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Dose–response characteristics of noninvasive ventilation in acute respiratory failure

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ABSTRACT Acute noninvasive ventilation (NIV) is a well-established therapy for acute respiratory failure but the dose–response characteristics of this therapy have not been defined. The aim of this study was to define this dose–response relationship.

This study was a retrospective review of patients receiving NIV for acute respiratory failure in a tertiary hospital respiratory high-dependency unit between July 2012 and June 2017. Mask-on time (rather than the period that NIV was in use) as the "dose" was compared with hospital survival as the "response".

654 patients were included, 594 (91%) with hypercapnic respiratory failure (HCRF). NIV was used for a median (interquartile range (IQR)) duration of 2.74 (1.51–4.73) days and median (IQR) mask-on time was 34 (18–60) h (56.1% (41.2–69.5%) of treatment time). There was evidence of a dose–response relationship in the HCRF group up to a ceiling of 24 h mask-on time, but not in the hypoxaemic respiratory failure (HRF) group. There was a difference in survival with as little as 2 h mask-on time (92% compared with 73%; p<0.001). Patients requiring NIV for 80–100% of therapy time had lower survival.

We conclude that there is evidence of a dose–response relationship between cumulative NIV usage (mask-on time) and survival from as little as 2 h to a ceiling of ~24 h in HCRF, but not in HRF.

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Introduction

Noninvasive ventilation (NIV) outside of the intensive care unit (ICU) is well established as a highly effective therapy for acute respiratory failure [1, 2]. The highest quality of evidence is seen in acute hypercapnic respiratory failure (HCRF) in chronic obstructive pulmonary disease (COPD) [3]. Despite consistent data showing the efficacy of NIV overall, there are very limited data on the dose–response characteristics of the therapy, especially related to therapy duration and intensity. Studies of NIV in acute respiratory failure most commonly report only the total period that therapy was offered rather than cumulative actual use (mask-on time). Where reported, the actual daily use of NIV is often only between 8 and 14 h in the first 24 h [3–7]. There are limited indirect data supporting a dose–response relationship in acute NIV. For example, more intensive NIV use (notably nocturnal NIV) was associated with better response to therapy in one study [8]. Studies on chronic nocturnal ventilation also indirectly suggest a dose–response relationship. A small number of studies in patients with motor neurone disease [9, 10], obesity hypoventilation [11] and restrictive chest wall disease [12] have suggested that survival benefits are only seen if average usage is greater than a threshold of $\geqslant$4 h per night.

Therefore, there is no evidence to guide this therapy, which is regarded as standard of care (in at least HCRF due to COPD) in terms of minimally effective or optimal durations of therapy. Furthermore, despite the absence of robust data on the dose–response characteristics of acute NIV, and specifically the minimal effective duration of therapy, health funding agencies utilise arbitrary thresholds in service funding models. In Australian public hospitals, for example, only acute NIV with cumulative actual usage (mask-on time) of $\geqslant$24 h is recognised for funding. In our institution (Princess Alexandra Hospital, Woolloongabba, Australia), 30–40% of acute NIV does not qualify for funding under current criteria.

The aim of this study was to determine the dose–response characteristics between the duration of acute NIV and survival, and to identify if there is a threshold for minimum duration of acute NIV associated with survival benefits.

Methods

The study was a single-centre, retrospective review of patients admitted to a tertiary hospital (Princess Alexandra Hospital) respiratory high-dependency unit (HDU) over a 5-year period (between July 1, 2012 and June 30, 2017). Patients requiring acute NIV for acute respiratory failure were included; however, patients stepped-down from the ICU were excluded. All data were collected prospectively and entered in an in-house database (FileMaker Pro; FileMaker, Santa Clara, CA, USA). The study was approved by the institutional Human Research Ethics Committee.

HCRF was defined as an acute elevation in arterial carbon dioxide tension >45 mmHg and acidosis defined as arterial pH <7.35. Hypoxaemic respiratory failure (HRF) was defined as an acute state with arterial oxygen tension <60 mmHg on room air (or, where room air measurements were not available, the requirement for oxygen to maintain pulse oximetry measurements >90%) with normal or low partial pressure of carbon dioxide [13]. Clinical data including age, sex, active comorbidities, admission arterial blood gas results, usual functional status (World Health Organization (WHO) Functional Class) and treatment outcomes (including escalation to ICU and in-hospital mortality) were recorded.

The duration of NIV therapy (therapy time) was defined as the total period that NIV was offered (including both mask-on and mask-off periods), and was calculated as the difference (in days) between commencement and final discontinuation of NIV. Mask-on time was defined as the actual usage of the therapy (in hours) during the admission, and was calculated from the differences in the device hour-meter readings at commencement and discontinuation of therapy. Mask-on proportion was defined as the proportion of the therapy time when NIV was actually in use and was calculated as the percentage of mask-on time/therapy time. The protocol of the respiratory HDU in our institution for the management of acute respiratory failure is continuous NIV with short breaks until the respiratory failure has corrected followed by progressive weaning of wakeful then nocturnal NIV as tolerated with discontinuation of the therapy altogether once the patient is clinically stable. Out-of-protocol discontinuation was defined as the ceasing of NIV before deemed clinical stable. The reasons for this discontinuation were recorded.

Outcome measures

The co-primary outcome measures were the dose–response relationships between hospital survival and the mask-on time (reflecting therapy "dose") in terms of 1) usage bands (mask-on time <4, 4–8, 8–16, 16–24 and >24 h) to calculate dose–response characteristics and 2) usage thresholds (mask-on time <2, <4, <8, <16, <24 and <48 h) to calculate minimally effective therapy duration. Secondary outcomes were the relationship between hospital survival and mask-on proportion in bands of 20% (<20%, 20–40% and 40–60%) as a measure of therapy "intensity", and the associations between mortality and clinical factors (age, sex, active comorbidities, WHO Functional Class and arterial blood gas parameters).

Statistical analysis

Statistical analysis was performed using SigmaPlot version 13 (Systat Software, San Jose, CA, USA). Data are presented as median (interquartile range (IQR)) as all variables were nonparametric. Continuous variables were compared by one-way ANOVA on ranks. Categorical parameters and proportions were compared using Chi-squared analysis. Multiple logistic regression analysis was used to identify clinical parameters (age, sex, ventilation duration, baseline arterial blood gas results and active comorbidities) associated with risk of death and odds ratios (95% confidence intervals) were calculated for the risk of mortality for these parameters. Log-rank Kaplan–Meier survival analysis was used to compare survival between groups. $p<0.05$ was considered significant.

Results

Patients

There were 654 patients with acute respiratory failure (594 (91%) with HCRF) admitted to the respiratory HDU and treated with acute NIV between July 1, 2012 and June 30, 2017. Clinical data are shown in table 1.

Patients were typically middle aged to elderly with almost equal sex distribution overall, but there was a significant male predominance in HRF. Active comorbidities differed between groups (table 1), with relatively more patients with COPD and obesity in the HCRF cohort, and more with pneumonia, lung cancer and interstitial lung disease in the HRF group. Usual functional status also differed between the groups, with relatively more HRF patients with a normal (WHO Functional Class I) pre-morbid functional status. There were also significant differences in arterial blood gas measurements between the cohorts as expected.

NIV parameters are shown in table 2. Median therapy duration with NIV (therapy days) was 2.74 days with a median mask-on time of 34 h (56.1% of therapy duration). There were no differences in these

TABLE 1 Clinical characteristics of the study cohort

	All patients	HCRF patients	HRF patients	p-value
Subjects	654	594	60	
Age years	64.3 (53.4–71.9)	55.2 (41.5–68.5)	64.9 (55.3–73.9)	0.79
Male:female (% male)	363:291 (55)	317:277 (53)	46:14 (77)	<0.001
Diagnoses				
COPD	375 (57)	360 (61)	15 (25)	<0.001
Asthma	35 (5)	34 (6)	1 (2)	0.30
Pneumonia	117 (18)	88 (15)	29 (48)	<0.001
LRTI	22 (3)	20 (3)	2 (3)	0.72
Bronchiectasis	27 (4)	26 (4)	1 (2)	0.51
Lung cancer	25 (3)	16 (3)	9 (15)	<0.001
Interstitial lung disease	15 (2)	4 (<1)	11 (18)	<0.001
Acute pulmonary oedema	41 (6)	35 (6)	6 (10)	0.33
Sleep disordered breathing	171 (26)	158 (27)	13 (22)	0.50
Obesity	243 (37)	231 (31)	12 (20)	0.006
Motor neurone disease	23 (4)	21 (4)	2 (3)	0.77
Admission gas exchange				
pH	7.43 (7.29–7.40)	7.34 (7.29–7.39)	7.44 (7.39–7.47)	<0.001
P_{aCO_2} mmHg	62.1 (53.0–75.0)	65.0 (55.0–76.0)	38.0 (32.5–43.0)	<0.001
P_{aO_2}/F_{IO_2}	220.0 (180.0–258.9)	222.7 (185.7–261.9)	147.2 (79.0–244.5)	<0.001
Mortality	68 (10.4)	47 (7.9)	21 (35.0)	<0.001
Patients requiring ICU	12 (2)	5 (<1)	7 (12)	<0.001
Subsequent mortality	5 (42)	1 (20)	4 (57)	0.30
Usual WHO Functional Class				
I	43 (7)	32 (5)	11 (18)	
II	311 (48)	284 (48)	27 (45)	<0.001
III	298 (46)	188 (32)	10 (17)	
IV	98 (15)	86 (15)	12 (20)	

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. HCRF: hypercapnic respiratory failure; HRF: hypoxaemic respiratory failure; COPD: chronic obstructive pulmonary disease; LRTI: lower respiratory tract infection; P_{aCO_2}: arterial carbon dioxide tension; P_{aO_2}: arterial oxygen tension; F_{IO_2}: inspiratory oxygen fraction; ICU: intensive care unit; WHO: World Health Organization. p-values refer to differences between HCRF and HRF cohorts.

TABLE 2 Noninvasive ventilation (NIV) characteristics and parameters

	All patients	HCRF patients	HRF patients	p-value
Subjects	654	594	60	
Duration of NIV therapy[#] days	2.74 (1.51–4.73)	2.76 (1.53–1.23)	2.25 (1.23–5.95)	0.56
Total mask-on time[¶] h	34.0 (18.0–60.0)	34.0 (18.2–60.0)	34.0 (10.0–60.0)	0.42
Proportion of mask-on time %	56.1 (41.2–69.5)	55.2 (41.5–68.5)	65.6 (33.7–85.2)	0.07
Settings				
Inspiratory pressure cmH_2O	18.0 (16.0–22.0)	19.0 (16.0–22.0)	15.0 (12.5–16.8)	<0.001
Expiratory pressure cmH_2O	10 (8–14)	10 (8–14)	8.5 (6.5–10.0)	0.07
Pressure support cmH_2O	8 (5–15)	8 (5–15)	6 (4–11)	<0.001
Out-of-protocol cessation of NIV[+]	37 (6)	29 (4)	8 (13)	0.02
Intolerance of treatment	20	18	2	
Change to palliative treatment intent	12	7	5	0.10
Treatment ineffective	5	4	1	

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. HCRF: hypercapnic respiratory failure; HRF: hypoxaemic respiratory failure. [#]: overall period where NIV was used (including mask-on and mask-off durations); [¶]: cumulative period where the therapy was actually in use; [+]: therapy was stopped before clinical stability was achieved. p-values refer to differences between HCRF and HRF cohorts.

measures between HCRF. Inspiratory pressure and pressure support (the difference between inspiratory and expiratory pressures) were higher in the HCRF cohort (both p<0.001), but there was no difference in expiratory pressure. Out-of-protocol (before clinically stable) cessation of NIV was more common in HRF (13% compared with 4%; p=0.016), although the reasons for the cessation were similar between groups (table 2).

In-hospital survival

Overall in-hospital mortality was 10.4% (7.9% in HCRF and 35.0% in HRF; p<0.001) (table 1). Survival was significantly lower in the HRF cohort. Clinical factors associated with an increased risk of death were active diagnoses of interstitial lung disease (OR 11.1 (95% CI 2.5–48.6); p<0.001) and lung cancer (OR 7.1 (95% CI 2.0–24.9); p=0.002). Obesity was associated with a reduced risk of death (OR 0.2 (95% CI 0.1–0.5); p<0.001).

Relationships between survival and mask-on time

Mask-on duration, *i.e.* the cumulative duration of actual use of mask ventilation, reflects the "dose" of NIV.

There was a dose–response relationship between survival and mask-on time (represented in bands of cumulative usage <4, 4–8, 8–16, 16–24 and >24 h) in the whole group (p<0.001), which was evident in only the HCRF cohort (p<0.001) and not the HRF group (p=0.55) (figure 1). There was no difference between 16 and 24 h and >24 h mask-on time in both the whole cohort and HCRF patients, suggesting a ceiling effect in the dose–response relationship.

There was also evidence of a dose–response relationship between survival and thresholds of mask-on time across a wider range of mask-on times (<2, <4, <8, <16, <24 and <48 h) (figure 2). The relationship was seen in the HCRF group across the range of thresholds from 4 to 24 h mask-on time (p=0.01), but was not present in the HRF group (p=0.73). There appeared to be incremental improvement in survival in the HCRF group above the threshold of 2 h mask-on time in the entire group and above 4 h mask-on time in the HCRF group. Survival was significantly better above mask-on times thresholds of 2 h (OR of death with mask-on time <2 *versus* ⩾2 h of 4.11 (95% CI 1.64–10.28); p=0.004), 4 h (OR 4.66 (95% CI 2.23–9.73); p<0.001), 8 h (OR 5.00 (95% CI 2.55–9.42); p<0.001) and 24 h (OR 3.23 (95% CI 1.75–5.93); p<0.001) (figure 3) There was no difference in survival between mask-on time ⩾48 *versus* <48 h (OR 0.42 (95% CI 0.16–1.08); p=0.09).

Relationships between survival and mask-on proportion

Mask-on proportion, *i.e.* the percentage of mask-on time/total therapy time, was used to indicate NIV "intensity".

There were significant differences in survival depending on the mask-on proportion (figure 4). There was significantly lower survival in patients with mask-on for >80% of therapy time. There was an inverse

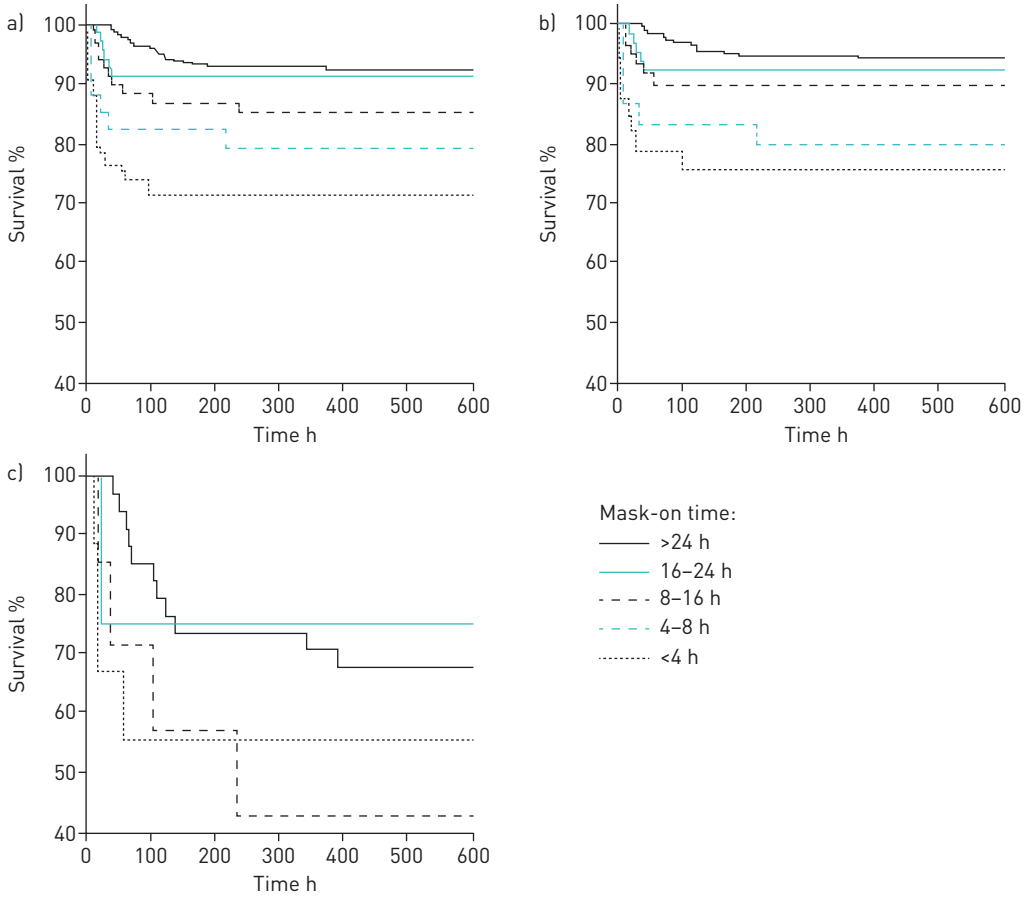

FIGURE 1 Survival stratified by type of respiratory failure and duration of mask-on time (noninvasive ventilation "dose") in bands of <4, 4–8, 8–16, 16–24 and >24 h. a) All patients, b) hypercapnic respiratory failure patients and c) hypoxaemic respiratory failure patients.

dose–response relationship in the HCRF cohort, with lower proportion of use associated with better survival. No patients with HCRF died where mask-on proportion was <20%. There were significant differences between mask-on proportions with HRF ($p<0.05$), with worst survival seen in patients with mask-on proportions of 80–100%, but there was no dose–response pattern. The mask-on proportion was significantly associated with admission WHO Functional Class (median (IQR): Class I 48.1% (39.6–65.4%), Class II 47.8% (39.5–64.2%), Class III 55.7% (40.5–65.5%) and Class IV 57.1% (43.2–72.1%); $p<0.001$). However, the differences in survival in the entire cohort remained significant after correction for functional status ($p<0.001$).

Discussion

NIV is the standard of care for acute HCRF in COPD, but to the best of our knowledge this is the first study to specifically assess the dose–response characteristics of this therapy. This study is also the first to accurately report mask-on time as the primary outcome rather than just total period available for use of NIV. Median mask-on time in this study was 34 h. NIV was utilised (mask-on) for 56% of the total therapy period. This was similar between the HCRF and HRF cohorts, although there was a trend for slightly greater proportion of use in HRF at 66% of therapy time. This usage is difficult to directly compare with other studies, but many studies have reported mask-on usage of between 6 and 8 h per day in the first 48 h of therapy [3, 4, 14, 15]. The median daily usage in our patients was >13 h. Inspiratory pressure was slightly higher in the HCRF cohort (19 *versus* 15 cmH_2O), but expiratory pressures were similar. Higher pressure support was therefore used in HCRF (8 *versus* 6 cmH_2O), which is an expected finding as pressure support is predominantly responsible for augmenting tidal volume and alveolar ventilation, therefore reducing arterial carbon dioxide levels.

There was a reasonably consistent dose–response pattern when considering bands of mask-on time (<4, 4–8, 8–16, 16–24 and >24 h) or thresholds of mask-on time (<2, <4, <8, <16, <24 and <48 h). These

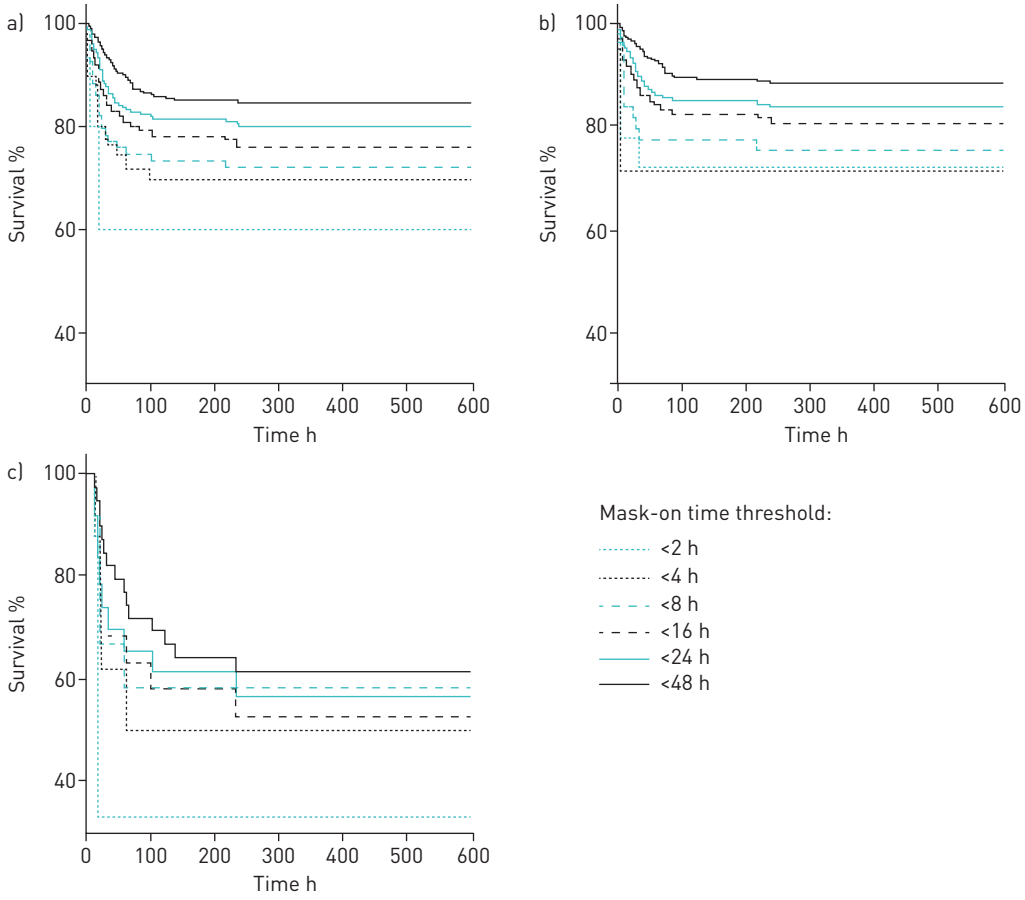

FIGURE 2 Survival stratified by type of respiratory failure and mask-on time thresholds of <2, <4, <8, <16, <24 and <48 h. a) All patients, b) hypercapnic respiratory failure patients and c) hypoxaemic respiratory failure patients.

dose–response relationships were seen only in the patients with HCRF and not those with HRF. The patterns seen in the overall group were heavily influenced by those seen in the HCRF cohort as these patients represented >90% of all patients. The whole group data suggest a ceiling effect at 24 h mask-on time (*i.e.* survival did not improve with higher usage). The evidence for this ceiling effect at 24 h was: 1) the absence of clinically significant differences in survival between mask-on times 16–24 and >24 h, and 2) the significant differences in survival between a mask-on time of <24 *versus* ⩾24 h, but no difference in survival between mask-on times of <48 *versus* ⩾48 h. There was a less clear lower threshold of the dose–response relationship. The data show that as little as 2 h mask-on time was associated with significantly lower mortality (7% *versus* 26%; p<0.001). There appears to be a stepwise improvement in survival with increased usage (figure 3a). There were only 10 patients altogether with a total mask-on time of <2 h, which may have affected the ability to identify a lower threshold of effect.

There was evidence of an inverse dose–response relationship between survival and the mask-on proportion in the HCRF cohort (p<0.001). Survival was lowest in patients with a mask-on proportion of 80–100% of NIV therapy time and best in patients with a mask-on proportion of <20% (where there were no deaths recorded). There were also significant differences in survival in the HRF cohort (p<0.05), with worst survival seen in the patients with a mask-on proportion of 80–100% of therapy time. However, there was no other dose–response relationship in the HRF cohort. Mask-on proportion was associated with more impaired WHO Functional Class on admission. The association between higher mask-on proportion and worse survival is most likely explained by the covariate of higher patient acuity and increased ventilator dependence. To the best of our knowledge, the relationship between survival and intensity of NIV use (reflected by the mask-on proportion) has not been previously reported.

Mortality overall was 10.4% (7.9% in the HCRF group and 35.0% in the HRF cohort), which is similar to other published data [3, 16, 17]. We observed significant associations between active comorbidities and survival. Others have also described lower survival in patients with interstitial lung disease [18] or lung malignancy [19] and improved survival in obesity [20].

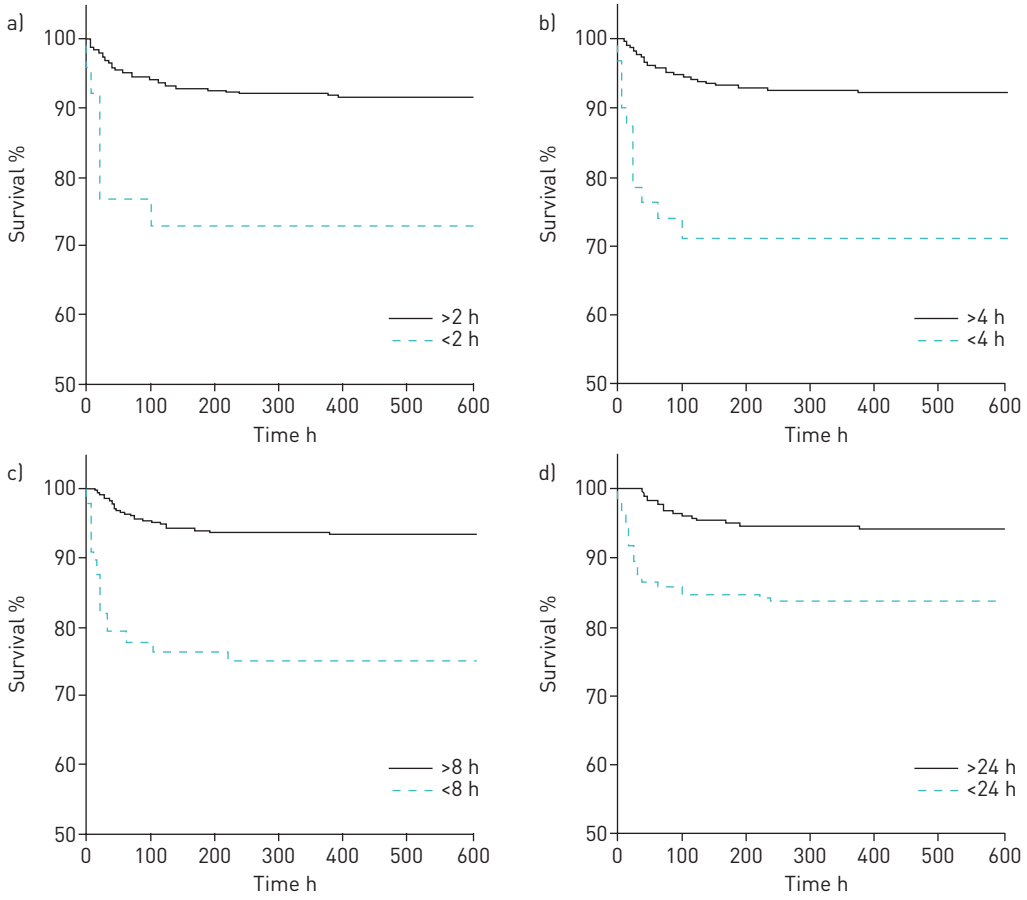

FIGURE 3 Survival stratified by threshold of mask-on time. a) >2 *versus* <2 h, b) >4 *versus* <4 h, c) >8 *versus* <8 h and d) >24 *versus* <24 h.

The study has a number of strengths and potential limitations. The size of the cohort is a strength of the study (654 patients). The recording of mask-on time based on an objective calculation from the hour-meter of the ventilator rather than observation is also a strength due to reduced risk of inaccurate measurements. The relatively small number of patients with HRF (reflecting the "real-world" incidence of respiratory failure through a respiratory HDU) is a limitation as the overall outcomes were mostly influenced by the HCRF cohort. However, the outcomes at least suggest that HCRF and HRF have different acute NIV dose–response characteristics. The main limitation of the study, as a retrospective cohort study, is that it can identify associations but not causality of the associations. Our data therefore cannot be used to determine if the differences in the duration and intensity of NIV are responsible for the observed differences in mortality, as a confounding factor may influence mortality and both duration and proportion of therapy use. Previous studies have highlighted that more rapid clinical improvement with NIV predicts better outcome [4, 21, 22]. In our case, the association between lower proportions of NIV use and improved survival may reflect a subgroup of patients with more rapid (spontaneous) clinical improvement and who were less "dependent" on ventilatory support for survival.

An understanding of the dose–response characteristics of acute NIV for acute respiratory failure potentially benefits the field in a number of respects. The demonstration of a dose–response relationship between the 2–4 and 24 h mask-on periods can be used together with clinical markers to help determine optimal timing for weaning of therapy. Identifying patients requiring significant proportion of times with ventilatory support (80–100% of therapy time based on our data) as a high risk for mortality may influence treatment decisions, including the need to escalate care to an ICU if appropriate. Finally, this study provides a more robust indication of effective therapy duration to inform agencies responsible for funding of care. Our data suggest that even 2 h of mask-on time influences survival and would be a more appropriate threshold for funding. In Australia, government funding for acute NIV is only provided for cumulative treatment of at least 24 h.

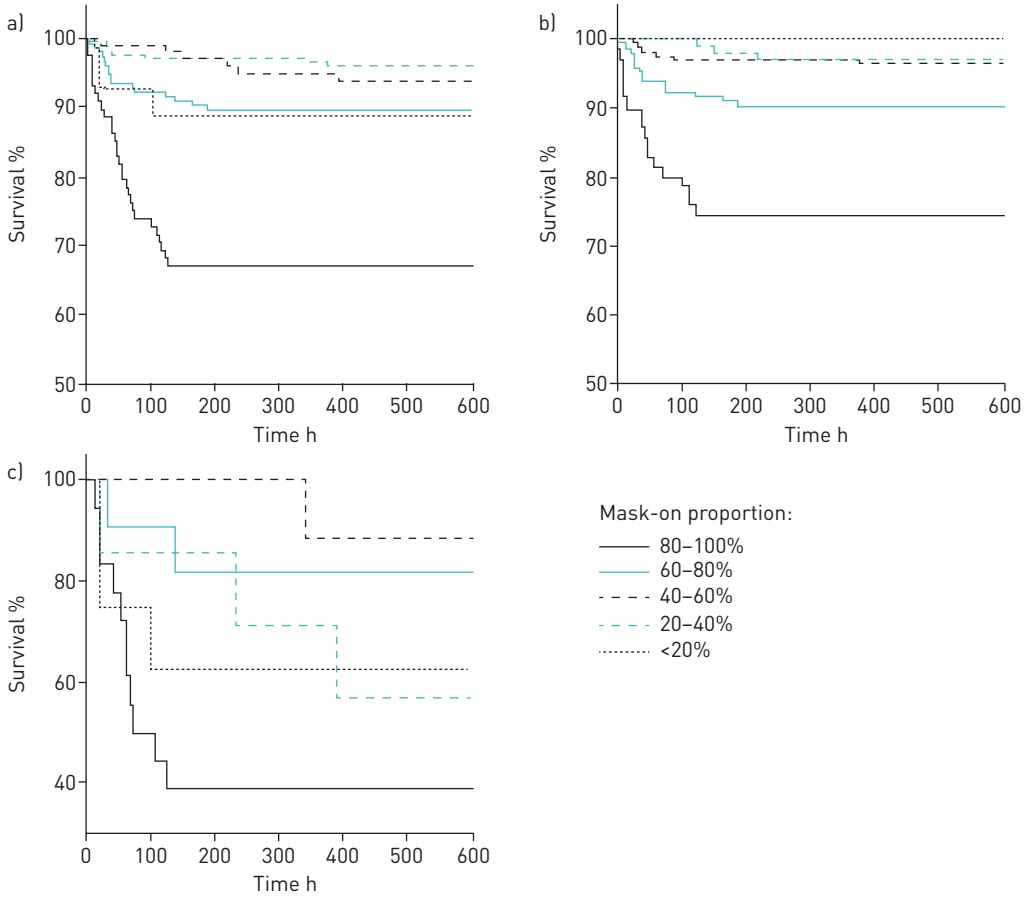

FIGURE 4 Survival stratified by type of respiratory failure and mask-on proportion (mask-on time relative to total therapy duration) calculated as mask-on time/(mask-on time+mask-off time) representing noninvasive ventilation "intensity". a) All patients, b) hypercapnic respiratory failure patients and c) hypoxaemic respiratory failure patients.

In summary, we have demonstrated a dose–response relationship between the duration of direct NIV use (mask-on time) in acute respiratory failure and hospital survival up to 24 h cumulative usage in HCRF. Benefits in survival are associated with as little as 2 h of this therapy. There is an association between reduced survival and increased proportion of usage in both HCRF and HRF, most likely reflecting underlying acuity of disease and dependence on ventilation.

Conflict of interest: None declared.

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