COVID-19 Special Report

Effectiveness of COVID-19 vaccine and Paxlovid treatment against SARS-Cov-2 infection related severe outcome and death during the Omicron variant outbreak; COV-EPI evaluation study in LTCFs

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Abstract

On November 5, 2021, Pfizer Inc. announced a treatment method using Paxlovid (nirmatrelvir + ritonavir) that could reduce the risk of hospitalization or death for confirmed patients with coronavirus disease 2019 (COVID-19). From February 6 to April 2, 2022, the incidence of COVID-19 as well as the effects of Paxlovid treatment and COVID-19 vaccine were analyzed in 2,241 patients and workers at five long term care facilities (LTCFs) during the outbreak of the Omicron variant of COVID-19.

Among the patients at LTCFs, the incidence of severe cases was 7.14% for those who did not receive Paxlovid and 3.69% for patients who did, and the fatality rates were was 5.61% and 3.53%, respectively. There was 51% (adjusted relative risk [aRR]=0.49; 95% confidence interval [CI]: 0.24-0.98) reduction in the rate of severe illness or death among patients who were administered Paxlovid compared with that noted among those who were not administered Paxlovid. In addition, the condition of 9.84% of patients who were not vaccinated progressed to severe illness, whereas the condition of only 3.27% of patients who completed the third vaccination progressed to severe illness; the fatality rates were 8.20% and 3.27%, respectively. Compared with patients who were unvaccinated, those who completed the third vaccination showed 71% (aRR=0.29; 95% CI: 0.13-0.64) reduction in the rate of severe illness or death and 65% (aRR=0.35; 95% CI: 0.15-0.79) reduction in the risk of death. Among patients at the LTCFs, the rates of severe illness or death and fatality were lower in the group that was administered Paxlovid than in the non-administered group, and these rates were also lower in the group that completed the third vaccination than in the unvaccinated group.

As the COVID-19 outbreak continues, the fatality rate has decreased; however, patients of LTCFs are still a high-risk group for COVID-19. The current countermeasures must first be supplemented through continuous analysis of the effects of vaccinations and the use of therapeutics at LTCFs and other facilities that are at high risk for severe COVID-19, while preparing for future outbreaks of COVID-19 and other infectious diseases.

Keywords: Coronavirus disease 2019 (COVID-19), Long term care facilities (LTCFs), Paxlovid, Effects of COVID-19 treatment, Effects of COVID-19 vaccine

Introduction

In November 2021, Pfizer Inc. announced a treatment using Paxlovid (nirmatrelvir + ritonavir) that could reduce the risk of hospitalization or death among confirmed patients with coronavirus disease 2019 (COVID-19). This treatment comprises an oral therapeutic agent and was developed to inhibit the action of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) proteolytic enzyme [1]. Pfizer reported that the risk of hospitalization or death could be reduced by approximately 89% with the use of Paxlovid [2].

In the Republic of Korea (ROK), the vaccination rate increased with the number of confirmed cases of COVID-19, and as of December 30, 2021, the number of individuals who completed the second vaccination was 82.7% [3]. However, as the Omicron variant is highly infectious, the cumulative number of confirmed cases reached 16,929,564 as of April 15, 2022 [4], with the mortality per 100,000 reaching 1.05 in the 4th week of February 2022, 1.74 in the 1st week of March, 2.61 in the 2nd week of March, and 3.79 in the 3rd week of March [5,6]. Therefore, management of the severe illness or death became necessary using therapeutic agents in the high-risk population. A previous study suggested the development of a convenient orally ingestible therapeutic agent along with the COVID-19 vaccine [7].

In the ROK, the use of Paxlovid, an orally ingestible therapeutic agent, began on January 14, 2022 [8], and the target subjects of the therapeutic agent expanded from individuals aged ≥60 years, immunocompromised individuals, and individuals in their 50s to include those in their 40s, following the rapid increase in the number of confirmed cases, as the Omicron variant became the dominant variant from February 21, 2022 [9]. As of March 3, 2022, the total number of Paxlovid doses used was 25,342, which included 20,827 doses for individuals under home treatment, 785 for residential treatment centers, and 3,730 for hospitals dedicated to infectious diseases [10]. Patients at long term care facilities (LTCFs) are at high risk of severe illness or death if COVID-19 is confirmed and therefore require a systematic analysis of major countermeasures, such as constant monitoring of patients as well as the use of vaccinations and therapeutic agents.

Therefore, this study aimed to identify the incidence of COVID-19 at five LTCFs that were managing confirmed cases of COVID-19 during the outbreak of the Omicron variant and to evaluate the preventive effects of COVID-19 vaccine and Paxlovid treatment on progression to severe COVID-19 among patients and workers at these LTCFs.

Method

Analysis was conducted among 2,241 patients and workers at five LTCFs with confirmed COVID-19 during the Omicron variant outbreak between February 6 and April 2, 2022. The number of confirmed cases and deaths was increasing for LTCFs, and the monitoring period was defined as the duration from the start of the outbreak until April 2, 2022, while the occurrence period was 38-52 days. Data were collected directly from each LTCF. The mean incidence rate in the entire study population was 71.93% (range: 58.6%-86.2%), and among the confirmed cases, 44.73% (range: 26.87%-63.00%) of patients and 0.2% (range: 0%-1.80%) of workers had been administered the therapeutic agent. Among the administered therapeutic agents, Paxlovid was used in 86.82% (range: 72.94%-100%), whereas Remdesivir and Regkirona were used in 13.18% (range: 12.44%-27.06%) of the subjects. Severe illness or death occurred in a minimum of 2 and a maximum of 19 patients, whereas death occurred in a minimum of 0 and a maximum of 18 patients. The detailed status of each LTCF is listed in Table 1.

Table 1. Status at five long term care facilities (LTCFs) with COVID-19 clusters (during the Omicron variant outbreak)

Category		Total	Busan A LTCF	Busan B LTCF	Seoul C LTCF	Jeonju D LTCF	Seoul E LTCF
Total		2,241	348	702	600	248	343
Confirmed cases		1,612	218	476	517	200	201
Incidence rate (%)		71.93	62.64	67.81	86.17	80.65	58.60
Received therapeutic agent (%)	Patients	721(44.73)	74(33.94)	255(53.57)	209(40.43)	126(63.00)	54(26.87)
	Workers	3(0.2)	0	0	0	0	3(1.80)
Type of therapeutic agent (%)	PAX[a]	626(86.82)	74(100)	186(72.94)	183(87.56)	126(100)	57(100)
	Other[b]	95(13.18)	-	69(27.06)	26(12.44)	-	-
Severity	Severe illness or death	43	19	13	6	2	3
	Death	38	18	12	6	2	0
Confirmed cases' occurrence period		February 6 -April 2	February 6 -April 1	February 6 -April 1	February 6 -April 2	February 17 -March 27	February 9 -April 2

[a] Paxlovid

[b] Remdesivir, Regkirona

Results

Among the total 2,241 subjects, 1,612 (71.93%) were infected, the condition of 43 (2.67%) subjects progressed to severe illness, and 38 (2.36%) subjects died. Among the total subjects, female subjects accounted for 68.23%, those aged ≥75 years accounted for 38.29%, and patients accounted for 51.81%. The preventive effect of vaccination was the highest (74.92%) among subjects who completed the third vaccination, followed by 14.37% among subjects who completed the second vaccination and 8.39% among subjects who only had the first vaccination. Among the infected subjects, 44.73% were administered the therapeutic agent, and the use of Paxlovid was the highest among subjects at 86.82%. The preventive effect of vaccination against the severe illness or death was the highest among subjects who completed the third vaccination at 73.82%, followed by 14.33% among subjects who completed the second vaccination and 9.18% among the unvaccinated subjects (Table 2).

General characteristics were compared according to the history of the use of therapeutic agents among patients of all LTCFs. Among subjects who received Paxlovid, 51.36% were female and 72.87% were aged ≥75 years; vaccinations were completed up to the third dose in 59.39% and the second dose in 21.67%. Followed by 14.77% subjects were unvaccinated. For other therapeutic agents, 53.68% subjects were male and 65.26% were aged ≥75 years; vaccinations were completed up to the second dose in 40.00%, the third dose in 36.84%. 21.05% subjects were unvaccinated. Among subjects who did not receive a therapeutic agent, 58.16% were female and 73.98% were aged ≥75 years; vaccinations were completed up to the third dose in 61.22% and the second dose in 17.86%. Followed by 15.31% subjects were unvaccinated (Table 3).

Among patients, the condition of 3.69% of those who received Paxlovid and 7.14% of unvaccinated patients progressed to severe illness; the fatality rate was 3.53% among those who received Paxlovid and 5.61% among those who used no agents. A crude relative risk was estimated using logistic regression analysis, and sex, age, and vaccination history were adjusted in the analysis model to compare the preventive effects of Paxlovid on severe illness or death among those who received Paxlovid and those who did not receive any treatment. There was 51% (aRR=0.49; 95% confidence interval [CI]: 0.24-0.98) reduction in the rate of severe illness or death among patients who were administered Paxlovid compared with that noted among those who were not administered Paxlovid (Table 4).

Among unvaccinated patients, the condition of 9.84% subjects progressed to severe illness compared with the condition of 3.27% subjects who completed the third vaccination; the fatality rate was 8.20% among the unvaccinated subjects and 3.27% among those who completed the third vaccination. A crude relative risk was estimated using logistic regression analysis, and sex, age, and therapeutic agent use history were included in the

Table 2. General characteristics and incidence in subjects

Category		Total		Infected		Incidence rate (%)
		Total	%	Total	%	
Total		**2,241**	**100%**	**1,612**	**100%**	**71.93**
Sex						
Male		712	31.77	563	34.93	79.07
Female		1,529	68.23	1,049	65.07	68.61
Age (years)						
〈60		726	32.40	448	27.79	61.71
60–74		657	29.32	494	30.65	75.19
≥75		858	38.29	670	41.56	78.09
Class						
Patients		1,161	51.81	914	51.81	78.73
Workers		1,080	48.19	698	48.19	64.63
Administration of therapeutic agent						
Total		–	–	721	44.73	100
Paxlovid		–	–	626	86.82	100
Regkirona		–	–	34	4.72	100
Remdesivir		–	–	61	8.46	100
Preventive effect of vaccination						
Unvaccinated		188	8.39	148	9.18	78.72
1 dose		52	2.32	43	2.67	82.69
2 doses	Total	322	14.37	231	14.33	71.74
	〈90 days	135	41.93	105	45.45	77.78
	≥90 days	187	58.07	126	54.55	67.38
3 doses	Total	1,679	74.92	1,190	73.82	70.88
	〈90 days	924	55.03	476	40.00	51.52
	≥90 days	755	44.97	714	60.00	94.57
Severity						
Severe illness or death		–	–	43	2.67	100
Death		–	–	38	2.36	100

analysis model to compare the preventive effects of vaccination on severe illness or death . Compared with unvaccinated patients, those who completed the third vaccination showed 71% (aRR=0.29; 95% CI: 0.13-0.64) reduction in the rate of severe illness or death and 65% (aRR=0.35; 95% CI: 0.15-0.79) reduction in the risk of death (Table 5).

This study examined the incidence of COVID-19 and the effectiveness of COVID-19 vaccine and Paxlovid treatment against SARS-Cov-2 infection among 2,241 patients and workers at five LTCFs during the Omicron variant outbreak

Table 3. General characteristics of all patients at LTCFs according to therapeutic agent used

Category	Paxlovid		Other[a]		No treatment		Other[a] vs Paxlovid	No treatment vs. Paxlovid
	Total	%	Total	%	Total	%	P-value	P-value
Total (n=914)	**623**	**100**	**95**	**100**	**196**	**100**		
Sex							0.359	0.096
Male	303	48.64	51	53.68	82	41.84		
Female	320	51.36	44	46.32	114	58.16		
Age (years)							0.107	0.182
〈60	38	6.10	11	11.58	18	9.18		
60-74	131	21.03	22	23.16	33	16.84		
≥75	454	72.87	62	65.26	145	73.98		
Vaccination status							〈.001	0.606
Unvaccinated	92	14.77	20	21.05	30	15.31		
1dose	26	4.17	2	2.11	11	5.61		
2doses Total	135	21.67	38	40.00	35	17.86		
2doses 〈90 days	67	49.63	22	57.89	11	27.59		
2doses ≥90 days	68	50.37	16	42.11	24	72.41		
3doses Total	370	59.39	35	36.84	120	61.22		
3doses 〈90 days	174	47.03	17	48.57	74	61.67		
3doses ≥90 days	196	52.97	18	51.43	46	38.33		
Severity								
Severe illness or death	23	3.69	6	6.32	14	7.14	0.226	0.042
Death	22	3.53	5	5.26	11	5.61	0.409	0.409

[a] Remdesivir, Regkirona

Table 4. Severity depending on Paxlovid use among all patients at LTCFs

Category	Total	Severe illness or death				Death			
	Total	Total	%	Crude relative risk (95% CI)	Adjusted relative risk[a] (95% CI)	Total	%	Crude relative risk (95% CI)	Adjusted relative risk[a] (95% CI)
All	**819**	**37**	**4.52**			**33**	**4.03**		
No treatment	196	14	7.14	1.00(Ref)	1.00(Ref)	11	5.61	1.00 (Ref)	1.00 (Ref)
Paxlovid administration[b]	623	23	3.69	0.50 (0.25-0.99)	0.49 (0.24-0.98)	22	3.53	0.62 (0.29-1.29)	0.62 (0.29-1.32)

[a] Adjusted for sex, age, and history of vaccination

[b] Paxlovid administered

Table 5. Severity according to vaccination status among patients at five LTCFs

Category	Total	Severe illness or death				Death			
	Total	Total	%	Crude relative risk (95% CI)	Adjusted relative risk[a] (95% CI)	Total	%	Crude relative risk (95% CI)	Adjusted relative risk[a] (95% CI)
Total	**819**	**37**	**4.52**			**33**	**4.03**		
Unvaccinated	122	12	9.84	1.00(Ref)	1.00(Ref)	10	8.20	1.00(Ref)	1.00(Ref)
1dose	37	1	2.70	0.26 (0.03-2.03)	0.29 (0.04-2.33)	0	0.00	-	-
2doses	170	8	4.71	0.45 (0.18-1.14)	0.46 (0.18-1.19)	7	4.12	0.48 (0.18-1.30)	0.47 (0.17-1.29)
3doses	490	16	3.27	0.31 (0.14-0.67)	0.29 (0.13-0.64)	16	3.27	0.38 (0.17-0.86)	0.35 (0.15-0.79)

[a] Adjusted for sex, age, and therapeutic agent use history

between February 6 and April 2, 2022. Similar to the findings of previous studies, the effects of the third vaccination as well as the reduction in the rates of severe illness or death and fatality following the use of the therapeutic agents were confirmed [1,2]. Among patients at the LTCFs, the rates of severe illness or death and fatality were lower in the group that was administered with Paxlovid than in the non-administered group, and these rates were also lower in the group that completed the third vaccination than in the unvaccinated group.

In the Paxlovid clinical trial, Pfizer Inc. reported that the risk of hospitalization or death in patients who received the treatment was reduced by approximately 89%. When compared with the results of our study, differences were noted in the study population and outcome variables, as the clinical trial was conducted on adult patients with COVID-19 who were not hospitalized but had a risk of severe illness or death , with a monitoring period of 28 days for hospitalization and death, and Paxlovid was administered within 3 or 5 days from the onset of symptoms [1,2]. We conducted the study with patients of LTCFs and included all deaths that occurred 28 days after the patients being confirmed in the analysis, as the COVID-19 outbreak was ongoing at the time at the LTCFs. Therefore, deaths due to other possible causes were not excluded in our study and we could not correct for the underlying diseases and conditions at the time of administration that could have affected mortality, even among patients at the same LTCF. In addition, there is a difference in outcome variables, in that our study included severe illness or death and death. In order to compensate for these limitations, future studies should expand the monitoring period and study population in the future.

In the Republic of Korea, BA.2, a subtype of the Omicron variant, became the dominant variant during the 4th week of March, 2022 [11], and new variants, such as recombination, continue to occur. Therefore, risk assessment of the new variant and rapid analysis of the effects of countermeasures must be conducted in a timely manner to minimize damage. To achieve this, the quarantine authorities are periodically analyzing the incidence of COVID-19 according to period, death, and the effects of vaccination among domestic LTCFs while identifying the epidemiologic characteristics and therapeutic effects in cluster cases. As such, our study has significance as it confirmed the effects of vaccination and Paxlovid treatment in reducing the rate of severe illness or death and fatality using the results adjusted for key factors related to death, such as age and vaccination

history, at five domestic LTCFs that had similar characteristics, as a part of the COVID-19 Epidemiological and Pharmaceutical Intervention evaluation in Long-Term Care Facilities (COV-EPI evaluation in LTCF). Specifically, under the COV-EPI evaluation in LTCF, we plan to (1) assess excess deaths using the status of incidence according to period and death; 2) evaluate preparedness compared with baseline through survey of facilities, manpower, and incidence; 3) evaluate risk factors and the effects of vaccination through in-depth investigations of cluster cases; and 4) assess the effects of reducing the severity of illness in patients through assessment of the efficacy of therapeutics. The Omicron variant has a lower fatality rate but a higher incidence rate than the Delta variant [12], resulting in a rapid surge of confirmed cases in addition to the increasing number of severe cases and deaths. Although the efficacy of vaccination has been confirmed for the Omicron variant [13], analysis of the effects of countermeasures at facilities that are vulnerable to infections must be continued to minimize the damage through intensive management of high-risk groups.

In addition, as the use of Paxlovid requires sufficient consideration, Central Disease Control Headquarters is currently distributing a guide for using COVID-19 treatment methods for the proper use of therapeutic agents and instructing the medical staff to check the feasibility of use by identifying the underlying diseases and concomitant medications through interviews [14]. In the future, adverse events, such as side effects following the use of the therapeutic agents, should also be examined so that the results can be used as source data for establishing policies on quarantine measures.

① What was previously known?

According to the press release from Central Disease Control Headquarters on February 21, 2022, the condition of 96.7% of domestic subjects who initially received Paxlovid did not progress to severe illness and death.

② What is newly learned?

During the Omicron variant outbreak, the incidence as well as the effects of vaccination and therapeutic agents could be specifically evaluated and confirmed at LTCFs with cluster cases that had similar characteristics. In addition, the reduction in the rate of severe illness or death and fatality was confirmed upon administration of Paxlovid.

③ What are the implications?

By continuously analyzing the effects of key measures, such as vaccinations and the use of therapeutic agents, following the outbreaks at LTCFs and facilities with high risk for COVID-19, the data can be used as reference for preparing response systems for the resurgence of the outbreak of COVID-19 and other infectious diseases.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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