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Research Paper

Clinical outcomes of different therapeutic options for COVID-19 in two Chinese case cohorts: A propensity-score analysis

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ABSTRACT

Background: The timing of administration of agents and use of combination treatments in COVID-19 remain unclear. We assessed the effectiveness of therapeutics in cohorts in Hong Kong SAR and Anhui, China.
Methods: We conducted propensity-score analysis of 4771 symptomatic patients from Hong Kong between 21st January and 6th December 2020, and 648 symptomatic patients from Anhui between 1st January and 27th February 2020. We censored all observations as at 13st December 2020. Time from hospital admission to discharge, and composite outcome of death, invasive mechanical ventilation or intensive care unit admission across 1) all therapeutic options including lopinavir-ritonavir, ribavirin, umifenovir, interferon-alpha-2b, interferon-beta-1b, corticosteroids, antibiotics, and Chinese medicines, and 2) four interferon-beta-1b combination treatment groups were investigated.
Findings: Interferon-beta-1b was associated with an improved composite outcome (OR=0.55, 95%CI 0.38, 0.80) and earlier discharge (−8.8 days, 95%CI −9.7, −7.9) compared to those not administered interferon-beta-1b. Oral ribavirin initiated within 7 days from onset was associated with lower risk of the composite outcome in Hong Kong (OR=0.51, 95%CI 0.29, 0.90). Lopinavir-ritonavir, intravenous ribavirin, umifenovir, corticosteroids, interferon-alpha-2b, antibiotics or Chinese medicines failed to show consistent clinical benefit. Interferon-beta-1b co-administered with ribavirin was associated with improved composite outcome (OR=0.50, 95%CI 0.32, 0.78) and earlier discharge (−2.35 days, 95%CI −3.65, −1.06) compared to interferon-beta-1b monotherapy.
Interpretation: Our findings support the early administration of interferon-beta-1b alone or in combination with oral ribavirin for COVID-19 patients.
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1. Introduction

Coronavirus Disease 2019 (COVID-19), caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in December 2019 [1,2]. Despite the ongoing global effort to find effective therapeutics, the only drug demonstrating survival benefit so far is dexamethasone, where it has been shown to reduce mortality by one-third in patients receiving invasive mechanical ventilation

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Research in Context

Evidence before this study

The SOLIDARITY and RECOVERY trials have shown the efficacy of single agents in Coronavirus disease (COVID-19) patients. Knowledge gaps remain regarding the timing of administration and combination treatment. We searched PubMed without language restriction for studies published from database inception until December 24, 2020, with the terms "SARS-CoV-2″ or "COVID-19″ and "antiviral" and "lopinavir-ritonavir" and "ribavirin" and "umifenovir" and "interferon" and "steroids" and "antibiotics" and "Chinese medicine" and "intensive care unit" or "invasive mechanical ventilation" or "mortality" or "death" or "length of stay". No relevant articles pertaining to different therapeutic options for COVID-19 was found.

Added value of this study

In this multi-centre, population-based, propensity-score analysis of 4771 consecutive symptomatic patients from Hong Kong Special Administrative Region and Anhui province of China, interferon-beta-1b use was associated with both an improved composite outcome and earlier discharge compared to non-interferon-beta-1b users, regardless of timing of administration. Oral ribavirin initiated within 7 days from onset were associated with lower risk of the composite outcome in Hong Kong. Interferon-beta-1b co-administered with ribavirin was associated with improved composite outcome and earlier discharge compared to interferon-beta-1b monotherapy.

Implications of all the available evidence

This study of symptomatic, mostly mildly to moderately ill, COVID-19 patients supported the early administration of interferon-beta-1b alone or in combination with oral ribavirin for COVID-19 patients.

and by 20% in those requiring oxygen support without intubation [3]. SOLIDARITY trial interim results suggest that remdesivir, hydroxychloroquine, lopinavir-ritonavir and interferon-beta produced little or no reduction in mortality, mechanical ventilation, and duration of hospital stay in hospitalized COVID-19 patients when compared to usual care [4].

Knowledge gaps remain regarding the timing of administration and combination treatment. While Cao and colleagues were first to show that lopinavir-ritonavir did not improve survival or hospital length of stay, compared with standard supportive care [5]; however, when used together with interferon-beta-1b and ribavirin, this triple therapy combination for patient hospitalized within 7 days of symptom onset has been shown to shorten viral shedding and hasten recovery and discharge, when compared to monotherapy with lopinavir-ritonavir [6]. For patients hospitalized more than a week after symptom onset, patients were randomized to either lopinavir-ritonavir only or in combination with ribavirin [6], thus the effect of interferon-beta-1b initiated 7 days after symptom onset remains uncertain.

In a retrospective non-randomised study, nebulised interferon-alpha-2b, either as monotherapy or in combination with umifenovir, was found to accelerate viral clearance in moderately ill COVID-19 patients, compared to those who used umifenovir alone [7]. An open-label, randomized trial evaluated interferon-beta-1a against standard supportive care in patients with severe COVID-19, and found no significant benefit in shortening hospital stay, intensive care unit stay, or duration of mechanical ventilation [8]. A currently ongoing trial evaluating SNG001, an oral inhalation version of interferon-beta revealed a 79% reduction in developing adverse outcomes with double the odds of recovery when compared to placebo [9]. Therefore interferon-beta given as a standalone drug or in combination with other antivirals may have the potential to achieve clinical benefits.

Here we present observational evidence based on complete case series from two large, population-based Chinese settings regarding the effectiveness of different therapeutic options, their timing of administration and drug combinations for treating COVID-19 infection.

2. Methods

2.1. Data sources and study populations

We analysed anonymised individual patient data from two consecutive case cohorts. The first cohort included data on all patients with confirmed COVID-19 admitted to 18 public hospitals in Hong Kong Special Administrative Region (HKSAR) of China between 21st January and 6th December 2020. The second cohort included data on consecutive patients admitted to 10 public hospitals in Anhui province of China, comprising 70.9% of all 990 laboratory-confirmed cases in that province, between 1st January and 27th February 2020. In both cohorts, all patients with positive polymerase chain reaction (PCR) results were admitted to hospital regardless of case severity, due to the relatively low case count in this region. Given that a relatively high number of testing per capita in both locations, these cohorts were highly representative of the respective locations, and included mild, moderate, severe, and critically ill cases as well as asymptomatic cases.

We excluded asymptomatic cases from this analysis because there are no indications to treat asymptomatic cases in both locations or indeed anywhere. The majority of asymptomatic cases were not given antivirals or interferons (72.8%) in our cohorts.

We classified patients based on the treatments they had received during the whole of their admission, as well as specified the timing of initiation of the different therapeutic options from the time of symptom onset. Given its demonstrated effectiveness as a single agent [9], we further selected patients who received interferon-beta-1b to explore the effects of combination treatment with other agents: 1) interferon-beta-1b monotherapy, 2) combination of interferon-beta-1b and lopinavir-ritonavir, 3) combination of interferon-beta-1b and ribavirin, and 4) triple combination of interferon-beta-1b, lopinavir-ritonavir, and ribavirin. Patients were observed from the time of admission until death, home discharge, or the censor date of 13th December 2020, whichever came first.

2.2. Outcomes definition

We considered the composite outcome of death, invasive mechanical ventilation or admission to intensive care unit (ICU) or high dependency unit (HDU); and the time from admission to discharge. The criteria for hospital discharge in both HKSAR and Anhui province were (i) two consecutive negative tests 24 h apart and (ii) clinically fit as determined by attending physician.

2.3. Data analysis

Descriptive statistics of baseline characteristics across treatment groups were presented with mean and standard deviation for continuous variables, and count and proportion for categorical variables.

To address missing baseline data in the two cohorts, multiple imputation by chained equations (MICE) [10] was used. Each missing value of laboratory data was imputed 20 times using other parameters such as sex, age, clinical severity defined by the WHO clinical

Table 1
Baseline characteristics and clinical outcomes of COVID-19 patients in Hong Kong Special Administrative Region (HKSAR) and Anhui province of China.

Characteristics	Hong Kong (n = 4771)		Anhui (n = 648)	
	N / Mean	% / SD	N / Mean	% / SD
Age, years				
<30	1041	(21.8%)	146	(22.5%)
30–65	2891	(60.6%)	459	(70.8%)
>65	839	(17.6%)	43	(6.6%)
Male sex	2300	(48.2%)	359	(55.4%)
Time from symptom onset to hospital admission, days				
<7	3681	(77.2%)	406	(62.7%)
≥7	1090	(22.9%)	242	(37.4%)
Pre-existing conditions				
Diabetes mellitus	592	(12.4%)	15	(2.3%)
Hypertension	1166	(24.4%)	80	(12.3%)
Chronic lung disease	223	(4.7%)	59	(9.1%)
Chronic heart disease	212	(4.4%)	16	(2.5%)
Chronic kidney disease	153	(3.2%)	5	(0.8%)
Liver disease	259	(5.4%)	27	(4.2%)
Malignancy	64	(1.3%)	4	(0.6%)
Long-term medications				
ACEI or ARB	513	(10.8%)	19	(2.9%)
Lipid-lowering agent	651	(13.6%)	3	(0.5%)
NSAID	450	(9.4%)	5	(0.8%)
Laboratory parameters on admission [normal range in HK; Anhui] †				
White blood cell, $\times 10^9$/L [3.7–9.2 $\times 10^9$/L; 3.5–9.5 $\times 10^9$/L]	5.5	2.0	5.3	2.3
Neutrophil, $\times 10^9$/L [1.7–5.8 $\times 10^9$/L; 1.8–6.3 $\times 10^9$/L]	3.5	1.8	3.5	2.1
Lymphocyte, $\times 10^9$/L [1.0–3.1 $\times 10^9$/L; 1.1–3.2 $\times 10^9$/L]	1.4	0.7	1.3	0.7
Platelet, $\times 10^9$/L [145–370 $\times 10^9$/L; 125–350 $\times 10^9$/L]	216.8	72.4	184.1	72.2
Lactate dehydrogenase, U/L [110–210 U/L; 120–250 U/L]	215.7	85.9	259.7	123.3
Creatine Kinase, U/L [26–192 U/L; 22–269 U/L]	145.6	274.2	106.0	301.8
Total Bilirubin, μmol/L [5–27 μmol/L; 3.4–21.0 μmol/L]	8.4	5.0	14.1	8.4
C-reactive Protein, mg/L [<5 mg/L; <8 mg/L]	17.3	34.6	25.0	34.5
Clinical outcomes				
Composite‡	331	(6.9%)	42	(6.5%)
Death	86	(1.8%)	2	(0.3%)
Invasive mechanical ventilation	152	(3.2%)	2	(0.3%)
Intensive care unit or high dependency unit admission	279	(5.8%)	42	(6.5%)
Clinical severity§				
Severe	304	(6.4%)	32	(4.9%)
Acute respiratory distress syndrome	154	(3.2%)	0	(0.0%)
Hospital length of stay, days	15.0	11.5	17.2	6.3

Note: ACEI = angiotensin converting enzyme inhibitor; ARB = Angiotensin II receptor blockers; NSAID = Nonsteroidal anti-inflammatory drugs; SD = standard deviation.
*Symptoms include fever, chills, sore throat, cough, runny nose, shortness of breath, headache, diarrhoea, nausea, vomiting, general weakness, irritability, confusion, muscular pain, chest pain, abdominal pain and joint pain.
† Laboratory parameters and hospital length of stay are presented in mean ± SD.
‡ Composite outcome consists of death, invasive mechanical ventilation, or intensive care unit admission.
§ Clinical severity is classified according to WHO Clinical Progress Scale.

progression scale [11], pre-existing conditions, and long-term medications.

Regression analyses were independently conducted for each therapeutic option including lopinavir-ritonavir, ribavirin, umifenovir, interferon-alpha-2b, interferon-beta-1b, corticosteroids (dexamethasone, hydrocortisone, methylprednisolone, and prednisolone), antibiotics, and Chinese medicines. To minimize potential confounding biases due to discrepancy in baseline characteristics, inverse probability of treatment weights (IPTW) using propensity scoring was applied to balance covariates for patients administered each treatment or not. A logistic regression model was performed to estimate the propensity scores for each treatment group and included the covariates of age, sex, clinical severity, pre-existing conditions, and baseline reading of lymphocyte count, platelet count, creatine kinase, total bilirubin, and C-reactive protein (CRP). The set of covariates was determined by at best minimising the residual confounding factors, and inclusion of covariates with data completion rates of >70% in both cohorts (Supplementary Table 1). Propensity score weights in each group were trimmed at the lowest and highest 1% (corresponding to the 1st and 99th percentiles). After propensity-score weighting, balance of baseline covariates between the treatment groups was further assessed using the standardized mean difference (SMD). SMDs of less than 0.2 implied sufficient balance between the groups [12]. Those baseline covariates with SMD≥0.2 were adjusted in the regression models. Bonferroni correction was accounted for comparisons of multiple independent treatments.

Logistic regression models adjusted with the IPTW using the propensity score were performed to estimate odds ratios of the composite outcome. To handle reverse causality, patients who presented with the composite outcome on or before the day of treatment initiation or at the time of hospital admission were excluded from the analysis of the composite outcome. among discharged patients, time from baseline to hospital discharge between treatment groups were compared by linear regression following the IPTW using propensity scoring. The regression analyses were repeated for therapeutic option initiated within 7 days and after 7 days of symptom onset. In interferon-beta-1b drug combination analysis, the regression analyses were repeated for each interferon-beta-1b drug combination group to identify the optimal timing of administration. For multiple comparison of interferon-beta-1b drug combination groups, p-values were corrected using the Bonferroni method.

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

2.4. 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, in both jurisdictions, individual patient informed consent was not required for this retrospective cohort study using anonymised data.

2.5. Role of the funding source

The funders did not have any role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

3. Results

3.1. Patient cohorts

There were 6803 and 702 patients with confirmed COVID-19 infection in HKSAR (diagnosed between 21st January and 6th December 2020) and Anhui province, China (diagnosed between 1st January and 27th February 2020), respectively. In this analysis, we included 4771 and 648 symptomatic and hospitalized patients with COVID-19 in HKSAR and Anhui, respectively. Baseline characteristics of patients in HKSAR and Anhui cohorts are shown in Table 1. Most characteristics after propensity scoring were balanced (Supplementary Table 2). Patients were treated in accordance with local guidelines in the two subsamples respectively, as shown in Table 2. However, there was no specific guidance concerning treatment initiation and types of drugs used in both locations. Duration from hospital admission to initiation of each therapeutic option, and duration from symptom onset to initiation of each therapeutic option in both cohorts are depicted in Fig. 1.

3.2. Composite outcome of death or serious complications

There were 86 (1.8%) deaths, 152 (3.2%) who required invasive mechanical ventilation and 279 (5.8%) admitted for ICU/HDU care in HKSAR; and 2 (0.3%), 2 (0.3%) and 42 (6.5%) in Anhui correspondingly. Table 3 shows that lopinavir-ritonavir was not associated with the composite outcome regardless of timing of administration in HKSAR cohort. Oral ribavirin initiated within 7 days from onset was associated with lower risk of the composite outcome (OR = 0.58, 95% CI 0.36, 0.92, p = 0.009) in Hong Kong. In Anhui, intravenous ribavirin when initiated within 7 days of onset was associated with a higher risk of the composite outcome (OR=5.59, 95% CI 2.72, 11.50, $p < 0.001$). Unifenovir showed no association with the composite outcome.

Interferon-alpha-2b, only available in Anhui, was unassociated with risk of the composite outcome. Interferon-beta-1b, only available in Hong Kong, was associated with improved composite outcome regardless of timing of initiation (OR = 0.55, 95% CI 0.38, 0.80, $p < 0.001$).

Corticosteroids were generally unassociated or associated with increased risk of the composite outcome for both cohorts, with the exception of hydrocortisone (OR = 0.27, 95% CI 0.11, 0.64, $p < 0.001$) in HKSAR. Antibiotics were associated with a higher risk of the

Table 2
Pharmaceutical interventions initiated to COVID-19 patients in Hong Kong SAR and Anhui province.

			Hong Kong (n = 4771)		Anhui (n = 648)	
Drug	Standard dosage in Hong Kong	Standard dosage in Anhui	N	(%)	N	(%)
Antivirals						
Lopinavir-ritonavir	400 mg/100 mg 2 times per day for 14 days; oral	400 mg/100 mg 2 times per day for max. of 10 days; oral	1600	(33.5%)	554	(85.5%)
Ribavirin	400 mg 2 times per day; oral	500 mg 2 to 3 times per day for max. of 10 days; intravenous	1366	(28.6%)	53	(8.2%)
Umifenovir	Not used in Hong Kong	200 mg 3 times per day for max. of 10 days; oral	0	(0.0%)	217	(33.5%)
Immunomodulators						
Corticosteroids			873	(18.3%)	171	(26.4%)
Dexamethasone	4 mg every 6 h; intravenous	5 - 10 mg once; intravenous	762	(16.4%)	5	(1.0%)
Hydrocortisone	25 - 300 mg daily*; intravenous 10 - 40 mg daily*; oral	Not used in Anhui	158	(3.9%)	0	(0.0%)
Methylprednisolone	250 mg once; intravenous	20 - 120 mg daily*; intravenous / oral	8	(0.2%)	123	(20.5%)
Prednisolone	2.5 - 30 mg daily*; oral	10 - 160 mg daily*; intravenous / oral	55	(1.4%)	50	(9.5%)
Interferon-α−2b	Not used in Hong Kong	50 mcg (5 million units) 2 times per day for 14 days; atomising inhalation	0	(0.0%)	495	(76.4%)
Interferon-β−1b	250mcg (8 million units) on alternate day for max. of 3 doses; subcutaneous	Not used in Anhui	2173	(45.5%)	0	(0.0%)
Antibiotics‡	NA	NA	1802	(37.8%)	377	(58.2%)
Chinese Medicines†	Not used in Hong Kong	Variable	0	(0.0%)	565	(87.2%)

Note: NA = not applicable.

* In divided doses if high doses are used.

† Chinese medicines include Lianhua Qingwen capsule, Shuanghuanglian oral liquid, Yu Ping Feng San, Shufeng Jiedu capsule, Qingfei paidu decoction, Kanggan mixture and other Chinese medicinal decoction and herbal medicine.

‡ Antibiotics initiated include Amikacin, Amoxicillin, Amoxicillin-Clavulanate, Ampicillin, Ampicillin-Sulbactam, Azithromycin, Benzylpenicillin, Cefazolin, Cefepime, Cefoperazone-Sulbactam, Cefotaxime, Ceftazidime-Avibactam, Ceftriaxone, Cefuroxime, Cephalexin, Ciprofloxacin, Clarithromycin, Clindamycin, Cloxacillin, Daptomycin, Doxycycline, Ertapenem, Ethambutol, Gentamicin, Isoniazid, Levofloxacin, Linezolid, Meropenem, Metronidazole, Minocycline, Neomycin, Nitrofurantoin, Ofloxacin, Piperacillin-Tazobactam, Rifampicin, Ticarcillin-Clavulanate, Trimethoprim-Sulfamethoxazole, Tobramycin, and Vancomycin.

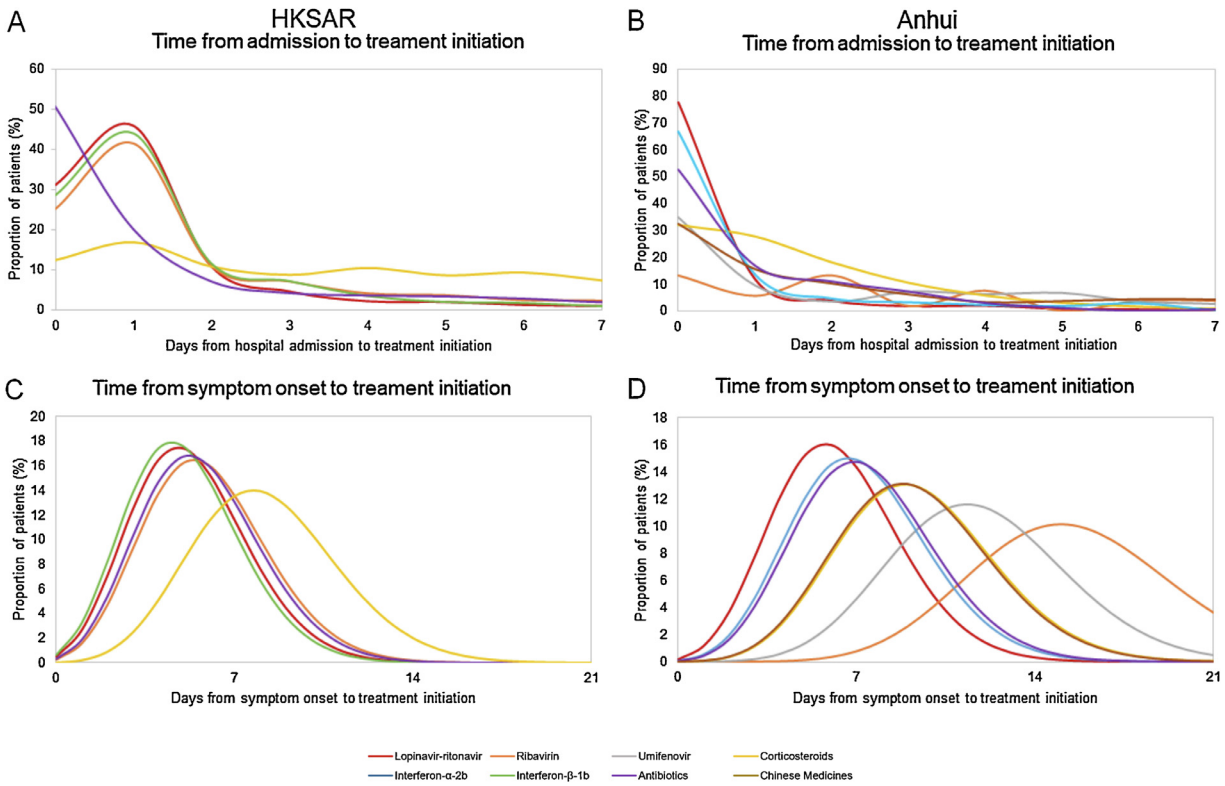

Fig. 1. Time from hospital admission to treatment initiation in (A) Hong Kong Special Administrative Region (HKSAR) and (B) Anhui province of China, and time from symptom onset to treatment initiation in (C) HKSAR and (D) Anhui province of China.

composite outcome in both HKSAR (OR = 2.74, 95% CI 1.56, 4.80, $p < 0.001$) and Anhui (OR = 7.16, 95% CI 1.60, 32.11, $p = 0.003$). Chinese medicines, only available in Anhui, were generally unassociated with risk of the composite outcome.

3.3. Length of stay

Table 4 shows that regardless of timing of administration, antivirals were either unassociated or associated with longer duration of hospitalisation in both cohorts. (−1.8 days, $p < 0.001$)

Interferon-beta-1b was associated with a shorter length of stay (−8.8 days, 95% CI −9.7, −7.9, $p < 0.001$; −8.4, 95% CI −9.4, −7.4, $p < 0.001$; −10.0, 95% CI −11.8, −8.1, $p < 0.001$), regardless of timing of administration. Interferon-alpha-2b, only available in Anhui, was generally unassociated with duration of hospitalisation.

Corticosteroids, antibiotics, Chinese medicines (Anhui only) were unassociated with hospitalisation duration or associated with a longer length of stay across both cohorts.

3.4. Interferon-beta-1b drug combinations

Among 2173 patients who ever received subcutaneous interferon-beta-1b, available in HKSAR only, 842, 689, and 465 were co-administered lopinavir-ritonavir, ribavirin, and both, respectively. Their characteristics were balanced after propensity score weighting (Supplementary Table 3).

Table 5 shows that interferon-beta-1b combined with ribavirin, compared to interferon-beta-1b alone, was associated with a lower risk of the composite outcome (OR = 0.50 95%CI 0.32, 0.78, $p < 0.001$) and a shorter length of stay (−2.35 days, 95% CI −3.65, −1.06, $p < 0.001$) regardless of timing of administration.

Table 6 further shows that when initiated within 3 days of symptom onset, this combination of interferon-beta-1b and ribavirin was unassociated with risk of the composite outcome when compared to later administration. It was however also associated with a longer length of stay (5.44 days, 95%CI 4.06, 6.81, $p < 0.001$) relative to later use.

4. Discussion

In this multi-centre, population-based, propensity-score adjusted analysis, we have shown that interferon-beta-1b and oral ribavirin was associated with improved outcomes in terms of survival/mechanical ventilation/intensive care and length of stay, especially when given early during the course of illness. Co-administration of oral ribavirin with interferon-beta-1b further reduced risk of the composite outcome but not the duration of hospitalisation among survivors.

Interferon-alpha-2b when administered within one week of symptom onset was unassociated with a lower risk of the composite outcome. When started after 7 days since symptom onset, it may be associated with an increase in the composite outcome of serious complications including death. These results are consistent with another recent retrospective study from the Chinese province of Hubei [13]. Timing of administration is likely critical given that its effect goes from anti-viral to pro-inflammatory if used beyond 7 days after symptom onset [6]. An integrated immune analysis identified a unique phenotype of highly impaired interferon type I response (i.e. no interferon-beta and low interferon-alpha production) among cases of severe COVID-19 illness [14]. These observations may provide the biological basis explaining our present results and justification for further consideration of associated therapeutic approaches [14]. There are ongoing trials evaluating interferons, alone and in combination with lopinavir-ritonavir, ribavirin, clofazimine and hydroxychloroquine [15].

Lopinavir-ritonavir, intravenous ribavirin and umifenovir were not associated with improvements in either specified outcome measure. Corticosteroids as a category were similarly disappointing,

Table 3
Composite outcome of death, invasive mechanical ventilation, or intensive care unit admission of COVID-19 patients in Hong Kong Special Administrative Region (HKSAR) and Anhui province of China.

	Hong Kong SAR									Anhui								
	Treatment						After weighting			Treatment						After weighting		
	No			Yes						No			Yes					
	N‡	Event	(%)	N‡	Event	(%)	OR	95% CI ¶	P-value¶	N‡	Event	(%)	N‡	Event	(%)	OR	95% CI¶	P-value¶
Interventions initiated regardless of timing of initiation																		
Lopinavir-ritonavir	3087	32	(1.0%)	1436	51	(3.6%)	1.27	(0.81, 1.98)	1.000	91	1	(1.1%)	540	24	(4.4%)	NA		
Ribavirin	3285	52	(1.6%)	1238	31	(2.5%)	0.58	(0.36, 0.92)	0.009	578	23	(4.0%)	53	2	(3.8%)	1.74	(0.85, 3.56)	0.267
Umifenovir	NA									421	22	(5.2%)	210	3	(1.4%)	0.84	(0.42, 1.69)	1.000
Corticosteroids	3865	7	(0.2%)	658	76	(11.6%)	1.74	(1.17, 2.58)	<0.001	470	4	(0.9%)	161	21	(13.0%)	2.64	(0.99, 7.05)	0.054
Dexamethasone	3865	7	(0.2%)	573	71	(12.4%)	3.49	(2.34, 5.20)	<0.001	470	4	(0.9%)	4	0	(0.0%)	NA		
Hydrocortisone	3865	7	(0.2%)	96	15	(15.6%)	0.27	(0.11, 0.64)	<0.001	NA								
Methylprednisolone	3865	7	(0.2%)	6	2	(33.3%)	3.79	(0.31, 46.13)	1.000	470	4	(0.9%)	114	14	(12.3%)	3.01	(1.06, 8.55)	0.031
Prednisolone	3865	7	(0.2%)	37	3	(8.1%)	0.88	(0.15, 5.27)	1.000	470	4	(0.9%)	48	9	(18.8%)	2.60	(0.79, 8.63)	0.231
Interferon-α−2b	NA									146	6	(4.1%)	485	19	(3.9%)	0.57	(0.21, 1.59)	1.000
Interferon-β−1b	2568	10	(0.4%)	1955	73	(3.7%)	0.55	(0.38, 0.80)	<0.001	NA								
Antibiotics	2946	5	(0.2%)	1577	78	(4.9%)	2.74	(1.56, 4.80)	<0.001	266	2	(0.8%)	365	23	(6.3%)	7.16	(1.60, 32.11)	0.003
Chinese Medicines	NA									79	4	(5.1%)	552	21	(3.8%)	0.96	(0.39, 2.40)	1.000
Interventions initiated within 7 days of symptom onset																		
Lopinavir-ritonavir	3087	32	(1.0%)	1109	40	(3.6%)	1.40	(0.88, 2.25)	0.370	91	1	(1.1%)	378	14	(3.7%)	NA		
Ribavirin	3285	52	(1.6%)	884	19	(2.1%)	0.51	(0.29, 0.90)	0.010	578	23	(4.0%)	18	2	(11.1%)	5.59	(2.72, 11.50)	<0.001
Umifenovir	NA									421	22	(5.2%)	76	0	(0.0%)	NA		
Corticosteroids	3865	7	(0.2%)	276	42	(15.2%)	1.57	(0.97, 2.55)	0.084	470	4	(0.9%)	56	6	(10.7%)	2.37	(0.67, 8.35)	0.460
Dexamethasone	3865	7	(0.2%)	225	37	(16.4%)	3.46	(2.10, 5.72)	<0.001	470	4	(0.9%)	0	0	(0.0%)	NA		
Hydrocortisone	3865	7	(0.2%)	42	6	(14.3%)	0.31	(0.09, 0.99)	0.046	NA								
Methylprednisolone	3865	7	(0.2%)	2	0	(0.0%)	NA			470	4	(0.9%)	39	4	(10.3%)	2.76	(0.69, 10.98)	0.337
Prednisolone	3865	7	(0.2%)	14	1	(7.1%)	NA			470	4	(0.9%)	17	2	(11.8%)	1.66	(0.21, 13.31)	1.000
Interferon-α−2b	NA									146	6	(4.1%)	310	4	(1.3%)	0.30	(0.07, 1.31)	0.198
Interferon-β−1b	2568	10	(0.4%)	1581	60	(3.8%)	0.60	(0.41, 0.88)	0.002	NA								
Antibiotics	2946	5	(0.2%)	1128	63	(5.6%)	3.10	(1.76, 5.43)	<0.001	266	2	(0.8%)	219	17	(7.8%)	8.99	(1.99, 40.58)	<0.001
Chinese Medicines	NA									79	4	(5.1%)	255	8	(3.1%)	1.04	(0.35, 3.11)	1.000
Interventions initiated after 7 days of symptom onset																		
Lopinavir-ritonavir	3087	32	(1.0%)	327	11	(3.4%)	1.01	(0.52, 1.94)	1.000	91	1	(1.1%)	162	10	(6.2%)	NA		
Ribavirin	3285	52	(1.6%)	354	12	(3.4%)	0.66	(0.36, 1.22)	0.556	578	23	(4.0%)	35	0	(0.0%)	NA		
Umifenovir	NA									421	22	(5.2%)	134	3	(2.2%)	1.29	(0.64, 2.56)	1.000
Corticosteroids	3865	7	(0.2%)	382	34	(8.9%)	1.85	(1.20, 2.87)	<0.001	470	4	(0.9%)	105	15	(14.3%)	2.78	(1.00, 7.74)	0.051
Dexamethasone	3865	7	(0.2%)	348	34	(9.8%)	3.50	(2.26, 5.43)	<0.001	470	4	(0.9%)	4	0	(0.0%)	NA		
Hydrocortisone	3865	7	(0.2%)	54	9	(16.7%)	0.24	(0.07, 0.79)	0.008	NA								
Methylprednisolone	3865	7	(0.2%)	4	2	(0.0%)	5.51	(0.44, 69.38)	0.556	470	4	(0.9%)	75	10	(13.3%)	3.14	(1.03, 9.58)	0.040
Prednisolone	3865	7	(0.2%)	23	2	(8.7%)	0.91	(0.08, 10.47)	1.000	470	4	(0.9%)	31	7	(22.6%)	3.02	(0.86, 10.60)	0.124
Interferon-α−2b	NA									146	6	(4.1%)	175	15	(8.6%)	1.08	(0.34, 3.44)	1.000
Interferon-β−1b	2568	10	(0.4%)	374	13	(3.5%)	0.39	(0.16, 0.91)	0.018	NA								
Antibiotics	2946	5	(0.2%)	449	15	(3.3%)	1.86	(0.82, 4.24)	0.322	266	2	(0.8%)	146	6	(4.1%)	4.44	(0.79, 24.99)	0.142
Chinese Medicines	NA									79	4	(5.1%)	297	13	(4.4%)	0.89	(0.30, 2.68)	1.000

Note: OR = Odds ratio; CI = confidence interval; NA = Not applicable.
†OR >1 (or <1) indicates the treatment was associated with higher (or lower) risk of composite outcome.
‡ The numbers of treated and non-treated patients may not total all patients in the respective cohorts as per Table 2 because those who presented with the composite outcome on or before the day of treatment initiation, or the day of admission were excluded from the analysis.
¶ Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.

Table 4
Time from admission to discharge for COVID-19 survivors receiving different pharmaceutical interventions in Hong Kong Special Administrative Region (HKSAR) and Anhui province of China.

	Hong Kong SAR									Anhui								
	Treatment						After weighting			Treatment						After weighting		
	No			Yes						No			Yes					
	N[§]	Mean	SD	N[§]	Mean	SD	Difference[†]	(95%CI)[¶]	P-value[¶]	N[§]	Mean	SD	N[§]	Mean	SD	Difference[†]	(95%CI)[¶]	P-value[¶]
Interventions initiated regardless of timing of initiation																		
Lopinavir-ritonavir	2835	12.3	9.0	1510	21.1	13.3	8.8	(8.1, 9.4)	<0.001	94	14.0	4.1	552	17.4	6.3	3.4	(2.6, 4.2)	<0.001
Ribavirin	3140	13.8	11.1	1205	21.2	13.7	7.4	(6.6, 8.1)	<0.001	593	16.9	6.2	53	18.3	6.2	1.4	(0.4, 2.3)	<0.001
Umifenovir	NA									430	16.5	6.0	216	18.6	7.5	2.1	(1.0, 3.1)	<0.001
Corticosteroids	3717	13.6	9.4	628	18.1	13.0	4.4	(3.7, 5.1)	<0.001	476	17.1	6.2	170	18.8	6.9	1.7	(0.7, 2.8)	<0.001
Dexamethasone	3717	13.6	9.4	525	17.0	12.6	3.3	(2.6, 4.1)	<0.001	476	17.1	6.2	5	17.3	2.8	0.2	(−3.6, 4.0)	1.000
Hydrocortisone	3717	13.6	9.4	117	19.0	13.6	5.4	(4.6, 6.1)	<0.001	NA								
Methylprednisolone	3717	13.6	9.4	6	27.1	13.8	13.5	(8.2, 18.7)	<0.001	476	17.1	6.2	122	17.7	6.1	0.6	(−0.5, 1.7)	1.000
Prednisolone	3717	13.6	9.4	43	23.2	21.7	9.5	(7.4, 11.6)	<0.001	476	17.1	6.2	49	20.9	7.8	3.8	(2.4, 5.2)	<0.001
Interferon-α−2b	NA									152	16.9	6.7	494	17.1	6.1	0.2	(−0.8, 1.2)	1.000
Interferon-β−1b	2420	23.9	17.8	1925	15.1	11.1	−8.8	(−9.7, −7.9)	<0.001	NA								
Antibiotics	2814	12.5	7.8	1531	17.1	12.3	4.6	(4.0, 5.2)	<0.001	270	16.3	5.7	376	17.8	6.7	1.5	(0.5, 2.5)	<0.001
Chinese Medicines	NA									82	15.5	5.4	564	17.2	6.3	1.7	(0.8, 2.6)	<0.001
Interventions initiated within 7 days of symptom onset																		
Lopinavir-ritonavir	2835	12.3	9.0	1164	21.3	13.0	9.0	(8.3, 9.7)	<0.001	94	14.0	4.1	383	17.8	6.3	3.9	(3.1, 4.7)	<0.001
Ribavirin	3140	13.8	11.1	852	21.7	13.5	7.9	(7.1, 8.7)	<0.001	593	16.9	6.2	18	18.8	5.3	1.9	(0.6, 3.1)	<0.001
Umifenovir	NA									430	16.5	6.0	76	16.1	4.4	−0.4	(−1.7, 0.8)	1.000
Corticosteroids	3717	13.6	9.4	268	19.9	15.1	6.2	(5.4, 7.1)	<0.001	476	17.1	6.2	58	17.9	6.2	0.9	(−0.5, 2.2)	0.765
Dexamethasone	3717	13.6	9.4	216	17.4	16.1	3.8	(2.6, 5.0)	<0.001	476	17.1	6.2	0	NA				
Hydrocortisone	3717	13.6	9.4	44	21.7	14.3	8.1	(7.1, 9.1)	<0.001	NA								
Methylprednisolone	3717	13.6	9.4	2	40.5	4.4	26.8	(16.6, 37.1)	<0.001	476	17.1	6.2	40	17.4	5.4	0.4	(−1.3, 2.0)	1.000
Prednisolone	3717	13.6	9.4	13	13.5	8.8	−0.1	(−3.0, 2.8)	1.000	476	17.1	6.2	18	18.8	7.2	1.7	(−0.4, 3.9)	0.240
Interferon-α−2b	NA									152	16.9	6.7	313	17.1	5.8	0.3	(−0.9, 1.4)	1.000
Interferon-β−1b	2420	23.9	17.8	1556	15.4	11.4	−8.4	(−9.4, −7.4)	<0.001	NA								
Antibiotics	2814	12.5	7.8	1073	17.8	12.3	5.3	(4.6, 5.9)	<0.001	270	16.3	5.7	222	18.1	6.6	1.8	(0.7, 2.9)	<0.001
Chinese Medicines	NA									82	15.5	5.4	257	17.0	6.1	1.5	(0.3, 2.6)	0.003
Interventions initiated after 7 days of symptom onset																		
Lopinavir-ritonavir	2835	12.3	9.0	346	20.6	13.9	8.3	(7.4, 9.1)	<0.001	94	14.0	4.1	169	16.3	6.3	2.3	(1.3, 3.3)	<0.001
Ribavirin	3140	13.8	11.1	353	20.4	14.0	6.6	(5.7, 7.5)	<0.001	593	16.9	6.2	35	18.0	6.6	1.1	(0.0, 2.2)	0.070
Umifenovir	NA									430	16.5	6.0	140	19.7	8.4	3.2	(2.0, 4.4)	<0.001
Corticosteroids	3717	13.6	9.4	360	16.7	11.0	3.1	(2.4, 3.8)	<0.001	476	17.1	6.2	112	19.2	7.1	2.1	(1.0, 3.3)	<0.001
Dexamethasone	3717	13.6	9.4	309	16.7	10.0	3.1	(2.2, 3.9)	<0.001	476	17.1	6.2	5	17.3	2.8	0.2	(−3.6, 4.0)	1.000
Hydrocortisone	3717	13.6	9.4	73	17.0	12.7	3.4	(2.5, 4.2)	<0.001	NA								
Methylprednisolone	3717	13.6	9.4	4	22.3	12.9	8.7	(2.6, 14.8)	<0.001	476	17.1	6.2	82	17.8	6.4	0.7	(−0.6, 2.0)	1.000
Prednisolone	3717	13.6	9.4	30	31.2	25.7	17.5	(14.7, 20.4)	<0.001	476	17.1	6.2	31	21.8	7.9	4.7	(3.1, 6.3)	<0.001
Interferon-α−2b	NA									152	16.9	6.7	181	16.9	6.7	0.0	(−1.4, 1.5)	1.000
Interferon-β−1b	2420	23.9	17.8	369	13.9	9.8	−10.0	(−11.8, −8.1)	<0.001	NA								
Antibiotics	2814	12.5	7.8	458	15.4	11.9	2.9	(2.1, 3.7)	<0.001	270	16.3	5.7	154	17.3	6.7	1.1	(−0.2, 2.3)	0.162
Chinese Medicines	NA									82	15.5	5.4	307	17.4	6.4	1.9	(0.8, 3.0)	<0.001

Note: CI = confidence interval; NA = Not applicable.

[†] Difference<0 (or >0) indicates the treatment was associated with shorter (or longer) time to discharge.

[§] The numbers of patients in each drug combination group may not total all patients in the respective cohort as per Table 2 because those who died during admission or not yet discharged were excluded from the analysis.

[¶] Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.

Table 5
Composite outcome of death, invasive mechanical ventilation, or intensive care unit admission of COVID-19 patients receiving different interferon-β−1b based drug combinations, and time from admission to discharge for COVID-19 survivors in Hong Kong Special Administrative Region (HKSAR) of China.

	Hong Kong SAR					
	Treatment			After weighting		
Composite outcome	N[‡]	Event	(%)	OR[†]	95% CI[¶]	P-value[¶]
Interferon-β−1b monotherapy	161	9	(5.6%)		(reference)	
Interferon-β−1b + ribavirin	634	16	(2.5%)	0.50	(0.32, 0.78)	<0.001
Interferon-β−1b + lopinavir-ritonavir	752	35	(4.7%)	0.88	(0.61, 1.28)	1.000
Interferon-β−1b + lopinavir-ritonavir + ribavirin	408	13	(3.2%)	1.11	(0.77, 1.59)	1.000
Time from admission to discharge for COVID-19 survivors	N[§]	Mean	SD	Difference[†]	95% CI[¶]	P-value[¶]
Interferon-β−1b monotherapy	156	15.5	12.3		(reference)	
Interferon-β−1b + ribavirin	550	13.2	8.4	−2.35	(−3.65, −1.06)	<0.001
Interferon-β−1b + lopinavir-ritonavir	775	16.6	12.4	1.10	(−0.15, 2.35)	0.020
Interferon-β−1b + lopinavir-ritonavir + ribavirin	444	23.6	16.1	8.10	(6.85, 9.34)	<0.001

Note: OR = Odds ratio; CI = confidence interval; NA = Not applicable.
[†] OR >1 (or <1) indicates the treatment was associated with higher (or lower) risk of composite outcome; Difference<0 (or >0) indicates the treatment was associated with shorter (or longer) time to discharge.
[‡] The numbers of patients in each drug combination group may not total all patients in the respective cohorts as per Table 2 because those who presented with the composite outcome on or before the day of treatment initiation, or the day of admission were excluded from the analysis.
[§] The numbers of patients in each drug combination group may not total all patients in the respective cohort as per Table 2 because those who died during admission or not yet discharged were excluded from the analysis.
[¶] Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.

Table 6
Composite outcome of death, invasive mechanical ventilation, or intensive care unit admission of COVID-19 patients initiating interferon-β−1b based drug combination at different time after symptom onset, and time from admission to discharge for COVID-19 survivors initiating interferon-β−1b based drug combination at different times in Hong Kong Special Administrative Region (HKSAR) of China.

	Treatment			After weighting		
Composite outcome	N[‡]	Event	(%)	OR[†]	95% CI[¶]	P-value[¶]
Interferon-β−1b + ribavirin						
initiated within 3 days of symptom onset	127	4	(3.1%)	1.36	(0.67, 2.76)	0.667
initiated between 3 and 7 days of symptom onset	362	8	(2.2%)		(reference)	
initiated after 7 days of symptom onset	145	4	(2.8%)	0.63	(0.26, 1.53)	0.489
Interferon-β−1b + lopinavir-ritonavir						
initiated within 3 days of symptom onset	194	11	(5.7%)	1.14	(0.67, 1.96)	1.000
initiated between 3 and 7 days of symptom onset	424	18	(4.2%)		(reference)	
initiated after 7 days of symptom onset	134	6	(4.5%)	0.73	(0.40, 1.33)	0.467
Interferon-β−1b + lopinavir-ritonavir + ribavirin						
initiated within 3 days of symptom onset	123	8	(6.5%)	4.47	(1.46, 13.68)	0.005
initiated between 3 and 7 days of symptom onset	227	3	(1.3%)		(reference)	
initiated after 7 days of symptom onset	58	2	(3.4%)	0.70	(0.15, 3.25)	1.000
Time from admission to discharge for COVID-19 survivors	**N[§]**	**Mean**	**SD**	**Difference[†]**	**95% CI ¶**	**P-value ¶**
Interferon-β−1b + ribavirin						
initiated within 3 days of symptom onset	112	18.2	14.9	5.44	(4.06, 6.81)	<0.001
initiated between 3 and 7 days of symptom onset	309	12.7	6.7		(reference)	
initiated after 7 days of symptom onset	129	11.9	7.2	−0.83	(−2.32, 0.65)	0.419
Interferon-β−1b + lopinavir-ritonavir						
initiated within 3 days of symptom onset	195	17.7	12.2	−0.02	(−1.41, 1.37)	1.000
initiated between 3 and 7 days of symptom onset	443	17.7	15.3		(reference)	
initiated after 7 days of symptom onset	137	14.5	8.2	−3.24	(−4.64, −1.84)	<0.001
Interferon-β−1b + lopinavir-ritonavir + ribavirin						
initiated within 3 days of symptom onset	123	26.7	20.4	4.15	(1.63, 6.67)	<0.001
initiated between 3 and 7 days of symptom onset	255	22.6	13.6		(reference)	
initiated after 7 days of symptom onset	66	20.4	14.9	−2.23	(−4.79, 0.32)	0.101

Note: OR = Odds ratio; CI = confidence interval; NA = Not applicable.
[†] OR >1 (or <1) indicates the treatment was associated with higher (or lower) risk of composite outcome; Difference<0 (or >0) indicates the treatment was associated with shorter (or longer) time to discharge.
[‡] The numbers of patients in each drug combination group may not total all patients in the respective cohorts as per Table 2 because those who presented with the composite outcome on or before the day of treatment initiation, or the day of admission were excluded from the analysis.
[§] The numbers of patients in each drug combination group may not total all patients in the respective cohort as per Table 2 because those who died during admission or not yet discharged were excluded from the analysis.
[¶] Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.

except for hydrocortisone. Dexamethasone consistently showed higher risks of the composite outcome and length of stay, regardless of timing of administration or study cohort. Given the earlier findings of the RECOVERY [3] and CoDEX [16] trials that show survival benefit only among those ill enough to warrant respiratory support, our two cohorts of mostly mild to moderately ill patients likely explain the discrepancy.

Although non-randomised trial reported azithromycin might reduce viral load in patients with non-severe COVID-19 [17], results of the COALITION II trial showed that addition of azithromycin to standard of care regimens was not associated with outcome improvement [18]. Our finding showed antibiotics did not show clear and consistent benefit for either outcome between the two cohorts. However, the heterogeneity of antibiotic types and absence of further information on bacterial super-infection, other than the highest CRP value during hospitalisation render further interpretation difficult. Likewise, it is hard to conclude that Chinese medicines provided clinical benefit, except perhaps when started later in the course of illness in certain patients. The lack of standardisation in both treatment options in an observational setting preclude drawing more definite conclusions.

Several key limitations bear mention. First, inherent to the observational design, despite propensity scoring to balance baseline characteristics, our findings are subject to the usual observational biases and cannot infer causation or definitive treatment effects. However, the likelihood that unmeasured confounders could affect the relationship between ribavirin and the composite outcome, between interferon-beta-1b and the composite outcome seemed unlikely, as indicated by E-values [19]. Our aim was to summarise the whole population experience of two large Chinese locations in order to provide comparison and context in interpreting ongoing trial results. Second, we cannot completely rule out the possibility of immortal time bias. However, no composite outcome was reported prior to hospital admission and antivirals and interferons were administered shortly after admission. We also excluded those who had composite outcome events on or before the day of treatment initiation, thus minimising the bias in favour of the treatment group. Third, our patient cohorts mostly represented the mild to moderate spectrum of COVID-19 presentations, albeit comprising consecutive, non-selected symptomatic cases from the designated treatment hospitals in the two locations. A majority of confirmed COVID-19 cases in mainland China were not classified as severe or critical [20], with similar distributions of clinical severity between our two cohorts. Hence, the study findings may be generalisable to those populations with similar casemix, including the whole of China and East Asia. Fourth, our data did not allow us to adequately evaluate other combinations of antivirals, immunomodulators, or antibiotics, perhaps administered at different stages of the course of illness, which in reality could be the preferred treatment strategy when no single agent appears to provide overwhelming or sufficient efficacy. Fifth, we did not have access to data on viral load trajectories or symptom resolution that could have enriched our observations. Finally, our study did not evaluate remdesivir or hydroxychloroquine /chloroquine. Remdesivir is the only direct antiviral to have shown efficacy against COVID-19. Neither HKSAR or Anhui had routine access to data of remdesivir administration during the period of observation. While the SIMPLE trials identified its benefits in shortening recovery time [21], which was not found in an earlier study [22], there is as yet evidence to demonstrate survival advantage. SOLIDARITY [4], RECOVERY [3] and a Cochrane review [23] found no evidence that either hydroxychloroquine or chloroquine was effective against SARS-CoV-2. Two trials even suggested a higher rate of adverse outcomes in those randomised to hydroxychloroquine [24,25]. Neither drug had been used in HKSAR or Anhui as part of COVID-19 treatment regimen.

In conclusion, our findings based on two complete case cohorts of symptomatic, mostly mildly to moderately ill COVID-19 patients support further randomised trials on the early administration of interferon-beta-1b alone and in combination with oral ribavirin. Other treatment therapies combined with interferon-beta-1b should also be further explored in an experimental setting.

Declaration of Interests

BJC reports honoraria from Sanofi Pasteur and Roche. The authors report no other potential conflicts of interest.

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Contributors

C.K.H.W. and E.Y.F.W. reviewed the literature, designed statistical analysis, conducted analyses, wrote the manuscript; S.L., Y.D., P.L., X. H., X.Z. and J.W. collected and compiled data. E.H.Y.L provided critical input to the statistical analyses and design. E.C.H.L and J.W. reviewed the literature and wrote the manuscript. B.J.C. constructed the study design, provided critical input to the statistical analyses, and wrote the manuscript. G.M.L. constructed the study design, supervised the study, wrote the manuscript and act as guarantor for the study. 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.

Data sharing statement

The databases are properties of the Hong Kong Hospital Authority Head Office, Hong Kong Centre for Health Protection, and Anhui provincial health commission.

Transparency statement

The manuscript's guarantor affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

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Supplementary materials

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References

[1] Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges. Int J Antimicrob Agents 2020;55(3):105924.

[2] Leung K, Wu JT, Liu D, Leung GM. First-wave COVID-19 transmissibility and severity in China outside Hubei after control measures, and second-wave scenario planning: a modelling impact assessment. Lancet 2020;395(10233):1382–93.

[3] The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. N Engl J Med 2020. doi: 10.1056/NEJMoa2021436.

[4] World Health Organization. "Solidarity" clinical trial for COVID-19 treatments. 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. [Access date 13 January 2021]

[5] Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382(19):1787–99.

[6] Hung IF, Lung KC, Tso EY, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet 2020;395(10238):1695–704.

[7] Zhou Q, Chen V, Shannon CP, et al. Interferon-α2b Treatment for COVID-19. Front Immunol 2020;11:1061.

[8] Davoudi-Monfared E, Rahmani H, Khalili H, et al. A randomized clinical trial of the efficacy and safety of Interferon β-1a in treatment of severe COVID-19. Antimicrob. Agents Chemother. 2020;64(9):e01061. 20.

[9] Monk PD, Marsden RJ, Tear VJ, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respir Med 2020. doi: 10.1016/S2213-2600(20)30511-7.

[10] White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. Stat Med 2011;30(4):377–99.

[11] Marshall JC, Murthy S, Diaz J, et al. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis 2020;20(8):e192–e7.

[12] Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J 2009;51(1):171–84.

[13] Wang N, Zhan Y, Zhu L, et al. Retrospective multicenter cohort study shows early interferon therapy is associated with favorable clinical responses in COVID-19 patients. Cell Host Microbe 2020;28(3):455–64 e2.

[14] Hadjadj J, Yatim N, Barnabei L, et al. Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. Science 2020;369(6504):718–24.

[15] Wadman M. Can interferons stop COVID-19 before it takes hold? Science 2020;369(6500):125–6.

[16] Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. JAMA 2020;324(13):1307–16.

[17] Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 2020;56(1):105949.

[18] Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. The Lancet 2020;396(10256):959–67.

[19] Haneuse S, VanderWeele TJ, Arterburn D. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. JAMA 2019;321(6):602–3.

[20] Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a Report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020;323(13):1239–42.

[21] Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. New Engl J Med 2020;383(19):1827–37.

[22] Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395(10236):1569–78.

[23] Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. Cochrane Database Syst Rev 2020(4):CD013587.

[24] Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;369:m1849.

[25] The RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. New Engl J Med 2020;383(21):2030–40.