PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A historical database cohort study addressing the clinical patterns prior to idiopathic pulmonary fibrosis (IPF) diagnosis in UK primary care
AUTHORS	Thickett, David; Voorham, Jaco; Ryan, Ronan; Jones, Rupert; Coker, Robina; Wilson, Andrew; Yang, Sen; Ow, Mandy; Raju, Priyanka; Chaudhry, Isha; Hardjojo, Antony; Carter, Victoria; Price, David

VERSION 1 – REVIEW

REVIEWER	Nils Hoyer Department of Respiratory Medicine, Herlev and Gentofte hospital, Copenhagen, Denmark
REVIEW RETURNED	10-Oct-2019

GENERAL COMMENTS	Thank you for the opportunity to review this well written paper. The authors address an important issue: the pre-diagnostic period in IPF. This real-world study has the strength that it includes data from primary care records, which are often not available to epidemiologic studies. However, it is limited by the purely descriptive nature and lack of control group for the analyses. In addition, for a retrospective cohort study, the population size is rather small. The most valuable message in the paper, in my opinion, is that the prevalence of symptoms (mainly cough and dyspnea) appear to rise several years prior to the IPF diagnosis. One important question is not sufficiently addressed by the authors: how do symptoms relate to the referral pattern (time to referral, time from first symptom to diagnosis etc.). Are there any patterns or risk factors for a delayed diagnosis? I suggest to include at least descriptive data about the referral patterns or time from symptom do final diagnosis in a revised version of the manuscript. Do the authors have data on a group that could be used as a control group? A comparison with the general population would greatly increase the useful information that can be extracted from this paper. Specific comments are listed below: Page 5, line 93: The authors have excluded patients with a competing lung disease which could contribute to the registered symptoms. However, there are more lung diseases, including asthma and COPD, which would cause dyspnea and cough. I would suggest exclusion of these patients. Alternatively, one could consider them in a separate sub-group. COPD patients would be

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	expected to have multiple consultations with cough and dyspnea, potentially leading to a false impression of an increased rate in IPF. Page 9, table 1: There was only a small percentage of patients with concomitant COPD. Could there have been an undiagnosed group? Do you have spirometry data available which could explain the relatively small number of COPD patients, considering the number of smokers and the age of the population? Page 11, table 3: I would be very interested in the results of the respiratory tests. Did the spirometry help in referring patients quickly? Were presenting symptoms related to a delayed diagnosis? Page 12, line 212: Error, please correct Page 14, line 227-231: The patterns of patient pathways should be supported by more data than a “visual assessment of individual patient timelines”. Otherwise, it should be removed.

REVIEWER	Minna Purokivi Kuopio University Hospital Kuopio, Finland
REVIEW RETURNED	21-Oct-2019

GENERAL COMMENTS	This is a very interesting paper! Diagnostic delay is still a significant problem with IPF patients. This data is based on information from free-text primary care records, Read codes and free text terms. It suggests that almost 80% of cases had a primary care visit due to respiratory symptoms one year prior to the specialist consultation preceding IPF diagnosis. Significant number of cases had respiratory symptoms (cough and dyspnoea) as mucm as 4-5 years before consultation. As the writers point out, cough and dyspnoea together should perform as a "red flag" for the primary care physician (especially when the inspiratory crackles are herad in chest auscultation.) This paper provides interesting real life data which confirms the earlier recognized need to educate primary care colleagues to take prolonged respiratory symptoms seriously and to suspect and identify also rare respiratory conditions like IPF. Minor comments: line 119 and 120 should obversation be observation? line 212: Error...? Is something missing from the text?

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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Nils Hoyer
Institution and Country: Department of Respiratory Medicine, Herlev and Gentofte hospital, Copenhagen, Denmark Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for the opportunity to review this well written paper. The authors address an important issue: the pre-diagnostic period in IPF. This real-world study has the strength that it includes data from primary care records, which are often not available to epidemiologic studies.
We thank the reviewer for this positive comment.

However, it is limited by the purely descriptive nature and lack of control group for the analyses. In addition, for a retrospective cohort study, the population size is rather small.

We acknowledge these limitations proposed by the reviewer. We have now added the limited population in our limitations in page 18 Line 342-344:
"Our additional selection criterion, requiring prior chest specialist consultation, also resulted in a reduced sample size."

We have also added the need for further research including a control group at the end of our conclusion, Page 20-21 Line 405-408:
"Further research comparing the clinical pathway of IPF patients with a control group of patients, as well as investigating whether spirometry led to a timelier referral to specialists may also be warranted."

The most valuable message in the paper, in my opinion, is that the prevalence of symptoms (mainly cough and dyspnea) appear to rise several years prior to the IPF diagnosis.

One important question is not sufficiently addressed by the authors: how do symptoms relate to the referral pattern (time to referral, time from first symptom to diagnosis etc.).

We agree with the reviewer that this is an important research question. Previously, we did not look into the associations between signs & symptoms and referral patterns as it was not part of our objectives (i.e. to characterise the pattern of signs, symptoms and other clinical predictors preceding IPF diagnosis). We have conducted an additional descriptive analysis for the length of time since the first symptoms of cough and dyspnoea until IPF diagnosis. We also plotted the cumulative probability of IPF diagnosis since the first cough or dyspnoea. These results have been added to the manuscript in Page 15 Line 262-268:

"Probability of IPF diagnosis from the first recording of symptoms
Analysis of probability for IPF diagnosis since the first recorded symptom of cough or dyspnoea included 463 patients (322 and 293 patients with cough and dyspnoea respectively). The mean (SD) time since the first cough was longer (6.3 [5.5] years) compared to since the first dyspnoea (4.3 [4.3] years). Cumulative probability of IPF diagnosis since the first recording of symptoms are illustrated as a life table (Supplementary Table E7) and a Kaplan-Meier plot (Supplementary Fig E5)."

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Are there any patterns or risk factors for a delayed diagnosis? I suggest to include at least descriptive data about the referral patterns or time from symptom do final diagnosis in a revised version of the manuscript.
We thank the reviewer for the suggestion. Although, this was outside the protocol of our current study. However, we have added a new descriptive post hoc analysis of the number of patients with different recording frequency of each symptoms (records/year) in our paper, Page 16 Line 245-247:

"The number of patients with at least a certain average symptom frequency in the period before IPF diagnosis (up to 12 years) are presented in Supplementary Table E6."

Do the authors have data on a group that could be used as a control group? A comparison with the general population would greatly increase the useful information that can be extracted from this paper.

We agree that a comparison with the general population might provide valuable insight towards the risk factors for IPF diagnosis. However, as mentioned above, this would fall outside of our primary objectives of characterising the pattern of signs, symptoms and other clinical predictors preceding IPF diagnosis. Consequentially, our study design includes only patients who had been diagnosed with IPF. Extraction of data of patients for a control group, designing the appropriate matching criteria and deciding the risk factors to investigate will require an entirely separate study. We will keep this in mind for further research. We added at the end of our manuscript, Page 20-21 Line 405-408:

"Further research comparing the clinical pathway of IPF patients with a control group of patients, as well as investigating whether spirometry led to a timelier referral to specialists may also be warranted."

Specific comments are listed below:

Page 5, line 93: The authors have excluded patients with a competing lung disease which could contribute to the registered symptoms. However, there are more lung diseases, including asthma and COPD, which would cause dyspnea and cough. I would suggest exclusion of these patients.

Alternatively, one could consider them in a separate sub-group. COPD patients would be expected to have multiple consultations with cough and dyspnea, potentially leading to a false impression of an increased rate in IPF.

We thank the reviewer for this suggestion. Our exclusion criteria were designed to select for patients with idiopathic pulmonary fibrosis as opposed to other types of pulmonary fibrosis such as sarcoid which could be confused with IPF. Asthma and COPD are both common disorders and misdiagnosis of IPF as either disease is a likely occurrence. We feel that including the asthma and COPD diagnoses may give an interest perspective to the patients' journey to a diagnosis of IPF. Regardless, the number of patients with asthma (n=24) and COPD (n=19) are too small to conduct separate analyses and thus unlikely to relevantly change our conclusion. We have added this into our discussion (Page 18, Line 349-353:

"We did not exclude asthma and COPD which may also present with symptoms of cough and dyspnoea. We felt that asthma and COPD are both common disorders and misdiagnosis of IPF as either symptom are likely, Regardless, the numbers of patients with asthma (n=24) and COPD (n=19) are too small to conduct separate analyses and are unlikely to relevantly change our conclusion."

Page 9, table 1: There was only a small percentage of patients with concomitant COPD. Could there have been an undiagnosed group? Do you have spirometry data available which could explain the

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relatively small number of COPD patients, considering the number of smokers and the age of the population?
The reviewer raised an interesting concern. The number of patients with COPD was based on the presence of a code for COPD diagnosis. However relatively uniquely in UK primary care a diagnosis of COPD has required spirometric confirmation since 2002 before it can be recorded. As such the UK may have less misdiagnosis of IPF as COPD than other health care systems. We have added this to our discussion in Page 18, Line 353-357:

"The small number of patients with concomitant COPD is likely due to the unique requirement of the UK primary care system since 2002 in which a diagnosis of COPD requires confirmation by spirometry. Consequentially, the UK may have less misdiagnosis of IPF as COPD than other health care systems."

Page 11, table 3: I would be very interested in the results of the respiratory tests. Did the spirometry help in referring patients quickly? Were presenting symptoms related to a delayed diagnosis?

It would indeed be interesting to see the impact of spirometry towards earlier diagnosis. However, that would be outside the scope of our study, as elaborated earlier. We shall keep this suggestion for our future studies as mentioned in Page 20-21, Line 405-408:

"Further research comparing the clinical pathway of IPF patients with a control group of patients, as well as investigating whether spirometry led to a timelier referral to specialists may also be warranted."

Page 12, line 212: Error, please correct
We have corrected this error.

Page 14, line 227-231: The patterns of patient pathways should be supported by more data than a "visual assessment of individual patient timelines". Otherwise, it should be removed.

To support this result, we have added a result on the number of patients with different recording frequency of each symptoms (records/year) in our paper, Page 14 Line 245-247:

"The number of patients with at least a certain average symptom frequency in the period before IPF diagnosis (up to 12 years) are presented in Supplementary Table E6."

Reviewer: 2
Reviewer Name: Minna Purokivi
Institution and Country:
Kuopio University Hospital
Kuopio, Finland
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

This is a very interesting paper! Diagnostic delay is still a significant problem with IPF patients. This data is based on information from free-text primary care records, Read codes and free text terms. It suggests that almost 80% of cases had a primary care visit due to respiratory symptoms one year prior to the specialist consultation preceding IPF diagnosis. Significant number of cases had respiratory symptoms (cough and dyspnoea) as much as 4-5 years before consultation. As the writers

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point out, cough and dyspnoea together should perform as a "red flag" for the primary care physician (especially when the inspiratory crackles are heard in chest auscultation. This paper provides interesting real life data which confirms the earlier recognized need to educate primary care colleagues to take prolonged respiratory symptoms seriously and to suspect and identify also rare respiratory conditions like IPF.

Minor comments:
line 119 and 120 should obversation be observation?
line 212: Error...? Is something missing from the text?

We thank the reviewer for the positive comments and for pointing out the typos. We have fixed the errors in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	MInna Purokivi Kuopio University Hospial Kuopio, Finland
REVIEW RETURNED	12-Feb-2020

GENERAL COMMENTS	The authors have conducted the corrections suggested by the reviewers. This has improved the manuscipt and I warmly recommend its publication.

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