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The Association Between PCV13 Vaccination and Hospital Admissions Due to Pneumonia or Sepsis: A cohort study in Patients with Hematological malignancies

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Abstract

Background: Patients with hematological malignancies receiving immunosuppressive therapy are at highest risk for invasive pneumococcal disease. Our goal was to investigate whether vaccinating hematological patients with pneumococcal 13-valent conjugated vaccine (PCV13) prior to therapy initiation is associated with decreased hospital admissions due to pneumonia or sepsis within 12 months.

Methods: A longitudinal retrospective cohort study was conducted at the Hematology Unit, Carmel Medical Center. Adult patients (>18 years), who were diagnosed between 1/1/2009 and 30/12/2019 with hematological malignancies and received immunosuppressive therapy were retrieved from the Electronic Health Medical Records. Patients were excluded if they received the PCV13 vaccination during or after initiation of the immunosuppressive therapy. A multivariate logistic regression model was performed to determine the association between PCV13 vaccination and hospital admission due to pneumonia or sepsis.

Results: The cohort included 616 patients, of these 418 (67%) patients weren't vaccinated and 198 (33%) were vaccinated. Within 12 months, 15.1% (n=63) of non-vaccinated patients compared to only 7.1% (n=14) of the vaccinated patients were hospitalized due pneumonia or sepsis. The logistic regression analysis demonstrated that receiving PCV13 vaccination is associated with reduced odds of 45% (OR 0.45, CI95%: 0.246-0.839, p =0.012) of being hospitalized due to pneumonia or sepsis in patients with hematological malignancies receiving immunosuppressive therapy.

Conclusion: This is the first study to demonstrate the contribution of PCV13 vaccine in patients with hematological malignancies receiving immunosuppressive therapy. Patients vaccinated with PCV13 had significantly reduce odds of hospitalization due to pneumonia or sepsis compared to non PCV13 vaccinated patients.

Article Summary:

Strengths and limitations of this study:

- First study to demonstrate the role of PCV13 vaccination in patient with hematological malignancies in reducing hospital admissions due to pneumonia or sepsis
- Demonstrate the effectiveness of vaccination prior to immunosuppressive therapy in patients with hematological malignancies.
- The study is not a randomized controlled study
- Control group consisted historical controls

Introduction

Hematological malignancies are the 5th cause of cancer in the US and the 4th cause of cancer related deaths (1). The lifetime probability to develop Non-Hodgkin Lymphoma (NHL) in the US is 1 in 42 for males, and 1 in 54 for females (1). The age adjusted mortality rate from NHL is 4.4/100,000 for females and 7.3/100,000 for males (1). The underlying malignancy and the immunosuppressive therapy place people at risk for severe infection, which is a frequent cause of death. Patients with Multiple Myeloma (MM), for example, have frequent infectious complications resulting in death in approximately 45% of the patients, two-thirds of these infections are due to pneumonia (2). In a national level US study, the cumulative incidence of severe sepsis was 43 cases per 1000 people living with NHL (3). The relative risk of severe sepsis in those with NHL was 10 times greater than observed in the non-cancer population (3).

In patients with hematological malignancies, several factors predispose to infectious complications, including immune deficiencies associated with the primary malignancy and the use of multiple lines of cytotoxic therapy that are frequently associated with prolong neutropenia and bone marrow failure. These complications usually lead to increased risk of serious infections requiring hospitalization (4) (5).

One of the most serious infectious complication is Invasive Pneumococcal Disease (IPD), defined as isolation of *Streptococcus Pneumonia* (SP) from a normally sterile body site (typically blood or cerebrospinal fluid) (6). Among adults with hematological malignancies, the IPD incidence is estimated to be 0.5% per year since diagnosis, 50-fold higher than in the general population (7).

Primary prevention of IPD relies on two available pneumococcal vaccines: The pneumococcal 13-valent conjugated vaccine (PCV13), and the pneumococcal 23-valent polysaccharide vaccine (PPSV23). A low antibody response to PPSV23 has been described in the general elderly population as well as in patients with hematologic malignancies, including patients with multiple myeloma and lymphoma (8). PCV13, however, demonstrates a greater immunogenicity through a T cell dependent response, leading to longer lasting immunologic memory (2).

The effectiveness of Pneumococcal Conjugate Vaccine (PCV13) in preventing pneumonia was demonstrated in the community based CAPITA study, with 84,496 adults over 65 years of age (9). The CAPITA study showed a vaccine efficacy of 45.6% to prevent community acquired pneumonia and 75% to prevent IPD (9). Other studies, performed with the PPSV23 have revealed less than 40% protective antibody levels after vaccination (10)(11).

The Infectious Diseases Society of America (IDSA), as well as other organizations, such as the Israel Ministry of Health (MoH), published recommendations regarding the vaccination of immunocompromised patients (8). The proper timing of immunization in cancer patients is a key component of achieving efficient vaccine protection. In general, patients with malignancy should receive the PPSV23 four to six weeks prior to chemotherapy, and no later than two weeks prior to chemotherapy initiation. The PCV13 vaccination is given as a single dose in addition to PPSV23(12,13).

The immune response following PCV13 vaccination in patients with hematological malignancies was evaluated (11,12). PCV13 vaccination in Chronic Lymphocytic Leukemia (CLL) patients, for example, induces an immune response in a considerable proportion of patients (58%) although less than in healthy controls (100%) (14). Individuals with Multiple Myeloma (MM) have historically received the PPSV23 vaccination, but this has usually resulted in a suboptimal immune response, most probably due to a defect in their humoral immunity system (2). Poor immune function and suboptimal response to pneumococcal vaccine, which contribute to the high rates and increased IPD- related mortality, were observed in patients with hematological malignancies and patients following organ or bone marrow transplantation (7).

Several unresolved questions are still present regarding the use of PCV13 in various groups of patients. The effectiveness of PCV13 vaccine in preventing IPD prior to the initiation of immunosuppressive therapy in patients with hematological malignancies has not been rigorously tested. Additionally, a paucity of data exists regarding the vaccine effectiveness in patients treated

with targeted therapy against B or T lymphocytes (15). In this paper we conducted a retrospective cohort design to assess whether vaccinating hematological patients with PCV13 prior to chemotherapy and/or biological therapy initiation is associated with decreased hospital admissions due to pneumonia or sepsis within 12 months.

Methods

***Study design and setting*:** A longitudinal retrospective cohort study was conducted at the Hematology Unit, Carmel Medical Center (CMC), Haifa, Israel, between January 1st, 2009 and December 30th, 2019. The data was retrieved from the Electronic Health Medical Records and the computerized databases of Clalit Health Services (CHS). Retrieved data included patients' clinical and personal characteristics, namely vaccination status, hospitalization (dates and cause), and type of therapy (chemotherapy and/or biological therapy). The study was approved by the Carmel Medical Center Helsinki Committee (CMC-20-0005) and by the Faculty of Social Welfare and Health Sciences Ethic Committee, University of Haifa (approval no. 351/20).

***Study population*:** The study population included patients with hematological malignancies (with the exception of acute leukemia patients). PCV13 vaccination was recommended to all patients as soon as it became available for general use, namely, as of June 1st, 2016. This retrospective analysis included two groups of patients: those who did not receive the PCV13 vaccination and patients who received PCV13 vaccination prior to initiation of immunosuppressive therapy.

Patient and public involvement:

This is a retrospective study and therefore there was no patient involvement.

Inclusion and exclusion criteria: The study included records of patients over 18 years old who have received chemotherapy and/or biological therapy. We excluded patients who were not members of CHS due to unavailability of follow-up data. We also excluded patients with acute leukemia, due to the paucity of patients and the aggressive nature of the disease, and patient who received the PCV13 vaccination after immunosuppressive therapy was commenced.

***Study variables*:** the dependent variable was the first hospitalization due to pneumonia or sepsis within 12 months after initiation of biologic therapy and/or chemotherapy. The decision regarding patient hospitalization due to pneumonia or sepsis was made according to the diagnosis on discharge documentation, based on the following criteria: fever, dyspnea, leukocytosis, and chest x-ray.

The independent variable was vaccination with PCV13.

Control variables included demographic variables such as age, gender, country of birth, marital status (e.g., married, single or lives alone), and place of living. General clinical variables included functional status according to ECOG (Eastern Cooperative Oncology Group) performance scale (16). Disease - specific clinical variables: age at treatment, primary hematological disease (Lymphoproliferative disease, Myeloproliferative disease and Multiple Myeloma); type of immunosuppressive therapy (chemotherapy and/or biological therapy); risk of severe neutropenia (<500 neutrophils/ul) - high, moderate or low (more than 7 days, less than 7 days, no neutropenia), and splenectomy status (17).

***Vaccination procedure*:** The PCV13 vaccination procedure was commenced at CMC on June 1st, 2016 and included an intramuscular injection of 0.5 ml of polysaccharides from 13 pneumococcal serotypes conjugated to a nontoxic diphtheria toxin (Prevenar, Pfizer USA).

Statistical Analyses: Descriptive statistics (frequency, means and standard deviation) were performed to describe patients' demographic and clinical characteristics. Statistical significance of differences and associations between vaccinated and non-vaccinated patients, and between those who were or were not hospitalized due to pneumonia or sepsis within 12 months of treatment initiation were analyzed using a *Student t test* for continuous variables and χ^2 *test* for categorical variables. To determine the contribution of the PCV13 vaccine to the risk for first hospitalization due to pneumonia or sepsis within 12 months, a multivariate logistic regression model controlling for known confounders was performed. Variables were entered into the regression model if a

statistical significant association (p-value < 0.05) was found in the bivariate associations with the dependent variable. All statistical analyses were carried out using SPSS statistical software version 23.

Extra data is available by emailing reginada2@clalit.org.il

Results

The study population included 616 patients, of these, 67% (n=418) patients who did not receive PCV13 vaccine and 33% (n=198) who received PCV13 vaccine prior to initiation of immunosuppressive therapy.

Table 1 describes the participants' socio-demographic and clinical characteristics. Among non-vaccinated patients: 36.8% were aged between 18–65 years, 32.8% were between 66–75 years, and 30.4% were older than 76 years (Table 1). In the vaccinated group 41.4% were aged between 18–65 years, 33.3% were between 66–75 years, and 25.3% were older than 76 years (p=0.372). More independent patients (according to ECOG performance score) were documented in the vaccinated patient's group compared to the non-vaccinated (98% vs. 91.1%, p=0.001). The most prevalent hematological diagnosis was Lymphoid Malignancy (76.1% among the non-vaccinated and 80.8% among the vaccinated), followed by Multiple Myeloma (16.3% among the non-vaccinated and 16.7% among the vaccinated), and Myeloid Malignancy (7.7% among the non-vaccinated and 2.5% among the vaccinated). Most of the patients had a moderate risk for neutropenic fever (non-vaccinated – 80.1%, vaccinated – 77.3%).

Table 2 presents the association between the demographic and clinical characteristics and the rate of hospitalization due to pneumonia or sepsis within 12 months after immunosuppressive therapy initiation. Among patients that were admitted within 12 months after therapy initiation, due to pneumonia or sepsis, non-vaccinated patients were the vast majority (81.8% vs. 18.2% p=0.005). A significant association was found between age at treatment and hospitalization rates. As

anticipated, in both groups patients older than 76 years of age had higher rates of hospitalization compared to younger patients between 18 and 65 years of age (p=0.014). The highest rates of hospitalization were found among the Myeloid Malignancy patients and Multiple Myeloma compared to Lymphoid Malignancy patients (p=0.01).

Table 3 shows a logistic regression analysis of factors associated with 12-month hospitalization due to pneumonia or sepsis. Vaccinated patients had reduced odds of hospitalization due to pneumonia or sepsis within 12 months since treatment initiation (OR=0.45, CI 95%: 0.246-0.839, P=0.012). Additionally, older age (76+) was associated with increased hospitalization odds relatively to the 19-65 age group (OR=2.082, CI 95%: 1.102-3.934, p=0.024). The type of hematological malignancy was not significantly associated with the odds of hospitalization.

Discussion

In this study we investigated the association between PCV13 vaccination and hospital admissions due to pneumonia or sepsis in a cohort of patients with hematological malignancies, within 12 months since initiation of therapy. This study is the first to demonstrate in a large cohort of patients with hematological malignancies that PCV13 vaccine administration prior to immunosuppressive therapy is associated with reduced odds for hospital admission due to pneumonia or sepsis, and that vaccination has a protective effect of 45.4% in preventing hospitalization. These significant results support the latest IDSA recommended guidelines to vaccinate patients with hematological malignancies with PCV13 prior to immunosuppressive therapy, which later have been also adopted by international officials, such as The Ministry of Health of Israel (18)(19).

Prior to our study, the effectiveness of PCV13 in preventing pneumonia was only demonstrated in the community based CAPITA study (20). Although patients undergoing immunosuppressive therapy were previously recommended to be vaccinated with PCV13 prior treatment initiation (12),

no study has demonstrated the clinical benefit in reducing severe pneumonia or sepsis, and hospital admissions following vaccination with PCV13 in these patients.

As anticipated, factors other than PCV13 vaccination also influence the risk of admission due to pneumonia or sepsis (21). In our cohort age >65 years old and the type of malignancy were associated with increased risk for hospital admission due to pneumonia or sepsis, in the bivariate analysis. The regression analysis demonstrated, however, that the PCV13 vaccination has a protective effect controlling for age and the type of malignancy. The IPD incidence among hematological malignancy patients is 0.5% per year which is 50-fold higher than in the general population (7). However, no data was found regarding hospitalization rates due to IPD or sepsis in patients with hematological malignancies.

Strengths and limitations: The main strength of our study is our ability to retrieve accurate information on all hospital admissions in a large cohort of patients treated in our medical center over a period of 10 years. Although we did not use a randomized control trial design, our findings demonstrate similarity in sociodemographic and clinical characteristics between vaccinated and non-vaccinated patients, except for type of disease, treatment modalities, and functional dependency. This difference might have been the result of differences in patients' age and thus differences by disease were no longer statistically significant after controlling for age groups in the multivariate regression. Treatment modalities differences between vaccinated and non-vaccinated treatment might be explained by the mix of patients' malignancies and changes in treatment protocols over the last decade, namely the use of a combination of biological and chemotherapy treatment. This change is in concomitant with patients' vaccination. Notably, these differences lost significance regarding hospital admission in the regression analysis.

This study demonstrates for the first time the association between PCV13 vaccination in a group of patients with high risk for infection, patients with hematological malignancies and adverse outcomes, such as infections requiring hospitalization. This simple procedure has a significant

implication on infectious complications related to the immunosuppressive therapy, hence has a great impact on the morbidity and maybe on mortality rates in these patients. Further research on large cohort of patients, stratifying by diverse risk factors and RCT design is needed in order to examine the PCV13 vaccination outcomes regarding hospitalization, survival rates, and economical costs.

Contribution Statement:

R.D. preform the data collection, analysis and writing the manuscript; E.D. E.S. M.P. designed the study analyzed the data and wrote the manuscript. There are no relevant conflict of interest for R.D.; E.D.; E.S.; M.P. The authors declare that they had no external or internal funding to perform the study.

Data sharing statement:

The authors confirm that the data supporting the findings of this study are available within the article. Identifiable Individual participant data will not be available however aggregated, anonymized data will be available on request from the corresponding author.

Ethics statement:

The study was approved by the Carmel Medical Center Helsinki Committee (CMC-20-0005) and by the Faculty of Social Welfare and Health Sciences Ethic Committee, University of Haifa (approval no. 351/20).

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Table 1: Demographic and clinical characteristics of vaccinated and non-vaccinated patients

Variable		Non-Vaccinated (n=418, 67%) N (%)	Vaccinated (n=198, 33%) N (%)	P value
Gender				0.219
	Male	229 (54.8%)	98 (49.5%)	
	Female	189 (45.2%)	100 (50.5%)	
Country of Birth				0.079
	Israel	209 (50%)	114(57.6%)	
	Not Israel	209 (50%)	84(42.4%)	
Living area				0.621
	City	318(76.1%)	147(74.2%)	
	Rural	100(23.9%)	51(25.8%)	
Family status				0.773
	Married	319(76.3%)	149(75.3%)	
	Not married	99(23.7%)	49(24.7%)	
Splenectomy				0.309
	Yes	6(1.4%)	1(0.5%)	
	No	412(98.6%)	197(99.5%)	
Hematological diagnosis				0.043
	Lymphoid Malignancy	318(76.1%)	160(80.8%)	
	Myeloid Malignancy	32(7.7%)	5(2.5%)	
	Multiple Myeloma	68(16.3%)	33(16.7%)	
Age at treatment				0.372
	19-65	154(36.8%)	82(41.4%)	
	66-75	137(32.8%)	66(33.3%)	
	76+	127(30.4%)	50(25.3%)	
ECOG performance score				0.001
	Dependent	37(8.9%)	4(2%)	
	Not Dependent	381(91.1%)	194(98%)	
Treatment type				0.035
	Chemotherapy	131(31.3%)	49(24.7%)	
	Biological	19(4.5%)	18(9.1%)	
	Combined treatment	268(64.1%)	131(66.2%)	
Risk Neutropenic fever				0.098
	High risk	65(15.6%)	28(14.1%)	
	Moderate risk	335(80.1%)	153(77.3%)	
	Low risk	18(4.3%)	17(8.6%)	

ECOG – Eastern Cooperative Oncology Group performance status

Table 2: Association between demographic and clinical characteristic and hospitalization rates due to pneumonia or sepsis within 12 months

	No Admission within 12 months	Admission within 12 months	P-value
	N (%)	N (%)	
Vaccination status			0.005
Vaccinated	184(43.1%)	14(18.2%)	
Non-vaccinated	335(65.9%)	63(81.8%)	
Gender			0.446
Male	283(52.5%)	44(57.1%)	
Female	256(47.5%)	33(42.9%)	
Hematological diagnosis			0.010
Lymphoid Malignancy	428(79.4%)	50(64.9%)	
Myeloid Malignancy	28(5.2%)	9(11.7%)	
Multiple Myeloma	83(15.4%)	18(23.4%)	
Country of Birth			0.410
Israel	286(53.1%)	37(48.1%)	
No Israel	253(46.9%)	40(51.9%)	
Family status			0.476
Not married	132(24.5%)	16(20.8%)	
Married	407(75.5%)	61(79.2%)	
Living area			0.972
City	407(75.5%)	58(75.3%)	
Rural	132(24.5%)	19(24.7%)	
ECOG performance score			0.359
Dependent	34(6.3%)	7(9.1%)	
Not Dependent	505(93.7%)	70(90.9%)	
Risk Neutropenic fever			0.975
High risk	81(15%)	12(15.6%)	
Moderate risk	427(79.2%)	61(79.2%)	
Low risk	31(5.8%)	4(5.2%)	
Splenectomy			0.886
No	533(98.9%)	76(98.7%)	
Yes	6(1.1%)	1(1.3%)	
Treatment type			0.635
Biological treatment	33(6.1%)	4(5.2%%)	
Chemotherapy treatment	154(28.6%)	26(33.8%)	
Combination treatment	352(65.3%)	47(61%)	
Age at treatment			0.014
19-65	218(40.4%)	18(23.4%)	
66-75	173(32.1%)	30(39%)	
76+	148(27.5%)	29(37.7%)	

*ECOG – Eastern Cooperative Oncology Group performance status

Table 3: Logistic regression analysis of factors associated with 12 month hospitalization due to pneumonia or sepsis

Variable	OR	95% CI (Lower	Upper)	P-value
Non-Vaccinated (reference)				
Vaccinated	0.454	0.246	0.839	0.012
Age at treatment				
19-65 (reference)				
66-75	1.915	1.022	3.588	0.043
76+	2.082	1.102	3.934	0.024
Hematological diagnosis				
Lymphoid Malignancy (reference)				
Multiple Myeloma	1.704	0.936	3.101	0.081
Myeloid Malignancy	2.092	0.919	4.762	0.079

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Word Count: 3135

Abstract

Objectives: Patients with hematological malignancies receiving immunosuppressive therapy are at highest risk for invasive pneumococcal disease. Our goal was to investigate whether vaccination of hematological patients with pneumococcal 13-valent conjugated vaccine (PCV13) prior to therapy initiation is associated with decreased hospital admissions due to pneumonia or sepsis within 12 months.

Design & Setting: A longitudinal retrospective cohort study was conducted at the Hematology Unit, Carmel Medical Center, Israel.

Participants: Information on adult patients (>18 years), who were diagnosed between 1/1/2009 and 30/12/2019 with hematological malignancies and received immunosuppressive therapy, was retrieved from the electronic health records. Patients with hematological malignancies who received the PCV13 vaccination during or after initiation of the immunosuppressive therapy were excluded from the study.

Outcome measures: A multivariate logistic regression model was performed to determine whether PCV13 vaccination is associated with fewer hospital admission due to pneumonia or sepsis.

Results: The cohort included 616 patients, of which 418 (67%) patients weren't vaccinated and 198 (33%) were vaccinated. Within 12 months, 15.1% (n=63) of non-vaccinated patients compared to only 7.1% (n=14) of the vaccinated patients were hospitalized due pneumonia or sepsis. The logistic regression analysis demonstrated that receiving PCV13 vaccination is associated with reduced odds of 45% (OR 0.45, 95%CI: 0.246-0.839, p=0.012) of being hospitalized due to pneumonia or sepsis in patients with hematological malignancies receiving immunosuppressive therapy.

Conclusion: This is the first observational study to demonstrate the association between PCV13 vaccination and hospital admissions in patients with hematological malignancies receiving immunosuppressive therapy. Patients receiving PCV13 vaccination before immunosuppressive

therapy initiation had significantly reduced odds of hospitalization due to pneumonia or sepsis compared to non PCV13 vaccinated patients.

Article Summary:

Strengths and limitations of this study:

- The study data is retrieved from Clalit Health Services database, which documents all types of vaccinations and hospital admissions.
- All hospital admissions due to pneumonia or sepsis were verified by the authors via review of the patient chart and discharge summary.
- The study is an observational, single-center study and causality cannot be directly inferred.
- The control group consisted of comparable historical controls.

Introduction

Hematological malignancies are the most common cause of cancer related deaths (1). The lifetime probability to develop Non-Hodgkin Lymphoma (NHL) in the US is 1 in 42 for males, and 1 in 54 for females (1). The age adjusted mortality rate from NHL is 4.4/100,000 for females and 7.3/100,000 for males (1). The underlying malignancy and the immunosuppressive therapy place people at risk for severe infection, which is a frequent cause of death. Patients with Multiple Myeloma (MM), for example, have frequent infectious complications resulting in death in approximately 45% of the patients, two-thirds of these infections are due to pneumonia (2). In a national level US study, the cumulative incidence of severe sepsis was 43 cases per 1000 people living with NHL (3). The relative risk of severe sepsis in those with NHL was 10 times greater than observed in the non-cancer population (3).

In patients with hematological malignancies, several factors predispose to infectious complications, including immune deficiencies associated with the primary malignancy and the use of multiple lines of cytotoxic therapy that are frequently associated with prolong neutropenia and bone marrow failure. These complications usually lead to increased risk of serious infections requiring hospitalization (4) (5).

One of the most serious infectious complication is Invasive Pneumococcal Disease (IPD), defined as isolation of *Streptococcus Pneumonia* (SP) from a normally sterile body site (typically blood or cerebrospinal fluid) (6). Among adults with hematological malignancies, the IPD incidence is estimated to be 0.5% per year since diagnosis, 50-fold higher than in the general population (7).

Primary prevention of IPD relies on two available pneumococcal vaccines: The pneumococcal 13-valent conjugated vaccine (PCV13), and the pneumococcal 23-valent polysaccharide vaccine (PPSV23). A low antibody response to PPSV23 has been described in the general elderly population as well as in patients with hematologic malignancies, including patients with multiple myeloma and lymphoma (8). PCV13, however, demonstrates a greater immunogenicity through a T cell dependent response, leading to longer lasting immunologic memory (2).

The effectiveness of Pneumococcal Conjugate Vaccine (PCV13) in preventing pneumonia was demonstrated in the community based CAPITA study, with 84,496 adults over 65 years of age (9). The CAPITA study showed a vaccine efficacy of 45.6% to prevent community acquired pneumonia and 75% to prevent IPD (9). Other studies, performed with the PPSV23 have revealed less than 40% protective antibody levels after vaccination (10)(11).

The Infectious Diseases Society of America (IDSA), as well as other organizations, such as the Israel Ministry of Health (MoH), published recommendations regarding the vaccination of immunocompromised patients (8). The proper timing of immunization in cancer patients is a key component of achieving efficient vaccine protection. In general, patients with malignancy should receive the PPSV23 four to six weeks prior to chemotherapy, and no later than two weeks prior to chemotherapy initiation. The PCV13 vaccination is given as a single dose in addition to PPSV23(12,13).

The immune response following PCV13 vaccination in patients with hematological malignancies was evaluated (11,12). PCV13 vaccination in Chronic Lymphocytic Leukemia (CLL) patients, for example, induces an immune response in a considerable proportion of patients (58%) although less than in healthy controls (100%) (14). Individuals with Multiple Myeloma (MM) have historically received the PPSV23 vaccination, but this has usually resulted in a suboptimal immune response, most probably due to a defect in their humoral immunity system (2). Poor immune function and suboptimal response to pneumococcal vaccine, which contribute to the high rates and increased IPD- related mortality, were observed in patients with hematological malignancies and patients following organ or bone marrow transplantation (7).

Several unresolved questions are still present regarding the use of PCV13 in various groups of patients. The effect of PCV13 vaccine in preventing IPD prior to the initiation of immunosuppressive therapy in patients with hematological malignancies has not been rigorously tested. Additionally, a paucity of data exists regarding vaccine effectiveness in patients treated with

targeted therapy against B or T lymphocytes (15). In this paper we conducted a retrospective cohort study to assess whether vaccination of hematological patients with PCV13 prior to chemotherapy and/or biological therapy initiation was associated with decreased hospital admissions due to pneumonia or sepsis within 12 months of therapy initiation.

Methods

***Study design and setting*:** A longitudinal retrospective cohort study was conducted at the Hematology Unit, Carmel Medical Center (CMC), Haifa, Israel, between January 1st, 2009 and December 30th, 2019. The data was retrieved from the electronic health records and the computerized databases of Clalit Health Services (CHS). Retrieved data included patients' clinical and personal characteristics, namely vaccination status, hospitalization (dates and cause), and type of therapy (chemotherapy and/or biological therapy). The study was approved by the Carmel Medical Center Helsinki Committee (CMC-20-0005) and by the Faculty of Social Welfare and Health Sciences Ethic Committee, University of Haifa (approval no. 351/20).

***Study population*:** The study population included patients with hematological malignancies (with the exception of acute leukemia patients). PCV13 vaccination was recommended to all patients as soon as it became available for general use, namely, as of June 1st, 2016. This retrospective analysis included two groups of patients: those who did not receive the PCV13 vaccination and patients who received PCV13 vaccination prior to initiation of immunosuppressive therapy.

Inclusion and exclusion criteria: The study included records of patients over 18 years old who have received chemotherapy and/or biological therapy. We excluded patients who were not members of CHS due to unavailability of follow-up data. We also excluded patients with acute leukemia, due to the paucity of patients and the aggressive nature of the disease, and patient who received the PCV13 vaccination after immunosuppressive therapy was commenced.

***Study variables*:** the dependent variable was the first hospitalization due to pneumonia or sepsis within 12 months after initiation of biologic therapy and/or chemotherapy. The EHR of our health

care system is very accurate in recording vaccination status. The decision regarding patient hospitalization due to pneumonia or sepsis was made according to the diagnosis on discharge documentation, based on the following criteria: fever, dyspnea, leukocytosis, and chest x-ray or chest CT. Accurate data regarding results of blood cultures was not available due to initiation of antibiotics therapy prior to drawing blood cultures in a significant proportion of patients. Therefore we could not accurately assess the proportion of positive blood cultures.

The independent variable was vaccination with PCV13.

Control variables included demographic variables such as age, gender, country of birth, marital status (e.g., married, single or lives alone), and place of living. General clinical variables included functional status according to ECOG (Eastern Cooperative Oncology Group) performance scale (16). Disease - specific clinical variables: age at treatment, primary hematological disease (Lymphoproliferative disease, Myeloproliferative disease and Multiple Myeloma); type of immunosuppressive therapy (chemotherapy and/or biological therapy); risk of severe neutropenia (<500 neutrophils/ul) - high, moderate or low (more than 7 days, less than 7 days, no neutropenia), and splenectomy status (17).

***Vaccination procedure*:** The PCV13 vaccination procedure was commenced at CMC on June 1st, 2016 and included an intramuscular injection of 0.5 ml of polysaccharides from 13 pneumococcal serotypes conjugated to a nontoxic diphtheria toxin (Prevenar, Pfizer USA).

Statistical Analyses: Descriptive statistics (frequency, means and standard deviation) were performed to describe patients' demographic and clinical characteristics. Statistical significance of differences and associations between vaccinated and non-vaccinated patients, and between those who were or were not hospitalized due to pneumonia or sepsis within 12 months of treatment initiation were analyzed using a *Student t test* for continuous variables and χ^2 *test* for categorical variables. To determine the contribution of the PCV13 vaccine to the risk for first hospitalization

due to pneumonia or sepsis within 12 months, a multivariate logistic regression model controlling for known confounders was performed. Variables were entered into the regression model if a statistical significant association (p-value < 0.05) was found in the bivariate associations with the dependent variable. All statistical analyses were carried out using SPSS statistical software version 23.

Patient and public involvement

There was no patient or public involvement.

Results

The study population included 616 patients, of these, 67% (n=418) patients who did not receive PCV13 vaccine and 33% (n=198) who received PCV13 vaccine prior to initiation of immunosuppressive therapy.

Table 1 describes the participants' socio-demographic and clinical characteristics. Among non-vaccinated patients: 36.8% were aged between 18–65 years, 32.8% were between 66–75 years, and 30.4% were older than 76 years (Table 1). In the vaccinated group 41.4% were aged between 18–65 years, 33.3% were between 66–75 years, and 25.3% were older than 76 years (p=0.372). More independent patients (according to ECOG performance score) were documented in the vaccinated patient's group compared to the non-vaccinated (98% vs. 91.1%, p=0.001). The most prevalent hematological diagnosis was Lymphoid Malignancy (76.1% among the non-vaccinated and 80.8% among the vaccinated), followed by Multiple Myeloma (16.3% among the non-vaccinated and 16.7% among the vaccinated), and Myeloid Malignancy (7.7% among the non-vaccinated and 2.5% among the vaccinated). Most of the patients had a moderate risk for neutropenic fever (non-vaccinated – 80.1%, vaccinated – 77.3%).

Table 2 presents the association between the demographic and clinical characteristics and the rate of hospitalization due to pneumonia or sepsis within 12 months after immunosuppressive therapy initiation. Among patients that were admitted within 12 months after therapy initiation, due to pneumonia or sepsis, non-vaccinated patients were the vast majority (81.8% vs. 18.2% p=0.005). A significant association was found between age at treatment and hospitalization rates. As anticipated, in both groups patients older than 76 years of age had higher rates of hospitalization compared to younger patients between 18 and 65 years of age (p=0.014). The highest rates of hospitalization were found among the Myeloid Malignancy patients and Multiple Myeloma compared to Lymphoid Malignancy patients (p=0.01).

Table 3 shows a logistic regression analysis of factors associated with 12-month hospitalization due to pneumonia or sepsis. Vaccinated patients had reduced odds of hospitalization due to pneumonia or sepsis within 12 months since treatment initiation (OR=0.45, CI 95%: 0.246-0.839, P=0.012). Additionally, older age (76+) was associated with increased hospitalization odds relatively to the 19-65 age group (OR=2.082, CI 95%: 1.102-3.934, p=0.024). The type of hematological malignancy was not significantly associated with the odds of hospitalization.

Discussion

In this study we investigated the association between PCV13 vaccination and hospital admissions due to pneumonia or sepsis in a cohort of patients with hematological malignancies, within 12 months since initiation of therapy. This study is the first to demonstrate in a large cohort of patients with hematological malignancies that PCV13 vaccine administration prior to immunosuppressive therapy is associated with reduced odds for hospital admission due to pneumonia or sepsis, and that vaccination was associated with a 55.6% reduction in odds of hospitalization. These significant results support the latest IDSA recommended guidelines to vaccinate patients with hematological malignancies with PCV13 prior to immunosuppressive therapy, which later have been also adopted by international officials, such as The Ministry of Health of Israel (18)(19).

For the study we used the Clalit Health Services data warehouse that comprises information from patients' electronic health records and administrative data. This is a unique database which encompasses all records of vaccinations in any care setting as well as patient's demographics, all clinic visits, disease characteristics, treatment, and hospital admissions. All vaccinations records were verified by the study authors including vaccine date.

Prior to our study, the effectiveness of PCV13 in preventing pneumonia was only demonstrated in the community based CAPITA study (20). Although patients undergoing immunosuppressive therapy were previously recommended to be vaccinated with PCV13 prior treatment initiation (12), no study has demonstrated the clinical benefit in reducing severe pneumonia or sepsis, and hospital admissions following vaccination with PCV13 in these patients.

As anticipated, factors other than PCV13 vaccination also influence the risk of admission due to pneumonia or sepsis (21). In our cohort age >65 years old and the type of malignancy were associated with increased risk for hospital admission due to pneumonia or sepsis, in the bivariate analysis. The regression analysis demonstrated, however, that the PCV13 vaccination has a protective effect controlling for age and the type of malignancy. The IPD incidence among hematological malignancy patients is 0.5% per year which is 50-fold higher than in the general population (7). However, no data was found regarding hospitalization rates due to IPD or sepsis in patients with hematological malignancies.

The main strength of our study is our ability to retrieve accurate information on all hospital admissions in a large cohort of patients treated in our medical center over a period of 10 years. To verify that the reason for hospital admissions was pneumonia or sepsis we reviewed the electronic health record of all study participants. Blood culture data was limited as in a significant proportion of patients the antibiotic treatment was initiated prior to drawing blood cultures. We therefore could not make any conclusion regarding the incidence of invasive pneumococcal infection. Although our retrospective study is inherently limited (compared with a randomized trial), our findings

demonstrate similarity in sociodemographic and clinical characteristics between vaccinated and non-vaccinated patients, except for type of disease, treatment modalities, and functional dependency. This difference might have been the result of differences in patients' age and thus differences by disease were no longer statistically significant after controlling for age groups in the multivariate regression. Treatment modalities differences between vaccinated and non-vaccinated treatment might be explained by the mix of patients' malignancies and changes in treatment protocols over the last decade, namely the use of a combination of biological and chemotherapy treatment. This change is in concomitant with patients' vaccination. Notably, these differences lost significance regarding hospital admission in the regression analysis.

This study demonstrates for the first time the association between PCV13 vaccination in a group of patients at high risk for infection—patients with hematological malignancies—and risk of adverse outcomes such as infections requiring hospitalization. Further research in large cohorts of patients, stratifying by diverse risk factors, and using randomized trial study designs, is needed in order to examine the PCV13 vaccination outcomes regarding hospitalization, survival rates, and economic impacts.

Contributors

R.D. preform the data collection, analysis and writing the manuscript; E.D. E.S. M.P. designed the study analyzed the data and wrote the manuscript.

Competing interests

We declare no relevant conflicts of interest.

Funding

The authors declare that they had no external or internal funding to perform the study.

Data availability statement

Identifiable individual participant data will not be available, however, aggregated, anonymized data will be available on request from the corresponding author.

Ethics statement

The study was approved by the Carmel Medical Center Helsinki Committee (CMC-20-0005) and by the Faculty of Social Welfare and Health Sciences Ethic Committee, University of Haifa (approval no. 351/20).

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Table 1: Demographic and clinical characteristics of vaccinated and non-vaccinated patients

Variable		Non-Vaccinated (n=418, 67%)	Vaccinated (n=198, 33%)	P value
		N (%)	N (%)	
Gender				0.219
	Male	229 (54.8%)	98 (49.5%)	
	Female	189 (45.2%)	100 (50.5%)	
Country of Birth				0.079
	Israel	209 (50%)	114(57.6%)	
	Not Israel	209 (50%)	84(42.4%)	
Living area				0.621
	City	318(76.1%)	147(74.2%)	
	Rural	100(23.9%)	51(25.8%)	
Family status				0.773
	Married	319(76.3%)	149(75.3%)	
	Not married	99(23.7%)	49(24.7%)	
Splenectomy				0.309
	Yes	6(1.4%)	1(0.5%)	
	No	412(98.6%)	197(99.5%)	
Hematological diagnosis				0.043
	Lymphoid Malignancy	318(76.1%)	160(80.8%)	
	Myeloid Malignancy	32(7.7%)	5(2.5%)	
	Multiple Myeloma	68(16.3%)	33(16.7%)	
Age at treatment				0.372
	19-65	154(36.8%)	82(41.4%)	
	66-75	137(32.8%)	66(33.3%)	
	76+	127(30.4%)	50(25.3%)	
ECOG performance score				0.001
	Dependent	37(8.9%)	4(2%)	
	Not Dependent	381(91.1%)	194(98%)	
Treatment type				0.035
	Chemotherapy	131(31.3%)	49(24.7%)	
	Biological	19(4.5%)	18(9.1%)	
	Combined treatment	268(64.1%)	131(66.2%)	
Risk Neutropenic fever				0.098
	High risk	65(15.6%)	28(14.1%)	
	Moderate risk	335(80.1%)	153(77.3%)	
	Low risk	18(4.3%)	17(8.6%)	

ECOG – Eastern Cooperative Oncology Group performance status

Table 2: Association between demographic and clinical characteristic and hospitalization rates due to pneumonia or sepsis within 12 months

	No Admission within 12 months	Admission within 12 months	P-value
	N (%)	N (%)	
Vaccination status			0.005
Vaccinated	184(43.1%)	14(18.2%)	
Non-vaccinated	335(65.9%)	63(81.8%)	
Gender			0.446
Male	283(52.5%)	44(57.1%)	
Female	256(47.5%)	33(42.9%)	
Hematological diagnosis			0.010
Lymphoid Malignancy	428(79.4%)	50(64.9%)	
Myeloid Malignancy	28(5.2%)	9(11.7%)	
Multiple Myeloma	83(15.4%)	18(23.4%)	
Country of Birth			0.410
Israel	286(53.1%)	37(48.1%)	
No Israel	253(46.9%)	40(51.9%)	
Family status			0.476
Not married	132(24.5%)	16(20.8%)	
Married	407(75.5%)	61(79.2%)	
Living area			0.972
City	407(75.5%)	58(75.3%)	
Rural	132(24.5%)	19(24.7%)	
ECOG performance score			0.359
Dependent	34(6.3%)	7(9.1%)	
Not Dependent	505(93.7%)	70(90.9%)	
Risk Neutropenic fever			0.975
High risk	81(15%)	12(15.6%)	
Moderate risk	427(79.2%)	61(79.2%)	
Low risk	31(5.8%)	4(5.2%)	
Splenectomy			0.886
No	533(98.9%)	76(98.7%)	
Yes	6(1.1%)	1(1.3%)	
Treatment type			0.635
Biological treatment	33(6.1%)	4(5.2%%)	
Chemotherapy treatment	154(28.6%)	26(33.8%)	
Combination treatment	352(65.3%)	47(61%)	
Age at treatment			0.014
19-65	218(40.4%)	18(23.4%)	
66-75	173(32.1%)	30(39%)	
76+	148(27.5%)	29(37.7%)	

*ECOG – Eastern Cooperative Oncology Group performance status

Table 3: Logistic regression analysis of factors associated with 12 month hospitalization due to pneumonia or sepsis

Variable	OR	95% CI (Lower	Upper)	P-value
Non-Vaccinated (reference)				
Vaccinated	0.454	0.246	0.839	0.012
Age at treatment				
19-65 (reference)				
66-75	1.915	1.022	3.588	0.043
76+	2.082	1.102	3.934	0.024
Hematological diagnosis				
Lymphoid Malignancy (reference)				
Multiple Myeloma	1.704	0.936	3.101	0.081
Myeloid Malignancy	2.092	0.919	4.762	0.079

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (page1)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page2)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page6)
Objectives	3	State specific objectives, including any prespecified hypotheses (page6)
Methods		
Study design	4	Present key elements of study design early in the paper(page7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (page 7) *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (page7) *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants (page7)
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (page7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case (page7)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable -not applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (page8)
Bias	9	Describe any efforts to address potential sources of bias- not applicable
Study size	10	Explain how the study size was arrived at (page7)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page7)
(pStatistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding page(7-8)
		(*b*) Describe any methods used to examine subgroups and interactions (page7-8)
		(*c*) Explain how missing data were addressed(page8)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed (page8) *Case-control study*—If applicable, explain how matching of cases and controls was addressed (page8) *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy (page8)
		(*e*) Describe any sensitivity analyses (page8)

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (page7)
		(b) Give reasons for non-participation at each stage (page7)
		(c) Consider use of a flow diagram (not applicable)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (page7)
		(b) Indicate number of participants with missing data for each variable of interest (page 7-8)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) (page 8)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time (page9)
		Case-control study—Report numbers in each exposure category, or summary measures of exposure (page 9)
		Cross-sectional study—Report numbers of outcome events or summary measures (page 9-10)
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (page 9-10)
		(*b*) Report category boundaries when continuous variables were categorized (not applicable)
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (not applicable)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (not applicable)
Discussion		
Key results	18	Summarise key results with reference to study objectives (page10)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 11-12)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (page 11-12)
Generalisability	21	Discuss the generalisability (external validity) of the study results (page12)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page13)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.