UNIVERSITI PUTRA MALAYSIA

USEFULNESS OF CENTOR SCORE FOR DIAGNOSIS OF GROUP A STREPTOCOCCAL PHARYNGO-TONSILLITIS AND PREVALENCE OF THE DISEASE IN MALAYSIA FROM 2016 TO 2017

ABDULRAHMAN MANSOOR MOHAMMED MUTHANNA

FPSK(M) 2018 1

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia in Fulfilment of the Requirements for the Degree of Master of Science

October 2017

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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October 2017

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Pharyngo-tonsillitis is very common in general practice and most of the cases are caused by viruses. One of the causes of pharyngo-tonsillitis is group A streptococcus, which has a strong indication for antibiotic treatment. It is difficult to distinguish between streptococcal pharyngo-tonsillitis from non-streptococcal according to the clinical findings. Nevertheless, up to 90% of the patients with sore throat might be treated with antibiotic. Over prescribing of antibiotics has very serious health effects with severe reactions and may promote antibiotic resistance and add significantly to the cost of health care. In Malaysia, Upper Respiratory Tract Infection (URTI) makes up nearly 30% of cases in primary care. Studies have shown trends of inappropriate prescribing of antibiotics for URTI in Malaysian primary care. Centor scoring is a guideline based on a set of criteria that help to identify the likelihood of streptococcal infections in patients with a sore throat. It was conducted to guide physicians to appropriately prescribe antibiotics for adults with pharyngo-tonsillitis. This study aims to describe the epidemiological pattern, etiology and its antibiotic susceptibility, clinical manifestation, antibiotic prescription among adults with sore throat and validity of Centor score in diagnosis group A streptococcal pharyngo-tonsillitis at three primary care clinics in Sepang, Selangor, Malaysia during 2016 to 2017. This cross-sectional study was conducted on 215 patients aged 18 and above with sore throat as one of the complaints at the three primary care clinics during December 2016 until April 2017. Throat swabs were collected from the patients for culture and analysis. Data on clinical manifestations, demographic characteristics, clinical information and throat sample results were analyzed using Chi-square test, and descriptive statistics. From all the participants (42.3% male, 57.7% female), (18.6% smokers, 81.4% non-smokers), (62.8%Malay, 30.2% Indian, 5.1% Chinese, 1.9 % others), 6 isolates (2.4%) were identified as GAS including 50% of those were associated with Centor score of 3 ($p < 0.001$), 50% were associated with Centor score

of 4 ($p < 0.001$), and 0% with Centor scores of 0,1 and 2. Centor criteria were clinical predictors that associated with group A streptococcal pharyngo-tonsillitis ($p < 0.001$). Pharyngo-tonsillitis was diagnosed in 130 (60.5%) of the total adult participants who complained with sore throat. Beta hemolytic streptococci and influenza A and B viruses were isolated from 37.1% and 3.8 % of total participants, respectively. Both Centor scores 3 and 4 had sensitivity of 50%, and specificity of 97.6% and 100%; respectively, positive predictive value 37.5% and 100%; respectively, negative predictive value 98.6% and 98.6%; respectively, positive likelihood ratio 20.5 and 50; respectively, negative likelihood ratio 0.5 and 0.5; respectively. The accuracy of Centor score 3 was 96.3% while the accuracy of Centor score 4 was 98.6%. Antibiotics were prescribed to 48 (22.3%) including 8.3% with group A streptococcus and 91.6% with non-group A streptococcus. A majority of prescribed antibiotics was associated with Centor scores of zero to one (75.0%). Antibiotic susceptibility testing revealed that all beta hemolytic streptococci isolates were susceptible to penicillin G, ampicillin, ofloxacin, cefepime, cefotaxime, ceftriaxone, vancomycin, and linezolid, but 40%, 2.4%, and 9.6% were resistant to tetracycline, clindamycin, and erythromycin, respectively. The current study has suggested that the Centor score is useful for diagnosis and decision making for antibiotic therapy of GAS pharyngo-tonsillitis leading to decrease the unnecessary antibiotic prescription, while achieving better levels of treatment.

Key words: Pharyngo-tonsillitis; Clinical score; Centor score; *Streptococcus pyogenes*; Group A beta-hemolytic streptococcus; antibiotic prescription

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

FAEDAH SKOR CENTOR UNTUK MENDIAGNOSIS FARINGO-TONSILITIS STREPTOKOKUS KUMPULAN A DAN PREVALENS PENYAKIT DI MALAYSIA DARI 2016 HINGGA 2017

Oleh

ABDULRAHMAN MANSOOR MOHAMMED MUTHANNA

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Faringo-tonsilitis biasa dijumpai di klinik primer dan kebanyakan kes disebabkan oleh virus. Salah satu punca jangkitan faringo-tonsilitis ialah streptokokus kumpulan A. Jangkitan ini adalah satu indikasi yang kukuh untuk rawatan menggunakan antibiotic. Tetapi, jangkitan ini sukar dibezakan antara faringo-tonsilitis streptokokus dan bukan-streptokokus menggunakan tanda-tanda klinikal sahaja. Walau bagaimanapun, sehingga 90% pesakit dengan sakit tekak mungkin dirawat dengan antibiotik. Dengan menetapkan antibiotik yang lebih ianya akan memberi kesan kesihatan yang sangat serius dengan tindak balas yang teruk dan boleh menggalakkan kerintangan antibiotik sekaligus menambah kos kepada penjagaan kesihatan. Di Malaysia, jangkitan saluran pernafasan atas (URTI) membentuk hampir 30% daripada kes di peringkat penjagaan primer. Kajian telah menunjukkan bahawa terdapat trend preskripsi antibiotik yang tidak sesuai untuk URTI di peringkat penjagaan primer Malaysia. Skor Centor adalah garis panduan berdasarkan satu set kriteria yang membantu untuk mengenal pasti kemungkinan jangkitan streptokokus pada pesakit yang mempunyai sakit tekak. Ia digunakan untuk membimbing para doktor untuk menetapkan antibiotik yang sesuai kepada orang dewasa dengan faringo-tonsilitis. Kajian ini bertujuan untuk menggambarkan corak epidemiologi, etiologi dan kerentanan antibiotik, manifestasi klinikal, preskripsi antibiotik di kalangan orang dewasa dengan sakit tekak dan kesahihan skor Centor dalam mendiagnosis faringo-tonsillitis streptokokus kumpulan A di tiga klinik klinik penjagaan primer di Sepang, Selangor, Malaysia pada 2016 hingga 2017. Satu kajian keratan rentas telah dijalakan di kalangan 215 pesakit berusia 18 tahun keatas yang mempunyai sakit tekak sebagai salah satu aduan di tiga klinik utama penjagaan pada Disember tahun 2016 hingga April tahun 2017. Calitan tekak telah dikumpulkan daripada sekumpulan pesakit bagi tujuan pengkulturan dan analisis. Data mengenai manifestasi klinikal, ciri-ciri demografi, maklumat klinikal dan hasil keputusan

calitan tekak dianalisis dengan menggunakan ujian Chi-square, dan statistik deskriptif. Daripada semua peserta (42.3% lelaki, 57.7% perempuan), (18.6% perokok, 81.4% bukan perokok), (62.8% Melayu, 30.2% India, 5.1% Cina, 1.9% lain-lain), 6 isolat (2.4%) telah dikenalpasti sebagai GAS, 50% daripada mereka yang mempunyai skor Centor 3 ($p < 0.001$), 50% dengan skor Centor 4 ($p < 0.001$), dan 0% dengan skor Centor 0,1 dan 2. Kriteria Centor adalah peramal klinikal yang berkaitan dengan faringo- tonsilitis streptokokus Kumpulan A ($p < 0.001$). Faringo-tonsilitis didiagnosis pada 130 (60.5%) dari jumlah peserta dewasa yang mengadu sakit tekak. Streptokokus beta hemolitik dan virus influenza A dan B telah diasingkan dari 37.1% dan 3.8% daripada jumlah peserta. Kedua-dua skor 3 dan 4 bagi permarkahan Centor mempunyai sensitiviti 50%; manakala kekhususan 97.6% dan 100% masing-masing, nilai ramalan positif 37.5% dan 100% masing-masing; nilai ramalan negatif 98.6% dan 98.6%; nisbah kemungkinan positif 20.5 dan 50; dan nisbah kemungkinan negatif 0.5 dan 0.5. Ketepatan skor Centor 3 adalah 96.3% manakala ketepatan skor Centor 4 adalah 98.6%. Antibiotik telah diberikan kepada 48 peserta (22.3%) termasuk 8.3% streptokokus kumpulan A dan 91.6% dengan streptokokus bukan kumpulan A. Majoriti antibiotik yang ditetapkan dikaitkan dengan skor Centor sifar hingga satu (75%). Ujian kerentanan antibiotik mendedahkan bahawa semua isolat streptokokus beta hemolitik adalah mudah terdedah kepada penisilin G, ampicillin, ofloxacin, cefepime, cefotaxime, ceftriaxone, vancomycin dan linezolid, tetapi 40%, 2.4%, dan 9.6% telah menunjukkan kerintangan kepada tetracycline, clindamycin, dan erythromycin. Kajian semasa mencadangkan bahawa skor Centor berguna bagi mendiagnosis dan membuat keputusan kepada terapi antibiotik untuk faringo- tonsilitis GAS yang membawa kepada penurunan preskripsi antibiotik yang tidak diperlukan, bagi mencapai tahap rawatan yang lebih baik.

Kata kunci: Faringo-tonsilitis; Skor klinikal; Skor Centor; *Streptococcus pyogenes*; Streptokokus beta hemolitik Kumpulan A; Preskripsi antibiotic

ACKNOWLEDGEMENTS

This work has been achieved with the help of Allah Almighty. I would like to express my deep gratitude and appreciation to my supervisor, Dr. Siti Zulaikha Zakariah, for her valuable and constructive suggestions and patient guidance during the planning and development of this research work. Also, I cannot express enough thanks to Associate Professor Dr. Rukman Awang Hamat, Dr. Nurainul Hana Shamsuddin and Dr. Faisal Ali for their professional guidance and valuable support, enthusiastic encouragement and useful critiques of this research work. Not forget as well, to thank all the nurses, physicians and lecturers in the Department of Medical Microbiology and Parasitology, Department of Family Medicine and three primary care clinics especially who have helped me regarding the sample collection.

I would like to thank my parents for their support and patience. They were always there cheering me up and stood by me through the good times and bad. I wish to thank my lovely sisters (DUNIA and DOA'A) for their supporting and encouragement with their best wishes.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

WHO	World Health Organization
CDC	Centers for Disease Control and Prevention
IMR	Institute for Medical Research
AAFP	American Academy of Family Physicians
PCR	Polymerase chain reaction
HIV	Human immunodeficiency virus
STSS	Streptococcal toxic shock syndrome
EBV	Epstein Barr Virus
HSN	Herpes simplex virus
AGN	Acute Glomerulonephritis
SPSS	Statistical package for the social science
GAS	Group A Streptococci
GBS	Group B Streptococci
GCS	Group C Streptococci
GFS	Group F Streptococci
GGS	Group G Streptococci
βHS	Beta haemolytic streptococci
RADT	Rapid Antigen detection test
ASO	Antistreptolysin-O
CRP	C-reactive protein
EES	Erythromycin Ethylsuccinate

CHAPTER 1

INTRODUCTION

1.1 Background

Pharyngo-tonsillitis is one of commonest upper respiratory tract infections and it is an inflammation involving both the tonsils and the pharynx wall caused by viral or bacterial infection (Mishra & Agrawal, 2012). Group A streptococcus (also known as *Streptococcus pyogene*s) is the most common and important bacteria cause an acute pharyngo-tonsillitis (Al-Moyed, 2011). Rhinovirus, influenza virus, adenovirus are the main viruses cause pharyngo-tonsillitis, present in 70-80% cases (Anjos et al., 2014). Sore throat, cough, nasal discharge, fever, swollen tonsils, and difficulty swallowing are the main signs and symptoms of pharyngo-tonsillitis. However, cough and nasal discharge are often associated with viral infections than bacterial infections (Anne & Zab, 2017). Serious complications of pharyngo-tonsillitis caused by group A streptococcus are rheumatic fever, scarlet fever, toxic shock syndrome and acute glomerulonephritis (Al-Moyed, 2011). More than 600 million cases annually have been diagnosed as pharyngo-tonsillitis worldwide. Acute pharyngo-tonsillitis is the second most commonly diagnosed pediatric illness. Group A Streptococcal infection frequently cause significant morbidity and are associated with significant mortality rates worldwide (World Health Organization, 2004). There are many ways to identify the organisms that are causing pharyngo-tonsillitis, such as culture of throat swab, rapid antigen detection tests and molecular diagnosis (PCR) (Cheesbrough, 2008). Viral pharyngo-tonsillitis is treated by a symptomatic relief, while bacterial pharyngo-tonsillitis may require the prescription of antibiotics such as penicillin, clindamycin or erythromycin. A specific treatment might be required if the complications occurred (Choby, 2009).

Antibiotics are prescribed for treating bacterial infections, not for viral illnesses. In general, antibiotics are safe, but should be prescribed by a physician after a careful clinical assessment. However, antibiotics that are taken unnecessarily may contribute to the development of antibiotic resistance (Andersson et al., 2016). The excessive use of antibiotics, an unnecessary antibiotic prescription and the diagnosis of pharyngo-tonsillitis adds an economic burden to the health care system around the world, as well as to patients and their families. For example, in the United Kingdom it is estimated that health costs for diagnosis of sore throat alone around 60 million Pound Sterling per year. Therefore, pharyngo-tonsillitis therapy has a great health and economic effects (Andersson et al., 2016). In Malaysia, because of the paucity of studies about sore throat, the economic impact of pharyngo-tonsillitis and its impact on the health are not known (Ministry of Health Malaysia, 2003).

1.2 Problem statement

According to World Health Organization, many people are probably facing the problem of sore throat each year, and a majority of physicians depend on the clinical findings to diagnose the upper respiratory tract infections (World Health Organization, 2004). However, previous studies have shown that clinical signs and symptoms alone cannot be used to rule out or diagnose pharyngo-tonsillitis with an adequate sensitivity and specificity, as it can mimic other type of diagnosis infections (Cardoso et al., 2013; Windfuhr et al., 2016; Júnior et al., 2014). Many physicians will automatically prescribe antibiotics based on clinical symptoms, but the Centers for Disease Control and Prevention (CDC) and American Academy of Family Physicians (AAFP) have instructed that antibiotics can only be given to patients with streptococcal pharyngo-tonsillitis to avoid any emergence of antimicrobial resistance among bacteria (Kuehn, 2013; Hersh et al., 2016).

Moreover, most of pharyngo-tonsillitis cases are caused by viruses and do not require antibiotics (Kuehn, 2013). Furthermore, diagnosis of the pathogens cause pharyngo-tonsillitis by throat culture has always been delayed. Ideally, the should be confirmed by throat swab culture, which usually takes two to three days for the bacterial growth to be identified (Uptona et al., 2017). During this period, the illness might be resolved or patients might suffer several complications such as scarlet fever, toxic shock syndrome, rheumatic fever and acute glomerulonephritis (Wong et al., 2013). Therefore, there is need a quick and effective diagnosis of pharyngo-tonsillitis on the first visit of the patients and determine if the patients need for antibiotic therapy.

Over prescribing of antibiotics has very serious health effects with severe reactions and may promote antibiotic resistance and add significantly to the cost of health care (Llor & Bjerrum, 2014). Furthermore, the resistance of antimicrobial lead to increase morbidity and mortality since resistance increases the risk of inappropriate therapy (Andersson, 2016). The risk is that the patients who do not receive appropriate therapy will have a longer period of disease or fatal effect; therefore, morbidity and transmission of the microorganism will increase due to the patients remain infectious for a long period (Centers for Disease Control and Prevention, 2014). Also, the increasing trend of antimicrobial resistance is a serious challenge in countries at all economic levels (Ventola, 2015). Therefore, there is a need to document the prescription practices of the physicians in the primary care clinics.

In Malaysia, data on the epidemiology of sore throat or pharyngo-tonsillitis with regard to its prevalence, socio- demographic data, aetiology of the pharyngo-tonsillitis and complications is very much lacking (Ministry of Health Malaysia, 2003). Therefore, there is a need to document pharyngo-tonsillitis with respects to its aetiology, risk factors and demographic data in Malaysia.

1.3 Significance of study

Pharyngo-tonsillitis is major public problems globally. Currently, group A streptococcal pharyngo-tonsillitis account for increasing morbidity and mortality. Unnecessarily antibiotic prescriptions add an economic burden not only on the individuals but also the health care system. Also, the risk factors that are associated with pharyngo-tonsillitis increases the risk of pharyngo-tonsillitis and has not been well studied. Centor score is a tool or guideline based on a set of criteria that help to identify the likelihood of streptococcal infections in patients with a sore throat. It was developed as a quick diagnosis of group A streptococcal pharyngo-tonsillitis in adult patients (Borchardt, 2013). Previous studies have shown that the Centor scoring system has an acceptable sensitivity and specificity and it can limit the over prescription of antibiotics, thus will reduce the emergence of antibiotic resistance as well as the cost of health care (Aalbers et al., 2011; Fine et al., 2012). Therefore, this study aims to determine the prevalence and factors associated with pharyngo-tonsillitis and the validity of Centor score to diagnose group A streptococcal pharyngo-tonsillitis among adult patients with sore throat in Sepang, Selangor, Malaysia. The findings in this study will help in understanding the prevalence of pharyngo-tonsillitis in Malaysia, contribute to the advancement of knowledge on this issue and also hope to be beneficial in further research. Furthermore, this study will be a reference to guide physicians to appropriately prescribe antibiotics for adults with pharyngo-tonsillitis in the local setting depending on Centor score.

1.4 Objectives

1.4.1 General objective

To describe the epidemiological pattern, etiology and its antibiotic susceptibility, clinical manifestation, antibiotic prescription among adults with sore throat and validity of Centor score in diagnosis group A streptococcal pharyngo-tonsillitis at three primary care clinics in Sepang, Selangor, Malaysia during 2016 to 2017.

1.4.2 Specific objectives

a. To determine the socio-demographic characteristics (age, gender, and ethnicity), and clinical information (smoking and chronic diseases which are hypertension, diabetes, asthma, chronic obstructive pulmonary disease, allergy, heart diseases and others), proportion of pharyngo-tonsillitis, acute pharyngo-tonsillitis, beta hemolytic streptococci (groups A, B, C, F and G) and influenza A and B viruses that are associated with pharyngo-tonsillitis among the participants.
b. To determine the association between the socio-demographic characteristics and the clinical information with pharyngo-tonsillitis.
c. To determine the validity of using Centor score for management of

sore throat and the association between clinical manifestations and Centor score with throat sample results.

d. To determine the types of prescribed antibiotics by the attending physician at the clinics with throat sample results and the association between Centor score and throat sample results with prescribed antibiotics

e. To determine the antimicrobial susceptibility patterns of beta hemolytic streptococci (groups A, B, C, F and G) that are associated with pharyngo-tonsillitis.

1.5 Research hypothesis

Based upon these data, it hypothesized that:

a. There is a significant association between socio-demographic data (age, gender and ethnicity) and pharyngo-tonsillitis.

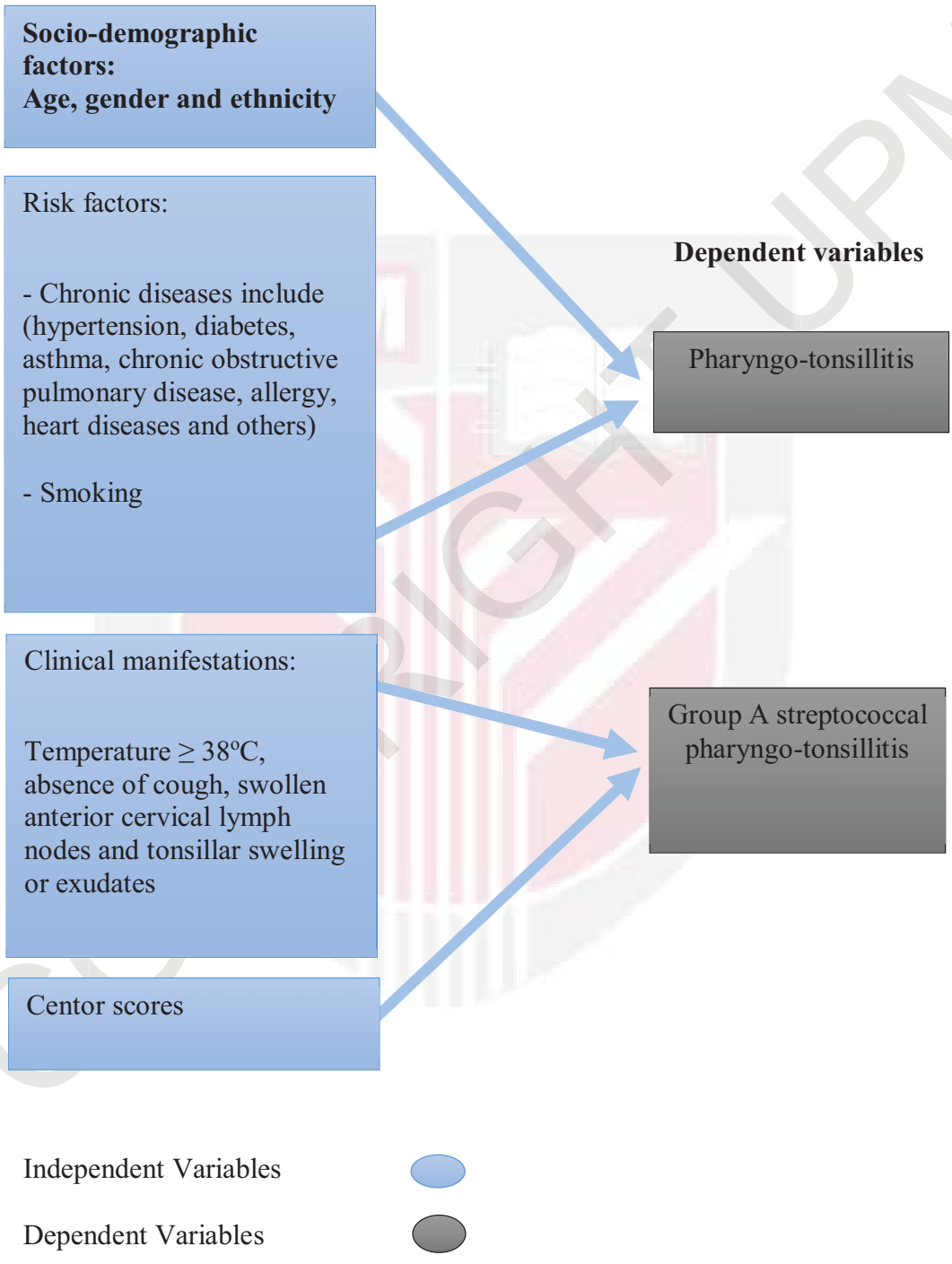
b. There is a significant association between the clinical information (smoking and chronic diseases which include hypertension, diabetes, asthma, chronic obstructive pulmonary disease, allergy, heart diseases and others) and pharyngo-tonsillitis.

c. There is a significant association between the clinical manifestations and Centor score with group A streptococcal pharyngo-tonsillitis.

1.6 Conceptual Framework

The development of pharyngo-tonsillitis is based on interplay of many correlated factors (Klug, 2014). Pharyngo-tonsillitis is an inflammation involving both the pharynx and tonsils most commonly caused by viral or bacterial infection (Wessels, 2011; Anjos et al., 2014). Pharyngo-tonsillitis reported to be influenced by socio-demographic, risk and environmental factors (Klug, 2017). Clinical manifestations including (Temperature $\geq 38^{o}C$, absence of cough, swollen anterior cervical lymph nodes and tonsillar swelling or exudates) and Centor score found to be associated with group A streptococcal pharyngo-tonsillitis (Centor et al., 1981).

Independent variables



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