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Intensive Care Needs of Chronic Pulmonary Disorders in ICU- Rate of Mortality and Health Care Quality of Life

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is characterized by expiratory airflow limitation that is not fully reversible. Acute respiratory failure, altered mental status, and hemodynamic instability associated with acute exacerbations of COPD are commonly encountered and require careful management in the intensive care unit (ICU). Noninvasive and invasive ventilator support in conjunction with pharmacotherapy can be lifesaving, although mortality remains high.

Aim: To investigate the mortality rate, characteristics and health-related quality of life of COPD patients admitted to Sri Shankaracharya Institute of medical sciences ICU and how the decision is made whether to use invasive or non-invasive intensive treatment of the newly admitted COPD patient in need of ventilator support.

Material and Methods: 70 patients admitted to ICU, Sri Shankaracharya Institute of medical sciences were included in the study and their detailed data, including Health-Related Quality of Life (HRQL) was assessed at the time of discharge, 3 months and 6 months post-discharge. A questionnaire was distributed to concerned ICUs personnel to define decisive factors in making the choice between invasive and non-invasive ventilation. The collected data and answers were analysed.

Results: 1.5-2% of all ICU admitted patients needed ventilation. The mean age of patients was 68 years and all were severely ill on admission, with high respiratory rates. There were more men than women. The short- and long term mortality was high despite intensive care treatment. The majority of patients were treated with Non-Invasive Ventilation (NIV) with a short hospital stay.

NIV seems to be preferable to invasive ventilation at admission for short and long term benefits. The health-related quality of life of COPD patients after treatment in ICUs is lower than in the general population. However, it does not decline between 3 and 6 months after ICU discharge. At the end of 6 months, the HRQL is quite similar to that of COPD patients not treated on the ICU.

Conclusions: Patients admitted to ICU for COPD are severely ill and have long term mortality despite ventilation and intensive care. NIV should be the first treatment modality after ICU admission and has short and long term benefits. Also, NIV doesn't increase mortality if failed. Health-related quality of life post-treatment is lower in such patients than the general population but similar to COPD patients not treated in ICU at 6 months post-discharge.

Key Words: COPD, HRQL, ICU, Mortality, Ventilation

INTRODUCTION

Chronic obstructive pulmonary disease is a relatively new entity in the field of medicine introduced in 1965[1] and is defined as a preventable and treatable disease with some significant extrapulmonary effects contributing to the severity in patients. The pulmonary component of the entity is distinguished by the irreversible and progressive limitation in airflow. This airflow inhibition is consociated with an abnormal inflammatory response of the lung to noxious particles or gases.[2] Main etiological factor is smoking.[2]

Several measurements are performed for COPD where most reliable is vital capacity either forced (FVC) or not forced (VC), or forced in one second Forced Expiratory Volume 1 (FEV1). A further spirometry measurement undergoing a renaissance is the inspiratory capacity (IC) i.e. the maximum volume of air that can be inspired from the

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end of quiet expiration [functional residual capacity (FRC) to total lung capacity (TLC)].[3] Lung volumes, in the majority of patients, do not provide much additional information.[4] COPD is not a stable disease. Patients can experience a sudden deterioration in their breathing, so-called "Acute Exacerbation of COPD" is an event in the natural course of disease characterised by a change in patient's baseline dyspnoea, cough, and/or sputum that is beyond normal day-to-day variations is acute in onset and may warrant a change in regular medication in COPD.[2] The treatment includes oxygen, bronchodilating agents, steroids, antibiotics, mucolytic agents, non-invasive and invasive ventilation, and in ICU care.[5]

Prevalence of COPD in the world is between 4 and 10 %.[6] Airflow limitation explains less than 10-25 % of the impact on the patient's quality of life.[7] Female smokers are more susceptible to smoke[8] and show an accelerated decline in FEV1.[9] Nutritional status of patients admitted to hospital with AECOPD is important for long-term prognosis. Low body mass index (BMI) is a marker of poor prognosis 38 and has an impact on long-term survival after the hospital.[10] Patients with low BMI are more difficult to wean from ventilator support compared to patients with normal weight.[11] Also, weight gain is a predictor of longer survival.[12]

Not all smokers develop COPD. It is believed to result from gene-environment interaction. Severe hereditary deficiency of alfa1-antitrypsin can lead to COPD.[2] At present, 192 COPD related genes are known, however, specific gene relation remain poorly understood FEV1 is used to define and stage COPD. However, the predictive value of FEV1 for mortality is weak when it is higher than 50 % of predicted value.[13,14]

Other systems have been developed that assess respiratory and systemic expressions of COPD to categorise and predict outcome including

- BODE index (BMI, Degree of airflow Obstruction, Dyspnoea and Exercise capacity).
- ADO index (Age, Dyspnoea, Obstruction).[15]
- DOSE index (Dyspnoea, Obstruction, Smoking status, and Exacerbation frequency).[16]

These indices can predict mortality, health status, hospital admissions, exacerbations and respiratory failure.[15] In 2006, it was stated that there are no reliable biomarkers for COPD.[17] However, elevated CRP, fibrinogen and leukocyte count can predict exacerbation in stable cases. Serum myeloperoxidase is related to a rapid decline in lung function.[18]

Pathophysiology of COPD affects several structures in lung involving airways, parenchyma and pulmonary vasculature. Four anatomic lesions predominate; emphysema, small airway remodelling, vascular remodelling associated with pulmonary hypertension, and excessive large airway mucus secretion (chronic bronchitis). Inhaled smoke leads to disruption of epithelial layer in airways leading to inflammation.[19] Affected airways cannot repair this damage. The clear function is reduced leading to impaired mucus clearance. Epithelial layer in airways is irritated by chronic inflammation leading to a persistent cough. Blood vessels in lungs are also affected leading to a thicker intimal layer. In later stages, there is reduced gas exchange and a larger dead space. This also affects elastic properties of the lung resulting in decreased elastic recoil and a change in chest wall mechanics to provide sufficient lung ventilation.[2] Air exchange occurs at higher lung volumes leading to an increase in chest size and FVC 1. A decline in FEV1 is closely related to the progress of emphysema, and the dynamic collapse of central airways is related to this reduction in FEV1. These changes contribute to three main symptoms of COPD; breathlessness, cough, and sputum production.[19]

COPD pathophysiology is also described in terms of a pathogenic triad of oxidative stress, protease-antiprotease imbalance, and inflammation which is believed to be influenced by genes and environmental factors.[20]

Pharmacologic therapy is used to prevent and control COPD symptoms, reduce the frequency and severity of exacerbations, improve health status and exercise tolerance. None of the existing medication has shown to modify long-term decline in lung function. Long term oxygen therapy for patients with hypoxia at rest increases survival time.[2] Drug therapy includes bronchodilators (long-acting ß-2stimulators, anticholinergics and methylxanthines) and inhalation of glucocorticosteroids infrequent exacerbations, though long term use should be avoided.

NIV is now used as first-line treatment in AECOPD and is indicated in moderate to severe dyspnoea with use of accessory muscles and paradoxical abdominal motion, moderate to severe acidosis (pH < 7.35) and/or hypercapnia (PaCO2, >6.0 kPa, >45 mm Hg), respiratory rate > 25 breaths/min. Indications for invasive ventilation are intolerance to NIV/ NIV failure, severe dyspnoea, respiratory rate >35 breaths/ min, life-threatening hypoxaemia, severe acidosis (pH <7.25) and/or hypercapnia (PaCO2 >8.0 kPa, >60 mm Hg), respiratory arrest, worsening of mental status despite optimal therapy, cardiovascular complications (hypotension, shock). NIV failure is often considered as the need for endotracheal intubation or death without endotracheal intubation.[21]

Prognosis of advanced COPD is very difficult to predict 126. Planning of ICU is important as it reduces stress, anxiety and depression. The in-hospital mortality rate in patients where ICU treatment is denied/ withdrawn is very high, between 80.3 to 95.4 %. Heterogeneity makes mortality prediction difficult. Health-related quality of life is an important predictor of survival.[22] Clinicians differ markedly in their decisions to admit and use of a type of ventilation in their prediction

of survival of identical patients.[23] With AECOPD admitted to ICU, premorbid variables have not shown to be predictive for intermediate survival. These include age; functional capacity; quality-of-life; male sex; oral steroids; spirometry; previous hospital or ICU admissions; body, BMI; smoking status; and long-term oxygen therapy. In milder COPD, cardiovascular diseases as an added comorbidity are more common causes of death than respiratory failure.[24]

The present prospective clinical trial was undertaken to investigate, in ICU admitted COPD patients, mortality rate, health-related quality of life and how the decision is made whether to use invasive or non-invasive ventilation of newly admitted COPD patient in need of ventilatory support.

MATERIALS AND METHODS

The present prospective clinical trial was undertaken at Department of Pulmonary Medicine, Sri Shankaracharya Institute of medical sciences and included 70 patients which were decided to be admitted in ICU for COPD/ AECOPD, in October 2019 and November 2019. The mean age of patients was 68 years with an age range of 57 years to 78 years. Out of 70 included patients, only 2 were females. Patients <30 years of age were excluded to minimize the inclusion of misclassified asthma. Also, patients with an associated medical history and systemic diseases such as diabetes, hypertension, and renal diseases were excluded to judge appropriate mortality rate. Ethical clearance was obtained from the Institutional Ethical Committee and informed consent was obtained from patients or attendants (in case the patient was not in a condition to give consent). Eligible patients had received mechanical ventilation ad ICU stay for more than 24 hours. Doctors, nurses and assistant nurses in ICU answered a questionnaire about factors having a possible influence on the decision to use immediate invasive ventilation in AECOPD patients. Patients were also analysed according to their health-related quality of life at the time of discharge, 3 months and 6 months after discharge from the ICU. The results were compared to HRQL of two reference groups from the general population, an age- and sex-adjusted reference population, and a reference group with COPD. Information regarding death was obtained from the ICU personnel.

Following measurements were recorded:

- Admissions in the ICU for patients with COPD
- Age in years
- Crude mortality risk within 90 days after admission to ICU
- Discharge time
- Gender: Female/ Male
- Length of stay on the ICU. Hours, days
- Vital status. Alive/ Dead
- Acute respiratory failure assessed as PaCO2 > 7 kPa or PaO2/ FiO2 < 26.7 kPa
- Arterial PaCO2. kPa
- Arterial PaO2. kPa
- Arterial PaO2/FiO2 ratio. kPa
- Arterial acid-base balance. pH
- Body Mass Index. Weight in kilos/ (length in metres) ^{2}
- Mode of ventilation: Non-invasive/ Invasive ventilation
- Time with invasive ventilation. Hours
- Time with non-invasive ventilation (NIV) Hours
- Length of stay, ICU. Days
- NIV failure rate. Intubation after initiation of NIV.
- Respiratory rate. Breaths per minute.

A questionnaire given to ICU personnel was based on a few items, it was based on what was relevant when choosing between non-invasive ventilation and invasive ventilation. The instructions to the respondents were as follows: to what extent is the decision to intubate the patient immediately after arrival on the ICU influenced by the following statements and were graded as

1. No or little significance.
2. Quite important.
3. Of great importance.
4. Most important.

The questionnaire was based on following parameters at the time of ICU admission which could affect the mode of ventilation and were separately solved by In-charge Doctor, Nurse and assistant nurse in ICU

- Severe dyspnoea
- Severe cough
- Copious secretions
- Doctor in- charge of the patient in the ICU
- Nurse in charge
- Assistant nurse in charge
- Gender
- Age
- Restlessness.
- State of consciousness
- Bodyweight: Thin, Normal weight, Obese
- Respiratory rate
- pH value in the arterial blood gas analysis
- PaCO2 value in the arterial blood gas analysis
- PaO2 value in the arterial blood gas analysis
- Base excess value in the arterial blood gas analysis
- Standard bicarbonate value in the arterial blood gas analysis
- Patient's activities of daily living before being admitted to the ICU
- The patient can inhale the nebulised medication
- Fever
- Elevated CRP
- Result of the patient's latest spirometry
- Personnel knowledge about current COPD guidelines

Also, Health-related quality of life (HRQL) was assessed I term of following variables I accordance with Short Form 36 Health Survey (SF-36).

The SF-36[25] was developed to investigate generic health concepts not specific to any age, disease or treatment group. It investigates physical, social and emotional functioning it has 36 questions and generates a health profile of eight sub-scale scores:

- Physical functioning (PF).
- Role limitations due to physical problems (RP).
- Bodily pain (BP).
- General health (GH).
- Vitality (VT).
- Social functioning (SF).
- Role limitations due to emotional problems (RE).
- Mental health (MH).

The scores on all sub-scales are transformed to a scale from 0 (worst score) to 100 (best score).

There are also two summary measures:

- Physical Component Summary Measure (PCS) consisting of values from PF (10 items); RP (4 items); BP (2 items); and GH (5 items).
- Mental Component Summary Measure (MCS) consisting of values from: VT (4 items); SF (2 items); RE (3 items); and MH (5 items).

The patient also answers two questions:

a. Compared to one year ago how would you rate your general health now?
b. In general, would you say your health is excellent, very good, good, fair or poor?

The collected data were statistically analysed

RESULTS

A total number of 70 patients that were admitted to ICU from Department of Pulmonary Medicine, Sri Shankracharya Institute of Medical Sciences due to COPD/ AECOPD I the month of October 2019 were included in this prospective clinical trial. Out of the included 70 patients, 68 were males and only two were females (Figure 1), the difference in gender variable was seen due to less prevalence of smoking among females in India. The mean age of patients was 68 years. The characteristics of patients are depicted in (Table 1: Demographic Characteristics of the study Patients).

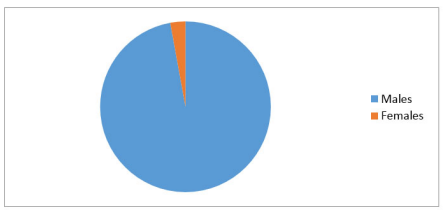


Figure 1: Gender Distribution.

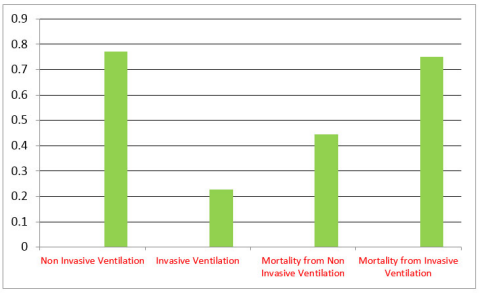
Table 1: Demographic Characteristics of the Study Patients

	Characteristics	COPD Patients (n=70)
1.	Age (mean)	68 years
2.	Gender	
a.	Male	68
b.	Female	2
3.	Body mass index, kg.m^{-2} (<18.5)	48
4.	Symptoms of anxiety at baseline	66
5.	Symptoms of depression at baseline	28
6.	Time since COPD diagnosis, months (range)	9-240
7.	Regular general practitioner visits	10
8.	Regular pulmonologist visits	48

In this study, 70 COPD patients admitted to ICUs in the institute were stratified according to the mode of ventilation. Out of these, nine patients (12.85 %) were intubated and invasively ventilated and 61 patients (87.14%) began with non-invasive ventilation. NIV failed in 7 patients (11.47 %). The mortality was high for both the groups, with a 6 months survival of 55.56% in the NIV group and 22.22% in the invasive ventilation group (Table 2 Ventilation and Mortality of study subjects in ICU) (Graph 1). Non-invasive ventilation was associated with increased survival, whereas increased age was associated with decreased survival. The mortality in the NIV fail group was not significantly different from survival in the invasive ventilation group.

Table 2: Ventilation and Mortality of study subjects in ICU

S. No	Parameter	Percentage
1.	Ventilation	
a.	Non Invasive Ventilation	77.14% (n= 54)
b.	Invasive Ventilation	22.85% (n= 16)
2.	Mortality (6 months post-discharge)	
a.	Non Invasive Ventilation	44.44% (n=24)
b.	Invasive Ventilation	75% (n=12)



Graph 1: Ventilation and Mortality in ICU.

Thereafter a questionnaire was given to ICU personnel with different professions (doctors, nurses and assistant nurses) in the ICU to study the relative importance of various factors that possibly influence the decision to use invasive ventilation immediately. The two groups did not differ in arterial blood gases, acid-base status or respiratory rate. The NIV group was significantly younger and had a lower BMI than patients that were intubated immediately. BMI was the only variable remaining associated with increased risk for intubation. The usage of NIV was not correlated to the presence of acidosis. Eighty-one cent of the patients with pH<7.35 were treated with NIV, and 78 % of the patients with severe acidosis pH<7.25 received NIV. Non-patient-related factors including a physician in charge, presence of guidelines, ICU workload were also deemed important for the decision to intubate immediately. There were small differences between professions in the ranking of the five most important factors in the questionnaire.

Table 3: Factors affecting Mode of Ventilation in ICU

Factors	High Weight By Pulmonologists	High Weight By ICU Nurses
BMI	+	+
pH < 7.35	+	+
severe dyspnoea	-	+
cough	-	-
ICU workload	-	-
Age	-	-
Restlessness	-	+
State of consciousness	+	+
Previous ICU history	+	-
Ability to inhale the nebulised medication	+	+
History of Corticosteroid Treatment	+	-
Fever	-	-
Spirometry Results	+	+
Elevated CRP	+	+
Personnel Knowledge about COPD Guidelines	+	+

Health-related quality of life (HRQL) in COPD patients treated on the ICU was also evaluated. Their results were compared to the HRQL of two other groups, a reference group with COPD (COPD-reference), and reference group without COPD from the general population (Non-COPD reference). HRQL was measured using the short form 36 Health Survey (SF- 36) questionnaires.

HRQL in the COPD-ICU group was always markedly lower compared to the Non-COPD reference group from the general population. In COPD-ICU patients where a complete follow-up was done, changes in HRQL over time were minor and did not decline further during 3 to 6 months after discharge. The SF-36 results in the COPD-ICU group were not statistically different from the COPD reference group. Patients that died during the study had a poorer HRQL. PF and SF scores were lower in this group of patients as compared to the other two references. HRQL in COPD patients 6 months after discharge from the ICU was quite similar to that of COPD patients not treated on the ICU.

DISCUSSION

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of mortality in the world and the US. COPD is a progressive disease and is associated with increased frequency and severity of exacerbations. Clinical manifestations of acute exacerbations are highly variable ranging from being a mild event requiring only outpatient treatment to being a life-threatening episode needing mechanical ventilatory support.

Mechanical ventilation, either invasive or non-invasive, is a life-saving measure in managing acute respiratory failure due to an acute exacerbation of COPD. However mechanical ventilation can be associated with significant morbidity and mortality. A good understanding of the underlying pathophysiologic mechanisms in acute exacerbation of COPD is very important in optimizing ventilatory strategies.

In one large multicenter cohort of patients admitted to 42 intensive care units across the US the frequency of mechanical ventilation was 47%.[26] This study was by the present study where all the patients among study population required mechanical ventilatory support.

In many cases of acute respiratory failure due to COPD, NIV can give the same benefits as the standard intubation and mechanical ventilation without the complications that are usually associated with the latter. As a result, patients treated with NIV have shorter stay, lower morbidity and incur lesser costs in a study. A Cochrane Database systematic review by Ram et al in 2004 concluded that NIV improved mortality, decreased the need for intubation and reduced the treatment failures has also been suggested in the present study where 81.74 % patients started with NIV and 67.57% survival rate was seen at the end of 6 months follow up.

In a previous study in literature, among all the ICU admissions in 2013, 8.53% ICU admissions were due to COPD.[27] This was in agreement with the present trial where the all the patients required Intensive care, ICU admission is attributed to reducing the risk of developing COPD and its exacerbation, the control of disease severity, including the control of risk factors such as smoking and exposure to air pollution

and occupational dust. ICU admission for severe life-threatening diseases such as COPD is beneficial in terms of assigning the better medical resources and treatment planning. Also in another study by Crisafulli E et al in 2018, it was concluded that severe AECOPD patients requiring hospitalization. Some treatments such as steroids and NIV (in patients admitted with a hypercapnic acute respiratory failure and respiratory acidosis) are supported by strong evidence of their efficacy.[28]

Health-related quality of life after ICU care is an important aspect to consider in severe illness such as COPD. All personnel involved in the care of patients with severe diseases in need of intensive care are interested in getting feedback about the recovery and subsequent life of their patients. It is also important to study HRQL to avoid the notion that ICU treatment of

COPD patients are futile and a burden for the patient and society. The study of HRQL is challenging as the methods used are quite new, HRQL in COPD patients is dependent on several factors such as dyspnoea, depression, anxiety and exercise tolerance. Clinically important differences in HRQL scores are not unanimously defined, there are various methods used. Nevertheless, it is important to describe the patient's situation after ICU care using objective measurements not restricted to just age, disease or treatment group.

The findings in the present study were different from what could be generally expected. COPD is a chronic and progressive disease; it could be expected to see a decline in HRQL over time in these patients. However, this was not the case; HRQL in this group of patients was low compared to the general population but did not decline further during 3 month period after discharge. After 6 months it was similar to the HRQL of COPD patients not treated in the ICU. Patients that died during the study had a poorer HRQL. In a study by Negi H et al[29] where they used a validated Hindi version of St George's Respiratory Questionnaire (SGRQ) was administered for self-assessment when the patients were clinically stable, authors concluded that HRQL of COPD patients was significantly impaired across stages. Marked impairment of HRQL was found even in patients with mild disease.[30] The results of these studies were not following the present study where HRQL improved over some time.

CONCLUSION

In the present study, ICU admitted patients for COPD and respiratory failure is high in short- as well as long-term despite intensive care provided in ICU. A first preferred choice for COPD patients admitted to ICU with respiratory failure is Non-invasive ventilation which showed better long-term outcome compared to immediate invasive ventilation in the present study. Various factors influenced the choice between NIV and invasive ventilation of patients with an acute COPD/AECOPD most important being body weight. The health-related quality-of-life (HRQL) of COPD patients admitted to the ICU is lower than in the general population, but does not decline further during the period 3 to 6 months after discharge. HRQL in COPD patients 6 months after discharge from the ICU was quite similar to that of COPD patients not treated on the ICU. However, the present study has few limitations as it did not follow the subjects over a longer period; hence they have difficulty in detecting rare or late adverse effects of treatment.

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REFERENCES

1. Pawar MRS and Abhang AS. Consumption of GSH with the Increase in Oxidative Stress in Chronic Obstructive Pulmonary Disease (COPD) Patients. Int. J. Cur. Res. Rev. 2017;9:25-9.
2. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007;176:532-55.
3. Pierce R. Spirometry: an essential clinical measurement. Aust Fam Physician 2005;34:535-9.
4. Ruppel GL. What is the clinical value of lung volumes? Respir Care 2012; 57:26-35.
5. Soto FJ, Varkey B. Evidence-based approach to acute exacerbations of COPD. Curr Opin Pulm Med 2003;9:117-24.
6. Lindberg A, Jonsson AC, Ronmark E, Lundgren R, Larsson LG, Lundback B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to doctor's diagnosis, symptoms, age, gender, and smoking habits. Respiration 2005;72:471-9.
7. Han MK, Agusti A, Calverley PM, Celli BR, Criner G, Curtis JL, Fabbri LM, Goldin JG, Jones PW, Macnee W, Make BJ, Rabe KF, Rennard SI, Sciurba FC, Silverman EK, Vestbo J, Washko GR, Wouters EF, Martinez FJ. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010; 182: 598-604.
8. Silverman EK, Weiss ST, Drazen JM, Chapman HA, Carey V, Campbell EJ, Denish P, Silverman RA, Celedon JC, Reilly JJ, Ginns LC, Speizer FE. Gender-related differences in severe, early-onset chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162:2152-8.
9. Gan WQ, Man SF, Postma DS, Camp P, Sin DD. Female smokers beyond the perimenopausal period are at increased risk of

chronic obstructive pulmonary disease: a systematic review and meta-analysis. Respir Res 2006;7:52.
10. Hallin R, Gudmundsson G, Suppli Ulrik C, Nieminen MM, Gislason T, Lindberg E, Brondum E, Aine T, Bakke P, Janson C. Nutritional status and long-term mortality in hospitalised patients with chronic obstructive pulmonary disease (COPD). Respir Med 2007;101:1954-60.
11. Li-Dong S, Chang-Sheng G, Zi-Yu Z. Explore the influence of BMI in the optimal time of weaning from sequential mechanical ventilation for severe chronic obstructive pulmonary disease. BMC Emerg Med 2013;13 Suppl 1: S1.
12. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1791-7.
13. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PM, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palange P, Parr D, Pistolesi M, Rennard SI, Rutten-van Molken MP, Stockley R, Sullivan SD, Wedzicha JA, Wouters EF. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31:416-69.
14. Celli BR. Predictors of mortality in COPD. Respir Med 2010;104:773-9.
15. Puhan MA, Garcia-Aymerich J, Frey M, Riet G, Anto JM, Agusti AG, Gomez FP, Rodriguez-Roisin R, Moons KG, Kessels AG, Held U. Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. Lancet 2009;374:704-11.
16. Jones RC, Donaldson GC, Chavannes NH, Kida K, Dickson-Spillmann M, Harding S, Wedzicha JA, Price D, Hyland ME. Derivation and validation of a composite index of severity in chronic obstructive pulmonary disease: the DOSE Index. Am J Respi Crit Care Med 2009;180:1189-95.
17. Franciosi LG, Page CP, Celli BR, Cazzola M, Walker MJ, Danhof M, Rabe KF, Della Pasqua OE. Markers of exacerbation severity in chronic obstructive pulmonary disease. Respir Res 2006;7:74.
18. Park HY, Man SF, Tashkin D, Wise RA, Connett JE, Anthonisen NA, Sin DD. The relation of serum myeloperoxidase to disease progression and mortality in patients with chronic obstructive pulmonary disease (COPD). PLoS One 2013;8:61315.
19. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 2004;364:709-21.
20. Fischer BM, Pavlisko E, Voynow JA. Pathogenic triad in COPD: oxidative stress, protease-antiprotease imbalance, and inflammation. Int J Chron Obstruct Pulmon Dis 2011;6:413-21.
21. Confalonieri M, Garuti G, Cattaruzza MS, Osborn JF, Antonelli M, Conti G, Kodric M, Resta O, Marchese S, Gregoretti C, Rossi A. A chart of failure risk for noninvasive ventilation in patients with COPD exacerbation. Eur Respir J 2005;25:348-55.
22. Celli BR, Cote CG, Lareau SC, Meek PM. Predictors of Survival in COPD: more than just the FEV1. Respir Med 2008;102:27-35.
23. Wildman MJ, O'Dea J, Kostopoulou O, Tindall M, Walia S, Khan Z. Variation in intubation decisions for patients with chronic obstructive pulmonary disease in one critical care network. Qjm 2003;96:583-91.
24. Alexander V, Pajanivel R, Menon KS, Prasath A. Prevalence of cardiac comorbidities and its relation to severity staging of chronic obstructive pulmonary disease. Int. J. Cur. Res. Rev. 2015;7:27-33.
25. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83.
26. Seneff MG, Wagner DP, Wagner RP, et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA. 1995;274:1852–7
27. Liao KM, Chen YC, Cheng KC, Wang JJ, Ho CH. Trends in intensive care unit admissions of COPD patients from 2003 to 2013 in Taiwan. Int J Chron Obstruct Pulmon Dis 2018;13:2007-12.
28. Crisafulli E, Ielpo A, Barbeta E, et al. Clinical variables predicting the risk of a hospital stay for longer than 7 days in patients with severe acute exacerbations of chronic obstructive pulmonary disease: a prospective study. Respir Res. 2018;13:36.
29. Negi H, Sarkar M, Raval AD, Pandey K, Das P. Health-related quality of life in patients with chronic obstructive pulmonary disease in North India. J Postgrad Med 2014;60:7-11.
30. Wacker ME, Jorres RA, Karch A, et al. Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities. BMC Pulm Med 2016;16:70.