Mortality and Healthcare Utilization of Patients with Compensated Hypercapnia

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Abstract

Rationale: Acute hypercapnic respiratory failure has been shown to be associated with worse outcomes for various disease states, but less is known about patients with compensated hypercapnic respiratory failure. Although these patients have a normal pH, it remains unknown whether chronically elevated partial pressures of carbon dioxide (PaCO2), irrespective of etiology, put patients at risk of adverse events.

Objectives: To understand the burden of and clinical factors associated with morbidity and mortality in patients with compensated hypercapnic respiratory failure.

Methods: We performed a query of the electronic medical record (EMR) to identify patients hospitalized at the University of Michigan from January 1 - December 31, 2018 who had compensated hypercapnia, using a PaCO2 $\geq$ 50 mmHg and pH 7.35 – 7.45 on arterial blood gas (ABG). We obtained demographic and clinical data from the EMR. Survival probabilities for PaCO2 subgroups (50.0-54.9; 55.0-64.9; ≥65.0 mmHg) were determined using the Kaplan-Meier product limit estimator. Cox proportional hazard models were constructed to test the association between PaCO2 and all-cause mortality.

Results: We identified 491 patients with compensated hypercapnia. The mean age was 60.5 ± 16.2. Patients were 57.4% male and 86.2% white. The mean pH and PaCO2 were 7.38 ± 0.03 and 58.8 ± 9.7 mmHg respectively. There were a total of 1,030 hospitalizations, with 44.4% of patients having 2 or more admissions. The median numbers of cumulative hospital and ICU days were 21.0 (IQR 11.0-38.0) and 7.0 (IQR 3.0-14.0) respectively. 217 patients (44.2%) died over a median of 592 days. In univariate analysis, every 5-mmHg increase in PaCO2 was associated with a higher risk of all-cause death (HR 1.09; 95% CI 1.03-1.16; p=0.004). This

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association was maintained after adjusting for age, sex, BMI, and the Charlson comorbidity index (HR 1.09 for every 5-mmHg increase in PaCO2; 95% CI 1.02-1.16; p=0.009). There was a statistically significant interaction between PaCO2 and BMI on mortality (p= 0.01 for the interaction term).

Conclusions: Patients with compensated hypercapnic respiratory failure have high mortality and healthcare utilization with higher PaCO2 associated with worse survival. Obese hypercapnic patients have higher risk of death with increases in PaCO2.

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Hypercapnia, defined as an elevated partial pressure of carbon dioxide (PaCO2) level above 45 mmHg at sea level, is a common problem presenting with symptoms of fatigue, confusion, and morning headache(1). Hypercapnia can present as either an acute state or develop into a chronic condition. Acute respiratory failure is particularly dangerous and often leads to admission to the intensive care unit (ICU). Patients with underlying chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome (OHS), neuromuscular disease, or thoracic cage abnormalities may develop compensated hypercapnic respiratory failure without acidosis. Acute hypercapnic respiratory failure is associated with worse outcomes in a variety of clinical settings, such as increased mortality in patients with COPD (2-4), acute respiratory distress syndrome (ARDS)(5), and those requiring mechanical ventilation in the ICU(6). Acute hypercapnia is also associated with a higher rate of intubation in patients with acute exacerbation of congestive heart failure (CHF)(7) and increased lengths of stay for patients admitted with pneumonia(8).

While these studies highlight the vulnerability of patients with acute hypercapnia, there is a paucity of literature on the clinical characteristics and outcomes of patients with compensated hypercapnia, and published studies are generally limited to specific disease states, such as COPD or OHS. In actual clinical practice, patients often have multiple comorbidities that predispose them to chronic hypoventilation. Studies looking at clinical outcomes of patients with compensated hypercapnic respiratory failure, irrespective of etiology, are limited, though Vonderbank et al reported a 1-year mortality rate of 32% for a cohort of 588 hypercapnic patients that were admitted for dyspnea or other pulmonary disease(9).

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The goal of this study is to characterize the demographics, spirometry, laboratory values, and outcomes among hospitalized patients with compensated hypercapnia. We hypothesized that patients with compensated hypercapnic respiratory failure experience increased morbidity and mortality in a dose-response relationship relative to their PaCO2 level.

Methods

Participants and Study Design

We first obtained Institutional Review Board approval at the University of Michigan (HUM00162425) and the project was exempt from informed consent. We performed a structured query of the electronic medical record (EMR) to identify adult patients meeting our inclusion criteria of at least one inpatient admission to the University of Michigan from January 1, 2018 to December 31, 2018 and compensated hypercapnic respiratory failure. We used a PaCO2 $\geq$ 50 mmHg and pH 7.35 – 7.45 on arterial blood gas (ABG) that was drawn during hospital admission as our inclusion criteria. We randomly selected 30 patients with a pH > 7.40 and carefully reviewed the EMR to ensure that we were not including patients with a primary metabolic alkalosis with respiratory compensation. None of these 30 patients had a primary metabolic process. When multiple ABGs were drawn and fit the inclusion criteria, a single sample with the highest PaCO2 value was recorded. The serum bicarbonate level was obtained from a basic metabolic panel that was drawn on the same day as the ABG. Using the EMR's problem list for each patient, we determined the prevalence of CHF (preserved and reduced ejection fraction), obstructive sleep apnea (OSA), neuromuscular disease, and COPD. We also

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determined the Charlson comorbidity index (CCI), which is a validated method of predicting mortality by weighting particular comorbid conditions(10).

We excluded patients less than 18 years of age or admissions to the psychiatric or inpatient rehabilitation hospital. We only analyzed data from patient care provided at the University of Michigan hospital. From the EMR, we obtained demographic data, body mass index (BMI), and most recent outpatient pulmonary function testing (PFT) preceding hospital admission.

Outcomes

We recorded the number of admissions, ICU days, and hospital days at the University of Michigan hospital over the course of 1 year following index admission. Need for invasive and non-invasive mechanical ventilation support was determined from inpatient records. Use of outpatient non-invasive ventilation (NIV), chronic tracheostomy, and long-term mechanical ventilation at the time of admission were extracted from the EMR. A patient was recorded as deceased if he or she died for any reason between January 1, 2018 and May 1, 2020. In addition to inpatient deaths, we included patients that died at home or a facility, such as long-term acute care facility or a hospice agency. Vital status up until May 1, 2020 was determined after review of the EMR, funeral home websites, and online newspapers.

Statistical Analysis

We described baseline characteristics for all participants and by PaCO2 subgroups (50.0-54.9; 55.0-64.9; and ≥ 65.0 mmHg) as means and standard deviations (SD) for continuous variables

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and as counts and proportions for categorical variables. For each PaCO2 subgroup, we estimated survival probabilities using the Kaplan-Meier product limit estimator. We then constructed univariable and multivariable Cox proportional hazards models with all-cause mortality as the outcome and PaCO2 as the predictor of interest. We adjusted models for age, sex, BMI, and CCI and evaluated for interactions between each of these variables and PaCO2. The proportional hazard assumption and the functional form of covariates assumption were met for all models. Analyses were performed in SAS 9.4 (Cary, NC, USA). A p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

We identified 491 unique patients with compensated hypercapnic respiratory failure that required inpatient admission in 2018. The mean age was 60.5 ± 16.2 years with 282 male patients (57.4%) and a predominantly white population (86.2%). The mean BMI was 30.6 ± 10.3 kg/m^2. The mean arterial pH and PaCO2 were 7.38 ± 0.03 and 58.8 ± 9.7 mmHg respectively. The mean serum bicarbonate level was 33.3 ± 4.6 mEq/L. For the 232 patients who had PFTs recorded in the system, the mean FVC and FEV1 were 57.4 ± 21.3 and 53.9 ± 24.0 percent predicted respectively. The mean CCI for the cohort was 5.53 ± 3.24. Among the 491 patients in the cohort, 220 (44.8%) had CHF, 110 (22.4%) had OSA, 36 (7.3%) had neuromuscular disease, and 170 (34.6%) had COPD (Table 1).

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Healthcare Utilization

Among this cohort, there was a total of 1,030 inpatient admissions, with 44.4% of patients having 2 or more admissions. Over a 12-month time period beginning on the initial ABG date, the median numbers of cumulative hospital and ICU days were 21.0 (IQR 11.0-38.0) and 7.0 (IQR 3.0-14.0) respectively. During their hospitalizations, 298 patients (60.7%) developed respiratory failure requiring invasive mechanical ventilation, and 96 patients (19.6%) required NIV. Only 120 patients (24.4%) in our total cohort were prescribed outpatient NIV therapy. For patients with PaCO2 50.0-54.9, only 16.7% were prescribed NIV, but for patients with a PaCO2 ≥ 65.0 mmHg, the rate increased to 40.4%.

Mortality

A total of 217 patients (44.2%) died over a median of 592 days. Survival probabilities decreased with increasing PaCO2 categories (Figure 1). In univariate analysis, every 5-mmHg increase in PaCO2 was associated with a higher risk of all-cause death (HR 1.09; 95% CI 1.03-1.16; p=0.004). This association was maintained after adjusting for age, sex, BMI, and CCI (HR 1.09 for every 5-mmHg increase in PaCO2; 95% CI 1.02-1.16; p=0.009) (Table 2). Higher age, lower BMI, and a higher CCI were also independently associated with mortality. In additional analyses on this model, there was a statistically significant interaction between PaCO2 and BMI on mortality (p= 0.01 for the interaction term). Therefore, the association between PaCO2 and mortality varied with BMI, with hazard ratios ranging from 0.95 (95% CI 0.84-1.08) for a BMI of 15 kg/m^2 to 1.66 (95% CI 1.21-2.28) for a BMI of 80 kg/m^2 with every 5-mmHg increase in PaCO2 (Table 3). Age and sex did not have significant interactions with PaCO2.

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Discussion

In this single center, retrospective study, we show that hospitalized patients with compensated hypercapnic respiratory failure have high mortality, and higher PaCO2 is associated with worsened mortality. We also demonstrate that this association varies with BMI as increasingly obese patients are at a higher risk of death with increasing PaCO2 levels. Our study also shows that patients with compensated hypercapnic respiratory failure have high levels of healthcare utilization, including ICU days and recurrent hospital admissions.

Given the metabolic compensation in chronic respiratory failure, a normal pH may lead clinicians to believe that these patients are not at risk for poor outcomes. While these patients may be safe from the acute dangers that arise from respiratory acidosis, our study shows that even short term, patients are extremely vulnerable. With nearly half of the patients dying in a 2.5-year period, this mortality rate exceeds that of many malignancies(11). Recent animal studies give some support as to why patients with chronic elevation in PaCO2 may be at high risk of death. CO2 is stored throughout the body in various compartments including blood, interstitium, and bone. Giosa et al used a pig model to show that when all compartments are saturated, further hypoventilation will more rapidly increase PaCO2 levels without reaching a steady state(12). For patients with chronically high levels of CO2, all compartments that store CO2, including slow compartments such as bone and fat, may be saturated, thereby leading to more rapid rises in PaCO2 and decreases in pH with any acute changes in minute ventilation. In addition, Gates et al used a mouse model to show that compensated hypercapnia negatively impacted the ability of alveolar neutrophils to phagocytose bacteria(13). Therefore, elevated

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PaCO2 alone may predispose patients to severe, life threatening infections. These biological mechanisms help explain why patients with compensated hypercapnia have such poor physiologic reserve. We believe that careful attention should be paid to these patients upon discharge given these findings.

In addition to being at increased risk of death, patients in our study had high levels of healthcare utilization, requiring prolonged hospitalizations with a median of 7.0 ICU days per patient. We noted high rates of respiratory failure requiring mechanical ventilation, either via endotracheal tube or NIV. These findings are of particular interest to hospital systems that may want to identify patients who are at high risk of ICU admission as well as hospital readmission. In our cohort, 218 (44.4%) of patients had 2 or more admissions to our hospital system over a 1 year follow up period, highlighting that a significant portion are at risk of being readmitted.

Furthermore, we noted an association between obese hypercapnic patients and death. Previous studies have shown that BMI can be predictive in detecting obesity hypoventilation syndrome(14-16), and that the presence of hypercapnia is a predictor of mortality in obese patients(17). However, in addition to hypercapnia being dangerous for patients who are obese, we showed that obesity is dangerous for patients who are hypercapnic. Increments of 5 mmHg of PaCO2 led to higher risk of death with increasing BMI when adjusted for age, sex, and CCI. This may be related to upper airway collapse(18), restrictive ventilatory defect(19), reduced functional residual capacity(20), and the myriad of other medical problems, such as heart disease and heart failure(21), associated with obesity. While these results may not be surprising to some, they are potentially useful for hospital systems to identify patients who may be at particularly high risk both during their hospital stays and immediately post discharge.

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Given the vulnerable nature of this patient population, it is important to know whether there is any potential therapy to improve the state of health for patients with compensated hypercapnic respiratory failure. Historically, the strongest indications for NIV include acute exacerbation of COPD and cardiogenic pulmonary edema(22). However, there are also numerous investigations that have studied the use of outpatient NIV for compensated hypercapnia secondary to COPD(23). Several clinical trials from patients with COPD have demonstrated a mortality benefit from chronic NIV therapy(24-27). In addition, NIV can help restore normocapnia(28), offload respiratory muscles, and improve dyspnea(29). It is important to note that many clinical trials investigating the benefit of outpatient NIV have focused on a specific disease state, such as COPD, OHS(30, 31), or neuromuscular disease(32, 33), rather than on multifactorial compensated hypercapnic respiratory failure. While there are not studies looking specifically at the benefits for NIV therapy in our heterogeneous population, chronic NIV use has been shown to improve PaCO2 levels, and therefore may be effective in bringing patients with compensated hypercapnia to a more stable state of health. We found that less than 25% of the cohort was prescribed outpatient NIV, although NIV was more frequently prescribed in patients with very severe hypercapnia. This indicates that clinicians may be recognizing potential benefits of NIV, albeit mostly at the extremes of disease.

We acknowledge several limitations to our study. First, our participants were all evaluated and treated at an academic medical center and may have different characteristics than patients treated in the community. Second, our study is limited by a retrospective design, and we did not delineate the etiology of hypercapnia, reason for admission, or cause of death. The etiology of hypercapnia can be sometimes difficult to attribute with certainty in the

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presence of multiple potentially contributing comorbidities. Our cohort may also include patients with mixed acid-base disturbances, as in patients with COPD and heart failure who are receiving diuretics. However, after carefully reviewing the EMR of 30 randomly selected patients with pH > 7.40, we found no patients with a primary metabolic process, suggesting that it is unlikely that elevations in PaCO2 were solely due to metabolic alkalosis. While patients were not defined by a primary reason for hypercapnia as in other studies, we believe our cohort represents a complex population of patients with multifactorial respiratory failure that represents actual clinical practice. Third, we only evaluated patients admitted to the hospital, signifying an overall sicker population at baseline. The prevalence of stable hypercapnic respiratory failure in the outpatient setting is not fully known and limited to smaller registry data(34). Our findings may not apply to patients with compensated hypercapnia who have not been hospitalized. Lastly, we only included admission data from our institution, given the various EMRs at outside facilities that do not utilize EPIC. Therefore, our data on healthcare utilization and admissions likely underestimates the magnitude of the problem.

Despite these limitations, our study highlights the vulnerability of this population and the need for further study in this area. Additional investigation is needed to determine the effects of outpatient NIV on mortality and hospital admissions for patients with compensated hypercapnic respiratory failure. Hospital systems may consider the use of triggers through the EMR to identify patients who may be at high risk of death and readmission. These triggers may include age, BMI, and PaCO2 as a way to alert a team to consult the pulmonary and/or palliative care teams given the high risk of short-term mortality. Finally, epidemiological studies

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of compensated hypercapnia in the outpatient setting are needed to understand whether patients who are not admitted to the hospital are at similar risk as our patient cohort.

In summary, our study shows that hospitalized patients with compensated hypercapnic respiratory failure have high rates of mortality and healthcare utilization. Inpatient clinicians should identify these patients as high risk despite their metabolic compensation. Healthcare providers may consider referral to pulmonology to explore the possibility of initiating NIV therapy.

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Figure Legend:

Figure 1. Kaplan-Meir plots of survival probabilities from initial arterial blood gas to end of study period.

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Table 1. Baseline characteristics of participants

	All (n = 491)	PaCO2 50.0-54.9 mmHg (n=221)	PaCO2 55.0-64.9 mmHG (n=171)	PaCO2 ≥ 65.0 mmHG (n=99)
Demographics				
Age (years)	60.5 ± 16.2	59.3 ± 16.3	60.8 ± 16.1	62.6 ± 16.2
Male	282 (57.4)	140 (63.3)	95 (55.6)	47 (47.5)
White	423 (86.2)	189 (85.5)	147 (86.0)	87 (87.9)
Body mass index (kg/m^2)	30.6 ± 10.3	30.8 ± 10.1	30.3 ± 9.5	30.7 ± 12.1
Comorbid conditions				
Charlson comorbidity index	5.53 ± 3.24	5.52 ± 3.40	5.54 ± 3.27	5.56 ± 2.83
Congestive heart failure	220 (44.8)	95 (43.0)	71 (41.5)	54 (54.5)
Obstructive sleep apnea	110 (22.4)	45 (20.4)	36 (21.1)	29 (29.3)
Neuromuscular disease	36 (7.3)	13 (5.9)	14 (8.2)	9 (9.1)
Chronic obstructive pulmonary disease	170 (34.6)	64 (29.0)	60 (35.1)	46 (46.5)
Laboratory values				
Arterial pH	7.38 ± 0.03	7.38 ± 0.03	7.38 ± 0.03	7.37 ± 0.03
PaCO2 (mmHg)	58.8 ± 9.7	51.7 ± 1.4	58.7 ± 2.9	74.6 ± 9.2
Serum bicarbonate (mEq/L)	33.3 ± 4.6	30.5 ± 3.8	34.1 ± 3.7	38.3 ± 2.3
Pulmonary function test†				
FEV1/FVC	68.5 ± 18.6	68.0 ± 18.3	70.5 ± 19.5	65.9 ± 17.5
FEV1 % predicted	53.9 ± 24.0	60.1 ± 23.7	54.7 ± 25.3	41.6 ± 17.2
FVC % predicted	57.4 ± 21.3	63.8 ± 19.8	57.1 ± 21.4	46.8 ± 19.9
Outpatient ventilation				
Invasive	17 (3.5)	4 (1.8)	7 (4.1)	6 (6.1)
Non-invasive	120 (24.4)	37 (16.7)	43 (25.1)	40 (40.4)

*Continuous variables presented as means ± standard deviations and categorical variables as counts (percentages)

**PaCO2: partial pressure of carbon dioxide

† Pulmonary function tests were only available for a subset of participants

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Table 2. Multivariable Cox regression model of all-cause mortality

	Hazard ratio	**95% confidence interval**	**p-value**
PaCO2 (per 5-mmHg increase)	1.09	1.02-1.16	0.009
Age (per 5-year increase)	1.07	1.01-1.13	0.01
Male vs. female	1.04	0.79-1.36	0.78
BMI (per 5-kg/m^2 increase)	0.91	0.85-0.98	0.01
Charlson comorbidity index (per 1-point increase)	1.14	1.09-1.19	<0.001

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Table 3. Association between a 5-mmHg higher PaCO2 and mortality at different BMIs

BMI (kg/m^2)	Hazard ratio	95% confidence interval
15	0.95	0.84-1.08
20	0.99	0.90-1.09
30	1.08	1.01-1.15
40	1.18	1.08-1.28
50	1.28	1.12-1.46
60	1.40	1.15-1.69
70	1.52	1.18-1.96
80	1.66	1.21-2.28

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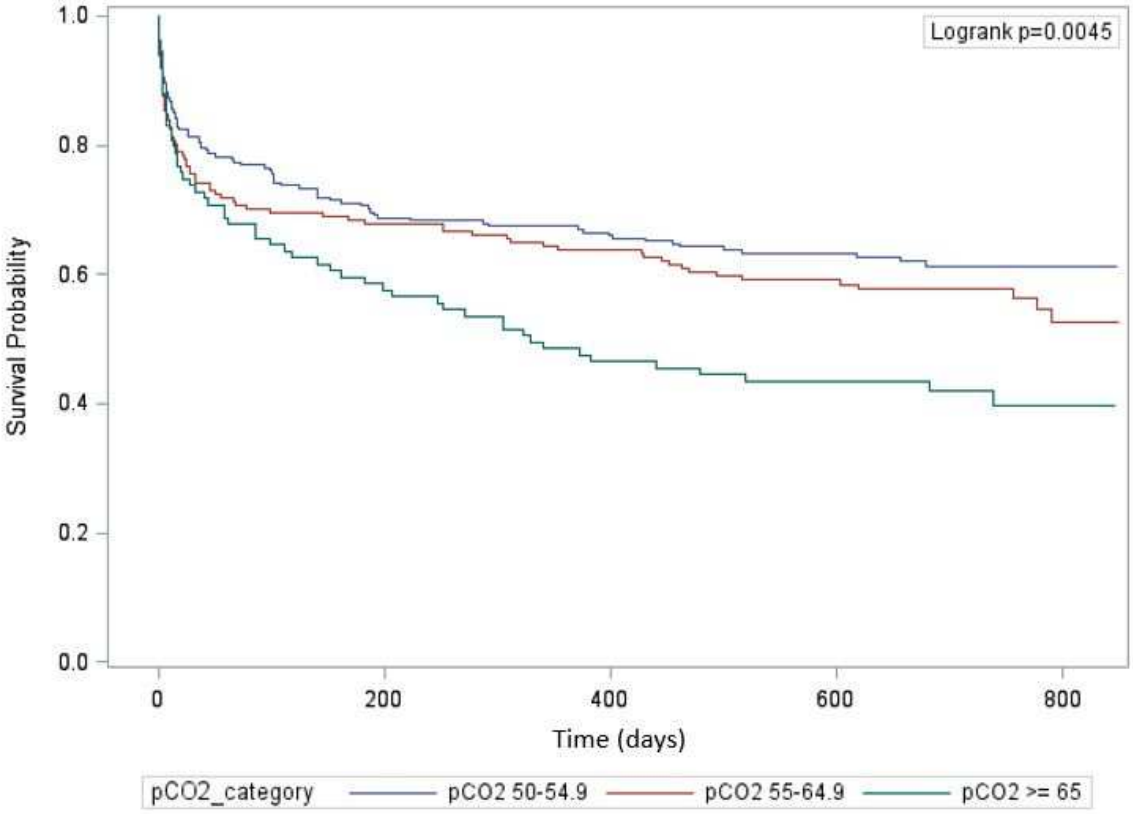

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