Twenty years of changes in the disease assessment method of the Global Initiative for Chronic Obstructive Lung Disease

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Abstract

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has been changing for nearly 20 years. GOLD has moved from single assessment using spirometry to a more comprehensive assessment of chronic obstructive pulmonary disease using spirometry, symptoms and exacerbation history. And subsequently, a new assessment system for chronic obstructive pulmonary disease separated spirometric grades from the old assessment system, and classified patients only according to their symptoms and history of exacerbation. The distribution, clinical characteristics, treatment, and prognosis of the new subgroups were different from the old ones. In this review, we will present a brief profile of changes made to the disease assessment method of GOLD, based on the relevant existing literature.

Keywords: Chronic obstructive pulmonary disease; Global Initiative for Chronic Obstructive Lung Disease; Disease assessment method

Introduction

The first version of the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), providing guidance for standardized diagnosis and treatment of chronic obstructive pulmonary disease (COPD), was released in 2001. GOLD 0 was defined as a high-risk period of COPD and included in the spirometric grading system. GOLD undergoes major revisions every 4 to 5 years and is updated every year. The most significant changes to GOLD have been related to the COPD disease assessment method. These changes were made in 2006, 2011, and 2017.

In 2006, GOLD updated the definition of COPD, evaluation by spirometry, and pathogenesis and treatment strategy of COPD; and classified COPD into four levels according to pulmonary function (GOLD I–GOLD IV).

In 2011, GOLD significantly updated the assessment method and management of COPD. In addition to the spirometric grading system, symptoms and exacerbation history were included in the comprehensive assessment.

GOLD 2017 updated the COPD definition, comprehensive assessment tools, treatment, and other aspects of COPD, resulting in more options for individualized treatment. The assessment system for COPD was once again revised, leading to removal of the spirometric grades from the updated assessment system. The updated assessment system classified patients according to their symptoms and exacerbation history exclusively.

GOLD 2018 retained the assessment tool of GOLD 2017, but history of exacerbation was modified to moderate (patient treated with short-acting bronchodilators plus antibiotics and/or oral corticosteroids), or severe (patient required hospitalization or visits to the emergency room) exacerbations. Severe exacerbations also included acute respiratory failure.

In the GOLD 2019 revision, initial treatment (based on ABCD) was separated from follow-up treatment (based on the patient's major treatable trait[s] and the currently used drugs). In addition, blood eosinophil count was introduced as a biomarker for estimating the efficacy of inhaled corticosteroids (ICSs) for the prevention of exacerbations.

In the GOLD 2020 revision, the disease assessment method remained the same. The key changes included: follow-up of non-pharmacologic treatments, factors to consider for

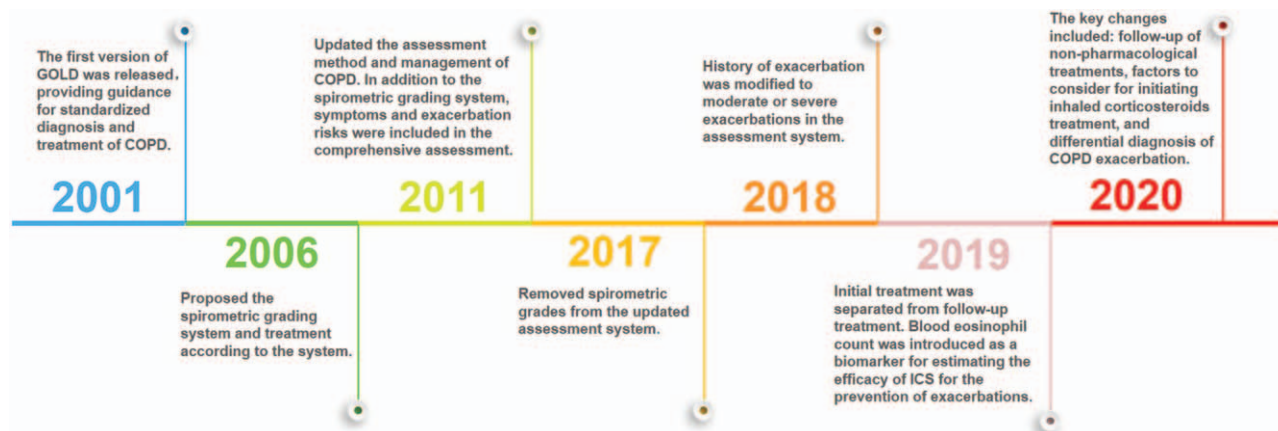| Access this article online	
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Figure 1: Twenty years of changes in GOLD. GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; COPD: Chronic obstructive pulmonary disease; ICS: Inhaled corticosteroids.
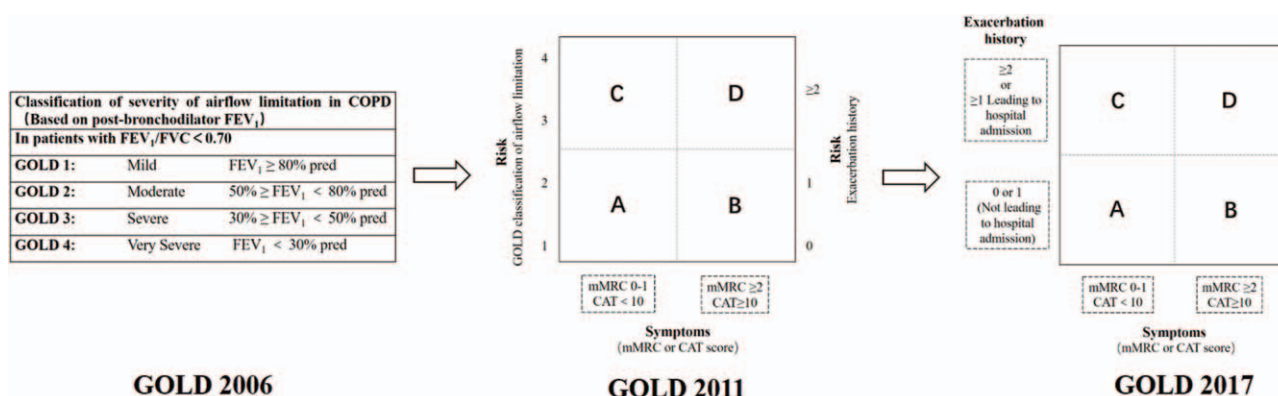

Figure 2: Key changes in the disease assessment method of GOLD. GOLD: Global Initiative for Chronic Obstructive Pulmonary Disease; COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in the first second; FVC: Forced vital capacity; Pred: Predicted; mMRC: Modified Medical Research Council dyspnea scale; CAT: Chronic Obstructive Pulmonary Disease Assessment Test.

initiating ICSs treatment, and differential diagnosis of COPD exacerbation.[1]

Twenty years of changes in GOLD are showed in Figure 1 and key changes in the disease assessment method are showed in Figure 2. The updates in GOLD changed COPD from a one-size-fits-all approach to personalized medicine, and improved the prognosis of COPD. In this review, we will investigate the value of the new disease assessment method in guiding treatment and prognosis.

Update of the Assessment System of COPD in GOLD

The ABCD assessment tool of the GOLD 2011 update was a major advance from the simple spirometric grading system of the earlier versions of GOLD. GOLD 2011 incorporated multi-modality assessment and symptom burden, and highlighted the importance of exacerbation prevention in the management of COPD. Evidence to support this classification system included: (1) patients with a high risk of exacerbations tend to be in GOLD categories 3 and 4 (severe or very severe airflow limitation) and can be identified quite reliably from their own history[2]; (2) higher exacerbation rates are associated with faster loss of forced expiratory volume in the first

second (FEV_1)[3] and greater worsening of health status[4]; (3) COPD Assessment Test (CAT) scores ≥ 10 are associated with significantly impaired health status.[5]

However, over time, studies found that there were some important limitations of GOLD 2011 disease assessment method: (1) The 2011 ABCD assessment tool was not superior to spirometric grades for mortality prediction or other important health outcomes[6-8]; (2) The prognosis of groups C and D was determined by two indicators: spirometry and exacerbation history. There were three subgroups. In subgroups C1 and D1, only spirometry was decreased. In subgroups C2 and D2, only exacerbation frequency was increased. In subgroups C3 and D3, spirometry was decreased and exacerbation frequency was increased. Patients had different risk characteristics according to the percentage of predicted FEV_1 value (FEV_1% pred) or the history of exacerbation.[9] The outcome of patients in group D was affected by these two indicators, which may cause confusion.[10] Population studies had shown that the subgroups C1 and D1 were the majority, and different therapies need to be used for these subgroups. (3) The results of spirometry cannot fully reflect individual clinical differences. The classification of spirometry can reflect the different severity of diseases in patients to some extent, but the clinical symptoms of

patients within each group differed substantially.[11] (4) Spirometry alone cannot accurately predict the risk of COPD. The frequency of exacerbation in patients with different spirometric grades varied greatly.[2,12,13] A previous study showed that 20% of patients with FEV$_1$% pred ≥50% had exacerbations ≥2 times in the past year, and 60% of patients with high risks of exacerbations had spirometry FEV$_1$% pred ≥50%.[14] FEV$_1$ itself has a large variability, so the use of FEV$_1$ as a predictor for risks of exacerbations or death at the individual patient level is not accurate enough.[6] The best predictor for frequent exacerbations is the exacerbation history.[2] (5) Depending on the patient's symptoms and history of exacerbations, regardless of spirometry, clinicians may in some cases prescribe initial treatment according to the refined ABCD groups.

To address these concerns, while at the same time maintaining consistency and simplicity for the practicing clinician, a new refined ABCD assessment tool was proposed in the GOLD 2017 report which separated spirometric grades from the ABCD groups. However, the combination of spirometry, symptoms, and exacerbation history remained critical for the diagnosis, prognosis, and treatment of COPD.

Changes due to the Update of the New Assessment System of COPD in GOLD

Changes in the distribution of subgroups under the new assessment system

The new assessment tool profoundly affected the distribution of patients in each group. Tudoric et al[15] analyzed data from the Phenotypes of COPD in Central and Eastern Europe (POPE) study, an international, multi-center, observational, and cross-sectional study of 3361 COPD subjects in ten countries in Central and Eastern Europe. The findings from that study indicated that 59 patients (1.8% of the entire cohort and 47.2% of group C) moved from group C to group A, and 686 patients (20.4% of the entire cohort and 35.6% of group D) moved from group D to group B, using GOLD 2017 as compared to GOLD 2016. This change was related to the reclassification of the patients in groups C and D solely on the basis of poor lung function, without the history of frequent exacerbation. Sun et al[16] stratified 1532 patients with COPD from 11 medical centers of seven provinces in China into old and new groups A to D, respectively, according to the GOLD 2011 and GOLD 2017 comprehensive assessment guidelines. The analyses revealed that 46.7% (500/1070) of patients in the high-risk groups were moved to the low-risk groups. As such, group C became the smallest group instead of group B. Cabrera López et al[17] prospectively enrolled and followed 819 patients with COPD for a mean of 5 years in Spain and the United States, and grouped these patients according to the modified Medical Research Council dyspnea questionnaire and exacerbation risks. Compared to GOLD 2015, GOLD 2017 classification significantly decreased the proportion of patients in groups C and D by half (20.5% vs. 11.2% and 24.6% vs. 12.9%), while the proportion of patients in groups A and B increased. Tan et al[18] analyzed data from the Canadian

Cohort of Obstructive Lung Disease, a population-based, non-interventional, longitudinal cohort that included 717 patients with COPD. Using the CAT score criteria and exacerbation risks, 69% of subjects previously classified as C by GOLD 2011 were reassigned to A in GOLD 2017 and 64% of subjects classified as D by GOLD 2011 were reassigned to B in GOLD 2017. On the whole, these studies clearly illustrated that the distribution of the GOLD 2017 assessment groups was different from that of GOLD 2011. More patients in the high-risk group were classified to the low-risk group according to GOLD 2017.

Clinical characteristics of the subgroups under the new assessment system

Sun et al[16] found that the new high-risk groups in GOLD 2017 demonstrated more characteristics associated with high risk of acute exacerbation and mortality than the old high-risk groups in GOLD 2011. Kobayashi et al[19] showed that patients with a high risk of exacerbation had a lower body mass index, more symptoms, used more respiratory medications, and had more severe airflow limitation than patients at low risk of exacerbation according to GOLD 2017. Tan et al[18] revealed that the mean declines in FEV$_1$ for GOLD 2017 categories B and D were significantly greater than A, after adjusting for covariate. The component of GOLD 2017 ABCD categories that was most significantly related to FEV$_1$ decline was decreased health status: CAT score ≥10. Hu et al[20] showed that subjects in groups B and D had significantly lower lung function, 6-min walk distance (6MWD), respiratory muscle strength, quality of life, and higher symptom scores and BODE index (body mass index, B; degree of air flow obstruction, O; dyspnea, D; exercise capacity, E), than subjects in group A in the comprehensive assessment according to the GOLD 2017 classification. Groups B and D may have greater disease severity. Cabrera López et al[17] found that D in the GOLD 2015 grading had a significantly higher BODE index than the rest of the grades; followed by grade B, grade C, and finally grade A. Significant changes in the GOLD 2017 classification resulted in groups D and B having similar values. BODE indexes in B and D were both significantly higher than that of group C, which in turn was higher than group A. The differences between groups B and D and groups A and C become less, thereby decreasing the value of the new assessment method.

Effect of the new assessment system on treatment

Hsieh et al[21] retrospectively analyzed patients with stable COPD in 11 participating hospitals across Taiwan, China. The pharmacologic concordance rate was 60.9% for GOLD 2011 and decreased to 44.9% for GOLD 2017. Over-treatment was found in 29.5% of patients according to GOLD 2011 and the rate increased to 46.1% when classified by the GOLD 2017. The major cause of over-treatment was unnecessary ICS, and the main cause of under-treatment was a lack of maintenance long-acting bronchodilators. Over-treatment was also observed in Cui et al's study[22] with 205 (71.9%) of the 285 patients and in Tudoric et al's study[15] with 490 (71.4%) of 686 patients who were reclassified from group D to group B treated

with ICS. Physicians should re-examine treatment patterns for patients reclassified into low-risk groups. An individualized approach in de-escalation of ICS should be applied. GOLD 2017 recognized that FEV_1 can be used to guide therapy in selected circumstances. In Tudoric et al's study,[15] 126 (18.4%) of patients who shifted from group D to group B had very severe bronchial obstruction (FEV_1 ≤30%). This might have important clinical implications, if these patients being classified as group B, were prescribed a single long-acting bronchodilator only. It is worth noting that GOLD suggested that spirometry may influence treatment decisions in patients with discrepancies between spirometry and the level of symptoms. The majority of patients who shift from group D to group B and have poor lung function should be treated with dual bronchodilation. The decision for introducing other recommended treatments (roflumilast, ICS, azithromycin) is most likely based on phenotypes (chronic bronchitis, combined with asthma, chronic infection), in addition to CAT scores and dyspnea. Accurate adherence to the GOLD 2017 report will likely promote dual bronchodilator treatments as the gold standard therapy for the majority of patients with COPD, thereby significantly narrowing the use of ICS. Changes leading to a "vertical" shift of distribution may affect the therapeutic decisions to a lower level. Clinicians should follow up the treatment of patients who were transferred to a low-risk group. Future studies are warranted to confirm whether the de-escalation of treatment is appropriate.[16]

GOLD 2019 offered major changes to the medication pathway, including initial treatment, management cycle, and follow-up treatment. Initial drug recommendations were made according to the ABCD group: group A, starts with a bronchodilator; group B, a single long-acting bronchodilator; group C, long-acting muscarinic antagonists; and group D, drug selection with reference to patients' CAT score and eosinophil level. The follow-up treatment was based on symptoms and exacerbations, but the recommendations do not depend on the patient's GOLD group at diagnosis.[1] For patients with more exacerbations, treatment with ICSs was recommended, taking into consideration the eosinophil level in the blood. The change of treatment mode provides personalized pharmacologic treatment and management for patients. Using GOLD 2019, Halpin et al[23] analyzed 11,409 patients with established COPD and 699 starting therapy, in the United Kingdom. The overall proportion in each GOLD group was similar after 2 years but there was substantial movement of patients between the groups. Long-acting muscarinic antagonist monotherapy was the commonest initial therapy in all GOLD groups. There was over-treatment during follow-up according to GOLD 2019 and escalation, de-escalation, or switching accounted for nearly 50%. Continued work is needed to improve the assessment and management of patients with COPD.

Prognostic significance of the new assessment system

Cabrera López et al[17] revealed that all-cause mortality at 5 years in the GOLD 2015 was higher in grade D, followed by grades B, C, and A. Grade A had significantly lower mortality rate than B, C, and D; while grade D had significantly higher mortality than grade C. Grades B and C had similar mortality. In the GOLD 2017, grade B and grade D had similar mortality rates while grade C and grade A had significantly lower mortality. The degree of obstruction measured by FEV_1% pred affected mortality within each grade. The new grading system decreases the ability to predict risk of death over 5 years. Han et al[24] found that the GOLD 2017 classification performed well by identifying individuals at risk of exacerbations, but its predictive ability for mortality was poor among patients with COPD. Combining spirometric staging with the grouping increased the predictive ability for all-cause and respiratory mortality. The results from Kobayashi et al[19] also provided evidence that the GOLD 2017 classification identifies patients with COPD at risk of exacerbations, including those requiring hospitalization, but had a poor ability to predict mortality. The classification of spirometry reflects the different severities of the disease. Although spirometry cannot fully reflect the individual clinical outcome (ie, wide variation), and GOLD 2017 separates spirometric grades from the ABCD system, FEV_1 is still a very important parameter at the population level in the prediction of important clinical outcomes such as mortality and hospitalizations.[1]

How to Optimize the Assessment System of COPD

After updating the assessment method, more than one-third of the patients in groups C and D were classified into groups A and B, and different symptom scoring tools were applied, with inconsistent grouping results.[25] Under-reporting the history of exacerbations can lead doctors to under-estimate future risk.[26] The patients at high risk of exacerbations in group B have not been screened out, and the adequacy of treatment warrants further investigation. The COPD assessment system in the future should be multi-dimensional, including the following aspects in addition to the evaluation of symptoms and exacerbation risks: (1) Classification of clinical phenotype: Clinical phenotypes of COPD vary considerably. Classical COPD phenotypes included chronic bronchitis, emphysema and the blue bloater. New COPD phenotypes included frequent exacerbator, the fast decliner, inflammatory phenotype, current smoker phenotype, the systemic or co-morbidities phenotype, asthma-COPD overlap syndrome, etc.[27] The frequency of exacerbations in patients with COPD with the chronic bronchitis phenotype has been shown to be significantly higher.[28,29] Comorbidity of COPD increased the risk of mortality.[30] The COPD-specific comorbidity test score of greater than or equal to 4 points increased mortality risk by 2.2-fold.[31] The "inflammatory" phenotypes such as the frequent exacerbator, chronic bronchitis, and those with a number of co-morbidities respond well to ICSs. In contrast, the emphysematous type with dyspnea and lung hyperinflation, and the fast decliner, respond better to dual bronchodilation[27]; (2) Evaluation of image phenotypes: Structural computed tomography (CT) could help to identify the emphysema and airways disease phenotypes; while functional CT could help to identify the gas trapping and ventilation phenotype and the perfusion phenotype. Magnetic resonance imaging using hyperpolarized noble gases and conventional methods has helped to better phenotype patients.[32] Pulmonary artery diameter to aorta diameter ratio (PA/A) >1 on chest CT has been associated with the risk of future exacerbations.[33] As

the severity of spirometric grade increased, CT showed an increase in emphysema area and a decrease in area of normal lung tissue. But as the severity of the disease increased, both the emphysema and normal areas decreased[34]; (3) BODE index: BODE index has good prognostic value.[35] 6MWD, representing exercise capacity in the index, helped to identify patients with COPD at high risk.[36] 6MWD and speed were prognostic predictors of COPD independent of the ABCD group[37]; (4) Comprehensive assessment of COPD in the Spanish guidelines: the Spanish guidelines presented four clinical phenotypes of high-risk patients including the non-exacerbator phenotype, the exacerbator phenotype with emphysema, the exacerbator phenotype with chronic bronchitis, and asthma-COPD overlap syndrome. The Spanish guidelines suggested a more individualized approach to the management of stable COPD.[35] Combination of these evaluations with the assessment system of GOLD can better explain the pathophysiologic status and provide a basis for individualized and precise treatment of patients with COPD.

Conclusions

After nearly two decades of revisions, GOLD has moved from single assessment using spirometry to a more comprehensive assessment of COPD (spirometry, symptoms, exacerbation history), and subsequently, the separation of spirometry from the ABCD groups. The new ABCD assessment tool highlights the importance of symptoms and exacerbation history. The ABCD assessment tool is useful for clinicians to make decisions on appropriate COPD therapy, but is not a good predictor of outcome. Spirometry, in conjunction with patient symptoms and history of moderate and severe exacerbations, remains vital for the diagnosis, prognosis and consideration of other important therapeutic approaches such as lung volume reduction or lung transplantation. Spirometry remains irreplaceable in the prediction of mortality and other important health outcomes at the population level. The effect of the changes in treatment strategy resulting from the modifications in the new assessment method, on the prognosis of patients, remains to be clarified. The assessment system could be optimized by further identifying phenotypes, which would help to establish a more personalized COPD management approach in the future.

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Conflicts of interest

None.

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