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ORIGINAL RESEARCH ARTICLE

Slower Recovery with Early Lopinavir/Ritonavir use in Pediatric COVID-19 Patients: A Retrospective Observational Study

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Abstract

Objectives There was initially insufficient understanding regarding suitable pharmacological treatment for pediatric Coronavirus Disease 2019 (COVID-19) patients. Lopinavir-ritonavir (LPV/r) was originally used for the treatment of Human Immunodeficiency Virus-1 (HIV-1) infection. It was also used in patients with severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS) with positive results. Nonetheless, results from recent randomized controlled trials and observational studies on COVID-19 patients were unfavorable. We sought to evaluate the clinical outcomes associated with early treatment with LPV/r for pediatric COVID-19 patients.

Study Design A total of 933 COVID-19 patients aged ≤ 18 years were admitted between 21 January 2020 and 31 January 2021 in Hong Kong. Exposure was receiving LPV/r within the first two days of admission. Time to clinical improvement, hospital discharge, seroconversion and hyperinflammatory syndrome, cumulative costs, and hospital length of stay were assessed. Multivariable Cox proportional hazard and linear models were performed to estimate hazard ratios (HR) and their 95% confidence intervals (CI) of time-to-event and continuous outcomes, respectively.

Results LPV/r users were associated with longer time to clinical improvement (HR 0.51, 95% CI 0.38–0.70; $p < 0.001$), hospital discharge (HR 0.51, 95% CI 0.38–0.70; $p < 0.001$) and seroconversion (HR 0.59, 95% CI 0.43–0.80; $p < 0.001$) when compared with controls. LPV/r users were also associated with prolonged hospital length of stay (6.99 days, 95% CI 6.23–7.76; $p < 0.001$) and higher costs at 30 days (US$11,709 vs US$8270; $p < 0.001$) as opposed to controls.

Conclusion Early treatment with LPV/r for pediatric COVID-19 patients was associated with longer time to clinical improvement. Our study advocates the recommendation against LPV/r use for pediatric patients across age groups.

1 Introduction

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected over 424 million people as of 23 February 2022 [1]. Although children with COVID-19 are found to exhibit milder clinical manifestations [2], rare but severe complications such as multisystem inflammatory syndrome in children (MIS-C) and infection-induced chilblains [3–5] may still pose a threat to the safety of these patients. MIS-C may eventually lead to or exacerbate hyperinflammatory syndrome and subsequent organ damage associated with severe COVID-19 [6, 7]. To date, there is still insufficient understanding regarding suitable pharmacological treatment for pediatric COVID-19 patients.

Together with the ongoing development of novel and specific pharmacological treatment, scientists are also trying to repurpose existing drugs which are approved for treatments of other infections owing to their known safety profile and pharmacology [8, 9]. One of the proposed medications is the cocktail therapy of lopinavir and ritonavir (LPV/r), which originally targeted Human Immunodeficiency Virus-1 (HIV-1). Lopinavir is the effective component which binds to the active site of the viral enzyme 3-chymotrypsin-like protease ($3CL^{pro}$), inhibiting RNA replication and viral proliferation

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Key Points

This territory-wide retrospective observational study aimed to study the clinical outcomes of pediatric COVID-19 patients receiving early treatment with lopinavir-ritonavir (LPV/r).

Treatment with LPV/r was associated with significantly longer time to clinical improvement, hospital discharge and longer hospital length of stay.

Our study advocates against the use of LPV/r in pediatric age groups.

of HIV-1 [10, 11]. Ritonavir is used to increase the half-life of lopinavir [11, 12]. In addition, LPV/r was selected as a potential candidate for COVID-19 treatment as it was shown to have in vitro activity against severe acute respiratory syndrome coronavirus (SARS-CoV) via the inhibition of $3CL^{pro}$ [11, 13, 14] and is active against Middle East respiratory syndrome-related coronavirus (MERS-CoV) [8, 13].

However, in the latest guidelines from National Institutes of Health (NIH) and World Health Organization (WHO), based on the results from randomized controlled trials (RCTs) in adult cohorts, administration of LPV/r is not recommended owing to the lack of significant clinical benefits [15, 16]. Three notable RCTs, the LOTUS trial in severe COVID-19 patients, the SOLIDARITY trial by the WHO consortium and the RECOVERY trial with only two pediatric patients out of 4859 patients all found that LPV/r was not associated with shorter time to clinical improvement and/or improved virologic outcomes [9, 17, 18]. However, contradicting results can be found in observational studies showing that LPV/r users are associated with slightly better outcomes [15, 19, 20].

With regards to the pharmacology of LPV/r on SARS-CoV-2, its efficacy in reducing SARS-CoV-2 reproduction was disputed as HIV-1 contains aspartic protease while SARS-CoV-2 contains cysteine protease [8, 21]. Additionally, as pediatric COVID-19 patients exhibit milder symptoms than adults, the potential benefits may not outweigh the possibility of adverse reactions [12, 18, 22, 23]. Moreover, results from the RCTs were inconclusive for the pediatric population as only two patients aged ≤ 18 years were included. Therefore, we conducted this retrospective observational study with the objective to evaluate the clinical outcomes associated with early treatment using LPV/r for children and adolescent patients with COVID-19.

2 Methods

2.1 Data Source and Study Population

A total of 993 pediatric (aged ≤18 years) patients diagnosed with COVID-19 (defined as positive SARS-CoV-2 viral nucleic acid detected using real-time reverse transcriptase-polymerase chain reaction [RT-PCR] assay, confirmed by the Department of Health Public Health Laboratory) admitted between 21 January 2020 and 31 January 2021 in Hong Kong were identified in our cohort. In Hong Kong, all confirmed COVID-19 cases were admitted for isolation purposes. Anonymous electronic medical records of patients diagnosed with COVID-19 were extracted from the Hong Kong Hospital Authority database.

With reference to the latest version of the Interim Drug Treatment Handbook for COVID-19 patients [24], oral LPV/r was additional to interferon-based regimens, and administered to infants (≥ 14 days of age), children and adolescents with a pediatric dose of lopinavir 300 mg/m^2 and ritonavir 75 mg/m^2 twice daily for 14 days. Treatment would be discontinued when patients encountered contraindications, serious adverse events, or fulfilled the requirement for hospital discharge [24, 25]. Patients had to meet both of the following two criteria for hospital discharge: (i) clinical conditions improved and afebrile; (ii) with two clinical specimens of the same type (e.g., respiratory or stool) tested negative for nucleic acid of SARS- CoV-2 by RT-PCR taken at least 24 hours apart. For patients who ever tested positive with a stool specimen, two negative stool specimens collected 24 hours apart and a period of 10 days since the onset of illness; or a positive test for SARS-CoV-2 antibody (i.e., anti-receptor binding domain [anti-RBD] immunoglobin G [IgG]/Abbott SARS-CoV-2 IgG) was necessary before release from isolation [25].

2.2 Treatment Exposure and Follow-Up Period

Exposure was defined as receiving LPV/r treatment within the first two days of admission. This reduces the possibility of selection bias from the difference in date of initiation of treatment among patients and immortal time bias from the difference between admission time and treatment initiation [26–28]. Patients who had initiated LPV/r after 2 days of hospital admission or did not receive LPV/r at all during hospitalization were classified as the non-exposure group. Patients were observed from the day of admission until in-hospital death, hospital discharge or data cut-off date of 30 April 2021, whichever came first.

2.3 Outcome Definition

WHO clinical progression scale provided a measure of severity from 0 (non-hospitalized, non-infected case) to 10 (dead) for COVID-19 patients [29]. Our primary outcome was defined as time to clinical improvement with regards to the WHO progression scale by at least 1 point. Secondary outcomes were hospital discharge; seroconversion (a composite outcome consisting of having a cycle threshold [Ct] value of ≥ 30 or positive IgG antibody); hyperinflammatory syndrome; hospital length of stay; and cumulative medical cost. The cumulative medical costs were calculated based on the unit cost of medication and healthcare services sourced from the Hong Kong SAR Government Gazette and Hospital Authority (Supplementary Table 1, see electronic supplementary material [ESM]).

2.4 Data Analysis

Descriptive statistics of baseline characteristics between the exposure and non-exposure groups were presented with mean and standard deviation for continuous variables, and count and proportion of categorical variables.

Baseline covariates of patients included duration of LPV/r use and time from admission to LPV/r initiation, age, sex, pre-existing comorbidities, long-term medication use, laboratory parameters, clinical severity measure by the WHO clinical progression scale, and in-hospital pharmacological and non-pharmacological treatments. Pre-existing comorbidities included ADHD, allergic rhinitis, asthma, autism, chronic heart disease, chronic kidney disease, depression, diabetes mellitus, glucose-6-phosphate dehydrogenase (G6PD) deficiency, hypertension, Kawasaki disease, liver disease, malignancy, obesity, vitamin D deficiency, and Charlson's Comorbidity Index (CCI). Concomitant medications included anticoagulants, antiplatelets, nonsteroidal anti-inflammatory drugs, and insulin. Criteria for COVID-19-associated hyperinflammatory syndrome [30] included macrophage activation, hematological dysfunction, coagulopathy, and hepatic inflammation. Laboratory parameters included were white blood cell, neutrophil, lymphocyte, platelet, lactate dehydrogenase (LDH), creatine kinase, total bilirubin, C-reactive protein (CRP), Ct value, estimated glomerular filtration rate (eGFR), alkaline phosphatase (ALP), alanine transaminase (ALT), and hemoglobin.

To minimize outcome bias due to discrepancy in baseline characteristics between the exposure and control, Inverse Probability of Treatment Weights (IPTW) using the propensity score was applied to balance covariates across treatment groups [31]. A logistic regression model was performed to calculate the propensity scores of each patient in the group and included the aforementioned covariates. After the propensity-score weighting, the balance of baseline covariates between the treatment groups was further assessed using the standardized mean difference (SMD). SMDs of ≤ 0.2 implied sufficient balance between the groups. Missing baseline covariates were addressed with Multiple Imputation by Chained Equations (MICE) and each missing value of laboratory data was imputed 20 times using other variables that may impact the outcome. Supplementary Table 2 lists the data completion rates of baseline characteristics before multiple imputation (see ESM).

Multivariable Cox proportional hazard models were performed to estimate standard hazard ratios (HR) and their 95% confidence intervals (CI) of event outcomes. In addition, time from the index date of admission to hospital discharge, and cumulative direct medical costs incurred between the groups were compared using the linear regression model following the IPTW using the propensity scores for COVID-19 survivors.

Subgroup analyses were conducted on the following: age (0–4, 5–12, and 13–18 years old), sex, and recipient of interferon-β-1b. Sensitivity analyses were also performed on three scenarios: extending the follow-up period to beyond hospital discharge; limiting the follow-up period to a maximum of 90 days; and performing the complete-case approach with the IPTW.

All statistical analyses were performed using STATA Version 16 (StataCorp LP, College Station, TX, USA). p values < 0.05 were considered statistically significant.

3 Results

3.1 Patient Cohort

Among a total of 933 patients aged ≤ 18 years who were admitted with COVID-19 between 21 January 2020 and 31 January 2021 in Hong Kong SAR, China, LPV/r was prescribed in 49 patients for its anti-viral properties. After multiple imputation and propensity score weighting, all the SMDs except for no oxygen therapy were balanced between groups with SMDs ≤ 0.2. The majority of the patients were admitted without oxygen therapy (score 4; 98%). 12 patients in the LPV/r group were also co-administered with interferon-β-1b within two days of admission. Baseline characteristics of the patients and their respective SMDs after multiple imputation and propensity score weighting are summarized in Table 1.

Overall, the median follow-up period of this patient cohort was 14 days and 29,454 person-days. The incidence rates of outcome events by exposure and control groups are presented in Supplementary Table 3 (see ESM).

Table 1 Baseline characteristics of hospitalized children and adolescent patients with COVID-19 in early treatment with lopinavir/ritonavir, control, and overall groups after multiple imputation

Baseline characteristics	Before weighting							After weighting				
	Overall (n = 933)		Lopinavir/ritonavir (n = 49)		Control (n = 884)		SMD	Lopinavir/ritonavir (n = 49)		Control (n = 884)		SMD
	N/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD		*N*/mean	%/SD	*N*/mean	%/SD	
Age, years[†]	10.0	5.9	11.5	6.8	9.9	5.8	0.28	10.5	6.6	9.9	5.8	0.10
0–4	234	(25.1%)	12	(24.5%)	222	(25.1%)		(26.3%)		(24.9%)		
5–12	327	(35.1%)	12	(24.5%)	315	(35.6%)		(29.6%)		(35.3%)		
13–18	372	(39.9%)	25	(51.0%)	347	(39.3%)		(44.1%)		(39.7%)		
Sex							0.11					0.08
Male	505	(54.1%)	24	(49.0%)	481	(54.4%)		(50.3%)		(54.3%)		
Female	428	(45.9%)	25	(51.0%)	403	(45.6%)		(49.7%)		(45.7%)		
Pre-existing comorbidities												
Charlson's Index[†,‡]	1.0	0.2	1.0	0.2	1.0	0.2	0.04	1.0	0.1	1.0	0.2	0.06
ADHD	4	(0.4%)	0	(0.0%)	4	(0.5%)	0.10	(0.0%)		(0.4%)		0.09
Allergic rhinitis	8	(0.9%)	0	(0.0%)	8	(0.9%)	0.14	(0.0%)		(0.9%)		0.13
Asthma	14	(1.5%)	1	(2.0%)	13	(1.5%)	0.04	(0.2%)		(1.5%)		0.15
Autism	4	(0.4%)	1	(2.0%)	3	(0.3%)	0.16	(1.8%)		(0.3%)		0.14
Chronic heart disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Chronic kidney disease	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Depression	3	(0.3%)	0	(0.0%)	3	(0.3%)	0.08	(0.0%)		(0.3%)		0.08
Diabetes mellitus	1	(0.1%)	0	(0.0%)	1	(0.1%)	0.05	(0.0%)		(0.1%)		0.05
G6PD deficiency	4	(0.4%)	0	(0.0%)	4	(0.5%)	0.10	(0.0%)		(0.4%)		0.09
Hypertension	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Kawasaki disease	1	(0.1%)	0	(0.0%)	1	(0.1%)	0.05	(0.0%)		(0.1%)		0.05
Liver disease	5	(0.5%)	0	(0.0%)	5	(0.6%)	0.11	(0.0%)		(0.6%)		0.11
Malignancy	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Obesity	18	(1.9%)	0	(0.0%)	18	(2.0%)	0.20	(0.0%)		(2.0%)		0.20
Vitamin D deficiency	2	(0.2%)	0	(0.0%)	2	(0.2%)	0.07	(0.0%)		(0.2%)		0.07
Long-term medications												
Anticoagulant	2	(0.2%)	0	(0.0%)	2	(0.2%)	0.07	(0.0%)		(0.4%)		0.09
NSAID	8	(0.9%)	0	(0.0%)	8	(0.9%)	0.14	(0.0%)		(0.9%)		0.13
Insulin	1	(0.1%)	0	(0.0%)	1	(0.1%)	0.05	(0.0%)		(0.1%)		0.05
Concomitant drug use within 2 days of admission												
Lopinavir/ritonavir	49	(5.3%)	49	(100.0%)	0	(0.0%)	NA	(100.0%)		(0.0%)		NA
Time from admission to lopinavir/ritonavir, days[†]	0.8	0.6	0.8	0.6	NA	NA	NA	0.8	0.6	NA	NA	NA
Duration of use of lopinavir/ritonavir, days[†]	6.0	4.3	6.2	4.3	NA	NA	NA	6.6	4.2	NA	NA	NA
Remdesivir	1	(0.1%)	0	(0.0%)	1	(0.1%)	0.05	(0.0%)		(0.1%)		0.05
Dexamethasone	1	(0.1%)	0	(0.0%)	1	(0.1%)	0.05	(0.0%)		(0.1%)		0.05
Tocilizumab	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Interferon-β-1b	17	(1.8%)	12	(24.5%)	5	(0.6%)	0.78	(2.0%)		(1.6%)		0.03

Table 1 (continued)

Baseline characteristics	Before weighting							After weighting				
	Overall ($n = 933$)		Lopinavir/ritonavir ($n = 49$)		Control ($n = 884$)		SMD	Lopinavir/ritonavir ($n = 49$)		Control ($n = 884$)		SMD
	N/mean	%/SD	*N*/mean	%/SD	*N*/mean	%/SD		*N*/mean	%/SD	*N*/mean	%/SD	
ECMO	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Dialysis	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
ICU admission	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Admission via emergency department	321	(34.4%)	23	(46.9%)	298	(33.7%)	0.27	(33.9%)		(34.3%)		0.01
Clinical severity on admission by WHO Clinical Progression Scale												
Score (range 0–10)[†]	4.0	0.3	4.0	0.0	4.0	0.3	0.01	4.0	0.0	4.0	0.3	0.01
No oxygen therapy (Score 4)	914	(98.0%)	49	(100.0%)	865	(97.9%)		(100.0%)		(97.9%)		
Supplemental oxygen without ventilation (Score 5–6)	19	(2.0%)	0	(0.0%)	19	(2.2%)		(0.0%)		(2.1%)		
Mechanical ventilation (Score 7–9)	0	(0.0%)	0	(0.0%)	0	(0.0%)		(0.0%)		(0.0%)		
Macrophage activation	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Haematological dysfunction	1	(0.1%)	1	(2.0%)	0	(0.0%)	0.20	(1.4%)		(0.0%)		0.17
Coagulopathy	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Hepatic inflammation	0	(0.0%)	0	(0.0%)	0	(0.0%)	NA	(0.0%)		(0.0%)		NA
Hyperinflammatory syndrome	1	(0.1%)	1	(2.0%)	0	(0.0%)	0.20	(1.4%)		(0.0%)		0.17
Laboratory parameters [normal range] †												
White blood cell, $\times 10^9$/L [3.7–9.2 $\times 10^9$/L]	6.4	2.4	6.2	2.2	6.4	2.4	0.06	6.0	2.4	6.4	2.4	0.14
Neutrophil, $\times 10^9$/L [1.7–5.8 $\times 10^9$/L]	3.2	1.7	3.4	1.7	3.2	1.7	0.14	3.1	1.6	3.1	1.7	0.01
Lymphocyte, $\times 10^9$/L [1.0–3.1 $\times 10^9$/L]	2.4	1.5	2.2	1.3	2.4	1.5	0.12	2.3	1.3	2.4	1.5	0.07
Platelet, $\times 10^9$/L [145–370 $\times$ 109/L]	270.2	78.7	275.8	89.6	269.9	78.1	0.07	259.3	82.3	270.0	79.0	0.13
Lactate dehydrogenase, U/L [110–210 U/L]	221.0	65.3	207.6	54.9	221.8	65.8	0.22	213.2	55.5	221.2	65.6	0.12
Creatine kinase, U/L [26–192 U/L]	127.2	214.7	104.7	76.5	128.4	219.8	0.11	109.8	84.7	127.3	218.2	0.08
Total bilirubin, µmol/L [5–27 µmol/L]	8.3	17.7	7.3	4.2	8.4	18.1	0.06	6.7	4.2	8.3	17.9	0.09
C-reactive protein, mg/L [< 5 mg/L]	2.7	12.5	3.0	6.0	2.7	12.8	0.02	1.8	3.3	2.7	12.6	0.08
Cycle threshold value, cycle	24.5	8.1	23.4	7.7	24.6	8.2	0.15	23.9	7.4	24.6	8.2	0.08
eGFR, mL/min/1.73m^2 [> 90 mL/min/1.73m^2]	336.9	495.3	302.7	234.8	338.8	505.9	0.07	313.5	218.5	337.0	501.7	0.05
ALP, U/L [30–120 U/L]	181.0	93.2	156.8	106.1	182.4	92.3	0.27	166.8	99.8	181.3	92.6	0.16
ALT, U/L [< 46.5 U/L]	23.2	24.3	23.2	20.7	23.2	24.5	0.00	19.2	9.5	23.2	24.4	0.17
Hemoglobin, g/dL [13.4–17.1 g/dL]	13.3	1.5	13.3	1.7	13.4	1.5	0.05	13.3	1.4	13.3	1.5	0.04

ACEI angiotensin converting enzyme inhibitor, *ADHD* attention-deficit/hyperactivity disorder, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *ARB* angiotensin receptor blockers, *AST* aspartate aminotransferase, *ECMO* extracorporeal membrane oxygenation, *eGFR* estimated glomerular filtration rate, *G6PD* glucose-6-phosphate dehydrogenase, *ICU* Intensive Care Unit, *NA* not applicable, *NSAID* nonsteroidal anti-inflammatory drugs, *SD* standard deviation, *SMD* standardized mean difference, *WHO* World Health Organization

[†]Age, Charlson's Index, clinical severity, and laboratory parameters on admission are presented in mean ± SD

[‡]The calculation of Charlson's Index does not include Acquired Immune Deficiency Syndrome (AIDS) SMD of < 0.2 indicates covariate balance between early treatment with lopinavir/ritonavir and control groups

Table 2 Comparison of clinical improvement on WHO clinical progression scale, hospital discharge, seroconversion, and hyperinflammatory syndrome outcomes between the two groups

	Before weighting		After weighting		
	Lopinavir/ritonavir	Control	Lopinavir/ritonavir vs control		
	% (*N*)	% (*N*)	HR†	95% CI	*p* value
Primary outcome					
Clinical improvement on WHO clinical progression scale by ≥ 1 point	100.0% (49)	100.0% (884)	0.51	(0.38–0.70)	< 0.001
Secondary outcome					
Hospital discharge	100% (49)	98.6% (884)	0.51	(0.38–0.70)	< 0.001
Seroconversion (Ct value ≥ 30 or IgG positive)	95.6% (45)	95.0% (847)	0.59	(0.43–0.80)	< 0.001
Hyperinflammatory syndrome	2.1% (48)	1.6% (884)	3.54	(0.49–25.38)	0.208

CI confidence interval, *Ct* cycle threshold, *HR* hazard ratio, *IgG* Immunoglobulin G, *WHO* World Health Organization

†HR >1 (or <1) indicates early treatment with lopinavir/ritonavir was associated with early (late) clinical improvement, hospital discharge, or seroconversion, or higher (lower) risk of hyperinflammatory syndrome, compared with the control group

3.2 Clinical Improvement, Hospital Discharge, and Seroconversion

Early treatment with LPV/r was associated with significantly longer time to clinical improvement as indicated by at least one-point score reduction on the WHO clinical progression scale (HR 0.51, 95% CI 0.38–0.70; $p < 0.001$), hospital discharge (HR 0.51, 95% CI 0.38–0.70; $p < 0.001$), seroconversion (HR 0.59, 95% CI 0.43–0.80; $p < 0.001$), and a longer hospital length of stay (6.99 days, 95% CI 6.23–7.76) when compared with controls (Table 2). Subgroup analyses, presented in Supplementary Table 4 (see ESM), reveal that significant overall results are mainly contributed by patients aged 13–18 years old (clinical improvement, HR 0.39, 95% CI 0.26–0.60, $p < 0.001$; hospital discharge, HR 0.39, 95% CI 0.26–0.60, $p < 0.001$; seroconversion, HR 0.47, 95% CI 0.31–0.71, $p < 0.001$), while sensitivity analyses (Supplementary Table 5, see ESM) are in line with the results for the main analysis. Figure 1a, b illustrate the clinical severity status and changes in WHO clinical progression scale score of LPV/r users and their control counterparts over the follow-up period (days 7, 15, and 30), respectively. A lower proportion of patients on LPV/r were discharged on days 7, 15 and 30 (Fig. 1a) and LPV/r patients had higher scores on day 15 ($p < 0.001$) and day 30 ($p < 0.001$) (Fig. 1b) than those in the control group. Kaplan-Meier survival curves for having at least 1-point clinical improvement on the WHO clinical progression scale, and seroconversion, are shown in Fig. 2.

3.3 Hyperinflammatory Syndrome

Insignificant outcomes for hyperinflammatory syndrome (HR 3.54, 95% CI 0.49–25.38) were produced for the main analysis, shown in Table 2. Sensitivity analyses were in line with the main analysis. However, the wide CI values indicate that interpretation should be conducted with caution.

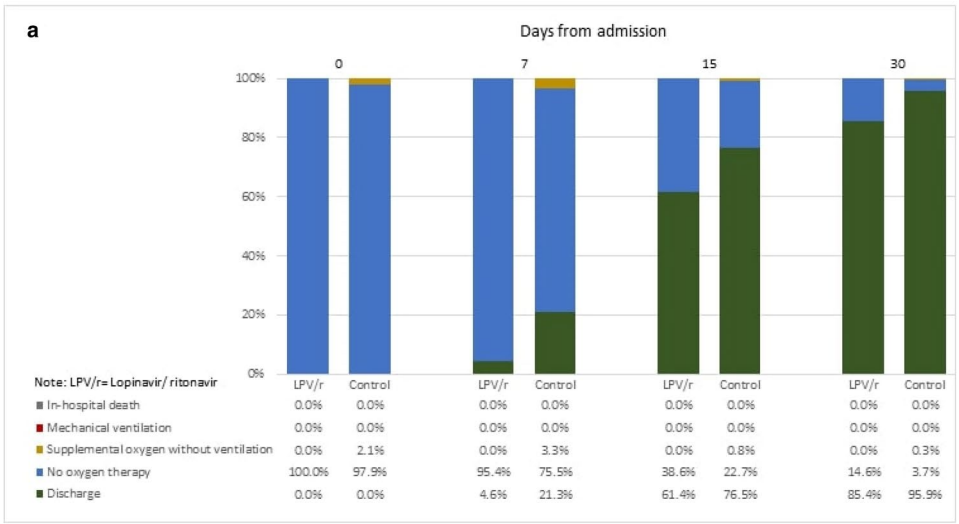
3.4 Cumulative Direct Medical Costs

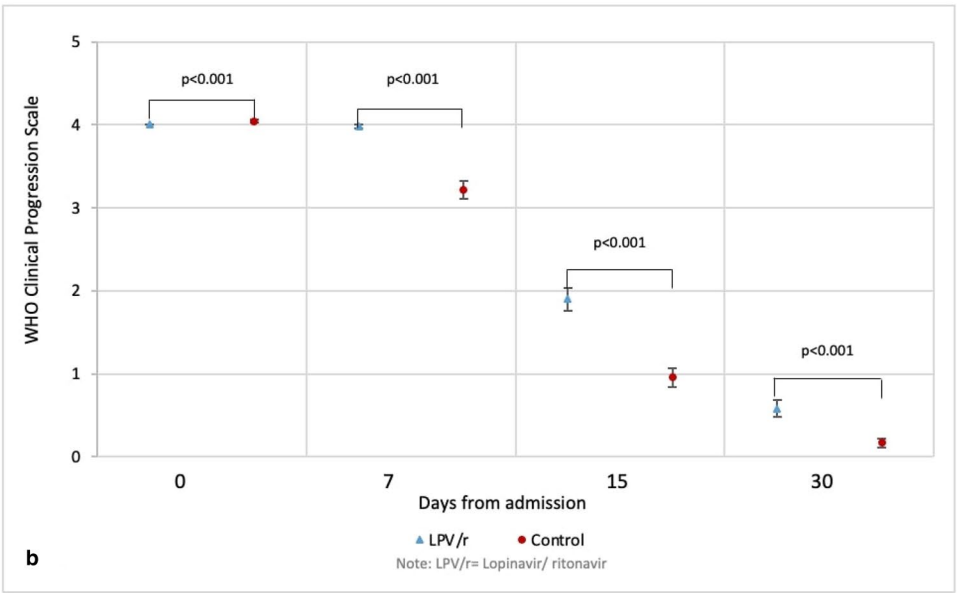
Figure 1c displays the average cumulative direct medical costs incurred by patients in the exposure and control groups over the 30-day follow-up period. LPV/r users incurred progressively higher costs from index date (US$744 vs US$718, $p < 0.001$) to day 30 (US$11,709 vs US$8270, $p < 0.001$) compared with their control counterparts.

4 Discussion

This study has identified a significant association between LPV/r use and longer time to clinical improvement, hospital discharge, seroconversion as well as hospital length of stay for hospitalized mild pediatric COVID-19 cases with early LPV/r use within 2 days of admission. Hyperinflammatory syndrome was implied, and LPV/r use was associated with significantly higher cumulative medical costs than control.

It is well documented that pediatric patients generally exhibit mild symptoms or are asymptomatic when infected and tend to have fewer complications [3–5, 32]. An epidemiological study carried out by Dong et al. reported proportions of severe cases do not exceed 11% per age group for pediatric patients aged ≤ 18 years [33], while a systematic review by de Souza et al. reported 82.3% cases were mild to moderate [34]. Results from our cohort supported this observation, with 98% of the cohort admitted with mild-to-moderate COVID-19; the need for mechanical ventilation or mortality were not reported. Additionally, biochemical profiles for pediatric patients were investigated by Bourgeois et al. in an international analysis of electronic health records,





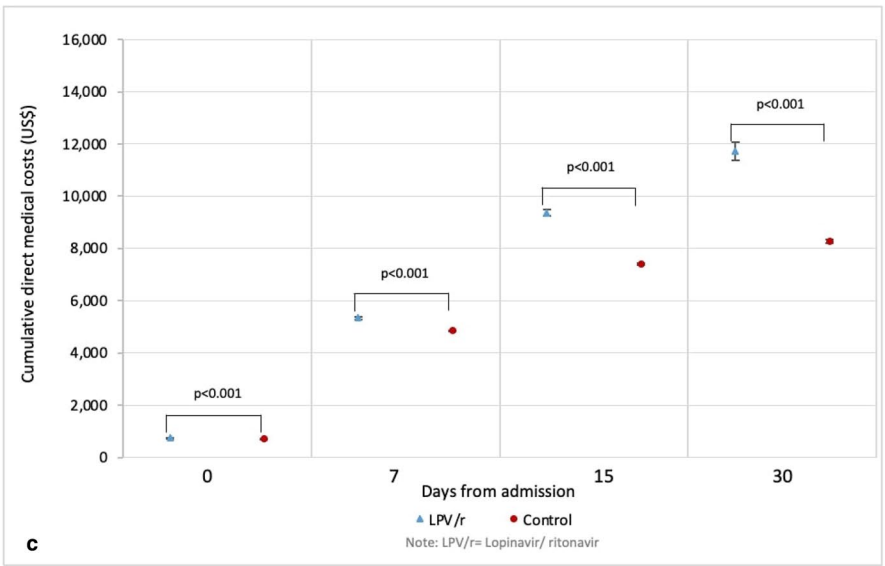


Fig. 1 Comparisons of **a** clinical status measured by WHO Clinical Progression Scale score, **b** WHO Clinical Progression Scale score, and **c** cumulative direct medical costs by days from baseline to day 30 between patients receiving early treatment with lopinavir/ritonavir and control group

showing elevated CRP and LDH, on average, with coagulation abnormalities (D-dimer) yet normal neutrophil and lymphocyte levels [35]. These results are in line with systematic reviews carried out by de Souza et al. and Henry et al., which investigated differences in laboratory parameters between mild and severe pediatric patients as well as those of adults and pediatric patients [34, 36]. Such trends are also in line with our analysis observing elevated LDH but normal values for neutrophil and lymphocyte count at baseline.

LPV/r was considered as one of the candidates for COVID-19 treatment owing to its efficacy exhibited in HIV and potentially in MERS and SARS treatment [37–40]. Early on during the pandemic in Hong Kong, LPV/r was used as a part of triple therapy for early treatment of COVID-19, consisting of interferon-β-1b and LPV/r ± ribavirin [41]. Additional to LPV/r, dexamethasone and remdesivir have been commonly used in patients with mild-to-moderate symptoms [42–45].

Consequently, in vitro studies were carried out and showed that lopinavir displays inhibitory activities against SARS-CoV-2. $3CL^{pro}$ of SARS-CoV-2 was soon realized to be 96.1% identical to the $3CL^{pro}$ of SARS-CoV-1 [46]. The association between LPV/r use and clinical improvement remains controversial in observational studies usually involving adult patients. A case study in Korea reported viral load reduction and improved clinical symptoms [19], and several other studies pointed towards reduced time to negative SARS-CoV-2 RNA detection, faster resolution of fever, and the effectiveness of LPV in disease recovery [20, 47]. In contrast, a nationwide comparative analysis [48] and the only observational study examining effects of LPV/r on outcomes of hospital length of stay and viral shedding time for mild-to-moderate pediatric COVID-19 patients (LPV/r users $n = 23$ vs control $n = 92$) demonstrated longer hospital length of stay and time to negative nasopharyngeal swab test. This observational study was comparable with our study; it had a similar cohort in terms of disease severity and results from both studies shared similarities with poorer outcomes for pediatric LPV/r users.

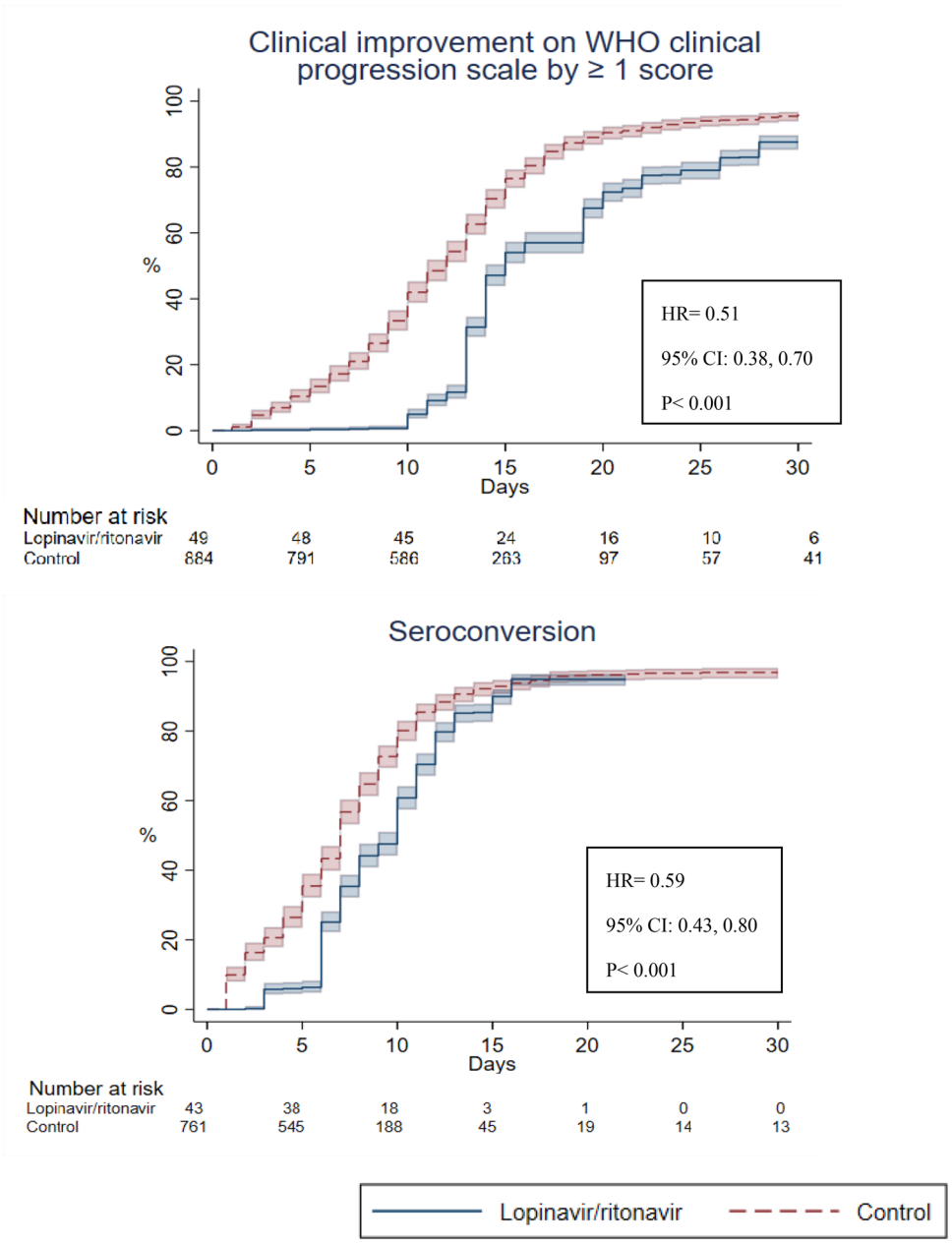
While there was successful main protease inhibition of SARS-CoV-2 in vitro, evidence is inconclusive on clinical improvement in COVID-19 patients. It was found that LPV can bind to the main protease according to computer simulation and exert an inhibitory effect with half maximal effective concentration (EC_{50}) of 16.4 μmol, with successful inhibition on its cytopathic activity [49]. Lopinavir consistently has a weaker inhibitory effect with SARS-CoV-1 and MERS coronavirus (MERS-CoV) when compared with HIV-1, despite successful inhibition on viral replication of all four viruses [49, 50]. However, such inhibition might not be translated to COVID-19 patients as there have been inconclusive results in clinical improvement and viral loads in the adult cohorts. This indicates a difference between in vivo and in vitro environments; for example, most in vitro methods employ bovine serum in the assay medium [51]. Experiments suggested that lopinavir has a plasma protein binding of > 98%, lowering the plasma concentration of free drug [52]. Therefore, it was hypothesized that lack of plasma protein binding in vitro might overestimate the protease inhibitory effect, explaining lack of improvement as illustrated in our cohort.

A mechanistic explanation for worse outcomes has been hypothesized to be infection-induced cytokine release and oxidative stress suppressing cytochrome P450 enzyme activity and associated gene expression [53, 54]. Moreover, ritonavir's mechanism of action is CYP3A4 inhibition for lopinavir's half-life extension [11]; hence, hepatic burden may be exacerbated by both inflammation and LPV/r-associated potential hepatotoxicity [55]. Our results may support this theory as elevated levels of ALP, one of the implied elevated biomarkers in COVID-19 patients with hepatocellular injury [56], were reported at baseline, perhaps indicating pre-admission SARS-CoV-2 infection-induced hepatic injury, hence potentially raising the risk for hyperinflammatory syndrome as an outcome [53, 54]. Despite this, our results for hyperinflammatory syndrome trend towards higher risk but have a wide CI, possibly due to the small number of events. These results should therefore be interpreted with caution [56].

Prior to our study, the LOTUS trial including severe adult COVID-19 patients reported that LPV/r use was not associated with time to clinical improvement and was associated with increased adverse events instead. The RECOVERY trial, which included two pediatric patients after removing the age restriction (> 18 years) from 9 May 2020, has also reported a lack of association between LPV/r use and reduction of 28-day mortality, length of stay, and risk of progressing to invasive mechanical ventilation. The SOLIDARITY trial, with an unknown number of pediatric patients, reported results that are in line with both aforementioned trials, with a joint mortality rate ratio of 1.01 (95% CI 0.91–1.13) [9, 17, 18]. Both the WHO and NIH have discouraged the use of LPV/r for COVID-19 patients owing to its lack of efficacy, with the WHO consulting seven trials containing 7429 adult participants. Hence, pediatric patients might be underrepresented by current guidelines [15, 16]. Therefore, a notable strength of our study is that it contributes to the knowledge on effectiveness of LPV/r for pediatric patients and advocates the recommendation against LPV/r use for pediatric patients across age groups.

Our study is not without its limitations. Firstly, most patients were admitted without oxygen therapy, hence this study could not account for outcomes for severe pediatric COVID-19 cases. Secondly, the exposure population of this study is very limited ($n = 49$), which could introduce biased results as well as difficulties in yielding significant

Fig. 2 Kaplan-Meier survival curves for at least 1-point clinical improvement on WHO clinical progression scale, and seroconversion



results when comparing clinical outcomes across different age groups in subgroup analysis. Thirdly, SARS-CoV-2 viral loads were represented by Ct values in this study. Despite a good correlation, direct quantitative measurements of viral loads would have been preferable if available. Fourthly, our study could not investigate the use of LPV/r with other concomitant drugs for COVID-19 due to limited use in this cohort. Lastly, residual confounding may not be fully removed due to the observational nature of this study.

5 Conclusion

Among pediatric patients hospitalized with COVID-19, LPV/r use was associated with longer time to clinical improvement, hospital discharge, seroconversion, and hospital length of stay. A trend towards higher risk of hyperinflammatory syndrome and significantly higher cumulative medical costs than controls was observed. Accordingly, it is advised that clinicians resort to other treatment modalities

for pediatric COVID-19 cases; however, studies with longer follow-up periods and larger sample sizes of different clinical severities are necessary to further elucidate the potential role of LPV/r in the deterioration of clinical outcomes.

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Declarations

Author Contributors' Statement Dr CKHW conceptualized, designed the study, reviewed and revised the manuscript. Mr MCHL, Miss ACYK and Miss AYCL searched literatures, drafted the initial manuscript, reviewed and revised the manuscript. Miss KTKL reviewed and revised the manuscript. Mr ICHA and Mr SHC conducted data analysis, reviewed and revised the manuscript. Miss XX, Mr EHYL and Prof. BJC reviewed and revised the manuscript. Dr MYWK provided clinical input.

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Conflict of interest Dr Wong, Mr Low, Miss Kwok, Miss Lui, Miss Lau, Mr Au, Mr Chung, Miss Xiong, Mr Lau, Prof. Cowling and Dr Kwan have no conflicts of interest to disclose.

Ethical approval and informed consent The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (Reference No. UW 20-493). Given the extraordinary nature of the COVID-19 pandemic, individual patient informed consent was not required for this retrospective cohort study using anonymized data.

Data sharing statement The data that support the findings of this study were provided by the Hong Kong Hospital Authority. Restrictions apply to the availability of these data, which were used under license for this study. Deidentified individual participant data will not be made available.

Availability of Data and Material The data that supported the findings of this study were provided by the Hong Kong Hospital Authority but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Hong Kong Hospital Authority.

Consent for publication All authors contributed to the interpretation of the analysis, critically reviewed and revised the manuscript, and approved the final manuscript as submitted. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Code availability All statistical analyses were performed using STATA Version 16 (StataCorp LP, College Station, TX).

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