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 13th 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...
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...
propensity 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 odds ratios of 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 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 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.

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, $10^9$/L [3.7–9.2 $10^9$/L; 3.5–9.5 $10^9$/L] | 5.5    | 2.0    | 5.3    | 2.3    |
| Neutrophil, $10^9$/L [1.7–5.8 $10^9$/L; 1.8–6.3 $10^9$/L] | 3.5    | 1.8    | 3.5    | 2.1    |
| Lymphocyte, $10^3$/L [1.0–3.1 $10^3$/L; 1.1–3.2 $10^3$/L] | 1.4    | 0.7    | 1.3    | 0.7    |
| Platelet, $10^9$/L [145–370 $10^9$/L; 125–350 $10^9$/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, $\mu$mol/L [0.5–7.0 $\mu$mol/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.

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).

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). Unifenvir 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

| Drug                  | Standard dosage in Hong Kong | Standard dosage in Anhui | Hong Kong (n = 4771) N (%) | Anhui (n = 648) 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%) |
| Unifenvir             | Not used in Hong Kong        | 200 mg 3 times per day for max. of 10 days; oral | 0 (0.0%) | 217 (33.5%) |
| **Immunomodulators** |                              |                          |                             |                        |
| Clemastine            | 4 mg every 6 h; intravenous  | 5 - 10 mg once; intravenous | 873 (18.3%) | 171 (26.4%) |
| Hydrocortisone        | 25 - 300 mg daily; oral      | Not used in Anhui        | 762 (16.4%) 5 (1.0%) | 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 (0.5%) |
| Interferon-α-2b       | Not used in Hong Kong        | 50 mg (5 million units) 2 times per day for 14 days; atomising inhalation | 0 (0.0%) | 495 (76.4%) |
| Interferon-β-1b       | 250 mcg (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.

1 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.

1 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, Mersopenem, Metronidazole, Minocycline, Neomycin, Nitrofurantoin, Ofloxacin, Piperacillin-Tazobactam, Rifampicin, Ticarcillin-Clavulanate, Trimethoprim-Sulfamethoxazole, Tobramycin, and Vancomycin.
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 |
|                               | N² Event (%)  | N² Event (%)   | OR 95% CI | P-value⁴       |
|                               |               |               |           |               |
| Interventions initiated regardless of timing of initiation |               |               |           |               |
| Lopinavir-ritonavir           | 3087 72 (1.0%)| 1436 51 (3.6%)| 1.27 (0.81, 1.98)| 1.000          |
| Ribavirin                     | 3285 52 (1.6%)| 1238 31 (2.5%)| 0.58 (0.36, 0.92)| 0.009          |
| Umifenovir                    | NA            |               |           |               |
| Corticosteroids               | 3865 7 (0.2%) | 658 76 (11.6%)| 1.74 (1.17, 2.58)| <0.001         |
| Dexamethasone                 | 3865 7 (0.2%) | 573 71 (12.4%)| 3.49 (2.34, 5.20)| <0.001         |
| Hydrocortisone                | 3865 7 (0.2%) | 96 15 (15.6%) | 0.27 (0.11, 0.64)| <0.001         |
| Methylprednisolone            | NA            |               |           |               |
| Prednisolone                  | 3865 7 (0.2%) | 37 3 (8.1%)   | 0.88 (0.15, 5.27)| 1.000          |
| Interferon-α-2b               | 2568 10 (0.4%)| 1955 73 (3.7%)| 0.55 (0.38, 0.80)| <0.001         |
| Antibiotics                   | NA            |               |           |               |
| Chinese Medicines             | 2946 5 (0.2%) | 1577 78 (4.9%)| 2.74 (1.56, 4.80)| <0.001         |
| Interventions initiated within 7 days of symptom onset |               |               |           |               |
| Lopinavir-ritonavir           | 3087 72 (1.0%)| 1109 40 (3.6%)| 1.40 (0.88, 2.25)| 0.370          |
| Ribavirin                     | 3285 52 (1.6%)| 884 19 (2.1%) | 0.51 (0.29, 0.90)| 0.010          |
| Umifenovir                    | NA            |               |           |               |
| Corticosteroids               | 3865 7 (0.2%) | 276 42 (15.2%)| 1.57 (0.97, 2.55)| 0.084          |
| Dexamethasone                 | 3865 7 (0.2%) | 225 37 (16.4%)| 3.46 (2.10, 5.72)| <0.001         |
| Hydrocortisone                | 3865 7 (0.2%) | 42 6 (14.3%)  | 0.31 (0.09, 0.99)| 0.46           |
| Methylprednisolone            | 3865 7 (0.2%) | 2 0 (0.0%)    | NA         |               |
| Prednisolone                  | 3865 7 (0.2%) | 14 1 (7.1%)   | NA         |               |
| Interferon-β-1b               | 2568 10 (0.4%)| 1581 60 (3.8%)| 0.60 (0.41, 0.88)| 0.002         |
| Antibiotics                   | NA            |               |           |               |
| Chinese Medicines             | 2946 5 (0.2%) | 1128 63 (5.6%)| 3.10 (1.76, 5.43)| <0.001         |
| Interventions initiated after 7 days of symptom onset |               |               |           |               |
| Lopinavir-ritonavir           | 3087 72 (1.0%)| 327 11 (3.4%) | 1.01 (0.52, 1.94)| 1.000          |
| Ribavirin                     | 3285 52 (1.6%)| 354 12 (3.4%) | 0.66 (0.36, 1.22)| 0.566          |
| Umifenovir                    | NA            |               |           |               |
| Corticosteroids               | 3865 7 (0.2%) | 382 34 (8.9%) | 1.85 (1.20, 2.87)| <0.001         |
| Dexamethasone                 | 3865 7 (0.2%) | 348 34 (9.8%) | 3.50 (2.26, 5.43)| <0.001         |
| Hydrocortisone                | 3865 7 (0.2%) | 54 9 (16.7%)  | 0.24 (0.07, 0.79)| 0.008          |
| Methylprednisolone            | 3865 7 (0.2%) | 4 2 (0.0%)    | NA         |               |
| Prednisolone                  | 3865 7 (0.2%) | 23 2 (8.7%)   | 0.91 (0.08, 10.47)| 1.000          |
| Interferon-α-1b               | 2568 10 (0.4%)| 374 13 (3.5%) | 0.39 (0.16, 0.91)| 0.018         |
| Antibiotics                   | 2946 5 (0.2%) | 449 15 (3.3%) | 1.86 (0.82, 4.24)| 0.322         |
| Chinese Medicines             | NA            |               |           |               |

Note: OR = Odds ratio; CI = confidence interval; NA = Not applicable.

|                               | Hong Kong SAR | Anhui          |
|                               | N² Event (%)  | N² Event (%)   | OR 95% CI | P-value⁴       |
|                               |               |               |           |               |
| Interventions initiated regardless of timing of initiation |               |               |           |               |
| Lopinavir-ritonavir           | 3087 72 (1.0%)| 1436 51 (3.6%)| 1.27 (0.81, 1.98)| 1.000          |
| Ribavirin                     | 3285 52 (1.6%)| 1238 31 (2.5%)| 0.58 (0.36, 0.92)| 0.009          |
| Umifenovir                    | NA            |               |           |               |
| Corticosteroids               | 3865 7 (0.2%) | 658 76 (11.6%)| 1.74 (1.17, 2.58)| <0.001         |
| Dexamethasone                 | 3865 7 (0.2%) | 573 71 (12.4%)| 3.49 (2.34, 5.20)| <0.001         |
| Hydrocortisone                | 3865 7 (0.2%) | 96 15 (15.6%) | 0.27 (0.11, 0.64)| <0.001         |
| Methylprednisolone            | NA            |               |           |               |
| Prednisolone                  | 3865 7 (0.2%) | 37 3 (8.1%)   | 0.88 (0.15, 5.27)| 1.000          |
| Interferon-α-2b               | 2568 10 (0.4%)| 1955 73 (3.7%)| 0.55 (0.38, 0.80)| <0.001         |
| Antibiotics                   | NA            |               |           |               |
| Chinese Medicines             | 2946 5 (0.2%) | 1577 78 (4.9%)| 2.74 (1.56, 4.80)| <0.001         |

Note: OR > 1 (or < 1) indicates the treatment was associated with higher (or lower) risk of composite outcome.

1 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.

2 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.

| Interventions initiated regardless of timing of initiation | Treatment | Hong Kong SAR | Anhui |
|-----------------------------------------------------------|-----------|---------------|-------|
| | N | Mean | SD | N | Mean | SD | Difference | (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Lopinavir-ritonavir | 2835 | 12.3 | 9.0 | 1510 | 21.1 | 13.3 | 8.8 | (8.1, 9.4) | <0.001 |
| Ribavirin | 3140 | 13.8 | 11.1 | 1205 | 21.2 | 13.7 | 7.4 | (6.6, 8.1) | <0.001 |
| Umifenovir | NA | | | | | | | | |
| Corticosteroids | 3717 | 13.6 | 9.4 | 628 | 18.1 | 13.0 | 4.4 | (3.7, 5.1) | <0.001 |
| Dexamethasone | 3717 | 13.6 | 9.4 | 525 | 17.0 | 12.6 | 3.3 | (2.6, 4.1) | <0.001 |
| Hydrocortisone | 3717 | 13.6 | 9.4 | 117 | 19.0 | 13.6 | 5.4 | (4.6, 6.1) | <0.001 |
| Methylprednisolone | 3717 | 13.6 | 9.4 | 6 | 27.1 | 13.8 | 13.5 | (8.2, 18.7) | <0.001 |
| Prednisolone | 3717 | 13.6 | 9.4 | 43 | 23.2 | 21.7 | 9.5 | (7.4, 11.6) | <0.001 |
| Interferon-2b | NA | | | | | | | | |
| Interferon-β-1b | 2420 | 23.9 | 17.8 | 1925 | 15.1 | 11.1 | −8.8 | (−9.7, −7.9) | <0.001 |
| Chinese Medicines | NA | | | | | | | | |
| Antibiotics | 2814 | 12.5 | 7.8 | 1531 | 17.1 | 12.3 | 4.6 | (4.0, 5.2) | <0.001 |
| Hydromorphone | NA | | | | | | | | |

#### Interventions initiated within 7 days of symptom onset

| Interventions initiated within 7 days of symptom onset | Treatment | Hong Kong SAR | Anhui |
|-------------------------------------------------------|-----------|---------------|-------|
| | N | Mean | SD | N | Mean | SD | Difference | (95% CI) | P-value |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Lopinavir-ritonavir | 2835 | 12.3 | 9.0 | 1164 | 21.3 | 13.0 | 9.0 | (8.3, 9.7) | <0.001 |
| Ribavirin | 3140 | 13.8 | 11.1 | 852 | 21.7 | 13.5 | 7.9 | (7.1, 8.7) | <0.001 |
| Umifenovir | NA | | | | | | | | |
| Corticosteroids | 3717 | 13.6 | 9.4 | 268 | 19.9 | 15.1 | 6.2 | (5.4, 7.1) | <0.001 |
| Dexamethasone | 3717 | 13.6 | 9.4 | 216 | 17.4 | 16.1 | 3.8 | (2.6, 5.0) | <0.001 |
| Hydrocortisone | 3717 | 13.6 | 9.4 | 44 | 21.7 | 14.3 | 8.1 | (7.1, 9.1) | <0.001 |
| Methylprednisolone | 3717 | 13.6 | 9.4 | 2 | 40.5 | 4.4 | 26.8 | (16.6, 37.1) | <0.001 |
| Prednisolone | 3717 | 13.6 | 9.4 | 13 | 13.5 | 8.8 | −0.1 | (−3.0, 2.8) | 1.000 |
| Interferon-α-2b | NA | | | | | | | | |
| Interferon-β-1b | 2420 | 23.9 | 17.8 | 1556 | 15.4 | 11.4 | −8.4 | (−9.4, −7.4) | <0.001 |
| Chinese Medicines | NA | | | | | | | | |
| Antibiotics | 2814 | 12.5 | 7.8 | 1073 | 17.8 | 12.3 | 5.3 | (4.6, 5.9) | <0.001 |
| Dexamethasone | 3717 | 13.6 | 9.4 | 360 | 16.7 | 11.0 | 3.1 | (2.4, 3.8) | <0.001 |
| Hydrocortisone | 3717 | 13.6 | 9.4 | 309 | 16.7 | 10.0 | 3.1 | (2.2, 3.9) | <0.001 |
| Methylprednisolone | 3717 | 13.6 | 9.4 | 73 | 17.0 | 12.7 | 3.4 | (2.5, 4.2) | <0.001 |
| Prednisolone | 3717 | 13.6 | 9.4 | 4 | 22.3 | 12.9 | 8.7 | (26.4, 14.8) | <0.001 |
| Interferon-α-2b | NA | | | | | | | | |
| Interferon-β-1b | 2420 | 23.9 | 17.8 | 369 | 13.9 | 9.8 | −10.0 | (−11.8, −8.1) | <0.001 |
| Chinese Medicines | NA | | | | | | | | |
| Antibiotics | 2814 | 12.5 | 7.8 | 458 | 15.4 | 11.9 | 2.9 | (2.1, 3.7) | <0.001 |
| Dexamethasone | 3717 | 13.6 | 9.4 | 30 | 31.2 | 25.7 | 17.5 | (14.7, 20.4) | <0.001 |
| Hydrocortisone | 3717 | 13.6 | 9.4 | 4 | 22.3 | 12.9 | 8.7 | (26.4, 14.8) | <0.001 |
| Methylprednisolone | 3717 | 13.6 | 9.4 | 30 | 31.2 | 25.7 | 17.5 | (14.7, 20.4) | <0.001 |
| Prednisolone | 3717 | 13.6 | 9.4 | 4 | 22.3 | 12.9 | 8.7 | (26.4, 14.8) | <0.001 |
| Interferon-α-2b | NA | | | | | | | | |
| Interferon-β-1b | 2420 | 23.9 | 17.8 | 369 | 13.9 | 9.8 | −10.0 | (−11.8, −8.1) | <0.001 |
| Chinese Medicines | NA | | | | | | | | |
| Antibiotics | 2814 | 12.5 | 7.8 | 458 | 15.4 | 11.9 | 2.9 | (2.1, 3.7) | <0.001 |

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

1. Difference <0 (or >0) indicates the treatment was associated with shorter (or longer) time to discharge.
2. 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.
3. Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.
who died during admission or not yet discharged were excluded from the analysis. Note: OR = Odds ratio; CI = confidence interval.

| Composite outcome | Treatment | N | Event (%) | OR | 95% CI | P-value<sup>a</sup> |
|-------------------|-----------|---|-----------|----|--------|----------------------|
| 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<sup>a</sup> |
|--------------------------------------------------------|---|------|----|------------|--------|----------------------|
| Interferon-β-1b monotherapy | | 156 | 15.5 | 12.3 | -2.35 | (-3.65, -1.06) | <0.001 |
| Interferon-β-1b + ribavirin | | 550 | 13.2 | 8.4 | 1.10 | (-0.15, 2.35) | 0.020 |
| 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.

<sup>a</sup> 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.

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 times in Hong Kong Special Administrative Region (HKSAR) of China.

| Composite outcome | Treatment | N<sup>b</sup> | Event (%) | OR | 95% CI | P-value<sup>a</sup> |
|-------------------|-----------|---|-----------|----|--------|----------------------|
| Interferon-β-1b + lopinavir-ritonavir | | 444 | 23.6 | 16.1 | 8.10 | (6.85, 9.34) | <0.001 |
| 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<sup>b</sup> | Mean | SD | Difference | 95% CI | P-value<sup>a</sup> |
|--------------------------------------------------------|---|------|----|------------|--------|----------------------|
| Interferon-β-1b + lopinavir-ritonavir | | 123 | 26.7 | 20.4 | 4.15 | (6.3, 6.67) | <0.001 |
| Interferon-β-1b + lopinavir-ritonavir + ribavirin | | 255 | 22.6 | 13.6 | -2.23 | (-4.79, 0.32) | 0.101 |

Note: OR = Odds ratio; CI = confidence interval; NA = Not applicable.

<sup>a</sup> 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.

<sup>b</sup> Adjusted confidence interval and p-value of Bonferroni correction for multiple comparison.
Anhui had routine access to data of remdesivir administration during hydroxychloroquine /chloroquine. Remdesivir is the only direct anti-observations. Finally, our study did not evaluate remdesivir or ...course of illness, which in reality could be the preferred treatment adequacy evaluate other combinations of antivirals, immunomodu-
lation experience of two large Chinese locations in order to provide adaption of the data; preparation, review, or approval of the manuscript; ...provide 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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