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Predictors of invasive mechanical ventilation requirement and mortality in hypercapnic respiratory failure: A retrospective analysis

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Abstract:

INTRODUCTION: While hypercapnic respiratory failure (HRF) has been widely studied in emergency department (ED) populations, the prognostic significance of metabolic compensation and lactate levels remains unclear. This study aimed to evaluate the association of creatinine, bicarbonate (HCO_3), chloride, and lactate levels with the need for invasive mechanical ventilation (IMV) and inhospital mortality in patients with HRF.

METHODS: This single-center, cross-sectional study included adult patients who presented to the ED with respiratory distress and arterial partial pressure of carbon dioxide >50 mmHg between 2020 and 2023. The relationships between initial laboratory parameters and clinical outcomes were analyzed.

RESULTS: A total of 420 patients were included (median age: 77 years [interquartile range: 68–85]; 51.4% female). The mortality rate among bedridden patients was 55.9% and 34.3% among patients diagnosed with pneumonia. Creatinine ≥1.6 mg/dL was associated with inhospital mortality (odds ratio [OR]: 3.7; 95% confidence interval [CI]: 2.044–6.696) and IMV requirement (OR: 2.323; 95% CI: 1.216–4.439). Lactate >1.5 mmol/L was also associated with higher mortality (OR: 10.441; 95% CI: 5.739–18.996). Delta HCO_3 (ΔHCO_3) <−7.5 mEq/L predicted mortality (OR: 2.965; 95% CI: 1.756–5.008) and IMV need (OR: 10.181; 95% CI: 5.709–18.156). Low ΔHCO_3, hemoglobin, pH levels, elevated lactate, creatinine levels, and immobility are the independent risk factors for mortality. The AUC values of lactate levels for predicting mortality were higher than those of pH (0.662 vs. 0.655).

CONCLUSIONS: In patients with HRF, ΔHCO_3, hemoglobin, pH, lactate and creatinine levels, and immobility are strong predictors of poor outcomes. Lactate is a robust and independent predictor of poor outcomes, with prognostic accuracy comparable to that of pH, and may be valuable for clinical risk stratification.

Keywords:

Anemia, bicarbonate, creatinine, hypercapnic respiratory failure, invasive mechanical ventilation, lactate, mortality

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Introduction

Hypercapnic respiratory failure (HRF) is one of the common causes of emergency department (ED) visits and is characterized by an arterial partial pressure of carbon dioxide ($PaCO_2$) exceeding 45–50 mmHg, accompanied by respiratory distress. Patients presenting with HRF often have a high risk of requiring invasive mechanical ventilation (IMV) and are associated with significant mortality.

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Box-ED section

What is already known on the study topic?

- Hypercapnic respiratory failure (HRF) is one of the most common respiratory emergencies encountered in the emergency department (ED).

What is the conflict on the issue? Has it importance for readers?

- The relationship between metabolic compensation, lactate levels, and poor prognosis in patients with HRF has not been fully clarified. Understanding these associations could improve risk stratification and management in the emergency setting.

How is this study structured?

- This observational study included adult patients who presented to the ED with respiratory distress and had a partial pressure of carbon dioxide level above 50 mmHg.

What does this study tell us?

- This study shows that patients with impaired renal function, anemia, elevated lactate levels, inadequate bicarbonate compensation, those who were bedridden, or those with a final diagnosis of pneumonia are more likely to require invasive mechanical ventilation and experience higher mortality rates. Lactate levels represent a valuable prognostic marker in patients with HRF.

Although numerous studies have investigated prognostic indicators in patients with HRF, the relationship between the effectiveness of metabolic compensation and clinical outcomes remains insufficiently elucidated. In patients with HRF, metabolic compensation is expected to be activated in response to respiratory acidosis resulting from elevated CO_2 levels. In the absence of renal dysfunction, these compensatory responses typically include increased bicarbonate (HCO_3) levels and decreased chloride (Cl) levels.[1] The prognostic significance of the delta HCO_3 (ΔHCO_3, difference between the actual HCO_3 level and expected HCO_3 level) and Cl levels has not yet been clearly established.[1-5] Although elevated lactate levels have been shown to be a poor prognostic factor in metabolic disturbances such as sepsis, acute renal failure, and hemorrhage, there is a lack of sufficient research in patients with HRF.[6,7]

The impact of the effectiveness of metabolic compensation on adverse outcomes in HRF patients represents a gap in the current literature. We aimed to identify the factors associated with inhospital mortality and the need for IMV in patients with HRF presenting to the ED, with particular focus on metabolic compensation parameters, including delta HCO_3, creatinine, Cl, hemoglobin, and initial lactate levels.

Methods

This retrospective, cross-sectional study was conducted at the ED of Dokuz Eylül University Hospital. Adult patients presenting to the ED with HRF between March 2020 and March 2023 were included. Eligibility criteria required patients to be aged 18 years or older and to have an arterial blood gas (ABG) analysis showing a $PaCO_2$ $\geq$50 mmHg within the first hour of ED admission.

Exclusion criteria were as follows: (1) hypercapnia due to central nervous system (CNS) depressant drug intoxication; (2) hypercapnia secondary to CNS or neuromuscular diseases; (3) trauma-related hypercapnia; (4) presentation following out-of-hospital cardiac arrest; (5) inaccessible outcome data; and (6) patients whose blood gas analyses were performed using venous samples.

The primary outcome of the study was inhospital mortality, and the secondary outcome was the need for IMV during the ED stay. Eligible patients were identified using the hospital's electronic health record system based on $PaCO_2$ levels. The study team reviewed patients' electronic medical records to collect data on demographics, comorbidities, vital signs at presentation, ABG parameters, other laboratory results, final diagnoses, and outcome data. All data were recorded in a standardized data collection form.

The expected HCO_3 levels were calculated based on the classification of hypercapnia as either acute or chronic. For acute hypercapnia, the expected HCO_3 was calculated as: 24 mEq/L + (1 mEq/L × [$PaCO_2$ –40]/10). For chronic hypercapnia, the expected HCO_3 was calculated as: 24 mEq/L + (4 mEq/L × [$PaCO_2$ –40]/10). The difference between the expected and measured HCO_3 levels was defined as ΔHCO_3. The expected HCO_3 value was calculated based on the 2021 Guideline for the Management of Chronic Obstructive Pulmonary Disease Exacerbations developed by the Emergency Medicine Association of Turkey/Turkish Thoracic Society Clinical Practice Guideline Task Force, as well as a previous study conducted by Marcy *et al*.[8,9] The final diagnosis and classification of hypercapnia as acute or chronic were determined by two members of the study team (SÖ and AT) based on patients' medical histories, previous hospital admission data, and blood gas analysis reports. In case of disagreement, a third physician (EA) adjudicated to reach a consensus.

Ethical approval for our study was obtained from the Ethics Committee of Dokuz Eylul University (Number: 7982, Date: December 4, 2023).

Analysis

SPSS 29.0 (IBM® Corporation, Armonk, New York, United States) was used for data analysis. Descriptive

statistics were presented as numbers and percentages for categorical variables. Differences in proportions of categorical variables between independent groups were analyzed using the Chi-square test or Fisher's exact test.

The normality of numerical variables was assessed using the Kolmogorov–Smirnov test. Numerical variables were expressed as mean and standard deviation if they followed a normal distribution, whereas those not following a normal distribution were presented as median and interquartile range (IQR). For comparisons of numerical variables between independent groups, the Student's *t*-test was used if the data were normally distributed, and the Mann–Whitney *U*-test was used if they were not.

Odds ratios (ORs) were calculated to evaluate the associations of pH, lactate, blood urea nitrogen (BUN), Cl, hemoglobin, HCO_3, ΔHCO_3, and platelet levels with the requirement for IMV and inhospital mortality. Receiver operating characteristic (ROC) analyses were conducted for pH, lactate, creatinine, HCO_3, and ΔHCO_3 to evaluate their predictive value for the requirement of IMV and inhospital mortality, with area under the curve (AUC) values reported. Univariate analyses were performed on the variables sex, platelet count, ΔHCO_3, HCO_3, hemoglobin, pH, lactate, creatinine, and immobility. Variables with $P < 0.2$ in the univariate analyses were subsequently included in a logistic regression model. The model's goodness-of-fit was assessed using the Hosmer–Lemeshow test, which yielded $P = 0.722$, indicating an adequate fit.

A confidence level of 95% was applied, and $P < 0.05$ was considered statistically significant.

Results

During the study period, a total of 1086 patients with a $PaCO_2$ level ≥50 mmHg were identified. Among them, 666 patients were excluded; as a result, 420 patients were included in the final analysis [Figure 1].

The median age of the patients was 77 years (IQR: 67–84), and 216 (51.4%) patients were female. The most common final diagnoses were decompensated heart failure ($n = 127$, 30.2%), pneumonia ($n = 105$, 25%), and acute exacerbation of COPD (AECOPD) ($n = 91$, 21.7%). Inhospital mortality was observed in 82 patients (19.5%), and IMV was required in 67 patients (16%) during their ED stay. A total of 288 patients (68.6%) were admitted to the intensive care unit (ICU). Non-IMV (NIMV) was applied to 212 of our patients (50.5%).

Table 1 summarizes the relationships between patients' demographic characteristics, comorbidities, vital signs

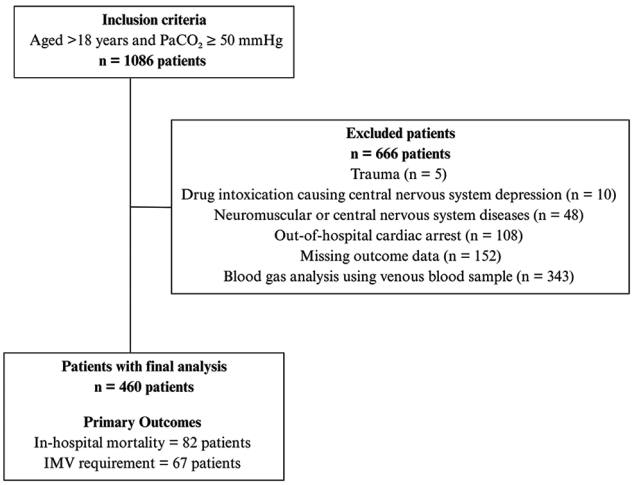

Figure 1: Patient flow diagram. $PaCO_2$: Partial pressure of carbon dioxide, IMV: Invasive mechanical ventilation

at ED admission, final diagnoses, and clinical outcomes. Mortality and IMV rates were significantly lower among patients with COPD, chronic hypercapnia, or those using home oxygen therapy or noninvasive ventilation. In contrast, bedridden patients and those with active malignancy had significantly poorer outcomes. The prognosis was more favorable in patients with AECOPD or heart failure compared with those with pneumonia. Table 2 compares ABG parameters and laboratory markers of metabolic compensation with patient outcomes. Elevated lactate, creatinine, and BUN, as well as lower HCO_3 and hemoglobin levels, were significantly associated with both increased mortality and higher IMV requirement.

Table 3 presents the optimal cutoff values of pH, lactate, creatinine, platelet count, HCO_3, ΔHCO_3, hemoglobin, and Cl levels for predicting inhospital mortality and the need for IMV. AUC values for pH, lactate, creatinine, ΔHCO_3, and HCO_3 in predicting mortality and the need for IMV are shown in Table 4. ROC curves for the need for IMV and inhospital mortality are shown in Figures 2 and 3.

Results of univariate and multivariate analyses evaluating major clinical variables and laboratory markers of metabolic compensation as predictors of inhospital mortality are shown in Table 5. Ten variables were included in the univariate analysis, of which eight were entered into the logistic regression model. Multivariate analysis demonstrated that ΔHCO_3, hemoglobin, pH, lactate, creatinine, and immobility were independent predictors of inhospital mortality.

Discussion

This study aimed to investigate the risk factors associated with the need for IMV and inhospital

Table 1: The relationship between patients' characteristics, comorbidities, and vital signs on admission with inhospital mortality and invasive mechanical ventilation requirement in the emergency department

	All patients, *n* (%)	Nonsurvivors, *n* (%)	Survivors, *n* (%)	*P*	IMV (+), *n* (%)	IMV (–), *n* (%)	*P*
All patients	420	82 (19.5)	338 (80.5)	-	67 (16)	353 (84)	-
Age (years)	77 (67–84)	82 (73–88)	76 (67–83)	<0.001	79 (68–85)	77 (67–84)	0.369
Female	216 (51.4)	41 (19)	175, (81)	0.773	33 (15.3)	183 (84.7)	0.698
Comorbidities							
Hypertension	238 (56.7)	46 (19.3)	192 (80.7)	0.908	36 (15.1)	202 (84.9)	0.597
COPD	203 (48.3)	24 (11.8)	179 (88.2)	<0.001	19 (9.4)	184 (90.6)	<0.001
Congestive heart failure	138 (32.9)	22 (15.9)	116 (84.1)	0.195	11 (8)	127 (92)	0.002
Diabetes	136 (32.4)	25 (18.4)	111 (81.6)	0.683	23 (16.9)	113 (83.1)	0.710
Coronary heart disease	88 (21)	15 (17)	73 (83)	0.509	18 (20.5)	70 (79.5)	0.195
Malignancy	63 (15)	25 (39.7)	38 (60.3)	<0.001	17 (27)	46 (73)	0.009
Cerebrovascular disease	14	7 (50)	7 (50)	0.003	8 (57.1)	6 (42.9)	<0.001
Chronic renal failure	54 (12.9)	15 (27.8)	39 (72.2)	0.101	11 (20.4)	43 (79.6)	0.342
Bed ridden	34 (8.1)	19 (55.9)	15 (44.1)	<0.001	16 (47.1)	18 (52.9)	<0.001
Chronic hypecarbia	209 (49.8)	29 (13.9)	180 (86.1)	0.004	20 (9.6)	189 (90.4)	<0.001
Oxygen use in home	140 (33.3)	17 (12.1)	123 (87.9)	0.007	10 (7.1)	130 (92.9)	<0.001
NIMV use in home	77 (18.3)	7 (9.1)	70 (90.9)	0.011	5 (6.5)	72 (93.5)	0.012
Vital parameters, median (IQR)							
Systolic blood pressure (mmHg)	146 (127 to 170)	126 (105 to 150)	150 (130 to 174)	<0.001	128 (100 to 157)	148 (130 to 170)	<0.001
Diastolic blood pressure (mmHg)	83 (75 to 97)	78 (70 to 90)	86 (77 to 100)	<0.001	79 (64 to 94)	84 (76 to 98)	0.015
Pulse rate (beats/min)	95 (82 to 112)	102 (86 to 121)	94 (82 to 110)	0.012	108 (87 to 123)	93 (82 to 110)	0.001
Respiratory rate (respiration/min)	23 (20 to 28)	24 (20 to 30)	22 (20 to 26)	0.122	28 (20 to 30)	22 (20 to 26)	<0.001
Temperature (°C)	36 (36 to 36.2)	36 (36 to 36.1)	36 (36 to 36.2)	0.976	36 (36 to 36.2)	36 (36 to 36.2)	0.460
Peripheral oxygen saturation (%)	84 (75 to 90)	85 (74 to 91)	84 (77 to 90)	0.854	80 (68 to 90)	85 (78 to 90)	0.022
Final diagnosis							
Decompensated heart failure	127 (30.2)	10 (7.9)	117 (92.1)	<0.001	11 (8.7)	116 (91.3)	<0.001
Pneumonia	105 (25)	36 (34.3)	69 (65.7)	<0.001	30 (28.6)	75 (71.4)	<0.001
Acute exacerbation of COPD	91 (21.7)	3 (3.3)	88 (96.7)	<0.001	5 (5.5)	86 (94.5)	<0.001

COPD: Chronic obstructive pulmonary disease, IMV: Invasive mechanical ventilation, NIMV: Noninvasive mechanical ventilation, IQR: Interquartile range

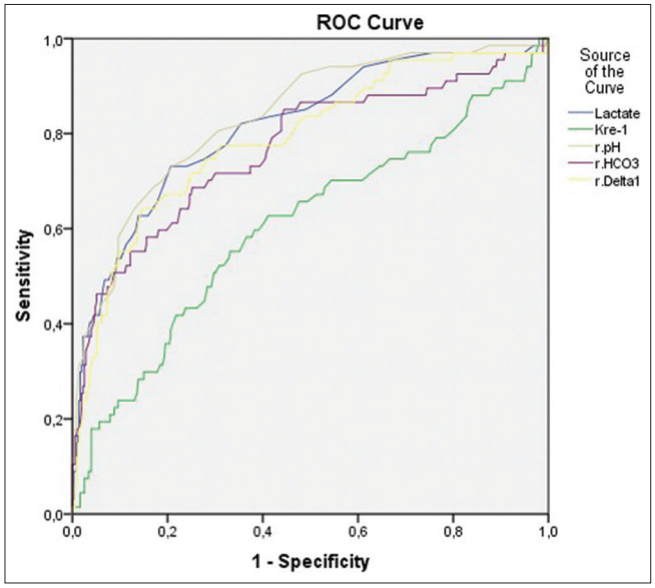

Figure 2: Receiver operating characteristic curve for invasive mechanical ventilation. ROC: Receiver operating characteristic, HCO_3: Bicarbonate

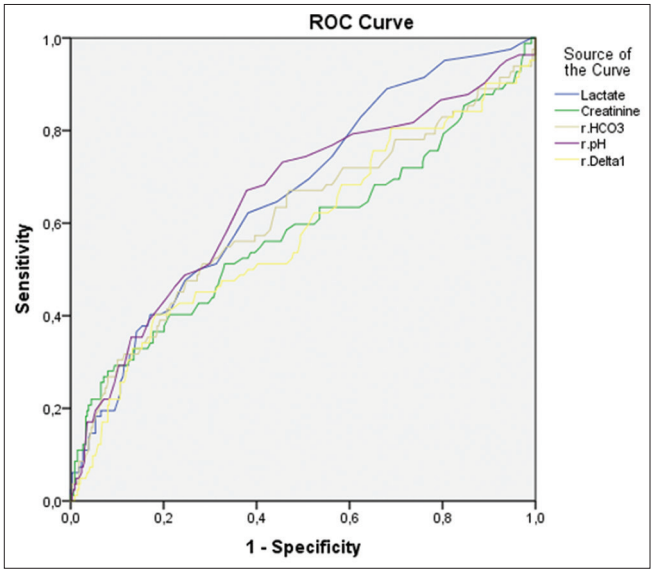

Figure 3: Receiver operating characteristic curve for inhospital mortality. ROC: Receiver operating characteristic, HCO_3: Bicarbonate

mortality in patients presenting to the ED with HRF. Particular attention was given to the role of metabolic compensation, which has not been extensively explored in previous literature. In addition, the prognostic value of lactate levels was assessed, given their potential association with disease severity and clinical outcomes in HRF.

Table 2: The relationship between patients' blood gas analysis, laboratory findings, and clinical outcomes

	All patients	Nonsurvivors	Survivors	*P*	IMV (+)	IMV (-)	*P*
pH	7.31 (7.23 to 7.36)	7.27 (7.16 to 7.33)	7.32 (7.26 to 7.37)	<0.001	7.19 (7.09 to 7.27)	7.33 (7.27 to 7.37)	<0.001
$PaCO_2$ (mmHg)	59.1 (53.4 to 68)	62.1 (54.6 to 71.5)	58.5 (53.1 to 67.3)	0.043	67.2 (57.5 to 79.3)	58.1 (53 to 66)	<0.001
PaO_2 (mmHg)	65.8 (53.6 to 89.9)	63.5 (51.9 to 99.8)	66.5 (53.7 to 87.2)	0.691	74.8 (57.9 to 108)	64.8 (53.2 to 82.6)	0.015
Lactate (mmol/L)	1.4 (1 to 2.2)	1.9 (1.2 to 3.4)	1.4 (1 to 1.9)	<0.001	3.1 (1.7 to 6.9)	1.3 (1 to 1.8)	<0.001
Base excess (mmol/L)	5.5 (2.1 to 8.6)	4.5 (−0.6 to 8.7)	5.8 (2.5 to 8.5)	0.098	3.4 (−4.7 to 7.6)	5.8 (2.6 to 8.6)	0.002
Oxygen saturation (%)	90.7 (83.9 to 95.3)	87.5 (78 to 94.5)	91.2 (85 to 95.4)	0.008	89.6 (78 to 96.1)	90.7 (84.5 to 95)	0.224
HCO_3 (mEq/L)	27.2 (22.6 to 30.2)	24.6 (18.1 to 29.4)	27.7 (23.8 to 30.2)	0.002	19.9 (15.7 to 26.9)	28 (24.4 to 30.5)	<0.001
ΔHCO_3 (mEq/L)	−2.3 (−6.9 to 0.2)	−3.7 (−9.9 to−0.6)	−2 (−6.2 to 0.4)	0.024	−9.5 (−13.6 to−4.3)	−1.6 (−5.3 to 0.7)	<0.001
Creatinine (mg/dL)	0.91 (0.7 to 1.22)	1.06 (0.66 to 1.9)	0.89 (0.71 to 1.17)	0.026	1.11 (0.73 to 1.52)	0.88 (0.69 to 1.17)	0.006
BUN (mg/dL)	22.3 (15.7 to 35.3)	33.7 (19.3 to 53.3)	21.3 (15.2 to 31.4)	<0.001	31.4 (17 to 48.2)	21.5 (15.5 to 32.9)	0.002
Chloride (mEq/L)	99 (95 to 102)	98 (93 to 103)	99 (95 to 102)	0.364	98 (93 to 104)	99 (95 to 102)	0.955
Hemoglobin (mg/dL)	12.3±2.3	11.4±1.9	12.5±2.3	<0.001	11.9±2.4	12.4±2.3	0.098
Platelet (10^3/uL)	258 (196 to 349)	294 (185 to 389)	256 (197 to 344)	0.540	318 (196 to 388)	255 (196 to 343)	0.187

IMV: Invasive mechanical ventilation, BUN: Blood urea nitrogen, HCO_3: Bicarbonate, $PaCO_2$: Partial pressure of carbon dioxide, PaO_2: Partial pressure of oxygen

Table 3: Optimal cutoff values of the predictors for mortality and invasive mechanical ventilation

Variables	Value	Mortality (+), *n* (%)	Mortality (–), *n* (%)	OR (95%CI)	Value	IMV (+), *n* (%)	IMV (–), *n* (%)	OR (95%CI)
pH	≥7.30	27 (11.4)	210 (88.6)	Reference	≥7.26	18 (6.1)	279 (93.9)	Reference
	<7.30	55 (30.1)	128 (69.9)	3.342 (2.006 to 5.567)	<7.26	49 (39.8)	74 (60.2)	10.264 (5.645 to 18.662)
Lactate (mmol/L)	<1.5	29 (13.4)	188 (86.6)	Reference	<2.0	18 (6.0)	280 (94.0)	Reference
	≥1.5	53 (26.1)	150 (73.9)	2.291 (1.388 to 3.780)	≥2.0	49 (40.2)	73 (59.8)	10.441 (5.739 to 18.996)
Creatinine (mg/dL)	<1.6	58 (16)	304 (84)	Reference	<1.6	51 (14.1)	311 (85.9)	Reference
	≥1.6	24 (41.4)	34 (58.6)	3.700 (2.044 to 6.696)	≥1.6	16 (27.6)	42 (72.4)	2.323 (1.216 to 4.439)
BUN (mg/dL)	<28	33 (12)	242 (88)	Reference	<28	28 (10.2)	247 (89.2)	Reference
	≥28	49 (33.8)	96 (66.2)	3.743 (2.269 to 6.176)	≥28	39 (26.9)	106 (73.1)	3.246 (1.899 to 5.548)
Chloride (mEq/L)	≤98	45 (22.1)	159 (77.9)	1.698 (1.005 to 2.870)	≤98	34 (16.7)	170 (83.3)	1.443 (0.816 to 2.554)
	98–107	27 (14.3)	162 (85.7)	Reference	98 to 107	23 (12.2)	166 (87.8)	Reference
	≥107	10 (37)	17 (63)	3.529 (1.463 to 8.517)	≥107	10 (37)	17 (63)	4.246 (1.735 to 10.386)
Hemoglobin (g/dL)	>9	74 (19.1)	314 (80.9)	Reference	>9	60 (15.5)	328 (84.5)	Reference
	≤9	8 (25)	24 (75)	1.414 (0.611 to 3.274)	≤9	7 (21.9)	25 (78.1)	1.531 (0.634 to 3.698)
HCO_3 (mEq/L)	≥24.7	41 (14.4)	244 (85.6)	Reference	≥24.7	21 (7.4)	264 (92.6)	Reference
	<24.7	41 (30.4)	94 (69.6)	2.596 (1.584 to 4.254)	<24.7	46 (34.1)	89 (65.9)	6.498 (3.677 to 11.482)
ΔHCO_3 (mEq/L)	≥−7.5	50 (15.2)	278 (84.8)	Reference	≥−7.5	25 (7.6)	303 (92.4)	Reference
	<−7.5	32 (34.8)	60 (65.2)	2.965 (1.756 to 5.008)	<−−7.5	42 (45.7)	50 (54.3)	10.181 (5.709 to 18.156)
Platelet (10^3/uL)	≤150	14 (37.8)	23 (62.2)	3.043 (1.479 to 6.263)	≤150	11, (29.7)	26, (70.3)	2.709 (1.256 to 5.846)
	150–450	58 (16.7)	290 (83.3)	Reference	150 to 450	47 (13.5)	301 (86.5)	Reference
	≥450	10 (28.6)	25 (71.4)	2.000 (0.912 to 4.388)	≥450	9 (25.7)	26 (74.3)	2.217 (0.978 to 5.023)

IMV: Invasive mechanical ventilation, BUN: Blood urea nitrogen, OR: Odds ratio, CI: Confidence interval, HCO_3: Bicarbonate

Respiratory acidosis, whether compensated or uncompensated, is a hallmark of HRF. It is reasonable to expect a worse prognosis in patients with impaired renal function, where metabolic (renal) compensation is insufficient. In the largest study to date involving 1768 patients with AECOPD, the presence of acute kidney injury (AKI) was associated with significantly higher rates of mechanical ventilation (both noninvasive and invasive), ICU admission, and inhospital mortality. Multivariable analysis showed that Stage 1, 2, and 3 AKI were associated with 1.9-, 2.1-, and 6.0-fold increased risks of inhospital mortality, respectively.[10] We also observed that patients with creatinine levels ≥2 mg/dL had a 4.7-fold higher risk of inhospital mortality and a 3.3-fold higher likelihood of requiring IMV. Similarly, Ucgun *et al*. found that elevated creatinine levels were an independent risk factor for mortality in ICU-admitted AECOPD patients.[4] In that study, patients with low HCO_3 levels (<20 mEq/L) had a mortality rate of 59%, whereas those with higher levels (>28 mEq/L) had a rate of 19%. Similarly, HCO_3 levels < 22 mEq/L were associated with a 2.4-fold increased risk of inhospital mortality and a 6.6-fold increased risk of requiring IMV. These results suggest that kidney function should be taken into account when predicting the prognosis of patients with HRF. It should be noted that patients with low HCO_3 levels and elevated creatinine values are more likely to experience a complicated clinical course. To evaluate the adequacy of metabolic compensation in respiratory acidosis, we calculated the expected

Table 4: Area under the curve values for pH, lactate, creatinine, ΔHCO_3, and HCO_3 in predicting mortality and the need for invasive mechanical ventilation

Variables	AUC	*P*	95% CI
IMV requirement			
pH	0.835	<0.001	0.780 to 0.890
Lactate	0.815	<0.001	0.755 to 0.875
Creatinine	0.605	0.006	0.525 to 0.686
ΔHCO_3	0.790	<0.001	0.726 to 0.854
HCO_3	0.768	<0.001	0.698 to 0.839
Mortality			
pH	0.655	<0.001	0.584 to 0.726
Lactate	0.662	<0.001	0.598 to 0.727
Creatinine	0.579	0.026	0.501 to 0.657
ΔHCO_3	0.580	0.024	0.505 to 0.655
HCO_3	0.612	0.002	0.536 to 0.687

IMV: Invasive mechanical ventilation, AUC: Area under the curve, CI: Confidence interval, HCO_3: Bicarbonate

Table 5: Univariate and multivariate analyses of predictors of inhospital mortality

Variables	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	*P*	OR	95% CI
Age	0.003	1.037	1.013 to 1.062	0.150	1.020	0.993 to 1.049
Sex	0.773	0.931	0.575 to 1.509	-	-	-
Platelet	0.406	1.522	0.566 to 4.094	-	-	-
ΔHCO_3	0.038	0.959	0.921 to 0.998	0.034	1.095	1.007 to 1.191
HCO_3	0.004	0.944	0.908 to 0.982	0.051	1.074	1.000 to 1.155
Hemoglobin	<0.001	0.793	0.708 to 0.889	0.011	0.841	0.737 to 0.961
pH	<0.001	0.011	0.001 to 0.082	0.002	<0.001	<0.001 to 0.034
Lactate	<0.001	1.203	1.101 to 1.315	0.023	1.168	1.021 to 1.337
Creatinine	<0.001	1.639	1.268 to 2.117	0.004	1.546	1.153 to 2.072
Immobility	<0.001	0.154	0.074 to 0.319	<0.001	0.210	0.091 to 0.484

OR: Odds ratio, CI: Confidence interval, HCO_3: Bicarbonate

HCO_3^- levels based on established formulas for acute and chronic hypercapnia. We then determined the ΔHCO_3 (measured minus expected). Negative ΔHCO_3 values indicated insufficient HCO_3 compensation. According to our literature review, only one study has investigated ΔHCO_3 levels in patients with HRF. This study examined 498 patients with AECOPD who required respiratory support. In patients with Stage I and II AKI (AKIN), the actual HCO_3 levels exceeded the expected values, whereas in patients with Stage III AKIN or those requiring hemodialysis, the actual HCO_3 levels remained below the expected levels. However, this study did not investigate the relationship between ΔHCO_3 levels and poor clinical outcomes.[9]

We identified the optimal discriminative cutoff value for ΔHCO_3 as −7.5 mEq/L. Patients with values below this threshold had approximately a 2.9-fold increased risk of requiring IMV and a 10-fold higher mortality rate. To the best of our knowledge, this is the first study to demonstrate an association between ΔHCO_3 levels and both the need for IMV and mortality.

Cl^- may also play a compensatory role in respiratory acidosis. An increase in Cl levels alone can cause a normal anion gap metabolic acidosis. Theoretically, in response to hypercapnia, the kidneys increase HCO_3^- reabsorption and production, leading to a decrease in serum Cl levels.[1] Therefore, in patients with respiratory acidosis who exhibit effective renal compensation, lower or normal Cl levels are expected. Terzano *et al*. investigated the factors influencing the need for NIMV in 68 hospitalized patients with HRF.[11] Contrary to expectations, the Cl levels in patients who required NIMV were lower than those in patients who did not (95 mmol/L vs. 100.2 mmol/L, $P < 0.001$). Among our patients, those with Cl levels within the range of 98–107 mEq/L had lower mortality and a reduced need for IMV compared to patients with hyperchloremia or hypochloremia. Specifically, in hyperchloremic patients, the OR for mortality was 3.5, and for IMV, it was 4.2.

In patients with chronic HRF, the presence of coexisting hypoxemia is common. Therefore, an increase in hemoglobin levels is expected to ensure adequate oxygen delivery to the tissues. However, since the underlying cause of chronic HRF is often a chronic disease, a significant proportion of patients may not achieve the expected polycythemic response due to anemia of chronic disease.[12] A study conducted on 300 hospitalized AECOPD patients found that 37% were anemic.[13] They reported that the mean survival time of anemic patients (defined as hemoglobin levels <13 g/dL in men and <12 g/dL in women) was 31 months (95% CI: 27.7–34.3), whereas the mean survival time of nonanemic patients was 41 months. Our study population included patients with pneumonia and congestive heart failure in addition to those with AECOPD. We demonstrated that anemia (hemoglobin levels below 9 g/dL) is an independent risk factor for mortality and the need for IMV.

Several studies have investigated the use of lactate levels as a prognostic marker in patients with HRF. Terzano *et al*. reported significantly higher admission lactate levels in patients requiring NIMV (3.1 vs. 0.7 mmol/L).[11] Durmuş *et al*. examined whether lactate clearance could help determine the need for hospitalization in patients presenting to the ED with AECOPD. Admission lactate levels were similar between groups, but follow-up showed 11.8% clearance in hospitalized versus 14.7%

in discharged patients.[14] Kasapoğlu *et al*. investigated the association between lactate levels and NIMV failure in patients with acute HRF. In this study, a lactate level >2.1 mmol/L was found to have an AUC of 0.680 (95% confidence interval [CI]: 0.578–0.791), with a sensitivity of 53.49% (95% CI: 38.6–68.4) and a specificity of 87.67% (95% CI: 80.1–95.2) for predicting NIMV failure.[15] In our study, elevated lactate levels at ED admission were identified as an independent risk factor for both the need for IMV and mortality. In patients with a lactate level >1.5 mmol/L, the ORs for mortality and IMV were 2.291 and 10.441, respectively.

pH is one of the most used laboratory parameters in clinical practice for predicting mortality and determining the need for NIMV in patients with HRF. According to our data, the lactate level measured at the time of ED admission is also a prognostically valuable parameter, at least as significant as pH. Furthermore, lactate levels demonstrated a higher AUC for predicting mortality compared with pH. This underscores the potential utility of lactate as a rapid and readily available marker for early risk stratification in emergency settings. While arterial pH is a well-established prognostic indicator in respiratory failure, the prognostic value of lactate in this specific context has been less thoroughly explored. Given the comparable OR observed in our study, we propose that lactate levels should be incorporated into clinical assessment algorithms alongside traditional blood gas parameters when evaluating patients with HRF.

Most previous studies on HRF have focused on ICU patients with AECOPD. However, Chung *et al*. showed that lower respiratory tract infections and congestive heart failure were also common causes of HRF in ED settings. In their study, mortality was lower in patients with COPD (OR: 0.59) and higher in those with lower respiratory tract infections (OR: 1.68).[5] In our cohort, AECOPD accounted for only 21.7% of HRF cases, and mortality in this group was just 3.3%, compared to 34.3% in patients with pneumonia and 7.9% in those with decompensated heart failure. The overall mortality rate among all patients was 19.5%. Among those using home oxygen therapy, mortality was 12.1%; in patients with chronic hypercapnia, it was 13.9%, and among those using home NIMV, it was 9.1%. These findings suggest that the prognosis of patients with isolated AECOPD without concomitant pneumonia or decompensated heart failure is significantly better than that of other HRF patients. It should be considered that patients with chronic hypercapnia due to COPD, who are already on home oxygen and NIMV therapy, tolerate hypercapnia relatively well. In contrast, hypercapnia that develops in the context of pneumonia or congestive heart failure appears to be a significantly poorer prognostic indicator.

Although this was not among our primary or secondary objectives, we found significantly higher mortality in bedridden patients. The need for NIMV (47.1%) and mortality rate (55.9%) in bedridden individuals were significantly higher compared to patients with comorbidities such as diabetes, active malignancy, or coronary artery disease. These findings indicate that the prognosis of HRF in bedridden patients is particularly poor.

Limitations

The primary limitation of our study is its single-center design and the retrospective nature of data collection from patient records, which may affect the generalizability of the findings and introduce potential information bias. Interrater reliability analysis was not conducted to assess the consistency between physicians' decisions regarding the final diagnosis and classification of hypercapnia as acute or chronic. The classification of hypercapnia as acute versus chronic is somewhat subjective and may also introduce bias. Furthermore, in cases where patients developed acute HRF, it is possible that metabolic compensation had not yet been fully established, potentially influencing some of the biochemical parameters analyzed.

Another important limitation is that due to high ICU bed occupancy, many patients received IMV or NIMV in the ED. This may have led to an underestimation of the total IMV requirement, as patients intubated after transfer might not have been captured. The lack of an external validation cohort and potential changes in clinical management over the 3-year study period should be considered. Since a power analysis was not conducted in our study, it is not known whether the sample size was adequate.

Due to the retrospective nature of the study, we were unable to standardize the indications for initiating IMV. Physicians' clinical experience and the individual patient's condition may have influenced the decision to start IMV, potentially introducing bias to the primary outcome.

Conclusions

In patients presenting to the ED with HRF, metabolic compensation status and initial lactate levels appear to be important prognostic indicators for both the need for IMV and inhospital mortality. Worse outcomes were associated with lower HCO_3 levels, elevated creatinine and lactate levels, and anemia. In addition, bedridden status and a final diagnosis of pneumonia were associated with significantly higher mortality rates and IMV requirements. Low ΔHCO_3, hemoglobin, pH levels, elevated lactate and creatinine levels, and immobility are the independent risk factors for mortality. These

findings highlight the importance of incorporating easily obtainable clinical and laboratory parameters, such as lactate, HCO_3, ΔHCO_3, and hemoglobin levels, into early risk stratification models for HRF patients.

Author contributions statement

ŞÖ (Conceptualization, Data curation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review and editing). EA (Conceptualization, Methodology, Project administration, Supervision, Visualization, Formal analysis, Writing – original draft, Writing – review and editing). SS (Conceptualization, Data curation, Supervision, Writing – original draft). AT (Conceptualization, Data curation, Supervision, Writing – original draft).

Conflicts of interest

None Declared.

Ethical approval

The study was approved by the ethics committee of Dokuz Eylül University (Number: 7982, Date: December 4, 2023).

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