

# To Identify Whether Anemia is related to Hospital Mortality in COPD Exacerbations

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## ABSTRACT

**Introduction:** Anemia of chronic disease (ACD) is an immune-driven abnormality associated with chronically very low levels of circulating hemoglobin that has been found to existing in various inflammatory diseases. The aim of this study evaluated whether the degree of anemia affects the survival of patients with COPD.

**Material and methods:** A Hospital based observational study concluded with 100 patients admitted in ICU of Mahatma Gandhi Medical College & Hospital, Jaipur during the period of January 2019 to June 2020 with COPD exacerbation. COPD diagnosis was established with GOLD clinical criteria. Anemia was defined as hemoglobin levels <12 gm/dL for female patients and <13 gm/dL for male patients according to the World Health Organization (WHO) anemia definition. Initial mechanical ventilation support type, failure in NIV, total duration of mechanical ventilation support, the lengths of ICU and hospital stays, and ICU and hospital mortality were recorded.

**Results:** Our study showed that the mean age in COPD patients was  $67.13 \pm 4.49$  years, male female ratio was 81:19. Mean pack year for these patients was  $69.84 \pm 9.62$ . Total 83 patients were on NIV out of these patients 40 patients had anemia and while remaining 43 patients were non anemic. Non anemic patients had higher NIV success rate (67.4%) in comparison to anemic patients(32.6%). This difference was highly significant ( $p < 0.001$ ). Mean GCS, Mean Hb and hematocrit was significantly lower ( $p < 0.05$  &  $p < 0.001$  respectively) in anemic patients ( $12.45 \pm 3.24$ ,  $10.97 \pm 1.04$  gm/dL,  $13.97 \pm 0.79$  gm/dL respectively) in comparison to non anaemic patients ( $14.05 \pm 2.12$ ,  $40.80 \pm 4.51$  gm/dl,  $43.84 \pm 5.03\%$  respectively). In this study 34 patients died while 66 patients survived. Mean hospital stay was significantly longer ( $p < 0.001$ ) in non survivors ( $30.18 \pm 4.50$  days) in comparison to survivors ( $15.05 \pm 5.07$  days). Mean GCS was significantly lower ( $p < 0.001$ ), mean albumin levels was significantly lower and CRP levels were significantly higher ( $p < 0.001$ ) in non survivors.

**Conclusion:** We can conclude from this study that anemia is related with increased mortality in acute COPD exacerbations and it is also associated with NIV failure.

**Keywords:** COPD, ICU, Mortality, NIV, Anemia

more than two successive years". American Thoracic Society (ATS) explained emphysema as an, "anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls".<sup>1</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) of late defined COPD as, "a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases".

Chronic Obstructive Pulmonary Disease (COPD), the fourth major cause of death worldwide. All round the world COPD is a major cause of chronic morbidity and mortality.

COPD is a persistent and progressive airflow restriction accompanied with increased chronic inflammatory response in the airways.<sup>2</sup> It has become comprehensible that COPD is not an isolated disease of the lungs. Instead, COPD is a complex interaction between airway obstruction and emphysema, systemic inflammation, comorbidities, and metabolism, which all contribute to prognosis.<sup>3</sup> Lately developed prognostic tools take this multifaceted pathology into consideration by incorporating systemic as well as lung-specific parameters.<sup>4</sup> Smoking and biomass exposure, along with genetic predisposition, are the prime risk factors for developing COPD.

Anemia is perceive to be present as comorbidity in numerous chronic disease states, and therefore, understanding its pathogenesis is salient. In recent years, anemia is also seen as a frequent comorbidity in COPD patients and correlated with reduced functional capacity, impaired standard of life, greater probability of hospitalization, and early mortality.<sup>5</sup>

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a name coined for the diseases that were earlier known as chronic bronchitis and emphysema. The British Medical Research Council (BMRC) defined chronic bronchitis as "daily productive cough for at least three consecutive months for

As per the WHO, "men with hemoglobin levels <13 g/dl and women with hemoglobin levels <12 g/dl are defined as anemic."<sup>6</sup> Any decrease in hemoglobin levels results in a corresponding reduction in the oxygen-carrying capacity of the blood. Impairment of this mechanism exerts a negative impact on clinical status.<sup>7</sup> The prevalence of anemia in patients with COPD varies from 7.5% to 33%,<sup>8</sup> and this variability might be due to various methods of studies, selection of patient group, and various definitions of anemia.<sup>9</sup> Anemia of chronic disease (ACD) is an immune-driven abnormality connected with chronically subsided levels of circulating hemoglobin that has been seen happen in various inflammatory diseases. The systemic inflammation that is now perceived as a feature of COPD makes it a possible cause of ACD. If present in COPD, anemia could aggravate dyspnea and limit exercise tolerance.<sup>10</sup>

The motive of our study was to recognize whether anemia is associated with hospital mortality in COPD exacerbations. We also aimed to assess whether the degree of anemia influence the survival of patients with COPD.

## MATERIAL AND METHODS

A Hospital based observational study done 100 patients admitted in ICU with COPD exacerbation who developed acute respiratory failure Department of Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur during the period of January 2019 to June 2020.

### Inclusion Criteria

- Diagnosis of COPD confirmed according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), from medical records.
- In patients for whom PFTs were unavailable, COPD diagnosis was confirmed with GOLD clinic criteria, {age >40 years, >10 pack-year smoking}, smoking or biomass history.
- Anaemia is defined as Haemoglobin levels <12 gm/dl for females patients and <13 gm/dl for male patients according to the World Health Organisation (WHO).

### Exclusion Criteria

- Suspected alternative cause for Respiratory failure such as Pulmonary Embolism, Severe Sepsis & Acute Respiratory Distress Syndrome.<sup>11</sup>
- Recent operation or Transfusion history
- Presence of a disease associated with bone marrow suppression (renal failure with glomerular filtration rate <30ml/min/1.73m<sup>2</sup>, malignancy, haematologic disorders).
- Patients who do not give consent for study.

### Procedure methodology:

Diagnosis of COPD was established, according to the Global initiative for chronic Obstructive Lung Disease (GOLD), from medical records, and if available pulmonary function tests (PFTs) within the previous year.<sup>9</sup> In patients for whom PFTs were unavailable, COPD diagnosis was established with GOLD clinical criteria (age >40 years, >10 pack-year smoking or biomass history).

Demographic characteristics (age, sex, smoking history), recent PFTs – if available, presence of comorbidities, use of long-term oxygen therapy and domiciliary NIV, duration of hospital stay prior to ICU admission, severity scores of Acute Physiology and Chronic Health Evaluation (APACHE) II and Glasgow Coma Scale (GCS) were recorded.

Laboratory data for admission arterial blood gas analysis, complete blood cell count, and serum CRP were collected. Anemia was defined as hemoglobin levels <12 gm/dL for female patients and <13 gm/dL for male patients according to the World Health Organization (WHO) anemia definition.<sup>12</sup> Data collection for mechanical ventilation and follow-up All patients had acute respiratory failure due to an exacerbation and were supported by either invasive (mechanical ventilation with endotracheal intubation) ventilation or NIV according to the degree of respiratory failure and the patient's clinical condition. NIV was performed by experienced ICU staff using pressure support mode through an oronasal mask. NIV failure was defined as requiring endotracheal intubation at any time.

Initial mechanical ventilation support type, failure in NIV, total duration of mechanical ventilation support, the lengths of ICU and hospital stays, and ICU and hospital mortality were recorded. For survivors, mortality was evaluated from the national death database system on January 2019 to June 2020.

## STATISTICAL ANALYSIS

Categorical variables between groups were compared with chi-square or Fisher's exact test, continuous variables were compared with Mann-Whitney *U*-test. The independent effect of anemia on hospital mortality was assessed with stepwise multivariate logistic regression analysis.

## RESULTS

Our study showed that the mean age in COPD patients was 67.13 ± 4.49 years, male female ratio was 81:19. Mean pack year for these patients was 69.84 ± 9.62 (table 1).

In this study 17 patients needed invasive mechanical ventilation while 83 patients were on non invasive ventilation (NIV) out of these 34 patients had NIV failure and shifted to IMV later course of disease.

Total 83 patients were on NIV out of these patients 40 patients had anemia and while remaining 43 patients were non anemic. Non anemic patients had higher NIV success rate (67.4%) in comparison to anemic patients(32.6%). This difference was highly significant (*p* <0.001) (table 2).

NIV successful patients had mean hospital stay, hemoglobin, hematocrit, albumin and CRP was 13.00 ± 3.97 days, 13.40 ± 1.34gm/dL, 45.74 ± 3.97%, 3.54 ± 0.31 gm/dL and 10.58 ± 2.58 mg/L respectively. In NIV failure patients had mean hospital stay, hemoglobin, hematocrit, albumin and CRP was 28.76 ± 5.73 days, 11.39 ± 1.69gm/dL, 38.47 ± 3.23%, 3.23 ± 0.33 gm/dL and 6.85 ± 3.11 mg/L respectively, Which was statistical significant in between NIV successful & NIV failure patients (table 3).

Mean FEV% was significantly lower (*p* <0.001), mean

hospital stay was significantly longer ( $p < 0.05$ ) in anemic patients ( $26.06 \pm 6.19\%$  &  $21.91 \pm 8.92$  days respectively) in comparison to non anaemic patients ( $32.74 \pm 6.22\%$  &  $18.26 \pm 8.09$  days) (table 4).

Mean GCS, Mean Hb and hematocrit was significantly lower ( $p < 0.05$  &  $p < 0.001$  respectively) in anemic patients ( $12.45 \pm 3.24$ ,  $10.97 \pm 1.04$  gm/dL,  $13.97 \pm 0.79$  gm/dL respectively)

<b>No. of cases (n)/%</b>	<b>100</b>
Age (years)	$67.13 \pm 4.49$
Male : Female	81:19
Pack-year	$69.84 \pm 9.62$ (50 – 90)

**Table-1:** General characteristics of COPD patients

in comparison to non anaemic patients ( $14.05 \pm 2.12$ ,  $40.80 \pm 4.51$  gm/dl,  $43.84 \pm 5.03\%$  respectively) (table 4).

In this study mean albumin levels was significantly lower and CRP levels were significantly higher ( $p < 0.05$ ) in anemic patients in comparison to non anaemic patients (table 4).

In this study 34 patients died while 66 patients survived. Mean hospital stay was significantly longer ( $p < 0.001$ ) in non survivors ( $30.18 \pm 4.50$  days) in comparison to survivors ( $15.05 \pm 5.07$  days). Mean GCS was significantly lower ( $p < 0.001$ ), mean albumin levels was significantly lower and CRP levels were significantly higher ( $p < 0.001$ ) in non survivors (table 5).

Mean Hb and hematocrit was significantly lower ( $p < 0.001$ )

General/ Clinical feature	NIV successful (n = 49)	NIV failure (n = 34)	t-value	P-value
Age (years)	$66.27 \pm 4.53$	$68.81 \pm 6.81$	-2.042	0.044
Hospital stay (days)	$13.00 \pm 3.97$	$28.76 \pm 5.73$	-14.815	<0.001
GCS	15.00	$10.29 \pm 3.02$	10.947	<0.001
FEV%	$30.74 \pm 6.63$	$28.11 \pm 7.35$	1.700	0.093
Hb (gm/dL)	$13.40 \pm 1.34$	$11.39 \pm 1.69$	6.034	<0.001
Haematocrit	$45.74 \pm 3.97$	$38.47 \pm 3.23$	8.835	<0.001
Albumin (gm/dL)	$3.54 \pm 0.31$	$3.23 \pm 0.33$	4.363	0.000
CRP (mg/L)	$6.85 \pm 3.11$	$10.58 \pm 2.58$	-6.167	0.000

P-value as obtained on applying Student's t-Test

**Table-2:** Comparison of General and Clinical features in patients grouped on the basis of NIV outcome

	NIV successful (n= 49)	NIV failure (n= 34)	X <sup>2</sup>	P-value
Anemic n (%)	16 (32.6)	24 (70.6)	27.424	<0.001
Non-anemic n (%)	33 (67.4)	10 (29.4)		

P-value as obtained on applying Chi-square test

**Table-3:** Distribution of patients on the basis of anaemia among groups based on NIV outcome

General/ Clinical feature	Anaemic (n = 53)	Non –anaemic (n = 47)	t-value	P-value
Age (years)	$66.47 \pm 4.65$	$68.74 \pm 4.33$	0.809	0.420
Hospital stay (days)	$21.91 \pm 8.92$	$18.26 \pm 8.09$	2.133	0.035
GCS	$12.45 \pm 3.24$	$14.05 \pm 2.12$	-2.882	0.005
FEV%	$26.06 \pm 6.19$	$32.74 \pm 6.22$	-5.374	<0.001
Hb (gm/dL)	$10.97 \pm 1.04$	$13.97 \pm 0.79$	-16.082	0.000
Haematocrit	$40.80 \pm 4.51$	$43.84 \pm 5.03$	-3.187	0.002
Albumin (gm/dL)	$3.30 \pm 0.33$	$3.49 \pm 0.37$	-2.714	0.008
CRP (mg/L)	$9.30 \pm 3.45$	$7.66 \pm 3.39$	2.392	0.019

P-value as obtained on applying Student's t-Test

**Table-4:** Comparison of General /Clinical on the basis of Anemia

General/ Clinical feature	Survivors (n = 66)	Non -survivors (n = 34)	P-value as obtained on applying Student's t-Test	P-value
Age (years)	$66.76 \pm 4.62$	$67.85 \pm 4.19$	-1.153	0.252
Hospital stay (days)	$15.05 \pm 5.07$	$30.18 \pm 4.50$	-14.670	<0.001
GCS	$14.26 \pm 2.08$	$11.16 \pm 3.12$	5.923	<0.001
Hb (gm/dL)	$12.79 \pm 1.73$	$11.59 \pm 1.59$	3.375	<0.001
Hematocrit	$44.20 \pm 4.57$	$38.40 \pm 3.22$	6.597	<0.001
Albumin (gm/dL)	$3.43 \pm 0.37$	$3.31 \pm 0.34$	1.578	0.118
CRP (mg/L)	$7.38 \pm 3.33$	$10.76 \pm 2.68$	-5.122	<0.001

P-value as obtained on applying Student's t-Test

**Table-5:** Comparison of General /Clinical on the basis of mortality

in non survivors ( $11.59 \pm 1.59$  gm/dL,  $44.20 \pm 4.57\%$ ) in comparison to survivors ( $12.79 \pm 1.73$  gm/dL,  $43.84 \pm 5.03\%$ ) (table 5).

## DISCUSSION

COPD is a major cause of health burden throughout the world.<sup>10</sup> COPD often coexists with other co morbidities such as cardiovascular diseases, osteoporosis, skeletal muscle dysfunction, depression, and anemia.<sup>13</sup> Comorbidities influences on potentiating the overall morbidity of COPD, leading to increased hospitalizations, health care costs, and eventually death. Anemia is a well-known co morbidity of COPD with a prevalence ranging from 12.3 to 23%.<sup>13,14</sup> Hemoglobin has been suggested as an easily measured prognostic indicator. Both low and high values of Hb are experienced in COPD, though the dispersal varies highly with the population studied. Historically, in the emergence of domiciliary oxygen, secondary polycythemia was a striking feature in COPD, but today the prevalence appear to be low.<sup>15</sup> Instead, anemia might be more common, with a reported prevalence of 6.2%–46.3%.<sup>16</sup>

In this study 100 cases were included. Mean age of this study for COPD patients was  $67.13 \pm 4.49$  years. It shows males were more affected than females due to COPD and it shows male preponderance of our study. Similar study was conducted by vipul garg et al<sup>17</sup> in 2016 which also showed male preponderance of COPD. Another study by Yeon-Mok Oh et al<sup>18</sup> 2017 found similar results.

In this study mean pack year for COPD patients was  $69.84 \pm 9.62$ . Out of 100 patients 44 patients were non smoker while remaining 56 patients were smoker either active or previous smoker. 21 patients were active smoker while 35 patients who quits smoking few months or year back.

### Clinical features according to NIV outcome

In this study mean age for NIV successful patients was  $66.27 \pm 4.53$  years and for NIV failure patients  $68.81 \pm 6.81$  years. Patients with NIV failure had higher mean age in comparison to NIV successful patients. This difference was statistically significant ( $p < 0.05$ ).

Average hospital stay for NIV successful patients was  $13.00 \pm 3.97$  days and for NIV failure patients  $28.76 \pm 5.73$  days. This difference was statistically significant ( $p < 0.001$ ). It shows patients in which NIV failure observed had long hospital stay as they shifted to IMV in comparison to patients who treated successfully on NIV.

Similar study conducted by Begum Ergan et al<sup>19</sup> in 2016 found similar results. They found mean hospital stay in NIV successful patient was 15.0 days while in NIV failure patients it was 23.5 days and this difference was also statistically significant ( $p$  value  $< 0.05$ )

Our results were in agreement of study conducted by Begum Ergan et al<sup>19</sup> in 2016 they observed NIV failure was more in the anemic patients when compared to the non anemic group (49% vs 22.6%, respectively;  $P = 0.001$ ). Another study conducted by Haja Mydin et al<sup>20</sup> in 2013 looked for prognostic factors in hypercapnic respiratory failure and showed that anemia was related to increased risk of NIV

failure.

Possible mechanism for that there is a relationship between muscle oxygenation and peak oxygen consumption varies extensively in COPD, and oxygen consumption is highly influenced by blood oxygenation and oxygen utilization level.<sup>21</sup> Anemic COPD patients also exhibit decreased diffusing capacity of oxygen corrected for hemoglobin. All these changes in transportation of oxygen lead to decrease in aerobic capacity and consequently skeletal muscle dysfunction in severe COPD during exercise. We can expect these changes to be more with patients with low hemoglobin levels, especially during episodes of exacerbations because of increased oxygen demand due to increased work of breathing and impaired cardiopulmonary interactions.

In this study Albumin for NIV successful and NIV failure patients was  $3.54 \pm 0.31$  gm/dL,  $3.23 \pm 0.33$  gm/dL. It shows lower value in NIV failure patients and this was significantly lower ( $p < 0.001$ ) and CRP in mean NIV successful patients was  $6.85 \pm 3.11$  mg/L and in NIV failure patients it was  $10.58 \pm 2.58$  mg/L. This was significantly high ( $p < 0.001$ ).

Our results were in concordance with study conducted by Begum Ergan et al<sup>19</sup> in 2016.

### NIV outcome in anemia

In our study we categorize patients according to anemic and non anemic patients and compared them on the basis of NIV success rate. In this study total 83 patients were on NIV out of these patients 40 patients had anemia and while remaining 43 patients were non anemic. Out of these 32.6% patients of anaemia had successful NIV in comparison 67.4% of non anaemic patients and 70.6% patients of anaemia had NIV failure while only 29.4% patients who had no anaemia. It shows anemic patients had significant NIV failure rate ( $p < 0.001$ ) in comparison to non anemic patients.

Mean age in anaemic and non anaemic patients were  $66.47 \pm 4.65$  years and  $68.74 \pm 4.33$  years respectively this difference was statistically non significant ( $p > 0.05$ ). it shows age matched comparison between anemic and non anemic patients of this study.

Mean FEV% in anaemic and non anaemic patients were  $26.06 \pm 6.19\%$  and  $32.74 \pm 6.22\%$  respectively. Mean FEV% was lower in anemic patients this difference was statistically significant ( $p < 0.001$ )

Similar study conducted by Begum Ergan et al<sup>19</sup> in 2016 found contradictory results as they found anemic patients were older than to non anemic patients. They also found that hemoglobin levels were correlated with FEV1% predicted and anemic patients had lower FEV1 than nonanemic patients which is consistent with previous studies (Ferrari M et al 2015)<sup>22</sup>.

In this study we found long hospital stay in anemic patients in comparison to non anemic patients. Hospital stay in anaemic and non anaemic patients was  $21.91 \pm 8.92$  days and  $18.26 \pm 8.09$  days respectively this difference was statistically significant ( $p < 0.05$ ).

Anne Pernille et al<sup>23</sup> in 2016 Patients without hemoglobin deficiency had shorter length of stay (median 1 [0–4] vs

5 [2–9] days,  $P=0.00001$ ) and reduced risk of death after discharge ( $P=0.02$ ),

When we compared GCS in anaemic and non anaemic patients it was significantly low ( $p<0.05$ ) in anemic patients in comparison to non anemic patients. In anemic patients mean GCS was  $12.45 \pm 3.24$  and in non anemic patients it was  $14.05 \pm 2.12$  this difference was statistically significant ( $p<0.05$ ).

In this study we found mean Hb in anaemic and non anaemic patients was  $10.97 \pm 1.04$  gm/dL,  $13.97 \pm 0.79$  gm/dL respectively and hematocrit was  $40.80 \pm 4.51\%$ ,  $43.84 \pm 5.03\%$  respectively this difference was statistically significant ( $p<0.001$ ). It shows lower Hb and hematocrit in anemic patients.

In this study mean albumin levels was significantly lower and CRP levels were significantly higher in anemic patients in comparison to non anemic patients. Mean albumin levels in anemic patients was  $3.30 \pm 0.33$  gm/dL and in non anemic patients it was  $3.49 \pm 0.37$  gm/dL and Mean CRP in anemic patients was  $9.30 \pm 3.45$  mg/L and in non anemic patients was  $7.66 \pm 3.39$  mg/L both these correlation as statistically significant ( $p<0.05$ ).

A study conducted by Yeon-Mok Oh et al<sup>18</sup> 2017 found similar results. They demonstrated that nutritional factors including a lower serum albumin level is more common in anemic patients in comparison to non anemic patients but they did not found difference in inflammatory markers such as leukocyte count and hs CRP. These markers did not exhibit differences between the two groups. Previous studies also reported that anemia mainly develops due to chronic inflammation in COPD because the low-grade systemic inflammation is associated with an increased risk of major comorbidities in COPD, irrespective of smoking. However, multiple factors have been suggested to cause anemia in COPD in addition to systemic inflammation these are: an increasing age, malnutrition and the use of certain medicines such as theophylline.

Yeon-Mok Oh et al<sup>18</sup> did not found any interrelation in inflammatory markers with the serum hemoglobin level.

### Mortality

In this study 34 patients died while 66 patients survived. Mean age in survivors was  $66.76 \pm 4.62$  years and in non survivors was  $67.85 \pm 4.19$  years. This difference was statistically non significant ( $p>0.05$ )

Mean hospital stay in survivors and non survivors were  $15.05 \pm 5.07$  and  $30.18 \pm 4.50$  days respectively this difference was statistically significant ( $p<0.001$ )

In this study mean GCS in survivors and non survivors were  $14.26 \pm 2.08$  and  $11.16 \pm 3.12$  respectively it shows higher GCS in patients who survived in comparison to patients who didn't survived. This difference was statistically significant ( $p<0.001$ ).

Mean albumin in survivors and non survivors was  $3.43 \pm 0.37$  gm/dL,  $3.31 \pm 0.34$  gm/dL respectively. It shows lower levels of albumin in non survivors in comparison to survivors. This difference was statistically significant ( $p<0.001$ ). Mean

CRP in survivors and non survivors was  $7.38 \pm 3.33$  mg/L,  $10.76 \pm 2.68$  mg/l respectively. It shows high level of CRP as an inflammatory marker in non survivors. This difference was statistically significant ( $p<0.001$ )

In this study mean Hb in survivors and non survivors was  $12.79 \pm 1.73$  gm/dL,  $11.59 \pm 1.59$  gm/dL respectively and hematocrit was  $44.20 \pm 4.57\%$ ,  $38.40 \pm 3.22\%$  respectively. It shows lower hemoglobin and lower hematocrit level in non survivors. This difference was statistically significant ( $p<0.001$ ). It shows in our study that anemia is a risk factor for mortality.

Anne Pernille et al<sup>23</sup> in 2016 This study demonstrates that low concentrations of hemoglobin are associated with increasing mortality after discharge in patients admitted for AECOPD. Another study by Yeon-Mok Oh et al<sup>18</sup> 2017 found similar results. They found that anemia was a significant factor associated with the survival of COPD in the Cox regression analysis. Their data showed that anemia was an independent factor to predict the survival of stable COPD in KOLD cohort. Previous studies with various cohorts reported that anemia is associated with a reduced survival in COPD.<sup>24</sup> In the cohorts with stable COPD recruited on an outpatient basis, anemia has not been proven to be a risk factor for mortality through multivariate analysis, even though the survival period was reported to be shorter in anemic COPD, Previous reports indicated the possibility for the correction of anemia to improve the functional outcomes of COPD by decreasing dyspnea and the work during breathing. However, further research on COPD is required to determine the relationship between anemia correction and long-term outcomes.

Rasmussen et al<sup>25</sup> evaluated COPD patients who needed invasive ventilation and they found that 54.8% of anemic COPD patients passed away within 30 days with a mortality risk ratio of 3.1 (95% CI 1.6–5.9). The result of anemia on COPD exacerbations was also assessed in the emergency room setting; a multicenter study performed in Canada showed anemia (hemoglobin, 10 gm/dL) was the strongest predictor (OR 4.9; 95% CI 2.1–11.7) of serious adverse events including death in patients admitted to the emergency room.<sup>26</sup> All these data suggested that, besides being an important predictor of long-term survival, anemia should also be considered as a risk factor for short-term mortality in severe COPD exacerbations.

Markoulaki et al<sup>27</sup> showed that a severe exacerbation itself caused transient changes in hemoglobin levels with a median decrease of 1.3 gm/dL. They found a negative correlation between hemoglobin and erythropoietin (EPO) levels which depicts increased EPO resistance during exacerbations. It is well known that erythropoietin resistance is directly correlated with the levels of inflammatory cytokines and therefore the level of systemic inflammation. Repeated exacerbations could cause further inhibition of erythropoiesis and due to this significant decrease in hemoglobin levels can occur in severe COPD. Thus, anemia could be accepted as a surrogate of severe systemic inflammation and might be helpful in identifying sicker patients.

## CONCLUSION

We can conclude from this study that anemia is associated with enhanced mortality in acute COPD exacerbations and it is also associated with NIV failure. Further studies are required to recognize the physiological significance of anemia in COPD exacerbations and its impact on clinical outcomes. Whether correction of anemia has beneficial effects in COPD patients is another challenging research question waiting to be answered.

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