Clinical and Epidemiological Dynamics of COVID-19 Prevention and Treatment with special focus on Chronic Obstructive Pulmonary Disease Patients

Ph.D. thesis

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1. Introduction

The Health Commission of Wuhan, China, reported cases of pneumonia of unknown origin on December 31, 2019. It was announced that a new strain of coronavirus had been isolated, later named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2). The virus was confirmed as the cause of COVID-19 (Coronavirus Disease 2019), which was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. In Hungary, the first confirmed COVID-19 case was reported on March 4, 2020, followed by the first SARS-CoV-2-related death on March 15. From the early stages of the pandemic, it became evident that SARS-CoV-2 primarily and most severely affects the lungs. As the pandemic evolved, there was an ongoing urgent need to explore evidence-based approaches to fight the spreading of the virus, reduce hospital admissions, and improve patient treatment related outcomes.

As the pandemic progressed, extensive efforts were made to identify effective treatments against SARS-CoV-2. Numerous antiviral, anti-inflammatory, and supportive therapies were tested in large scale clinical trials and observational real-world studies. Among these, remdesivir, a nucleotide analog antiviral, emerged as one of the first approved treatments for COVID-19, showing promise in shortening recovery time in hospitalized patients. In addition to the therapeutic advancements, mass vaccination programs played a crucial role in controlling the spread of the virus. In Hungary, COVID-19 vaccines became publicly available in January 2021, leading to widespread immunization efforts. To assess vaccine effectiveness and long-term protection, extensive observational studies were initiated. One of the largest national-scale initiatives was the HUN-VE workgroup, established to evaluate the real-world impact of COVID-19 vaccines the whole population of Hungary.

2. Objectives

1. Evaluate the impact of a 5-day RDV treatment on 30- and 60-day all-cause mortality in hospitalized COVID-19 patients, focusing on those with more severe clinical conditions.

2. Identify patient subgroups benefiting most from RDV treatment. Determine which specific groups show the most significant benefits from RDV therapy in a hospital setting

3. Investigate if primary vaccination series and booster doses reduce the risk of hospital admission and 28-day all-cause mortality due to the SARS-CoV-2 delta VOC among the Hungarian elderly population.

4. Analyze VE against SARS-CoV-2 infection and hospitalization in COPD patients and in a matched non-COPD cohort and assess VE waning.

3. Methods

Observational cohort studies were conducted to assess the impact of COVID-19 treatments and vaccinations using real-world data from Hungary. Data were analyzed retrospectively. For the study investigating remdesivir (RDV) treatment the COVID registry of the Department of Pulmonology, Semmelweis university was used. In the two studies focusing on vaccine effectiveness (VE) a nationwide COVID registry was utilized which consisted of data regarding comorbidities, vaccinations, hospitalizations and death.

3.1. Study investigating RDV treatment in hospital setting

For this study the observational period was during the second and third waves of the pandemic (September 1, 2020 – April 30, 2021). The study population consisted of all inpatients hospitalized with COVID-19 at the department. Two propensity score-matched cohorts were compared: patients receiving additional RDV therapy versus a matched control group receiving only standard of care (SOC). The primary outcome was the effect of a 5-day RDV regimen on 30- and 60-day all-cause mortality. As a secondary objective multivariate analyses were performed to investigate the benefit of different patient groups (by sex, age, Charlson comorbidity index, etc.)

3.2. The populational studies focusing on VE

The second and third studies investigated VE in higher-risk populations. The first focused on the elderly (65 years or older) with the observational period between 23 August, 2021 and 5 December, 2021. The second on COPD patients and an exact matched non-COPD cohort, with a longer observational period between 23 August, 2021 and 5 January, 2022. Individuals with previous infection were excluded.

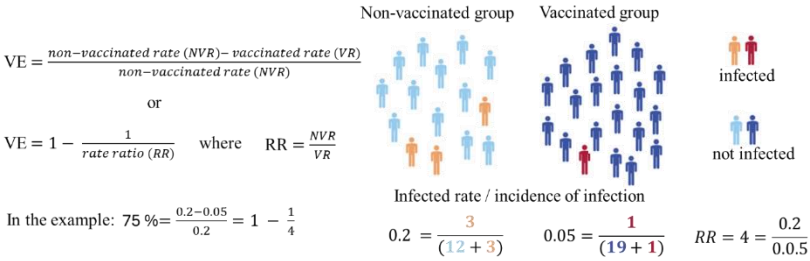
In both studies the main outcomes were VE against SARS-CoV-2 infection, and associated COVID-19 hospitalization. Primary and booster vaccinated populations were assessed respectively.

The first study additionally included VE against 28-day all-cause mortality as a secondary outcome and focused on the additional benefit of booster vaccinations.
While the second study investigated the change in VE over time after the last does of vaccine received. As a secondary analysis the difference of VE and its change was analyzed between the COPD and the matched non-COPD group.

3.3 Statistical Methods

For statistical analysis, propensity score matching (PSM) was applied in the first study to create comparable treatment groups. Differences between matched cohorts were assessed using independent t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed variables, and Chi-square tests for categorical data. To analyze time-to-event outcomes, Kaplan-Meier survival estimates were used for visualizing survival distributions, while Cox proportional hazards regression models were applied to evaluate risk factors and treatment effects, adjusting for potential confounders. VE was calculated from the relative reduction in infection and hospitalization rates among vaccinated individuals compared to unvaccinated controls (see Figure 1)

3.4 Figure 1: Calculation of Vaccine effectiveness with an example



4. Results

4.1 Findings related to the use of 5-day RDV therapy against COVID-19 in hospital setting

During the observation period, 974 patients were admitted to COVID-19 wards at Semmelweis University's Pulmonology Department. Excluding 19 early discharges, 417 received remdesivir. Propensity score matching (based on sex, age, baseline NEWS2, and Charlson comorbidity index (CCI) formed two cohorts (RDV and SOC) of 370 cases each, leaving 47 unmatched. Baseline characteristics and p-values are shown in Table 1

4.1.1. *Table 1 Baseline patient characteristics*

	Group RDV (n=370)	**Group SOC** (n=370)	**P**
Sex			
Female	151 (40.8%)	151 (40.8%)	1.000
Male	219 (59.2%)	219 (59.2%)	
VOC			
original	134 (36.2%)	237 (64.1%)	<0.001
alpha variant	236 (63.8%)	133 (35.9%)	
Age			
Mean (SD)	62.2 (14.63)	63.19 (15.92)	0.375
WHOS			
3 (Hospitalized)	0 (0.0%)	57 (15.4%)	<0.001
4 (Supplementary O2)	356 (96.2%)	306 (82.7%)	
5 (High-Flow O2)	14 (3.8%)	7 (1.9%)	

Continuation of Table 3.

	Group RDV (n=370)	**Group SOC** (n=370)	**P**
Charlson index			
1-3	209 (56.5%)	204 (55.1%)	
4-6	111 (30.0%)	114 (30.8%)	0.933
7-	50 (13.5%)	52 (14.1%)	
Comorbidities			
Malignancy	31 (8.4%)	44 (11.9%)	0.113
Hypertension	220 (59.5%)	217 (58.6%)	0.823
Diabetes	115 (31.1%)	81 (21.9%)	0.005
Heart failure	44 (11.9%)	55 (14.9%)	0.235
Asthma	34 (9.2%)	22 (5.9%)	0.095
COPD	54 (14.6%)	67 (18.1%)	0.196
Anemia	20 (5.4%)	44 (11.9%)	0.002
Parenchymal involvement on the initial CT (%)			
<15	89 (24.1%)	189 (51.1%)	
15-50	183 (49.5%)	107 (28.9%)	<0.001
50<	84 (22.7%)	47 (12.7%)	
missing	14 (3.8%)	27 (7.3%)	

More patients received RDV during the alpha VOC wave. Age, sex, and CCI were balanced between groups. The RDV group had more type 2 diabetes cases, while anemia was more common in Group SOC. Greater lung involvement on baseline CT and higher oxygen need in the RDV group supported the hypothesis of patients with more severe disease.

4.1.2. Table 2 Primary and Secondary outcomes

	Group RDV (n=370)	**Group SOC** (n=370)	**P**
Primary outcomes			
30-day all-cause mortality	49 (13.2%)	74 (20.0%)	0.014
60-day all-cause mortality	58 (15.7%)	84 (22.7%)	0.015
Secondary outcome			
Orientation of discharge			
Death	36 (9.7%)	60 (16.2%)	
Higher intensity care unit	38 (10.3%)	33 (8.9%)	0.031
Discharge from the hospital	296 (80.0%)	277 (74.9%)	

The RDV group had lower mortality and more escalations to intensive care, despite a more severe baseline profile.

4.1.3. Secondary Analysis

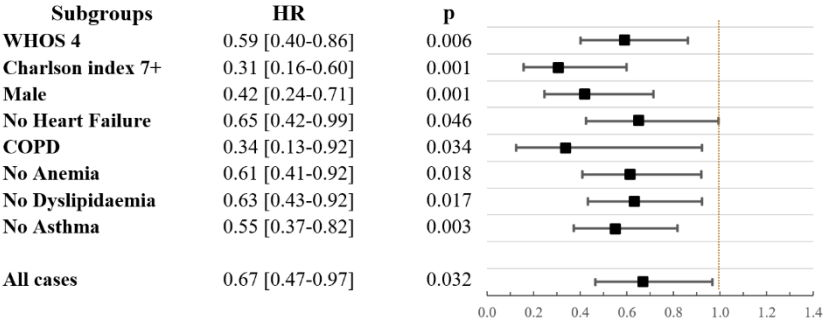
Beyond assessing RDV's general efficacy, the study aimed to identify patient subgroups benefiting most. Univariate analysis evaluated RDV's impact on in-hospital mortality across age, sex, WHOS, CCI, lung involvement, and comorbidities. Table 3 highlights subgroups with significant differences. The absence of statistical benefit in age groups may reflect imbalance or limited power.

RDV significantly reduced in-hospital mortality in WHOS 4 but not WHOS 5 patients. Benefit was seen in multimorbid (CCI ≥7), male, non-diabetic, and COPD patients. The effect in those without heart failure or anemia likely reflects cohort composition. Overall, RDV lowered mortality risk by around 30% with a relative risk (RR) of 0.69 [0.51 – 0.93].

4.1.4. *Table 3 RR by subgroups for in-hospital mortality*

Subgroups by		Mortality (n/n) RDV			Mortality (n/n) SOC			Relative Risk
WHOS								
4		53	/	356	79	/	306	**0.58 [0.42-0.79]**
5		5	/	14	2	/	7	1.25 [0.32-4.90]
Charlson index								
0-3		16	/	209	12	/	204	1.30 [0.63-2.68]
4-6		23	/	111	35	/	114	0.67 [0.43-1.07]
7≤		19	/	50	37	/	52	**0.53 [0.36-0.79]**
Sex								
Male		26	/	219	50	/	219	**0.52 [0.34-0.80]**
Female		32	/	151	34	/	151	0.94 [0.61-1.44]
Comorbidities								
Malignancy	+	10	/	31	21	/	44	0.68 [0.37-1.23]
	-	48	/	339	63	/	326	0.73 [0.52-1.03]
Hypertension	+	44	/	220	59	/	217	0.74 [0.52-1.04]
	-	14	/	150	25	/	153	0.57 [0.31-1.06]
Diabetes	+	22	/	115	24	/	81	0.65 [0.39-1.07]
	-	36	/	255	60	/	289	**0.68 [0.47-0.99]**
Heart Failure	+	18	/	44	25	/	55	0.90 [0.57-1.42]
	-	40	/	326	59	/	315	**0.66 [0.45-0.95]**
COPD	+	8	/	54	23	/	67	**0.43 [0.21-0.89]**
	-	50	/	316	61	/	303	0.79 [0.56-1.10]
Anemia	+	10	/	20	21	/	44	1.05 [0.61-1.79]
	-	48	/	350	63	/	326	**0.71 [0.50-1.00]**
All cases		58	/	370	84	/	370	**0.69 [0.51-0.93]**

4.1.4.*Figure 2 Hazard ratios of different characteristics for all-cause mortality in the hospitalized COVID-19 patients*



A multivariate logistic regression model was built using variables with significant group differences and those showing substantial distinctions in the univariate analysis. The final model included RDV therapy, sex, VOC, and comorbidities as binomial variables, with age and CCI as continuous variables. Lung involvement was excluded due to too much missing data. Hazard ratios for mortality were calculated for the total population and key subgroups. The analysis confirmed RDV's benefit. An HR of 0.67 could be interpreted as a 33% reduction in the hazard of in-hospital death among patients receiving RDV plus SOC compared to those who only received SOC, after adjusting for potential confounders

4.2 Results of the nationwide retrospective study investigating vaccination efficacy in the elderly population

At start, 769 477 men and 1 214 699 women were enrolled. After excluding previously infected individuals, the population was categorized as unvaccinated, primary vaccinated, or booster vaccinated. Those without a full regimen were excluded. Initially, there were 322,836 unvaccinated, 1,571,803 primary vaccinated, and 36,567 booster vaccinated individuals. By December 5, 2021, 41,093 infections were recorded (13,006 unvaccinated, 28,087 vaccinated), with hospitalizations in 5,087 unvaccinated and 6,056 vaccinated cases. Hospitalization-associated 28-day mortality was 0.420 in unvaccinated and 0.307 in vaccinated individuals. By the end of follow-up, 281,422 remained unvaccinated, 684,164 primary vaccinated, and 945,967 booster vaccinated. VE results are in Table 4.

4.2.1. *Table 4 Vaccine effectiveness against infection, hospitalization and 28-day all-cause mortality of primary and booster vaccinations compared to the unvaccinated without prior infections*

	VE against Infection	VE against COVID-19 hospitalization	VE against 28-day all-cause mortality
Primary vaccinated	**48.88 [47.75 - 49.97]**	**71.55 [70.41 - 72.65]**	**79.87 [78.48 - 81.17]**
Booster vaccinated	**82.95 [82.35 - 83.54]**	**92.71 [92.12 - 93.27]**	**94.24 [93.42 - 94.98]**

4.3 Results of the nationwide retrospective study focusing on vaccine effectiveness amongst COPD patients

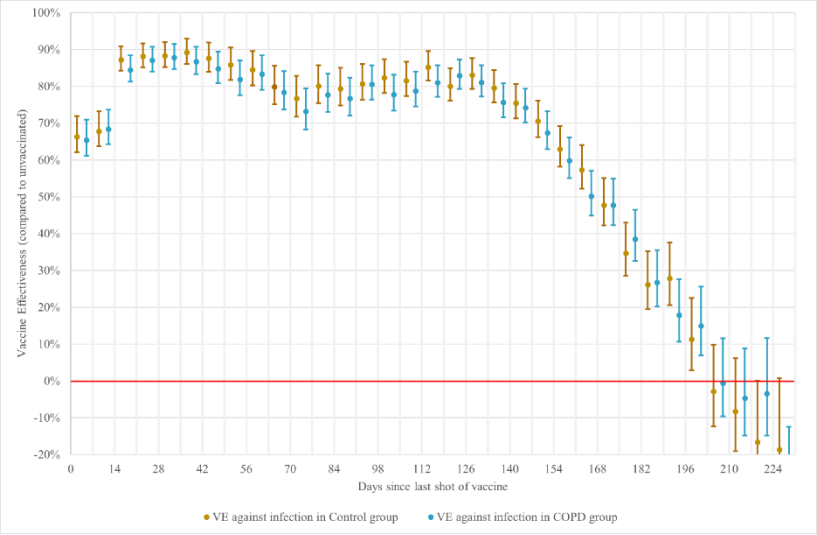
The study included COVID registry cases aged 18–100 with COPD. Of the 189 998 eligible patients, 186 981 were matched with non-COPD controls, forming a study population of 373 962. Both groups had a female/male ratio of 52.2 to 47.8 and similar average age (COPD: 66.67 ±12.66, non-COPD: 66.73 ±12.67 years, p>0.05). Matching included comorbidities, with Type 2 diabetes (23.5%), malignancy (15.1%), peripheral vascular disease (11.8%), heart failure (9.9%), and history of angina (14.7%) being the most common. Immunization status was also balanced in the two group, both groups encorporating a population of 7.3% with prior infection, 20.3% unvaccinated, 64.0% primary vaccinated, and 8.4% booster vaccinated. For the calculation of VE previously infected were excluded. Results of VE, with the average time since last dose, are shown in Table 5.

4.3.1.*Table 5 Mean VE against infection and COVID hospitalization during the delta VOC by groups*

	PRIMARY VACCINATED		BOOST VACCINATED	
	Matched	COPD	Matched	COPD
VE against Infection:	46.8% [43.5% - 49.9%]	45.6% [42.3% - 48.7%]	86.1% [84.7% - 87.5%]	83.6% [82.0% - 85.1%]
VE against Hospitalization:	72.1% [67.5% - 76.2%]	58.0% [52.6% - 63.0%]	92.6% [90.5% - 94.5%]	88.8% [86.3% - 91.1%]
Average time since last dose received (days)	240.67 ±57.82	239.06 ±59.79	69.3 ±45.16	69.89 ±45.74

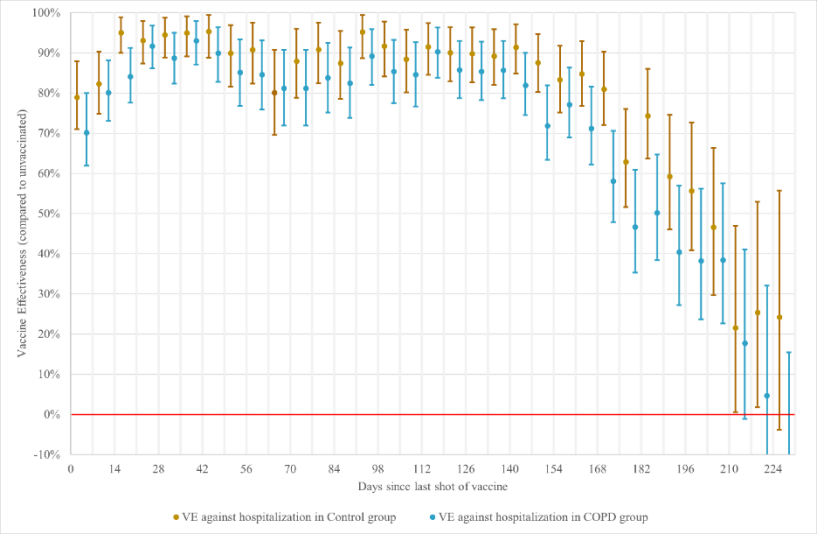
VE changes were assessed by calculating daily average risks for unvaccinated cases and risks by days since last vaccine dose for vaccinated individuals. A homogeneous risk distribution was assumed for unvaccinated cases, allowing VE calculation for a given time period using daily risks. Weekly VE changes are shown against infection in Figure 3 and against hospitalization in Figure 4

4.3.2. *Figure 3 VE against infection by 7-day time intervals since last given vaccination dose*



Initially, VE exceeded 80% against infection in both groups, indicating strong early protection. Over time, VE declined, with infection protection dropping below 50% by week 25 and approaching 0% by week 30.

4.3.3. *Figure 4 VE against hospitalization (B) by 7-day time intervals since last given vaccination dose*



VE against hospitalization were even better, exceeding 90%, and declined more gradually than infection but still neared 0% after 7 months. Higher-resolution analysis (5-day intervals) revealed a statistically significant decline, with VE decreasing by 3.5 percentage points per 5 days in controls and 4.5 in COPD cases. However, clinical significance remains questionable, as VE against hospitalization became negligible in both groups after 30 weeks.

5. Conclusions

This dissertation addresses key aspects of in hospital COVID-19 treatment and vaccine effectiveness, focusing on outcomes in specific patient groups.

1) In hospitalized COVID-19 patients needing supplemental oxygen 5-day RDV treatment reduced 30- and 60-day all-cause compared to those, only receiving SOC.
2) Particular benefit of the RDV treatment was observed in male, non-diabetic or elderly patients and those with multiple comorbidities.
3) Booster vaccinations among the Hungarian elderly population during the delta variant confirmed that booster doses significantly reduce the risk of hospitalization and 28-day all-cause mortality.
4) VE in a cohort of COPD patients to a matched non-COPD cohort no significant difference in the rate of VE decline between the two groups was identified. However, the length of meaningful protection in the COPD and the non-COPD group lasted for around 120-130 days, and significant effectiveness against hospitalization was lost roughly after 210 days in both groups.

6. Bibliography of the candidate's publications

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∑IF: 34,8 + 27,8 = 62,6