HISTORY OF MANUSCRIPT PUBLICATION
(Asian J Pharm Clin Res,)

IMPACT OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION

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PROGRAM STUDI ADMINISTRASI KESEHATAN
FAKULTAS KESEHATAN DAN TEKNOLOGI
UNIVERSITAS MUHAMMADIYAH KLATEN

AUTHOR KORESPONDENSI
ARTIKEL JURNAL INTERNASIONAL

Judul Artikel : Impact Of Environmental Tobacco Smoke Exposure On Adults With Asthma Exacerbation

Identitas Jurnal Ilmiah :

a. Nama Jurnal : Asian J Pharm Clin Res,
b. Nomor ISSN : Online - 2455-3891 Print - 0974-2441
c. Volume, Nomor, Bulan Tahun : Vol 12, Issue 3, 2019
d. Penerbit : Innovare Academics Sciences Pvt. Ltd
e. DOI artikel (jika ada) : http://dx.doi.org/10.22159/ajpcr.2019.v12i3.28498
f. Alamat Web Jurnal :
https://innovareacademics.in/journals/index.php/ajpcr/article/view/28498
g. Terindeks di : Scopus (Disc), DOAJ, Google scholar

Riwayat Artikel

NO	PERIHAL	TANGGAL
1	Active Submissions	12 Juli 2018
2	Bukti Received Manuscript	14 Juli 2018
3	Revision Required (1st Round)	9 Agustus 2018
4	Revision Reminder	17 Agustus 2018
5	Revision Required (2nd Round)	10 September
6	Revision Reminder	20 September
7	Manuscript Acceptance **(LoA)**	13 Desember 2018
8	Proofing Of Paper For Checking	19 Februari 2019
9	Respons To Checking Proofing	19 Februari 2019
10	Bukti Konfirmasi published	Maret 2019

Lampiran Pendukung :

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Sutaryono_Manuscript Submission

sutar yono <sutar.on@gmail.com> 12 Juli 2018 pukul 15.40
Kepada: editor@ajpcr.com

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I hereby would like to submit an original paper to be published as a Research Paper at the Asian Journal of Pharmaceutical and Clinical Research, as follows:
Title : Impact of Environment Tobacco Smoke Exposure in Adults with Asthma Exacerbation
Authors : Sutaryono, Hartono, Ari Probandari, Prabang Setyono
Principal investigator: Sutaryono
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Print ISSN- 0974-2441 Online ISSN- 2455-3891
INNOVARE ACADEMIC SCIENCES Knowledge to Innovation

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ICV 2016 = 104.84
Print ISSN- 0974-2441
Online ISSN- 2455-3891

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Impact per Publication (IPP): 0.588

SCImago Journal Rank (SJR): 0.22

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2 Bukti Received Manuscript 14 Juli 2018

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[AJPCR] 28498

editor ajpcr <editorajpcr@gmail.com> 14 Juli 2018 pukul 17.00
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3 Revision Required (1st Round) 9 Agustus 2018

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status/AJPCR/28498

editor ajpcr <editorajpcr@gmail.com> 9 Agustus 2018 pukul 13.39
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IMPACT OF ENVIRONMENT TOBACCO SMOKE EXPOSURE ~~IN~~ON ADULTS WITH ASTHMA EXACERBATION

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ABSTRACT

Objective: Environment Tobacco Smoke (ETS) exposure in the household is dangerous ~~for~~to infants and children. Nicotine residue inhaled in the respiratory tract metabolized into cotinine which ~~can cause~~has the possibility of causing inflammation ~~so it~~which can ~~cause an~~result in asthma exacerbation. The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

Methods: A cohort study was carried out among 114 asthma patients aged 12-18 years old at three hospitals ~~in~~ from January 2016 ~~until~~to March 2017. Data was obtained using self reported questionnaires and cotinine urine test. The data analysis ~~used~~was carried with the use of *Cox Proportional Hazard Model* with 95% confidence interval.

Results: ~~During~~The result of the ~~study period,~~research showed that 57% of the patients got the trigger (event~~), consisting~~). The respondents consisted of 61.5% of female, ~~and the~~ average age of 15 years, 50.8% of upper secondary education, 55.4% of body mass index BMI normal~~,~~ and 63.1% low economic status persons. Median survival for the ETS-exposed group was in 9th ~~weeks~~week, while the median survival for the ETS non-exposed group was more than 12 weeks. Multivariate exposure of ETS with asthma exacerbation was HR, 2.17; 95% CI, 1.23-3.83, p = 0.008 and gender HR, 1.72; 95% CI, 1.04-2.85, p = 0.035.

Conclusion: Environment Tobacco Smoke (ETS) exposure in the household increases the risk of asthma exacerbation. Controlling the environment and ~~educationof~~education of children to avoid ETS exposure should be intensified.

Keywords: asthma, exacerbation, environmental tobacco smoke, cotinine

INTRODUCTION

~~The epidemiological~~Epidemiological studies show that smoking is a global health problem and it is seen as a risk factor for the emergence of various medical disorders, especially ~~noncommunicable~~some non-communicable diseases [1]. Environment Tobacco Smoke (ETS) ~~is one~~has to do with the pollution of the ~~pollutants in the room or~~ environment, mostly rooms, with tobacco smokes and that is why it is usually referred ~~to~~Secondhand~~to~~ as Second Hand Smoke (SHS). It ~~is associated~~comes with ~~the impact~~devastating impacts such as cardiovascular death

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and respiratory diseases, infections, behavioral problems, low birth weight, sudden infant death syndrome, and cancer [2, 3]. Groups that are particularly vulnerable to this secondhand smoke are children, so they are easily affected by asthma, pneumonia, sinusitis, and different allergies.

Globally, about 40% of children with respiratory problems got them from smoking parents, as a result of this, about 28% of children deaths were associated with ETS in 2004 [2], people who]. People that smokes are at risk of developing diabetes mellitus, cigarette smoking habitbe as well as be at increased risk of cancer of the bladder, cancer [4, 5]. Exposure to tobacco smoke quickly damages can cause heart attacks, strokes, and even sudden death. Smoking. It was found that smoking causes about 85% of lung cancers in the United States [6]. Sympathetic overactivity may lead to cardiovascular disease development in smokers, that cigarette. Cigarette smoking also has adverse effect on serum ferritin and other hematologic parameters, and serumferritin isserum ferritin has been discovered to be one of the most reliable indicators of iron status [7, 8]. The cox proportional hazard model showedshows higher hazard ratio for smokers [9].

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One of the major effects of ETS that can causeresult in death is asthma, where asthma. Asthma is a chronic inflammatory disease of the respiratory tract characterized by wheezing, coughing, and chest tightness due to respiratory tract blockages. Epidemiological study of asthma reveals that the prevalence from several countries ranged from 1% to 18% [10], while, nationally, in Indonesia it showed 4.5% [11]. Asthma is caused by many factors, genetic which include gene, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization, Bodybody weight, hypertension and tobacco exposure. These are the main risk factors associated with childhood-onset asthma [12, 13].

Leftover cigarette smoke on surfaces does not evaporate into the air, however, there is nicotine residue attached to the dust or stuff around us, such as clothes, carpets, walls, furniture or chairs. Nicotine dust is not going to disappear in a short time so it will be inhaled by others even though the smoker has left the place [14, 15].

More than 5200 chemical components are found in cigarette smoke in the form of the particles and steam [16]. These chemicals are dangerous whichand can increase allergies in cause damages to the respiratory tract, so itin such a way that they can block overall breathing work [17]. One of thosethese chemicals is nicotine thatand it has a secondary immunomodulatory effect of eosinophil function, by inhibiting the release of pro-inflammatory cytokines from macrophages [18, 19].

ETS exposure in the household can increase the severity of asthma in children because beingwhile they are on the floor inhaled, they inhale dust of carpet, mildew, mite and others which are equivalent to sucking four cigarettes a day. Over 90% of children spend their time indoors so thatand because of the ETS, indoor air pollution gives more harmful health effects than outdoor air pollution [20].

ETS exposure in the household can be inhaled through the breath into the alveoli and then spread into the blood circulation if not stopped. In the metabolism, there is *CYP2A6* genes, which are genes encoding P450 2a6 of cytochrome enzyme. This enzyme is responsible for 70% untilto 90% of nicotine metabolism in blood to cotinine [21-24]. Therefore, ETS exposure can be assessed through cotinine measurement in urine, serum, or saliva.

Nicotine in cigarette smoke can trigger inflammation because it has a direct effect on neutrophils and macrophages ~~by activating~~through the activation of *nicotinic acetylcholine receptors (nAChR)* in nerve cells as well as non-nerve cells such as monocytes and endothelia [25]. Several studies have also shown an increase in neutrophil inflammation in the bronchi~~,~~ and an increased number of neutrophils will trigger an increase in eosinophils, which will secrete inflammatory mediators that play a significant role ~~during~~in triggering asthma ~~triggers~~. Decreased IgE serum, blood eosinophils and *fractional exhaled nitric oxide* (FeNO) non-smoker's and former smoker's ages had higher *thymic stromal lymphopoietin* (TSLP) than those that never ~~smokers~~smoke. In addition, goblet cell numbers will increase and hypersecretion of mucus in the respiratory tract [26]. Cigarette smoking ~~increased~~increases plasma IL-6 and TNF-α concentrations in smokers~~, the~~. The oxidative stress resulting from the elevated serum ~~they~~ can oxidize membrane lipids and proteins and , consequently-, increase the expression of these inflammatory factors [27].

This study ~~analyzes~~analyzed the harmful effects of ETS exposure on survival ~~in~~of people with asthma. We ~~hypothesize~~hypothesized that asthma ~~patient~~patients affected by ETS exposure will get more rapidly trigger or exacerbation than asthma patient that are not affected by ETS.

The novelty of this study is to assess the risk impact associated with exposing children living with asthma to cigarette smoke environment in the family. We hypothesize that asthmatic children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

METHODS

Study Design

A cohort study was carried out among 114 asthma patients from three hospitals~~, named~~ -, Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia ~~since~~from January 2016 ~~-~~to March 2017 with inclusion of some criteria. The research was carried out on respondents between the ages of 12~~-~~ and 18 year ~~and carried out survival~~. Survival analysis was carried out for asthma exacerbation.

Research Ethics

We conducted a written informed consent before the data collection. The research ethics ~~was~~were obtained from Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.

Data Collection

~~To obtain the~~The data of respondents related to demography, BMI and history of Environmental Tobacco Exposure (ETS) in the household were based on self ~~reported by~~report gotten through interview and questionnaire at the ~~initial~~beginning of the research. The history of cigarette use includes the presence of smokers at home and number of cigarettes per day (1 to 10, 11 to 19, 20 to 29, and more than 30 per day). ~~Our event evaluates~~Data was evaluated at 12 weeks or 3 months through self ~~reported~~report or medical records ~~of~~from the hospital to obtain sensory time analysis data. Urine sampling was also done in ~~early~~early research on every subject. Urine samples were used to determine levels of Cotinine ~~using~~with the use of *Enzyme-*

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Linked Immunosorbent Assay (ELISA) method [28-31]. Urine cotinine analysis data ~~are~~were classified into two categories which are: lower than 15ng/ml also known as non-exposed and higher than 15ng/ml also known as exposed [28].

Data Analysis

~~A demographic~~Data on demography, body mass index (BMI), cigarette use and cotinine concentration were obtained ~~by using~~with the use of frequency distribution and percentage.~~We used~~ We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariate *Cox proportional Hazard* models were fitted using all the covariates, yielding Hazard ratios (HRs) 95% confidence interval with SPSS software.

RESULTS

Based on medical ~~record~~records from three hospitals; Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkelmas) Klaten, Central Java, Indonesia ~~since~~from January 2016 to March 2017. The total number of asthma patients in the three health care ~~facilities were~~ facilities were 4872 ~~patients, especially~~with the number of children with asthma ~~were~~ recorded to be 726. There were 114 children who fulfilled the criteria and they were used as samples. During the research period, it was found that the trigger status (event) was 57% and the sensor was 43%. Survival time ~~was~~showed that 50% respondent suffered the trigger in the 10th week, while the ETS-exposed group was in the 9th week.

Baseline characteristics as a single predictor of asthma exacerbation are summarized in Table 1. Cohort survival time showed that most of the respondents who suffered events were 61.5% ~~of~~ female, ~~and~~at the average age of 15 years, 50.8% of upper secondary education, 55.4% of BMI normal, income ~~<$~~ < $105 (63.1%). Cotinine test as ETS biomarker showed that high concentration of cotinine suffered more events (75.4%).

Table 1. The Baseline of Sociodemographic Characteristics, ETS Exposure and Triger in Adults with Asthma Exa erbation

Variable	Event		Sensor		p-value*
	n	%	n	%	
Age					
12-15	30	46.15	32	65.31	0.067
16-18	35	53.85	17	34.69	
Mean, SD	15 ± 2.5				
Gender					
Female	40	61.54	20	40.82	0.065
Male	25	38.46	29	59.18	
Education					
Primary	32	49.23	33	67.35	0.056
Upper Secondary	33	50.77	16	32.65	
BMI					

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Normal	36	55.38	20	40.82	0.186
Abnormal	29	44.62	29	59.18	
Income					
<$ 105	41	63.08	24	48.98	0.124
≥$ 105	24	36.92	25	51.02	
Cotinine					
≥ 15 ng/ml	49	75.38	26	53.06	0.010
< 15 ng/ml	16	24.62	23	46.94	

* The Log rank test (Mantel Cox) was used for all other characteristics; BMI : body mass index

The result of multivariate analysis with *cox regression* (*Cox Proportional Hazard Model)* showed that ~~from~~ some variables, cotinine concentration and ~~demografi~~demographic variable (gender) have significant correlation with asthma exacerbation (HR, 2.17; 95% CI, 1.23-3.83) and (HR, 1.72; 95% CI, 1.04-2.85).

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Table 2. Results of the Multivaria e Analysis for overall survival

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Variable	Level	HR (95% CI)	p-value*
Gender	(female vs. male)	1.721 (1.040-2.849)	0.035
Cotinine	(≥ 15 ng/ml and < 15 ng/ml)	2.168(1.226-3.832)	0.008

HR : hazard ratio; CI : confidence interval
* The cox regression (Cox Proportinal Hazard Model)

DISCUSSION

Median survival for both ETS-exposed and non-exposed groups ~~are~~were 10 weeks. It shows that patients with asthma exacerbation will suffer the trigger in the 10th week. Asthma patients with ETS-exposed will rapidly suffer the trigger in the 9th week, while patients with ETS non-exposed were more than 12 weeks. The result has the similarity as the other research that find an average rate of asthma trigger ~~rate as~~to be 14 weeks or 3.5 months per year [32].

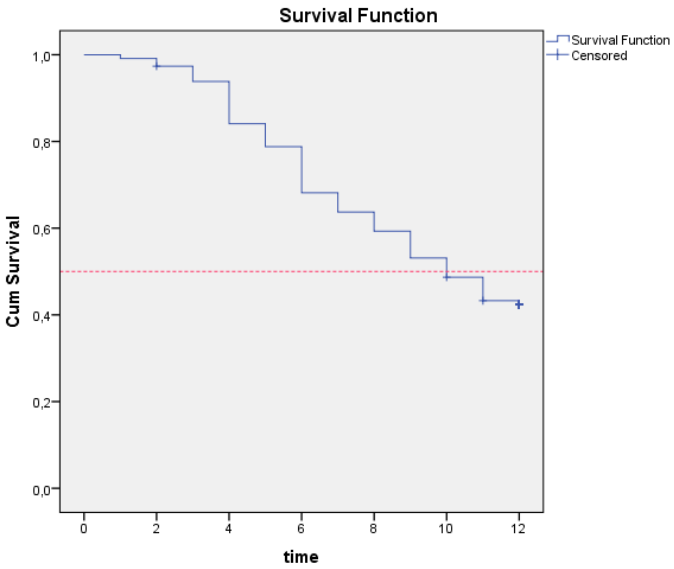

Fig.1 Survival curve for the asthma exacerbation for all groups

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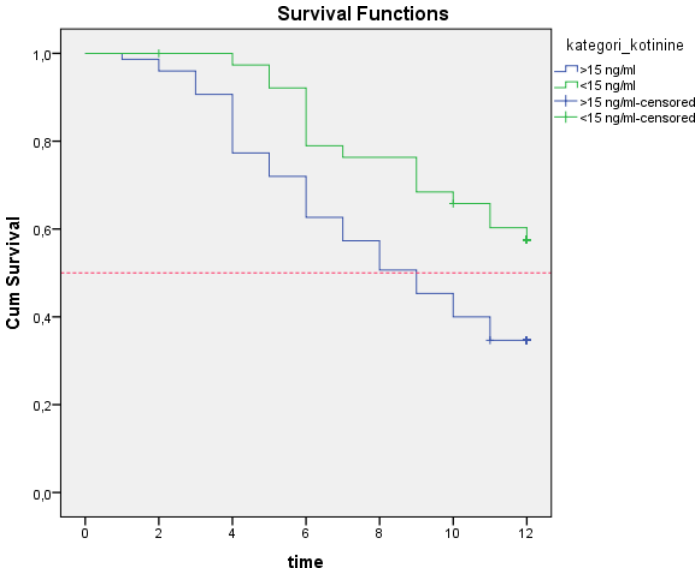

Fig. 2 Survival curve for the asthma exacerbation and cotinine ETS exposure.

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Hazard survival ETS with urinary cotinine concentration of biomarker and frequency on the trigger of asthma exacerbation was HR, 2.17; 95% CI, 1.226-3.832, p = 0.008. The result of this research shows that ETS exposure measured with urine cotinine level in children suffering asthma has risk 2 of having asthma exacerbation more rapidly when compared ~~by~~to children with non-~~exposed~~exposure of cigarette smoke. There is a research that has proved that mothers who smoke increase fourfold response to histamine, as well as high level of cotinine increase the risk of acute asthma exacerbation ~~by1~~by 1.8-fold [33]. Children with ETS-exposed have the higher risk of having uncontrolled asthma with OR= 3.20; 95% CI= 1.40 to 6.90 [34].

Children who live in homes with smoking members have increased ~~the~~ cotinine level when compared ~~to~~with those ~~who live~~living in homes with no smokers. It shows that ETS exposure is associated with the increasing urinary cotinine and acute exacerbation asthma trigger as well as decreasing lung function of FEV1 and ratio of FVC [35]. Around 87,9% of nontobacco consumers in the United States had detectable ~~acquire~~acquired serum cotinine levels. Nearly 40% of children aged 2 months to 2 years are living with at least one smoker, and perhaps, their condition is exacerbated by ETS exposure [36].

A series of epidemiological surveys provide strong evidence of the relationship between parental smoking and prevalence of asthma in school age children [37, 38]. A recent study and meta-analysis of 76 studies have assessed ~~that~~ the effects of pre-or post-natal second-hand smoke exposure is associated with a 21% to 85% increased risk of asthma incident ~~asthma~~ [39]. The strongest effect from prenatal maternal smoking on asthma in children aged 2 years old has CI 95% OR=1,85 (1.3-2,5). In adolescence and adults, exposure to passive smoke is also associated with the prevalence of asthma [25].

The increase of urinary cotinine concentration is affected by the number of smokers ~~at home~~in an household and the number of ~~smoked~~ cigarettes smoked. The result showed that the existing home smokers have cotinine concentrations >15ng/ml at most. Category of heavy smokers or higher number of cigarettes >20 cigarettes per day, are as shown in the following table:

Table 3. ETS Status at home and Cotinine Concentration

ETS Household	Cotinine	
	≥ 15 ng/ml	< 15 ng/ml
Home with smoker	50 (66.7)	7 (17.9)
Home without smoker	25 (33.3)	32 (82.1)

ETS : Environment Tobacco Smoke

Table. 4 Number of Cigarettes and Cotinine Concentration

Number of cigarette	Cotinine	
	> 15 ng/ml	< 15 ng/ml
< 4	6 (12)	3 (42.9)
5 - 9	11 (22)	1 (14.3)
10 - 19	16 (32)	1 (14.3)
20 - 29	17 (34)	2 (28.6)

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The variability of each individual against the pattern of cotinine metabolism due to exposure to existing nicotine is quite ~~varied~~different. Therefore, it is possible ~~if~~that there may be existence of cotinine in an household where there is no smoke ~~at home but cotinine still exists.~~ This ~~is due~~may be attributed to exposure of the inhabitant(s) to cigarette smoke outside the home and other metabolism factors such as genetic variation, race, sex, use of oral contraceptives or other estrogen-containing hormones, renal and drug failure, including anticonvulsants and rifampin as well as from ~~food~~foods they ate [23, 40].

The main physiological features of asthma exacerbation are airways constriction and airflow obstruction, which are reversible. It is produced as a result of contraction of bronchial smooth muscle, edema and hypersecretion of mucus. Various trigger factors can lead to exacerbations. Acute bronchoconstriction caused by allergens occurs as a result of the release of mediators from mast cells [41]. The nature of tobacco smoke as inhalants, which are inhaled and exposed directly to the airway, causes a risk factor that has relationship with asthma exacerbation events in children [17, 42].

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8 + and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43]

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04-2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi et al., Conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environtment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller, however, long-term use of this medication has side effects. Tamarindusindica L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed in order to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

CONCLUSION

This research ~~showed~~revealed that environment tobacco smoke exposure in the household increases the risk of asthma exacerbation. Since children with asthma should have good survival and quality of life, it is, therefore, ~~it is important~~necessary and expedient to control the environment and ~~education of~~educate children to avoid ETS Exposure.

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ACKNOWLEDGMENTS

We would like to thank Directors of the Center for Healthy Lung Community Surakarta, Dr. Moewardi Hospital Surakarta, and the Lung Health Center Klaten, Indonesia for ~~giving the~~granting us permission.We also thank all enumerators and laboratory technicians for assisting ~~the~~in the process of collecting data ~~collection~~.

AUTHORS' CONTRIBUTIONS

~~all Authors~~All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono ~~design a~~designed the framework, ~~plan~~planned sample preparation and carry out data collection in the field. Hartono contributed ~~the lead~~ in writing the script and ~~supervising~~supervision of all activities. All authors ~~discuss~~discussed and ~~provide~~provided critical feedback on ~~the~~this text.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper

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4 Revision Reminder 17 Agustus 2018

August 27, 2018

To
Dr. Anurekha Jain
Editor in Chief
Asian Journal of Pharmaceutical and Clinical Research

Subject: Re-Submission of research article (Appended and revised submission point-by-point) for the publication in Asian Journal of Pharmaceutical and Clinical Research

Dear Dr. Anurekha Jain
We are grateful to you for the opportunity to resubmit this substantial revision of our manuscript titled **IMPACT OF ENVIRONMENT TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION** as a resubmission for consideration of publication in Asian Journal of Pharmaceutical and Clinical Research.

For reviewer information, this version of manuscript comprises all the detailed and substantial information that has been raised in major and minor concerns. For instance, in this submission, we have rearranged manuscript as per recommendation by the reviewer (rewriting and proof-reading). We are thankful to reviewer concern and incorporated all the changes as per the recommendations by reviewer and feel confident that this body of work is now substantially improved our revised manuscript. We have included all the concerns in the revised version of the manuscript according to the recommendations of referee's and hope this work is now sufficient to answer the scientific questions to qualify the standard of this Asian Journal of Pharmaceutical and Clinical Research.

Thank you for your consideration!

Sincerely yours,
Authors

Answer to Reviewer ;

1. Put two citations from IJPPS
Response: Thanks for the comments. We have included quotes from IJPPS (References No. 13 and 27).

1. *Reference 13.* Rina A, Eff Y. Incidence of Hypertension in Asthma Patients Who Treated With Beta-2 Agonists Bronchodilators. *Int J Pharm Pharm Sci*. 2017;9(4):2-5.
2. *Reference 27.* B. A. R. Mshimesh, Effects of etoricoxib, zileuton, and their combination on urinary PGE-M and LTE4 levels in iraqi smokers: A comparative study. *Int. J. Pharm. Pharm. Sci.*, vol. 8, no. 6, pp. 182–187, 2016

2. Need to reduce grammatical mistakes
   Response: Thank you. We have reviewed and sent to professional native proofreading service.

3. Referencing is required as per format
   Response: We have adjusted the reference according to the format specified

4. Editing and formatting is required as per journal
   Response: Thank you. We have adjusted the script format according to the guideline of journal, which includesa as follows:
   1. *Title page*
   2. *Abstract*
   3. *Introduction*
   4. *Materials and methods*
   5. *Results*
   6. *Discussion*
   7. *Conclusion*
   8. *Acknowledgement*
   9. *References*

5. Please add two citations from our other journal ijpps highlight with red color and also add two points conflicts of interests or authors contribution.
   Response:
   1. *We have added a quote from the IJPPS journal and we also have marked the red as in our response the first point (references 13, 27).*
   2. *We have also added conflicts of interests*
      "The authors declare that there is no conflict of interests regarding the publication of this paper."
   3. *We have already added this text that we have resubmitted to the contribution authors as suggested.*
      "All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono designed the framework, planned sample preparation and carry out data collection in the field. Hartono contributed in writing the script and supervision of all activities. All authors discussed and provided critical feedback on this text."

6. There is no need of structural abstract in a review article
   Response: we need to say that our abstract structure has been adapted to the original article format, with the arrangement:
   1. *Objective*
   2. *Methods*
   3. *Results*
   4. *Conclusion*
   5. *Keywords*

Original Article

IMPACT OF ENVIRONMENT TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION

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ABSTRACT

Objective: Environment Tobacco Smoke (ETS) exposure in the household is dangerous to infants and children. Nicotine residue inhaled in the respiratory tract metabolized into cotinine which has the possibility of causing inflammation which can result in asthma exacerbation. The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

Methods: A cohort study was carried out among 114 asthma patients aged 12-18 years old at three hospitals from January 2016 to March 2017. Data was obtained using self reported questionnaires and cotinine urine test. The data analysis was carried with the use of Cox Proportional Hazard Model with 95% confidence interval.

Results: The result of the research showed that 57% of the patients got the trigger (event). The respondents consisted of 61.5% of female, average age of 15 years, 50.8% of upper secondary education, 55.4% of body mass index (BMI) normal and 63.1% low economic status persons. Median survival for the ETS-exposed group was in 9^{th} week, while the median survival for the ETS non-exposed group was more than 12 weeks. Multivariate exposure of ETS with asthma exacerbation was hazard ratio (HR), 2.17; 95% CI, 1.23-3.83, p = 0.008 and gender HR, 1.72; 95% CI, 1.04-2.85, p = 0.035.

Conclusion: Environment tobacco smoke exposure in the household increases the risk of asthma exacerbation. Controlling the environment and education of children to avoid ETS exposure should be intensified.

Keywords: Environmental tobacco smoke, cotinine, survival, asthma, exacerbation

INTRODUCTION

Epidemiological studies show that smoking is a global health problem and it is seen as a risk factor for the emergence of various medical disorders, especially some non-communicable diseases [1]. Environment Tobacco Smoke (ETS) has to do with the pollution of the environment, mostly rooms, with tobacco smokes and that is why it is usually referred to as

Second Hand Smoke (SHS). It comes with devastating impacts such as cardiovascular death and respiratory diseases, infections, behavioral problems, low birth weight, sudden infant death syndrome and cancer [2, 3]. Groups that are particularly vulnerable to this secondhand smoke are children, so they are easily affected by asthma, pneumonia, sinusitis and different allergies.

Globally, about 40% of children with respiratory problems got them from smoking parents, as a result of this, about 28% of children deaths were associated with ETS in 2004 [2]. People that smokes are at risk of developing diabetes mellitus as well as be at increased risk of cancer of the bladder [4, 5]. Exposure to tobacco smoke can cause heart attacks, strokes, and even sudden death. It was found that smoking causes about 85% of lung cancers in the United States [6]. Sympathetic overactivity may lead to cardiovascular disease development in smokers. Cigarette smoking also has adverse effect on serum ferritin and other hematologic parameters and serum ferritin has been discovered to be one of the most reliable indicators of iron status [7, 8]. The cox proportional hazard model shows higher hazard ratio for smokers prognostic impact in patients with lung Adenocarcinoma[9].

One of the major effects of ETS that can result in death is asthma. Asthma is a chronic inflammatory disease of the respiratory tract characterized by wheezing, coughing, and chest tightness due to respiratory tract blockages. Epidemiological study of asthma reveals that the prevalence from several countries ranged from 1% to 18% [10], while, nationally, in Indonesia it showed 4.5% [11]. Asthma is caused by many factors which include gene, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization, body weight, hypertension and tobacco exposure. These are the main risk factors associated with childhood-onset asthma [12, 13].

Leftover cigarette smoke on surfaces does not evaporate into the air, however, there is nicotine residue attached to the dust or stuff around us, such as clothes, carpets, walls, furniture or chairs. Nicotine dust is not going to disappear in a short time so it will be inhaled by others even though the smoker has left the place [14, 15].

More than 5200 chemical components are found in cigarette smoke in the form of particles and steam [16]. These chemicals are dangerous and can cause damages to the respiratory tract, in such a way that they can block overall breathing work [17]. One of these chemicals is nicotine and it has a secondary immunomodulatory effect of eosinophil function, by inhibiting the release of pro-inflammatory cytokines from macrophages [18, 19].

ETS exposure in the household can increase the severity of asthma in children because while they are on the floor, they inhale dust of carpet, mildew, mite and others which are equivalent to sucking four cigarettes a day. Over 90% of children spend their time indoors and because of the ETS, indoor air pollution gives more harmful health effects than outdoor air pollution [20].

ETS exposure in the household can be inhaled through breath into the alveoli and then spread into the blood circulation if not stopped. In the metabolism, there is CYP2A6 genes, which are genes encoding P450 2a6 of cytochrome enzyme. This enzyme is responsible for 70% to 90% of nicotine metabolism in blood to cotinine [21-24]. Therefore, ETS exposure can be assessed through cotinine measurement in urine, serum or saliva.

Nicotine in cigarette smoke can trigger inflammation because it has a direct effect on neutrophils and macrophages through the activation of nicotinic acetylcholine receptors (nAChR) in nerve cells as well as non-nerve cells such as monocytes and endothelia [25]. Several studies have also shown an increase in neutrophil inflammation in the bronchi and an increased number of neutrophils will trigger an increase in eosinophils, which will secrete inflammatory mediators that play a significant role in triggering asthma. Decreased IgE serum, blood eosinophils and fractional exhaled nitric oxide (FeNO) non-smoker's and former smoker's ages had higher thymic stromal lymphopoietin (TSLP) than those that never smoke. In addition, goblet cell numbers will increase and hypersecretion of mucus in the respiratory tract [26]. The presence of cotinine urine levels in smokers has a positive relationship to increased levels of PGE-M and LTE4. This plays a role in inflammation and carcinogenesis[27].

The novelty of this study is to assess the risk impact associated with exposing children living with asthma to environment tobacco smoke in the family. We hypothesize that asthmatic children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

METHODS

Study Design

A cohort study was carried out among 114 asthma patients from three hospitals - Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017 with inclusion of some criteria. The research was carried out on respondents between the ages of 12 and 18 year. Survival analysis was carried out for asthma exacerbation.

Research Ethics

We conducted a written informed consent before the data collection. The research ethics were obtained from Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Indonesia.

Data Collection

The data of respondents related to demography, BMI and history of environmental tobacco exposure in the household were based on self report gotten through interview and questionnaire at the beginning of the research. The history of cigarette use includes the presence of smokers at home and number of cigarettes per day (1 to 10, 11 to 19, 20 to 29, and more than 30 per day). Data was evaluated at 12 weeks or 3 months through self report or medical records from the hospital to obtain sensory time analysis data. Urine sampling was also done in early research on every subject. Urine samples were used to determine levels of Cotinine with the use of Enzyme-Linked Immunosorbent Assay (ELISA) method [28-31]. Urine cotinine analysis data were classified into two categories which are: lower than 15 ng/ml also known as non-exposed and higher than 15ng/ml also known as exposed [28].

Data Analysis

Data on demography, BMI, cigarette use and cotinine concentration were obtained with the use of frequency distribution and percentage. We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariate Cox proportional Hazard models

were fitted using all the covariates, yielding Hazard ratios (HRs) 95% confidence interval with SPSS software.

RESULTS

Based on medical records from three hospitals; Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017. The total number of asthma patients in the three health care facilities were 4872 with the number of children with asthma recorded to be 726. There were 114 children who fulfilled the criteria and they were used as samples. During the research period, it was found that the trigger status (event) was 57% and the sensor was 43%. Survival time showed that 50% respondent suffered the trigger in the 10^{th} week, while the ETS-exposed group was in the 9^{th} week.

Baseline characteristics as a single predictor of asthma exacerbation are summarized in Table 1. Cohort survival time showed that most of the respondents who suffered events were 61.5% female, at the mean age of 15 years, 50.8% of upper secondary education, 55.4% of BMI normal, income < $105 (63.1%). Cotinine test as ETS biomarker showed that high concentration of cotinine suffered more events (75.4%).

Table 1. The Baseline of Sociodemographic Characteristics, ETS Exposure and Triger in Adults with Asthma Exacerbation

Variable	Event		Sensor		p-value*
	n	%	n	%	
Age					
12-15	30	46.15	32	65.31	0.067
16-18	35	53.85	17	34.69	
Mean, SD	15 $\pm$ 2.5				
Gender					
Female	40	61.54	20	40.82	0.065
Male	25	38.46	29	59.18	
Education					
Primary	32	49.23	33	67.35	0.056
Upper Secondary	33	50.77	16	32.65	
BMI					
Normal	36	55.38	20	40.82	0.186
Abnormal	29	44.62	29	59.18	
Income					
<$ 105	41	63.08	24	48.98	0.124
$\geq$ $ 105	24	36.92	25	51.02	
Cotinine					
$\geq$ 15 ng/ml	49	75.38	26	53.06	0.010
< 15 ng/ml	16	24.62	23	46.94	

* The Log rank test (Mantel Cox) was used for all other characteristics; BMI : body mass index

The result of multivariate analysis with cox regression (Cox Proportional Hazard Model) showed that some variables, cotinine concentration and demographic variable (gender) have significant correlation with asthma exacerbation (HR, 2.17; 95% CI, 1.23-3.83) and (HR, 1.72; 95% CI, 1.04-2.85).

Table 2. Results of the Multivariate Analysis for overall survival

Variable	Level	HR (95% CI)	p-value*
Gender	(female vs. male)	1.721 (1.040-2.849)	0.035
Cotinine	(≥ 15 ng/ml and < 15 ng/ml)	2.168(1.226-3.832)	0.008

HR : hazard ratio; CI : confidence interval
* The cox regression (Cox Proportinal Hazard Model)

DISCUSSION

Median survival for both ETS-exposed and non-exposed groups were 10 weeks. It shows that patients with asthma exacerbation will suffer the trigger in the 10th week. Asthma patients with ETS-exposed will rapidly suffer the trigger in the 9th week, while patients with ETS non-exposed were more than 12 weeks. The result has the similarity as the other research that find an average rate of asthma trigger to be 14 weeks or 3.5 months per year [32].

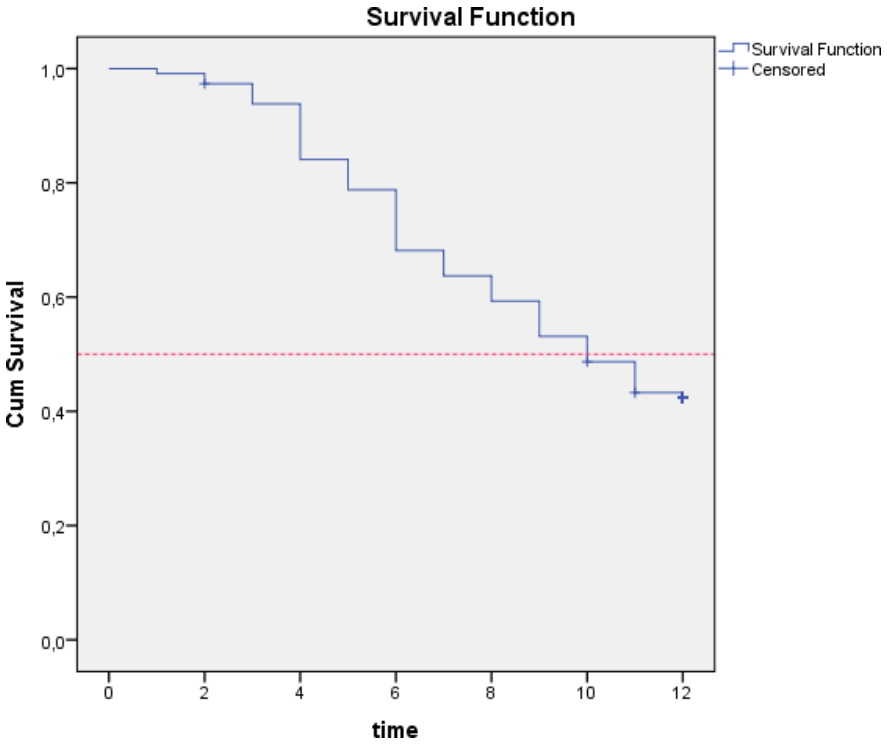

Fig.1 Survival curve for the asthma exacerbation for all groups

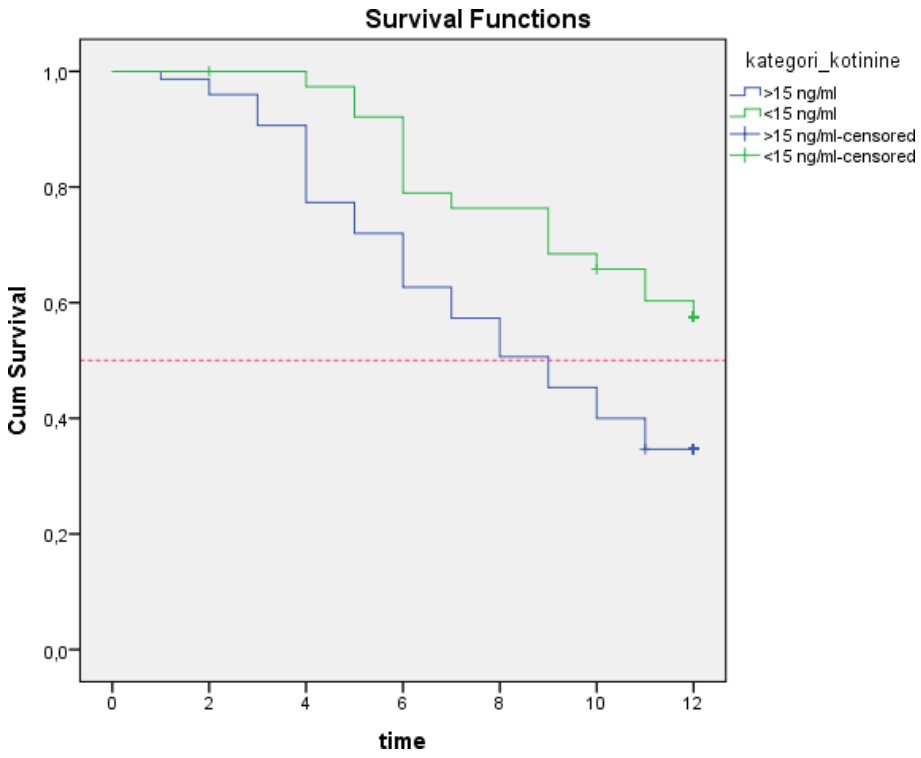

Fig. 2 Survival curve for the asthma exacerbation and cotinine ETS exposure.

Hazard survival ETS with urinary cotinine concentration of biomarker and frequency on the trigger of asthma exacerbation was HR, 2.17; 95% CI, 1.226-3.832, p = 0.008. The result of this research shows that ETS exposure measured with urine cotinine level in children suffering asthma has risk 2 of having asthma exacerbation more rapidly when compared to children with non-exposure of cigarette smoke. There is a research that has proved that mothers who smoke increase fourfold response to histamine as well as high level of cotinine increase the risk of acute asthma exacerbation by 1.8-fold [33]. Children with ETS-exposed have the higher risk of having uncontrolled asthma with OR= 3.20; 95% CI= 1.40 to 6.90 [34].

Children who live in homes with smoking members have increased cotinine level when compared with those living in homes with no smokers. It shows that ETS exposure is associated with the increasing urinary cotinine and acute exacerbation asthma trigger as well as decreasing lung function of FEV1 and ratio of FVC [35]. Around 87.9% of nontobacco consumers in the United States had detectable acquired serum cotinine levels. Nearly 40% of children aged 2 months to 2 years are living with at least one smoker, and perhaps, their condition is exacerbated by ETS exposure [36].

A series of epidemiological surveys provide strong evidence of the relationship between parental smoking and prevalence of asthma in school age children [37, 38]. A recent study and meta-analysis of 76 studies have assessed the effects of pre-or post-natal second-hand smoke exposure is associated with a 21% to 85% increased risk of asthma incident [39]. The strongest effect from prenatal maternal smoking on asthma in children aged 2 years old has CI 95% OR=1,85 (1.3-2,5). In adolescence and adults, exposure to passive smoke is also associated with the prevalence of asthma [25].

The increase of urinary cotinine concentration is affected by the number of smokers in an household and the number of cigarettes smoked. The result showed that the existing home smokers have cotinine concentrations >15 ng/ml at most. Category of heavy smokers or higher number of cigarettes >20 cigarettes per day are as shown in the following table:

Table 3. ETS Status at home and Cotinine Concentration

ETS Household	Cotinine	
	≥ 15 ng/ml	**< 15 ng/ml**
Home with smoker	50 (66.7)	7 (17.9)
Home without smoker	25 (33.3)	32 (82.1)

ETS : Environment Tobacco Smoke

Table. 4 Number of Cigarettes and Cotinine Concentration

Number of cigarette	Cotinine	
	≥ 15 ng/ml	**< 15 ng/ml**
< 4	6 (12)	3 (42.9)
5 - 9	11 (22)	1 (14.3)
10 - 19	16 (32)	1 (14.3)
20 - 29	17 (34)	2 (28.6)

The variability of each individual against the pattern of cotinine metabolism due to exposure to existing nicotine is quite different. Therefore, it is possible that there may be existence of cotinine in an household where there is no smoke. This may be attributed to exposure of the inhabitant(s) to cigarette smoke outside the home and other metabolism factors such as genetic variation, race, sex, use of oral contraceptives or other estrogen-containing hormones, renal and drug failure, including anticonvulsants and rifampin as well as from foods they ate [23, 40].

The main physiological features of asthma exacerbation are airways constriction and airflow obstruction, which are reversible. It is produced as a result of contraction of bronchial smooth muscle, edema and hypersecretion of mucus. Various trigger factors can lead to exacerbations. Acute bronchoconstriction caused by allergens occurs as a result of the release of mediators from mast cells [41]. The nature of tobacco smoke as inhalants, which are inhaled and exposed directly to the airway, causes a risk factor that has relationship with asthma exacerbation events in children [17, 42].

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8 + and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43]

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04-2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi et al., Conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environtment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller, however, long-term use of this medication has side effects. Tamarindusindica L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed in order to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

CONCLUSION

This research revealed that environment tobacco smoke exposure in the household increases the risk of asthma exacerbation. Since children with asthma should have good survival and quality of life, it is, therefore, necessary and expedient to control the environment and educate children to avoid ETS Exposure.

ACKNOWLEDGMENTS

We would like to thank Directors of the Center for Healthy Lung Community Surakarta, Dr. Moewardi Hospital Surakarta, and the Lung Health Center Klaten, Indonesia for granting us access to facilities for this study.We also thank all enumerators and laboratory staff for assisting in the process of collecting data.

AUTHORS' CONTRIBUTIONS

All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono designed the framework, planned sample preparation and carry out data collection in the field. Hartono contributed in writing the script and supervision of all activities. All authors discussed and provided critical feedback on this text.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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5 Revision Required (2nd Round) 10 September

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- Discussion could not be found. Only results have been given. Authors should make comparison with previously reported such works to emphasize importance of the presented work.
- Authors should add/replace at least 2 references from International Journal of Pharmacy and Pharmaceutical Sciences and may be at least one from IJAP, IJCPR and JCR etc.

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6 Revision Reminder 20 September

Solo, September 20, 2018

To
Dr. Anurekha Jain
Editor in Chief
Asian Journal of Pharmaceutical and Clinical Research

Dear Dr. Anurekha Jain
The authors appreciate all comments from the editor to our manuscript. Herewith, we would like to resubmit the revised manuscript and our responses to the editor's comments point by point. The manuscript had been re-check for the English editing.

We thank that our manuscript has been recommended for publication on the upcoming AJPCR topic, we hereby enclose proof of payment. For academic purposes, would you like to send me the acceptance letter stating that our manuscript has been accepted by AJPCR.

Thank you for your consideration!

With kind regards,
Authors

Response to the editor ;

1. Format, Abbreviations, Symbol and units, Table and Figure, should be rectified. See latest issue of AJPCR
   Response : We revised the reviewer comment's as it is suggested

2. Abstract: Rewrite Abstract which should be structural (Divide it into Objective, Methods, Results, and Conclusion)
   Response: we need to say that our abstract structure has been adapted to the original article format, with the arrangement : Objective, Methods, Results,Conclusion, Keywords. We added the objective ;
   The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

3. References: References are out of format. Uniformity must be ensured in all the references. It should be made strictly as per Instructions toAuthors. Journal's title should be non italic, abbreviated without use of full stop.
   Response: We have adjusted the reference according to the format specified

4. Introduction: What is rationale and novelty of study? It should be mentioned.
   Response: Thank you, We revised of the manuscript as you suggested. The red colour in the paragraph are new sentences.

   The novelty of this study is to assess the risk impact associated with exposing children living with asthma to environment tobacco smoke in the family. We hypothesize that asthmatic

children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

5. Discussion could not be found. Only results have been given. Authors should make comparison with previously reported such works to emphasize importance of the presented work.
Response: We added previous research result as the references, and elaborate them in discussion.

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8 + and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43]

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04-2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi et al., Conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environtment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller, however, long-term use of this medication has side effects. Tamarindusindica L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed in order to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

6. Authors should add/replace at least 2 references from International Journal of Pharmacy and Pharmaceutical Sciences and may be at least one from IJAP, IJCPR and JCR etc
Response Thanks for the comments. We have included quotes from IJCPR (References No. 44 and 45).
    1) *References 44.* Prakruthi GM, Bharathi DR, Yogananda R. A Case Control Study On Determinants Of Childhood Asthma In School Chil-Dren Of Chitradurga City. Int J Curr Pharm Res. 2018;10(3):11–5.
    2) *References 45.* Mahmudah RA, Adnyana IK, Kurnia N. Anti-Asthma Activity Of Tamarind Pulp Extract (Tamarindus Indica L.). Int J Curr Pharm Res. 2017;9(3):3–6.

Original Article

IMPACT OF ENVIRONMENT TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION

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ABSTRACT

Objective: Environment Tobacco Smoke (ETS) exposure in the household is dangerous to infants and children. Nicotine residue inhaled in the respiratory tract metabolized into cotinine which has the possibility of causing inflammation which can result in asthma exacerbation. The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

Methods: A cohort study was carried out among 114 asthma patients aged 12-18 years old at three hospitals from January 2016 to March 2017. Data was obtained using self reported questionnaires and cotinine urine test. The data analysis was carried with the use of Cox Proportional Hazard Model with 95% confidence interval.

Results: The result of the research showed that 57% of the patients got the trigger (event). The respondents consisted of 61.5% of female, average age of 15 years, 50.8% of upper secondary education, 55.4% of body mass index (BMI) normal and 63.1% low economic status persons. Median survival for the ETS-exposed group was in 9th week, while the median survival for the ETS non-exposed group was more than 12 weeks. Multivariate exposure of ETS with asthma exacerbation was hazard ratio (HR), 2.17; 95% CI, 1.23-3.83, p = 0.008 and gender HR, 1.72; 95% CI, 1.04-2.85, p = 0.035.

Conclusion: Environment Tobacco Smoke exposure in the household increases the risk of asthma exacerbation. Controlling the environment and education of children to avoid ETS exposure should be intensified.

Keywords: environmental tobacco smoke, cotinine, survival, asthma, exacerbation

INTRODUCTION

Epidemiological studies show that smoking is a global health problem and it is seen as a risk factor for the emergence of various medical disorders, especially some non-communicable diseases [1]. Environment Tobacco Smoke (ETS) has to do with the pollution of the environment, mostly rooms, with tobacco smokes and that is why it is usually referred to as Second Hand Smoke (SHS). It comes with devastating impacts such as cardiovascular death and respiratory diseases, infections, behavioral problems, low birth weight, sudden infant death

syndrome and cancer [2, 3]. Groups that are particularly vulnerable to this secondhand smoke are children, so they are easily affected by asthma, pneumonia, sinusitis and different allergies.

Globally, about 40% of children with respiratory problems got them from smoking parents, as a result of this, about 28% of children deaths were associated with ETS in 2004 [2]. People that smokes are at risk of developing diabetes mellitus as well as be at increased risk of cancer of the bladder [4, 5]. Exposure to tobacco smoke can cause heart attacks, strokes, and even sudden death. It was found that smoking causes about 85% of lung cancers in the United States [6]. Sympathetic overactivity may lead to cardiovascular disease development in smokers. Cigarette smoking also has adverse effect on serum ferritin and other hematologic parameters and serum ferritin has been discovered to be one of the most reliable indicators of iron status [7, 8]. The cox proportional hazard model shows higher hazard ratio for smokers prognostic impact in patients with lung Adenocarcinoma[9].

One of the major effects of ETS that can result in death is asthma. Asthma is a chronic inflammatory disease of the respiratory tract characterized by wheezing, coughing, and chest tightness due to respiratory tract blockages. Epidemiological study of asthma reveals that the prevalence from several countries ranged from 1% to 18% [10], while, nationally, in Indonesia it showed 4.5% [11]. Asthma is caused by many factors which include gene, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization, body weight, hypertension and tobacco exposure. These are the main risk factors associated with childhood-onset asthma [12, 13].

Leftover cigarette smoke on surfaces does not evaporate into the air, however, there is nicotine residue attached to the dust or stuff around us, such as clothes, carpets, walls, furniture or chairs. Nicotine dust is not going to disappear in a short time so it will be inhaled by others even though the smoker has left the place [14, 15].

More than 5200 chemical components are found in cigarette smoke in the form of particles and steam [16]. These chemicals are dangerous and can cause damages to the respiratory tract, in such a way that they can block overall breathing work [17]. One of these chemicals is nicotine and it has a secondary immunomodulatory effect of eosinophil function, by inhibiting the release of pro-inflammatory cytokines from macrophages [18, 19].

ETS exposure in the household can increase the severity of asthma in children because while they are on the floor, they inhale dust of carpet, mildew, mite and others which are equivalent to sucking four cigarettes a day. Over 90% of children spend their time indoors and because of the ETS, indoor air pollution gives more harmful health effects than outdoor air pollution [20].

ETS exposure in the household can be inhaled through breath into the alveoli and then spread into the blood circulation if not stopped. In the metabolism, there is CYP2A6 genes, which are genes encoding P450 2a6 of cytochrome enzyme. This enzyme is responsible for 70% to 90% of nicotine metabolism in blood to cotinine [21-24]. Therefore, ETS exposure can be assessed through cotinine measurement in urine, serum or saliva.

Nicotine in cigarette smoke can trigger inflammation because it has a direct effect on neutrophils and macrophages through the activation of nicotinic acetylcholine receptors *(nAChR)* in nerve cells as well as non-nerve cells such as monocytes and endothelia [25]. Several studies have also shown an increase in neutrophil inflammation in the bronchi and an increased number of neutrophils will trigger an increase in eosinophils, which will secrete inflammatory mediators that play a significant role in triggering asthma. Decreased IgE serum, blood eosinophils and fractional exhaled nitric oxide (FeNO) non-smoker's and former

smoker's ages had higher thymic stromal lymphopoietin (TSLP) than those that never smoke. In addition, goblet cell numbers will increase and hypersecretion of mucus in the respiratory tract [26]. The presence of cotinine urine levels in smokers has a positive relationship to increased levels of PGE-M and LTE4. This plays a role in inflammation and carcinogenesis[27].

The novelty of this study is to assess the risk impact associated with exposing children living with asthma to environment tobacco smoke in the family. We hypothesize that asthmatic children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

METHODS

Study Design

A cohort study was carried out among 114 asthma patients from three hospitals - Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017 with inclusion of some criteria. The research was carried out on respondents between the ages of 12 and 18 year. Survival analysis was carried out for asthma exacerbation.

Research Ethics

We conducted a written informed consent before the data collection. The research ethics were obtained from Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Indonesia.

Data Collection

The data of respondents related to demography, BMI and history of environmental tobacco exposure in the household were based on self report gotten through interview and questionnaire at the beginning of the research. The history of cigarette use includes the presence of smokers at home and number of cigarettes per day (1 to 10, 11 to 19, 20 to 29, and more than 30 per day). Data was evaluated at 12 weeks or 3 months through self report or medical records from the hospital to obtain sensory time analysis data. Urine sampling was also done in early research on every subject. Urine samples were used to determine levels of Cotinine with the use of Enzyme-Linked Immunosorbent Assay (ELISA) method [28-31]. Urine cotinine analysis data were classified into two categories which are: lower than 15 ng/ml also known as non-exposed and higher than 15ng/ml also known as exposed [28].

Data Analysis

Data on demography, BMI, cigarette use and cotinine concentration were obtained with the use of frequency distribution and percentage. We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariate Cox proportional Hazard models were fitted using all the covariates, yielding Hazard ratios (HRs) 95% confidence interval with SPSS software.

RESULTS

Based on medical records from three hospitals; Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017. The total number of asthma patients in the three health care facilities were 4872 with the number of children with asthma recorded to be 726. There were 114 children who fulfilled the criteria and they were used as

samples. During the research period, it was found that the trigger status (event) was 57% and the sensor was 43%. Survival time showed that 50% respondent suffered the trigger in the 10^{th} week, while the ETS-exposed group was in the 9^{th} week.

Baseline characteristics as a single predictor of asthma exacerbation are summarized in Table 1. Cohort survival time showed that most of the respondents who suffered events were 61.5% female, at the mean age of 15 years, 50.8% of upper secondary education, 55.4% of BMI normal, income < $105 (63.1%). Cotinine test as ETS biomarker showed that high concentration of cotinine suffered more events (75.4%).

Table 1. The Baseline of Sociodemographic Characteristics, ETS Exposure and Triger in Adults with Asthma Exacerbation

Variable	Event		Sensor		p-value*
	n	%	n	%	
Age					
12-15	30	46.15	32	65.31	0.067
16-18	35	53.85	17	34.69	
Mean, SD	15 ± 2.5				
Gender					
Female	40	61.54	20	40.82	0.065
Male	25	38.46	29	59.18	
Education					
Primary	32	49.23	33	67.35	0.056
Upper Secondary	33	50.77	16	32.65	
BMI					
Normal	36	55.38	20	40.82	0.186
Abnormal	29	44.62	29	59.18	
Income					
<$ 105	41	63.08	24	48.98	0.124
≥$ 105	24	36.92	25	51.02	
Cotinine					
≥ 15 ng/ml	49	75.38	26	53.06	0.010
< 15 ng/ml	16	24.62	23	46.94	

* The Log rank test (Mantel Cox) was used for all other characteristics; BMI : body mass index

The result of multivariate analysis with cox regression (Cox Proportional Hazard Model) showed that some variables, cotinine concentration and demographic variable (gender) have significant correlation with asthma exacerbation (HR, 2.17; 95% CI, 1.23-3.83) and (HR, 1.72; 95% CI, 1.04-2.85).

Table 2. Results of the Multivariate Analysis for overall survival

Variable	Level	HR (95% CI)	p-value*
Gender	(female vs. male)	1.721 (1.040-2.849)	0.035
Cotinine	(≥ 15 ng/ml and < 15 ng/ml)	2.168(1.226-3.832)	0.008

HR : hazard ratio; CI : confidence interval

* The cox regression (Cox Proportinal Hazard Model)

DISCUSSION

Median survival for both ETS-exposed and non-exposed groups were 10 weeks. It shows that patients with asthma exacerbation will suffer the trigger in the 10th week. Asthma patients with ETS-exposed will rapidly suffer the trigger in the 9th week, while patients with ETS non-exposed were more than 12 weeks. The result has the similarity as the other research that find an average rate of asthma trigger to be 14 weeks or 3.5 months per year [32].

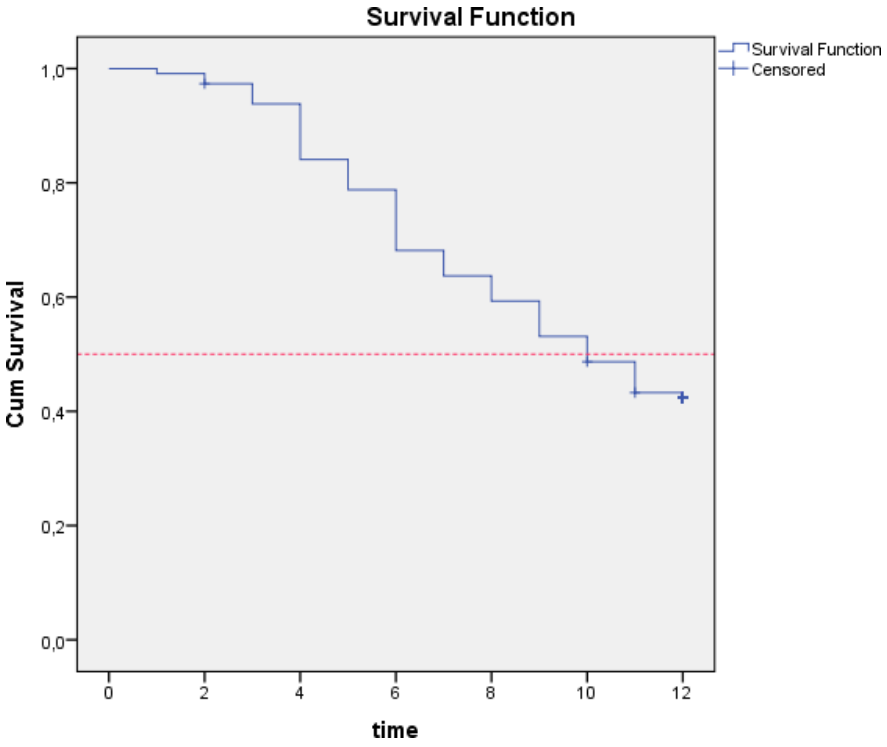

Fig.1 Survival curve for the asthma exacerbation for all groups

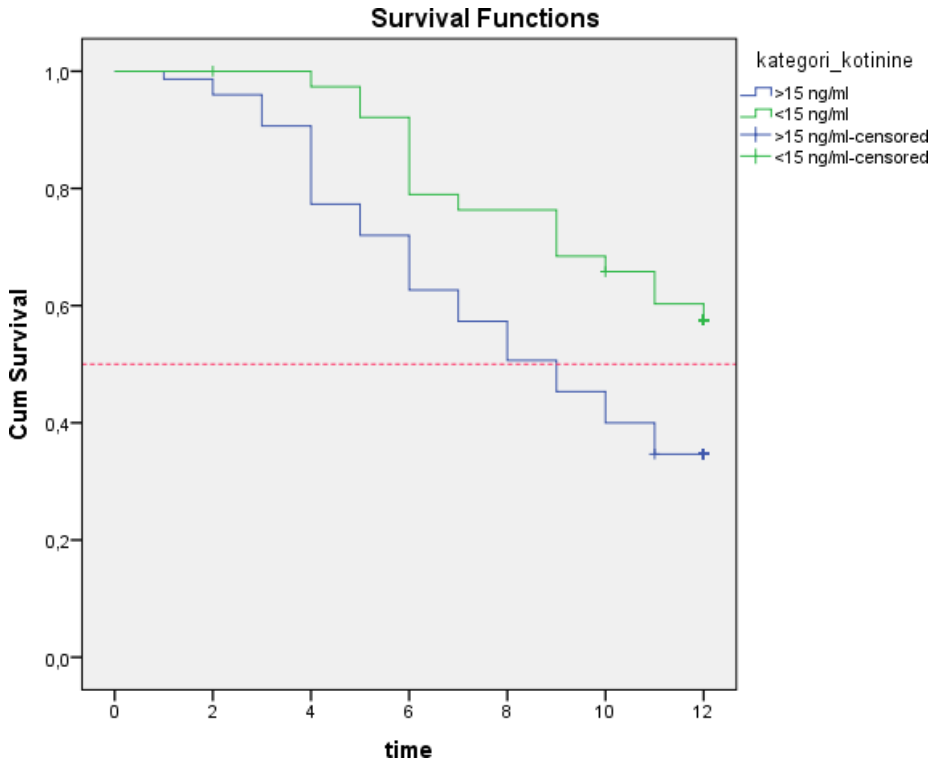

Fig. 2 Survival curve for the asthma exacerbation and cotinine ETS exposure.

Hazard survival ETS with urinary cotinine concentration of biomarker and frequency on the trigger of asthma exacerbation was HR, 2.17; 95% CI, 1.226-3.832, p = 0.008. The result of this research shows that ETS exposure measured with urine cotinine level in children suffering asthma has risk 2 of having asthma exacerbation more rapidly when compared to children with non-exposure of cigarette smoke. There is a research that has proved that mothers who smoke increase fourfold response to histamine as well as high level of cotinine increase the risk of acute asthma exacerbation by 1.8-fold [33]. Children with ETS-exposed have the higher risk of having uncontrolled asthma with OR= 3.20; 95% CI= 1.40 to 6.90 [34].

Children who live in homes with smoking members have increased cotinine level when compared with those living in homes with no smokers. It shows that ETS exposure is associated with the increasing urinary cotinine and acute exacerbation asthma trigger as well as decreasing lung function of FEV1 and ratio of FVC [35]. Around 87.9% of nontobacco consumers in the United States had detectable acquired serum cotinine levels. Nearly 40% of children aged 2 months to 2 years are living with at least one smoker, and perhaps, their condition is exacerbated by ETS exposure [36].

A series of epidemiological surveys provide strong evidence of the relationship between parental smoking and prevalence of asthma in school age children [37, 38]. A recent study and meta-analysis of 76 studies have assessed the effects of pre-or post-natal second-hand smoke exposure is associated with a 21% to 85% increased risk of asthma incident [39]. The strongest effect from prenatal maternal smoking on asthma in children aged 2 years old has CI 95% OR=1,85 (1.3-2,5). In adolescence and adults, exposure to passive smoke is also associated with the prevalence of asthma [25].

The increase of urinary cotinine concentration is affected by the number of smokers in an household and the number of cigarettes smoked. The result showed that the existing home

smokers have cotinine concentrations >15 ng/ml at most. Category of heavy smokers or higher number of cigarettes >20 cigarettes per day are as shown in the following table:

Table 3. ETS Status at home and Cotinine Concentration

ETS Household	Cotinine	
	≥ 15 ng/ml	< 15 ng/ml
Home with smoker	50 (66.7)	7 (17.9)
Home without smoker	25 (33.3)	32 (82.1)

ETS : Environment Tobacco Smoke

Table. 4 Number of Cigarettes and Cotinine Concentration

Number of cigarette	Cotinine	
	≥ 15 ng/ml	< 15 ng/ml
< 4	6 (12)	3 (42.9)
5 - 9	11 (22)	1 (14.3)
10 - 19	16 (32)	1 (14.3)
20 - 29	17 (34)	2 (28.6)

The variability of each individual against the pattern of cotinine metabolism due to exposure to existing nicotine is quite different. Therefore, it is possible that there may be existence of cotinine in an household where there is no smoke. This may be attributed to exposure of the inhabitant(s) to cigarette smoke outside the home and other metabolism factors such as genetic variation, race, sex, use of oral contraceptives or other estrogen-containing hormones, renal and drug failure, including anticonvulsants and rifampin as well as from foods they ate [23, 40].

The main physiological features of asthma exacerbation are airways constriction and airflow obstruction, which are reversible. It is produced as a result of contraction of bronchial smooth muscle, edema and hypersecretion of mucus. Various trigger factors can lead to exacerbations. Acute bronchoconstriction caused by allergens occurs as a result of the release of mediators from mast cells [41]. The nature of tobacco smoke as inhalants, which are inhaled and exposed directly to the airway, causes a risk factor that has relationship with asthma exacerbation events in children [17, 42].

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8 + and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43]

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04-2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi et al., Conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environtment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller, however, long-term use of this medication has side effects. Tamarindusindica L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed in order to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

CONCLUSION

This research revealed that environment tobacco smoke exposure in the household increases the risk of asthma exacerbation. Since children with asthma should have good survival and quality of life, it is, therefore, necessary and expedient to control the environment and educate children to avoid ETS Exposure.

ACKNOWLEDGMENTS

We would like to thank Directors of the Center for Healthy Lung Community Surakarta, Dr. Moewardi Hospital Surakarta, and the Lung Health Center Klaten, Indonesia for granting us access to facilities for this study.We also thank all enumerators and laboratory staff for assisting in the process of collecting data.

AUTHORS' CONTRIBUTIONS

All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono designed the framework, planned sample preparation and carry out data collection in the field. Hartono contributed in writing the script and supervision of all activities. All authors discussed and provided critical feedback on this text.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Vol 12, Issue 3, 2019

Research Article

IMPACT OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION

AQ1

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Received: 14 July 2018, Revised and Accepted: 13 December 2018

ABSTRACT

Objective: Environment tobacco smoke (ETS) exposure in the household is dangerous to infants and children. Nicotine residue inhaled in the respiratory tract metabolized into cotinine which has the possibility of causing inflammation which can result in asthma exacerbation. The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

Methods: A cohort study was carried out among 114 asthma patients aged 12–18 years old at three hospitals from January 2016 to March 2017. Data were obtained using self-reported questionnaires and cotinine urine test. The data analysis was carried with the use of cyclooxygenase proportional hazard model with 95% confidence interval (CI).

Results: The result of the research showed that 57% of the patients got the trigger (event). The respondents consisted of 61.5% of female, average age of 15 years, 50.8% of upper secondary education, 55.4% of body mass index (BMI) normal, and 63.1% low economic status persons. Median survival for the ETS-exposed group was in a 9th week, while the median survival for the ETS non-exposed group was >12 weeks. Multivariate exposure of ETS with asthma exacerbation was hazard ratio (HR), 2.17; 95% CI, 1.23–3.83, p=0.008 and gender HR, 1.72; 95% CI, 1.04–2.85, p=0.035.

Conclusion: ETS exposure in the household increases the risk of asthma exacerbation. Controlling the environment and education of children to avoid ETS exposure should be intensified.

Keywords: Environmental tobacco smoke, Cotinine, Survival, Asthma, Exacerbation.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i3.28498

INTRODUCTION

Epidemiological studies show that smoking is a global health problem and it is seen as a risk factor for the emergence of various medical disorders, especially some non-communicable diseases [1]. Environment tobacco smoke (ETS) has to do with the pollution of the environment, most rooms, with tobacco smokes, and that is why it is usually referred to as second-hand smoke. It comes with devastating impacts such as cardiovascular death and respiratory diseases, infections, behavioral problems, low birth weight, sudden infant death syndrome, and cancer [2,3]. Groups that are particularly vulnerable to this secondhand smoke are children, so they are easily affected by asthma, pneumonia, sinusitis, and different allergies.

Globally, about 40% of children with respiratory problems got them from smoking parents, as a result of this, about 28% of children deaths were associated with ETS in 2004 [2]. People that smokes are at risk of developing diabetes mellitus as well as be at increased risk of cancer of the bladder [4,5]. Exposure to tobacco smoke can cause heart attacks, strokes, and even sudden death. It was found that smoking causes about 85% of lung cancers in the United States [6]. Sympathetic overactivity may lead to cardiovascular disease development in smokers. Cigarette smoking also has an adverse effect on serum ferritin, and other hematologic parameters and serum ferritin have been discovered to be one of the most reliable indicators of iron status [7,8]. The cyclooxygenase (Cox) proportional hazard model shows a higher hazard ratio (HR) for smokers prognostic impact in patients with lung adenocarcinoma [9].

One of the major effects of ETS that can result in death is asthma. Asthma is a chronic inflammatory disease of the respiratory tract characterized by wheezing, coughing, and chest tightness due to respiratory tract blockages. Epidemiological study of asthma reveals that the prevalence of several countries ranged from 1% to 18% [10], while, nationally, in Indonesia, it showed 4.5% [11]. Asthma is caused by many factors which include gene, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization, body weight, hypertension, and tobacco exposure. These are the main risk factors associated with childhood-onset asthma [12,13].

Leftover cigarette smoke on surfaces does not evaporate into the air; however, there is nicotine residue attached to the dust or stuff around us, such as clothes, carpets, walls, furniture, or chairs. Nicotine dust is not going to disappear in a short time, so it will be inhaled by others even though the smoker has left the place [14,15].

More than 5200 chemical components are found in cigarette smoke in the form of particles and steam [16]. These chemicals are dangerous and can cause damages to the respiratory tract, in such a way that they can block overall breathing work [17]. One of these chemicals is nicotine, and it has a secondary immunomodulatory effect of eosinophil function, by inhibiting the release of pro-inflammatory cytokines from macrophages [18,19].

ETS exposure in the household can increase the severity of asthma in children because while they are on the floor, they inhale dust of carpet, mildew, mite, and others which are equivalent to sucking four cigarettes a day. Over 90% of children spend their time indoors, and because of the ETS, indoor air pollution gives more harmful health effects than outdoor air pollution [20].

ETS exposure in the household can be inhaled through breath into the alveoli and then spread into the blood circulation if not stopped. In the metabolism, there are CYP2A6 genes, which are genes encoding P450 2a6 of cytochrome enzyme. This enzyme is responsible for 70%–90% of nicotine metabolism in blood to cotinine [21-24]. Therefore, ETS exposure can be assessed through cotinine measurement in urine, serum, or saliva.

Nicotine in cigarette smoke can trigger inflammation because it has a direct effect on neutrophils and macrophages through the activation of nicotinic acetylcholine receptors in nerve cells as well as non-nerve cells such as monocytes and endothelial [25]. Several studies have also shown an increase in neutrophil inflammation in the bronchi and an increased number of neutrophils will trigger an increase in eosinophils, which will secrete inflammatory mediators that play a significant role in triggering asthma. Decreased IgE serum, blood eosinophils, and fractional exhaled nitric oxide non-smoker's and former smoker's ages had higher thymic stromal lymphopoietin than those that never smoke. In addition, goblet cell numbers will increase and hypersecretion of mucus in the respiratory tract [26]. The presence of cotinine urine levels in smokers has a positive relationship to increased levels of PGE-M and LTE4. This plays a role in inflammation and carcinogenesis [27].

The novelty of this study is to assess the risk impact associated with exposing children living with asthma to ETS in the family. We hypothesize that asthmatic children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

METHODS

Study design

A cohort study was carried out among 114 asthma patients from three hospitals - Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta, and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017 with the inclusion of some criteria. The research was carried out on respondents between the ages of 12 and 18 years. Survival analysis was carried out for asthma exacerbation.

Research ethics

We conducted a written informed consent before the data collection. The research ethics were obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Indonesia.

Data collection

The data of respondents related to demography, BMI, and history of environmental tobacco exposure in the household were based on self-report gotten through interview and questionnaire at the beginning of the research. The history of cigarette use includes the presence of smokers at home and number of cigarettes per day (1 to 10, 11 to 19, 20 to 29, and >30/day). Data were evaluated at 12 weeks or 3 months through self-report or medical records from the hospital to obtain sensory time analysis data. Urine sampling was also done in early research on every subject. Urine samples were used to determine levels of cotinine with the use of Enzyme-Linked Immunosorbent Assay method [28-31]. Urine cotinine analysis data were classified into two categories which are: <15 ng/mlalso known as non-exposed and higher than 15 ng/ml also known as exposed [28].

Data analysis

Data on demography, BMI, cigarette use, and cotinine concentration were obtained with the use of frequency distribution and percentage. We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariate Cox Proportional Hazard Models were fitted using all the covariates, yielding HRs 95% confidence interval (CI) with SPSS software.

RESULTS

Based on medical records from three hospitals; Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta, and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017. The total number of asthma patients in the three health-care facilities was 4872 with the number of children with asthma recorded to be 726. There were 114 children who fulfilled the criteria, and they were used as samples. During the research period, it was found that the trigger status (event) was 57% and the sensor was 43%. Survival time showed that 50% respondent suffered the trigger in the 10th week, while the ETS-exposed group was in the 9th week.

Baseline characteristics as a single predictor of asthma exacerbation are summarized in Table 1. Cohort survival time showed that most of the respondents who suffered events were 61.5% female, at the mean age of 15 years, 50.8% of upper secondary education, 55.4% of BMI normal, and income <$105 (63.1%). Cotinine test as ETS biomarker showed that a high concentration of cotinine suffered more events (75.4%).

The result of multivariate analysis with Cox regression (Cox proportional hazard model) showed that some variables, cotinine concentration and demographic variable (gender) have significant correlation with asthma exacerbation (HR, 2.17; 95% CI, 1.23–3.83) and (HR, 1.72; 95% CI, 1.04–2.85) (Table 2).

DISCUSSION

Median survival for both ETS-exposed and non-exposed groups was 10 weeks. It shows that patients with asthma exacerbation will suffer the trigger in the 10th week. Asthma patients with ETS-exposed will rapidly suffer the trigger in the 9th week, while patients with ETS non-exposed were >12 weeks. The result has the similarity as the other research that finds an average rate of asthma trigger to be 14 weeks or 3.5 months/year (Figs. 1 and 2) [32].

Table 1: The baseline of sociodemographic characteristics, ETS exposure, and trigger in adults with asthma exacerbation

Variables	Event	Sensor	p value*
	n (%)	n (%)	
Age			
12–15	30 (46.15)	32 (65.31)	0.067
16–18	35 (53.85)	17 (34.69)	
Mean±SD	15±2.5		
Gender			
Female	40 (61.54)	20 (40.82)	0.065
Male	25 (38.46)	29 (59.18)	
Education			
Primary	32 (49.23)	33 (67.35)	0.056
Upper secondary	33 (50.77)	16 (32.65)	
BMI			
Normal	36 (55.38)	20 (40.82)	0.186
Abnormal	29 (44.62)	29 (59.18)	
Income			
<$ 105	41 (63.08)	24 (48.98)	0.124
>$ 105	24 (36.92)	25 (51.02)	
Cotinine			
>15 ng/ml	49 (75.38)	26 (53.06)	0.010
<15 ng/ml	16 (24.62)	23 (46.94)	

*The log-rank test (Mantel Cox) was used for all other characteristics. BMI: Body mass index, ETS: Environment tobacco smoke, Cox: Cyclooxygenase

Table 2: Results of the multivariate analysis for overall survival

Variable	Level	HR (95% CI)	p value*
Gender	(Female vs. Male)	1.721 (1.040–2.849)	0.035
Cotinine	(>15 ng/ml and<15 ng/ml)	2.168 (1.226–3.832)	0.008

*The Cox regression (Cox Proportional Hazard Model). HR: Hazard ratio, CI: Confidence interval, Cox: Cyclooxygenase

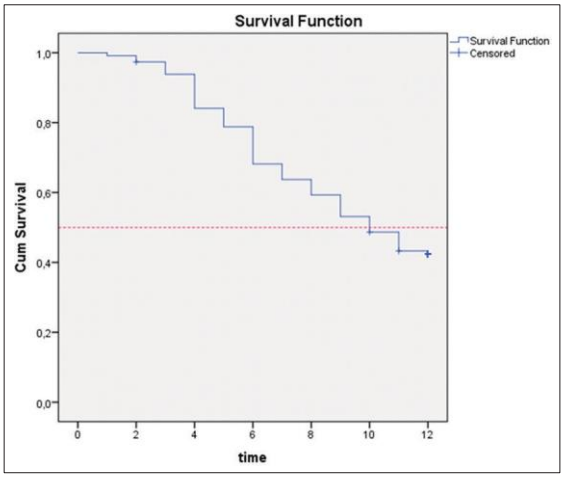

Fig. 1: Survival curve for the asthma exacerbation for all groups

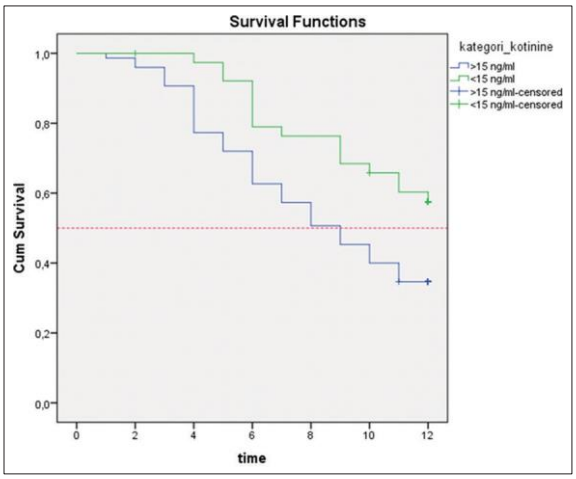

Fig. 2: Survival curve for the asthma exacerbation and cotinine environment tobacco smoke exposure

Hazard survival ETS with urinary cotinine concentration of biomarker and frequency on the trigger of asthma exacerbation was HR, 2.17; 95% CI, 1.226–3.832, p=0.008. The result of this research shows that ETS exposure measured with urine cotinine level in children suffering asthma has risk 2 of having asthma exacerbation more rapidly when compared to children with non-exposure of cigarette smoke. There is a research that has proved that mothers who smoke increase four-fold response to histamine as well as high level of cotinine increase the risk of acute asthma exacerbation by 1.8-fold [33]. Children with ETS-exposed have the higher risk of having uncontrolled asthma with OR=3.20; 95% CI=1.40–6.90 [34].

Children who live in homes with smoking members have increased cotinine level when compared with those living in homes with no smokers. It shows that ETS exposure is associated with the increasing urinary cotinine and acute exacerbation asthma trigger as well as decreasing lung function of forced expiratory volume in 1 s and the ratio of forced vital capacity [35]. Around 87.9% of nontobacco consumers in the United States had detectable acquired serum cotinine levels. Nearly 40% of children aged 2 months to 2 years are living with at least one smoker, and perhaps, their condition is exacerbated by ETS exposure [36].

A series of epidemiological surveys provide strong evidence of the relationship between parental smoking and the prevalence of asthma in school-age children [37,38]. A recent study and meta-analysis of 76 studies have assessed that the effects of pre- or post-natal second-hand smoke exposure are associated with a 21–85% increased risk of asthma incident [39]. The strongest effect of prenatal maternal smoking on asthma in children aged 2 years old has CI 95% OR = 1.85 (1.3–2.5). In adolescence and adults, exposure to passive smoke is also associated with the prevalence of asthma [25].

The increase of urinary cotinine concentration is affected by the number of smokers in a household, and the number of cigarettes smoked. The result showed that the existing home smokers have cotinine concentrations >15 ng/ml at most. Category of heavy smokers or higher number of cigarettes >20 cigarettes per day areas is shown in Tables 3 and 4.

The variability of each individual against the pattern of cotinine metabolism due to exposure to existing nicotine is quite different. Therefore, it is possible that there may be the existence of cotinine in a household where there is no smoke. This may be attributed to exposure of the inhabitant(s) to cigarette smoke outside the home and other metabolism factors such as genetic variation, race, sex, use of oral contraceptives or other estrogen-containing hormones, renal, and drug failure, including anticonvulsants and rifampin as well as from foods they ate [23,40].

The main physiological features of asthma exacerbation are airways constriction and airflow obstruction, which are reversible. It is produced as a result of the contraction of bronchial smooth muscle, edema, and hypersecretion of mucus. Various trigger factors can lead to exacerbations. Acute bronchoconstriction caused by allergens occurs as a result of the release of mediators from mast cells [41]. The nature of tobacco smoke as inhalants, which are inhaled and exposed directly to the airway, causes a risk factor that has a relationship with asthma exacerbation events in children [17,42].

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8+ and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43].

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04–2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi *et al*. conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller; however, long-term use of this medication has side effects. *Tamarindus indica* L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

CONCLUSION

This research revealed that ETS exposure in the household increases the risk of asthma exacerbation. Since children with asthma should have good survival and quality of life, it is, therefore, necessary and expedient to control the environment and educates children to avoid ETS Exposure.

Table 3: ETS status at home and cotinine concentration

ETS Household	Cotinine	
	≥15 ng/ml	<15 ng/ml
Home with smoker	50 (66.7)	7 (17.9)
Home without smoker	25 (33.3)	32 (82.1)

ETS: Environment tobacco smoke

Table 4: Number of cigarettes and cotinine concentration

Number of cigarette	Cotinine	
	≥15 ng/ml	<15 ng/ml
<4	6 (12)	3 (42.9)
5–9	11 (22)	1 (14.3)
10–19	16 (32)	1 (14.3)
20–29	17 (34)	2 (28.6)

ACKNOWLEDGMENTS

We would like to thank Directors of the Center for Healthy Lung Community Surakarta, Dr. Moewardi Hospital Surakarta, and the Lung Health Center Klaten, Indonesia, for granting us access to facilities for this study. We also thank all enumerators and laboratory staff for assisting in the process of collecting data.

AUTHORS' CONTRIBUTIONS

All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono designed the framework, planned sample preparation and carry out data collection in the field. Hartono contributed in writing the script and supervision of all activities. All authors discussed and provided critical feedback on this text.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Vol 12, Issue 3, 2019

Online - 2455-3891
Print - 0974-2441

Research Article

IMPACT OF ENVIRONMENTAL TOBACCO SMOKE EXPOSURE ON ADULTS WITH ASTHMA EXACERBATION

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Received: 14 July 2018, Revised and Accepted: 13 December 2018

ABSTRACT

Objective: Environment tobacco smoke (ETS) exposure in the household is dangerous to infants and children. Nicotine residue inhaled in the respiratory tract metabolized into cotinine which has the possibility of causing inflammation which can result in asthma exacerbation. The impact created by the exposure of ETS on children suffering from asthma is the sole objective of this research work.

Methods: A cohort study was carried out among 114 asthma patients aged 12–18 years old at three hospitals from January 2016 to March 2017. Data were obtained using self-reported questionnaires and cotinine urine test. The data analysis was carried with the use of Cox proportional hazard model with 95% confidence interval (CI).

Results: The result of the research showed that 57% of the patients got the trigger (event). The respondents consisted of 61.5% of female, average age of 15 years, 50.8% of upper secondary education, 55.4% of body mass index (BMI) normal, and 63.1% low economic status persons. Median survival for the ETS-exposed group was in a 9th week, while the median survival for the ETS non-exposed group was >12 weeks. Multivariate exposure of ETS with asthma exacerbation was hazard ratio (HR), 2.17; 95% CI, 1.23–3.83, p=0.008 and gender HR, 1.72; 95% CI, 1.04–2.85, p=0.035.

Conclusion: ETS exposure in the household increases the risk of asthma exacerbation. Controlling the environment and education of children to avoid ETS exposure should be intensified.

Keywords: Environmental tobacco smoke, Cotinine, Survival, Asthma, Exacerbation.

 DOI: http://dx.doi.org/10.22159/ajpcr.2019.v12i3.28498

INTRODUCTION

Epidemiological studies show that smoking is a global health problem and it is seen as a risk factor for the emergence of various medical disorders, especially some non-communicable diseases [1]. Environment tobacco smoke (ETS) has to do with the pollution of the environment, most rooms, with tobacco smokes, and that is why it is usually referred to as second-hand smoke. It comes with devastating impacts such as cardiovascular death and respiratory diseases, infections, behavioral problems, low birth weight, sudden infant death syndrome, and cancer [2,3]. Groups that are particularly vulnerable to this secondhand smoke are children, so they are easily affected by asthma, pneumonia, sinusitis, and different allergies.

Globally, about 40% of children with respiratory problems got them from smoking parents, as a result of this, about 28% of children deaths were associated with ETS in 2004 [2]. People that smokes are at risk of developing diabetes mellitus as well as be at increased risk of cancer of the bladder [4,5]. Exposure to tobacco smoke can cause heart attacks, strokes, and even sudden death. It was found that smoking causes about 85% of lung cancers in the United States [6]. Sympathetic overactivity may lead to cardiovascular disease development in smokers. Cigarette smoking also has an adverse effect on serum ferritin, and other hematologic parameters and serum ferritin have been discovered to be one of the most reliable indicators of iron status [7,8]. The cyclooxygenase (Cox) proportional hazard model shows a higher hazard ratio (HR) for smokers prognostic impact in patients with lung adenocarcinoma [9].

One of the major effects of ETS that can result in death is asthma. Asthma is a chronic inflammatory disease of the respiratory tract characterized by wheezing, coughing, and chest tightness due to respiratory tract blockages. Epidemiological study of asthma reveals that the prevalence of several countries ranged from 1% to 18% [10], while, nationally, in Indonesia, it showed 4.5% [11]. Asthma is caused by many factors which include gene, family history of allergy and asthma, viral respiratory infections, bacterial colonization, allergic sensitization, body weight, hypertension, and tobacco exposure. These are the main risk factors associated with childhood-onset asthma [12,13].

Leftover cigarette smoke on surfaces does not evaporate into the air; however, there is nicotine residue attached to the dust or stuff around us, such as clothes, carpets, walls, furniture, or chairs. Nicotine dust is not going to disappear in a short time, so it will be inhaled by others even though the smoker has left the place [14,15].

More than 5200 chemical components are found in cigarette smoke in the form of particles and steam [16]. These chemicals are dangerous and can cause damages to the respiratory tract, in such a way that they can block overall breathing work [17]. One of these chemicals is nicotine, and it has a secondary immunomodulatory effect of eosinophil function, by inhibiting the release of pro-inflammatory cytokines from macrophages [18,19].

ETS exposure in the household can increase the severity of asthma in children because while they are on the floor, they inhale dust of carpet, mildew, mite, and others which are equivalent to sucking four cigarettes a day. Over 90% of children spend their time indoors, and because of the ETS, indoor air pollution gives more harmful health effects than outdoor air pollution [20].

ETS exposure in the household can be inhaled through breath into the alveoli and then spread into the blood circulation if not stopped. In the metabolism, there are CYP2A6 genes, which are genes encoding P450 2a6 of cytochrome enzyme. This enzyme is responsible for 70%–90% of nicotine metabolism in blood to cotinine [21-24]. Therefore, ETS exposure can be assessed through cotinine measurement in urine, serum, or saliva.

Nicotine in cigarette smoke can trigger inflammation because it has a direct effect on neutrophils and macrophages through the activation of nicotinic acetylcholine receptors in nerve cells as well as non-nerve cells such as monocytes and endothelial [25]. Several studies have also shown an increase in neutrophil inflammation in the bronchi and an increased number of neutrophils will trigger an increase in eosinophils, which will secrete inflammatory mediators that play a significant role in triggering asthma. Decreased IgE serum, blood eosinophils, and fractional exhaled nitric oxide non-smoker's and former smoker's ages had higher thymic stromal lymphopoietin than those that never smoke. In addition, goblet cell numbers will increase and hypersecretion of mucus in the respiratory tract [26]. The presence of cotinine urine levels in smokers has a positive relationship to increased levels of PGE-M and LTE4. This plays a role in inflammation and carcinogenesis [27].

The novelty of this study is to assess the risk impact associated with exposing children living with asthma to ETS in the family. We hypothesize that asthmatic children who are exposed to ETS in the family will experience an asthma exacerbation faster than those who are not exposed to ETS in the family.

METHODS

Study design

A cohort study was carried out among 114 asthma patients from three hospitals - Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta, and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017 with the inclusion of some criteria. The research was carried out on respondents between the ages of 12 and 18 years. Survival analysis was carried out for asthma exacerbation.

Research ethics

We conducted a written informed consent before the data collection. The research ethics were obtained from the Ethics Committee of the Faculty of Medicine, Universitas Sebelas Maret, Indonesia.

Data collection

The data of respondents related to demography, BMI, and history of environmental tobacco exposure in the household were based on self-report gotten through interview and questionnaire at the beginning of the research. The history of cigarette use includes the presence of smokers at home and number of cigarettes per day (1 to 10, 11 to 19, 20 to 29, and >30/day). Data were evaluated at 12 weeks or 3 months through self-report or medical records from the hospital to obtain sensory time analysis data. Urine sampling was also done in early research on every subject. Urine samples were used to determine levels of cotinine with the use of Enzyme-Linked Immunosorbent Assay method [28-31]. Urine cotinine analysis data were classified into two categories which are: <15 ng/mlalso known as non-exposed and higher than 15 ng/ml also known as exposed [28].

Data analysis

Data on demography, BMI, cigarette use, and cotinine concentration were obtained with the use of frequency distribution and percentage. We used the Log-rank test to evaluate the difference in time-to-event endpoints between patient groups. Multivariate Cox Proportional Hazard Models were fitted using all the covariates, yielding HRs 95% confidence interval (CI) with SPSS software.

RESULTS

Based on medical records from three hospitals; Center for Healthy Lung Community (BBKPM), Surakarta, Dr. Moewardi Hospital, Surakarta, and Lung Health Center (Balkesmas) Klaten, Central Java, Indonesia from January 2016 to March 2017. The total number of asthma patients in the three health-care facilities was 4872 with the number of children with asthma recorded to be 726. There were 114 children who fulfilled the criteria, and they were used as samples. During the research period, it was found that the trigger status (event) was 57% and the sensor was 43%. Survival time showed that 50% respondent suffered the trigger in the 10th week, while the ETS-exposed group was in the 9th week.

Baseline characteristics as a single predictor of asthma exacerbation are summarized in Table 1. Cohort survival time showed that most of the respondents who suffered events were 61.5% female, at the mean age of 15 years, 50.8% of upper secondary education, 55.4% of BMI normal, and income <$105 (63.1%). Cotinine test as ETS biomarker showed that a high concentration of cotinine suffered more events (75.4%).

Table 1: The baseline of sociodemographic characteristics, ETS exposure, and trigger in adults with asthma exacerbation

Variables	Event	Sensor	p value*
	n (%)	n (%)	
Age			
12–15	30 (46.15)	32 (65.31)	0.067
16–18	35 (53.85)	17 (34.69)	
Mean±SD	15±2.5		
Gender			
Female	40 (61.54)	20 (40.82)	0.065
Male	25 (38.46)	29 (59.18)	
Education			
Primary	32 (49.23)	33 (67.35)	0.056
Upper secondary	33 (50.77)	16 (32.65)	
BMI			
Normal	36 (55.38)	20 (40.82)	0.186
Abnormal	29 (44.62)	29 (59.18)	
Income			
<$ 105	41 (63.08)	24 (48.98)	0.124
>$ 105	24 (36.92)	25 (51.02)	
Cotinine			
>15 ng/ml	49 (75.38)	26 (53.06)	0.010
<15 ng/ml	16 (24.62)	23 (46.94)	

*The log-rank test (Mantel Cox) was used for all other characteristics. BMI: Body mass index, ETS: Environment tobacco smoke, Cox: Cyclooxygenase

The result of multivariate analysis with Cox regression (Cox proportional hazard model) showed that some variables, cotinine concentration and demographic variable (gender) have significant correlation with asthma exacerbation (HR, 2.17; 95% CI, 1.23–3.83) and (HR, 1.72; 95% CI, 1.04–2.85) (Table 2).

Table 2: Results of the multivariate analysis for overall survival

Variable	Level	HR (95% CI)	p value*
Gender	(Female vs. Male)	1.721 (1.040–2.849)	0.035
Cotinine	(>15 ng/ml and<15 ng/ml)	2.168 (1.226–3.832)	0.008

*The Cox regression (Cox Proportional Hazard Model). HR: Hazard ratio, CI: Confidence interval, Cox: Cyclooxygenase

DISCUSSION

Median survival for both ETS-exposed and non-exposed groups was 10 weeks. It shows that patients with asthma exacerbation will suffer the trigger in the 10th week. Asthma patients with ETS-exposed will rapidly suffer the trigger in the 9th week, while patients with ETS non-exposed were >12 weeks. The result has the similarity as the other research that finds an average rate of asthma trigger to be 14 weeks or 3.5 months/year (Figs. 1 and 2) [32].

Hazard survival ETS with urinary cotinine concentration of biomarker and frequency on the trigger of asthma exacerbation was HR, 2.17;

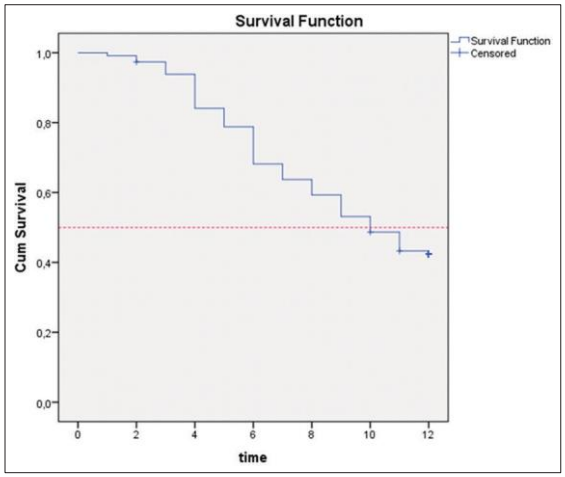

Fig. 1: Survival curve for the asthma exacerbation for all groups

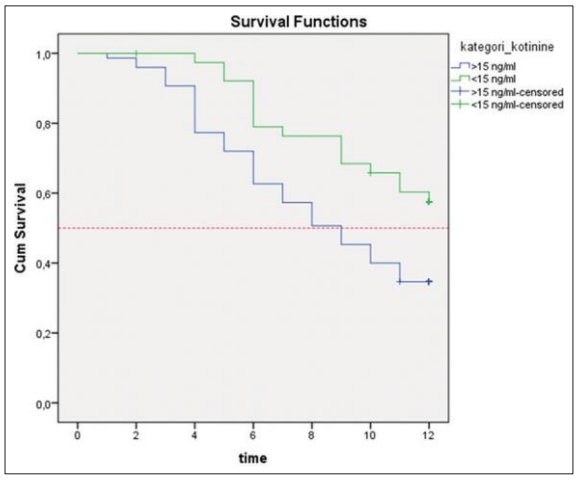

Fig. 2: Survival curve for the asthma exacerbation and cotinine environment tobacco smoke exposure

95% CI, 1.226–3.832, p=0.008. The result of this research shows that ETS exposure measured with urine cotinine level in children suffering asthma has risk 2 of having asthma exacerbation more rapidly when compared to children with non-exposure of cigarette smoke. There is a research that has proved that mothers who smoke increase four-fold response to histamine as well as high level of cotinine increase the risk of acute asthma exacerbation by 1.8-fold [33]. Children with ETS-exposed have the higher risk of having uncontrolled asthma with OR=3.20; 95% CI=1.40–6.90 [34].

Children who live in homes with smoking members have increased cotinine level when compared with those living in homes with no smokers. It shows that ETS exposure is associated with the increasing urinary cotinine and acute exacerbation asthma trigger as well as decreasing lung function of forced expiratory volume in 1 s and the ratio of forced vital capacity [35]. Around 87.9% of nontobacco consumers in the United States had detectable acquired serum cotinine levels. Nearly 40% of children aged 2 months to 2 years are living with at least one smoker, and perhaps, their condition is exacerbated by ETS exposure [36].

A series of epidemiological surveys provide strong evidence of the relationship between parental smoking and the prevalence of asthma in school-age children [37,38]. A recent study and meta-analysis of 76 studies have assessed that the effects of pre- or post-natal second-hand smoke exposure are associated with a 21–85% increased risk of asthma incident [39]. The strongest effect of prenatal maternal smoking on asthma in children aged 2 years old has CI 95% OR = 1.85 (1.3–2.5). In adolescence and adults, exposure to passive smoke is also associated with the prevalence of asthma [25].

The increase of urinary cotinine concentration is affected by the number of smokers in a household, and the number of cigarettes smoked. The result showed that the existing home smokers have cotinine concentrations >15 ng/ml at most. Category of heavy smokers or higher number of cigarettes >20 cigarettes per day areas is shown in Tables 3 and 4.

Table 3: ETS status at home and cotinine concentration

ETS Household	Cotinine	
	≥15 ng/ml	**<15 ng/ml**
Home with smoker	50 (66.7)	7 (17.9)
Home without smoker	25 (33.3)	32 (82.1)

ETS: Environment tobacco smoke

Table 4: Number of cigarettes and cotinine concentration

Number of cigarette	Cotinine	
	≥15 ng/ml	**<15 ng/ml**
<4	6 (12)	3 (42.9)
5–9	11 (22)	1 (14.3)
10–19	16 (32)	1 (14.3)
20–29	17 (34)	2 (28.6)

The variability of each individual against the pattern of cotinine metabolism due to exposure to existing nicotine is quite different. Therefore, it is possible that there may be the existence of cotinine in a household where there is no smoke. This may be attributed to exposure of the inhabitant(s) to cigarette smoke outside the home and other metabolism factors such as genetic variation, race, sex, use of oral contraceptives or other estrogen-containing hormones, renal, and drug failure, including anticonvulsants and rifampin as well as from foods they ate [23,40].

The main physiological features of asthma exacerbation are airways constriction and airflow obstruction, which are reversible. It is produced as a result of the contraction of bronchial smooth muscle, edema, and hypersecretion of mucus. Various trigger factors can lead to exacerbations. Acute bronchoconstriction caused by allergens occurs as a result of the release of mediators from mast cells [41]. The nature of tobacco smoke as inhalants, which are inhaled and exposed directly to the airway, causes a risk factor that has a relationship with asthma exacerbation events in children [17,42].

Our study found that children who lived with smokers tend to have high levels of cotinine and were more likely to experience asthma attacks compared to children who lived in smoke-free homes. These results prove that cigarette smoke triggers inflammation in the respiratory tract which causes asthma attacks exacerbation. Several studies have shown that an increase in the neutrophils inherent the airways will lead to an increase in eosinophils, which will release inflammatory mediators that play a role when asthma attacks [26]. People exposed to cigarettes will find an increase in T lymphocytes, especially CD8+ and macrophages along the airway wall, increased neutrophils in airway secretions, and peripheral airway infiltration with mononuclear cells and macrophages [43].

We also found the female gender more prone to having an asthma exacerbation HR attack, 1.72; 95% CI, 1.04–2.85). During our study of 114 children, the respondents were mostly girls (61.5%) and men (38.5%). Prakruthi *et al*. conducted a study which proved that women were more prone to asthma than men, out of 90 children examined, 66.7% females had asthma while 33.3% men were affected [44].

Tobacco smoke exposure may happen in a home (including childhood exposure from parents, siblings, other family members or from the environment). The best recommendation for individuals who have children with asthma exacerbations is the drug reliever and controller; however, long-term use of this medication has side effects. *Tamarindus indica* L. plants have been studied, and this plant can improve respiratory and anti-asthmatic patterns [45]. Proper preventive efforts and educational controls should be employed to stop smoking. The efforts of public health agencies through their regulations aimed at banning smoking in homes have successfully reduced ETS exposure.

CONCLUSION

This research revealed that ETS exposure in the household increases the risk of asthma exacerbation. Since children with asthma should have good survival and quality of life, it is, therefore, necessary and expedient to control the environment and educates children to avoid ETS Exposure.

ACKNOWLEDGMENTS

We would like to thank Directors of the Center for Healthy Lung Community Surakarta, Dr. Moewardi Hospital Surakarta, and the Lung Health Center Klaten, Indonesia, for granting us access to facilities for this study. We also thank all enumerators and laboratory staff for assisting in the process of collecting data.

AUTHORS' CONTRIBUTIONS

All authors in this manuscript have contributed to the research. Sutaryono and Ari Probandari designed the research model, analyzed the data and compiled the manuscript. Sutaryono assisted by Prabang Setyono designed the framework, planned sample preparation and carry out data collection in the field. Hartono contributed in writing the script and supervision of all activities. All authors discussed and provided critical feedback on this text.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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