ARTICLE DETAILS

<table>
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<th>TITLE (PROVISIONAL)</th>
<th>Correlation between symptoms and objective findings may improve the symptom-based diagnosis of chronic rhinosinusitis for primary care and epidemiologic studies</th>
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<td>AUTHORS</td>
<td>Park, Do-Yang; Lee, Eun Jung; Kim, Ji Hoon; Kim, Yoo Suk; Jung, Chan Min; Kim, Kyung-Su</td>
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VERSION 1 - REVIEW

<table>
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<tr>
<th>REVIEWER</th>
<th>Wytske Fokkens</th>
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<td>REVIEW RETURNED</td>
<td>13-Aug-2015</td>
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GENERAL COMMENTS

This very large study aimed to evaluate the symptomatic predictors of CRS for primary care and epidemiologic studies by comparing nasal endoscopic findings from a large-scale nation-wide epidemiologic study, the Korean National Health & Nutrition Examination Survey (KNHANES).

Background:

It is suggested that EPOS does not suggest epidemiological and primary care definitions for CRS. This is incorrect and should be adjusted.


M & M: who exactly did the endoscopy? I recently reviewed another paper from the same group and the same Survey where it was indicated that the endoscopy was done by residents. Now it is otolaryngologists. I wonder whether in the study (also more than 7000 people) and this study different methods have been used. Please comment.

 Apparently only pus or polyps in the middle meatus were taken as positive sign of CRS. This is not equivalent to common definitions of endoscopic signs of disease (like e.g, in CRS). This is a limitation of the study that should be discussed.

Results:
- the population included is surprisingly old. Please comment.
- the prevalences of the separate symptoms is extremely low (lower than all other data on prevalence also other Korean data) and the data from the same group on the same survey. This is not mentioned in the text and should be discussed.
- I miss the most relevant odds ratio: the prediction of the symptoms as suggested in EPOS. This would be: odds ratio for: 1 + 2 or 1 + 3 or 1 + 4 or 2 + 3 or 2 + 4 (EPOS epidemiological definition in figures). If the authors can come up with this ratio that would be very interesting. For now the odds ratio’s that they calculated do not seem to be very relevant because they do not show to be better than prediction based on EPOS

The authors might be interested to use the following two references:

REVIEWER
Bibi Lange
Department of Otorhinolaryngology
Odense University Hospital
Denmark

REVIEW RETURNED
19-Aug-2015

GENERAL COMMENTS
Comments to the author

This is a well written paper with an important aim - to evaluate the symptomatic predictors of CRS for primary care and epidemiologic studies.

It should be mentioned in the manuscript that EPOS 2012 already describes a definition of CRS for epidemiology studies/General Practice. This paper tries to go one step further - to evaluate the importance of each of the 4 symptoms and their combination in relation to the clinical-based CRS diagnosis.

The difference between the symptom-based CRS diagnosis and the clinical-based CRS diagnosis should be clearly stated. Otherwise the aim is confusing. This study is relevant in our attempt to close the gap between the symptom-based and clinical-based diagnosis.

This study evaluates the correlation between symptoms and objective findings. It is correctly concluded that reduction or loss of smell is highly correlated to positive nasal endoscopic findings. In this way it can be indirectly assumed that persons with reduction or loss of smell are more likely having clinical-based CRS which requires a positive rhinoscopy. However, the correlation to CRS is not analysed. Having a positive rhinoscopy is not the same as having CRS. See e.g. reference nr 17 where they compare symptoms with CRS.

It is not describe how many persons had CRS and the CRS diagnosis is not included in the analysis.
The title, aim and conclusion should be revised not to include "symptomatic predictors of chronic rhinosinusitis". The correlation between each symptom and the clinical CRS diagnosis is not analysed but can only be assumed through the correlation with the objective findings. Something like: "Correlation between symptoms and objective findings may improve the symptom-based diagnosis of chronic rhinosinusitis for primary care and epidemiologic studies", would be more correct. Please reconsider.

Do we know how many were in medical treatment/nasal steroid and if medical treatment could influence the correlation between symptoms and objective findings?

It would be interesting also to know the correlation between symptoms and each of the objective findings – polyps/discharge. Could this be included in the result section or in a table?

Both the European and American guidelines have 3 objective findings. Why is oedema not included? Please include oedema or explain and discuss why it is excluded.

Page 10, line 37: reference nr 15 does not emphasis on reduction or loss of smell. The paper discuss the mechanism of symptoms but does not highlight smell.

The paper by Tomassen P, et al.: Reliability of EP3OS symptom criteria and nasal endoscopy in the assessment of chronic rhinosinusitis - a GA(2) LEN study. Allergy 2010 Nov 17, could be used as an updated reference when debating the correlation between symptom/symptom-based CRS and positive rhinoscopy.

In the result section it is described that combination of symptoms showed higher odds ratios than individual symptoms. The importance of combination of symptoms should be included in the conclusion as it maybe even more relevant for the clinician than the reduction of smell as a single symptom.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1.

1. It is suggested that EPOS does not suggest epidemiological and primary care definitions for CRS. This is incorrect and should be adjusted

   ➔ We have clarified and should adjusted several sentences in the ‘Background’ section according to your comments as below:

   “Despite these clinical guidelines incorporating all symptomatic, endoscopic, and radiologic criteria, in certain conditions, such as in primary care and epidemiological studies, the use of medical devices and resources for nasal endoscopy and radiologic examination is impractical. Moreover, excessive consumption of medical devices and resources is connected to the escalation of health care costs. Thus, the above currently used symptom-based diagnosis of CRS should be better designed for use in primary care and epidemiologic studies.”

2. I miss referral to the study of Tomassen (Tomassen P, Newson RB, Hoffmans R, Lotvall J, Cardell

→ We have added and discussed your recommended article, according to your comments, in the ‘Background’ section as below.

“Tomassen et al. reported the reliability of EP3OS symptom criteria and nasal endoscopy determined using data from the Global Allergy and Asthma European Network (GA2LEN) survey. In this report, 62% of enrolled subjects with positive symptoms showed positive nasal endoscopic findings, and 38% of enrolled subjects with negative symptoms showed positive nasal endoscopic findings. Thus, symptom-based CRS was statistically associated with positive endoscopy. If the relative value of each symptom is considered, combinations of symptoms can provide greater reliability in the diagnosis of CRS.”

3. M & M: who exactly did the endoscopy? I recently reviewed another paper from the same group and the same Survey where it was indicated that the endoscopy was done by residents. Now it is otolaryngologists. I wonder whether in the study (also more than 7000 people) and this study different methods have been used. Please comment.

→ We have clarified and changed several sentences in the ‘Material and Methods’ section according to your comments.

“The visiting survey team was composed of four medical experts, including an otolaryngology resident who performed the clinical evaluations in a well-equipped mobile medical examination bus. The residents had been educated and trained for the standardization of the examination by the Korean Society of Otorhinolaryngology-Head and Neck Surgery.”

4. Apparently only pus or polyps in the middle meatus were taken as positive sign of CRS. This is not equivalent to common definitions of endoscopic signs of disease (like e.g. in CRS). This is a limitation of the study that should be discussed.

→ The oedema or mucosal obstruction findings were excluded in the physical examination of KNHANES because nasal mucosal shrinkage was done for better visualization of the nasal cavity and reduction of pain during examination. We think that it may be a limitation of this study. We have modified the ‘Discussion’ section according to your comments.

“In terms of limitations, nasal polyps and mucopurulent discharge from the middle meatus were regarded as positive findings; however, oedema of the middle meatus was not regarded, as nasal mucosal shrinkage was performed for better visualization of the nasal cavity and reduction of pain during examination. This difference in the diagnostic criteria was related to a low incidence of positive endoscopic findings in this study.”

5. The population included is surprisingly old. Please comment.

→ According to the 2010 Population and Housing Census in Korea, the mean age of the total population was 38.1 years old. Even considering that this study was conducted on adults over 19 years of age, the mean age of this study (50.2 years old) is somewhat old. The cause of this old age...
is not clear; thus, it is also a limitation of our study. We have added these comments in the
‘Discussion’ section.

“According to the 2010 Population and Housing Census in Korea, the mean age of the total
population was 38.1 years old. Even considering that this study was conducted on adults over 19
years of age, the mean age of this study (50.2 years old) was somewhat high. As the cause of this old
age is not clear, it is also a limitation of our study.”

6. The prevalences of the the separate symptoms is extremely low (lower than all other data on
prevalence also other Korean data) and the data from the same group on the same survey. This is not
mentioned in the text and should be discussed

➔ We have added and discussed your recommended article, according to your comments, in the
‘Discussion’ section.

“The prevalence of CRS symptoms in this study is lower than other reports. In Tomassen et al.’s
report, the prevalence of symptoms was 6.9% to 13.3%. However, in this study, the prevalence of
symptoms was 0.1% to 2.4%. The subjects of Tomassen et al.’s report were selected based on the
results of a CRS questionnaire in the first cross-sectional phase; conversely, the subjects of the
present study came from a general population and were selected using a multistage cross-sectional
and stratified sampling design. This difference in enrollment may have contributed to the difference in
results.”

7. I miss the most relevant odds ratio: the prediction of the symptoms as suggested in EPOS. This
would be: odds ratio for: 1 + 2 or 1 + 3 or 1 + 4 or 2 + 3 or 2 + 4 (EPOS epidemiological definition in
figures). If the authors can come up with this ratio that would be very interesting. For now the odds
ratio’s that they calculated do not seem to very relevant because they do not show to be better than
prediction based on EPOS.

➔ We have added and reinforced our manuscript with your comments in the ‘Results’ section as
shown below.

“The combination of nasal blockage, facial pain/pressure, and reduction or loss of smell was found to
have the highest odds ratio (6.392 [95% CI 0.845–48.349]). However, this combination was not
statistically significant due to its low incidence (p = 0.0723). Thus, the combination of facial
pain/pressure and reduction or loss of smell had the highest odds ratio with statistical significance
(4.154 [95% CI 1.004–17.197]; p = 0.0494).”

8. The authors might be interested to use the following two references:
1. Vandenhende-Szymanski C, Hochet B, Chevalier D, Mortuaire G. Olfactory cleft opacity and CT
score are predictive factors of smell recovery after surgery in nasal polyposis. Rhinology.
2. Leong SC, Tsang HK, Wilkie MD, Banhegyi G. Characterisation of patients with endoscopy-
negative, computer tomography-negative midfacial segment pain using the sino-nasal outcome test.
Among the recommended articles, the first article (Vandenhende-Szymanski et al.) was a useful reference for our manuscript in terms of supporting an olfactory pathophysiology. Therefore, we have cited this article in the ‘Discussion’ section.

Reviewer 2.

1. The difference between the symptom-based CRS diagnosis and the clinical-based CRS diagnosis should be clearly stated. Otherwise the aim is confusing. This study is relevant in our attempt to close the gap between the symptom-based and clinical-based diagnosis.

We have clarified and changed the sentences of the ‘Background’ section according to your comments.

“This study aimed to evaluate the correlation between symptoms and objective findings of chronic rhinosinusitis to improve its symptom-based diagnosis for primary care and epidemiologic studies by using data from a large-scale nation-wide epidemiologic study, the Korean National Health & Nutrition Examination Survey (KNHANES).”

2. However, the correlation to CRS is not analysed. Having a positive rhinoscopy is not the same as having CRS. See e.g. reference nr 17 where they compare symptoms with CRS.

We agree with your opinion. For the diagnosis of CRS, both symptoms and signs found via endoscopy or CT scan are necessary. In this study, we attempted to evaluate the correlation between symptoms and objective findings of chronic rhinosinusitis. This study did not compare symptoms and symptom combinations with clinical guidelines that incorporated all symptomatic, endoscopic, and radiologic criteria. The reference also attempted to find a clinical predictor of CRS, and the result was similar to ours. Our study is more important than this reference because the subjects of our study were selected from a general population by using a multistage cross-sectional and stratified sampling design. This content was added to the ‘Discussion’ section.

“In contrast to other epidemiologic studies, this study did not include sinus CT scans. This is an inevitable limitation of primary care and epidemiologic studies and precluded the comparison of symptoms, endoscopic findings, and/or CT scan images. Thus, our study did not compare symptoms and symptom combinations with clinical guidelines that incorporated all symptomatic, endoscopic, and radiologic criteria.

3. It is not describe how many persons had CRS and the CRS diagnosis is not included in the analysis.

We have added the data in the ‘Results’ section according to your comments.

“1011 subjects (3.46% of total subjects) were given a symptom-based diagnosis of CRS.”

4. Something like: “Correlation between symptoms and objective findings may improve the symptom-based diagnosis of chronic rhinosinusitis for primary care and epidemiologic studies”, would be more correct. Please reconsider.
Based on your opinion, we have modified the title of our study and changed the results and conclusion of the abstract as below.

“Results: Of the four symptoms, reduction or loss of smell was the most significantly related to positive endoscopic findings in multivariable analysis (odds ratio: 1.936). The combinations of symptoms showed higher odds ratios than individual symptoms, and combinations of reduction or loss of smell with other symptoms were statistically more reliable for positive endoscopic findings than other combinations. Conclusions: According to our results, reduction or loss of smell was the most significantly related to positive nasal endoscopic findings. Therefore, symptom-based diagnosis of CRS can be improved by considering reduction or loss of smell as an important symptom for endoscopic findings of CRS.”

5. Do we know how many were in medical treatment/nasal steroid and if medical treatment could influence the correlation between symptoms and objective findings?

→ Unfortunately, no KNHANES data were related to medical treatment or nasal steroids.

6. It would be interesting also to know the correlation between symptoms and each of the objective findings – polyps/discharge. Could this be included in the result section or in a table?

→ It is a good idea to observe the symptoms and each objective finding. However, the aim of this study focused on the correlation of each symptom and combination of symptoms with the endoscopic findings. If we had observed the correlation between symptoms and each objective finding, the aim of this study would have become more confusing. Thus, such observations will be performed in a later study.

7. Both the European and American guidelines have 3 objective findings. Why is oedema not included? Please include oedema or explain and discus why it is excluded.

→ The oedema or mucosal obstruction findings were excluded in the physical examination of KNHANES because nasal mucosal shrinkage was done for better visualization of the nasal cavity and reduction of pain during examination. We think that it may be a limitation of this study. We have modified the ‘Discussion’ section according to your comments.

“In terms of limitations, nasal polyps and mucopurulent discharge from the middle meatus were regarded as positive findings; however, oedema of the middle meatus was not regarded, as nasal mucosal shrinkage was performed for better visualization of the nasal cavity and reduction of pain during examination. This difference in the diagnostic criteria was related to a low incidence of positive endoscopic findings in this study.”

8. Page 10, line 37: reference nr 15 does not emphasis on reduction or loss of smell. The paper discus the mechanism of symptoms but does not highlight smell.

→ We have deleted that reference.

the assessment of chronic rhinosinusitis - a GA(2) LEN study. Allergy 2010 Nov 17, could be used as an updated reference when debating the correlation between symptom/symptom-based CRS and positive rhinoscopy.

⇒ We have added and discussed your recommended article, according to your comments, in the ‘Background’ section as shown below.

“Tomassen et al. reported the reliability of EP3OS symptom criteria and nasal endoscopy determined using data from the Global Allergy and Asthma European Network (GA2LEN) survey. In this report, 62% of enrolled subjects with positive symptoms showed positive nasal endoscopic findings, and 38% of enrolled subjects with negative symptoms showed positive nasal endoscopic findings. Thus, symptom-based CRS was statistically associated with positive endoscopy. If the relative value of each symptom is considered, combinations of symptoms can provide greater reliability in the diagnosis of CRS.”

10. In the result section it is described that combination of symptoms showed higher odds ratios than individual symptoms. The importance of combination of symptoms should be included in the conclusion as it maybe even more relevant for the clinician than the reduction of smell as a single symptom.

⇒ We have added and reinforced our manuscript based on your comments in the ‘Results’ section as shown below.

“The combination of nasal blockage, facial pain/pressure, and reduction or loss of smell was found to have the highest odds ratio (6.392 [95% CI 0.845–48.349]). However, this combination was not statistically significant due to its low incidence (p = 0.0723). Thus, the combination of facial pain/pressure and reduction or loss of smell had the highest odds ratio with statistical significance (4.154 [95% CI 1.004–17.197]; p = 0.0494).”

GENERAL COMMENTS

It is correct that this study did not aim to evaluate the correlation between the subjective symptoms and each of the objective findings. Your next study looking into this will be interesting. However, it might be assumed that having polyps is more correlated to reduced sense of smell or nasal blockage, and nasal discharge is more correlated to nasal drip. If such a difference do exist it could be questioned how the lack of looking for mucosal oedema influence your results. E.g. if mucosal oedema is highly correlated to nasal blockage the importance of reduced smell is overestimated in your study. As oedema is part of the international guidelines, I think it is important to make further comments regarding how excluding oedema might influence your results. Resulting in a lower incidence of positive endoscopic findings is too short. The example above is one way it might influence, maybe there are more! Comments could be added in the limitation section where you mention oedema or in the
In the discussion section the prevalence of symptoms is described as 0.1 – 2.4%. The prevalence of each symptom is not found in the text or in the table? As discussed the prevalence of symptoms is lower than found by Tomassen et al. (and Hastan et al) which you explain by difference in sampling method. Can you please explain in comments to the reviewer (or refer to a paper explaining this) why your sampling method results in this lower prevalence - or is the prevalence of nasal symptoms actual lower in Korea than in Europe?

VERSION 2 – AUTHOR RESPONSE

Thank you for your constructive comment for this study and keen interest towards the later study design.

1. As oedma is part of the international guidelines, I think it is important to make further comments regarding how excluding oedema might influence your results. Resulting in a lower incidence of positive endoscopic findings is too short. The example above is one way it might influence, maybe there are more! Comments could be added in the limitation section where you mention oedema or in the discussion section.

⇒ We clarified and changed the sentences of the ‘Discussion’ section according to your comments as below.

“If mucosal oedema was included in diagnostic criteria of CRS, the prevalence of CRS would have been more increased. This difference in the diagnostic criteria in this study was related to a low incidence of positive endoscopic findings. The presence of mucosal oedema in middle meatus will cause certain discrepancies in the prevalence of CRS since it can increase the possibility of olfactory dysfunction. Therefore, the exclusion of mucosal oedema in the diagnostic criteria is an important limitation in this study.”

2. In the discussion section the prevalence of symptoms is described as 0.1 – 2.4%. The prevalence of each symptom is not found in the text or in the table? As discussed the prevalence of symptoms is lower than found by Tomassen et al. (and Hastan et al) which you explain by difference in sampling method. Can you please explain in comments to the reviewer (or refer to a paper explaining this) why your sampling method results in this lower prevalence - or is the prevalence of nasal symptoms actual lower in Korea than in Europe?

⇒ We have clarified and changed the comments regarding the prevalence of each symptoms and added in the ‘Results’ section as below.

GA2LEN study (enrolled baseline data in two noted reference articles: Tomassen et al. and Hastan et al.) was conducted by mail survey method. However, KNHANES was conducted by visiting survey method for populations selected by systematic sampling. Mail survey method have disadvantages of low response rate, limited investigation results due to linguistic behavior, and restricted control of responders’ environments. In this context, responders having related diseases are more willing to reply to the survey positively. This response bias contributes to a higher positive response rate of CRS symptoms. On the contrary, the visiting survey method of KNHANES contains a relatively large amount of questionnaires regarding the health and disease issues. Our study was a part of survey
with many other health-related questionnaires and this fact can result in the habitual effect or irrelevance effect of the responders. Thus, the enrolled population is liable to make more negative responses for each survey questions. This comment has been added to the ‘Discussion’ section as below.

Ref.)

“The prevalence of symptoms was 0.6% to 5.7% (nasal drip: 4.9%, nasal blockage: 5.7%, facial pain: 0.6%, and reduction or loss of smell: 5.2%).”

“The prevalence of CRS symptoms in this study is lower than other reports. In the report by Tomassen et al., the prevalence of symptoms was 6.9% to 13.3% whereas the prevalence of symptoms in the present study was 0.6% to 5.7%. The subjects of the report by Tomassen et al. were selected based on the results of a CRS questionnaire in the first cross-sectional phase by mail survey; conversely, the subjects of the present study came from a general population and were selected using a multistage cross-sectional and stratified sampling design with visiting survey. This difference in enrollment may have contributed to the difference in the prevalence.”