1 (1.6)	0	
Capecitabine	6 (9.5)	6 (9.5)	
Tegafur / Gimeracil / Oteracil	2 (3.2)	0	
Fluoropyrimidine+oxaliplatin (n=48)			
FOLFOX	6 (9.5)	13 (20.6)	
CAPEOX	14 (22.2)	15 (23.8)	

Values are presented as median (range) or number (%). CAPEOX, capecitabine and oxaliplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, fluorouracil, leucovorin, and oxaliplatin.

incubated for 2 hours at room temperature. After washing, the plates were incubated for 2 hours at room temperature with goat anti-human IgG-alkaline phosphatase conjugate (Southern Biotech). Then, the plates were washed 5 times with PBS-T, followed by adding 100  $\mu$ L/mL of AP substrate reagent (1 mg/mL p-nitrophenyl phosphate in the diethanolamine substrate buffer). When the color changed, 50  $\mu$ L of 3 N NaOH was added as a stop solution. The absorbance was read at 405 nm (test wavelength) and 690 nm (reference wavelength) using a microplate reader (Molecular Devices). Data were analyzed using the standardized curve-fit four-parameter logistic method (4-PL) in the pneumococcal ELISA manual.

#### 4. Statistical analysis

Categorical variables, analyzed using the chi-squared test (or Fisher exact test as appropriate), are presented as numbers and percentages. Continuous variables, analyzed using the Mann-Whitney U test, are presented as medians and ranges. OPA titers and specific IgG concentrations by ELISA are expressed as geometric means with 95% confidence intervals (CIs). Geometric mean titers (GMTs), their mean

fold increases, and geometric mean concentrations (GMCs) of specific IgG titers were analyzed using the Student's t test. Factors associated with global protection and global response were analyzed using a logistic regression model, with results expressed as odds ratio and 95% CIs. SPSS ver. 26.0 (IBM Corp.) was used for all statistical analyses. A p-value < 0.05 indicated statistical significance.

## Results

### 1. Patients characteristics

Among the 92 patients enrolled in the previous study, 63 participated in this long-term follow-up study. Arm A comprised 29 patients, while arm B included 34 patients. Baseline characteristics, including age, sex, Eastern Cooperative Oncology Group performance status, cancer stage, cancer type, and chemotherapeutic regimen, did not significantly differ between the two arms (Table 1). All participants in both groups completed their standard adjuvant chemotherapy courses.

**Table 2.** Serial changes of GMTs of MOPA

Serotype	Arm	Pre-vaccination (n=62)			1 Month (n=62)			3 Years (n=59)			5 Years (n=51)		
		GMT	95% CI	p-value	GMT	95% CI	p-value	GMT	95% CI	p-value	GMT	95% CI	p-value
5	A	6	4-10	0.258	408	165-1,011	0.862	103	39-272	0.544	72	28-188	0.587
	B	4	3-6		369	183-746		72	36-143		53	30-94	
6B	A	667	214-2,082	0.960	8,555	5,186-14,113	0.381	3,297	1,763-6,164	0.576	2,713	1,148-6,412	0.912
	B	644	295-1,406		10,930	8,317-14,363		4,102	2,581-6,519		2,866	1,720-4,777	
18C	A	115	57-234	0.996	4,672	2,814-7,758	0.716	1,082	564-2,074	0.720	936	425-2,062	0.740
	B	115	51-257		5,422	2,999-9,804		1,293	647-2,582		774	353-1,696	
19A	A	535	235-1,216	0.364	7,690	3,874-15,264	0.998	2,018	984-4,142	0.864	1,860	812-4,260	0.692
	B	344	203-583		7,696	5,511-10,747		2,176	1,318-3,592		1,522	862-2,688	

CI, confidence interval; GMT, geometric mean titer; MOPA, multiplex opsonophagocytosis assay.

**2. Immunogenicity assays**

**1) Geometric mean titers of OPA**

For the four serotypes, the GMTs of OPA significantly increased one month after vaccination. Although GMTs decreased over time, they remained above the pre-vaccination levels. No significant difference was observed between the arms (Table 2).

**2) Fold increase in post-vaccination GMTs of OPA**

The fold increase in GMTs peaked one month after vaccination, with most values decreasing to below half in 3 years (Table 3). However, GMTs were stabilized between 3 and 5 years post-vaccination. Additionally, no significant difference in fold increase was noted between the arms (Table 3).

**3) Seroprotection and seroconversion based on the OPA**

One month after vaccination, seroprotection rates exceeded 80% for all four serotypes. For serotypes 6B, 18C, and 19A, seroprotection rates consistently remained above 80% in both arms. In contrast, seroprotection rates for serotype 5 decreased to around 50% in both arms (Fig. 1A, S1 Table). Similar to our previous study, seroconversion rates varied significantly depending on the serotypes. Contrary to the seroprotection rate results, seroconversion rates for serotype 5 were higher compared to other serotypes, remaining sustained after 5 years (Fig. 1B, S1 Table). No significant differences in seroprotection and seroconversion were observed between the two arms.

**4) Geometric mean concentration of specific IgG titers**

Among the 13 pneumococcal serotypes, specific IgG titers significantly increased after vaccination for all serotypes, except for serotype 3. GMCs for serotypes 1, 6B, 7F, 14, 18C, and 19A decreased by > 50% after 3 years. GMCs for serotypes 4, 5, 6A, 9V, 19F, and 23F were maintained or showed a slow decline in three and 5 years. Comparing both arms, only the GMC for serotype 4 at one month was significantly different (arm A vs. B, 1.46 [95% CI, 0.94 to 2.26] vs. 2.49 [95% CI, 1.96 to 3.15]; p=0.041). GMCs for other serotypes were similar at 3 and 5 years between both arms (Table 4, S2 Fig.).

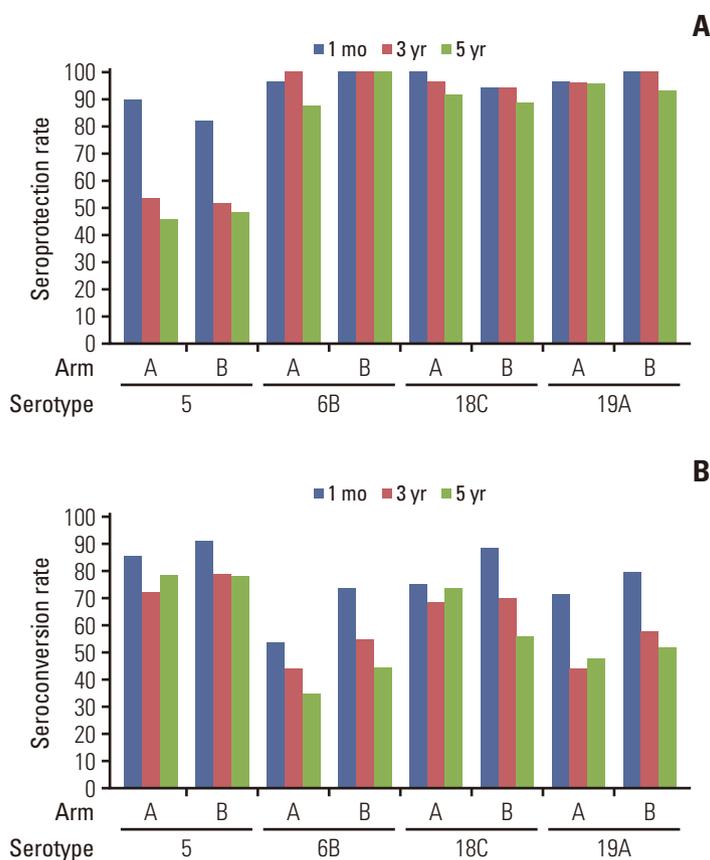
**5) Global protection and global response**

Global protection rates were higher than the pre-vaccination level at 90% (arm A vs. B, 91.7% vs. 96.3%; p=0.575). In arm B, all patients met the criteria for global protection after vaccination, which was consistently maintained even after 5 years. Although some patients in arm A did not meet the criteria, most had global protection, showing no significant difference between the two groups. Conversely, global response rates were the highest one month after vaccination and then continued to decline. More than half of patients in

**Table 3.** Serial changes of fold increase of MOPA: fold increase in post-vaccination GMTs

Serotype	Arm	1 Month (n=62)			3 Years (n=58)			5 Years (n=50)		
		Geometric mean fold increase	95% CI	p-value	Geometric mean fold increase	95% CI	p-value	Geometric mean fold increase	95% CI	p-value
5	A	67.8	1.8-2,513.0	0.617	19.1	0.3-1,148.4	0.894	17.2	0.2-1,715.8	0.898
	B	90.4	5.1-1,608.6		17.7	0.7-480.3		16.0	0.6-418.3	
6B	A	12.8	0.8-196.1	0.665	7.1	0.5-104.8	0.920	4.2	0.2-76.3	0.896
	B	17.0	2.7-105.0		6.7	0.7-62.7		4.0	0.5-34.4	
18C	A	40.6	15.7-104.5	0.808	11.3	3.3-38.7	0.945	11.1	1.4-88.7	0.927
	B	47.2	21.6-103.0		11.8	3.3-42.2		10.4	1.6-68.7	
19A	A	14.4	0.4-546.9	0.316	4.8	0.1-246.8	0.615	4.2	0.0-745.5	0.640
	B	22.4	1.0-522.9		6.1	0.1-306.8		5.5	0.0-715.8	

CI, confidence interval; GMT, geometric mean titer; MOPA, multiplex opsonophagocytosis assay.



**Fig. 1.** Seroprotection (A) and seroconversion (B) rates of arms A and B at 1 month, 3 years, and 5 years after the PCV13 vaccination.

both groups maintained their global response to vaccination. No significant difference was observed between both arms in the global response across all periods (Table 5).

Logistic regression analyses were conducted to assess the impact of each factor on global protection and global

response. Timing of vaccination (2 weeks before vs. the same day), age, sex, cancer site (gastric cancer vs. colorectal cancer), performance status, cancer stage (I-II vs. III-IV), and the type of chemotherapy regimen (monotherapy vs. doublet chemotherapy) had no significant impact on global protec-

**Table 4.** GMCs of specific IgG titers

Serotype	Arm	Pre-vaccination			1 Month			3 Years			5 Years		
		GMC	95% CI	p-value	GMC	95% CI	p-value	GMC	95% CI	p-value	GMC	95% CI	p-value
1	A	2.24	1.68-2.98	0.340	5.63	3.97-7.99	0.178	0.59	0.45-0.78	0.329	0.65	0.49-0.86	0.663
	B	1.79	1.28-2.52		8.11	5.55-11.84		0.70	0.57-0.87		0.60	0.47-0.76	
3	A	0.85	0.64-1.14	0.487	0.43	0.31-0.59	0.935	0.35	0.27-0.45	0.402	0.28	0.23-0.35	0.510
	B	0.75	0.60-0.94		0.44	0.34-0.57		0.40	0.32-0.50		0.31	0.26-0.37	
4	A	0.61	0.47-0.80	0.633	1.46	0.94-2.26	0.041	1.50	1.07-2.10	0.978	1.27	0.84-1.91	0.610
	B	0.57	0.47-0.69		2.49	1.96-3.15		1.49	1.20-1.84		1.11	0.85-1.45	
5	A	0.56	0.42-0.74	0.536	1.47	0.98-2.20	0.177	3.98	2.56-6.20	0.661	3.78	2.43-5.86	0.735
	B	0.49	0.37-0.65		2.10	1.53-2.87		4.48	3.34-6.01		3.47	2.78-4.35	
6A	A	1.34	0.93-1.92	0.681	4.23	2.76-6.49	0.919	5.09	3.50-7.42	0.493	4.74	3.41-6.59	0.923
	B	1.20	0.85-1.70		4.08	2.46-6.78		5.93	4.79-7.34		4.85	3.85-6.11	
6B	A	1.16	0.75-1.79	0.826	5.77	3.56-9.34	0.382	2.56	1.55-4.23	0.797	2.16	1.35-3.45	0.529
	B	1.09	0.73-1.62		7.60	5.14-11.24		2.77	2.02-3.80		1.78	1.24-2.57	
7F	A	1.87	1.34-2.60	0.727	7.01	4.80-10.24	0.197	2.73	1.95-3.81	0.361	2.42	1.64-3.55	0.515
	B	2.04	1.43-2.90		9.42	7.38-12.01		3.35	2.54-4.42		2.04	1.48-2.81	
9V	A	1.95	1.36-2.79	0.421	7.12	4.87-10.39	0.078	6.07	4.28-8.61	0.814	5.60	3.91-8.04	0.698
	B	2.38	1.74-3.25		10.41	8.53-12.69		6.36	5.09-7.95		5.16	4.17-6.39	
14	A	13.15	9.46-18.28	0.502	27.70	18.72-41.00	0.865	4.44	3.29-6.00	0.716	4.06	3.04-5.44	0.749
	B	11.35	8.62-14.95		28.87	22.24-37.48		4.81	3.65-6.33		3.80	2.81-5.13	
18C	A	4.71	3.86-5.73	0.137	15.62	11.72-20.81	0.269	3.56	2.77-4.58	0.528	2.94	2.10-4.10	0.947
	B	3.86	3.25-4.58		19.37	15.10-24.85		3.95	3.23-4.84		2.99	2.27-3.95	
19A	A	10.38	8.03-13.42	0.662	29.76	19.34-45.79	0.253	4.15	2.98-5.78	0.519	3.41	2.25-5.16	0.867
	B	9.61	7.57-12.19		42.70	27.60-66.06		4.81	3.59-6.43		3.57	2.62-4.85	
19F	A	1.05	0.80-1.37	0.683	3.60	2.41-5.38	0.272	5.31	3.54-7.97	0.766	4.93	3.14-7.75	0.411
	B	0.97	0.74-1.26		4.91	3.40-7.09		5.76	4.04-8.21		3.85	2.67-5.57	
23F	A	0.88	0.60-1.28	0.747	2.75	1.71-4.41	0.150	2.30	1.56-3.39	0.401	2.07	1.44-2.97	0.831
	B	0.96	0.68-1.34		4.21	3.02-5.86		2.82	2.13-3.73		2.17	1.64-2.88	

CI, confidence interval; GMC, geometric mean concentration.

**Table 5.** Global protection and global response by specific IgG titers

	Arm A	Arm B	p-value
<b>Global protection</b>			
Pre-vaccination	22/24 (91.7)	26/27 (96.3)	0.595
1 month	23/24 (95.8)	27/27 (100)	0.471
3 years	24/26 (92.3)	33/33 (100)	0.190
5 years	24/26 (92.3)	27/27 (100)	0.236
<b>Global response</b>			
1 month	19/24 (79.2)	25/27 (92.6)	0.232
3 years	12/22 (54.5)	20/26 (76.9)	0.131
5 years	12/21 (57.1)	11/20 (55.0)	> 0.99

Values are presented as number (%).

tion and global response following PCV13 vaccination across all periods (Table 6).

### 3. Cases of pneumococcal infections

No cases of invasive pneumococcal diseases or pneumococcal pneumonia were identified among the study participants throughout the follow-up.

## Discussion

Our previous study demonstrated that PCV13 immunogenicity is adequate in patients with gastric and colorectal cancer undergoing adjuvant chemotherapy [8]. Contrary to the general recommendations suggesting delayed vaccination during chemotherapy, we found that the antibody response to PCV13 in cancer patients receiving the vaccine concurrently with chemotherapy was not inferior to those who were vaccinated 2 weeks before starting chemotherapy [8]. To the best of our knowledge, this is the first study conducting a 5-year follow-up of PCV13 vaccination in patients with solid tumors undergoing chemotherapy. This study reaffirms that the timing of vaccination relative to chemotherapy does not significantly influence PCV13 immunogenicity in this patient population. Additionally, PCV13 demonstrates sustained immunogenicity over 5 years, with global protection maintained in most patients.

The MOPA analysis demonstrated significant rises in GMTs and fold increases in functional antibodies for four serotypes one month after vaccination. Although GMTs declined after 5 years, they remained higher than the pre-vaccination levels. Furthermore, ELISA results for all subtypes showed remarkable immunogenicity in cancer patients receiving chemotherapy. Jackson et al. [15] reported PCV13 immunogenicity in immunocompetent and pneumococcal vaccine-naïve patients using OPA assays one month after PCV13 vaccination. Their results were comparable to those

of our immunocompromised cohort [15]. In another study involving immunocompetent adults (B1851020 Study Group, NCT00521586), OPA and ELISA analyses were performed one month and 5 years after vaccination. While some antibody titers in our study were lower than in that study, most titers were comparable [16]. Hence, PCV13 demonstrates sustained immunogenicity, effectively protecting against invasive pneumococcal disease even in patients undergoing adjuvant chemotherapy.

Despite the high global protection rates observed for 5 years, the pre-vaccination global protection rates in this study were already over 90%. The concept of global protection, commonly used in studies involving immunocompromised patients [10-14], may require reassessment as a reliable measure of immunogenicity. Actually, unlike in children, the serotype-specific protective threshold of the pneumococcal vaccine has not been established in adults [17]. Over time, the global response rates declined, although more than half of the patients still demonstrated a global response 5 years after vaccination. Therefore, PCV13 immunogenicity diminishes over time, particularly for pneumococcal serotypes 1, 14, 18C, and 19A, which exhibited a marked decline in antibody levels after 3 and 5 years. Given the invasive potential of these serotypes, the observed decline raises the question of whether revaccination is necessary to maintain protection in this population.

Patient factors, such as age, sex, and performance status, did not influence immunogenicity. Additionally, contrary to previous recommendations, administering the vaccine concurrently with chemotherapy did not impact short- and long-term immunogenicity. This result also supports the recommendation for pneumococcal vaccination in cancer patients regardless of chemotherapy timing. This finding is crucial for simplifying vaccination protocols in solid tumor patients undergoing cytotoxic chemotherapy, allowing them to receive necessary immunizations without delaying their treatment.

Table 6. Factors associated with global protection and global response

Variable	Pre-vaccination			1 Month			3 Years			5 Years		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
<b>Factors associated with global protection</b>												
Arm B	2.12	0.16 to 27.22	0.566	> 999.99	< 0.01 to > 999.99	0.998	> 999.99	< 0.01 to > 999.99	0.995	> 999.99	< 0.01 to > 999.99	0.995
Age ≥ 65 years	> 999.99	< 0.01 to > 999.99	0.999	1.75	< 0.01 to > 999.99	> 0.99	< 0.01	< 0.01 to > 999.99	0.996	< 0.01	< 0.01 to > 999.99	0.996
Female	0.64	0.05 to 8.38	0.735	> 999.99	< 0.01 to > 999.99	0.998	> 999.99	< 0.01 to > 999.99	0.996	> 999.99	< 0.01 to > 999.99	0.996
Gastric (vs. CRC)	> 999.99	< 0.01 to > 999.99	0.999	0.43	< 0.01 to > 999.99	> 0.99	0.66	< 0.01 to > 999.99	> 0.99	> 999.99	< 0.01 to > 999.99	> 0.99
ECOG PS 1 (vs. 0)	< 0.01	< 0.01 to > 999.99	0.999	< 0.01	< 0.01 to > 999.99	0.999	< 0.01	< 0.01 to > 999.99	0.999	< 0.01	< 0.01 to > 999.99	0.999
Higher stage (vs. I-II)	0.55	0.04 to 8.29	0.666	< 0.01	< 0.01 to > 999.99	0.998	< 0.01	< 0.01 to > 999.99	0.998	< 0.01	< 0.01 to > 999.99	0.998
Doublet chemotherapy	2.24	0.14 to 34.81	0.565	< 0.01	< 0.01 to > 999.99	0.998	< 0.01	< 0.01 to > 999.99	0.998	< 0.01	< 0.01 to > 999.99	> 0.99
<b>Factors associated with global response</b>												
Arm B	-	-	-	3.92	0.56 to 27.26	0.168	2.79	0.80 to 9.60	0.106	0.82	0.20 to 3.30	0.778
Age ≥ 65 years	-	-	-	> 999.99	< 0.01 to > 999.99	0.999	0.49	0.07 to 3.39	0.472	1.96	0.29 to 13.42	0.495
Female	-	-	-	3.12	0.41 to 23.91	0.275	1.26	0.27 to 5.98	0.769	0.84	0.20 to 3.55	0.815
Gastric (vs. CRC)	-	-	-	3.17	0.11 to 91.06	0.501	> 999.99	< 0.01 to > 999.99	0.999	1.40	0.10 to 19.89	0.804
ECOG PS 1 (vs. 0)	-	-	-	1.75	0.10 to 32.16	0.706	0.76	0.04 to 14.88	0.856	0.54	0.05 to 6.45	0.625
Higher stage (vs. I-II)	-	-	-	0.72	0.10 to 5.14	0.739	1.40	0.30 to 6.57	0.671	0.37	0.09 to 1.56	0.174
Doublet chemotherapy	-	-	-	0.47	0.40 to 5.46	0.546	0.10	0.01 to 1.12	0.062	1.43	0.21 to 9.80	0.714

CI, confidence interval; CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; OR, odds ratio.

However, this study has some limitations. The relatively small sample size (63 patients) and the inclusion of only certain cancer types may limit the generalizability of the findings. Furthermore, the study did not evaluate the impact of newer chemotherapy agents, such as immune checkpoint inhibitors, which could influence vaccine responses by altering the immune response dynamics. Additionally, refining the methodologies used to assess vaccine immunogenicity, such as incorporating more sensitive biomarkers, could better predict the long-term effectiveness of pneumococcal vaccination [18].

Future studies should investigate the optimal timing for revaccination in oncology patients, especially given the observed decline in antibody titers over time, which might affect long-term protection against pneumococcal disease. Additionally, research on various cancer types and differing chemotherapy objectives, such as palliative versus curative intent, could provide a broader understanding of pneumococcal vaccination effectiveness in these populations. Such studies could lead to more tailored vaccination schedules for patients undergoing diverse cancer treatments.

In conclusion, this study demonstrates that PCV13 vaccination induces long-term immunity against vaccine-type pneumococci with the potential to improve vaccine efficacy in patients undergoing adjuvant chemotherapy for gastric and colorectal cancer. Vaccination timing relative to chemotherapy initiation does not significantly impact the long-term immunogenicity of pneumococcal vaccination. However, the gradual decline in antibody levels over time suggests that some patients may require revaccination to maintain adequate protection. Further research is needed to establish the optimal revaccination timing in this vulnerable population.

### Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (<https://www.e-crt.org>).

### Ethical Statement

The institutional review board of Chonnam National University Hwasun Hospital approved this study (CNUHH-2018-171). This trial was conducted following the Declaration of Helsinki, with all patients providing written informed consent.

### Author Contribution

Conceived and designed the analysis: Song JY, Bae WK.

Collected the data: Kim HJ, Bang H, Shim HJ, Hwang JE, Cho SH, Chung IJ, Kang SJ, Kim JG, Beom SH, Jang AY, Song JY, Bae WK.

Contributed data or analysis tools: Kim HJ, Jang AY, Song JY, Bae WK.

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### Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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