A Case Report on a 29-Year-Old Male with Difficult to Treat Bronchial Asthma in Exacerbation: Rediscovering Asthma COPD Overlap Syndrome (ACOS)

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Abstract

Background: Asthma chornic obstructive pulmonary disorder (COPD) overlap syndrome (ACOS) was formally described by the joint project of global initiative for asthma (GINA) and global Initiative for chronic obstructive lung disease (GOLD) as persistent airflow limitation with several features usually associated with both asthma and COPD. ACOS is identified by the features shared with both asthma and COPD. The underlying cause though remains unknown, hence the project did not offer current formal definition.

Case: This is a case of a 29-year-old male, asthmatic with an eight - pack year smoking history who presented with chronic obstructive respiratory symptoms with non significant improvement on control of exacerbation despite standard maximal therapy. Diagnostic tests such as pulmonary function Tests, 2D Echo, chest CT scan and even assay for alpha 1 anti trypsin were done to rule out for other disease entities and prognosticate the patient's condition leading to the diagnosis of asthma COPD overlap syndrome (ACOS).

Conclusion: ACOS as a disease entity is still under debate and still has no current formal definition due to lack of specific biomarkers and lack of defining characteristics. Despite this, management should not be compromised since these patients often present with higher rates of exacerbations, hospitalization, associated co morbid illness and mortality. Treatment therefore is individualized.

Keywords: asthma, COPD, bronchial asthma, ACOS

Introduction

Historically, asthma and chornic obstructive pulmonary disorder (COPD) have been considered as separate and unique diseases with distinct characteristics. Classically, asthma has been characterized by reversible airways obstruction and COPD by fixed, less reversible, or irreversible airways obstruction. These definitions however have undergone major revisions recently. Even though asthma and COPD can be and are often appropriately separated as clinical entities, there are times when they are clinically and physiologically indistinguishable.

Clinicians often encounter difficult to treat bronchial asthma cases despite maximal therapy especially among smoker patients. These patients often present with less reversible or even irreversible airflow obstruction often seen in COPD. Further classification to several phenotypes has been formulated making asthma and COPD distinction less well defined. They often share clinical features that showed similar responses to the available treatments for asthma to COPD and vice versa, and these may have prognostic implications.

Clinically, asthma COPD overlap syndrome (ACOS) usually corresponds to asthmatic smokers who develop non-fully reversible airway obstruction[1], however, when the previous history of asthma is unknown, the diagnosis of ACOS may be difficult due to the lack of specific biomarkers.

The Joint Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines in 2014 defined ACOS as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD[1]. The syndrome is identified by the features that it shares with both asthma and COPD[1]. The underlying cause though remains unknown, hence did not offer current formal definition.

This report then aims to present a case of a young male patient who manifested with unresponsive asthmatic symptoms that are not relieved with maximal medications. On work up, obstructive airway disease was confirmed but could not be attributed to purely bronchial asthma alone. The findings also suggest features of a COPD however with non significant smoking pack years to really conclude COPD, hence managed as ACOS. Restrictive lung component

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though was also noted that could have contributed to the patient's underlying lung condition.

Case Presentation

Patient is a 29-year-old male who came in at the Emergency Department with shortness of breath. Patient was clinically diagnosed case of bronchial asthma for three years that was partly controlled as per GINA Guidelines maintained on salmeterol + fluticasone 250.0mcg / 25.0mcg metered dose inhaler (MDI) with poor compliance. The history of present illness started one month prior to admission when the patient experienced increasing severity of dyspnea associated with physical activity relieved by rest and / or inhaler. Three days prior to admission had worsening severity of dyspnea with associated non productive cough. Few hours prior to admission, patient had persistent shortness of breath with no relief with salmeterol + fluticasone MDI hence admitted. Pertinent negatives include the absence of associated fever, diaphoresis, chest pain, weight loss nor orthopnea.

Patient was previously treated with pulmonary tuberculosis (PTB) in 2012 and was able to complete the standard six months HRZE/HR regimen. There were no history of allergy to any food and drugs nor eczema. He is a previous eight - pack year smoker who started at 14 years old and stopped at 24 years old and who has been chronically exposed to a second - hand smoker. Patient also had history of drug abuse with marijuana with the last intake approximately two months prior to the admission and usual intake approximately twice a year for five years. The family members showed no history of asthma, allergy, atopy or any pulmonary and cardiac diseases.

He was seen at the Emergency Room conscious coherent speaks in phrases with vital signs as follows: BP 130/80; HR 107; RR 24; Temperature 36.9; SaO2 82% taken at room air.Pertinent physical examination showed an apex beat at sixth ICS left anterior axillary line and chest findings of symmetric chest expansion, no retraction, (+) fair air entry (+) wheezes bilateral lung fields.

Chest Xray showed fibrotic densities with cystic lucencies on bilateral upper lungs that has been stable as compared from his previous chest xray (the findings signify PTB with bullae formation). There was cardiomegaly with cardiothoracic ratio of 0.6. Pulmonary hyperaeration was also noted.

Results of the electrocardiogrgam (ECG) revealed sinus tachycardia with right ventricular hypertrophy. Patient was admitted with primary working impression of bronchial asthma in exacerbation and PTB treatment completed in 2012. Medications were started such as hydrocortisone

Table I. Complete blood count with platelet count

	Patient Value	Reference Values
Hemoglobin	15.0	14.0 – 18.0
Hematocrit	48	40 – 54
RBC	4.8	5.0 – 6.4
WBC	7.1	4.0 – 11.0
Segmenter	63	50 – 70
Lymphocyte	22	20 – 40
Eosinophil	1	2 – 4
Monocyte	13	2 – 5
Basophi	0	0 – 1
Platelet	211	150 – 450

Table II. Arterial blood gas (ABG) taken at 10 lpm via face mask. Partly compensated respiratory acidosis with more than adequate oxygenation

	Patient	Reference Values
pH	7.29	7.35 – 7.45
pCO2	77.4	35 – 45
pO2	159.7	80 – 100
HCO3	36.4	22 – 26
SaO2	98.8	

given at 4.0 mg/kg/body weight thru IV, salbutamol + ipratropium nebulization every hour and as needed for dyspnea and aminophylline drip at dose 0.4/kg given thru IV. On the initial hospital stay, patient was clinically improving, hence, nebulization was decreased and aminophylline was shifted to doxofylline. Hydrocortisone was later shifted to oral prednisone. The ABGs though showed persistently compensated to partly compensated respiratory acidosis. However, during the later part of hospital stay, patient had been noted of intermittent repeated bouts of exacerbation and consistent respiratory acidosis. Despite of persistent hypercarbia, patient was not intubated because patient is clinically stable and comfortable post-nebulization with inhaled short acting beta agonist combined with anticholinergic agent. Furthermore the patient presents with an ABG consistent of a chronic hypercarbia that could be probably due to chronic obstruction (as suggested by compensatory increase in HCO3). Compliance and proper technique of the use of medications were regularly checked. Additional medications such as montelukast, budesonide nebulization and tiotropium 18 mcg/cap one cap via hand inhaler were also started however did not offer significant improvement in the overall control of exacerbation. Diagnostic work ups were done to further characterize the patient's clinically insignificant improvement despite maximal therapy for asthma.

Table III. Series of ABGs at the ward

	Day 1	Day 2	Day 3	Day 4
pH	7.388	7.35	7.368	7.21
pCO2	70.7	67.7	59.8	88.6
pO2	73.2	106.5	111.6	98.1
HCO3	38.7	36.4	33.8	44.7
SaO2	93.2	97.54	98.3	96.5

Table IV. Pulmonary fuction test #1

Parameter	Predicted	Pre Broncho-dilator	Post Broncho-dilator	Change
FEV1/FVC (%)	79	43	38	
FEV1 Liters (%)	3.93	0.40 (10%)	0.41 (10%)	2 (2%)
FVC Liters (%)	4.88	0.93 (19%)	1.09 (22%)	22 (18%)

Interpretation: Very Severe airflow obstruction with no significant response to post bronchodilator study

The findings suggest an irreversibility of airway obstruction as evidenced by FEV1/FVC ratio that was less than 0.7 (Patients value 0.43) and a non significant post bronchodilator response with FEV1 that is less than 12% and / or 200mL (Patient's value: 2%). A possible a component of restricted airway is also entertained as reflected by decrease in FVC, however this is not very sensitive.

The 2D Echo findings are suggestive of a right sided heart failure probably due to the underlying pulmonary disease that is yet to be investigated. The Chest CT scan findings are consistent with bronchiectatic changes probably from the result of previous PTB that could be responsible for the restrictive component of the pulmonary disease.

Despite the maximal treatment with long acting inhaled bronchodilator and inhaled corticosteroid along with long acting antimuscarinic agent and a phosphodiesterase inhibitor, patient still experienced repeated bouts of dyspnea, hypoxemia with associated uncompensated respiratory acidosis in ABG. Compliance with medications as well as proper technique of inhaler use were frequently checked and emphasized. Incentive spirometry was also tried but still of no significant control of the exacerbation. Additional work up were done as seen in Table V.

Interpretation

1. Very severe airway obstruction.
2. No significant response to post bronchodilator study with restrictive component
3. Severe decrease in DLCO
4. Lung volumes: Low VC, IC, TLC; High RV

Table V. Pulmonary fuction test #2

Parameter	Predicted	Pre Broncho-dilator	Post Broncho-dilator	Change
FEV1/FVC (%)	80	41	34	
FEV1 Liters (%)	3.96	0.34 (9%)	0.34 (9%)	1
FVC Liters (%)	4.90	0.84 (17%)	1.03 (21%)	22

Diffusion		
	Reference	Patient
DLCO (mmol/Kpa min)	7.6	1.5
VA	6.42	1.79

Lung Volume		
	Reference	Patient
Vital Capacity (L)	4.9	1.28
Inspiratory Capacity (L)	3.23	0.84
Expiratory Reserve Volume (L)	1.61	0.43
Residual Volume (L)	1.59	2.56
Total Lung Capacity (L)	6.30	3.84

The pulmonary tests were repeated to give a more complete picture of the lung function. Irreversible airway obstruction is again noted, now with values of DLCO and lung volumes. The decrease in DLCO can be significantly correlated several disease entities in relation to FEV1 and FVC values and a decreased value of DLCO is commonly seen in emphysema. The low lung volumes in particular the low Total Lung Capacity (TLC) signify a restrictive lung disease. The elevated Residual Volume (RV) may indicate air trapping, commonly seen in obstructive lung diseases.

Among young adults who have pulmonary function test showing low DLCO in the presence of airway obstruction may indicate a possibility of cystic fibrosis or alpha1-antitrypsin deficiency. The assay test for alpha1-antitrypsin deficiency was tested in this patient and yield negative result.

Given the described clinical presentation of the patient as well as the series of laboratory and diagnostics done lead to the diagnosis of the so-called ACOS.

Discussion

Even before the joint project of GINA and GOLD in defining and characterizing ACOS, the clinical syndrome has been described in several countries both in prospective and retrospective studies. A two-stage multi center study in Italy described physician diagnosed ACOS to be more prevalent in older age occurring at 1.6% among 20 – 44 years old age

class and 4.5% among 65 – 84 years old age class. It also described that patients with ACOS presented with higher frequency of respiratory symptoms, functional limitation and hospitalization[2]. This may imply significant economic burden than in cases of asthma or COPD alone.

An epidemiological study in Poland had a study that involved 384 pulmonary specialists who enrolled a total of 12,103 patients in the period from March 2012 to September 2013 and described ACOS. It emphasized that there is no universally recognized diagnostic criteria for ACOS and that profile of patients is markedly different across the studies. However, patients with ACOS were described to have more severe course of the disease, with more symptoms, more exacerbations and more frequent hospitalizations, and portends a poorer prognosis[3]. There has been also a report of more frequent presence of concomitant diseases, metabolic and circulatory disorder. In particular, eighty five percent have been diagnosed with concomitant arterial hypertension (62.9%) and metabolic diseases (46.4%) such as metabolic syndrome, obesity, type 2 diabetes (Brzostek, et.al., 2014). The study though was non interventional[3].

The usual temporal profile of patients with ACOS was described in a retrospective study from January 2000 to March 2012 among 650 patients that were followed up at Tottori University Hospital in Japan. In this retrospective study, ACOS patients are commonly older, male, current and past smoking histories. They usually have low FEV1/FVC values and low FEV1 % predicted values. Patients also had a higher percentage of malignant disease and the mortality among all patients was higher in patients with ACOS than those with asthma[4].

The Joint GINA and GOLD Project described ACOS based on the findings among available studies and characterize the syndrome with a step wise diagnosis and treatment. Common asthma symptoms of ACOS include paroxysmal dyspnea with wheezing, and good response to inhaled steroids and COPD symptoms include long-lasting reduction in FEV1< 80% after administering a bronchodilator and chronic productive cough[1]. These characteristics were seen in our patient. The physical exam of ACOS patient may be normal but most patients will present with evidence of hyperinflation and other features of chronic lung disease or respiratory insufficiency and abnormal auscultation (wheeze and/or crackles)[1]. However, the guideline set by GINA and GOLD did not provide any specific criteria for diagnosing the syndrome with the disclaimers such as "final diagnosis is left to the physicians" and a "similar number" of overlapping features common to asthma and COPD support the diagnosis of the syndrome. The GINA and GOLD Project still provided a step- wise approach in diagnosis and management of ACOS as follows:

STEPWISE APPROACH TO DIAGNOSIS OF PATIENTS WITH RESPIRATORY SYMPTOM[1]

STEP 1: Does the patient have chronic airway disease?
- CXR or CT scan may be normal especially in early stages
- Hyperinflation, airway wall thickening, hyper lucency, bullae
- May identify or suggest an alternative or additional diagnosis

E.g. bronchiectasis, tuberculosis, interstitial lung disease, cardiac failure

STEP 2: Syndromic Diagnosis in Adults
- Compare the number of features for diagnosis of COPD versus asthma
- Several positive features (three or more) for either asthma and COPD suggest the diagnosis
- If there are "similar" number for both asthma and COPD, consider the diagnosis of ACOS

STEP 3: : Spirometry
- Essential if chronic airway disease is suspected
- Confirms chronic airflow limitation
- More limited value in distinguishing between asthma with fixed airflow limitation, COPD and ACOS

STEP 4: Initial Therapy
- GINA and GOLD failed to set out clear guidelines for the treatment
- If syndromic assessment suggests ACOS, start treatment as for asthma pending further investigation
  - First-line treatment: Inhaled Corticosteroids
  - Doses adjusted to the severity of the disease
- COPD component
  - Combined individualized bronchodilator therapy

A case report of ACOS in South Korea by Lee, et.al.[5], 2015 emphasized the statement of Tho, et.al.[6], that the definitive diagnosis of ACOS can often be postponed with follow-up monitoring. This is because most clinical features favoring asthma or COPD are based on the patient's history and present laboratory findings, but persistent airflow limitation, which is one of the clinical features favoring COPD, requires time to confirm[7]. Thus, as shown in this case, when ACOS is suspected in patients with asthma and limitation, of follow-up lung function test after regular inhaled therapy is necessary to confirm the presence of persistent airflow limitation.

Though the GINA and GOLD Joint Project failed to set out clear guidelines for the treatment of ACOS, as part on the stepwise approach the following treatment recommendations are enumerated for patients with ACOS[1].

- If the syndromic assessment suggests asthma or ACOS, or there is significant uncertainty about the diagnosis of COPD, it is prudent to start treatment as for asthma until further investigation has been performed to

Table VI. Characteristics observed and/or documented in our patient[1]

Features if present suggest:	Asthma	COPD
Age of onset	✔ Before age 20 years	After age of 40 years
Pattern of symptoms	✔ Variation over minutes, hours or days Worse during night or early morning ✔ Triggered by exercise, emotions including laughter, dust or exposure to allergens	Persistent despite treatement ✔ Good and bad days but always daily symptoms and exertion dyspnea Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	Record of variable airflow limitation(spirometry or peak flow)	✔ Record of persistent airflow limitation (FEV1/ FVC <0.70 post BD)
Lung function between symptoms	Normal	✔ Abnormal
Past history or family history	✔ Previous doctor diagnosis of asthma Family history of asthma and other allergic conditions (allergic rhinitis or eczema)	Previous doctor diagnosis of COPD, chronic bronchitis or emphysema ✔ Heavy exposure to risk factors: tobacco, smoker, biomass fuels
Time course	✔ No worsening of symptoms over time. Variation in symptoms either seasonally or from year to year ✔ May improve spontaneously or have an immediate response to bronchodilators or to ICS over weeks	Symptoms slowly worsening over time (progressive course over years) Rapid acting bronchodilator treatment provide only limited relief
Chest x-ray	Normal	✔ Severe hyperinflation

confirm or refute this initial position

- Treatments will include an ICS (in a low or moderate dose, depending on level of symptoms)
- A long-acting beta2-agonist (LABA) should also be continued (if already prescribed), or added
- However, it is important that patients should not be treated with a LABA without an ICS (often called LABA monotherapy) if there are features of asthma.

- If the syndromic assessment suggests COPD, appropriate symptomatic treatment with bronchodilators or combination therapy should be commenced, but not ICS alone (as monotherapy)[1].

- Treatment of ACOS should also include advice about other therapeutic strategies including[1]:
  - Smoking cessation
  - Pulmonary rehabilitation
  - Vaccinations
  - Treatment of comorbidities, as advised in the respective GINA and GOLD reports

The guideline was further supported by the study of Kostikas, et.al. that recommends the aggressive treatment of both asthma and COPD. The optimal bronchodilation and the appropriate dose of ICS must be adjusted for disease severity. Most consensus papers recommend the use of long-acting beta agonist (LABA)/ ICS combination therapy. The term "Triple therapy" (LAMA, LABA, and ICS) can be given among patients with more severe symptoms and more frequent exacerbations[4]. Furthermore, reduced response to ICS was seen especially patients with COPD who continue to smoke or those who smoke and have asthma, hence the importance to advise smoking cessation.

Prognosis of ACOS is different from asthma or COPD alone, It was described in a retrospectively collected data for in patients (age >40 years) with exacerbation of COPD and/or asthma in 1073 hospitals across Japan between July 2010 and May 2013 from national database by Yamauchi, et.al[8]. Patients with COPD alone had higher mortality and asthma alone had lower mortality than those with ACOS. The higher mortality with ACOS is associated with high doses of corticosteroids requirements, the absence of the asthmatic component and presence of the COPD component.

Clinical Correlation

The case presented was diagnosed of Asthma COPD Overlap Syndrome (ACOS) on the basis of the above clinical features checked on Step 2 (Syndromic Diagnosis in Adults) as suggested by the Joint Guidelines of GINA and GOLD in diagnosis of ACOS. The number smoking pack years is not significant enough to diagnose the patient of COPD. The patient's use of marijuana did not appear to have significant effect on patient's clinical condition, though the restrictive lung disease as a result of previous PTB could contribute to the patient's lung function. According to the Division of Pulmonary and Critical Care Medicine of UCLA published in 2013 by American Thoracic Society, habitual use of marijuana alone does not appear to lead

Table VII. Differences between asthma, COPD and ACOS using spirometric variables[1]

Spirometric variable	Asthma	COPD	ACOS
Normal FEV1/FVC pre- or post-BD	Compatible with asthma	Not compatible with diagnosis (GOLD)	Not compatible unless other evidence of chronic airflow limitation
Post-BD FEV1/FVC <0.7	Indicates airflow inflammation; may	Required for diagnosis by GOLD criteria	Usual in ACOS
FEV1=80% predicted	Compatible with asthma (good control, or interval between symptoms	Compatible with GOLD category A or B if post BD FEV1/FEV <0.7	Compatible with mild ACOS
FEV1<80% predicted	Compatible with asthma, A risk factor for exacerbations	Indicate severity of airflow limitation and risk of exacerbations and morality	Indicates severity of airflow limitation and risk of exacerbations and mortality
Post-BD increase in FEV1 >12% and 200 mL from baseline (reversible airflow limitation)	Usual at some time in course of asthma; not always present	Common in COPD and more likely when FEV is low, but consider ACOS	Common in ACOS , and is more likely when FEV is low
Post-BD increase in FEV1 >12% and 400 mL from baseline	High probability of asthma	Unusual in COPD. Consider ACOS	Compatible with diagnosis of ACOS

Table VIII. Specialized investigations to determine asthma vs. COPD[1]

Investigation	Asthma	COPD
DLCO	Normal or slightly elevated	Often reduced
Arterial blood gases	Normal between exacerbations	In severe COPD, may be abnormal between exacerbations
Airway hyperresponsive	Not useful on its own in distinguishing asthma and COPD	
High resolution CT scan	Usually normal; may shoe air trapping and increased airway wall thickness.	Air trapping emphysema; may show bronchial wall thickening and features of pulmonary hypertension
High resolution CT scan	Usually normal; may shoe air trapping and increased airway wall thickness.	Air trapping emphysema; may show bronchial wall thickening and features of pulmonary hypertension
Tests for atopy (sigE and/or skin prick tests)	Not essential for diagnosis; increases probability of asthma	Conforms to background prevalence; does not rule out COPD
FENO	If high (>50ppb) supports eosinophilic inflammation	Usually normal. Low in current smokers
Blood eosinophilia	Supports asthma diagnosis	May be found during exacerbations
Spolum inflammatory cell analysis	Role in differential diagnosis not established in large populations	

to significant abnormalities in lung function when assessed either cross - sectionally or longitudinally, except for possible increases in lung volumes and modest increases in airway resistance of unclear clinical significance and therefore of no clear link to chronic obstructive pulmonary disease has been established. Although, the presentation of ACOS theoretically would be more of an obstructive rather a restrictive pattern, one cannot undermine the underlying restrictive arm of the lung disease of the patient as seen in the Chest CT scan result. Important implication would be a more aggressive treatment management focused not only on ACOS but also for the structural lung disease created by the post TB bronchiectatic changes.

Furthermore, patient presented with pulmonary arterial hypertension as evidenced by the 2D Echo findings that were seen as a very common co morbid illness among patients with ACOS across the studies described previously.[3,6] The type of pulmonary hypertension of our patient can be classified as WHO Class three (Hypoxia Induced secondary to Lung Disease). The AHA ACC 2009 recommends that treatment patients under this classification should have a treatment that is directed at the underlying lung disease[9] that include bronchodilator and anti-inflammatory therapy, and most importantly, oxygen that was provided to the patient upon discharge. With the primary pulmonary disease that presented with a difficult to control obstructive symptoms, patient was given triple therapy (combination long acting beta agonist + inhaled corticosteriod + long acting

muscarinic antagonist) as suggested by the study of Kostikas, et.al.,[4] and by GINA and GOLD Guideline[1] in the form of salmeterol + fluticasone 250.0mcg/25.0mcg MDI at two puffs twice a day and tiotropium 18.0mcg cap given once a day via hand inhaler, respectively. Additional medications such as Montelukast, a leukotriene receptor antagonist given 10.0mg tab one tab once daily and doxofylline, a phosphodiesterase inhibitor given 400.0mg tab one tab three times a day were also prescribed on discharge. There was no particular mention on the guideline on what specific bronchodilator or inhaled steroids must be used in patients suspected with ACOS, hence the use of such medications above were on the basis of the readily available drugs at the hospital. Furthermore, patient was also consistently advised of compliance and correct use of inhaled medications.

Conclusion

ACOS should be suspected among male patients with previous or current smoking history that presents with chronic obstructive symptoms that are difficult to treat, intractable to maximal medications and are characterized atypically with both symptoms of COPD and Asthma that cannot be attributed to a single entity. Series of Pulmonary Function Tests is recommended if not yet previously done to further exemplify and prognosticate airway irreversibility and detect possible concomitant restrictive lung disease component. Additional diagnostics such as Chest CT scan and 2D Echo are also recommended to further typify if patient has structural lung disease and if with concomitant cardiac comorbid illness and / or complication. Inhaled corticosteroid remains as first line treatment if still with pending diagnosis to cover for the asthmatic symptoms. Long Acting Beta Agonists (LABA) are usually added for the COPD symptoms and are adjusted depending on clinical response. Additional medications such as Long Acting Muscarinic Antagonist (LAMA), phosphodiesterase inhibitor and leukotriene receptor antagonist can be added as necessary. Given these, still there is no current recommendation standard treatment protocol in patients diagnosed with ACOS, hence relying the addition of medications based on clinical response thus implying individualized approach. Close monitoring and follow up are also recommended since patients with ACOS often have higher rates of exacerbations, hospitalization, associated co morbid illness and mortality rate.

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