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Prognostic Value of Oxygenated Hemoglobin Assessed during Acute Exacerbations of Chronic Pulmonary Disease

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Keywords
Acute exacerbations of chronic obstructive pulmonary disease · Oxygenated hemoglobin · Chronic obstructive pulmonary disease

Abstract
Background: Oxygenated hemoglobin(OxyHem) is a simple-to-measure marker of oxygen content capable of predicting all-cause mortality in stable chronic obstructive pulmonary disease (COPD). ***Objectives:*** We aimed to analyze its predictive value during acute exacerbations of COPD (AECOPD). ***Methods:*** In this retrospective study, data from 227 patients discharged after severe AECOPD at RoMed Clinical Center Rosenheim, Germany, between January 2012 and March 2018, was analyzed. OxyHem (hemoglobin concentration [Hb] × fractional SpO_2, g/dL) was calculated from oxygen saturation measured by pulse oximetry and hemoglobin assessed within 24 h after admission. The follow-up (1.7 ± 1.5 years) covered all-cause mortality, including readmissions for severe AECOPD. ***Results:*** During the follow-up period, 127 patients died, 56 due to AECOPD and 71 due to other reasons. Survivors and non-survivors showed differences in age, FVC % predicted, C-reactive protein, hemoglobin, Cr, Charlson Comorbidity Index (CCI), and OxyHem ($p < 0.05$ each). Significant independent predictors of survival were BMI, Cr or CCI, FEV_1 % predicted or FVC % predicted, Hb, or OxyHem. The predictive value of OxyHem ($p = 0.006$) was

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superior to that of Hb or SpO_2 and independent of oxygen supply during blood gas analysis. OxyHem was also predictive when using a cutoff value of 12.1 g/dL identified via receiver operating characteristic curves in analyses including either the CCI (hazard ratio 1.85; 95% CI 1.20, 2.84; $p = 0.005$) or Cr (2.04; 95% CI 1.35, 3.10; $p = 0.001$) as covariates. ***Conclusion:*** The concentration of OxyHem provides independent, easy-to-assess information on long-term mortality risk in COPD, even if measured during acute exacerbations. It therefore seems worth to be considered for broader clinical use.

Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive, debilitating condition, and estimated to become the third-leading worldwide cause of death in 2020 [1, 2]. Various measures, such as the BMI and the degree of airflow obstruction and dyspnea, or integrative scores such as the BODE ndex have been shown to be relevant for COPD prognosis under stable conditions [3–5]. In contrast, the use of blood gas analyses (BGAs) has been largely restricted to the acute, unstable situation [6]. Recently, however, we found that they carry prognostic information also under stable conditions [7]. Of special interest is the oxygen content of the blood (CaO_2), which is given by the hemoglobin concentration (Hb), oxygen saturation (SaO_2 or SpO_2), and partial pressure of oxygen (PaO_2) [8]. Due to the minor contribution from solved oxygen, CaO_2 is practically equivalent to the simpler measure "oxygenated hemoglobin" (OxyHem), which is the concentration of OxyHem (g/dL) obtained by multiplying Hb with fractional SaO_2 [2], alternatively SpO_2. This measure has the great advantage that it can be determined without the need for arterial or capillary BGAs and the respective equipment.

The predictive value of OxyHem in stable COPD, especially for mortality [2], has been shown in the large prospective COPD cohort Systemic Consequences – Comorbidities Network (COSYCONET) [9]. OxyHem was found to be independent of other predictors such as age, BMI, airflow obstruction, or cardiovascular comorbidities. The marker was furthermore independent from oxygen supply during BGA assessments [2]. This robustness raised the question whether it would be useful for long-term prediction also when assessed under unstable conditions, for example, during a visit due to acute deterioration of the disease or a severe exacerbation requiring hospitalization. To answer this question, we analyzed data collected within the first 24 h after admission for COPD exacerbation, that is, under unstable conditions. The outcome measure was long-term mortality after discharge from the hospital.

Methods

Study Population

The study comprised a retrospective analysis of patients admitted between January 2012 and March 2018 to the RoMed Clinical Center Rosenheim, Germany. From a computerized database, all files of patients admitted due to acute COPD exacerbation were retrieved and coded in line with the 10th revision of the International Classification of Diseases (ICD-10; J44.0: COPD with acute exacerbation unspecified, or J44.1: COPD with acute lower respiratory tract infections).

Selection Criteria

All patients discharged with information from follow-up were included in the analyses. The follow-up comprised subsequent hospital admissions at RoMed Clinical Center Rosenheim for respiratory and non-respiratory causes. It was determined whether patients died at the last admission recorded in the files, or whether they left the hospital alive. Data from patients admitted to other hospitals was not included due to the lack of comparable data. A comparison of patients, for whom no follow-up information could be obtained, and those included in the present study did not show significant differences regarding age or the severity of COPD.

Lung Function Measurements and BGA

Lung function was assessed within 24 h after admission and comprised spirometry and body plethysmography performed according to established guidelines [10–12], using Global Lung Function Initiative (GLI) reference values [13]. BGAs were also performed within 24 h. The values of PaO_2, $PaCO_2$, and pH were obtained from direct arterial puncture or from arterialized capillary blood from the earlobe [14]. For analysis, we took the values of SpO_2 as measured by pulse oximetry, using standard clips placed over a fingertip or earlobe. CaO_2 was calculated as $1.34 \times Hb \times \text{fractional } SpO_2 + 0.0031 \times PaO_2$ [15]. The concentration of OxyHem (g/dL) was calculated as $Hb \times \text{fractional } SpO_2$ [2].

Laboratory Values

Laboratory values as determined within the first 24 h of admission were extracted from the hospital electronic database. The numbers of leukocytes ($\times 10^9$/L) and erythrocytes (Ery/pL), and the values of hemoglobin (g/dL), hematocrit (%), C-reactive protein (CRP) (mg/dL), and Cr (mg/dL) were considered for analysis. Measures that were only assessed in case of suspected conditions, such as d-dimers, NT-pro-BNP, or troponine, were not considered due to their limited availability.

Comorbidities

Comorbidities were extracted from the hospital electronic database according to the 10th revision of the International Classification of Diseases, and prognostically relevant comorbidities were summarized using the Charlson Comorbidity Index (CCI) [16]. In its computation, age was omitted, if age was carried as explicit predictor.

Table 1. Characteristics of the study cohort (n = 227)

Variable	All N = 227	Survivors N = 100	Non-survivors N = 127	p value
Sex (f/m)	111/116	54/46	57/70	0.109
Age, yr	71.3±9.0	69.0±8.6	73.2±9.0	**≤0.001**
BMI, kg/m^2	26.1±6.4	26.9±6.5	25.4±6.3	0.092
Pack years	45.2±23.9	44.0±22.9	45.9±25.2	0.784
FEV_1 % predicted (GLI)	42.1±15.5	44.3±16.3	40.2±14.6	0.060
FVC %predicted (GLI)	58.0±17.0	63.0±15.8	53.7±16.9	**≤0.001**
FEV_1/VCmax, %	49.8±12.1	48.5±12.0	50.8±12.2	0.175
SpO_2, %	92.8±4.8	93.4±3.7	92.3±5.5	0.091
PaO_2, mm Hg	68.9±15.3	69.5±15.0	68.4±15.6	0.595
$PaCO_2$, mm Hg	44.2±10.4	43.7±10.1	44.7±10.7	0.481
pH	7.4±0.1	7.4±0.0	7.4±0.1	0.100
BE, mmol/L	2.3±4.5	2.5±4.1	2.0±4.8	0.415
CaO_2, mL/dL	17.2±2.6	17.9±2.3	16.7±2.7	**≤0.001**
OxyHem, g/dL	12.7±1.9	13.2±1.7	12.3±2.0	**≤0.001**
CRP, mg/dL	2.5±4.1	1.6±3.0	3.3±4.7	**0.002**
Leukocytes, ×10^9/L	10.2±3.7	9.8±3.4	10.4±3.9	0.237
Erythrocytes, n/pL	4.5±0.6	4.6±0.6	4.4±0.6	**0.014**
Hemoglobin, g/dL	13.7±1.9	14.2±1.8	13.3±2.0	**≤0.001**
Hematocrit, %	41.1±5.2	42.1±4.9	40.3±5.4	**0.009**
Cr, mg/dL	1.1±0.7	0.9±0.4	1.2±0.9	**≤0.001**
GFR, mL/min	71.5±26.2	78.6±20.9	65.9±28.7	**≤0.001**
LTOT	105/227 (46.2%)	46/100 (46%)	59/127 (46.4%)	1.000
LTOT flow, L/min	2.2±0.7	2.3±0.8	2.2±0.7	0.542
NIV	55/227 (24.2%)	29/100 (29.0%)	26/127 (20.5%)	0.161
CCI	5.0±1.9	4.6±1.7	5.3±1.9	0.004

The table shows mean values, SDs, or absolute numbers and percentages in case of sex, LTOT, and NIV. p values are given explicitly. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SpO_2, arterial oxygen saturation as measured by pulse oximetry; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; BE, base excess; CaO_2, oxygen content of blood; OxyHem, oxygenated hemoglobin; CRP, C-reactive protein; GFR, glomerular filtration rate; NIV, noninvasive ventilation; CCI, Charlson Comorbidity Index (including age); SD, standard deviation; GLI, Global Lung Function Initiative.

Statistical Analysis

We described categorical data using frequencies and percentages, and continuous data via mean values and standard deviations. To compare the groups of deceased versus surviving patients, Fisher's exact test for categorical variables and Student's t test for continuous variables were used, as appropriate. Cox proportional hazard regression analysis was employed to evaluate the independent prognostic value of OxyHem assessed upon admission for acute exacerbations of COPD (AECOPD) on long-term mortality, always keeping sex, age, and BMI as covariates, and selectively including other predictors such as lung function, leukocyte number, or the CCI. In these analyses, OxyHem was kept as the continuous variable. Alternatively, it was analyzed as the binary variable, defined via an optimal cutoff value that was identified by the receiver operating characteristic (ROC) analysis of OxyHem against life status within the follow-up period, using the Youden-Index as a criterion. All statistical tests were two sided, and p values <0.05 were considered statistically significant. Statistical analyses were performed with SPSS version 25 (IBM Corp., Armonk, NY, USA).

Results

Characteristics of Survivors and Non-Survivors

The median follow-up time was 1.7 ± 1.5 years (±SD), and 227 patients with severe exacerbations requiring hospital admission were included. Their mean (±SD) age was 71.3 ± 9.0 years, the FEV_1 at admission 42.1 ± 15.5 % predicted, and 111 (48.9%) were female. Overall, 127 patients (55.9%) died during follow-up in the center, among them 56 (44.1%) due to another acute exacerbation of COPD and 71 (55.9%) due to other conditions. Patients' characteristics stratified for survivors and non-survivors are presented in Table 1. Non-survivors were significantly older and had lower FVC % predicted. Concerning SpO_2, PaO_2, $PaCO_2$, pH, or BE, no significant differences between groups were observed. However, CaO_2 and its

Table 2. Cox proportional hazard regression analysis for mortality risk including BMI, FEV1 % predicted, and OxyHem ≤12.1 g/dL as a binary variable, and either Cr (upper subtable) or CCI (lower subtable)

Predictor	*B*	SE	HR	95% CI for HR		*p* value
				lower	upper	
With Cr						
BMI (kg/m^2)	−0.047	0.017	0.954	0.923	0.986	0.005
OxyHem ≤ 12.1 (g/dL)	0.713	0.213	2.040	1.345	3.095	0.001
Cr (mg/dL)	0.246	0.103	1.279	1.044	1.566	0.017
FEV_1 (%predicted)	−0.014	0.007	0.986	0.973	0.999	0.042
With CCI						
BMI (kg/m^2)	−0.058	0.018	0.944	0.912	0.977	0.001
OxyHem ≤ 12.1 (g/dL)	0.613	0.219	1.847	1.202	2.838	0.005
CCI > 3 (points)	0.220	0.083	1.246	1.059	1.466	0.008
FEV_1 (%predicted)	−0.016	0.007	0.984	0.971	0.997	0.019

The table shows the results of the Cox regression analysis for mortality risk. The mean follow-up time was 1.7 years. Sex, age, BMI, CCI (without age), and FEV_1 % predicted were included as covariates. *B* indicates the unstandardized estimate and HR is expressed as (= exp[*B*]). SE, standard error; HR, hazard ratio; CI, confidence interval; CCI, Charlson Comorbidity Index; OxyHem, oxygenated hemoglobin; FEV1, forced expiratory volume in 1 s.

marker OxyHem were significantly lower in non-survivors compared to survivors (16.7 ± 2.7 vs. 17.9 ± 2.3 mL/dL and 12.3 ± 2.0 vs. 13.2 ± 1.7 g/dL, respectively; $p \leq 0.001$ each). Moreover, non-survivors had a worse kidney function, higher levels of CRP, and lower hematocrit values, with lower Hb and erythrocyte number ($p < 0.05$ each). Patients who died from AECOPD had more severe airflow limitation in terms of FEV_1 % predicted and a lower comorbidity burden compared to those who died from other causes, while no significant differences were observed in terms of conventional BGA or OxyHem (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000513440).

Comorbidities

A summary of frequent comorbidities stratified for survivors and non-survivors is presented in the online suppl. Table 2. The most frequent comorbidities according to ICD-10 codes were cardiovascular, metabolic, renal, and mental disorders. More than half of all patients had cardiovascular comorbidities, with the diagnoses of "arterial hypertension" in 49.8%, "congestive heart failure" in 34.4%, "hypertensive heart disease" in 22.9%, and "atrial fibrillation or atrial flutter" in 19.8% of cases. The most prevalent metabolic disorders were "type 2 diabetes mellitus" in 23.8%, "other hypothyroidism" in 14.1%, "disorders of lipoprotein metabolism and other lipidemias" in 13.7%, and "disorders of purine and pyrimidine metabolism" in 7.0%. For single comorbidities, significant differences between survivors and non-survivors occurred for "other pulmonary heart diseases" and renal impairment in terms of diagnosed "CKD" or "glomerular disorders in diseases classified elsewhere," that were overall present in 5.7, 18.5, and 6.2%, respectively. The comorbidity burden (including age) if summed up using the CCI was significantly higher in non-survivors compared to survivors with 4.6 ± 1.7 versus 5.3 ± 1.9 points ($p = 0.004$).

ROC Curves

ROC curves showed OxyHem as a significant mortality predictor with an area under the curve of 0.642 (95% CI 0.570–0.714; $p < 0.0001$) and an optimal cutoff value of 12.1 g/dL according to the Youden Index (online suppl. Fig. 1).

Cox Proportional Hazard Regression Analyses

In all analyses, age, sex, and BMI were carried as potential covariates. FEV_1 % predicted, FVC % predicted, Cr, CCI, Hb, and OxyHem were significant ($p < 0.05$ each) predictors, if added as single variables to the set of covariates. Leukocyte number and CRP were not relevant and omitted from further analyses. When comparing FEV_1 % predicted and FVC % predicted, as highly correlated measures of lung function, FVC was significant but FEV_1 was no more. Regarding Cr versus CCI as indicators

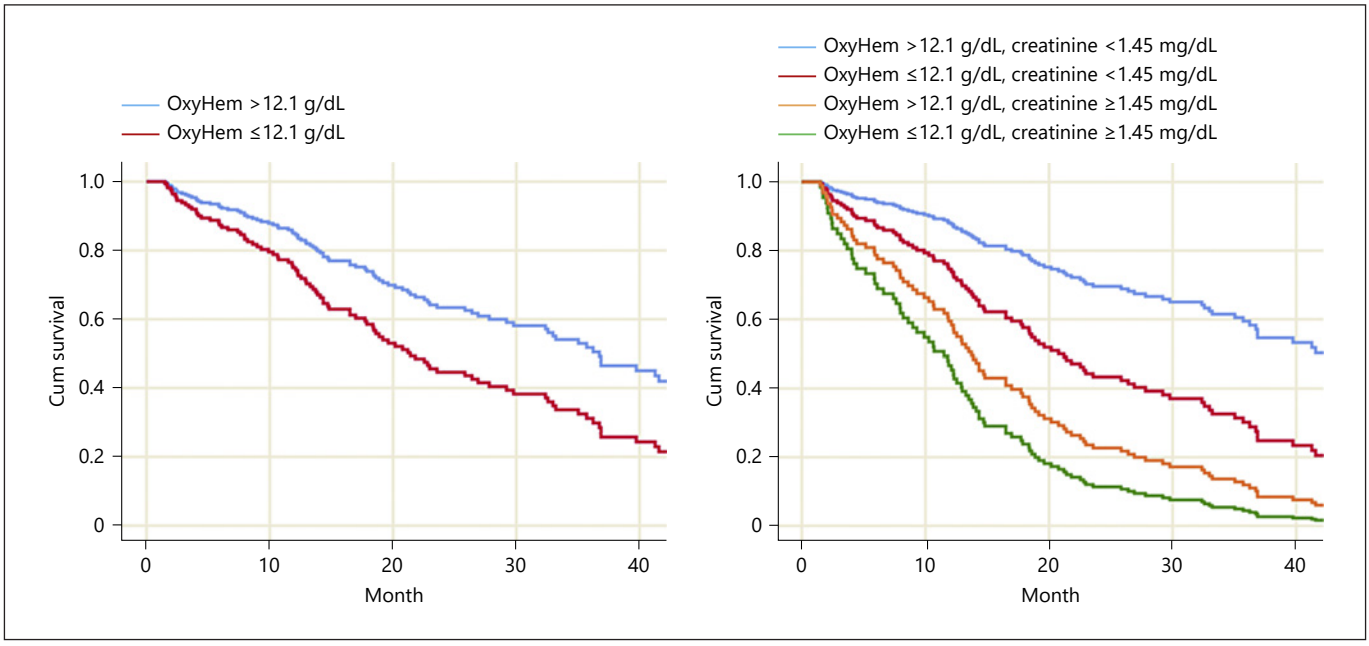

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Fig. 1. Cox proportional hazards cumulative survival curves, stratified for OxyHem >12.1 g/dL (left panel) or for the combination of OxyHem >12.1 g/dL and Cr ≥1.45 mg/dL (right panel). BMI, FEV1 % predicted, and Cr were carried as covariates. The HRs for the binary OxyHem and binary Cr are given in Table 2, upper subtable. OxyHem, oxygenated hemoglobin; HR, hazard ratio.

of comorbidity, the CCI was superior to Cr. OxyHem and Hb were closely related to each other by the way OxyHem is computed; when comparing them, OxyHem was significant but Hb was not . SpO_2 was not a significant predictor.

To identify the best ones among these correlated predictors, we performed a stepwise (forward) Cox regression analysis with OxyHem, CCI, and FVC % predicted. OxyHem was significant ($p = 0.006$), in addition to BMI ($p = 0.002$), CCI ($p = 0.026$), and FVC % predicted ($p = 0.021$). The result for OxyHem was robust ($p = 0.001$) when replacing the CCI by Cr ($p = 009$) and FVC % predicted by FEV_1 % predicted ($p = 0.033$). When performing a forward selection with all the variables mentioned in the initial analysis, BMI, FEV_1 % predicted, Cr, and OxyHem remained as only predictors showing that these physiologically meaningful predictors were also statistically consistent (online suppl. Table 3). Moreover, the predictive value of OxyHem was independent of the condition of oxygen supply during BGA (online suppl. Table 4), whereby the numerical value of the OxyHem coefficient was virtually unchanged. A direct comparison of OxyHem with Hb was difficult due to the high degree of collinearity. If performed stepwise, always OxyHem was selected and Hb was removed (also see below).

Following the results of the ROC analysis, the continuous OxyHem was then replaced by a binary variable defined via the cutoff value of 12.1 g/dL. This resulted in a hazard ratio for OxyHem of 2.04 (95% CI 1.35, 3.10; $p = 0.001$), when using Cr as the covariate. In a stepwise forward approach with all variables mentioned above, the CCI was slightly superior to Cr regarding its predictive value. In this case, the hazard ratio for OxyHem being below 12.1 g/dL was 1.85 (95% CI 1.20, 2.84; $p = 0.005$). Thus, the results for OxyHem were statistically robust. They are given in Table 2 when including either Cr or CCI as the covariate. Survival curves for OxyHem are shown in Figure 1, either alone or in combination with a Cr cutoff value of 1.45 mg/dL. It can be seen that OxyHem was of particular value in patients with lower Cr levels, while at high Cr levels, Cr dominated. Comparisons between Hb and OxyHem were limited by the high degree of collinearity between these 2 indices, particularly if continuous measures were used. This could be partially remedied by using indicator variables. The optimal ROC-determined cutoff value for Hb regarding mortality was 13.0 g/dL, and the result of a Cox regression analysis including the 2 predictors showed that OxyHem was still statistically significant ($p = 0.006$) but Hb was not ($p = 0.3305$). A similar result was obtained when including the covari-

ates BMI, Cr, and FEV_1 % predicted, or when choosing higher or lower cutoff values for Hb. All results indicated OxyHem to be a robust predictor and superior to Hb.

Discussion

The concentration of OxyHem is a novel, simple-to-measure marker of the oxygen content of blood and was recently identified as an independent outcome predictor in stable COPD [2]. The present study set out to investigate the predictive value of OxyHem for long-term mortality when assessed at the beginning of an acute COPD exacerbation, that is, within 24 h after admission. We included data from patients discharged from the hospital and assessed their outcomes at the last of their following hospital admissions within a follow-up period of 1.7 ± 1.5 years. Based on findings from previous work [2], we aimed to assess the predictive robustness of OxyHem and to compare it to other laboratory and functional markers.

The major finding of our analysis was that OxyHem is a significant predictor of long-term mortality if assessed during an acute exacerbation, including if determined with oxygen supply during BGA. Its predictive value was independent of other established risk factors such as BMI, kidney function, and FEV_1. Furthermore, it was superior to that of Hb alone [17, 18]. These results add to our previous findings obtained in patients with stable COPD in the COSYCONET cohort. Out of a broad panel of blood gas measures, comorbidities and inflammatory markers, OxyHem and leukocyte count were identified as those biomarkers that reflected the current burden of the disease and predicted significant disease-related outcomes, including mortality [2]. In the present study, leukocyte count did not play a role, similar to CRP, and this was probably due to the fact that under unstable clinical conditions leukocyte count is quite variable and thus not suitable as a long-term predictor.

COPD is often accompanied by comorbidities that significantly contribute to disease burden and outcomes [19–21]. Almagro and colleagues [22] identified the quality of life, marital status, depressive symptoms, prior hospital admission, and comorbidities as prognostic relevant after hospital admission for acute exacerbations of COPD. The multidimensional CODEX index developed to estimate survival chances in patients hospitalized for COPD exacerbation includes the age-adjusted CCI, obstruction, dyspnea, and previous severe exacerbations [23]. Clinical practice shows that in the acute setting these measures are often not completely available. There is also no algorithm for deriving an estimate of long-term risk from the acute setting. This was one of the reasons why we focused on most simple, readily available measures such as OxyHem and Cr that have been shown to be predictive for long-term risk at least under stable conditions [2, 7]. Our study population presented with a broad panel of comorbidities, especially cardiovascular, metabolic, renal, and mental diseases, but only pulmonary hypertension and kidney diseases had a relevant impact on mortality, if considered as single comorbidities. In line with these findings, Cr was significantly elevated in the non-survivor group, and correspondingly it was an outcome predictor for mortality independently from OxyHem. We previously elucidated the associations of blood gases, renal, and respiratory function with exacerbation rate in stable COPD, using a network analysis [7]. Kidney dysfunction had direct and indirect effects on exacerbations, whereby the indirect effects were mainly mediated via base excess and oxygen content, CaO_2. CaO_2 has an impact on COPD comorbidities, as tissue oxygenation, mandatory for every organ system, depends on both the circulatory capacity and the oxygen transport capacity of the blood [24]. The role of CaO_2, as well as its greater relevance compared to PaO_2 or SaO_2, was underlined in a recent study on cognitive impairment in COPD [25]. Other interactions regarding CaO_2 involve hypoxic pulmonary vasoconstriction and an increase of cardiac output in response to a reduced oxygen transport capacity, possibly leading to overstrain of the cardiovascular system, especially in patients with preexisting congestive heart failure or pulmonary hypertension.

The current GOLD guidelines recommend the use of pulse oximetry for all COPD patients with clinical signs suggestive for respiratory failure or right heart failure, additionally BGAs is recommended if SpO_2 is below 92% (https://goldcopd.org/2021-gold-reports/). However, the potential predictive value of SpO_2 or biomarkers derived from BGA has been not addressed in international recommendations so far.

OxyHem and Cr were independent predictors of mortality. The impact of kidney disease on COPD outcome can be explained by pathophysiological interactions between lung and kidney, as well as interactions with other comorbidities including cardiovascular diseases [20]. Comorbid kidney disease substantially contributes to other common systemic disease manifestations, such as malnutrition, muscle wasting, acid-base balance disturbances, and anemia [7, 26]. The present data indicate that in the absence of kidney disease, OxyHem was a particularly powerful predictor, whereas in the presence of kidney

disease this disorder dominated the prognosis, although a low OxyHem still had an additional predictive value. Kidney function may affect OxyHem via its effects on the hemoglobin level that was also a powerful predictor of mortality. The analysis faced the problem of the very high collinearity of Hb and OxyHem, as consequence of its definition. In stepwise analyses, the continuous OxyHem always dominated hemoglobin, which has not provided additional information, and the simultaneous inclusion of 2 optimal binary variables that were less correlated with each other, clearly underlined the dominance of OxyHem. Compared to hemoglobin, OxyHem confers additional information originating from SaO_2, but SaO_2 itself was not predictive in any way. Surprisingly, even the application of oxygen during the determination of blood gases including that of SaO_2 did not affect the predictive value of OxyHem. It also had no predictive value per se, for example, through correlation with other risk factors. This suggests that OxyHem satisfies some requirements of a biomarker suitable for clinical use.

It directly quantifies the burden of the disease on future outcomes [27] via its close relation to oxygen content that is relevant for proper organ function; whether it is also useful for targeting interventions in COPD patients, such as long-term oxygen therapy and measures against anemia, and for evaluation of their effects, has to be determined in future studies. The same is true for its potential application in other chronic disorders.

Limitations

The present study has limitations arising from its design as a retrospective analysis. A comparison of patients, for whom no follow-up information could be obtained, and those included in the present study did not show significant differences regarding age or the severity of COPD. Thus, there is no reason suggesting a bias toward the results of the present analysis, particularly those obtained for OxyHem. We also did not have reliable information on the precise cause of death in those patients who did not die from AECOPD. The data indicate that there were some differences between these 2 groups, which were plausible in terms of the lung function and cardiac comorbidity. The 2 groups were too small to yield a meaningful result in separate analyses. The strength of the present study is that all data were obtained in the same hospital under comparable conditions.

The values of PaO_2, $PaCO_2$, and pH were obtained from arterialized capillary blood from the earlobe, an established method to avoid arterial puncture [14]. Commonly, arterial BGA is considered as gold standard for the assessment of SaO_2, while in the present study pulse oximetry (SpO_2) was used. The 2 measures are not equivalent, as large SpO_2 to SaO_2 differences have been observed especially in critically ill patients. [28] In this case, SaO_2 might be sensitive to biochemical alterations in the blood and not as predictive as SpO_2. Our data show that OxyHem was predictive when computed via SpO_2, that is, without the need for capillary BGA, which favors potential practical applications and is of interest, as our initial analysis [2] performed in patients with COPD used SaO_2 but only under stable conditions. Saturation measured by co-oximetry could be superior to SpO_2, better reflecting local biochemical conditions at the oxygen-demanding tissues. Thus, further studies should aim to better describe and confirm the physiological and clinical value of different measures of SaO_2.

Conclusions

The concentration of OxyHem provided easy-to-assess information on long-term mortality risk in COPD, especially if assessed during acute exacerbations. It was independent from other predictors such as comorbidity burden, kidney function, and lung function and not sensitive to oxygen supply during BGA. It was also superior to the conventional marker of Hb from which it can be easily computed by taking into account fractional SaO_2. Thus, OxyHem appears as a robust marker well suited for clinical use.

Statement of Ethics

According to the guidelines of the Ethical Committee of the University of Regensburg to which the study was announced, no explicit approval was necessary for this retrospective study.

Conflict of Interest Statement

C.F. Hinke, R.A. Jörres, F. Bornitz, H. Watz, M. Kreuter, F.J.F. Herth, K. Kahnert, C. Kellerer, S. Budweiser, and F.C. Trudzinski have nothing to disclose with regard to this study. R. Bals reports grants and personal fees from AstraZeneca and Boehringer Ingelheim; personal fees from GlaxoSmithKline; Grifols, Novartis, and CSL Behring; grants from the German Federal Ministry of Education and Research (BMBF) Competence Network Asthma and COPD (ASCONET); Sander Stiftung; Schwiete Stiftung; Krebshilfe; and Mukoviszidose eV, outside the submitted work. P. Alter reports grants from the German Federal Ministry of Education and Research (BMBF) Competence Network Asthma and COPD (ASCONET) and from AstraZeneca GmbH; grants and non-financial

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Author Contributions

Felix Hinke collected the data, which are part of his medical doctoral dissertation. He was involved in the design of the study, analysis, and interpretation of data, drafting of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Rudolf A. Jörres was involved in the analysis and interpretation of data, drafting and critical revision of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work. Peter Alter, Robert Bals, F. Bornitz, Felix Herth, Kathrin Kahnert, Christina Kellerer, Hendrik Watz, Stephan Budweiser, and Franziska Trudzinski were involved in the interpretation of data and critical revision of the manuscript, approved the final submitted version, and agreed to be accountable for all aspects of the work.

References

1 Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006 Nov;3(11):e442.
2 Trudzinski FC, Jörres RA, Alter P, Kahnert K, Waschki B, Herr C, et al. Associations of oxygenated hemoglobin with disease burden and prognosis in stable COPD: results from COSYCONET. Sci Rep. 2020 Jun 29;10(1):10544.
3 Burrows B, Earle RH. Prediction of survival in patients with chronic airway obstruction. Am Rev Respir Dis. 1969 Jun;99(6):865–71.
4 Domingo-Salvany A, Lamarca R, Ferrer M, Garcia-Aymerich J, Alonso J, Félez M, et al. Health-related quality of life and mortality in male patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2002 Sep 1;166(5):680–5.
5 Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004 Mar 4;350(10):1005–12.
6 Gungor S, Kargin F, Irmak I, Ciyiltepe F, Acartürk Tunçay E, Atagun Guney P, et al. Severity of acidosis affects long-term survival in COPD patients with hypoxemia after intensive care unit discharge. Int J Chron Obstruct Pulmon Dis. 2018;13:1495–506.
7 Trudzinski FC, Kahnert K, Vogelmeier CF, Alter P, Seiler F, Fähndrich S, et al. Combined effects of lung function, blood gases and kidney function on the exacerbation risk in stable COPD: results from the COSYCONET cohort. Respir Med. 2019 Jul–Aug;154:18–26.
8 Köhler D. CaO2-Wert zur Beurteilung der Sauerstoff-Organversorgung: Klinische Bedeutung des Sauerstoffgehaltes. Dtsch Arztebl Int. 2005 Jul 18;102(28–9):2026.
9 Karch A, Vogelmeier C, Welte T, Bals R, Kauczor HU, Biederer J, et al. The German COPD cohort COSYCONET: aims, methods and descriptive analysis of the study population at baseline. Respir Med. 2016 May;114:27–37.
10 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug;26(2):319–38.
11 Criee CP, Berdel D, Heise D, Kardos P, Kohler D, Leupold W, et al. [Recommendations on spirometry by Deutsche Atemwegsliga]. Pneumologie. 2006 Sep;60(9):576–84.
12 Criée CB, Heise D, Jörres D, Kardos RA, Köhler P, Leupold D, et al. Empfehlungen zur Ganzkörperplethysmographie (Bodyplethysmographie) Teil II. Atemw Lungenkrkh. 2009;349–70.
13 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324–43.
14 Langlands JH, Wallace WF. Small blood-samples from ear-lobe puncture: a substitute for arterial puncture. Lancet. 1965 Aug 14;2(7407):315–7.
15 Duke JW, Davis JT, Ryan BJ, Elliott JE, Beasley KM, Hawn JA, et al. Decreased arterial PO2, not O2 content, increases blood flow through intrapulmonary arteriovenous anastomoses at rest. J Physiol. 2016 Sep 1;594(17):4981–96.
16 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83.
17 Kollert F, Tippelt A, Müller C, Jörres RA, Porzelius C, Pfeifer M, et al. Hemoglobin levels above anemia thresholds are maximally predictive for long-term survival in COPD with chronic respiratory failure. Respir Care. 2013 Jul;58(7):1204–12.
18 Schneckenpointner R, Jörres RA, Meidenbauer N, Kollert F, Pfeifer M, Budweiser S. The clinical significance of anaemia and disturbed iron homeostasis in chronic respiratory failure. Int J Clin Pract. 2014 Jan;68(1):130–8.
19 Divo M, Cote C, de Torres JP, Casanova C, Marin JM, Pinto-Plata V, et al. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012 Jul 15;186(2):155–61.
20 Trudzinski FC, Alqudrah M, Omlor A, Zewinger S, Fliser D, Speer T, et al. Consequences of chronic kidney disease in chronic obstructive pulmonary disease. Respir Res. 2019 Jul 12;20(1):151.
21 Waschki B, Alter P, Zeller T, Magnussen C, Neumann JT, Twerenbold R, et al. High-sensitivity troponin I and all-cause mortality in patients with stable COPD: an analysis of the COSYCONET study. Eur Respir J. 2020;55(2):1901314.
22 Almagro P, Calbo E, Ochoa de Echagüen A, Barreiro B, Quintana S, Heredia JL, et al. Mortality after hospitalization for COPD. Chest. 2002 May;121(5):1441–8.
23 Almagro P, Soriano JB, Cabrera FJ, Boixeda R, Alonso-Ortiz MB, Barreiro B, et al. Short- and medium-term prognosis in patients hospitalized for COPD exacerbation: the CODEX index. Chest. 2014 May;145(5):972–80.
24 MacIntyre NR. Tissue hypoxia: implications for the respiratory clinician. Respir Care. 2014 Oct;59(10):1590–6.
25 von Siemens SM, Perneczky R, Vogelmeier CF, Behr J, Kauffmann-Guerrero D, Alter P, et al. The association of cognitive functioning as measured by the DemTect with functional and clinical characteristics of COPD: results from the COSYCONET cohort. Respir Res. 2019 Nov 14;20(1):257.
26 Webster AC, Nagler EV, Morton RL, Masson P. Chronic kidney disease. Lancet. 2017 Mar 25;389(10075):1238–52.
27 Taylor DR. Risk assessment in asthma and COPD: a potential role for biomarkers? Thorax. 2009 Mar;64(3):261–4.
28 Van de Louw A, Cracco C, Cerf C, Harf A, Duvaldestin P, Lemaire F, et al. Accuracy of pulse oximetry in the intensive care unit. Intensive Care Med. 2001 Oct;27(10):1606–13.