Original article

Non-invasive versus invasive mechanical ventilation for respiratory failure in severe acute respiratory syndrome

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Keywords: *acute respiratory failure* · *infection control* · *invasive mechanical ventilation* · *non-invasive ventilation* · *severe acute respiratory syndrome*

Background Severe acute respiratory syndrome is frequently complicated by respiratory failure requiring ventilatory support. We aimed to compare the efficacy of non-invasive ventilation against invasive mechanical ventilation treating respiratory failure in this disease.

Methods Retrospective analysis was conducted on all respiratory failure patients identified from the Hong Kong Hospital Authority Severe Acute Respiratory Syndrome Database. Intubation rate, mortality and secondary outcome of a hospital utilizing non-invasive ventilation under standard infection control conditions (NIV Hospital) were compared against 13 hospitals using solely invasive ventilation (IMV Hospitals). Multiple logistic regression analyses with adjustments for confounding variables were performed to test for association between outcomes and hospital groups.

Results Both hospital groups had comparable demographics and clinical profiles, but NIV Hospital (42 patients) had higher lactate dehydrogenase ratio and worse radiographic score on admission and ribavirin-corticosteroid commencement. Compared to IMV Hospitals (451 patients), NIV Hospital had lower adjusted odds ratios for intubation (0.36, 95% CI 0.164 – 0.791, $P = 0.011$) and death (0.235, 95% CI 0.077 – 0.716, $P = 0.011$), and improved earlier after pulsed steroid rescue. There were no instances of transmission of severe acute respiratory syndrome among health care workers due to the use of non-invasive ventilation.

Conclusion Compared to invasive mechanical ventilation, non-invasive ventilation as initial ventilatory support for acute respiratory failure in the presence of severe acute respiratory syndrome appeared to be associated with reduced intubation need and mortality.

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Severe acute respiratory syndrome (SARS) due to a novel coronavirus (SARS-CoV) emerged in November 2002 and caused outbreaks worldwide. In Hong Kong it affected 1755 individuals including 386 health care workers (HCW), and caused 299 deaths.[1] Acute respiratory failure (ARF) is common in SARS cases, with high rates of intensive care (20% – 38%), assisted ventilation (59% – 100%),[2-7] and mortality among invasively ventilated patients (34% – 53% at 28 days).[2-4,6] Non-invasive ventilation (NIV) is successful in treating ARF due to various causes, and is associated with reduced rates of intubation and nosocomial infection.[8,9] Case series from Mainland China,[10-15] Vietnam[16] and Hong Kong, China[17] had described the use of NIV in treating ARF in SARS, with reported mortality of 6% among NIV-treated patients.[17]

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The Hospital Authority developed the SARS Database in 2003, and subsequently received funding in 2004 from the Research Council of the Hong Kong Government Health, Welfare and Food Bureau for the general management and maintenance of the Database.

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The Hong Kong Hospital Authority (HA) manages all public hospitals in the territory and develops and maintains the HA SARS Database for the complete cohort of patients who fulfilled the World Health Organization criteria for probable SARS.[18] This is to our knowledge the second largest and most comprehensive database on SARS in the world. With the objective of investigating the efficacy of NIV in this disease, the Database was utilized to compare the outcomes of ARF patients supported initially with NIV against those treated solely with invasive mechanical ventilation (IMV).

METHODS

Study subjects

ARF was defined in our study by the presence of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). ARDS and ALI were defined according to the lowest ratio of arterial partial pressures of oxygen (PaO_2) divided by the fractional inspired oxygen concentration (FiO_2) administered (P/F ratio) each day, being >26.7 – 40 kPa (>200 – 299 mmHg) for ALI and ≤26.7 kPa (≤200 mmHg) for ARDS.[19] All ARF patients were identified from the HA SARS Database.

Inclusion criteria were: (1) ever developed ARF during hospitalization for SARS; (2) aged 15 – 74 years; and (3) received combination therapy (ribavirin-corticosteroid) for SARS.

Exclusion criteria were: (1) deceased patients who had never been admitted to intensive care unit (ICU) because of prior "Do not resuscitate" (DNR) orders; (2) no admission neutrophil count; (3) received Kaletra (lopinavir plus ritonavir); or (4) intubated before starting combination therapy.

Study design

Retrospective comparison of outcomes in terms of intubation and mortality was performed on two patient groups identified by hospital: NIV Hospital, the treatment protocol[17,20,21] of which stipulated NIV as initial ventilatory support; and IMV Hospitals, comprising all others (totaling 13) in which only IMV was used.

Data sources and definitions

From the HA SARS Database, the following data were retrieved: Demographics; laboratory (including laboratory evidence of SARS according to WHO criteria[22]); pharmacy; admission and discharge from on-line information systems; symptom onset dates; co-morbidity; daily observations of clinical parameters; and use of NIV and/or IMV. Co-morbidity was defined as chronic obstructive pulmonary disease, ischemic heart disease, cerebrovascular disease, malignancy, diabetes mellitus, chronic renal failure and chronic liver disease. Due to laboratory variations in reference ranges of lactate dehydrogenase (LDH), measured values divided by upper limits of respective normal ranges (LDH ratio) were used for comparison.

Respiratory assessment: to avoid undue HCW exposure to SARS patients, arterial blood gas testing was not routinely performed prior to intubation (unpublished data from HA SARS Database). PaO_2 were estimated from oxygen saturation (SpO_2) values obtained by pulse oximetry using the standard oxygen dissociation curve at 37℃, barometric pressure and $PaCO_2$ 40 mmHg,[23] and each liter of nasal oxygen was assumed to raise FiO_2 by 0.035.

Radiological assessment: two radiologists, both blinded to clinical information, together scored chest radiographs semi-quantitatively on admission; commencement of combination therapy and pulsed steroid rescue; peak radiographic involvement; and prior to discharge or death. Differences were rectified by consensus. Each lung was divided into three zones (upper, middle and lower), with extent of opacification scored as: 0 = 0%, 1 = 1% – 25%, 2 = 26% – 50%, 3 = 51% – 75%, 4 = 76% – 100% (maximum 24).

Intervention was defined as initiation of ventilatory support in the form of either NIV or IMV.

As described by Cheung et al,[17] all HCW exposed to NIV were monitored and investigated for evidence of SARS by serology after informed consent.

Management of SARS

All SARS patients in NIV Hospital were treated with a standard treatment protocol[17,20,21] summarized as follows: combination therapy for SARS was commenced only when there were respiratory and/or radiographic deterioration despite two days of broad-spectrum antibiotics to cover community-acquired pneumonia. Hypoxemia was treated with

nasal oxygen to maintain SpO_2 at 93% – 96%. Should rapid clinical and radiographic deterioration occur notwithstanding, pulsed steroid rescue (methylprednisolone 500 mg twice daily) would be administered intravenously for two days, and NIV would be commenced under infection control conditions listed below if oxygen above 5 liters per minute (LPM) failed to maintain target SpO_2. NIV applied on March 7 – 9, 2003 to the index SARS case in ICU with high (6 – 8 per hour) air change (ACH) had not resulted in SARS transmission to HCW, even though the same patient was later found to have infected 10 staff in a general ward (< 6 ACH) on March 2 – 7, 2003.

Pharmacologic therapy for SARS in IMV Hospitals was similar to NIV Hospital but with variable timing, types and dosages of corticosteroid among hospitals (Unpublished data from HA SARS Database). While infection control measures were similar among all HA hospitals after April 2003, a report about possible increased SARS transmission from nebulized therapy[22] resulted in strict avoidance of NIV as another potentially aerosol-generating procedure in IMV hospitals. Intubation followed by IMV would thus be instituted should ARF continue to deteriorate. Criteria for intubation could not be obtained from the Database.

NIV delivery and criteria for intubation in NIV Hospital[17]

NIV was delivered from a positive airway pressure system with independent positive inspired (iPAP) and expiratory (ePAP) pressures [BiPAP(r) S/T-D or BiPAP(r) S/T-D30, Respironics Inc., USA]. IPAP was adjusted to achieve respiratory rates below 25 breaths per minute and exhaled tidal volumes above 6 ml/kg. EPAP was adjusted to achieve target oxygenation with minimum carbon dioxide re-breathing. Criteria for intubation were intolerance to NIV; patient fatigue; or when supplemental oxygen at 12 LPM failed to maintain at least 93% SpO_2 while on NIV.

Infection control measures for NIV[17]

To decrease leakage and possible environmental contamination due to aerosol generation from SARS patients, viral-bacterial filters (Airlife, Allegiance; Sterivent, Tyco; Filta-Guard, DCH Healthcare) were placed between facial masks and exhalation devices providing round-the-tube outflow (Whisper-Swivel Ⅱ, Respironics). In accordance with standard infection control recommendations,[23] patients were cared in isolation cubicles in centrally air-conditioned SARS wards or ICU. Window-type exhaust ventilation fans created negative-pressure unidirectional airflow at 12 ACH per hour from the clean nursing station to patient areas and then the atmosphere. In early March 2003, HCW wore surgical masks and observed meticulous hand-washing technique. From late March to mid-April, full personal protective equipment (PPE) were worn including surgical or N-95 masks, protective eye-wear, full-faced shields, caps, gowns with full sleeve coverage, surgical gloves and shoes covers. From mid-April to early June, only HCW in direct contact with patients on NIV wore powered air purifying respirator systems (Air-Mate, 3M, USA).

Outcome measures

Primary outcome measures were need for intubation following failed NIV versus intubation in IMV Hospitals, and mortality in each hospital group. Secondary outcomes for each group included the time from specific events (ARF, pulsed steroid rescue, peak FiO_2, intervention) to clinical improvement, defined as maintenance of SpO_2 above 90% for at least four consecutive days without oxygen or after reduction by at least 50% of peak FiO_2 above room air.

Statistical analysis

To compare baseline characteristics and clinical and radiographic profiles between hospital groups on admission, commencement of combination therapy and intervention, and time to specific events as defined, descriptive statistics in terms of proportion, median, mean and standard deviation were compiled. Chi-square test or Fisher exact test, where appropriate, was performed to test for differences in proportions and Wilcoxon rank-sum test for differences in median values between groups. Non-parametric tests were adopted because patient number in NIV Hospital was small.

To test for association between outcome and hospital groups, Chi-square tests and multiple logistic regressions were performed for each primary outcome measure. The latter multivariable analyses were performed to adjust for demographics and confounding variables reported to affect outcome: age, sex, co-morbidity, admission neutrophil reading;[5,6,21,24-26] and time from symptom onset to ARF. Secondary outcome measures were compared using Wilcoxon rank-sum test. A two-

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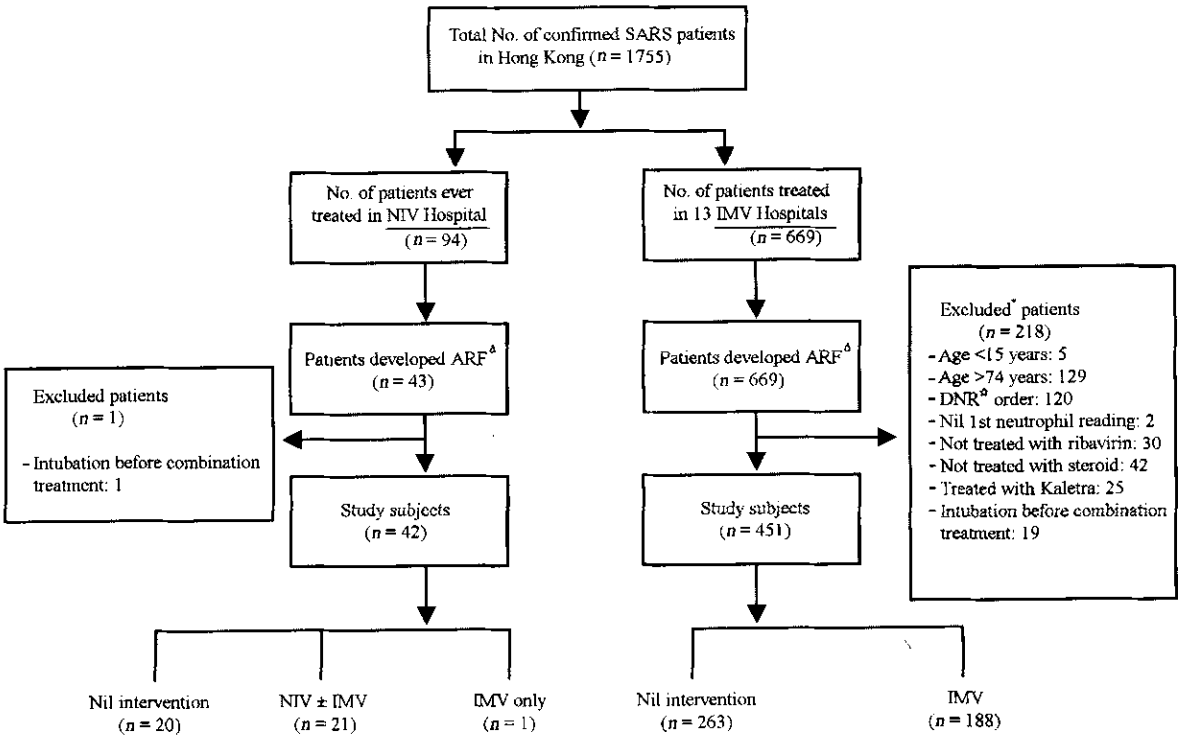

Fig. * Excluded due to one or more reasons; △ ARF: acute respiratory failure; ☆ DNR: do not resuscitate; # because of sudden collapse from post-SARS nosocomial sepsis.

sided *P* value of less than 0.05 was considered statistically significant for all test statistics. All analyses were performed using Statistical Analysis System (SAS) version 8.2 software.

RESULTS

Of 1755 SARS patients in the Database, 1462 (83.3%) had laboratory confirmed disease according to WHO criteria.[27] In total, 712 developed ARF of whom 219 were excluded from analysis (Fig.). A total of 493 patients were thus analyzed, including 42 from NIV Hospital and 451 from IMV Hospitals.

Compared to the Hong Kong study on NIV in SARS,[17] the NIV Hospital cohort included two additional patients (NIV being administered respectively for pulmonary edema and weaning post-extubation) and three episodes (foregoing episodes plus a third for pulmonary edema in a patient with a prior successful NIV episode for SARS). Both patients with pulmonary oedema failed NIV and died from cardiovascular comorbidities. In summary, 21 patients received 22 NIV episodes as initial ventilatory support, while the twenty-second patient with severe nosocomial sepsis post-SARS only received NIV post-extubation. Similar details on IMV Hospitals' patients were not available from the Database.

Apart from significantly higher LDH ratio in NIV Hospital, the groups did not differ on admission in terms of demographics, co-morbidity and laboratory-confirmed disease (Table 1). On ribavirin-corticosteroid commencement, however, the following were significantly higher in NIV Hospital: LDH ratio, proportion with ARF and use of supplemental oxygen. At the time of intervention, on the contrary, IMV Hospitals had significantly higher proportion of ARDS and FiO_2 >50% (Table 2). Timing from symptom onset to development of ARF, peak FiO_2 and pulsed steroid rescue was similar ($P > 0.05$) in the two groups (time from symptom onset was median of 11 days for NIV Hospital compared to 10 days for IMV Hospitals; peak $FiO_2$13 vs 13 days; and pulsed steroid rescue 10 vs 8 days). Apart from at discharge/death, radiographic scores were significantly higher for NIV Hospital at all time-points studied (median of 6 vs 2 for IMV Hospitals on admission, $P < 0.0001$; 8.5 vs 4 scores on commencement of combination therapy, $P < 0.0001$; 13 vs 7 on first pulsed steroid rescue, $P < 0.0001$ and 18 vs 15 scores on peak lung opacification, $P = 0.01$). Despite a trend towards

more intervention in NIV Hospital, it had significantly fewer patients on IMV (21.4% vs 41.2% for IMV Hospitals, $P=0.012$), with lower overall and post-intervention mortalities (9.5% vs 25.1%, $P=0.024$ and 18.2% vs 58.6%, $P=0.0003$ respectively). Only 8/21 NIV-treated patients (38%) subsequently required intubation.

Multiple Logistic regression analysis (Table 3) confirmed that adjusted odds ratios (OR) for adverse outcomes were lower for NIV Hospital, being 0.36 for IMV requirement (95% CI 0.164 – 0.791, $P=0.011$) and 0.235 for death (95% CI 0.077 – 0.716, $P=0.011$). Older age and ARF developing more than 15 days after symptom onset were also independent adverse prognostic indicators.

Table 4 shows that, compared to IMV Hospitals, median time from symptoms onset to intubation was significantly longer among patients from NIV Hospital, who also improved earlier after pulsed steroid rescue.

As reported by Cheung et al,[17] none of 105 HCW exposed to NIV acquired SARS. Those who consented for blood taking (102/105) had uniformly negative serology for SARS-CoV.

Table 1. Profile of study patients from NIV Hospital and IMV Hospitals on admission

	NIV Hospital	IMV Hospitals	*P* value
Number of subjects	42	451	
Age (years, meidan)	47	44	0.10
Distribution of age (%)			
15 – 44 years	40.5	52.5	
45 – 64 years	45.2	34.4	0.30
65 years and above	14.3	13.1	
Male(%)	45.2	49.7	0.58
With comorbidities (%)	23.8	17.7	0.33
Laboratory-confirmed SARS (%)	95.2	88.9	0.29
Laboratory readings			
White cell count (10^9/L, median)	5.95	5.90	0.84
Neutrophil count (10^9/L, median)	4.75	4.53	0.84
Lymphocyte count (10^9/L, median)	0.85	0.80	0.87
LDH ratio* (median)	1.39	1.07	0.002
Respiratory status#			
Non-ARF (%)	76.2	87.0	
ARF (ALI + ARDS) (%)	23.8	13.0	0.05
ARDS (%)	2.4	5.4	0.71
FiO_2 > 0.21 (%)	19.0	10.7	0.13
FiO_2 > 0.50 (%)	0	1.6	1.00

* LDH ratio = actual values divided by the upper limit of normal reference range in the laboratory of each hospital studied. Missing data on admission: from three patients of NIV Hospital and 72 of IMV Hospitals. # Respiratory status = ratio of PaO_2 to FiO_2 (P/F ratio). ARDS = 26.6 kPa (199 mmHg) or less, ALI = 26.7 – 39.9 kPa (200 – 299) mmHg, Non-ARF = 40 kPa (300 mmHg) or more.

Table 2. Laboratory findings and respiratory status of study subjects on commencement of steroid treatment and of intervention (NIV or IMV)

	Combination treatment★			Intervention		
	NIV Hospital (*n*=42)	IMV Hospitals (*n*=451)	*P* value	NIV Hospital (*n*=42)	IMV Hospitals (*n*=451)	*P* value
Laboratory readings						
White cell count* (10^9/L, median)	5.60	5.60	0.81	10.55	12.90	0.06
Neutrophil count# (10^9/L, median)	4.40	4.40	0.92	9.75	12.00	0.13
Lymphocyte count△ (10^9/L, median)	0.70	0.70	0.54	0.40	0.50	0.17
LDH ratio☆ (median)	1.71	1.21	0.010	2.21	2.03	0.44
Respiratory status▲						
Non-ARF (%)	61.9	80.3		–	0.5	
ARF (ALI + ARDS) (%)	38.1	19.7	0.005	100.0	99.5	
ARDS (%)	9.5	8.6	0.78	54.6	80.1	0.013
FiO_2 > 0.21 (%)	50.0	24.7	0.0004	100.0	100.0	
FiO_2 > 0.50 (%)	0	4.5	0.24	22.7	68.3	< 0.0001

* White cell count missing data (i) Commencement of combination treatment: from one patient of NIV Hospital and 14 of IMV Hospitals; (ii) IMV/NIV commencement: from one patient of IMV Hospitals. # Neutrophil missing data (i) Commencement of combination treatment: from one patient of NIV Hospital and 15 of IMV Hospitals; (ii) IMV/NIV commencement: from three patients of IMV Hospitals. △ Lymphocyte missing data (i) Commencement of combination treatment: from one patient of NIV Hospital and 15 of IMV Hospitals; (ii) IMV/NIV commencement: from three patients of IMV Hospitals. ☆ LDH ratio = Actual values divided by the upper limit of normal reference range in the laboratory of each hospital studied. Missing data (i) Commencement of combination treatment: from 7 of NIV Hospital and 129 of IMV Hospitals; (ii) Starting IMV/NIV: from 59 of IMV Hospitals. ▲ Respiratory status = Ratio of PaO_2 to FiO_2 (P/F ratio). ARDS = 26.6 kPa (199 mmHg) or less, ALI = 26.7 – 39.9 kPa (200 – 299 mmHg, Non-ARF = 40 kPa (300 mmHg) or more. ★ Combination treatment = Ribavirin + Corticosteroid.

Table 3. Multiple logistic regression analyses on adverse outcome parameters among ARF patients from NIV Hospital and IMV Hospitals (n=493)

	Need for any form of ventilatory support			Need for IMV			Death		
	Adj OR	(95% CI)	*P* value	Adj OR	(95% CI)	*P* value	Adj OR	(95% CI)	*P* value
Age (per 10 years increase)	1.276	(1.092, 1.490)	0.002	1.250	(1.069, 1.461)	0.005	1.667	(1.375, 2.020)	<0.0001
Sex (M vs F)	1.195	(0.819, 1.744)	0.36	1.150	(0.786, 1.684)	0.47	1.452	(0.916, 2.302)	0.11
Comorbidity (Yes vs No)	0.998	(0.582, 1.713)	1.00	1.008	(0.587, 1.732)	0.98	1.236	(0.688, 2.220)	0.48
First Neutrophil count (per 10^9/L increase)	1.028	(0.962, 1.100)	0.41	1.030	(0.963, 1.102)	0.39	1.050	(0.976, 1.130)	0.19
Days from symptom onset to first respiratory failure									
8–10 vs 7 days	1.337	(0.797, 2.244)	0.27	1.320	(0.786, 2.215)	0.29	1.287	(0.722, 2.292)	0.39
11–14 vs 7 days	0.596	(0.355, 1.001)	0.051	0.605	(0.358, 1.023)	0.06	0.576	(0.309, 1.073)	0.08
>15 vs 7 days	0.281	(0.135, 0.586)	0.001	0.319	(0.153, 0.665)	0.002	0.197	(0.070, 0.558)	0.002
Hospital group (NIV vs IMV)	1.619	(0.830, 3.161)	0.16	0.360	(0.164, 0.791)	0.011	0.235	(0.077, 0.716)	0.011

Adj OR = adjusted odds ratio. M: male, F: female.

Table 4. Time from symptom onset to intervention for all patients and time from events/intervention to clinical improvement for patients with intervention (days)

	NIV Hospital (n=42)	IMV Hospitals (n=451)	*P* value
Time to NIV (n=9 in NIV Hospitals, median)	13		
Time to IMV (n=9 in NIV Hospitals, 186 in IMV Hospitals, median)	21	11	0.003
Time to NIV/IMV (n=22 in NIV Hospitals, 186 in IMV Hospitals, median)	12	11	0.85
Time from peak FiO_2 (n=18 in NIV Hospitals, 119 in IMV Hospitals, median)	3	3	0.45
Time from pulsed methylprednisolone (MP) (n=17 in NIV Hospitals, 88 in IMV Hospitals, median)	5	10	0.005
Time from NIV (n=16 in NIV Hospitals, median)	4		
Time from IMV (n=6 in NIV Hospitals, 117 in IMV Hospitals, median)	3.5	4	0.78
Time from NIV/IMV (n=18 in NIV Hospitals, 117 in IMV Hospitals, median)	4	4	0.98

Clinical improvement = reduction of oxygen requirement by 50% of (peak FiO_2 −0.21) or cessation of oxygen supplementation for at least four days.

DISCUSSION

To our knowledge, this is the first retrospective comparison of patient outcomes following the use of NIV against IMV in SARS-related ARF. Patients were drawn from the Hong Kong HA SARS Database, which contains comprehensive information on the second largest SARS patient cohort in the world.[1] All study patients had suffered uniformly from ARF and received similar pharmacotherapy for SARS, with strict exclusion of potential bias such as DNR orders precluding ICU admission and the use of non-steroidal immunomodulatory agents and Kaletra, the latter of which may have beneficial effect on outcome.[28,29]

Apart from significantly higher LDH, ARF proportion, oxygen use and radiographic scores in NIV Hospital on admission and on commencing combination therapy, the two groups were similar in demographics, blood picture and time course of disease progression. Since higher admission LDH[6,21] and radiographic scores[30,31] independently predicted adverse outcome while ARF contributed to mortality in SARS,[6] NIV Hospital appeared to have more severe SARS pre-intervention, although severe disease on starting combination therapy may also reflect compliance to its treatment protocol.[20] In contrast, ARDS and FiO_2 > 0.5 were proportionately higher in IMV Hospitals on intervention, suggesting that intubation was only performed in the presence of gross ARF. On the other hand, NIV Hospital had apparently less severe disease on intervention because its protocol

mandated NIV use much earlier in the course of ARF.[17,20] The trend for more frequent intervention in NIV Hospital broadly agrees with its more severe respiratory, laboratory and radiographic parameters pre-intervention, with half of its patients being already ill enough to be described as suffering from "critical SARS", for whom ventilatory support in the form of NIV would be recommended.[32] Furthermore, since NIV was indicated if pulsed steroid rescue failed to control disease progression,[17,20] significantly faster improvement after pulsed steroid in NIV Hospital can be explained by early and successful support or reversal of ARF by NIV, such that only 38% of study patients eventually required intubation.

Both univariate and multivariate analyses showed that patients from NIV Hospital were significantly less likely to require intubation and had lower post-intervention and overall mortalities, suggesting that early NIV initiation may be comparatively more effective than IMV in the management of ARF in SARS. Older age and ARF developing over 15 days from symptom onset, but not other reported prognostic factors[5,6,21,24-26] included as confounding factors in our model, also predicted all adverse outcomes. Since our analysis was performed on a large and homogeneous ARF cohort, it is not surprising that the resulting prognostic factors are different from those obtained from smaller series with mixed disease severity. Since SARS-related ARF is reported to peak on Day 8 after symptom onset,[2,3] late-onset ARF after Day 15 would more likely be due to complications such as nosocomial sepsis, which is associated with poor outcome,[33] than to SARS *per se*. Compared to IMV, morbidity and mortality associated with NIV are low,[9] and NIV success has been reported in immunosuppressed ARF patients.[34,35] Since over 90% of Hong Kong SARS patients had received corticosteroids (unpublished data from HA SARS Database), and since both SARS and corticosteroid result in immunosuppression, we believe that reduction in infective complications attributable to NIV was of paramount importance in contributing to mortality reduction.

NIV was used in 6 of 13 ventilated patients in the only SARS outbreak in Vietnam[16] and was frequently used in China to treat SARS-related ARF,[10-15] but comparisons between NIV and MV and reports on SARS transmission risks are lacking. Most studies described the effectiveness of low levels of continuous positive airway pressure (CPAP), with reduction of intubation by about two-thirds[11,13] similar to our own findings. The 9.5% overall mortality of uniformly ARF patients in NIV Hospital compares well with that of the largest Chinese cohort utilizing NIV (188 of 250 patients), which reported an overall mortality of 10%,[13] whereas eventual SARS-related mortality of intubated patients (58.6%) in our IMV Hospital is similar to that (45% at 28 days) of a Canadian series.[2] A review of five SARS cohorts reported an aggregate short-term (mean 12 – 26.8 days) mortality of 26% for patients on IMV,[7] while our study showed mortality among NIV patients to be 18.2% in the long term. The literature thus supports our finding that, when compared to IMV, NIV as initial ventilatory support could confer significant mortality reduction in SARS-related ARF.

A Canadian study reported a non-significant association for SARS transmission risk and NIV (1/6 exposed HCW against 2/28 non-exposed, risk ratio 2.33, $P = 0.5$) but a much higher and statistically significant risk ratio of 13.29 (6/14 exposed HCW against 2/62 non-exposed, $P = 0.003$) for intubation.[36] Despite this, NIV is still being recommended to be avoided in SARS.[7,37,38] Our NIV Hospital had established negative-pressure environment with high air change. Its HCW wore surgical masks initially but were provided with appropriate PPE[17,23] as the organism and modes of transmission became known. There were no NIV-related SARS transmissions, and standard PPE was as effective as more sophisticated respirators used later in the outbreak. With standard environmental precautions and infection control measures, therefore, experience to date suggests that NIV is much safer for HCW than endotracheal intubation. In the presence of low overall patient mortalities following NIV use[10-17] and mortality advantage compared to IMV in the current analysis, we submit that neither patients nor HCW would be well-served should intubation and IMV remain endorsed as the only mode of ventilatory support for SARS. We also submit that, since specific therapy is lacking in this disease,[39,40] early NIV application may provide safe and effective support for ARF while waiting for the disease to abate spontaneously or respond to immunomodulatory therapy.[11,20,21,40]

Our study is limited by being retrospective in nature, with small number of patients in NIV Hospital and absence of a control group. There are however no

large-scale controlled studies in SARS, and comparable demographics and near-comparable pre-intervention clinical parameters in our ARF groups may enhance the validity of our analyses. Indeed, lower admission LDH ratios and radiographic scores in IMV Hospitals should bias towards better outcomes in this group, which however was not found on detailed analyses. Respiratory status could only be estimated due to lack of blood gas data, but bias was not introduced since the same assumptions and approximations were uniformly applied to both groups. Finally, though combined corticosteroid-ribavirin was prescribed to all patients, variations in treatment protocols existed between the two groups and among IMV Hospitals. By the time of intervention, however, all but one patient had developed ARF, attesting to the appropriateness of patient inclusion and decisions for ventilatory support in this study.

In conclusion, analysis of patients from the Hong Kong Hospital Authority SARS Database revealed that, compared to invasive mechanical ventilation, early application of non-invasive ventilation as initial support for SARS-related acute respiratory failure appeared to be associated with significantly reduced need for intubation and mortality. Under currently recommended infection control conditions, non-invasive ventilation did not result in any SARS-coronavirus transmission among health care workers in our study.

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