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Lowering PCO2 with Non-invasive Ventilation is Associated with Improved Survival in Chronic Hypercapnic Respiratory Failure

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Abstract:

Background: Chronic hypercapnic respiratory failure is associated with high mortality. While prior work has demonstrated a mortality improvement with high intensity non-invasive ventilation in chronic obstructive pulmonary disease, it is unclear whether a partial pressure carbon dioxide (PCO2) reduction strategy is associated with improved outcomes in other populations of chronic hypercapnia

Methods: The objective of this study was to investigate the association between PCO2 reduction (using transcutaneous partial pressure of carbon dioxide as an estimate for arterial PCO2) and survival in a broad population of individuals treated with NIV for chronic hypercapnia. We hypothesized that reductions in PCO2, would be associated with improved survival. Therefore, we performed a cohort study of all subjects evaluated from February 2012 to January 2021 for NIV initiation/optimization due to chronic hypercapnia at a home ventilation clinic in an academic center. We used multivariable Cox proportional hazard models with time-varying coefficients and PCO2 as a time-varying covariate to test the association between PCO2 and all-cause mortality adjusting for known cofounders

Results: The mean age of 337 subjects was 57 ± 16 years; 37% female and 85% white. In univariate analysis, survival probability increased with reductions in PCO2 to <50 mm Hg after 90 days, and these remained significant after adjusting for age, sex, race, body mass index, diagnosis, Charlson comorbidity index, and baseline PCO2. In the multivariable analysis, patients who had a < 50 mm Hg had a reduced mortality risk of 94% between 90-179 days (HR=0.06; 95% CI: 0.01 – 0.50), 69% between 180 – 364

days (HR=0.31; 95% CI: 0.12 – 0.79), and 73% for 365 -730 days (HR = 0.27; 95% CI: 0.13 – 0.56).

Conclusion: Reduction in PCO2 from baseline for subjects with chronic hypercapnia on NIV is associated with improved survival. Management strategies should target the greatest attainable reductions in PCO2.

Introduction

Elevated partial pressures of carbon dioxide (PCO2) levels are associated with increased mortality and morbidity [1,2]. While the causes are likely multifactorial, the association could be indirectly related to the severity of underlying disease (irrespective of the etiology) or directly through several pathophysiologic mechanisms. For example, elevated PCO2 may hinder both skeletal muscle repair and host defenses against bacterial infections, leading to increased mortality [3,4]. In addition, overloaded body tissue stores of CO2 can result in a rapid, potentially intolerable further PCO2 increments in response to an increase in CO2 production or reduction in CO2 removal [5].

In the setting of chronic alveolar hypoventilation, non-invasive ventilation (NIV) can offload respiratory muscles while increasing alveolar ventilation to improve CO2 clearance and reduce excess total body CO2 stores [5]. NIV has been shown to improve survival in many conditions including chronic obstructive pulmonary disease (COPD) [6-8], obesity hypoventilation syndrome (OHS) [9-11], and amyotrophic lateral sclerosis (ALS) [12]. While the importance of outpatient NIV therapy is becoming increasingly recognized [13,14], there remains little data regarding optimal treatment strategies and targets.

Transcutaneous carbon dioxide (PtcCO2) monitors are non-invasive devices that provide a real-time proxy for PCO2 levels [15]. Their reliability and portability provide clinicians with a convenient, practical tool to follow PCO2. Aarrestad et al reported that PtcCO2 monitoring reflects PCO2 in stable patients receiving NIV [16,17] with limits of agreements within the proposed ranges [18,19].

The purpose of this study was to determine whether reductions in PCO2 (using PtcCO2 as an estimate for arterial PCO2) achieved through NIV are associated with improved survival in a sample of subjects with mixed etiologies of chronic hypercapnia. We hypothesized that reducing PCO2 levels through NIV is associated with improved survival and that the survival benefit is dose-dependent based on the magnitude of PCO2 decrease from baseline.

Methods

We conducted a retrospective cohort study of adult subjects (≥ 18 years) with chronic hypercapnic respiratory failure of any cause assessed for NIV initiation or optimization by the Assisted Ventilation Clinic at a reference academic center.

Using existing clinic patient databases, we identified all subjects with a first-time encounter with the Assisted Ventilation Clinic between February 2012 and January 2021. The first encounter was defined as either the first outpatient clinic visit or an inpatient encounter in which the Assisted Ventilation Clinic was consulted for the initiation of NIV. We included subjects with chronic hypercapnia at the first encounter who were initiated or maintained on NIV. Chronic hypercapnia was defined as partial pressure of carbon dioxide in arterial blood (PaCO2) > 45 mmHg with a pH > 7.35 on a blood sample obtained

by arterial puncture in the inpatient setting, or PtcCO2 >45 mmHg using PtcCO2 monitoring in a stable state as an outpatient. We excluded patients requiring invasive mechanical ventilation (tracheostomized patients) at first visit, those who were not initiated on NIV and patients lost to follow-up.

Follow-up PCO2 measurements over a 2-year period were performed using PtcCO2 monitoring. We used EMR chart review to identify demographic characteristics, comorbidities, and clinical data.

All outpatient visits included a PtcCO2 reading while the subject was at rest breathing spontaneously without assistance unless clinical status required continuous mechanical ventilation. PtcCO2 measurements were performed using a SenTec Digital Monitor (SenTec AG, Therwil, Switzerland). The PtcCO2 sensor was applied to the patient forehead at 42º C for at least 5–10 minutes, and the value at steady-state was recorded

At each clinic visit, assessments were made by the pulmonary clinician and respiratory therapist. Based on PtcCO2 levels and device downloads, recommendations were made to either continue current management strategies, adjust ventilator settings, or increase hours of use. For subjects who had no change or an increase in PtcCO2 from baseline during the follow-up period, the clinical notes were reviewed to determine the reasons for the lack of PtcCO2 improvement. The institutional review board approved this study (HUM00162425) and waived the informed consent requirement for data collection.

The primary outcome was all-cause mortality within two years of the initial encounter. We determined vital status by reviewing the EMR, funeral home websites, and

online obituaries. All subjects were followed from the date of the first encounter to death, the last visit, or August 30, 2021, whichever came first with a maximum follow-up time of 730 days. Patients were considered lost to follow-up when his/her vital status within the last six months of the censoring date was unknown.

We described baseline characteristics using means (standard deviations [SD]) or medians (interquartile range [IQR]) for continuous variables and as counts (percentage) for categorical variables. We performed univariate and multivariable Cox proportional hazard models. To minimize immortal time bias [20], we included time-varying PCO2 levels in the Cox proportional hazards models. To determine PCO2 associations at different time intervals, we used time-varying coefficients of PCO2 in the Cox proportional hazards models [21].

For the multivariable models, we adjusted for potential confounders that were associated with disease progression, need for NIV, and overall survival in chronic respiratory failure, such as primary diagnosis for NIV indication, age, sex, race, body mass index (BMI), Charlson comorbidity index (CCI), and baseline PCO2. Primary diagnosis was considered the primary reason for chronic respiratory failure. We examined the proportional hazard assumption of PCO2 within each time interval through Schoenfeld residual plots [22,23].

We performed subgroup analyses using the aforementioned approach to examine associations with mortality, including ALS versus non-ALS subjects and those with both baseline PaCO2 and PtcCO2 values versus baseline PtcCO2 values alone. Missing data was handled using multiple imputation. We considered all P values of less than 0.05 as

statistically significant. We performed all analyses using Stata version 15.0 (StataCorp, LP).

Results

We identified 337 unique subjects who were evaluated by the Assisted Ventilation Clinic for NIV initiation or optimization with baseline hypercapnia **(Table 1),** We excluded 81 patients who were receiving invasive mechanical ventilation at the time of first visit **(Figure 1).** The mean age was 57 ± 16 years; 125 (37%) were female and 285 (85%) were white. The most common causes of chronic respiratory failure were neuromuscular disorders (NMD) other than ALS and restrictive thoracic disorders (41%), followed by ALS (16%), OHS (14%), spinal cord injury (12%), and COPD (12%). Additional diagnoses (central congenital hypoventilation, pleural disease, cystic fibrosis, bronchiectasis) were categorized as “other” (5%). The mean baseline PCO2 was 57 ± 10 mmHg, with 40% ranging between 50-59 mmHg. A majority of initial encounters occurred in the outpatient setting (78%). Forty-four percent of the cohort was already using NIV upon referral to the Assisted Ventilation Clinic. The median follow-up time was 730 days (IQR, 600-730). Regarding missing data, we had one subject only in which BMI could not be calculated (height was missing throughout the chart).

Among the different diagnostic subgroups, mean baseline PCO2 levels were highest in subjects with COPD (66 ± 13 mmHg) and lowest in those with ALS (51 ± 6 mm Hg). Subjects initially encountered as inpatients had higher PCO2 levels than those encountered as outpatients. Irrespective of the diagnosis, mean PCO2 was reduced for subjects in all subgroups at 0-90 days, 90-180 days, 180-365 days, 365-540 days, and

540-730 days after the first encounter. The mean PCO2 was < 50 mmHg for surviving subjects in all primary diagnosis subgroups across both initial assessment locations at 1 and 2 years except for COPD **(Table 2)**.

We found a 23% all-cause mortality within two years of the first evaluation by the Assisted Ventilation Clinic. In the univariate analysis, we found significant associations between mortality and the diagnoses of ALS (hazard ratio, 10.60; 95% CI: 4.60-13.30) and COPD (hazard ratio, 4.37; 95% CI: 1.68-6.34). Female sex, higher age, BMI >= 30 kg/m2, and higher CCI, were associated with mortality**.**

Survival probabilities increased after 90 days based on the percent reduction in PCO2 from baseline (**Figure 2)**. In the multivariate analysis, we found a 92% reduction in mortality between 180-364 days (HR=0.08, 95% CI: 0.01 – 0.64) for patients with a reduction of > 20% from the baseline PCO2. We did not find statistically significant differences in the other deciles of PCO2 reduction or at < 180 days. However, after 365 days, we found a 77% reduction in mortality in patients who had a reduction in PCO2 between 10-19.9% (HR=0.23; 95% CI: 0.08– 0.65), and a 76% reduction in those who had a reduction in PCO2 > 20% (HR = 0.24; 95% CI: 0.09 – 0.62) **(Table 3)**.

Similarly, absolute values of PCO2 <50 mm Hg after 90 days were associated with improved survival **(Figure 3).** After adjusting for age, sex, race, BMI, primary diagnosis, CCI, and baseline PCO2, there remained an increase in survival probability after 90 days for subjects who attained a PCO2 <50 mmHg. In the multivariable analysis, we found a 94% reduction in mortality between 90-179 days (HR=0.06; 95% CI: 0.01 – 0.50), a 69% reduction in mortality between 180 – 364 days (HR=0.31; 95% CI: 0.12 – 0.79), and a

73% reduction in mortality between 365-730 days (HR = 0.27; 95% CI: 0.13 – 0.56) for subjects who attained a PCO2 <50 mmHg (**Table 4**).

To examine the potential effect modification of ALS, a disease with high short-term mortality, we performed a subgroup analysis considering subjects with **(Supplementary Figures 1 and 2 and Supplementary Table 1)** and without ALS **(Supplementary Figures 3 and 4)**. Due to the imperfect correlation between PtcCO2 and arterial PCO2, we analyzed survival considering those who had only PtcCO2 measurements at baseline (**Supplementary Figure 5).** Similarly, we analyzed survival NIV naïve patients only **(Supplementary Table 2 and Supplementary Figure 6).** All subgroup analyses yielded similar results to our primary analysis.

Forty-two subjects were unable to achieve any reduction in PCO2 from baseline in 6-12 months. Of these 42 subjects, 12 (29%) were non-adherent with therapy, defined as consistently less than 4 hours of daily usage. The remaining 30 subjects (71%) were still unable to achieve a reduction in PCO2 despite greater than 4 hours of consistent daily usage.

Discussion

In this single-center, retrospective study of subjects with chronic hypercapnic respiratory failure, we found a strong correlation between reduction in diurnal PCO2 by means of NIV and 2-year mortality. A reduction in PCO2 to <50 mm Hg by 3-6 months was associated with improved survival. In addition, increasing percent reduction in PCO2 from baseline was also associated with improved survival.

Baseline hypercapnia can be a marker for more severe cardiovascular-pulmonary or multi-organ system disease. Although the cause-effect relationship between PCO2 reduction and 2-year mortality cannot be ascertained from this retrospective study, there are compelling reasons to suspect that improving diurnal PCO2 in a dose-response manner could explain the prolonged survival.

Elevated PCO2 directly impairs alveolar fluid reabsorption [24], epithelial cell regeneration [25], cytokine expression [26], and phagocytosis [27] independent of extracellular pH. In mice infected with P. aeruginosa and Influenza A, hypercapnia is associated with increased mortality, independent from blood pH [4,28]. The authors attributed these findings to the effects of hypercapnia on neutrophil and macrophage activity, suggesting that patients with chronic hypercapnia may be predisposed to developing life-threatening bacterial and viral infections. This is supported by observational studies of community-acquired pneumonia that have demonstrated an association between hypercapnia and increased ICU admission, intubation, and mortality [29,30].

In addition to its effects on host defenses, elevated PCO2 has harmful effects on the respiratory pump. Hypercapnia, in both animal and human studies, has been shown to have direct effects on skeletal muscle function. Hypercapnia directly leads to catabolic muscle wasting while also impairing muscle regeneration in respiratory and non-respiratory skeletal muscles [3,31]. Patients with conditions leading to alveolar hypoventilation may develop functional neuromuscular weakness. Adverse effects on brain function have been identified [32-34]. In addition, chronic hypercapnia increases total body tissue stores of PCO2, rendering patients vulnerable to acid-base and

cardiorespiratory decompensation in the event of impairments in PCO2 removal or modest acute increases in PCO2 production as might occur during a febrile illness [5].

Our study showed that although PCO2 could be reduced within the first 3 months after the first visit, its impact in survival became evident with sustained PCO2 reductions. This was seen in both the analyses of percent PCO2 reduction as well as the PCO2 reduction to below 50 mm Hg. These findings may simply be due to the infrequency of deaths within the first 3 months of evaluation. However, this greater survival benefit over time may also represent the time needed to affect host defenses and skeletal muscle function. Future studies looking at these factors in response to PCO2 reduction in humans are warranted. Our findings suggest that future studies in hypercapnic respiratory failure should aim to explore the reduction in PCO2 and maintain the PCO2 reduction over time.

Wilson et al demonstrated that, in hospitalized patients with compensated hypercapnia, higher levels of PCO2 were associated with increased mortality even when adjusted for severity of illness [2]. In contrast to our study, Wilson et al studied a population mostly comprised by patients with OSA, COPD and heart failure, while only a minority had neuromuscular disease. In our study 57% of the population had a primary neuromuscular diagnosis as the cause for hypercapnic respiratory failure. Given the poor prognosis in specific neuromuscular disorders such as ALS, we performed sensitivity analyses excluding this subgroup finding a consistent signal for survival benefit in those who decreased PCO2 levels to < 50 mmHg. Regarding the subgroup analysis in ALS patients, although there was a trend toward improved survival, we are heavily limited in our ability to detect statistically significant differences due to the small sample size of this subgroup

Both in univariate and multivariable analyses, baseline PCO2 level was not significantly associated with higher mortality. This could reflect that PCO2 correction mitigates the mortality risk attributable to baseline hypercapnia. The fact that during the follow-up period we were able to achieve mean PCO2 levels of 50 mm Hg for all baseline PCO2 categories, (including the most extreme cases of PCO2>70 mmHg) could account for the neutral effect of baseline hypercapnia in mortality and supports the notion that hypercapnia is modifiable risk factor rather than just a marker of severity. In addition, a change of PCO2 may be more indicative of trajectory of the disease and reflect outcomes more strongly than a snapshot in time such as a baseline PCO2.

While there is increasing evidence of the benefits of NIV on quality of life and symptom burden [35], little is known about how specific NIV management strategies impact survival. NIV for the management of chronic respiratory failure has focused primarily on hours of usage per day as opposed to specific physiologic variables. Adherence goals have been derived largely from insurance coverage criteria for the use of continuous positive airway pressure (CPAP) therapy for sleep apnea [36] and studies have shown a mortality benefit in patients using NIV for greater than 4 hours per day [12,37]. However, 4 hours may grossly underestimate the hours of use needed to achieve normocapnia. Patients' ventilatory needs may vary from a few hours/days to 24 hours/day depending on the severity of the disease and underlying pathophysiology. Therefore, while hours of use may be sufficient for CPAP therapy secondary to OSA, our study bolsters the argument for a shift in the way we manage NIV in chronic respiratory failure towards prioritizing PCO2 over hourly usage alone.

It is unknown whether targeting an absolute CO2 threshold (for example < 50 mmHg) or a CO2 percentage reduction has superior outcomes. Given the equipoise, we feel this creates a clinical research question that is ripe for a future randomized control trial comparing CO2 reduction strategies in patients with chronic hypercapnia. Until further evidence is available, the "ideal" strategy may depend on degree of baseline CO2 elevation, comorbidities, patient comfort with NIV settings, and aligning treatment strategy with patient goals of care

Arterial blood gas testing remains the gold standard for PCO2. However, there are many barriers to its regular use in the outpatient setting including access to a blood gas analyzer and patient discomfort. PtcCO2 monitors provide an alternative, non-invasive method for longitudinal monitoring of alveolar ventilation. PtcCO2 has been shown to correlate with PCO2 with limits of agreement of -6 to 6 mm Hg when using modern sensors placed on the earlobe at a temperature of 42ºC) [38]. This technique is practical for trending PCO2 during titration of NIV. In addition, PtcCO2 has been used to diagnose respiratory failure in neuromuscular diseases and to aid in the decision-making of inpatient NIV initiation in a small case series [39]. High cost likely hinders the dissemination of PtcCO2 monitors. End-tidal pressure of expired CO2 (PetCO2) also provides non-invasive continuous monitoring of PCO2 levels amenable to an outpatient setting. PetCO2 is less costly than PtcCO2, making it a potentially attractive non-invasive option. However, the accuracy of PetCO2 is limited by inherent differences in PaCO2 and PetCO2 due to dead space, the effect of increasing age and ventilation/perfusion (V/Q) mismatch, and decreasing with large tidal volume [40]. Therefore, PetCO2 may be error-prone in spontaneously breathing patients for 2 reasons: 1) patients with chronic

respiratory failure have frequent V/Q mismatches, and 2) patients requiring continuous NIV will experience mask leakage with measurements [41]. Finally, serum bicarbonate has been used as a surrogate for blood PCO2 levels and may give a general sense of responses to NIV. However, primary metabolic alkalosis, including the use of diuretics, may limit its practical use for the monitoring of alveolar ventilation.

We were unable to reduce PCO2 at 6-12 months in 12% of our hypercapnic subjects. Some subjects did not use NIV regularly or for sufficient hours per day to reduce diurnal PCO2. Others had such severe thoracic or lung disease that we were unable to achieve settings that effectively reversed hypercapnia. Such difficulties highlight the complexities involved in personalizing the management of chronic respiratory failure to each patient. PtcCO2 should be used in conjunction with a full understanding of device downloads to optimize home mechanical ventilation strategies. An inability to reduce PCO2 despite adjustments to ventilator settings and increasing hourly usage should prompt discussing advanced goals of care planning including tracheostomy and/or palliative care for symptom management and end-of-life care planning.

We acknowledge several limitations of our study. Due to the study's retrospective design, we cannot attribute causality or exclude the role of unmeasured confounders in the outcome. The subjects in our single-center study were followed in a specialized clinic with expertise in home mechanical ventilation and PtcCO2 monitoring. Therefore, our findings are prone to selection bias and may not be generalizable to settings with fewer resources. The majority of PCO2 measurements were taken using a PtcCO2 monitor which is prone to bias compared to the gold standard arterial blood gases. In addition, the

placement of the transcutaneous sensor on the forehead has not been widely studied [40] and could have introduced measurement bias.

Conclusion

PCO2 reductions are associated with improved survival in chronic hypercapnic respiratory failure, a condition associated with high mortality. Given the strong association between improved PCO2 and survival, our study sets the rationale for larger prospective studies exploring this association and its potential role in improving clinically meaningful outcomes. In addition, our study highlights the importance of a home mechanical ventilation program with integrated PtcCO2 monitoring. Future work should focus on PtcCO2 technology dissemination to a wider clinical audience to facilitate multicenter cohort studies on how PtcCO2 reduction affects clinical outcomes including hospitalizations and readmissions.

References

1. Vonderbank S, Gibis N, Schulz A, Boyko M, Erbuth A, Gürleyen H, Bastian A. Hypercapnia at hospital admission as a predictor of mortality. Open Access Emerg Med 2020;12 (7):173–180
2. Wilson MW, Labaki WW, Choi PJ. Mortality and Healthcare Use of Patients with Compensated Hypercapnia. Ann Am Thorac Soc. 2021;18(12):2027-2032.
3. Shiota S, Okada T, Naitoh H, Ochi R, Fukuchi Y. Hypoxia and hypercapnia affect contractile and histological properties of rat diaphragm and hind limb muscles. Pathophysiology. 2004;11(1):23-30.

4. Gates KL, Howell HA, Nair A, Vohwinkel CU, Welch LC, Beitel GJ, et al. Hypercapnia impairs lung neutrophil function and increases mortality in murine pseudomonas pneumonia. Am J Respir Cell Mol Biol. 2013;49(11):821-828.

5. Giosa L, Busana M, Bonifazi M, Romitti F, Vassalli F, Pasticci I, et al. Mobilizing Carbon Dioxide Stores. An Experimental Study. Am J Respir Crit Care Med. 2021; 203(3):318-327.

6. Köhnlein T, Windisch W, Köhler D, Drabik A, Geiseler J, Hartl S, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014; 2(9):698-705.

7. Murphy PB, Rehal S, Arbane G, Bourke S, Calverley PMA, Crook AM, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017;317(6):2177-2186.

8. Wilson ME, Dobler CC, Morrow AS, Beuschel B, Alsawas M, Benkhadra R, et al. Association of Home Noninvasive Positive Pressure Ventilation With Clinical Outcomes in Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. JAMA. 2020;323(2):455-465.

9. Mokhlesi B, Masa JF, Afshar M, Almadana Pacheco V, Berlowitz DJ, Borel JC, et al. The Effect of Hospital Discharge with Empiric Noninvasive Ventilation on Mortality in Hospitalized Patients with Obesity Hypoventilation Syndrome. An Individual Patient Data Meta-Analysis. Ann Am Thorac Soc. 2020;17(5):627-637.

10. Pérez de Llano LA, Golpe R, Ortiz Piquer M, Veres Racamonde A, Vázquez Caruncho M, Caballero Muinelos O, Alvarez Carro C. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005; 128(8):587-594.

11. Blankenburg T, Benthin C, Pohl S, Bramer A, Kalbitz F, Lautenschläger C, et al.Survival of Hypercapnic Patients with COPD and Obesity Hypoventilation Syndrome Treated with High Intensity Non Invasive Ventilation in the Daily Routine Care. Open Respir Med J. 2017;11(11):1131-1140.

12. Ackrivo J, Hsu JY, Hansen-Flaschen J, Elman L, Kawut SM. Noninvasive Ventilation Use Is Associated with Better Survival in Amyotrophic Lateral Sclerosis. Ann Am Thorac Soc. 2021;18(3):486-494.

13. Orr JE, Coleman JM 3rd, McSparron JI, Owens RL, Macrea M, Drummond MB, et al. Summary for Clinicians: Clinical Practice Guideline for Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease. Ann Am Thorac Soc. 2021;18(3):395-398.

14. Windisch W, Geiseler J, Simon K, et al; on behalf of the Guideline Commission. German National Guideline for Treating Chronic Respiratory Failure with Invasive and Non-Invasive Ventilation - Revised Edition 2017: Part 2. Respiration. 2018;96(2):171-203.

15. Ackrivo J, Geronimo A. Transcutaneous carbon dioxide monitoring in ALS: Assessment of hypoventilation heats up.(editorial) Muscle Nerve. 2022;65(4):371-373.

16. Aarrestad S, Tollefsen E, Kleiven AL, Qvarfort M, Janssens JP, Skjønsberg OH. Validity of transcutaneous PCO2 in monitoring chronic hypoventilation treated with non-invasive ventilation. Respir Med. 2016;112(3):112-118.

17. Georges M, Rabec C, Monin E, Aho S, Beltramo G, Janssens JP, Bonniaud P. Monitoring of noninvasive ventilation: comparative analysis of different strategies. Respir Res. 2020;21(1):324.

18. Bendjelid K, Schütz N, Stotz M, Gerard I, Suter PM, Romand JA. Transcutaneous PCO2 monitoring in critically ill adults: clinical evaluation of a new sensor. Crit Care Med. 2005;33(10):2203-2206.

19. Restrepo RD, Hirst KR, Wittnebel L, Wettstein R. AARC clinical practice guideline: transcutaneous monitoring of carbon dioxide and oxygen: 2012. Respir Care. 2012;57(11):1955-1962.

20. Vail EA, Gershengorn HB, Wunsch H, Walkey AJ. Attention to Immortal Time Bias in Critical Care Research. Am J Respir Crit Care Med. 2021;203(10):1222-1229.

21. Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models.(editorial) Ann Transl Med. 2018;6(7):121.

22. Schoenfeld D.Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika.1980; 67(4): 145-153

23. Boher JM, Filleron T, Giorgi R, Kramar A, Cook RJ. Goodness-of-fit test for monotone proportional subdistribution hazards assumptions based on weighted residuals. Stat Med 2017;36(1):362–377.

24. Shigemura M, Lecuona E, Sznajder JI. Effects of hypercapnia on the lung. J Physiol. 2017;595(8):2431-2437.

25. Vohwinkel CU, Lecuona E, Sun H, Sommer N, Vadász I, Chandel NS, Sznajder JI. Elevated CO(2) levels cause mitochondrial dysfunction and impair cell proliferation. J Biol Chem. 2011;286(43):37067-37076.

26. Wang N, Gates KL, Trejo H, Favoreto S Jr, Schleimer RP, Sznajder JI et al. Elevated CO2 selectively inhibits interleukin-6 and tumor necrosis factor expression and decreases phagocytosis in the macrophage. FASEB J. 2010;24(7):2178-2190.

27. Casalino-Matsuda SM, Nair A, Beitel GJ, Gates KL, Sporn PH. Hypercapnia Inhibits Autophagy and Bacterial Killing in Human Macrophages by Increasing Expression of Bcl-2 and Bcl-xL. J Immunol. 2015;194(11):5388-5396.

28. Casalino-Matsuda SM, Nair A, Beitel GJ, Gates KL, Sporn PH. Hypercapnia Suppresses Macrophage Antiviral Activity and Increases Mortality of Influenza A Infection via Akt1. J Immunol. 2020;205(2):489-501.

29. Sin DD, Man SF, Marrie TJ. Arterial carbon dioxide tension on admission as a marker of in-hospital mortality in community-acquired pneumonia. Am J Med. 2005;118(7):145-150.

30. Laserna E, Sibila O, Aguilar PR, Mortensen EM, Anzueto A, Blanquer JM, et al. Hypocapnia and hypercapnia are predictors for ICU admission and mortality in hospitalized patients with community-acquired pneumonia. Chest. 2012;142(11):1193-1199.

31. Korponay TC, Balnis J, Vincent CE, Singer DV, Chopra A, Adam AP, et al. High CO2 Downregulates Skeletal Muscle Protein Anabolism via AMP-activated Protein Kinase α2-mediated Depressed Ribosomal Biogenesis. Am J Respir Cell Mol Biol. 2020;62(1):74-86.

32. Xu F, Uh J, Brier MR, Hart J Jr, Yezhuvath US, Gu H, et al. The influence of carbon dioxide on brain activity and metabolism in conscious humans. J Cereb Blood Flow Metab. 2011;31(1):58-67.

33. Thesen T, Leontiev O, Song T, Dehghani N, Hagler DJ Jr, Huang M, et al. Depression of cortical activity in humans by mild hypercapnia. Hum Brain Mapp. 2012;33(3):715-726.

34. Burgraff NJ, Neumueller SE, Buchholz KJ, LeClaire J, Hodges MR, Pan L, et al. Brainstem serotonergic, catecholaminergic, and inflammatory adaptations during chronic hypercapnia in goats. FASEB J. 2019;33(12):14491-14505.

35. Tsolaki V, Pastaka C, Kostikas K, Karetsi E, Dimoulis A, Zikiri A, Koutsokera A, et al. Noninvasive ventilation in chronic respiratory failure: effects on quality of life. Respiration. 2011;81(5):402-410.

36. Mokhlesi B, Won CH, Make BJ, Selim BJ, Sunwoo BY; ONMAP Technical Expert Panel.. Optimal NIV Medicare Access Promotion: Patients With Hypoventilation

Syndromes: A Technical Expert Panel Report From the American College of Chest Physicians, the American Association for Respiratory Care, the American Academy of Sleep Medicine, and the American Thoracic Society. Chest. 2021;160(11):e377-e387.

37. Patout M, Lhuillier E, Kaltsakas G, Benattia A, Dupuis J, Arbane G, et al. Long-term survival following initiation of home non-invasive ventilation: a European study. Thorax. 2020;75(11):965-973.

38. Conway A, Tipton E, Liu WH, Conway Z, Soalheira K, Sutherland J, Fingleton J. Accuracy and precision of transcutaneous carbon dioxide monitoring: a systematic review and meta-analysis. Thorax. 2019;74(2):157-163.

39. Quigg KH, Wilson MW, Choi PJ. Transcutaneous CO2 monitoring as indication for inpatient non-invasive ventilation initiation in patients with amyotrophic lateral sclerosis. Muscle Nerve. 2022;65(4):444-447.

40. Huttmann SE, Windisch W, Storre JH. Techniques for the measurement and monitoring of carbon dioxide in the blood. Ann Am Thorac Soc. 2014;11(4):645-652.

41. Storre JH, Bohm P, Dreher M. Clinical impact of leak compensation during non-invasive ventilation. Respir Med 2009; 103(10):1477–1483.

Figures

Figure 1. Flow Diagram of Cohort.

Figure 2. Two-year survival by the percentage of PCO2 change for the entire cohort of hypercapnic patients. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, primary diagnosis, and initial PCO2. Likelihood ratio test of equality p= <0.001.

Figure 3. Two-year survival by absolute PCO2 higher on lower than 50 mmHg for the entire cohort of hypercapnic patients. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, primary diagnosis, and initial PCO2. Likelihood ratio test of equality p= <0.001.

Quick Look

Current Knowledge

Chronic compensated hypercapnia is associated with increased mortality and morbidity. In the setting of chronic alveolar hypoventilation, non-invasive ventilation can offload respiratory muscles while increasing alveolar ventilation and reducing excess total body PCO2 stores.

What This Paper Contributes To Our Knowledge

The reduction in PCO2 levels using non-invasive ventilation is associated with improved survival in chronic hypercapnic respiratory failure. Larger reductions in PCO2 had a stronger association with survival. Reductions of PCO2 to levels < 50 mmHg were achieved in most of the patients.

Table 1. Cohort characteristics (*N*=337)

Variable	Summary Statistics
Age at first visit, yr	57 ±16
Sex, F, *n* (%)	125 (37)
Race, *n* (%)	
White	285 (85)
Black	39 (11)
Asian	6 (2)
Other	7 (2)
BMI class, *n* (%)	
<18.5 kg/m^2	30 (9)
18.5-24.9 kg/m^2	82 (24)
25-29.9 kg/m^2	69 (21)
≥30 kg/m^2	155 (46)
Primary diagnosis, *n* (%)	
ALS	56 (16)
Other NMD / RTD	138 (41)
COPD	40 (12)
Spinal cord injury	39 (12)
OHS	48 (14)
Other	16 (5)
Charlson comorbidity index	2.0 (1.0, 4.0)
Non-invasive ventilation start location, *n*(%)	
Outpatient	262 (78)
Inpatient	75 (22)
Baseline non-invasive ventilation use	
Naïve	189 (56)
Prior use	148 (44)
Baseline CO_2, mmHg	
<50	87 (26)
50-59	134 (40)
60-69	83 (24)
≥70	33 (10)
Vital status at 2 years	
Alive	260 (77)
Deceased	77 (23)

Definition of abbreviations: BMI = body mass index; ALS = amyotrophic lateral sclerosis; NMD = neuromuscular disease; RTD = restrictive thoracic disorder; COPD = chronic obstructive pulmonary disease; OHS = obesity hypoventilation syndrome; CO_2 = carbon dioxide.
Summary statistics are mean ± SD or median (25th–75th percentiles) unless otherwise indicated.

Table 2. Carbon dioxide averages by time and group

	n (%)	CO_2, (mmHg) baseline	CO_2, (mmHg) 0-90 days	CO_2, (mmHg) 90-180 days	CO_2, (mmHg) 180-365 days	CO_2, (mmHg) 365-540 days	CO_2, (mmHg) 540-730 days
All subjects	337 (100)	57 ±10	55 ±9	50 ±8	48 ±7	47 ±8	46 ±8
Primary diagnosis							
ALS	56 (16)	51 ±6	51 ±6	47 ±6	45 ±6	44 ±6	44 ±6
Other NMD / RTD	138 (41)	55 ±9	54 ±9	50 ±8	47 ±6	46 ±6	46 ±7
COPD	40 (12)	66 ±13	62 ±11	55 ±9	54 ±10	53 ±10	52 ±10
Spinal cord injury	39 (12)	56 ±7	54 ±7	49 ±7	46 ±7	46 ±6	46 ±6
OHS	48 (14)	61 ±11	60 ±10	52 ±8	49 ±9	47 ±10	46 ±10
Other	16 (5)	59 ±9	57 ±8	51 ±6	48 ±6	47 ±6	43 ±4
NIV start location							
Outpatient	262 (78)	55 ±9	54 ±9	50 ±7	48 ±7	47 ±7	46 ±8
Inpatient	75 (22)	63 ±12	59 ±11	50 ±10	48 ±9	47 ±9	46 ±8
NIV experience							
Prior NIV	189 (56)	58 ±10	54 ±9	50 ±7	48 ±7	47 ±7	47 ±8
NIV Naïve	148 (44)	56 ±10	56 ±10	50 ±9	48 ±8	47 ±8	45 ±8
Baseline CO_2, mmHg							
<50	87 (26)	47 ±2	47 ±3	46 ±4	45 ±5	44 ±5	43 ±5
50-59	134 (40)	54 ±3	53 ±4	49 ±6	47 ±6	46 ±6	46 ±7
60-69	83 (24)	64 ±3	61 ±5	53 ±9	50 ±9	49 ±10	48 ±10
≥70	33 (10)	79 ±9	74 ±10	59 ±10	55 ±10	51 ±10	50 ±9

Definition of abbreviations: ALS = amyotrophic lateral sclerosis; NMD = neuromuscular disease; RTD = restrictive thoracic disorder; COPD = chronic obstructive pulmonary disease; OHS = obesity hypoventilation syndrome; NIV = noninvasive ventilation; CO_2 = carbon dioxide.
Data are mean ± SD unless otherwise indicated.

Table 3. Results of 2-year survival analysis adjusted for percent change in CO_2 (*N*=337)

	Univariate Analysis			Multivariable Analysis		
Variable	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Age at diagnosis, per decade	1.54	1.30 – 1.83	<0.001	1.16	0.87 – 1.55	0.31
Female sex	1.91	1.22 – 2.99	0.004	1.51	0.91 – 2.52	0.11
Race						
White	--	--	--	--	--	--
Black	0.42	0.15 – 1.15	0.09	1.24	0.42 – 3.71	0.70
Asian	2.69	0.85 – 8.54	0.09	2.51	0.68 – 9.25	0.17
Other	0.54	0.08 – 3.90	0.54	1.07	0.14 – 8.43	0.95
Body mass index class (kg/m^2)						
<18.5	1.65	0.81 – 3.38	0.17	2.90	1.28 – 6.56	0.011
18.5 - 24.9	--	--	--	--	--	--
25 - 29.9	1.35	0.74 – 2.47	0.34	1.81	0.90 – 3.63	0.10
≥30	0.51	0.28 – 0.94	0.03	1.00	0.49 – 2.01	0.99
Primary diagnosis						
Other NMD / RTD	--	--	--	--	--	--
ALS	10.60	4.60 – 13.30	<0.001	10.90	5.21 – 22.78	<0.001
COPD	4.37	1.68 – 6.34	<0.001	2.51	1.09 – 5.78	0.031
Spinal cord injury	*	*	*	*	*	*
OHS	1.02	0.28 – 1.94	0.53	1.17	0.38 – 3.61	0.79
Other	2.59	1.25 – 5.37	0.011	6.42	2.15 – 19.14	0.001
Charlson comorbidity index, per 1-point increase	1.17	1.07 – 1.29	0.001	1.08	0.89 – 1.32	0.43
NIV experience						
NIV Naïve	--	--	--			
Prior NIV	0.82	0.52 – 1.30	0.41			
Location of NIV Start						
Outpatient	--	--	--			
Inpatient	1.12	0.67 – 1.88	0.68			
Baseline CO_2 (mmHg)						
<50	--	--	--	--	--	--
50-59	0.96	0.57 – 1.63	0.88	2.64	1.41 – 4.92	0.002
60-69	0.57	0.29 – 1.13	0.11	1.49	0.62 – 3.55	0.37
≥70	0.81	0.35 – 1.89	0.63	3.18	0.98 – 10.32	0.05
Percent change in CO_2						
<180 Days						
No change or increase	--	--	--	--	--	--
<10% Decrease	0.74	0.09 – 5.94	0.78	0.67	0.08 – 5.47	0.71
10 – 19.9% Decrease	1.47	0.40 – 5.39	0.56	1.00	0.26 – 3.84	> 0.99
≥20% Decrease	0.56	0.12 – 2.61	0.46	0.55	0.11 – 2.76	0.47
180 – 364 Days						
No change or increase	--	--	--	--	--	--
<10% Decrease	1.41	0.51 – 3.88	0.51	1.08	0.37 – 3.12	0.89
10 – 19.9% Decrease	0.48	0.13 – 1.75	0.27	0.39	0.10 – 1.46	0.16
≥20% Decrease	0.09	0.01 – 0.69	0.021	0.08	0.01 – 0.65	0.018

≥365 Days						
No change or increase	--	--	--	--	--	--
<10% Decrease	0.48	0.16 – 1.43	0.19	0.33	0.10 – 1.07	0.06
10 – 19.9% Decrease	0.30	0.11 – 0.81	0.018	0.23	0.08 – 0.65	0.006
≥20% Decrease	0.25	0.11 – 0.59	0.001	0.24	0.09 – 0.62	0.003

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; ALS = amyotrophic lateral sclerosis, NMD = neuromuscular disease; RTD = restrictive thoracic disorder; COPD = chronic obstructive pulmonary disease; OHS = obesity hypoventilation syndrome, NIV = noninvasive ventilation, CO_2 = carbon dioxide. *hazard ratios are not estimable because no patient with spinal cord injury died during the follow-up

*

Table 4. Results of 2-year survival analysis adjusted for absolute CO_2 above or below 50 mmHg (*N*=337)

	Univariate Analysis			Multivariable Analysis		
Variable	**HR**	**95% CI**	**P Value**	**HR**	**95% CI**	**P Value**
Age at diagnosis, per decade	1.54	1.30 – 1.83	<0.001	1.15	0.87 – 1.54	0.33
Female sex	1.91	1.22 – 2.99	0.004	1.60	0.96 – 2.64	0.07
Race						
White	--	--	--	--	--	--
Black	0.42	0.15 – 1.15	0.09	1.28	0.44 – 3.75	0.65
Asian	2.69	0.85 – 8.54	0.09	2.93	0.79 – 10.9	0.11
Other	0.54	0.08 – 3.90	0.54	1.13	0.15 – 8.68	0.91
Body mass index class (kg/m^2)						
<18.5	1.65	0.81 – 3.38	0.17	2.39	1.03 – 5.53	0.042
18.5 - 24.9	--	--	--	--	--	--
25 - 29.9	1.35	0.74 – 2.47	0.34	1.94	0.99 – 3.80	0.053
≥30	0.51	0.28 – 0.94	0.03	1.05	0.51 – 2.14	0.90
Primary diagnosis						
Other NMD / RTD	--	--	--	--	--	--
ALS	10.60	4.60 – 13.30	<0.001	11.26	5.38 – 23.60	<0.001
COPD	4.37	1.68 – 6.34	<0.001	2.49	1.09 – 5.67	0.030
Spinal cord injury	*	*	*	*	*	*
OHS	1.02	0.28 – 1.94	0.53	0.99	0.32 – 3.03	0.98
Other	2.59	1.25 – 5.37	0.011	4.73	1.58 – 14.18	0.006
Charlson comorbidity index, per 1-point increase	1.17	1.07 – 1.29	0.001	1.11	0.91 – 1.34	0.30
NIV experience						
NIV Naïve	--	--	--			
Prior NIV	0.82	0.52 – 1.30	0.41			
Location of NIV Start						
Outpatient	--	--	--			
Inpatient	1.12	0.67 – 1.88	0.68			
Baseline CO_2 (mmHg)						
<50	--	--	--	--	--	--
50-59	0.96	0.57 – 1.63	0.88	1.33	0.69 – 2.56	0.40
60-69	0.57	0.29 – 1.13	0.11	0.62	0.26 – 1.45	0.27
≥70	0.81	0.35 – 1.89	0.63	0.76	0.26 – 2.28	0.63
Time-varying CO2 (mmHg)						
≥50 per time interval	--	--	--	--	--	--
<50 between 0 – 89 days	0.83	0.26 – 2.64	0.75	0.43	0.11 – 1.75	0.24
<50 between 90 – 179 days	0.10	0.01 – 0.84	0.033	0.06	0.01 – 0.50	0.009

<50 between 180 – 364 days	0.44	0.18 – 1.07	0.07	0.31	0.12 – 0.79	0.014
<50 after 365-730 days	0.35	0.18 – 0.68	0.002	0.27	0.13 – 0.56	<0.001

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; ALS = amyotrophic lateral sclerosis, NMD = neuromuscular disease; RTD = restrictive thoracic disorder; COPD = chronic obstructive pulmonary disease; OHS = obesity hypoventilation syndrome, NIV = noninvasive ventilation, TCO_2 = transcutaneous carbon dioxide.
*hazard ratios are not estimable because no patient with spinal cord injury died during the follow-up

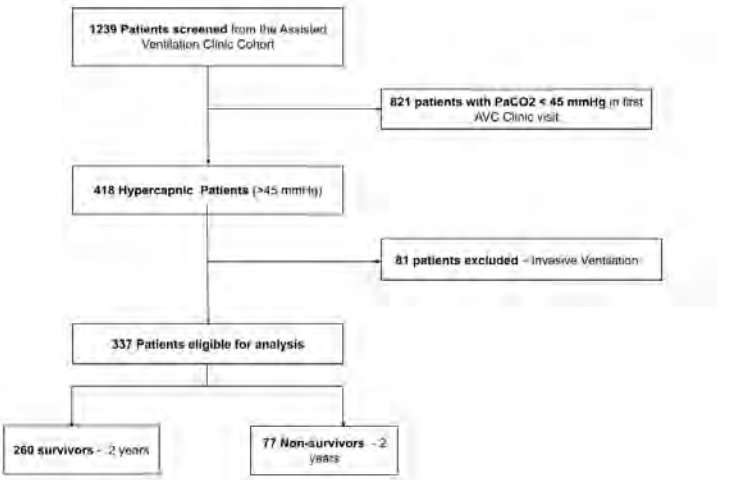

Figure 1. Flow Diagram of Cohort.

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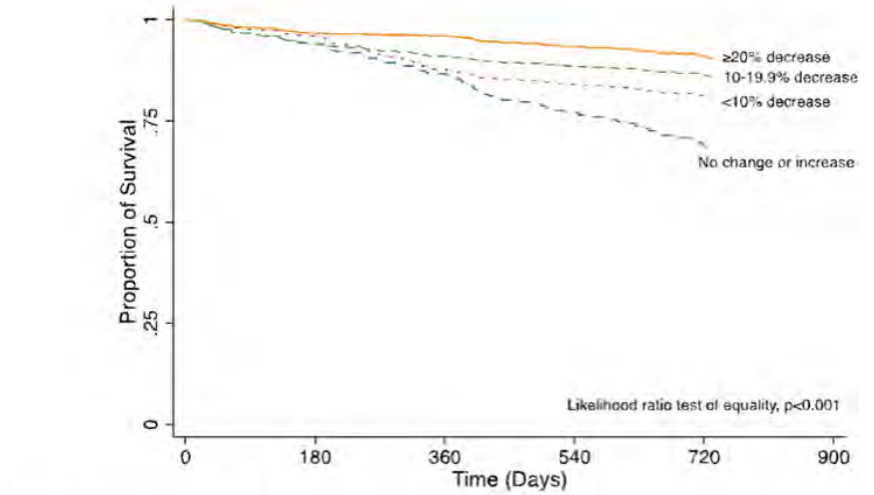

Number at risk					
No change or increase	82	65	54	41	30
<10% decrease	43	42	42	35	27
10 – 19.9% decrease	81	77	73	65	59
≥20% decrease	131	129	126	117	107

Figure 2. Two-year survival by absolute PCO2 higher on lower than 50 mmHg for the entire cohort of hypercapnic patients

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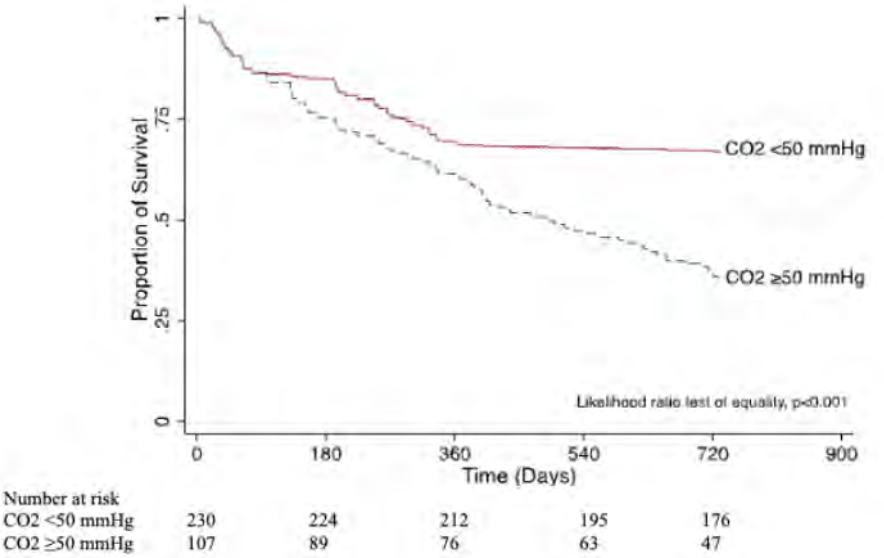

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Supplemental Table 1. Hazard Ratios for survival of ALS patients **only** (*N*=56)

Variable	HR	p-value	95% CI
Time-varying CO2 (mmHg)			
≥50 per time interval	---	---	---
< 50 between 0-89 days	0.18	0.033	0.39 – 0.87
< 50 between 90-179 days	0.04	0.007	0.004 – 0.43
<50 between 180 – 364 days	0.14	0.004	0.04 – 0.54
CO2 50 mmHg at 365 --730 days	0.25	0.082	0.05 –1.18
Age per decade	1.14	0.652	0.64 – 2.05
Female	1.66	0.197	0.76 – 3.63
BMI (kg/m^2)			
<18.5	0.62	0.612	0.10 – 3.85
25-29.9	1.91	0.166	0.76 –4.79
>30	0.71	0.550	0.23 – 2.14
Race			
White	---	---	---
Black	6.31	0.760	0.34 – 4.33
CCI	1.04	0.828	0.68 – 1.61
Initial CO2 (mmHg)			
<50	---	---	---
50-59	0.99	0.993	0.45 – 2.16
60-69	0.69	0.580	0.19 – 2.48

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; ALS = amyotrophic lateral sclerosis, , CO_2 = carbon dioxide.

Supplemental Table 2. Hazard Ratios for survival of NIV naive patients **only** (*N*=189)

Variable	HR	P-value	95% CI
Time-varying CO2 (mmHg)			
≥50 per time interval	--	--	--
< 50 between 0-89 days	0.14	0.017	0.26 – 0.71
< 50 between 90 - 179 days	0.14	0.10	0.014 – 1.44
<50 between 180 – 364 days	0.33	0.050	0.11 – 1.00
<50 between 365 – 730 days	0.11	<0.001	0.04 – 0.35
Age per decade	1.49	0.07	0.96 – 2.32
Female	2.71	0.007	1.31 – 5.63
Body mass index (kg/m^2)			
<18.5	2.29	0.15	0.73 – 7.19
18.5 – 24.9	--	--	--
25-29.9	3.91	0.005	1.50 –10.12
>30	1.85	0.24	0.66 – 5.16

Race			
White	--	--	--
Black	1.21	0.76	0.34 – 4.33
Asian	4.82	0.037	1.09 – 21.20
Other	2.31	0.45	0.25 – 20.95
CCI	0.094	0.70	0.727 – 1.23
Diagnosis			
Other NMD/RTD	--	--	--
ALS	10.30	<0.001	3.99 – 26.60
COPD	3.83	0.014	1.30 – 11.26
OHS	0.79	0.78	0.15 – 4.10
Other	9.98	0.003	2.14 – 46.59
Initial CO2 (mmHg)			
<50	--	--	--
50-59	1.22	0.65	0.50 – 2.99
60-69	0.65	0.44	0.22 – 1.91
>70	0.83	0.797	0.20 – 3.40

Definition of abbreviations: HR = hazard ratio; CI = confidence interval; ALS = amyotrophic lateral sclerosis, NMD = neuromuscular disease; RTD = restrictive thoracic disorder; COPD = chronic obstructive pulmonary disease; OHS = obesity hypoventilation syndrome, NIV = noninvasive ventilation, CO_2 = carbon dioxide.

*

Supplementary Figure 1. Two-year survival by absolute CO2 higher on lower than 50 mmHg for patients with ALS. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, and initial CO2. Likelihood ratio test of equality p= 0.09.

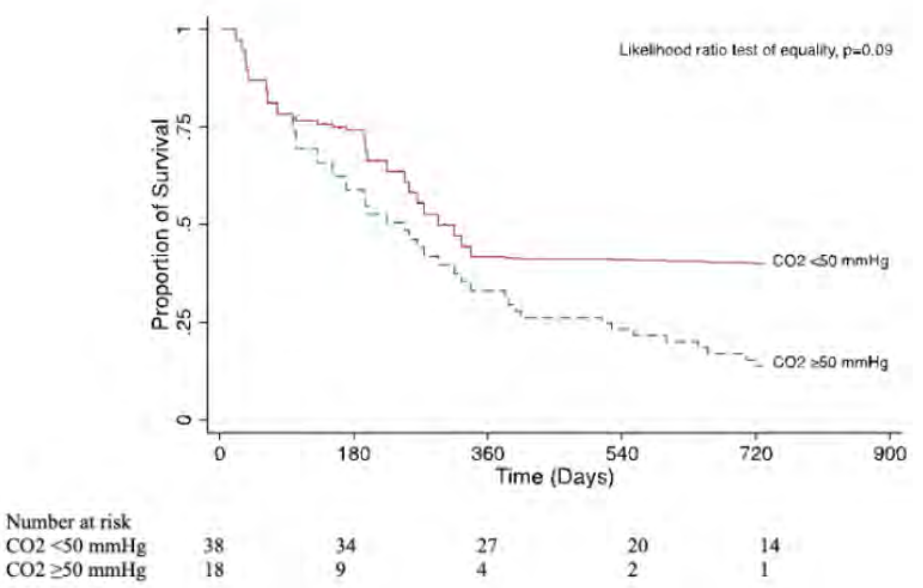
Supplementary Figure 2. Two-year survival by the percentage of PCO2 change for patients with ALS. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, and initial CO2. Likelihood ratio test of equality non-significant.

Supplementary Figure 3. Two-year survival by absolute CO2 higher on lower than 50 mmHg for patients without ALS. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, and initial CO2. Likelihood ratio test of equality p= <0.001.

Supplementary Figure 4. Two-year survival by the percentage of PCO2 change for patients without ALS. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, and initial CO2.

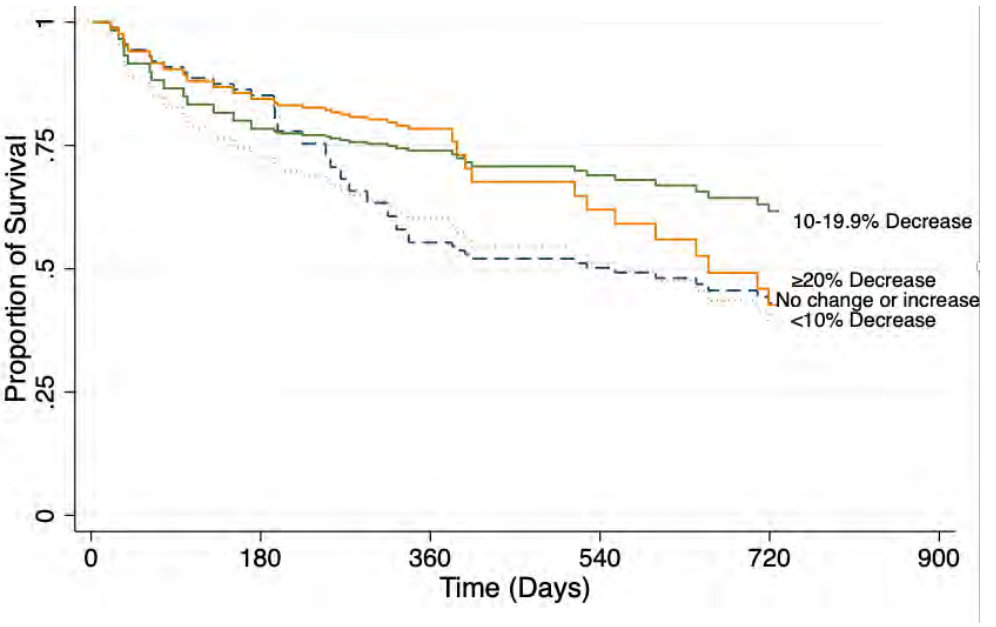
Supplementary Figure 5. Two-year survival by absolute CO2 higher on lower than 50 mmHg for patients with TCO2 at diagnosis only. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, primary diagnosis, and initial CO2. Likelihood ratio test of equality p= <0.001.

Supplementary Figure 6. Two-year survival by absolute CO2 higher on lower than 50 mmHg for NIV naïve patients only. Model adjusted for age sex, body mass index, race, Charlson Comorbidity Index, primary diagnosis, and initial CO2. Likelihood ratio test of equality p= <0.001.



Number at risk					
CO2 <50 mmHg	38	34	27	20	14
CO2 ≥50 mmHg	18	9	4	2	1

70x43mm (300 x 300 DPI)



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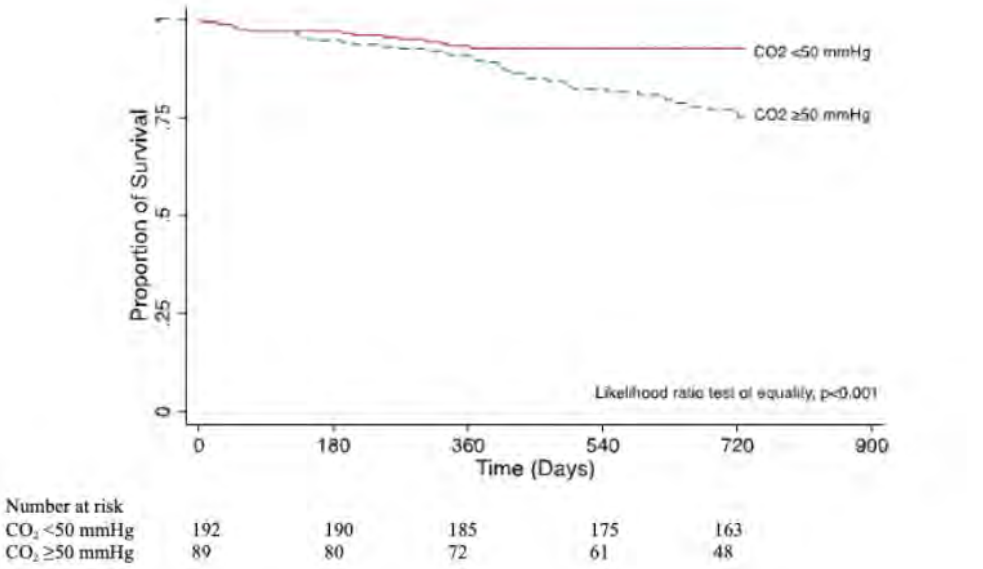

Number at risk					
CO_2 <50 mmHg	192	190	185	175	163
CO_2 ≥50 mmHg	89	80	72	61	48

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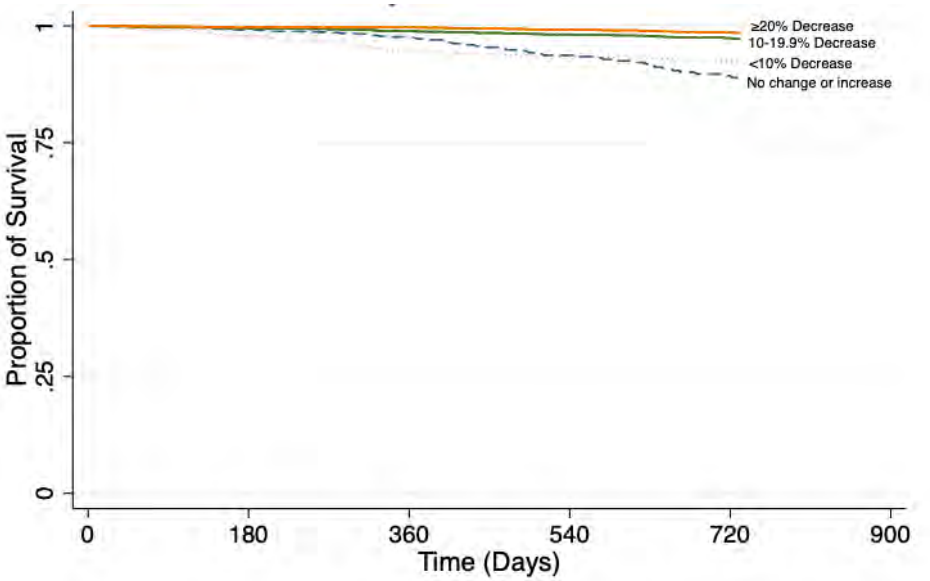

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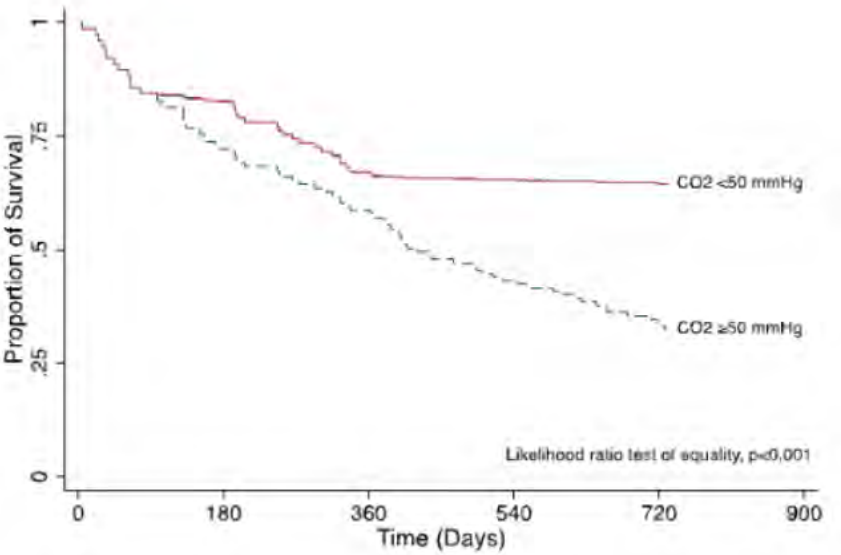

Number at risk					
CO_2 <50 mmHg	230	219	205	188	170
CO_2 ≥50 mmHg	101	83	72	59	45

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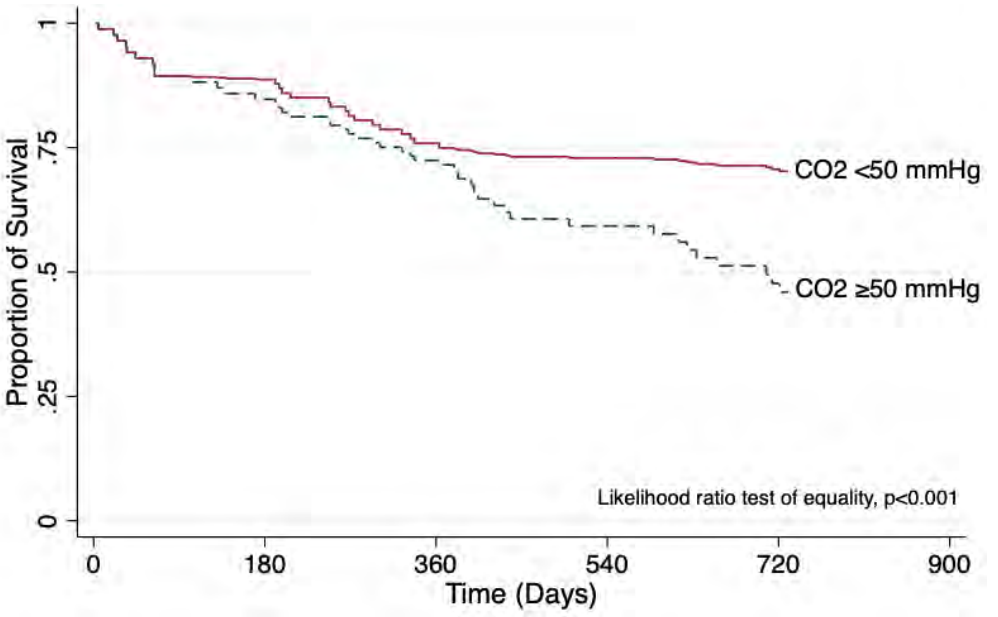

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