



Potential impact of combined influenza and pneumococcal vaccines on the severity of respiratory illness in COVID-19 infection among type 2 diabetic patients

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Abstract

To retrospectively assess the impact of regular yearly administration of recombinant influenza and single administration of pneumococcal conjugate vaccines on the occurrence of serious respiratory infection including COVID-19 in patients with type 2 diabetes mellitus. Hundred patients with type 2 diabetes mellitus were given Vaxigrip and Pevnar13[®] vaccines and were evaluated by comprehensive clinical review, airflow screening questionnaire, and routine laboratory investigations with follow-up during the COVID-19 pandemic and compared to a control group of diabetic patients with the same inclusion criteria ($n = 100$). After Vaxigrip and Pevnar13, there is a significant improvement in respiratory symptoms and a decrease in the airflow screening questionnaire ($p = 0.0001$) with a significant improvement in inflammatory parameters as neutrophil-lymphocyte ratio, ESR, CRP, and platelet count. Four patients had mild COVID-19 (4%), mainly gastrointestinal with no complications. Twenty-one out of 32 (65.6%) patients in the control group had severe COVID-19. The hazard ratios of significant respiratory tract infection and death due to COVID-19 were 2.29 and 10.24 in the non-vaccinated control ($p = 0.001$). The severity of COVID-19 in diabetes correlated with HBA1C ($p = 0.007$), combined Vaxigrip and Pevnar13 vaccination ($p = 0.0001$), serum creatinine ($p = 0.001$), neutrophil-lymphocyte ratio ($p = 0.001$), and thrombocytopenia ($p = 0.003$). The present study suggested that the combination of Pevnar13 and Vaxigrip may be related to decreased occurrence of serious respiratory infections including COVID-19. Further randomized control trials may be needed to establish a direct causation between the two and clarify these associations.

Keywords Influenza · Pneumococcal vaccines · COVID-19 · Diabetes mellitus

Introduction

Newly developed viral epidemics put a significant and challenging economic burden on healthcare systems. The potency of the vaccine is determined by disease control, which relies on the age and immunocompetence of the patient [1].

Previous experience in SARS-CoV-infected patients demonstrated a significant innate immune response as a cause of SARS-CoV-mediated disease. Neutralizing antibody response to SARS-CoV spike (S) glycoprotein is protective, including memory B cells, but it is short-lived in cured patients. Severe depletion of T cells had been demonstrated during the acute stage of this illness [2].

Lymphopenia is a laboratory feature of severity [3] with a substantial decline in CD4 + T, CD8 + T, natural killer cells (NK), and B cell lymphocytes as the most critical characteristics of immune dysfunction in COVID-19 [4]. It was explained by direct infection of T cells and macrophages through ACE2 receptor-mediated viral entry, the aggressive inflammatory release of cytokine-favored T cell exhaustion, spleen, and lymph node invasion by the virus, and lactic acidemia that might occur in sepsis and cause inhibition to lymphocyte proliferation [5, 6].

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CD8 + T cell reaction can surpass CD4 + T cell reaction with high expression of CD69, CD38, and CD44 and enhanced expression of OX40 (CD134) and OX40L (CD252); when compared to healthy subjects, the latter is one of TNFR/TNF family members which can stimulate T cells promoting sustained T cell clonal expansion and survival making it a promising target for enhancing protection against viral infection [7].

In *OX40* $-/-$ mice, CD4 + T cell proliferation and the number of IFN- γ -producing CD4 + and number of CD4 + T cells infiltrating the lungs of influenza virus-infected *OX40* $-/-$ mice was reduced [8].

With the progression of COVID-19, lymphocyte dysfunction could be represented with the exhaustion of T lymphocyte and NK cells with upregulation of programmed cell death protein-1 (PD1), T cell immunoglobulin domain, and killer cell lectin-like receptor subfamily C member 1 (NKG2A) [9].

Neutrophils and neutrophil/lymphocyte ratio are considerably higher as lymphocyte loss may boost secondary bacterial infections that may be polymicrobial, adding more serious and bad outcomes of the disease [10].

Cytokines are increasingly produced, mainly IL-1 β , IL-2, IL-6, IL-10, interferon-inducible protein-10 (IP10), IFN- γ , and TNF- α in severe cases [11]; this cytokine storming can initiate inflammatory-triggered multi-organ dysfunction, mainly adult respiratory distress syndrome (ARDS), respiratory failure, hepatic, renal and myocardial injury with elevated corresponding biochemical markers [12].

SARS-CoV-2-specific antibodies (IgM and IgG) can be detected in the first week of illness in less than 40%, which may approach 100% after 2 weeks of the onset of infection [13].

Patients who are susceptible to serious respiratory complications, mainly pneumonia and its sequelae as hospitalization and death, are the elderly, patients with chronic diseases as chronic obstructive airway disease, ischemic heart disease, diabetes mellitus, chronic liver disease, and pregnant women, so they have the highest priority of vaccination [14].

Vaccines that improve the immunological integrity of the respiratory system, such as Inactivated Influenza Vaccine Trivalent Types A and B (Split Virion) [VAXIGRIP[®]] containing three strains of influenza virus developed by culture on embryonic eggs [15].

It has been shown to induce specific IgG antibodies to H1N1 and H3N2 influenza viruses, respectively, with a substantial improvement in post-vaccination B cell counts; influenza vaccination should be given annually as immunity diminishes over the next year [16].

Vaccination may be suboptimal in the elderly due to a progressive decrease in humoral and cell-mediated immunity, aging of the immune system with a significant reduction

in the efficacy of natural killer (NK) cells, defective differentiation, and performance of B and T lymphocytes [17, 18].

Pneumococcal conjugate vaccine (PCV) which is composed of pneumococcal capsular polysaccharides covalently bound to a protein that is almost identical to diphtheria toxin (cross-reactive material 197 [CRM197]; a non-toxic form of diphtheria toxoid) which enhances the conversion of T-cell-independent free-polysaccharide immune response to T-cell-dependent immune response [19] leading to maturation of B cell response and the development of B cell memory [20].

Conjugated polysaccharides stimulate mucosal immunity that eradicates the nasopharyngeal reservoir. Prevnar13 contains 13 capsular types; it is given as 0.5 ml intramuscularly [21, 22].

Prevnar13[®] vaccine has been indicated for adults with the risk of invasive pneumococcal infection with extended efficacy to protect from bacteremia, meningitis, and acute otitis media. Influenza vaccine can be administered with pneumococcal polysaccharide vaccine using separate syringes at different injection sites [23, 24].

In diabetes mellitus, protective vaccines are recommended due to the increased risk of drug-resistant influenza and pneumococcal disease, especially if the patients are older with decreased immunity and impaired respiratory function, confirming the importance of immunization; it was recommended that influenza and pneumococcal vaccines should be given for all diabetic patients [25].

In the current study, we retrospectively evaluated the impact of routine and regular yearly administration of recombinant influenza and single administration of Prevnar13 vaccines in high-risk patients with type 2 diabetes mellitus on the occurrence of serious respiratory infection including COVID-19.

Research design and methods

1-Patient selection

This is a retrospective and observational study from January 2016 to September 2020; the clinical data of 100 diabetic patients were retrospectively evaluated (Fig. 1); they were accustomed to receive regularly and yearly Vaxigrip[®] [Inactivated Influenza Vaccine Trivalent Types: 2 type A and 1 type B], 0.5 ml in the deltoid region, together with Prevnar13[®] vaccine once every 3–5 years, 0.5 ml intramuscular in the other deltoid region.

Sample size

The internal medicine department serves nearly 1000 patients per year (3000 over the period of the study), and nearly 25% of them present with repeated respiratory tract

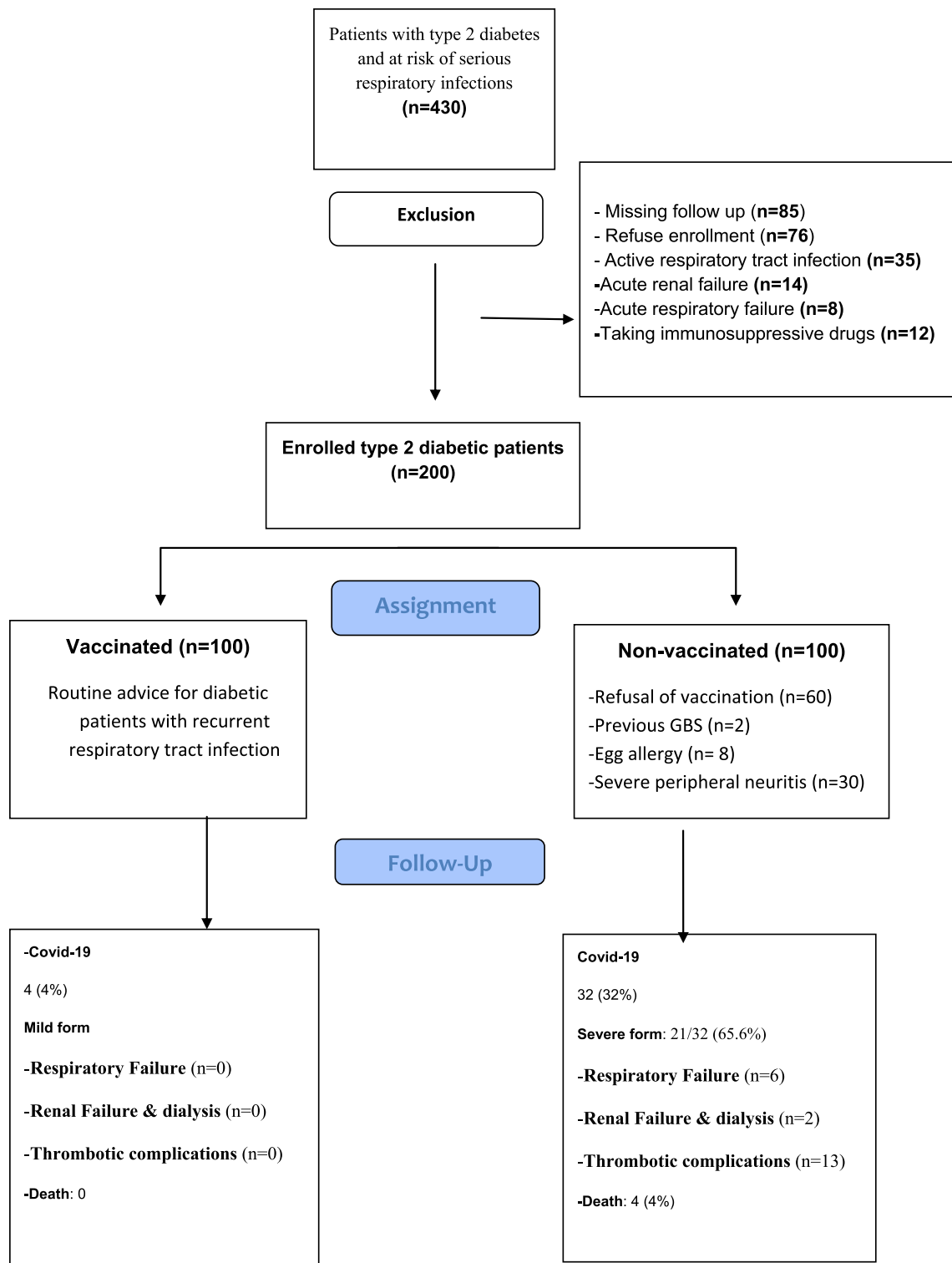


Fig. 1 Flowchart of the studied groups

infection, so with a margin of error of 9.78%, a confidence level of 95%, a response distribution of 50%, and a power of 80%, the recommended sample size was at least 100 patients in each arm with $p < 0.05$.

Inclusion criteria

Patients with type 2 diabetes and at risk of serious respiratory infections, mainly elderly, are included; other comorbidities

include ischemic heart disease, bronchial asthma, and renal failure; also, patients with recurrent seasonal influenza and recurrent trachea-bronchitis were included.

Patients with a previous history of allergy to the utilized vaccines, egg allergy, Guillain–Barré syndrome, current active upper respiratory tract infection, and severe peripheral neuritis were excluded.

As a routine step in the care of these patients, we advised them to receive these vaccines and oral consent was obtained from all patients to share their data in this research.

Control group

One hundred type 2 diabetic patients who fulfilled the inclusion criteria but did not receive both studied vaccines due to refusal of vaccination ($n=60$), previous Guillain–Barré syndrome ($n=2$), egg allergy ($n=8$), and severe peripheral neuritis ($n=30$) were matched for age and sex and shared a similar exposure.

Patients were evaluated by:

- Comprehensive clinical examination, including vital signs and clinical characteristics of renal, heart, or respiratory diseases, had been reported.
- Features of COVID-19: Mild COVID-19 is manifested by fever, malaise, cough, headache, myalgia, and diarrhea, loss of smell and taste without dyspnea, or abnormal chest radiology. Moderate COVID-19 is manifested

as any symptom of the mild disease and lung ultrasound and radiology features with oxygen saturation (SpO_2) $\geq 94\%$ on room air. Severe COVID-19 presented with $\text{SpO}_2 < 94\%$ on room air, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) < 300 mm Hg, respiratory rate $> 30/\text{min}$, or lung affection $> 50\%$. Critical COVID-19 is characterized by respiratory failure, septic shock, and/or multiple organ failure [26].

- Airflow screening questionnaire (Fig. 2) [27] was evaluated before vaccination and every 6 months post-vaccination with comparison; a score > 25 implied obstruction of airflow.
- Routine laboratory investigations included liver function tests, coagulation profile, renal function tests, complete blood count, C reactive protein, and D dimer level.
- PCR for the nasopharyngeal swab of the suspected cases

Well-trained personnel had performed the sampling. The positive results suggested SARS-CoV-2 infection, but bacteria and other virus-induced co-infection could not be excluded. The negative results could not exclude SARS-CoV-2 infection and should be judged by combining clinical observation; patients who suffered from fever, sore throat, dyspnea, and cough with confirmed exposure to confirmed cases, with typical chest computerized tomography (CT) findings, are highly suggestive of COVID-19 [28].

Patient name		
1. Have you smoked at least 100 cigarettes in your life?	<input type="checkbox"/> 0 No <input type="checkbox"/> 20 Yes	<input type="checkbox"/>
2. Have you been told by your healthcare provider that you have anxiety (nervousness)?	<input type="checkbox"/> 0 No <input type="checkbox"/> 3 Yes	<input type="checkbox"/>
3. How often do you have chest tightness, a sense of suffocation or an inability to take a deep breath?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 A little of the time <input type="checkbox"/> 2 Some of the time <input type="checkbox"/> 3 Most of the time	<input type="checkbox"/>
4. How often do your breathing problems or shortness of breath limit you in performing your usual activities, including your job, housework, school work or routine daily activities?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 A little of the time <input type="checkbox"/> 2 Some of the time <input type="checkbox"/> 3 Most of the time	<input type="checkbox"/>
5. How often do you feel frustrated because of your breathing problems or shortness of breath?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 A little of the time <input type="checkbox"/> 2 Some of the time <input type="checkbox"/> 3 Most of the time	<input type="checkbox"/>
6. In the past 3 months, how often have you had a cough in the morning?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 A little of the time <input type="checkbox"/> 2 Some of the time <input type="checkbox"/> 3 Most of the time	<input type="checkbox"/>
7. In the past 3 months, how often have you had noisy breathing (whistle, rattle, wheeze) while sleeping?	<input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 A little of the time <input type="checkbox"/> 2 Some of the time <input type="checkbox"/> 3 Most of the time	<input type="checkbox"/>
		Total score
		<input type="checkbox"/>

Fig. 2 Airflow screening questionnaire

Lung ultrasound

Features highly suggestive of COVID-19 are confluent and isolated B lines, thickened irregular pleural lines, sub-pleural pulmonary consolidations, and air bronchogram [29].

High-resolution CT chest

Features in CT may show ground-glass opacities, with a rounded morphology and peripheral lung affection [30].

Follow-up

The first patient had received Pevnar13 in January 2016, and the last patient in October 2019; 15 patients received a second dose of Pevnar13 after 3 years from the last dose.

The first patient who had received the first dose of Vaxigrip in January 2016 and the last one in October 2019 had been given Vaxigrip yearly; they were followed up after the first dose of vaccines to detect the impact of both vaccines on the occurrence of respiratory complications and on systemic inflammatory parameters by laboratory evaluation every 4 months; they were encouraged to consult us in case of any respiratory distress, and during COVID-19 pandemic they were followed strictly from January 2020 until September 2020; any suspected case was evaluated clinically and by lung ultrasound and then referral for CT chest when indicated.

Study outcome

- The time from the first recurrence of respiratory tract infection or life-threatening chest infections after vaccination up to death or the end of the study period (September 1, 2020), whichever came first.
- Incidence of COVID-19 and complications including death in the vaccinated patients when compared to the non-vaccinated patients.

Statistical analysis

All statistical analyses were performed using the SPSS version 20 software (SPSS Inc., Chicago, IL, USA). Shapiro–Wilk test was used to test the distribution of data. Independent samples' Student's *t* test was used to compare between the study and control groups of normally distributed variables, while Mann–Whitney *U* test was used for non-normally distributed variables. The chi-square or Fisher's exact tests were used for categorical variables when appropriate. The paired *t* test was appropriately used. *P* value < 0.05 was considered significant. Survival analysis was performed using Kaplan–Meier test; the significance of the curves was assessed using log-rank test. Cox proportional hazard

analysis was used to estimate the hazard ratio of COVID-19-related adverse events and death.

Results

One hundred patients had received the combined vaccines [yearly Vaxigrip from 2016 till 2019, 85 patients received Pevnar13 once and 15 patients received a second dose after 3 years]; all the patients in the study group were diabetic; 34 patients were treated with insulin Mixtard (soluble insulin 30% and isophane insulin 70%) 56.3 ± 23.6 units daily, 66 patients were on oral hypoglycemic agents (glimepiride $n = 39$, glyburide $n = 27$, vildagliptin $n = 66$), and 48% were smokers. They had received the vaccines due to recurrent bronchopneumonia ($n = 39$), ischemic heart disease ($n = 25$), renal impairment ($n = 12$), and recurrent seasonal influenza ($n = 24$).

They were compared with a control group of patients with type 2 diabetes mellitus who did not receive the vaccines due to their refusal of vaccination, allergic reaction to influenza vaccine or egg allergy, and severe peripheral neuritis for fear of its aggravation. Forty-two patients had recurrent bronchitis, recurrent bronchopneumonia ($n = 15$), ischemic heart disease ($n = 26$), and renal impairment ($n = 17$).

They were treated with insulin Mixtard (soluble insulin 30% and isophane insulin 70%) 52.2 ± 13.5 units daily ($n = 46$), 54 patients were on oral hypoglycemic agents (glimepiride $n = 21$, glyburide $n = 12$, metformin $n = 21$, vildagliptin $n = 54$), and 44% were smokers. The baseline laboratory characteristics of both groups are shown in Table 1.

Tables 2 and 3 show the impact of Vaxigrip and Pevnar13 on the airflow screening questionnaire and laboratory parameters of the studied patients when compared to the control group at the end of follow-up, including the incidence and complications of COVID-19 in both groups.

The patients who were followed up after combined vaccinations showed a significant improvement in respiratory tract symptoms as dyspnea, cough, expectoration, and quality of life guided by a significant decrease in the airflow screening questionnaire (14.1 ± 2.7 post-vaccination vs. 24.15 ± 5.43 pre-vaccination = 0.0001) and highly significant reduction when compared to the control group presented with respiratory symptoms (14.1 ± 2.7 vs. 26.5 ± 7.45 , $p = 0.0001$).

In the study group, 12 patients had developed mild upper respiratory tract infection in the form of tracheobronchitis after 18.5 ± 9.5 months of follow-up, which responded well to levofloxacin 750 mg for 5 days; however, 17 patients of the control group developed lower respiratory tract infections (8 patients needed hospitalization and 9 patients needed 14.5 ± 3.8 days of broad spectrum antibiotics ($p = 0.0005$, $\chi^2 = 11.977$)).

Table 1 Baseline characteristics of patients in the study and control groups

	Control (n=100)	Case (n=100)	p
<i>F/M</i>	28/72	22/78	0.147
Age	56.03 ± 10.9	57.5 ± 10.5	0.73
BMI (kg/m ²)	31.4 ± 1.8	31.9 ± 1.5	0.16
Smoking	48 (48%)	44 (44%)	0.3
Airflow screening questionnaire	24.15 ± 5.43	24.53 ± 6.2	0.196
AST IU/L	49.3 ± 9.9	41.9 ± 10.2	0.86
ALT IU/L	57.9 ± 11.1	47.9 ± 21.8	0.001
Total bilirubin mg/dl	0.94 ± 0.41	1.03 ± 0.36	0.34
Albumin gm/dl	4.7 ± 0.42	5.1 ± 0.24	0.001
INR	0.93 ± 0.11	1.09 ± 0.19	0.1
Creatinine mg/dl	1.156 ± 0.24	1.17 ± 0.27	0.234
WBC (10 ³ /ul)	8.9 ± 2.1	11.7 ± 2.08	0.699
lymphocytes (10 ³ /ul)	2.96 ± 0.72	1.97 ± 0.62	0.257
NLR	4.67 ± 1.3	5.8 ± 0.95	0.001
Hemoglobin gm/dl	12.5 ± 0.98	11.4 ± 1.33	0.039
Platelet count (10 ³ /ul)	186.9 ± 12.8	158.6 ± 26.5	0.001
FBS mg/dl	197.9 ± 30.2	208.9 ± 23.8	0.1
HBA1c %	8.9 ± 0.46	9.4 ± 0.6	0.11
<i>ESR</i>			
1st Hour	50.9 ± 11.4	68.2 ± 22.05	0.001
2st Hour	78.2 ± 9.3	87.2 ± 27.1	0.001
CRP g/l	10.1 ± 1.3	9.6 ± 2.4	0.0012
D-Dimer (ng/dl)	344.8 ± 115.4	398.4 ± 94.1	0.088

INR International normalized ratio; *NLR* Neutrophil–lymphocyte ratio; *CRP* C-reactive protein

Table 2 Impact of Vaxigrip and Pevnar13 on airflow screening questionnaire and laboratory parameters of the studied patients

	Post-vaccination	Pre-vaccination	p
Airflow screening questionnaire	24.15 ± 5.43	14.1 ± 2.7	0.0001
WBC (10 ³ /ul)	8.9 ± 2.1	5.64 ± 0.81	0.0001
Lymphocytes (10 ³ /ul)	2.96 ± 0.72	3.3 ± 0.92	0.008
NLR	4.67 ± 1.3	1.87 ± 0.4	0.0001
Platelets (10 ³ /ul)	186.9 ± 12.8	205 ± 43.4	0.0001
<i>ESR</i>			
First hour	50.9 ± 11.4	24.1 ± 9.8	0.001
Second hour	78.2 ± 9.3	33.9 ± 15.2	0.001
CRP g/l	10.1 ± 1.3	5.4 ± 1.27	0.0001
D-Dimer (ng/dl)	344.8 ± 115.4	158.5 ± 59.3	0.0001

Four patients (4%) in the study group had developed mild COVID-19 during the period of follow-up in COVID-19 pandemic from January 2020 till September 2020, in the form of low-grade fever and gastrointestinal symptoms (abdominal pain, diarrhea, loss of taste, and smell) without respiratory manifestations; the data were collected by clinical examination of suspected cases and evaluation of COVID-19 questionnaire including high-grade fever, body aches, gastrointestinal symptoms, sense of smell and taste, and respiratory manifestations after being informed

to report any suspicious symptoms confirmed by laboratory findings, lung ultrasound, and CT chest.

No recorded complications in the COVID-19-infected patients with a significant reduction in inflammatory parameters as leucocytes count, neutrophil–lymphocyte ratio, platelet count, C-reactive protein, and D-dimer levels when compared to the pre-vaccination values (Table 2).

A significant number (32%) in the control group had COVID-19 infection with a significant increase in inflammatory and coagulation parameters, which was severe in 21/32 (65.6%) patients and complicated with respiratory

Table 3 Impact of Vaxigrip and Prevnar13 on airflow screening questionnaire and laboratory parameters of the studied patients when compared to control group at the end of follow-up

	Control group	Study group	<i>p</i>
Airflow screening questionnaire	26.5 ± 7.45	14.1 ± 2.7	0.0001
WBC (10 ³ /ul)	16.47 ± 1.3	5.64 ± 0.81	0.0002
Lymphocytes (10 ³ /ul)	1.3 ± 0.34	3.3 ± 0.92	0.0001
NLR	8.1 ± 1.9	1.87 ± 0.4	0.0001
Platelet count (10 ³ /ul)	122.4 ± 28.2	205 ± 43.4	0.001
<i>ESR</i>			
First hour	81.3 ± 24.1	24.1 ± 9.8	0.0001
Second hour	101.8 ± 19.6	33.9 ± 15.2	0.001
CRP g/l	35.2 ± 8.4	5.4 ± 1.27	0.0001
D-Dimer (ng/dl)	1288 ± 322.5	158.5 ± 59.3	0.0001
COVID-19 (<i>n</i> , %)	32 (32%)	4 (4%)	0.0001
<i>Complications</i>			
Respiratory failure (<i>n</i> =6)	6	0	0.0022
Renal failure and dialysis (<i>n</i> =2)	2	0	0.33
Thrombotic complications (<i>n</i> =13)	13	0	0.00001
Death (<i>n</i> =4)	4	0	0.0286

NLR: Neutrophil–lymphocyte ratio; CRP C-reactive protein

failure in 6 patients, renal failure and dialysis in 2 patients, thrombotic complications in 13 [DVT (*n*=3), myocardial infarction (*n*=5), pulmonary embolism (*n*=4), cavernous sinus thrombosis (*n*=1)], and death (*n*=4); lung ultrasound was highly efficient in directing diagnosis and confirmed by high-resolution CT chest (Fig. 3).

The impact of giving vaccination to diabetic patients on survival and occurrence of major events as serious respiratory tract infections including COVID-19 and death was analyzed by Kaplan–Meier survival curve (Fig. 4). The hazard ratio (HR) of getting significant respiratory tract infection was 2.29 higher in the non-vaccinated control group when compared to the vaccinated diabetic patients (95% CI: 0.39–4.8, *p*=0.001); HR of death due to COVID-19 was 10.24 times higher in the non-vaccinated control group when compared to the vaccinated diabetic patients (95% CI: 0.45–21.8, *p*=0.001).

The severity of COVID-19 in patients with diabetes had been correlated with HbA1C (*r*=0.422, *p*=0.007), combined Vaxigrip and Prevnar13 vaccination (*r*=−1.12, *p*=0.0001), serum creatinine (*r*=0.537, *p*=0.001), neutrophil–lymphocyte ratio (*r*=0.597, *p*=0.001), and thrombocytopenia (*r*=0.377, *p*=0.003).

Discussion

Patients with chronic respiratory illnesses have altered lung functions and may have other comorbidities like cardiovascular disease, diabetes, chronic renal failure, and malignant conditions, rendering these patients highly vulnerable to viral or bacterial infection [30].

Prevnar13 had been recommended for all adults who are at high risk of respiratory tract infection, with underlying medical conditions or immunosuppression in more than 25 countries [31]. The efficacy of the pneumococcal vaccine in diabetic patients might reach 84% and does not decline with increasing duration after vaccination. The vaccine was highly cost-effective in preventing pneumococcal infection in older patients [32]; it was safe, with enhanced immunogenicity [33].

Influenza vaccination in patients with diabetes enhances B-lymphocytes function and antibody production, leading to a reduction in hospitalizations due to complications and the rate of deaths in more than half of the cases [34].

A large study of mortality in COVID-19 had revealed that poor glycemic control (HbA1c more than 10%) before hospital admission was associated with a higher risk of in-hospital death compared with those with HbA1c of less 6.5% [35].

Hyperglycemia at admission was associated with radiological severity, worse outcome including ICU admission, mechanical ventilation, or death, when compared with patients with normal glucose level, denoting that improving glycemic control is the most important target whether the patient is diabetic or not [36].

The mortality was significantly higher in patients with diabetes or uncontrolled hyperglycemia during their hospital stay (30%) than those with euglycemia (6%), and these patients had higher rates of neutrophilia, lymphopenia, higher C-reactive protein, and pro-calcitonin with higher risks for diabetic ketoacidosis and hyperglycemic hyperosmolar syndrome [37]; this rapid metabolic deterioration could be explained by marked affection of insulin-secreting ability of the pancreas, together with the metabolic paralysis mediated by the cytokine release, viral affinity to ACE2 receptors in the pancreatic β -cells, and anorexia that prevent regular administration of anti-diabetic drugs [38, 39].

The current study assessed the impact of combined influenza and Prevnar13 vaccination in diabetic patients with recurrent respiratory tract infections on systemic inflammation, and the possible protection from COVID-19; it had revealed that the combination of both vaccines had significantly improved respiratory symptoms, with marked improvement in systemic inflammation parameters when evaluated regularly during the period of follow-up.

It was suggested that both vaccines might improve the outcomes in the form of significant reductions in numbers

Fig. 3 Lung ultrasound with corresponding computed tomography of the chest, A: normal lungs with horizontal A lines, B: normal CT chest, C: sub-pleural pulmonary consolidation 2.7 cm with isolated B lines, D: CT chest showed ground-glass opacities

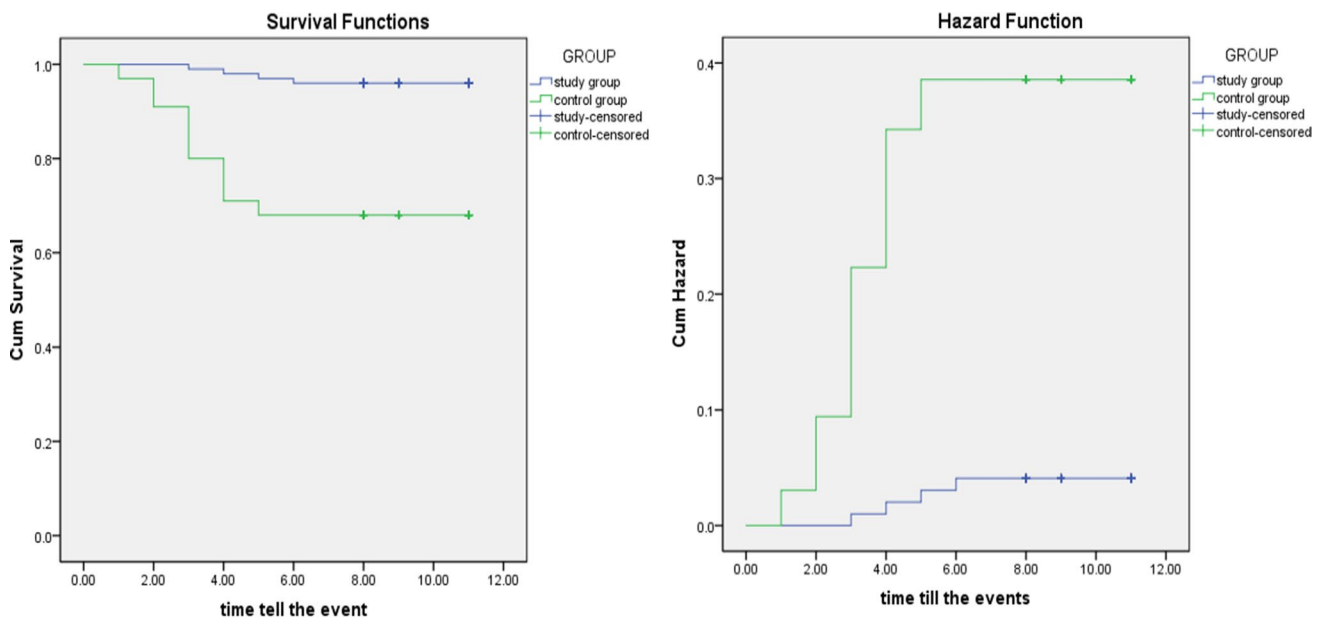
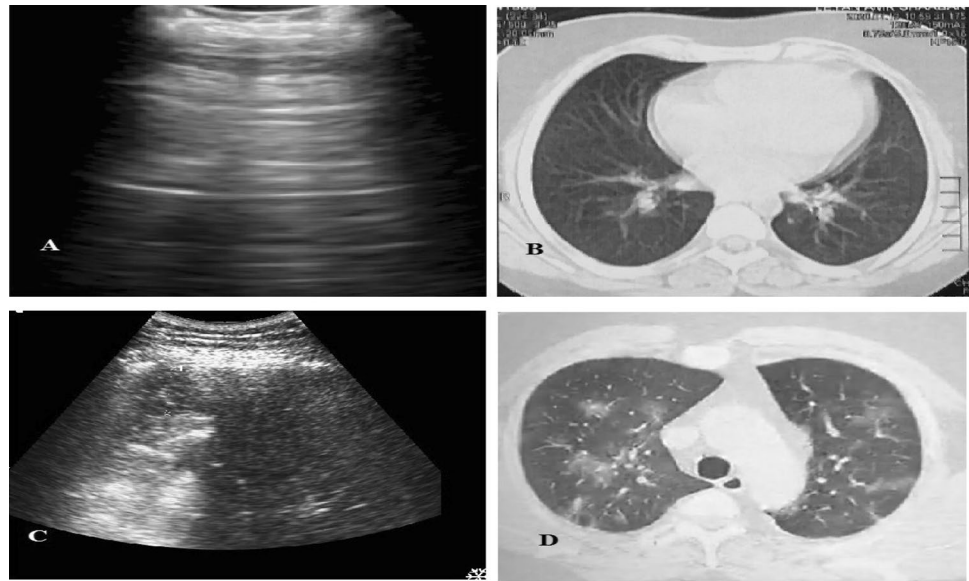


Fig. 4 The impact of adding combined influenza and pneumococcal conjugate vaccines on risk of serious respiratory infections including COVID-19 in the treated and control patients

of patients presented with bronchopneumonia which was mild infection that responded to medications in a short period of time; however, 17% of patients in the control group developed significant lower respiratory tract infections that needed hospitalization in 8 patients ($p = 0.0005$, $\chi^2 = 11.977$).

Our results were supported by the fact that influenza vaccine caused a significant reduction in rate of pneumonia (32%), hospitalization, and the risk of death by 50% [40] and also reduced the morbidity and mortality in patients with cardiac disease in 37% [40].

The Community-Acquired Pneumonia Immunization Trial in Adults (CAPITA) had shown the effectiveness of the pneumococcal conjugate vaccine in older patients, and data had indicated that the pneumococcal and influenza vaccines might reduce community-acquired pneumonia and acute exacerbations in patients with the chronic respiratory disease [41–43].

Four (4%) patients in the study group had developed mild COVID-19, mainly gastrointestinal, without respiratory manifestations with no recorded complications and a significant reduction in inflammatory markers; however,

significant number (21%) in the control group had severe COVID-19 infection with life-threatening complications and death in 4 patients, reflecting the potential protective role of combining both studied vaccines against COVID-19, both groups had the same environmental exposure and the same preventive measures and comorbid conditions.

In agreement with our results is the concept that influenza and pneumococcal vaccines can prevent the numbers of pneumococcal and influenza hospital admissions, reduces the needed care for non-COVID-19 patients, and minimizes possible superadded infections, preventing a considerable amount of COVID-19-related mortality [44], and this is supported by the fact that there is a lower rate of SARS-CoV-2 in children who were infected with influenza or had been vaccinated [45].

The extended protection of both studied vaccines can be explained by direct stimulation of Toll-like receptor (TLR), eliciting both humoral and T cell responses, production of specific natural killer (NK) cells, with enhanced long-term memory, and possible activation of OX40 and OX40L [46, 47].

The limitations of the current study are its retrospective evaluation and the limited information about the other treatments that the patients received in both the vaccination and control group. In addition, there is a lack of practical methods to measure the antibody titers of both vaccines. Further, the detailed analysis of some essential risk factors of type 2 diabetes as physical inactivity and dietary habits was deficient as there was a shortage of such data in the obtained medical records. We think that the study sample size might not be large enough to reflect more accurate results regarding this issue. All patients were selected from only one, albeit large, hospital. Further future randomized control trials are required to study these associations and confirm them and could build upon these retrospective data from our study. Randomized control trials could establish direct causation more reliably.

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Declarations

Conflict of interest The authors that they have declare no conflict of interest.

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