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Effectiveness of Ribavirin and Corticosteroids for Severe Acute Respiratory Syndrome

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ABSTRACT

OBJECTIVE: Ribavirin and corticosteroids were used widely as front-line treatments for severe acute respiratory syndrome; however, previous evaluations were inconclusive. We assessed the effectiveness of ribavirin and corticosteroids as the initial treatment for severe acute respiratory syndrome using propensity score analysis.

METHODS: We analyzed data on 1755 patients in Hong Kong and 191 patients in Toronto with severe acute respiratory syndrome using a generalized propensity score approach.

RESULTS: The adjusted excess case fatality ratios of patients with severe acute respiratory syndrome receiving the combined therapy of ribavirin and corticosteroids within 2 days of admission, compared with those receiving neither treatment within 2 days of admission, were 3.8% (95% confidence interval, -1.5 to 9.2) in Hong Kong and 2.1% (95% confidence interval, -44.3 to 48.5) in Toronto.

CONCLUSIONS: Our results add strength to the hypothesis that the combination of ribavirin and corticosteroids has no therapeutic benefit when given early during severe acute respiratory syndrome infection. Further studies may investigate the effects of these treatments later in disease course.

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The severe acute respiratory syndrome outbreak in 2002 and 2003 infected more than 8000 people in 29 territories with an overall worldwide case fatality ratio of 9.6%.[1] Hong Kong and Toronto bore a significant proportion of the global case burden, together accounting for 25% of all "probable cases."[1] Although there have been only sporadic human infections with the severe acute respiratory syndrome coronavirus since the first global outbreak,[2] the pos-

sibility of widespread reemergence cannot be ruled out given the continued trading and consumption of palm civets, a likely animal reservoir.[3,4] Meanwhile, severe acute respiratory syndrome-like coronaviruses are endemic in bats in Hong Kong and southern China.[5,6]

Ribavirin has broad activity against many DNA and RNA viruses.[7] Corticosteroids can be protective against extensive inflammatory lung damage.[8,9] Therefore, these 2 drugs were recommended for use as front-line treatments during the outbreak, although not without controversy.[10] Evaluation of the effectiveness of these 2 drugs in the treatment of severe acute respiratory syndrome has consisted largely of uncontrolled studies and small hospital cohorts. A recent meta-analysis confirmed that there are few reliable data on which to base future treatment decisions in severe acute respiratory syndrome, largely because of the lack of adjustment for important confounding variables in evaluative studies published to date.[11] Although randomized controlled trials would provide more conclusive evidence, they cannot be conducted unless large future out-

breaks occur,[12] and in the meantime it is critical that current recommendations, both for the treatment of patients and for the identification of those agents that should be prioritized for testing in future trials, are based on the best available data.

We analyzed data on patients with severe acute respiratory syndrome from Hong Kong and Toronto to assess and compare the treatment efficacies, as measured by mortality reduction, of early administration of ribavirin alone, corticosteroids alone, or both in combination. We used propensity score analysis to adjust for potential confounding effects, an approach that has been proposed as the most valid analytic strategy for observational data in the absence of a randomized design[13] and has been used to evaluate drug effectiveness in many observational studies.[14-18] In addition to providing important evidence-based guidance for future human cases of severe acute respiratory syndrome, our work may serve as a template for the evaluation of treatment efficacies for other emerging infectious diseases.

CLINICAL SIGNIFICANCE

- Previous evaluations on the effectiveness of ribavirin and corticosteroids in treating severe acute respiratory syndrome were inconclusive.

- On the basis of a large dataset with 25% of global severe acute respiratory syndrome cases and properly adjusted for treatment selection bias, the combination of ribavirin and corticosteroids was found to have no significant beneficial effect in the initial treatment of patients with severe acute respiratory syndrome.

We included all patients in Hong Kong. In Toronto the outbreak occurred in 2 waves (first wave: March 2 to April 21; second wave: April 22 to June 10),[22] and ribavirin was not used at all during the second wave because of clinical experience in the first wave.[12] In this analysis we require that each patient had the opportunity to be treated with ribavirin or corticosteroids, and therefore we excluded the 94 patients in Toronto who were admitted to hospital during the second wave. We excluded the 12 patients (0.6%) in Hong Kong and 2 patients (1%) in Toronto who died within 2 days of admission.

Statistical Analysis

In randomized controlled trials, the randomization process should on average balance patient characteristics across treatment groups, and comparison of crude event rates across treatment groups should be unconfounded,[23] although adjustment for potential confounders may improve precision.[24] However, in situations in which treatment assignment is not random, but may depend on patients' presenting characteristics and clinical course, failure to appropriately adjust for such factors may lead to misleading findings. Standardization or stratification can be carried out for each characteristic but is typically not feasible when there are a large number of potential confounders. Regression adjustment is often used provided there are sufficient events; a simple rule of thumb is 20 events (eg, deaths) per potential confounder.[25]

An alternative approach is the use of propensity score analysis.[13] Under this approach, a model is specified to explain the assignment of treatments in terms of patient characteristics. The predicted probabilities, or "propensity scores" from this model are in turn incorporated in a successive model to assess the association between the treatment and the outcome of interest. In the latter model, the estimate of the treatment effect should reflect adjustment for differences in the observed patient characteristics between treatment groups.

To study the relative effects on mortality of the 4 treatment groups, namely, neither drug, ribavirin alone, corticosteroids alone, or both drugs, we used a generalized propensity score approach that can allow for more than 2 treatment choices.[26] We estimated the propensity scores using a multinomial regression model adjusting for the key patient characteristics at admission as described above and 3 other factors, including calendar date of onset, onset-to-admission delay, and admitting hospital. Because some prognostic factors were only available for a subset of approximately 30% of the patients in Hong Kong and 60% of

MATERIALS AND METHODS

Data Sources

We analyzed an integrated database containing clinical and epidemiologic details on all 1755 patients in Hong Kong reported to have "probable severe acute respiratory syndrome" according to the World Health Organization definition,[19] derived from the Hong Kong Hospital Authority Electronic Severe Acute Respiratory Syndrome system and the Hong Kong Department of Health's Master list.[19,20] For the Toronto data, the Canadian Severe Acute Respiratory Syndrome Research Network conducted a retrospective cohort study of all probable severe acute respiratory syndrome cases among adults (age ≥ 16 years) admitted to a hospital during the outbreak.[20,21] Medical charts were reviewed by trained research staff, and clinical, radiographic, and laboratory data were double entered into a database.

Key patient characteristics at hospital admission that were extracted from these 2 sources included gender, age, occupation, preexisting comorbid conditions, calendar date of symptom onset, delay between symptom onset and admission, lactate dehydrogenase level, chest radiograph findings, neutrophil count, platelet count, lymphocyte count, and oxygen saturation. We classified patients into 4 treatment groups based on whether they had started a course of ribavirin, corticosteroids, both ribavirin and corticosteroids, or neither drug within 2 days of admission to hospital.

the patients in Toronto,[20] we used multiple imputation to make best use of all available data in the propensity score model.[27-30] Ten datasets were constructed on the basis of all clinical, demographic, and outcome variables with imputed values based on a generalized additive model and predictive mean matching (function aregImpute in R library Hmisc). We used chi-square tests to evaluate whether the propensity scores were able to balance observed covariates across treatment groups. We then weighted the observed individual outcome by the inverse estimated propensity scores to infer adjusted case fatality ratios in each treatment arm.[26] We used case-resampling bootstrap with 1000 repetitions in each imputed dataset to estimate 95% confidence intervals (CIs) for the case fatality ratios.[31]

For the primary analysis we focused on treatment choice within 2 days of hospital admission, because early treatment decisions were most likely based on patient characteristics at hospital admission as opposed to later treatment decisions that also would have been affected by the effects of initial treatments and the subsequent course of illness. We carried out sensitivity analyses to examine the effectiveness of treatment assignments within 1 to 5 days of admission. Further technical details of the methods are described in the Appendix. All analyses were conducted in R version 2.3.1.[32]

This study received ethics approval from the institutional review boards of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, Hong Kong; McMaster University, Hamilton, Ontario; the University of Toronto, Toronto; and all Toronto-area hospitals where data were collected.

RESULTS

Table 1 summarizes the patient characteristics in Hong Kong and Toronto, by treatment within 2 days of admission. More detailed comparison of the characteristics is given in Appendix Table 1. There were statistically significant differences ($P < .001$) in all demographic variables across the 4 treatment groups in Hong Kong, whereas clinical variables were relatively more balanced across groups. For patients in Toronto, the distribution of characteristics was more balanced across treatment groups, especially in demographic variables, but there were greater differences in delay between symptom onset and admission, lactate dehydrogenase level, and neutrophil count ($P \le .05$). In Hong Kong and Toronto, 301 (17.3%) and 25 (12.6%) deaths occurred in total, respectively. The crude case fatality ratios were higher in the patients untreated with ribavirin or corticosteroids within 2 days of admission (23.3% and 20.0%, respectively) compared with those treated with ribavirin and corticosteroids within 2 days of admission (12.6% and 12.8%, respectively). The crude combined treatment effect of ribavirin and corticosteroids in Hong Kong and Toronto, in terms of absolute risk reduction, was 10.7% and 7.2%, respectively.

Table 1 Characteristics at Hospital Admission of All Patients with Probable Severe Acute Respiratory Syndrome in Hong Kong and Patients Infected in the First Phase of the Toronto Epidemic[a] (Onset before April 22, 2003)

Characteristic	Hong Kong (n = 1743)								Toronto (n = 191)					
	Neither Treatment	(%)	Ribavirin Only	(%)	Corticosteroids Only	(%)	Ribavirin and Corticosteroids	(%)	Neither Treatment	(%)	Ribavirin Only	(%)	Ribavirin and Corticosteroids	(%)
Men	379	(50.5)	85	(42.1)	23	(45.1)	286	(38.7)	16	(35.6)	40	(37.4)	18	(46.2)
Age ≤ 39 y	297	(39.5)	123	(60.9)	19	(37.3)	403	(54.5)	18	(40.0)	43	(40.2)	14	(35.9)
Age 40-49 y	124	(16.5)	36	(17.8)	6	(11.8)	172	(23.3)	9	(20.0)	26	(24.3)	9	(23.1)
Age 50-59 y	73	(9.7)	15	(7.4)	7	(13.7)	93	(12.6)	7	(15.6)	16	(15.0)	7	(17.9)
Age 60-69 y	70	(9.3)	14	(6.9)	8	(15.7)	30	(4.1)	4	(8.9)	13	(12.1)	5	(12.8)
Age > 69 y	187	(24.9)	14	(6.9)	11	(21.6)	41	(5.5)	7	(15.6)	9	(8.4)	4	(10.3)
Health care worker	120	(16.0)	72	(35.6)	7	(13.7)	205	(27.7)	14	(31.1)	48	(44.9)	16	(41.0)
With preexisting comorbid conditions	220	(29.3)	28	(13.9)	18	(35.3)	90	(12.2)	11	(24.4)	18	(16.8)	5	(12.8)
Data on comorbid conditions missing	2	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Died	175	(23.3)	18	(8.9)	15	(29.4)	93	(12.6)	9	(20.0)	10	(9.3)	5	(12.8)

[a]Only 3 patients were treated with corticosteroids in Toronto and were excluded.
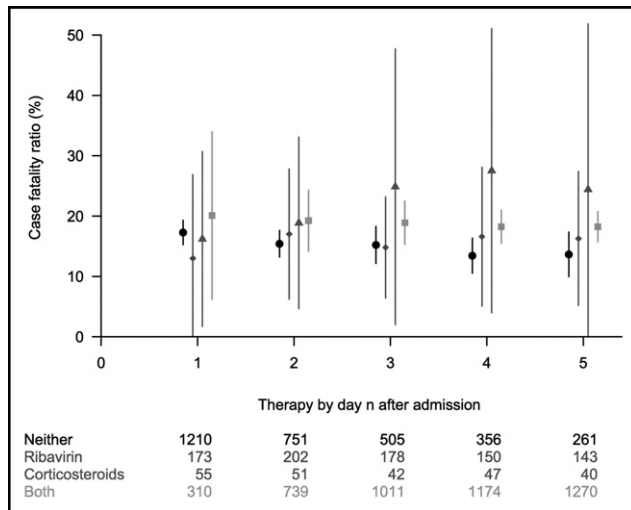
Figure 1 Estimated case fatality ratios and associated 95% CIs for alternative treatment strategies in Hong Kong (*circle:* neither treatment; *diamond:* ribavirin only; *triangle:* corticosteroids only; *square:* both treatments) within 1 to 5 days of hospital admission of all patients with probable severe acute respiratory syndrome, using generalized propensity score analysis.

In Hong Kong, younger patients, health care workers, those with a longer delay between symptom onset and admission, and those with earlier calendar date of symptom onset were more likely to be treated with both ribavirin and corticosteroids (Appendix Table 2). In Toronto, patients with younger age, longer delay between symptom onset and admission, high lactate dehydrogenase level, or hazy chest radiograph were more likely to be treated with both ribavirin and corticosteroids. After adjustment for propensity scores, balance was achieved among all patient characteristics (test for heterogeneity across treatment groups not explained by propensity score, $P > .24$ for all covariates in Hong Kong; $P > .10$ for all covariates in Toronto).

Table 2 shows the estimated case fatality ratio by treatment group in Hong Kong and Toronto based on the generalized propensity score weighting. By adjusting for patient characteristics, the model predicted that the overall case fatality ratio would have been highest (19.2%) if all patients in Hong Kong had been treated with both ribavirin and corticosteroids within 2 days of admission, whereas it would have been lowest (15.4%) if no Hong Kong patients had been treated with ribavirin or with corticosteroids within 2 days of admission. The difference in case fatality ratios was 3.8% (95% CI, -1.5 to 9.2, $P = .16$), which suggests at most no effectiveness of combined therapy with ribavirin and corticosteroids, and is inconsistent with even a mildly beneficial effect of these treatments. The results for Toronto were generally consistent albeit with wide confidence bounds because of the relatively small sample size (Table 2), and the adjusted excess case fatality ratios for ribavirin and corticosteroids versus neither treatment within

2 days of admission was 2.1% (95% CI, -44.3 to 48.5, $P = .93$).

In sensitivity analyses, Figures 1 and 2 show the estimated case fatality ratios in Hong Kong and Toronto, respectively, for 5 separate analyses in which patients were grouped by the treatment they had received within days of hospital admission for $d = 1, 2, \ldots, 5$. For Hong Kong, the estimated case fatality ratios were consistent with the main results in Table 2 and generally stable across the different cutoffs, except for the small numbers of patients receiving corticosteroids only. Appendix Table 3 shows the estimated adjusted odds ratio of case fatality ratios among treatments, based on conventional multinomial logistic regression models on 10 imputed datasets. For Hong Kong, the estimated odds ratio is consistent with the main results in Table 2, where patients treated with both ribavirin and corticosteroids had a higher case fatality ratio and the difference was marginally statistically significant. For Toronto, the results were not statistically significant with wide CIs.

DISCUSSION

During the 2003 severe acute respiratory syndrome outbreaks in Hong Kong and Toronto, ribavirin and corticosteroids were widely used, although no controlled studies of their effectiveness were performed because of the novelty of the causative agent. This study used propensity score methods to estimate the effectiveness of ribavirin and corticosteroids for severe acute respiratory syndrome early in the course of disease, adjusting for differences in patient characteristics between treatment arms.[11] For example, the most significant factors associated with severe acute respiratory
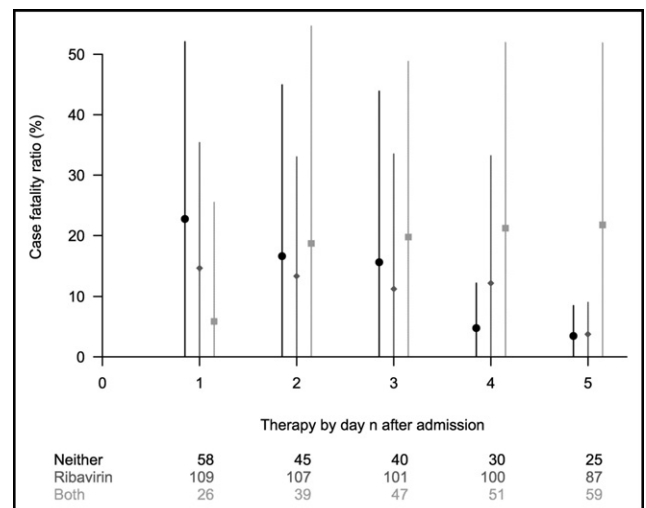
Figure 2 Estimated case fatality ratios and the associated 95% CIs under alternative treatment strategies in Toronto (*circle:* neither treatment; *diamond:* ribavirin only; *triangle:* corticosteroids only; *square:* both treatments) within 1 to 5 days of hospital admission of all patients with probable severe acute respiratory syndrome, using generalized propensity score analysis.

Table 2   Case Fatality Ratios and Associated 95% Confidence Intervals in Hong Kong and Toronto by Treatment Received within 2 Days of Hospital Admission, Estimated by Generalized Propensity Score Analysis

Treatment	Hong Kong			Toronto		
	Case Fatality Ratio[a] (%)	95% CI	P Value[b]	Case Fatality Ratio[a] (%)	95% CI	P Value[b]
Neither ribavirin nor corticosteroids	15.4	(13.2-17.6)	—	16.6	(0.0-44.9)	—
Ribavirin	17.0	(6.2-27.8)	.77	13.4	(0.0-33.0)	.85
Corticosteroids	18.9	(4.6-33.1)	.64	—	—	—
Both	19.2	(14.2-24.3)	.16	18.7	(0.0-54.7)	.93

CI = confidence interval.

[a]Each case fatality ratio is the predicted case fatality ratio had *all* severe acute respiratory syndrome cases been assigned to the corresponding treatment group.

[b]P value for a difference in case fatality ratio compared with no treatment.

syndrome fatality in Hong Kong are age more than 60 years old, preexisting comorbid conditions, and non-health care worker status,[19,33] all of which were more commonly present for patients not receiving ribavirin or corticosteroids (Table 1). The high crude case fatality ratio for patients receiving neither treatment was likely because of this case mix that was fully adjusted in our propensity score analysis.[12]

We did not find any evidence that early treatment with both ribavirin and corticosteroids was beneficial to patients in general, which is consistent with previous studies.[34-37] By observing that there were higher case fatality ratios for the ever treated patients but lower case fatality ratios in patients treated within 2 days on hospital admission, it is possible that treatment decisions made later during hospitalization depended on whether patients' health status was improving or deteriorating rather than baseline clinical characteristics. Without detailed data on clinical progression, which we do not have, we cannot assess the potential benefits of therapies later in the clinical course and in particular as rescue treatment. It is always easier to act with the benefit of hindsight, and our results should not be taken as a criticism of those early prescribing decision but rather as an evaluation of treatment strategies based on information that has since become available. This also points to the need for common data-collection protocols and specification of a standardized dataset (or minimum dataset), which may facilitate integration of data during the initial period of epidemics and allow more comprehensive retrospective analyses after epidemics.

Early in the severe acute respiratory syndrome epidemic when the causative agent was still unknown, ribavirin, along with other broad-spectrum antibiotics, was used in Hong Kong and Toronto because of its in vitro activity against a broad spectrum of viral agents. On this basis, it was thought that ribavirin had the potential to suppress acute viral replication in the early phase of severe acute respiratory syndrome.[38,39] Early treatment with ribavirin was considered important because the viral load in patients with severe acute respiratory syndrome peaked at day 10 after symptom onset,[9] and the peak level was independently associated with mortality.[40] However, the in vivo inhibitory effect of ribavirin at clinically achievable doses remains controversial, significant adverse events are associated with ribavirin,[37,41] and our findings suggest that it is unlikely that ribavirin had any significant beneficial effect on patient outcome.

Corticosteroids were used to reduce pulmonary damage because of the immune-mediated inflammatory responses that usually started in the second week.[9,42] However, early corticosteroids treatment during the stage of viral replication may have suppressed the immune response and allowed a higher peak viral level.[43,44] The clinical effectiveness of corticosteroid therapy has not been established for severe acute respiratory syndrome[45,46] or acute respiratory distress syndrome,[47] and corticosteroids use in severe acute respiratory syndrome was associated with aspergillus superinfection, avascular necrosis, reduced bone mineral density, and other long-term adverse outcomes.[48-50]

LIMITATIONS

A limitation of our analysis is that a propensity score model cannot adjust for unmeasured confounding variables and that the unconfoundedness assumption of propensity score models is inherently untestable. However, given that our analysis included and balanced the most important variables that have been identified as predictive of survival,[20,34,51] the best effort was made to control for potential confounders. Our data on treatment assignments are limited to information on the first date of ribavirin use and the first date of corticosteroid use; therefore, we have been unable to investigate alternative strategies of treatment administration, for example, whether corticosteroids were pulsed or not or variations in dosage or duration of treatment. We do not have data on other treatments, such as lopinavir/ritonavir, which was associated with improved clinical outcomes in a small uncontrolled study,[52] or traditional Chinese medicine.[53] The main analyses were based on treatment choice within 2 days of admission; however, results were consistent when treatment within 1, 3, 4, or 5 days of admission was considered. A further limitation is the presence of substantial proportions of missing data on some clinical variables. We implemented multiple imputation to use all

available data in the analysis, which is considered the gold standard approach,[54] and the estimated treatment effects were consistent with those estimated in a complete case analysis (data not shown). Another limitation is that outcomes other than death were not considered; common side effects such as avascular necrosis due to corticosteroid therapy might have a significant impact on long-term quality of life, but such outcomes were not considered in this study.[48,49] A more complete comparison between treatments should consider both nonfatal adverse drug effects and quality of life. A complete dataset including disease progression and all clinical events (eg, ventilation) was not available. Finally, our analyses were based on patients with probable severe acute respiratory syndrome according to the World Health Organization definition.[55] We adopted this definition rather than laboratory confirmation because the latter definition may be potentially biased toward including more survivors, particularly in the early cases.[19]

CONCLUSIONS

On the basis of a large sample from 2 epicenters, our results add strength to the hypothesis that the combination of ribavirin and corticosteroids has no significant beneficial effect in the treatment of severe acute respiratory syndrome. In the absence of further evidence, clinicians should not use ribavirin and corticosteroids to treat severe acute respiratory syndrome because to the best of our knowledge, they provide no benefit in terms of survival. Investigators should consider other promising therapies in the event of another outbreak of severe acute respiratory syndrome, and ideally protocols would be in place to evaluate alternative treatments in randomized trials.

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APPENDIX

For the primary analysis that compares all 4 treatment choices within the first 2 days after admission, we applied a multivariable multinomial regression model to estimate the propensity scores for each of the 4 treatment alternatives, including variables that were likely to be influential in early treatment decisions. The latter included the following known prognostic factors: age, gender, health care worker, presence of comorbid condition, hospital, delay in admission, onset date, lactate dehydrogenase level, chest radiograph, oxygen saturation on room air, neutrophil count, platelets, and lymphocyte count,[20] and 3 other factors that may have been potentially important in treatment assignment, including date of onset, onset-to-admission delay, and hospital. Because some prognostic factors were only available for a subset of up to approximately 30% of the patients in Hong Kong and 60% of the patients in Toronto,[20] we used multiple imputation to facilitate inclusion of these factors in the propensity score model.[27] The resulting propensity scores were then used to weigh the case fatality ratios in each treatment group, allowing estimation of the mean causal effect,[26] that is, for each treatment group we estimated the overall case fatality ratios had all patients been assigned to that particular treatment. Let p_{it} be the estimated propensity score for patient i with treatment t, D_i be 1 for a death outcome for patient i, and I be an indicator function; then the propensity score-adjusted case fatality ratio for each treatment t is given by:

$$CFR_t = \frac{1}{n}\sum_{i=1}^{n}\frac{D_i I(T_i = t)}{p_{it}}$$

Appendix Table 1   Characteristics at Hospital Admission of all Patients with Probable Severe Acute Respiratory Syndrome in Hong Kong and Patients Infected in the First Phase of the Toronto Epidemic[a] (Onset before April 22, 2003)

Characteristic	Hong Kong								Toronto					
	Neither Treatment	(%)	Ribavirin Only	(%)	Corticosteroids Only	(%)	Ribavirin and Corticosteroids	(%)	Neither Treatment	(%)	Ribavirin Only	(%)	Ribavirin and Corticosteroids	(%)
Gender														
Women	372	(49.5)	117	(57.9)	28	(54.9)	453	(61.3)	29	(64.4)	67	(62.6)	21	(53.8)
Men	379	(50.5)	85	(42.1)	23	(45.1)	286	(38.7)	16	(35.6)	40	(37.4)	18	(46.2)
Age, y														
≤39	297	(39.5)	123	(60.9)	19	(37.3)	403	(54.5)	18	(40.0)	43	(40.2)	14	(35.9)
40-49	124	(16.5)	36	(17.8)	6	(11.8)	172	(23.3)	9	(20.0)	26	(24.3)	9	(23.1)
50-59	73	(9.7)	15	(7.4)	7	(13.7)	93	(12.6)	7	(15.6)	16	(15.0)	7	(17.9)
60-69	70	(9.3)	14	(6.9)	8	(15.7)	30	(4.1)	4	(8.9)	13	(12.1)	5	(12.8)
>69	187	(24.9)	14	(6.9)	11	(21.6)	41	(5.5)	7	(15.6)	9	(8.4)	4	(10.3)
Health care worker														
Yes	120	(16.0)	72	(35.6)	7	(13.7)	205	(27.7)	14	(31.1)	48	(44.9)	16	(41.0)
No	631	(84.0)	130	(64.4)	44	(86.3)	534	(72.3)	31	(68.9)	59	(55.1)	23	(59.0)
Preexisting comorbid conditions														
Yes	220	(29.3)	28	(13.9)	18	(35.3)	90	(12.2)	11	(24.4)	18	(16.8)	5	(12.8)
No	529	(70.4)	174	(86.1)	33	(64.7)	649	(87.8)	34	(75.6)	89	(83.2)	34	(87.2)
Data missing	2	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Delay in admission, d														
≤0	229	(30.5)	26	(12.9)	19	(37.3)	60	(8.1)	19	(42.2)	6	(5.6)	1	(2.6)
1-2	190	(25.3)	79	(39.1)	10	(19.6)	233	(31.5)	11	(24.4)	18	(16.8)	10	(25.6)
3-4	189	(25.2)	64	(31.7)	10	(19.6)	214	(29.0)	8	(17.8)	30	(28.0)	11	(28.2)
≥5	143	(19.0)	33	(16.3)	12	(23.5)	232	(31.4)	7	(15.6)	53	(49.5)	17	(43.6)
Symptom onset date														
February 15 to March 23	238	(31.7)	25	(12.4)	16	(31.4)	161	(21.8)	—		—		—	
March 24 to March 29	126	(16.8)	27	(13.4)	10	(19.6)	296	(40.1)	—		—		—	
March 30 to April 9	171	(22.8)	39	(19.3)	11	(21.6)	186	(25.2)	—		—		—	
April 9 to May 31	216	(28.8)	111	(55.0)	14	(27.5)	96	(13.0)	—		—		—	
Lactate dehydrogenase level[b]														
Greater than upper limit of normal	299	(39.8)	85	(42.1)	22	(43.1)	329	(44.5)	6	(13.3)	46	(43.0)	14	(35.9)
Normal	311	(41.4)	105	(52.0)	20	(39.2)	345	(46.7)	20	(44.4)	31	(29.0)	15	(38.5)
Data missing	141	(18.8)	12	(5.9)	9	(17.6)	65	(8.8)	19	(42.2)	30	(28.0)	10	(25.6)

Appendix Table 1 Continued

Characteristic	Hong Kong								Toronto					
	Neither Treatment	(%)	Ribavirin Only	(%)	Corticosteroids Only	(%)	Ribavirin and Corticosteroids	(%)	Neither Treatment	(%)	Ribavirin Only	(%)	Ribavirin and Corticosteroids	(%)
Chest radiograph														
Normal	44	(5.9)	26	(12.9)	4	(7.8)	82	(11.1)	5	(11.1)	22	(20.6)	15	(38.5)
Haziness	63	(8.4)	20	(9.9)	2	(3.9)	164	(22.2)	—		—		—	
Pneumonic consolidation	53	(7.1)	7	(3.5)	5	(9.8)	66	(8.9)	28	(62.2)	68	(63.6)	19	(48.7)
Data missing	591	(78.7)	149	(73.8)	40	(78.4)	427	(57.8)	12	(26.7)	17	(15.9)	5	(12.8)
Neutrophil count[c]														
Less than lower limit of normal	10	(1.3)	5	(2.5)	0	(0.0)	16	(2.2)	1	(2.2)	12	(11.2)	6	(15.4)
Normal	99	(13.2)	34	(16.8)	7	(13.7)	245	(33.2)	31	(68.9)	79	(73.8)	28	(71.8)
Greater than upper limit of normal	14	(1.9)	2	(1.0)	1	(2.0)	20	(2.7)	6	(13.3)	9	(8.4)	5	(12.8)
Data missing	628	(83.6)	161	(79.7)	43	(84.3)	458	(62.0)	7	(15.6)	7	(6.5)	0	(0.0)
Platelet count[d]														
Less than lower limit of normal	42	(5.6)	11	(5.4)	5	(9.8)	98	(13.3)	7	(15.6)	22	(20.6)	13	(33.3)
Normal	85	(11.3)	37	(18.3)	3	(5.9)	195	(26.4)	32	(71.1)	83	(77.6)	25	(64.1)
Data missing	624	(83.1)	154	(76.2)	43	(84.3)	446	(60.4)	6	(13.3)	2	(1.9)	1	(2.6)
Lymphocyte count[e]														
Less than lower limit of normal	87	(11.6)	27	(13.4)	7	(13.7)	214	(29.0)	32	(71.1)	88	(82.2)	33	(84.6)
Normal	21	(2.8)	7	(3.5)	1	(2.0)	30	(4.1)	3	(6.7)	10	(9.3)	4	(10.3)
Data missing	643	(85.6)	168	(83.2)	43	(84.3)	495	(67.0)	10	(22.2)	9	(8.4)	2	(5.1)
Oxygen saturation														
<95%	8	(1.1)	0	(0.0)	2	(3.9)	9	(1.2)	13	(28.9)	40	(37.4)	13	(33.3)
≥95%	130	(17.3)	52	(25.7)	8	(15.7)	295	(39.9)	29	(64.4)	62	(57.9)	25	(64.1)
Data missing	613	(81.6)	150	(74.3)	41	(80.4)	435	(58.9)	4	(6.7)	5	(4.7)	1	(2.6)
Outcome														
Death	175	(23.3)	18	(8.9)	15	(29.4)	93	(12.6)	9	(20.0)	10	(9.3)	5	(12.8)
Recovery	576	(76.7)	184	(91.1)	36	(70.6)	646	(87.4)	36	(80.0)	97	(90.7)	34	(87.2)

[a] Only 3 patients were treated with corticosteroids only in Toronto and were excluded.
[b] Lactate dehydrogenase level (upper limit of normal: > 225 U/L).
[c] Neutrophil count (lower limit of normal = 2.0 × 109 cells/L; upper limit of normal = 7.5 × 109 cells/L).
[d] Platelet count (lower limit of normal = 150 × 109 cells/L).
[e] Lymphocyte count (lower limit of normal = 1.5 × 109 cells/L).

Appendix Table 2 Factors Associated with Treatment Assignment of Probable Severe Acute Respiratory Syndrome Cases in Hong Kong and in the First Phase of the Epidemic[a] (Onset before April 22, 2003) in Toronto, with Associated Confidence Intervals for the Estimated Odds Ratio[b] in the Propensity Score Multinomial Regression Model, Based on 10 Imputed Datasets

| | Hong Kong | | | | | | Toronto | | | |
| | Ribavirin Only | | Corticosteroids Only | | Ribavirin and Corticosteroids | | Ribavirin Only | | Ribavirin and Corticosteroids | |
Characteristic	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Intercept[c]	0.04	(0.01-0.17)	0.07	(0.01-0.69)	0.18	(0.07-0.44)	0.2	(0.02-1.30)	0	(0.00-0.24)
Gender										
Women	1		1		1		1		1	
Men	0.84	(0.59-1.2)	0.72	(0.39-1.32)	0.72	(0.57-0.92)	0.9	(0.34-2.25)	1.4	(0.45-4.56)
Age, y										
≤39	1		1		1		1		1	
40-49	0.63	(0.39-1.01)	0.74	(0.28-1.95)	1.12	(0.82-1.53)	0.5	(0.15-1.65)	0.5	(0.13-2.14)
50-59	0.45	(0.23-0.87)	1.33	(0.50-3.54)	1.2	(0.81-1.78)	0.7	(0.19-2.76)	0.9	(0.18-4.73)
60-69	0.6	(0.29-1.25)	1.54	(0.55-4.31)	0.5	(0.30-0.85)	1.2	(0.24-5.96)	1	(0.14-6.51)
>69	0.21	(0.10-0.45)	0.65	(0.22-1.88)	0.38	(0.23-0.62)	0.8	(0.13-5.32)	1.1	(0.11-10.9)
Health care worker										
No	1		1		1		1		1	
Yes	1.67	(1.02-2.74)	0.95	(0.34-2.66)	2.45	(1.73-3.48)	2.6	(0.95-7.12)	2.1	(0.63-6.87)
Preexisting comorbid conditions										
No	1		1		1		1		1	
Yes	0.79	(0.44-1.40)	1.37	(0.61-3.07)	1.03	(0.71-1.51)	1.6	(0.36-7.51)	1.1	(0.18-6.90)
Delay in admission, d										
≤0	1		1		1		1		1	
1-2	2.99	(1.72-5.19)	0.55	(0.23-1.33)	2.59	(1.74-3.86)	8.5	(1.77-40.4)	22	(1.64-286)
3-4	3.22	(1.81-5.73)	0.56	(0.23-1.38)	2.65	(1.76-3.99)	15	(3.22-66.9)	29	(2.26-372)
≥5	3.08	(1.61-5.87)	0.97	(0.39-2.42)	4.96	(3.22-7.64)	25	(5.21-123.1)	37	(2.84-493)
Symptom onset date										
February 15 to March 23	1		1		1		—		—	
March 24 to March 29	2.68	(1.36-5.27)	1.19	(0.47-2.99)	3.52	(2.48-5.00)	—		—	
March 30 to April 9	4.22	(2.28-7.79)	1.17	(0.47-2.93)	2.66	(1.86-3.81)	—		—	
April 9 to May 31	16.36	(9.17-29.2)	1.33	(0.52-3.4)	2.12	(1.42-3.16)	—		—	
Lactate dehydrogenase level[d]										
Normal	1		1		1		1		1	
High	1.5	(0.97-2.3)	1.11	(0.56-2.19)	1.44	(1.06-1.94)	4.9	(1.58-14.9)	4.3	(1.09-16.9)
Chest radiograph										
Normal	1		1		1		1		1	
Haziness	0.87	(0.45-1.66)	0.73	(0.23-2.33)	0.97	(0.66-1.42)	—		—	
Pneumonic consolidation	0.81	(0.44-1.50)	0.81	(0.28-2.34)	0.88	(0.59-1.30)	1.1	(0.35-3.39)	4	(1.09-14.4)
Neutrophil count[e]										
Less than lower limit of normal	1		1		1		1		1	
Normal	0.86	(0.34-2.16)	1.08	(0.17-6.83)	1.24	(0.62-2.48)	0.4	(0.08-2.02)	0.9	(0.13-5.56)
Greater than upper limit of normal	0.74	(0.18-3.02)	0.87	(0.06-12.2)	1.25	(0.53-2.96)	2.8	(0.38-20.0)	6.4	(0.72-57.2)
Platelet count[f]										
Normal	1		1		1		1		1	
Less than lower limit of normal	0.92	(0.57-1.49)	1.32	(0.52-3.37)	1.04	(0.74-1.46)	0.7	(0.22-2.01)	1.5	(0.40-5.32)

Appendix Table 2   Continued

	Hong Kong						Toronto			
	Ribavirin Only		Corticosteroids Only		Ribavirin and Corticosteroids		Ribavirin Only		Ribavirin and Corticosteroids	
Characteristic	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Lymphocyte count										
Normal	1		1		1		1		1	
Less than lower limit of normal	0.98	(0.49-1.95)	1.28	(0.44-3.69)	1.18	(0.79-1.77)	0.8	(0.18-4.02)	0.8	(0.12-5.10)
Oxygen saturation										
≥95%	1		1		1		1		1	
<95%	0.76	(0.20-2.9)	1.25	(0.31-5.12)	0.99	(0.50-1.95)	1.6	(0.55-4.87)	1.4	(0.37-5.27)

OR = odds ratio; CI = confidence interval.

[a]Only 3 patients were treated with corticosteroids only in Toronto and were excluded.

[b]OR represents the relative odds of the corresponding treatment choice versus no treatment, relative to the reference group. An OR of 0.84 for men under "ribavirin only" means that men has 16% less odds than women to be treated with ribavirin only instead of no treatment.

[c]Intercept represents the baseline relative odds of the corresponding treatment choice versus no treatment.

[d]Lactate dehydrogenase level (high: > 231 U/L).

[e]Neutrophil count (lower limit of normal = 2.0×10^9 cells/L; upper limit of normal = 7.5×10^9 cells/L).

[f]Platelet count (lower limit of normal = 150×10^9 cells/L).

Appendix Table 3   Odds Ratios and Associated 95% Confidence Intervals in Hong Kong and Toronto by Treatment Received within 2 Days of Hospital Admission, Estimated by Multinomial Logistic Regression Models

	Hong Kong			Toronto		
Treatment	OR	95% CI	P Value[a]	OR	95% CI	P Value[a]
Neither ribavirin nor corticosteroids	Reference	—	—	Reference	—	—
Ribavirin	0.76	(0.35-1.62)	.43	0.42	(0.06-2.98)	.35
Corticosteroids	1.34	(0.52-3.45)	.49	—	—	—
Both	1.52	(0.94-2.47)	.08	0.54	(0.06-4.65)	.53

OR = odds ratio; CI = confidence interval.

[a]P value for the odds of death relative to no treatment, adjusted for other demographic and clinical covariates.