Peer Review File

Reviewer: 1

Comment 1:

Research hypothesis / introduction - The Introduction i quite short and does not allow the reader understand the reason why this study was conducted. Why COPD? Why this issue? Is there in your country a particular interest in this disease? Is COPD a public health problem in your country? Was an initiative to improve management of COPD conducted? Which kind of initiative? When? At what level (local, regional national?). Who did it and how? Did the Authors hypothesise that this initiative could have improved the COPD management? Did the Authors hypothesise that this initiative could have differential impact on different “medical care institutions”? Introduction should be enriched with a deeper description of the importance of the issue under study, adding some references and information on evidence-based guidelines you refer to for the COPD management, and on your health care service organization and context. Improving the background and the rationale of this study is important.

Reply 1:

Thank you very much for your valuable comment. We admit that the introduction does not allow the reader understand the reason. We are sorry for this.

This study is a report of the result of 3 years nationwide quality assessment program performed by government. This quality assessment program was initiated by Health Insurance Review and Assessment Service (HIRA). South Korea has one universal national health insurance system. HIRA is a governmental institution whose main role is to judge whether claims from all hospitals are appropriate.

As we mentioned in the manuscript, the prevalence of COPD is 13.4% and associated medical costs were 1,245 million in 2015. Moreover, according to the Statistics Korea, COPD was 8th cause of death in 2018 (1). However, in spite of this burden, COPD is underdiagnosed and undertreated in South Korea. According to Korean National Health and Nutrition Examination Survey, among subjects who were confirmed as COPD by spirometry, only 2.4% reported having been diagnosed with COPD and 2.1% treated (2). Also, according to the analysis of HIRA data, PFT were not routinely performed and the prescription rate of inhaler was low (3). Adherence of inhaler was also very low in even high-grade COPD patients (4). In order to solve these problems, HIRA initiated nationwide quality assessment program since 2014. The main purpose of this program is to increase the quality of COPD management in South Korea.

HIRA hypothesize implement of nationwide quality assessment program will improve COPD management, especially in primary care clinic. For example, PFT ratio in primary and secondary care facilities were only 11.1% while 40.6% in tertiary (3). Percentage of use of

long acting muscarinic antagonist (LAMA) in primary and secondary was 8.1% while 32.7% in tertiary (3).

Changes in the text:

We have added this instruction in revised manuscript (see Page 5 & Page 6, 1st ~ 6th line).

Comment 2:

Aim - This work is only descriptive, it is rather a report. The aim stated at pg 3 lines 38-39 is not correct. The study does not “improve patients management, reduce progression to severe status, and minimize medical care expense”. Please re-formulate the aim.

Reply 2:

We do agree with the comment. Indeed, this manuscript is a summary of the results of three years’ quality assessments in HIRA. With the permission of HIRA, we have integrated and summarized three years’ results in this manuscript. The purpose of quality assessment by HIRA is to improve management, reduce progression, and minimize expense. Thus, we have changed the sentence as follows: Here, we have reported the results of nationwide quality assessment performed with the aims of improving patient management, reducing progression to severe status, and minimizing medical care expenses.

Changes in the text: Page 6, 4th line

Comment 3:

Methods section - This section is not structured and lack of important details. It should be improved and enriched with operative details, it should be divided in paragrafs to describe carefully the study design, procedures and variables definition.

Reply 3:

We have re-structed method as suggested. We have added more detailed information regarding the quality assessment program.

Changes in the text: Page 6, 8th ~ Page 8, 9th line

Comment 4:

Health care organization and source of data – Since in each country the organization of health services is different, more details should be given about your health care context. Which is Health Insurance Review and Assessmant Service? Is it a governamental institution? Or private? What are claim data (pg 3 line 42)? Hospitalization? Emergency visits? Specialistic

care? Primary care? Drugs? All those? Please describe which datasets are available in your country, who is authorized to use them, at what level (regional / national). How did you link all these datasets? Did you you use standardzed methodology? Please give details on procedures and references. What is the quality of your datasets? Do you have any information or did you conduct previous studies on data quality? About drugs, did you have any specific registry? Did you have information of pharmacy prescriptions? Or what? Which/ how many pharmacies? What classification codes did you use for (5-7)drugs? Please clarify.

Reply 4:

South Korea has one universal national health insurance system. HIRA is a governmental institution whose main role is to examine the claim data. HIRA decide whether to reimburse or not. Almost all Koreans are covered by one single insurance system and this is a mandatory. Every single detailed claim data for almost all Koreans is included in this database. This includes hospitalization, emergency visits, specialist care, GP care, public hospital, private hospital, all drugs, and cost. Corresponding author (Rhee CK) has utilized this database and published in many SCI(E) journals including Thorax and JACI in Practice (3-5, 8-34). All of claim data from 50 million people is stored in HIRA.

Information regarding all medication used in Korea is available in HIRA data. The classification codes for drugs is open to public and available at HIRA homepage (www.hira.or.kr). We have used 530 codes for the identification of drugs used in this study. LABA included formoterol, indacaterol, vilanterol, and salmeterol. SABA included fenoterol, procaterol, salbutamol, and terbutaline. LAMA included aclidinium, tiotropium, and umeclidinium. SAMA included ipratropium. ICS included budesonide, beclomethasone, beclomethasone, ciclesonide, and fluticasone. PDE4 included roflumilast.

Comment 5:

Settings - Plaese clarify what you mean with “medical care institutions”. Hospital? Community level services? Located in town / cities / rural places? How many are they? Are they in some way “linked” for the managenet of COPD? Given COPD is a complex disease and the management needs specialistc and amultidisciplinary team, do all these services and professionals work in a collaborative way? See also point 1. Please clarify.

Reply 5:

Since HIRA data include all hospitals in Korea, entire medical care institutions in South Korea were included in the analysis. Among all hospitals in Korea, the number of hospitals included in quality assessment was 6,691 in 2014, 6,722 in 2015, and 6,470 in 2016. These hospitals were selected based on enroll criteria (ICD-10 cod with prescription of COPD medication). Any medical facilities where COPD patients were managed were enrolled in quality assessment. We have added these methods and results in revised manuscript.

We are sorry that whether there are specialists and multidisciplinary teams in all of these

hospitals. We cannot identify this information via claim data.

Changes in the text: Page 7, 7th ~ 9th line.

Comment 6:

Design - The study design is not clear. Is it a longitudinal cohort study? Did the Authors identify three different cohorts in the three different “assessement period “? What does it mean “assessment period”? What is the date of enrollement for each cohort? Did you perform a follow up? How long was it? Was the same time-window for each individulal under study? This point is crucial, there is no information on time-window, dates and follow up, please clarify.

Reply 6:

HIRA have analyzed three different cohorts during the three different assessment period. First assessment period is from May 2014 to April 2015. Second is from May 2015 to April 2016 and third is May 2016 to April 2017. HIRA has reviewed all the claim data which was generated during the assessment period and identified COPD patients. Quality assessment was performed for the hospitals who managed COPD patients during each assessment period. All claim data during each year was analyzed. All patients were followed for one year (each assessment period). We have added this method in revised manuscript.

Changes in the text: Page 6, 14th ~ 19th line.

Comment 7:

Population under study - COPD criteria definition are quite original. Can you give some information on the validity of your COPD case definition? Who made the COPD diagnosis? Pneumologists / generic physicians? Was pulmonary function tests used to identify all COPD cases? In which period was identified the population / what date / what time? COPD may have different levels of severity and the management is different according to the stages. This point is crucial. Do you have an idea of distribution of the different stages? Did you include asthma in the COPD case definition? All these points have an impact on interpretation of results. Please clarify.

Reply 7:

The working definition of COPD in this study was made by airway specialists in Korea including corresponding author (Rhee CK) in 2013. This definition was validated through the comparison of Korean National Health and Nutrition Examination Survey (KNHANES) prevalence of COPD which was confirmed by spirometry. This working definition of COPD has been utilized in many SCI(E) publications (3, 4, 6-8, 10, 16, 20-22, 28, 33, 34). Each COPD patients in this study was identified during assessment period (1 year).

We agree that COPD may have different levels of severity. Rhee CK and airway specialists invented criterion to identify COPD severity by HIRA data (4, 21). However, this classification was not used in quality assessment. We are sorry that we cannot analyze the distribution of the different stages in this data.

Asthma was not excluded in this study.

We have added these details in the revised manuscript.

Changes in the text: Page 7, 6^{th} ~ 7^{th} line.

Comment 8:

Variable definition / outcomes / exposure/ confounders - This part is poor, operative definition of all the variables of interest is lacking. It is difficult to understand the quality and validity of all these measures. Please clarify this crucial point.

Reply 8:

As we described in our manuscript, COPD medication was identified by HIRA data. HIRA data contains all the detailed information regarding the medication. LABA included formoterol, indacaterol, vilanterol, and salmeterol. SABA included fenoterol, procaterol, salbutamol, and terbutaline. LAMA included aclidinium, tiotropium, and umeclidinium. SAMA included ipratropium. ICS included budesonide, beclomethasone, beclomethasone, ciclesonide, and fluticasone. PDE4 included roflumilast.

Rate of PFT was also analyzed by HIRA data. Every single information regarding the performance PFT is also stored in HIRA data because this is a claim data. Without claim, the fees cannot be reimbursed. Thus, there is no missing data in HIRA. PFTs in this study includes spirometry without flow-volume curve, spirometry with flow-volume curve, cardiopulmonary exercise test, bronchial provocation test, and bronchodilator test.

The visit rate is also identified by HIRA data. We can easily calculate the number of visits of COPD patients. We also already described the type medical instructions in our original submission. We also can easily analyze and calculate the number of admission and cost by utilization of HIRA data. All the detailed information of outcome of this study is available without missing in HIRA database.

COPD visit was defined by the presence of ICD-10 codes J43-44 (except J43.0) for primary or first subsidiary diagnosis in outpatient claim data.

The percentage of COPD patients who admitted hospital was analyzed. COPD admission was defined by the presence of ICD-10 codes J43-44 (except J43.0) for primary or first subsidiary diagnosis in the claim data of admission. All admissions regardless of hospital type were calculated.

Outpatient medical care expenses were calculated by adding up all the costs of the COPD claim data. Medical expenses by COPD was defined by the presence of ICD-10 codes J43-44

(except J43.0) for primary or first subsidiary diagnosis in the claim data. It includes costs for medical examination and consultation during the outpatient visit. Cost for medication was not included.

We have added the definition of visit, admission, and expenses in the revised manuscript.

Changes in the text: Page 7, 22nd line. Page 8, 1st ~ 10th line.

Comment 9:

Drugs used to identify COPD and describe adherence - The Authors included short term bronchodilators, why? They are not recommended in guidelines for the care of COPD. I do not think it is correct. What COPD guidelines did the Authors refer to build the drug adherence indicator? Therapy is not the same for the different COPD stages. I think the outcome variable is not correct in its generic formulation and referring to the overall COPD population (early stages and severe stages together).

Reply 9:

GOLD recommendation was a reference. Short acting bronchodilator was recommended in group A in previous GOLD documents. Since the rate of inhaler use was very low in Korea, HIRA decided to included SABA/SAMA in quality assessment. We agree your opinion and maybe in the future, we hope HIRA will only include long acting bronchodilator.

We do agree with your opinion that treatment is not the same for the different COPD stages. However, this was a nationwide quality assessment program and main purpose is to increase the management quality of GPs. It is a shame that Korean GPs do not even prescribe inhalers to COPD patients (not only long acting but also short acting). Korean government considered this as a very serious problem and initiated quality assessment program to improve this ashamed situation in Korea.

Comment 10:

Functional pulmonary tests - They are necessary for the first diagnosis, but in the severe cases – with high level of flow obstruction and symptoms - is not necessary to be done more times in a year. What COPD guidelines did the Authors refer to build this outcome indicator? Again, I think the outcome variable is not correct in its generic formulation and referring to the overall COPD population (early stages and severe stages together).

Reply 10:

GOLD document has recommended PFT FU at least once in a year (for example, GOLD 2020, P. 97.). HIRA adapted this recommendation and included in quality assessment program.

Comment 11:

Medical care institutions - Are you sure they define COPD cases in the same way /same quality? Do they use the same data recording? What is the reason for comparing different institutions / what rationale? COPD is a disease which needs integrated care, which way is the care for COPD organized in your country? Please give more details. See also point 5.

Reply 11:

We absolutely agree with your opinion. We do not think GPs do not define COPD cases in the same way/quality with specialists. However, the prevalence of COPD in Korea is 13.4%. There are so many COPD patients that they cannot be solely managed by specialists. This is why HIRA has been implementing quality assessment program. The main purpose is to increase the quality of GPs. It will be ideal that all GPs provide integrated care, however, it is far from the reality in Korea. The urgent goal of COPD management in Korea is to increase the rate of inhaler use and PFT performance especially in primary care clinic.

Comment 12:

Statistical analysis - This part is poor. There are no statistical measures to interpret differences over time and across institutions.

Reply 12:

This is a report of government-initiated program and there was no comparison between groups. As you can observe, there is no *P* value in this manuscript. No comparison has been performed in quality assessment program. We are very sorry that HIRA did not perform statistical comparison. I think this is a certainly limitation of this study. We are very sorry for this. We have added this limitation in revised manuscript.

Changes in the text: Page 11, 21st ~ 23rd line.

Comment 13:

Results - Most of them they are descriptive, good for a technical report, too many for a scientific paper. Lines 108-113 which are “admitted patients?? admitted where? This outcome was not previously described in the Methods section? Expences? All these measures are additional and generate confusion.

Reply 13:

We are sorry for the missing of the definitions of outcomes.

COPD admission was defined by the presence of ICD-10 codes J43-44 (except J43.0) for primary or first subsidiary diagnosis in the claim data of admission. All admissions regardless of hospital type were calculated.

Outpatient medical care expenses were calculated by adding up all the costs of the COPD claim data. Medical expenses by COPD was defined by the presence of ICD-10 codes J43-44 (except J43.0) for primary or first subsidiary diagnosis in the claim data. It includes costs for medical examination and consultation during the outpatient visit. Cost for medication was not included.

We have added the definition of admission and expenses in the revised manuscript.

Changes in the text: Page 8, 3rd ~ 10th line.

Comment 14:

Discussion – Since the research hypothesis and aims are not clearly stated and methodology poorly described, the interpretion of results and understanding the implication is difficult.

Reply 14:

We have added the hypothesis and aims in revised manuscript.

Changes in the text: Page 5, 23rd line. Page 6, 4th line.

Reviewer: 2

Comment 1:

The inclusion criteria: in the manuscript, the point 4 and 5 of the inclusion criteria was to confirm the included patients who had the history of received medical treatment, this would exclude some COPD patients who did not receive inhalation therapy, especially for stage 1 COPD patients, definitely influenced the results of this study for evaluating nationwide quality assessment of treatment for COPD.

Reply 1:

We do agree with your opinion. In fact, HIRA also has considered this problem. Thus, HIRA has included oral medication such as methylxanthine and systemic beta agonist to define COPD. Also, short acting bronchodilator was included in the lists of the medications used to define COPD. These prevent to exclude early mild patients in nationwide quality assessment. However, during the quality assessment, HIRA only monitored percentage of inhaler prescription.

Comment 2:

COPD medications: in this manuscript, the authors only included the information of inhalant drugs for COPD patients, indeed, as one of the most important therapy, inhalation therapy is very effective and apply wildly in patients with COPD, however, there are also other medication ways, such as oral administration, to be used for stable COPD patients, why did the authors not record it.

Reply 2:

Thank you very much for your comment. We agree that medication other than inhaler can be used in COPD patients. That is why HIRA define COPD patients by the use of not only inhaler but also oral medication. However, the aim of quality assessment in Korea is to increase the use of inhaler. The use of inhaler was low in Korea. For example, percentage of use of LAMA in primary and secondary was 8.1% while 32.7% in tertiary (3). We have added the aims of quality assessment and reference of low use of inhaler in Korea in revised manuscript.

Changes in the text: Page 6, 1^{st} ~ 6^{th} line.

Comment 3:

Information of revisit: in the manuscript, the authors only recorded the revisit rate of the included patients who visited the same medical care institution, to our knowledge, some patients may select different medical care institutions for further treatment. For the criteria, that of excluding these patients may lead to bias of data analysis.

Reply 3:

Thank you very much for your valuable comment. We absolutely agree with your opinion. We are sorry that we did not consider this critical point. We admit that we may exclude patients who selected different medical care institutions for better treatment. We think this is a certainly limitation of this study. We have added this limitation in revised manuscript.

Changes in the text: Page 11, 23rd line.

Comment 4:

Table 1, 2: in table 1, we found that the number of patients with COPD treated in primary healthcare clinic decreased during the following three years, and the number in tertiary hospital and general hospital increase obviously. In general, most COPD patients should be admitted mostly in primary healthcare clinic for medical treatment, which can save medical resources and more effectively monitoring and be helpful for COPD patients who use inhalation medication regularly. If more patients are admitted in tertiary hospitals which provide specialized medical services to patients with severe diseases, which means increased more severe patients occurred during the 3 years or some stable patients expended extra medical resources who were in tertiary hospitals or general hospitals may be solved in primary healthcare clinic. If the situation is existed, the conclusion of this manuscript may be doubtful.

Reply 4:

Thank you very much for your valuable comment. We do agree that COPD patients should be mainly managed in primary clinic. However, we partly agree with your opinion. It is true that the number of COPD patients managed in primary clinic decreased. However, it is not due to quality assessment. In fact, this phenomenon is not limited to COPD. It is a serious problem in Korean medical system. Access to specialist is very easy in Korea. There has been no barrier for patients to go to tertiary hospital. Korean Patients tend to visit tertiary hospital more and more every year.

Apart from this problem, two important outcomes (use of inhaler and performance of PFT) of quality assessment improved during three years. We think this improvement resulted from the implementation of quality assessment program.

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