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ANAEMIA IN CHRONIC RESPIRATORY FAILURE

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ABSTRACT

Background: In patients with severe chronic obstructive pulmonary disease (COPD), anaemia is common and associated with impaired long-term survival and quality of life. Whether anaemia is also prevalent in patients with other severe, non-inflammatory respiratory diseases has not yet been systematically tested.

Methods: In 595 patients with obstructive (OD, 54.8%) or restrictive disease (RD, 45.2%) and chronic respiratory failure (CRF), anthropometric data, laboratory parameters, lung function, blood gases and co-morbidities were assessed prior to initiation of home mechanical ventilation. Patients were classified as anaemic based on haemoglobin (Hb) levels (Hb <12/13g/dl, female/male). Patients with known causes for anaemia were excluded.

Results: In patients with CRF the prevalence of anaemia was 13.3% and not different between RD (11.5%) and OD (14.7%) ($p=0.276$). A sex-related difference occurred only in OD (7.9% (f) versus 17.3% (m); $p=0.035$). Patients with OD and anaemia presented with higher age ($p=0.003$), pH ($p=0.014$) and arterial oxygen pressure (PaO_2) ($p=0.012$), lower body-mass index (BMI) ($p=0.011$) and total protein ($p=0.012$), and higher rates of coronary heart disease ($p=0.01$), cardiac arrhythmia ($p=0.014$) and diabetes mellitus ($p=0.003$) in comparison to non-anaemic patients. In patients with RD anaemia was associated with higher age, ($p=0.008$), pH ($p=0.011$) and lower leucocytes numbers ($p=0.006$).

Conclusions: Anaemia is frequent not only in COPD but also in other severe respiratory diseases combined with CRF. It was associated with advanced age, several co-morbidities, impaired nutritional state and elevations of pH and PaO_2 , probably due to hyperventilation. Its prognostic impact has to be elucidated in future studies.

Word count of abstract: 248

Key words: Respiratory failure; anaemia; prognostic factors; COPD; restrictive disease.

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3 **What is already known about this topic?**
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6 Anaemia is highly prevalent in COPD and associated with increased long-term mortality. In
7
8 contrast, the prevalence of anaemia has not yet been tested in other severe, non-inflammatory
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10 respiratory diseases.
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15 **What does this article add?**
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18 The prevalence of anaemia was high in COPD but also in other severe respiratory diseases,
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20 even after exclusion of relevant co-morbidities. These findings suggest that anaemia is a
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22 common phenomenon in patients with severe chronic respiratory disease, which has a
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24 multifactorial origin and is not only explained by systemic inflammation.
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INTRODUCTION

Anaemia of chronic disease (ACD) is one of the most frequent forms of anaemia which is often observed in patients with infections, cancer and chronic inflammatory or autoimmune diseases. The underlying mechanisms are complex, including dysregulation in iron homeostasis and erythropoietin production, impaired proliferation of erythroid progenitor cells and reduced life span of red blood cells. Moreover, ACD often is superimposed by malnutrition, bleeding, renal failure and effects of medication or interventions (1). In patients with chronic renal failure, congestive heart failure, or malignant diseases, anaemia has been shown to be associated with impaired quality of life and prognosis (2-4).

A retrospective analysis of patients with chronic obstructive pulmonary disease (COPD) receiving long-term oxygen therapy (LTOT) has revealed that anaemia is also common in severe COPD, being linked to morbidity and survival (5). Moreover, a prospective study of stable COPD patients with a wide range of airflow limitation reported haemoglobin levels of <13 g/dl in 17% of patients, whereby anaemia acted as a risk factor for dyspnoea, functional capacity and mortality (6). However, a limitation of these investigations appeared to be that co-morbidities relevant for anaemia were not excluded. Thus COPD is associated with many co-morbidities (7), not only renal failure (8), which could substantially contribute to anaemia. In addition, the clinical significance and pathogenesis of anaemia in COPD are still under discussion. Erythropoietin resistance secondary to systemic inflammation has been proposed as a contributor (9), but a number of other mechanisms, such as malnutrition or oxidative stress, may also play a role in severe forms of the disease (10), as well as medication, such as theophylline (11).

Based on these considerations we aimed to assess the prevalence of anaemia in a large group of patients with severe respiratory diseases of different aetiologies, to compare this with the prevalence found in COPD and to identify risk factors linked to anaemia. All patients were of comparable clinical state with regard to the fact that they received home mechanical

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ventilation (HMV) due to chronic respiratory failure (CRF). To reduce the bias by confounders, patients with known causes for anaemia were strictly excluded from the analysis.

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METHODS

Study population

Patients who were discharged with HMV due to CRF from the Donaustauf Hospital, Centre for Pneumology, University of Regensburg, between April 1992 and March 2007 were identified from a data base. Since January 2002 data entry was performed prospectively. The underlying disorders were classified as obstructive disorders (OD) (COPD or overlap syndrome) or restrictive disorders (RD) including obesity-hypoventilation syndrome (OHS), thoracic restrictive diseases (TRD), neuromuscular disorders (NMD), and mixed respiratory disease (predominately interstitial lung diseases). The diagnosis of COPD was based on clinical history, symptoms, a ratio of forced expiratory volume in one second (FEV_1) to inspiratory vital capacity (VC) of $<70\%$, and FEV_1 being $<50\%$ predicted. In case of $FEV_1 >50\%$ (and $FEV_1/VC <70\%$) and in the presence of chronic hypercapnia, patients were classified as “overlap syndrome” (OL) (12). OHS was defined as obesity ($BMI >30 \text{ kg/m}^2$) plus daytime hypercapnia ($PaCO_2 \geq 45 \text{ mm Hg}$) and symptoms of hypoventilation (13).

Selection criteria

Only patients with complete blood count data prior to initiation of HMV were included. Based on the fact that intensive care or endotracheal intubation is associated with repeated blood withdrawal or blood loss due to interventions, we also excluded all patients who had undergone invasive ventilation before initiation of HMV. It has been shown, that the prevalence of renal anaemia in patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 ml/min/1.73m² is low (14), thus only patients with eGFR $<30 \text{ ml/min/1.73 m}^2$ were excluded. Further exclusion criteria were known malignancies/haematological disorders within the last 5 years, surgeries, interventions, accidents or haemorrhage within the last 3 months; additional chronic inflammatory, infectious or autoimmune diseases; previous

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3 gastrointestinal resection that could evoke malabsorption; substitution of iron, folate or
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5 vitamin B₁₂; preceding withdrawal of blood due to polyglobulia or blood transfusion.
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8 9 *Measurements*

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11 All data were assessed at the beginning of the hospital stay. Routine blood parameters
12 including haemoglobin (Hb), haematocrit (Hk), leukocyte number, C-reactive protein (CRP),
13 creatinine and total protein (if available) were documented upon admission. Patients were
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15 classified as anaemic (Hb<12 g/dl in females, Hb<13 g/dl in males) (15) or normal. BMI was
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17 calculated as weight(kg)/height(m)². Glomerular filtration rate was estimated by the
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19 “Modification of Diet in Renal Disease (MDRD)” study equation, as this formula is known to
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21 be more accurate especially in older and obese patients than the Cockcroft-Gault equation (16).
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Chronic renal failure was defined by an eGFR <60 ml/min/1.73 m². Daytime capillary
blood gas values (pH, arterial oxygen pressure (PaO₂), arterial carbon dioxide pressure
(PaCO₂), base excess (BE)) were determined prior to HMV therapy from the hyperaemic
earlobe. Only values acquired without additional oxygen supplementation were used.
Spirometry and bodyplethysmography were performed according to guidelines of the
American Thoracic Society (ATS) / European Respiratory Society (ERS) (17) using ERS
reference values (18). Co-morbidities, such as coronary heart disease, left heart failure,
cardiac arrhythmias, arterial hypertension and diabetes mellitus, as well as concomitant
medication, such as inhaled bronchodilators, theophylline or anti-hypertensive medication,
were documented. The presence of acute infection, such as pneumonia or lower urinary tract
infection, was derived from clinical findings and/or CRP levels >20mg/dl.

55 56 57 58 59 60 *Statistical analysis*

The results are shown as median and quartiles. For the comparison of groups, the Mann-Whitney U-test or t-test was used in case of continuous variables, and Fisher’s exact test for categorical variables. Parameters which were significant different between anaemic and non-

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3 anaemic patients, and disease category (OD versus RD) as binary variable, were evaluated by
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5 multivariate regression analyses to identify independent factors. A p-value <0.05 was
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7 considered statistically significant. Calculations were performed using PASW statistics 17.0
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10 (Chicago, IL, USA).
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RESULTS

Study population

Within the study period 966 patients were discharged with HMV. In total, 939 patients showed appropriate laboratory data prior to initiation of HMV. The exclusion of patients with co-morbidities possibly contributing to anaemia (**Figure 1**) resulted in a study population of 595 patients aged from 21 to 84 years. OD (n=326; 54.8%) comprised severe COPD (n=304) and overlap syndrome (n=22). RD (n=269; 45.2%) comprised OHS (n=120), TRD (n=80), NMD (n=48) and other respiratory disease (n=21) (**Table 1**).

Prevalence of anaemia in different chronic respiratory diseases

The overall prevalence (n=595) of anaemia was 13.3% (n=79), without significant difference between OD (14.7%) and RD (11.5%) (p=0.276), or between COPD (15.1%) and RD (11.5%) (p=0.221). However, the prevalence of anaemia was significantly different between TRD (6.3%) and COPD (15.1%) (p=0.041), NMD (20.8%) and TRD (6.3%) (p=0.021) and OD (14.7%) and TRD (6.3%) (p=0.043). In contrast, the prevalence did not show significant differences between overlap syndrome (9.1%), OHS (10.8%) and other respiratory diseases (14.3%) (**Figure 2**). Only in OD the prevalence of anaemia differed between females and males (7.9% versus 17.3%; p=0.035), whereas no such differences occurred in the total group (p=0.081) or in patients with RD (p=1.0) (**Figure 3**).

Characteristics of patients with anaemia in chronic respiratory diseases

Patients with OD and anaemia showed higher age (p=0.003), pH (p=0.014) and arterial oxygen pressure (PaO₂) (p=0.012), lower BMI (p=0.011) and total protein (p=0.012), and higher rates of male sex (p=0.035) coronary heart disease (p=0.01), cardiac arrhythmia (p=0.014) and diabetes mellitus (p=0.003) in comparison to non-anaemic patients with OD.

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3 Moreover, anaemic patients with OD showed less intake of theophylline ($p < 0.001$). In
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5 anaemic patients with RD, there were higher age ($p = 0.008$), pH ($p = 0.011$) and lower
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7 leukocyte numbers ($p = 0.006$) as compared to non-anaemic patients with RD (**Table 2**).
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10 Stepwise multivariate regression analysis of all patients, including OD versus RD as
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12 binary variable, revealed that age ($p = 0.012$), pH ($p = 0.002$) and PaO_2 ($p = 0.006$) but not the
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14 disease category were independently associated with anaemia. In OD only pH ($p = 0.011$) and
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16 PaO_2 ($p = 0.013$) were independently associated with anaemia, while in RD leukocyte number
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18 ($p = 0.035$) and pH ($p < 0.001$) were independent predictors of anaemia (**Table 3**).
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DISCUSSION

This study demonstrates that anaemia, a treatable condition, is highly prevalent in patients with CRF irrespective of the underlying disease. Anaemia was associated with age, nutritional indices and blood gas indices. In view of the heterogeneity of the study population these results suggest, that not only systemic inflammation, but also conditions associated with respiratory failure itself, contributes to the development of anaemia in respiratory diseases.

Anaemia is known to be a common feature in COPD. When defining anaemia via haemoglobin levels, prevalence rates between 13% (Hb<13 g/dl) (21) and 17% (Hb<13.5 g/dl for male, Hb<12.0 g/dl for female) have been reported (6). In line with this our data show a prevalence of 15.1% in COPD, if anaemia was defined based on WHO criteria (Hb<12 g/dl for females and Hb<13 g/dl for males) (15). Remarkably, this percentage did not vary much when patients with overlap syndrome were included (14.9%). Using the same definition for anaemia, a prevalence of 23.1% has been found in a population of 312 hospitalised COPD patients (9). In severe COPD (n=80) the prevalence of anaemia (13.9%) was similar to our results, while it was higher in less severe disease (9). Possibly, hypoxemia which often is present in more severe forms of the disease and which is known as stimulus for erythropoiesis acts against the development of anaemia. This might may also explain why a lower prevalence of anaemia was found in patients with COPD who were candidates for LTOT (12.6% in men, 8.2% in women), apart from the fact that in this study haematocrit had been used as criterion (<39% in men, <36% in women) (5). As in the present investigation, the prevalence of anaemia reported in this study was also higher in males with COPD.

To the best of our knowledge, the prevalence of anaemia in patients with CRF due to other respiratory diseases than COPD has not been systematically studied so far. Our data reveal that in severe restrictive disease anaemia is nearly equally frequent, as the overall prevalence in non-COPD was 11.5% and not significantly different from that in OD or COPD. Nevertheless there were differences between diseases within this group. The highest

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3 prevalence was found in patients with NMD (20.8%) and “other respiratory diseases” (14.3%;
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5 predominantly interstitial lung disease), whereas patients with TRD showed the lowest
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7 prevalence (6.3%). In COPD anaemia reflects prognosis (19). Correspondingly, in non-COPD
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9 patients anaemia also appears to be inversely related to long-term survival, as this is known to
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11 be best in patients with CRF due to TRD and often worse in patients with lung fibrosis or
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13 NMD such as amyotrophic lateral sclerosis. In view of this it is surprising, that also in patients
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15 with OHS anaemia was observed in a considerable number of patients.
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20 The current study was not designed to elucidate causative mechanisms regarding
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22 anemia. Phenomenologically, anaemic patients with OD showed higher age, lower BMI and
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24 total protein, and a higher rate of relevant co-morbidities. Among these, diabetes mellitus
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26 could be causal for anaemia (20) and the development of coronary heart disease and cardiac
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28 arrhythmias probably favoured by it.
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32 ACD is a frequent phenomenon in patients with acute or chronic immune activation
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34 (21). Interleukin-1, interleukin-6, tumor necrosis factor- α and interferon- γ are involved in the
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36 underlying mechanism (1). These cytokines also take part in the pathogenesis of COPD (22)
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38 and therefore could contribute to the development of anaemia in COPD (5;10;23). In addition,
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40 an imbalance between the erythropoietin-stimulating effect of hypoxia and inflammation-
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42 induced erythropoietin resistance resulting in anaemia has been proposed in COPD (10). Our
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44 finding, that anaemia is present in severe respiratory disease largely irrespective of the
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46 underlying disorder suggests that inflammation probably is not the major driver of anaemia.
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48 Thus, anaemia was also prevalent in disorders such as NMD, TRD or OHS, which are
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50 commonly considered as non-inflammatory.
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56 Among the mechanisms evoking anaemia in CRF, malnutrition probably plays a major
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58 role. Actually, haematocrit has been found to be positively correlated with BMI (5).
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60 Correspondingly, in our study patients with OD and anaemia presented with lower BMI and

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3 total protein. However, neither BMI nor total protein was associated with anaemia in RD.
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5 This was confirmed in an additional analysis excluding OHS patients (data not shown).
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7 Malnutrition, especially vitamin deficiency, is however also reflected in measures beyond
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9 BMI and total protein. It occurs frequently in NMD, such as duchenne muscular dystrophia
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11 (24), due to dysphagia and/or dyspnoea and needs to be treated by gastrostomy tube feeding
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13 (25). Similarly, in anorexia nervosa, anaemia is common, and weight loss is associated with
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15 the disappearance of hematopoietic cells and an increased fat fraction in bone marrow (26).
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17 This may be associated with lower leukocyte numbers, as in anaemic patients with RD in our
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19 study. Anaemia is also frequent in the elderly and often of unknown cause (27).
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21 Correspondingly, age was also associated with lower haemoglobin in the present study, in line
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23 with previous results in COPD (5;6). Taken together, these data suggest that anaemia in these
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25 patients is of multifactorial origin.
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32 Dyspnoea is a known symptom in anaemia. We found a higher PaO₂ and pH, and a
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34 lower PaCO₂ in anaemic patients. Among these, PaO₂ and pH were independently associated
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36 with anaemia in OD, both of them possibly based on hyperventilation. Anaemia in COPD is
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38 linked to morbidity and mortality (5;6), and anaemic patients with COPD and respiratory
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40 failure might benefit from blood transfusion (28;29). In patients with heart failure exercise
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42 capacity improves after rising haemoglobin level (30). Thus, in addition to worsening tissue
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44 oxygenation, anaemia could increase the work of breathing and thereby contribute to the
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46 impairment of the nutritional status and prognosis in CRF.
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52 Our study is limited by its partially retrospective design, which hampers the causative
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54 interpretation. **Moreover, there might have been potential confounders of anaemia which**
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56 **became evident only at a later time and were not detected in our retrospective data**
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58 **analysis.** Not only patients with stable disease were included. It appeared, however, that acute
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60 infection was not associated with a higher prevalence of anaemia. Another limitation is the
lack of a control group. An age-matched control cohort is difficult to define and was not

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3 available in the present setting. Finally, within the spectrum of restrictive diseases the number
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5 of patients was low which affects the accuracy of the prevalence estimates in the subgroups.
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9 In summary, this study systematically examined the prevalence of anaemia in a large
10 cohort of patients with CRF and different types of underlying respiratory disorder. Our data
11 indicate that anaemia is nearly as prevalent in restrictive diseases as in COPD. These results
12 underline the assumption that in the development of severe respiratory disorder anaemia is a
13 regular phenomenon of multifactorial origin and not only due to systemic inflammation.
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17 **Practical clinicians should be aware of the high prevalence of anaemia and hence be**
18 **ready to screen for nutritional deficiencies and related co-morbidities in patients with**
19 **severe respiratory disease prior to the development of manifest anaemia. The clinical**
20 **impact of anaemia in the different chronic respiratory diseases and effect of a correction**
21 **of haemoglobin on clinical outcomes should be addressed in future prospective trials.**
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AUTHORS CONTRIBUTIONS

F.K. participated in study design, statistical evaluation and data interpretation and wrote the manuscript. C.M. and A.T. collected the data, helped in statistical evaluation and data interpretation. R.A.J. helped in statistical evaluation of the data, their interpretation and participated in writing the manuscript. D.H. participated in study design and critical revision of the manuscript. C.P. helped in critical revision of the manuscript and data interpretation. M.P. participated in data interpretation and the initiation of the study, enabled the realization and supervised its performance. S.B. initiated the study, helped writing the manuscript and participated in statistical evaluation, study design and data interpretation.

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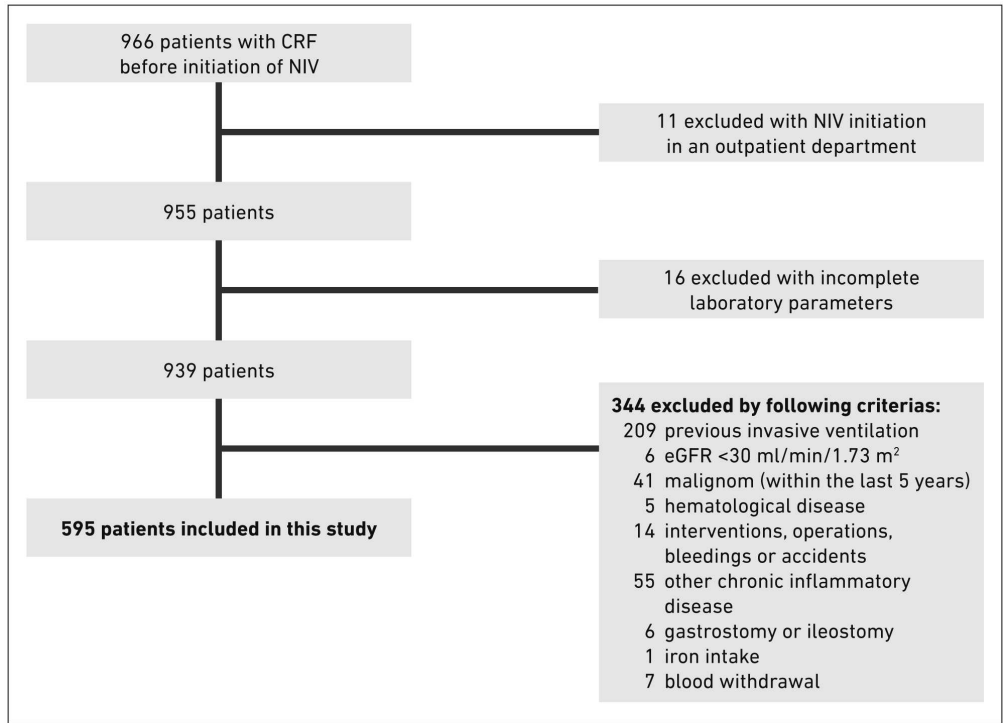


Figure 1. Selection of study population.
Definition of abbreviations: NIV=non-invasive ventilation; eGFR=estimated glomerular filtration rate.

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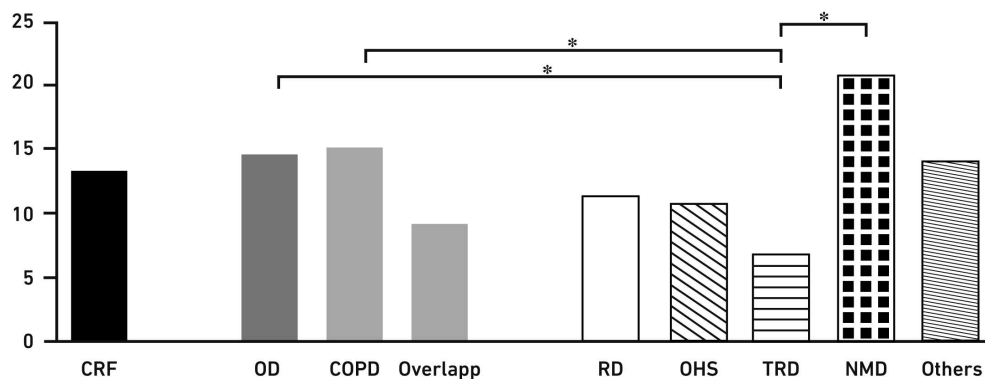


Figure 2. Prevalence of anaemia in different chronic respiratory diseases (n=595). The prevalence of anaemia in patients with OD (n=326) was not different compared to RD (n=269) (p=0.276). In patients with TRD (n=80) there was a significantly lower prevalence of anaemia in comparison to OD (n=326) (*p=0.043), COPD (n=304) (*p=0.041) and NMD (n=48) (*p=0.021). Definition of abbreviations: CRF=chronic respiratory failure; OD=obstructive disease; RD=restrictive diseases; COPD=chronic obstructive pulmonary diseases; OHS=obesity-hypoventilation-syndrome; NMR=neuromuscular diseases; TRD=thoracic-restrictive diseases.

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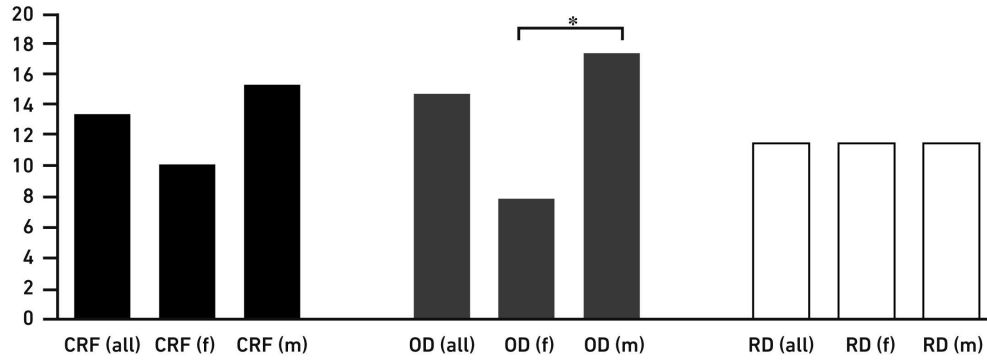


Figure 3. Prevalence of anaemia in patients with CRF (n=595), OD (n=326) and RD (n=269), stratified according to sex. The prevalence of anaemia was significant higher in males with OD (n=41) compared to females with OD (n=7) (*p=0.035).
 Definition of abbreviations: CRF=chronic respiratory failure; OD=obstructive disease; RD=restrictive diseases; f=female; m=male.

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TABLES

Table 1. Patients' characteristics (n=595) with either obstructive or restrictive diseases.

Variable	N	Obstructive disease (OD)	N	Restrictive Disease (RD)	P value [§]
N (% of total group)		326 (54.8 %)		269 (45.2 %)	
Sex (F/M)		89/237		130/139	<0.001
Age (years)	326	66.3 (59.5; 71.5)	269	60.8 (50.0; 68.4)	<0.001
BMI (kg/m ²)	324	28.0 (21.9; 33.6)	265	34.7 (25.7; 43.2)	<0.001
Previous LTOT (n/%)		149/45.7		51/19.0	<0.001
Laboratory parameters					
Haemoglobin (g/dl)	326	14.5 (13.2; 16.0)	269	14.7 (13.3; 16.4)	0.255
Haematocrit (%)	326	44.0 (40.0; 49.0)	269	45.0 (40.0; 51.0)	0.366
Leucocytes (10 ³ /ml)	326	9.3 (7.5; 11.7)	269	7.7 (6.4; 9.5)	0.000
CRP (mg/dl)	323	7.6 (4.5; 22.4)	264	5.2 (4.5; 15.7)	0.058
Creatinine (mg/dl)	326	0.9 (0.8; 1.1)	269	0.8 (0.7; 1.0)	0.001
eGFR (ml/min/1.73 m ²)	326	87.1 (69.5; 102.4)	269	91.5 (68.5; 115.2)	0.063
Total protein (g/dl)	293	6.6 (6.1; 7.1)	244	6.7 (6.2; 7.2)	0.043
Lung function parameters					
FVC (%predicted)	317	52.1 (44.0; 61.4)	255	54.1 (38.0; 67.2)	0.801
FEV ₁ (%predicted)	317	30.8 (23.1; 40.4)	255	50.0 (35.8; 64.0)	<0.001
Blood gas values without oxygen supply					
pH	182	7.42 (7.39; 7.45)	209	7.42 (7.39; 7.45)	0.842
PaO ₂ (mmHg)	182	49.0 (43.0; 55.0)	209	52.0 (46.0; 61.0)	<0.001
PaCO ₂ (mmHg)	182	53.0 (48.0; 58.0)	209	50.0 (46.0; 56.0)	0.006
BE (mmol/l)	182	7.6 (4.7; 10.2)	209	6.3 (4.2; 9.1)	0.013
Co-morbidities					
Chronic renal failure [#] (n/%)		47/14.4		44/16.4	0.568
Coronary heart disease (n/%)		52/16.0		19/7.1	0.001
Left heart failure (n/%)		56/17.2		22/8.2	0.001
Cardiac arrhythmias (n/%)		48/14.7		24/8.9	0.032
Arterial hypertension (n/%)		140/42.9		139/51.7	0.039
Diabetes mellitus (n/%)		79/24.2		66/24.5	1.000
Acute infection (n/%)		90/27.6		59/21.9	0.128

Table 2. Characteristics of anaemic versus non-anaemic patients (n=595).

Variable	Obstructive disease		P value [§]	Restrictive disease		P value [§]
	Anaemic	Non-Anemic		Anemic	Non-Anemic	
N (%)	48 (14.7 %)	278 (85.3 %)		31 (11.5 %)	238 (88.5 %)	
Sex (F/M)	7/41	82/196	0.035	15/16	115/123	1.000
Age (years)	70.40 (62.6; 73.9)	65.6 (58.6; 70.8)	0.003	65.7 (59.5; 71.4)	60.1 (49.1; 67.5)	0.008
BMI (kg/m ²)	24.4 (20.9; 29.8)	28.6 (22.5; 33.9)	0.011	33.7 (25.7; 43.4)	35.0 (25.6; 43.1)	0.813
Previous LTOT (n/%)	22/45.8	127/45.7	1.000	7/22.6	44/18.5	0.626
Laboratory parameters						
Haemoglobin (g/dl)	11.9 (10.9; 12.5)	14.8 (13.7; 16.2)	<0.001	11.5 (10.8; 12.0)	15.1 (13.7; 16.6)	<0.001
Haematocrit (%)	36.0 (33.3; 38.0)	45.0 (42.0; 50.0)	<0.001	35.0 (32.0; 37.0)	46.0 (41.0; 52.0)	<0.001
Leucocytes (10 ³ /ml)	9.4 (7.7; 11.9)	9.3 (7.5; 11.7)	0.873	6.6 (5.3; 8.4)	7.8 (6.6; 9.5)	0.006
CRP (mg/dl)	8.7 (3.5; 39.7)	7.5 (4.5; 21.7)	0.851	6.1 (4.5; 33.9)	5.2 (4.5; 15.0)	0.433
Creatinine (mg/dl)	0.9 (0.7; 1.1)	0.9 (0.8; 1.1)	0.780	0.9 (0.7; 1.0)	0.8 (0.7; 1.0)	0.284
eGFR (ml/min/1.73 m ²)	86.2 (63.8; 117.1)	87.1 (69.7; 102.0)	0.975	88.6 (57.8; 105.8)	91.8 (69.9; 116.1)	0.234
Total protein (g/dl)	6.4 (5.8; 6.7)	6.6 (6.2; 7.1)	0.012	6.3 (6.0; 7.0)	6.7 (6.3; 7.2)	0.132
Functional parameters						
VC (%predicted)	49.0 (36.4; 58.9)	53.1 (45.0; 61.8)	0.050	55.6 (41.7; 67.4)	53.9 (37.4; 67.5)	0.544
FEV ₁ (%predicted)	29.5 (22.6; 40.7)	31.0 (23.8; 40.4)	0.527	51.3 (42.8; 58.5)	49.2 (34.3; 64.1)	0.469
Blood gas values without oxygen supply						
pH	7.45 (7.40; 7.49)	7.41 (7.38; 7.44)	0.014	7.45 (7.41; 7.46)	7.41 (7.39; 7.44)	0.011
PaO ₂ (mmHg)	54.5 (46.0; 63.3)	48.0 (42.0; 55.0)	0.012	57.0 (49.0; 66.8)	52.0 (45.5; 60.0)	0.056
PaCO ₂ (mmHg)	48.5 (40.8; 56.5)	53.0 (48.0; 58.0)	0.090	48.0 (39.8; 53.8)	50.0 (46.0; 56.0)	0.057
BE (mmol/l)	7.2 (4.2; 16.5)	7.6 (4.7; 10.2)	0.951	5.9 (2.9; 10.6)	6.4 (4.3; 9.0)	0.597
Co-morbidities						
Chronic renal failure [#] (n/%)	10/20.8	37/13.3	0.183	9/29.0	35/14.7	0.066
Coronary heart disease (n/%)	14/29.2	38/13.7	0.010	5/16.1	14/5.9	0.053
Left heart failure (n/%)	6/12.5	50/18.0	0.414	3/9.7	19/8.0	0.727
Cardiac arrhythmias (n/%)	13/27.1	35/12.6	0.014	4/12.9	20/8.4	0.498
Arterial hypertension (n/%)	21/43.8	119/42.8	1.000	21/67.7	118/49.6	0.084
Diabetes mellitus (n/%)	20/41.7	59/21.2	0.003	9/29.0	57/23.9	0.513
Acute infection (n/%)	17/35.4	73/26.3	0.221	10/32.3	49/20.6	0.165
Medication						
Anticholinergic agents (n/%)	39/81.3	228/82.0	0.842	9/29.0	58/24.4	0.659
β ₂ -Sympathomimetics (n/%)	45/93.8	250/89.9	0.594	9/29.0	84/35.3	0.552
Steroids (inhalative) (n/%)	29/60.4	186/66.9	0.411	6/19.4	52/21.8	1.000
Steroids (systemic) (n/%)	31/64.6	166/59.7	0.632	4/12.9	43/18.1	0.619
Theophylline (n/%)	14/29.2	158/56.8	<0.001	5/16.1	63/26.5	0.274
ACE-blockers (n/%)	19/39.6	120/43.2	0.752	13/41.9	105/44.1	0.850
Angiotensin-II-blockers (n/%)	3/6.3	17/6.1	1.000	4/12.9	16/6.7	0.264
Beta-blockers (n/%)	6/12.5	21/7.6	0.258	10/32.3	41/17.2	0.053
Calcium-antagonists (n/%)	10/20.8	42/15.1	0.392	5/16.1	47/19.7	0.810
Digitalis (n/%)	11/22.9	54/19.4	0.561	4/12.9	33/13.9	1.000
Diuretics (n/%)	45/93.8	223/80.2	0.024	25/80.6	182/76.5	0.821

Table 3. Stepwise binary logistic multivariate regression analysis for the presence of anaemia**A. All patients with CRF**

Independent variable	Odds ratio (95% CI)	P value
Age (years)	0.954 (0.920-0.990)	0.012
pH	<0.001 (<0.001-0.006)	0.002
PaO ₂ (mmHg)	0.957 (0.927-0.987)	0.006

B. Patients with OD

Independent variable	Odds ratio (95% CI)	P value
pH	<0.001 (<0.001-0.041)	0.011
PaO ₂ (mmHg)	0.931 (0.879-0.985)	0.013

C. Patients with RD

Independent variable	Odds ratio (95% CI)	P value
Leukocyte number (10 ³ /μl)	1.306 (1.019-1.674)	0.035
PaO ₂ (mmHg)	<0.001 (0.001-0.098)	0.020