Survival analysis of asthma patients attended to at Chitungwiza Central Hospital in Zimbabwe

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Research article

Keywords: asthma, hazard ratio, survival, mortality, Zimbabwe.

Posted Date: November 26th, 2019

DOI: https://doi.org/10.21203/rs.2.17794/v1

Abstract

Background Asthma is one of the leading global public health problems with an estimated 300 thousand deaths occurring annually worldwide. Deaths due to asthma in Zimbabwe reached 1 301 or 1.02% of total deaths in 2014. The association between asthma survival and socio-demographic and pathologic factors has not been done in Zimbabwe. We aimed to determine the survival of asthma patients at Chitungwiza Central Hospital in Zimbabwe over a period of 20 years. Methods Records for 158 asthma patients were analysed in this retrospective cohort study. The patient records were sampled from the computerised health information department at the hospital. Data were collected using a patient record checklist which was divided into four sections: (i) demographic information, (ii) clinical characteristics of asthma patients, (iii) health service utilization and (iv) asthma self-management. Descriptive data analysis was performed using the Kaplan Meier survival function curves. The Kaplan Meier survival curves were differentiated by the log-rank test, median survival times and mortality rates. Significant hazard ratios were used for multivariate cox regression model and a test on proportional hazards assumption based on Schoenfeld residuals was conducted. Results The total follow-up time was 2208 person years. The majority of the participants (60.7%) were female. The mortality rate was 61.4%. The median age at death was 25.5 years (IQR; 21-34). Smoking history [p=<0.001], presence of respiratory disease and cardiovascular disease [p=0.002] were significantly associated with higher mortality. Having an income level

Background

Asthma is global public health problem. [1]. It is a heterogeneous disease characterised by chronic inflammation of the airway and often bronchoconstriction. The symptoms of asthma include chest tightness, wheezing, shortness of breath and cough which vary over time and in intensity with variable expiratory airflow limitations [2]. Globally 334 million people worldwide suffer from asthma with approximately over 300 thousand deaths worldwide [3]. Twenty-two million disability-adjusted life years (DALYs) are lost annually and children with untreated asthma miss much of their primary school education which leads to reduced educational opportunities and increased time off work for parents resulting in the negative impacts on the economy through loss of productivity [3].

Asthma accounts for an estimated 80% of deaths in the low to middle income countries [4, 5]. The all age group adjusted death rate was 16.81 per 100,000 of population for asthma in Zimbabwe and the country was ranked number 15 in the world [6, 7].

Asthma has been associated with increased hospital admission over the past 25 years in South Africa with reports of 25-200 times increase of admission [8]. In Zimbabwe asthma is attributed to 253.5 deaths per 100 000 men and 185.8 deaths per 100 000 women among those aged 80 years and above [7]. This suggests need for improved quality of treatment for patients with asthma.

Deaths as a result of asthma are infrequent but are of serious concern because many of them are preventable [9]. Most asthma deaths are among older adults, although comparisons of mortality rates have a tendency to focus on children and younger adults.

Over the past 50 years, death rates in the young age groups have varied markedly in many high-income countries, attributed to modifications in medical care for asthma, especially the introduction of novel asthma medications. However, anecdotal evidence for Zimbabwe revealed that deaths among asthma patients was high at Chitungwiza Central hospital, hence a retrospective clinical cohort study was conducted among asthma patients to analyse asthma survival trends from 1997 to 2017.

Methods

Setting

The study was conducted at Chitungwiza Central Hospital in Zimbabwe. The hospital has a bed capacity of 500 beds including general, specialised, maternity and emergency care beds. Patients with acute asthma are cared for in the causality department from where they may be admitted to medical or paediatric wards if indicated. More complex cases of asthma such as status asthmaticus are managed in the high dependence unit.

Data Collection

Data were collected using the KoBO Collect, which an open source platform that is utilised when collecting and analysing data. Data collectors were trained on how to use the KoBo Collect Toolbox before actual data collection commenced on 29th of November 2018 ending on 16th of December 2018. All available asthma patient records from 1997 to 2017 were captured from the health information and records department at the hospital. This was done using computer based application systems which included the Systems Application Product (SAP) for admitting and discharging patients as well as the district health information system (DHIS). We collected data using a patient record checklist which was divided into four sections: (i) demographic information, (ii) clinical characteristics of asthma patients, (iii) health service utilization and (iv) asthma self-management. Additionally, we extracted data on asthma deaths from the death certificates and post-mortem results which were in the patients' files.

Sample size determination and sampling techniques

For this study we calculated a minimum sample size of 157. However there were a total of 158 records which had reported death as an outcome hence we included all the 158 records in our analysis. Since the prevalence of mortality with asthma was not known we used a hazard ratio (HR) of 50% to calculate the sample size. The sample size was determined using Stata version 14. This was based on the following formula

H_0: S1(t)=S2(t), alpha =0.0500 (two sided), s1=0.4000 s2=0.6325, hratio=0.5000, power=0.8000, p1=0.333 and withdrawal =10.00%. (see Formlua 1 in the Supplementary Files)

Data Analysis

The data collected was transferred to an Excel 2013 spreadsheet for cleaning and coding. We used the Stata Version 13 package for analysing data. Descriptive statistics were performed on the demographic characteristics which included gender, employment status and smoking history.

Clinical characteristics, health services utilization and asthma self-management were also descriptively analysed. Comparisons of survival times for asthma patients by these different characteristics was performed using the Kaplan Meier survival function curves. Further analysis of the cohort was done using bivariate cox regression models. Significant hazard ratios were then used for multivariate Cox regression model. Finally a test on proportional hazards based on Schoenfeld residuals was done to check if the model was consistent to Cox regression assumptions

Ethical Considerations

Permission to conduct the study was given by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE613/18) and also by Medical Research Council of Zimbabwe (A/2352). Gatekeepers' permission was granted by Zimbabwe Ministry of Health and Child Care and Chitungwiza Central Hospital. The community advisory board for Chitungwiza allowed the study to be conducted. Data captured through mobile electronic devices did not capture personal identifying information for the patient records and only computer generated codes were used for each participant record.

Results

Demographic characteristics of the asthma cohort: 1997-2017.

A total of 158 records were collected for an asthma cohort which was analysed for a 20 years follow up period. Table 1 shows characteristics of the cohort focusing on smoking history, place of death and cause of death. The analysis included 153 asthma patients. The median age of cohort between sexes (male 18.5 [IQR 11-23]: female 19 [IQR13-25]; p=0.330). The total follow up period was 2208 person years (males [891 person years]: females [1317 person years]). Total mortality of 61.4% was reported among the participants in the cohort. There was no significant difference in the median age at death by sex 25.5[21-34], [p=0.340]. The median age at death by sex was 25 [19-32] for males and 26[21-37] for females. Participants in the cohort did not show any significant difference in their level of education by gender [p=0.474] and marital status [p=0.121].The study showed 46.2% of participants reported an income between US$201 and US$500, there was no significant difference in the level of income between males and females [p=0.232]. More males (53.2%) confirmed smoking history, there was a significant difference between males and females who never smoked [p=<0.001]. More (90.4%) asthma patients died at a health facility. There was no gender bias, males and females [p=0.677].

Causes of death among asthma patients

The main (46.8%) cause of death in the cohort of asthma patients was respiratory diseases followed by HIV, diabetes and kidney disease with (23.4%). Differences in the cause of death by gender were statistically significant in both respiratory and cardiovascular diseases (p=0.006), whilst mortality due to diseases of the Gastroesophageal reflux disease (GERD) and HIV, diabetes and kidney diseases were common in both sex (Table 1).

Table 1: Characteristics for the asthma patients cohort: 1997-2017

ategory	Total Sample (158)	Male (n=62) 39.3%	Female(n=96) 60.7%	p value
.ge at enrolment median [IQR)	19(13-25)	18.5(11-23)	19(13-25)	0.330
otal follow up period	**2208person years**	891person years	317person years	
otal Mortality n (%)	94 (61.4)	-		-
Iortality by Sex, n (%)			-	
Iale	37(61.7)			0.960
emale	57(61.3)			
.ge at death, median [IQR]	25.5[21-34]	25[19-32]		0.340
evel of Education n (%)			26[21-37]	
[ever attended	6(3.8)	2(3.2)		0.748
rimary	12(7.6)	7(11.3)	4(4.2)	0.158
econdary	124(78.5)	46(74.2)	5(5.2)	0.289
ertiary	16(10.1)	7(11.3)	78(81.3)	0.699
Iarital Status			9(9.4)	
ivorced	20(12.7)	7(11.3)		0.685
Iarried	69(43.7)	27(43.6)	13(13.5)	0.980
ingle	42(26.6)	21(33.9)	42(43.8)	0.096
/idowed	27(17.1)	7(11.3)	21(21.9)	0.121
ıcome Level			20(20.8)	
$100	37(23.4)	14(22.6)		0.839
100-$200	30(19.0)	13(21.0)	23(24.0)	0.606
201-$500	73(46.2)	25(40.3)	17(17.7)	0.232
$500	18(11.4)	10(16.1)	48(50.0)	0.131
moking history			8(8.3)	
urrent/former	56(35.4)	33(53.2)		<0.001
[ever Smoked	102(64.6)	29(46.8)	23(24.0)	<0.001
lace of death			73(76.0)	
[ome	9(9.6)	4(10.8)		0.677
[ospital/Clinic	85(90.4)	33(89.2)	5(8.8)	
ause of death			52(91.2)	
ardiovascular disease	9(9.6)	0		0.001
astroesophageal Reflux disease	19(20.2)	6(16.2)	9(15.8)	0.314
IV, Diabetes, Kidney disease	22(23.4)	8(21.6)	13(22.8)	0.670
espiratory disease (Pneumonia,	44(46.8)	23(62.2)	14(24.6)	0.002
ronchitis,			21(36.8)	

Clinical characteristics of the asthma patients

Table 2 shows the clinical characteristics of the asthma patients. Controlled asthma was defined as the extent to which the various manifestations of asthma are reduced or removed by asthma treatment. The proportion of patients who died with asthma during the period of interest was significantly higher in those with uncontrolled asthma [p=0.040]. Participants in the cohort did not show any significant difference in the regularity of their use of maintenance medications [p=0.421] and adherence to asthma medications [p=0.476].A history of asthma exacerbation significantly correlated with mortality [p=<0.001]. When compared to use of beclomethasone inhaler, participants who had used the Seretide accuhaler were significantly less likely to have died during the follow up period [p=0.026]. Majority (57.5%) of those who died with asthma had a history of atopy (eczema/hay fever). There was no significant differences in the proportion of those asthma patients who died whilst on asthma medications. Majority (63.9%) reported not having a history of emphysema/chronic bronchitis.

Table 2: Clinical characteristics of the asthma patients (cohort) n=153

Category	Dead n=94	Alive n=59	P value
Asthma controlled			
Yes	41(43.6)	36(61.0)	**0.018**
No	53(56.4)	23(39.0)	
Regular use of maintenance medications			
Yes	59(62.8)	38(64.4)	
No	35(37.2)	21(35.6)	**0.421**
Adherence to asthma medications			
Yes	53(56.4)	33(55.9)	
No	41(43.6)	26(44.1)	**0.476**
History of Exacerbation			
Yes	78(83.0)	43(72.9)	
No	16(17.0)	16(27.1)	**0.067**
Use of corticosteroid inhaler			
Yes	53(56.4)	33(55.9)	
No	41(43.6)	26(44.1)	**0.476**
Type of corticosteroid inhaler used			
Beclamethasone	31(58.5)	14(42.4)	**0.026**
Seretide accuhaler	22 (41.5)	19 (57.6)	
History of emphysema/chronic bronchitis			
Yes	29(30.9)	28(47.5)	
No	65(69.1)	31(52.5)	**0.294**
History of Atopy			
Eczema/ Hay fever	54(57.5)	26(44.1)	
No	40(42.6)	33(55.9)	**0.05**
Medications			
Ever taken Beclamethasone	9(9.6)	4(6.8)	**0.546**
Ever taken Ipratropium	14(14.9)	5(8.5)	**0.243**
Ever taken Prednisolone	40(42.6)	27(45.8)	**0.697**
Ever taken theophylline	17(18.1)	11(18.6)	**0.978**
Ever taken 3 or more medications	14(14.9)	12(20.3)	**0.387**

Health services utilisation by asthma patients

The significant factors associated with mortality were not seeing the same doctor or specialist doctor and a history of having visited a doctor for their asthma in the past 2 years [p=<0.001]. Those who visited

emergency department for severe asthma attack and also those who got admitted to hospital because of asthma attack had a significantly high mortality rate [<0.001].

Table 3 Health Service Utilisation by asthma patients

ategory	Dead n=94	Alive n=59	p value
ee same doctor for asthma			
es	6(6.4)	1(1.7)	0.088
lo	88(93.6)	58(98.3)	
ee specialist doctor for asthma			
es	23(24.5)	13(22.0)	<0.001
lo	71(75.5)	46(78.0)	
isited a doctor for asthma in the past 2 years			
es	88(93.6)	55(93.2)	<0.001
lo	6(6.4)	4(6.8)	
isited emergency department for asthma in the past two			
ears	80(85.1)	52(88.1)	
es	14(14.9)	7(11.9)	<0.001
lo			
dmitted to hospital for asthma treatment in the past 2	86(91.5)	50(84.8)	<0.001
ears	8(8.5)	9(15.2)	
es			
lo			

The Kaplan Meier survival curves (Fig 1) showed significant differences of smokers and non smokers in the first 10 years follow up period (p=0.004). However, there was no significant difference for the last 10 years follow up period. Smokers had a median survival of 15 person years while the non smokers had a median survival time of 16 person years

Kaplan Meier survival curves for clinical characteristics of asthma patients.

The Kaplan Meier survival curves (Fig 2) below showed significant differences (p=0.009) in survival during a follow up period of 20 years. Patients who had controlled asthma had a median survival time of 19 person years compared to those uncontrolled who had a median survival time of 13 person years. The mortality rate amongst those controlled was 4/100 whereas for those uncontrolled had a mortality rate was 6/100 over the 20 year follow up period.

The log-rank test for equality of survival times between patients with asthma who used Beclomethasone inhaler and Seretide Accuhaler showed that Seretide Accuhaler users had significantly higher survival

(p=0.04). The use of Seretide Accuhaler resulted in significantly lower mortality rate (4/100) compared to Beclamethasone inhaler whose mortality rate was 6/100 over the 20 year follow up period (p=0.04). (Fig 3). Review of records on the use of Seretide Accuhaler and Beclamethasone inhaler showed that patients who were using Seretide Accuhaler had it prescribed in the private setting.

There were significant differences between asthma patients who indicated history of eczema, hay fever and lack thereof (p=0.03) (Fig 4). However, the incidence rates of those with a history of eczema or those without was the same (4/100). Patients who had a history of hay fever had the least median survival time (12 person years) for the follow up period of 20 years while those with with history of eczema had a median survival time of 16 person years.

The participants' survival time also differed by diagnosed conditions. Those diagnosed with respiratory conditions (Pneumonia and Bronchitis) had the highest incidence death rate of 6/100 patients over the 20-year follow-up period. Gastroesophageal reflux diseases had an incidence death rate of 5/100 patients, whilst the lowest was in cardiovascular diseases (3/100 patients). HIV, diabetes and kidney diseases contributed to combined incidence death rate of 4/100 patients of the follow-up period.

Survival times for asthma patients according to health services utilization

Regardless of the log-rank test showing lack of significance between survival times of participants who see the same doctor or different doctors over the 20 year follow-up period, seeing the same doctor had a mortality rate of 5/100 compared to those participants who sought help from different doctors whose mortality rate was 8/100 persons over a 20 year follow-up period. Seeing a specialist doctor in the first 10 years had a better survival compared to seeing the specialist doctor during the last 10 years. Those who did not see a specialist doctor had a median survival time of 17 person years. However, there were no significant differences (p=0.647).

The log-rank test for identifying differences in Kaplan Meier Curves on asthma patients according to doctor visited in the past 2 years did not show significant differences. However, the follow-up period of 5 and 15 years depicted some significant difference between those who visited a doctor in the past two years and those who did not visit a doctor in the past two years.

Investigation on the clinical characteristics on the survival of asthma patients showed that uncontrolled asthma was significantly contributing to death, with the hazard ratio of 1.68(p=0.01). Thus, a patient with uncontrolled asthma was 68% more likely to die compared to those who had it under control. Significant hazard ratios also included the use of Beclamethasone inhaler as compared to Seretide accuhaler. Patients who used Beclamethasone inhaler were 1.75 times more likely to die at any given time over the follow-up period as compared to those using seretide accuhaler. Also, patients with a history of atopy (Hay fever) were 1.93 times more likely to die compared with to those without a history of atopic conditions. Furthermore, the use of Ipratropium was a borderline significant hazard ratio with an estimate of 1.98(p=0.07).

In bivariate analysis, seeing the same primary care doctor and a specialist doctor were a risk factor. Those patients seeing different doctors were 48% less likely to die compared to those who were being seen by the same doctor and referred to a specialist doctor. (Table 5).

Table 5: Bivariate cox regression models for demographic characteristics, clinical characteristics, health service utilisation and asthma self-management

Variable	Hazard Ratio (95% CI)	P-value
Demographic Characteristics		
Gender		
Female	Reference	
Male	0.96(0.63-1.45)	0.83
Employment Status		
Unemployed	Reference	
Employed	0.66(0.45-1.01)	0.05*
Income Status		
$100-$200	Reference	
$201-$500	1.37(0.73-2.61)	0.33
<$100	3.08(1.57-6.04)	0.001*
>$500	1.89(0.83-4.30)	0.14
Smoking History		
Non-Smoker	Reference	
Smoker	1.16(0.76-1.78)	0.49
Clinical Characteristics		
Asthma Control		
Yes	Reference	
No	1.68(1.11-2.52)	0.01*
Regular use of maintenance medications		
Yes	Reference	
No	1.09(0.72-1.66)	0.68
Adherence to asthma medications		
Yes	Reference	
No	0.99(0.66-1.49)	0.98
Use of corticosteroids inhalers		
Seretide Accuhaler	Reference	
Beclamethasone inhaler	1.75(1.01-3.04)	0.045*
History of atopy		
No	Reference	
Eczema	1.16(0.72-1.88)	0.54
Hay fever	1.93(1.17-3.18)	0.01*
Asthma medications used		
Ever taken >3	Reference	
Prednisolone	1.24(0.67-2.28)	0.49
Theophylline	1.31(0.64-2.65)	0.46
Beclomethasone	1.45(0.63-3.35)	0.39

Ipratropium	1.98(0.94-4.16)	0.07
Health service utilization		
See same doctor for asthma		
Yes	Reference	
No	0.52(0.23-1.19)	0.12
See specialist for severe asthma		
Yes	Reference	
No	1.11(0.69-1.77)	0.68
Admitted to hospital in the past 2 years		
No	Reference	
Yes	1.39(0.68-2.88)	0.37
Visited a doctor in the past 2 years		
Yes	Reference	
No	1.11(0.48-2.54)	0.81
Asthma Self-Management		
Know which medications to take in severe asthma		
Yes	Reference	
No	1.06(0.66-1.70)	0.80
Have written down instructions about when to call for help in severe asthma attack		
Yes	Reference	
No	0.87(0.55-1.40)	0.58
Know when to call for help in a severe asthma attack		
Yes	Reference	
No	0.91(0.61-1.37)	0.65

Multivariate cox proportional hazards analysis

A multivariate cox proportional hazard analysis showed that after controlling for smoking, history of atopy, the above factors were significant to explain the survival of asthma patients. The model showed that the most significant risk factor for mortality was seeing different doctors (p=0.005). However, those who were admitted in the past 2 years were 3.6 times more likely to die due to uncontrolled asthma after adjusting for other factors (smoking, history of atopy

Discussion

The aim of this study was to determine the survival of asthma patients at a Zimbabwean Central Hospital over a period of 20 years. To the authors' knowledge, this is the first study to analyse survival of asthma patients attended to at any public hospital in Zimbabwe.

This retrospective clinical cohort study revealed that the mortality rate amongst patients with asthma who were followed up for 20 years was high. Higher mortality rates were observed among males compared to females. These findings are comparable to those reported in Brazil [10] and Australia [11]. The reasons why males were are at higher risk of death were unclear but could be related to non-adherence to medication and poor health-seeking behaviour. Another plausible explanation for higher male mortality in our setting could be due to gendered differences around smoking behaviour in Zimbabwe with more males being smokers than their female counterparts. Results from this study showed that a history of smoking was a risk factor for death among asthma patients. Previous research has demonstrated that lifetime tobacco consumption increases the risk of death from asthma [12].

Our results revealed that most of the patients died at a health care facilities as was observed in Brazil [10]. Such findings are unsurprising since patients with severe symptoms of asthma are more likely to be hospitalized.

Concurrent affliction by two or more conditions has more adverse outcomes in asthma. This was shown in our study where the co-occurrence of respiratory diseases and cardiovascular disease was significantly related to mortality, a phenomenon that has also been reported in other settings where respiratory disorders were shown to exacerbate death among asthma patients [11] [12].

A major finding was that uncontrolled asthma was related to mortality. This mandates the implementation of interventions targeting the control of asthma severity within the community and healthcare institutions. This study suggests that clinical characteristics of asthma patients including lack of asthma control, history of atopy and use of beclamethasone inhaler were associated with high mortality. These clinical characteristics of asthma patients might be related to severity of the condition. In addition, our findings also suggest that patients who consulted a specialist doctor and who visited an emergency department because of asthma in the past 2 years had significantly higher mortality rates. This suggests a link between uncontrolled asthma and mortality. These results echo those reported in Australia and New Zealand [16]. According to Fernandes et al. [10], a lack of asthma control is a risk factor for mortality among individuals with severe asthma.

Although, this study was conducted in only one of Zimbabwe's five central hospitals, it is the only study that has looked at survival of asthma patients. We however recommend that future studies to explore the situation prevailing in other settings within the country to have a better understanding of the survival of asthma patients.

Conclusion

The study concluded that having a smoking history, respiratory disease, cardiovascular disease and uncontrolled asthma were risk factors for death among asthma patients. Those patients that presented having an atopic history and who had visited emergency departments as a result of their asthma had high risk of mortality with asthma compared to those that were alive after the 20 years follow-up period.

There is need to institute measures aimed at reducing co-morbidity of asthma and cardiovascular diseases and controlling asthma severity in healthcare institutions.

Abbreviations

BREC: Biomedical Research Ethics Committee; CI: Confidence Interval; DALYs: Disability adjusted life years; DHIS: District Health Information Systems; GERD: Gastroesophageal reflux disease; HIV: Human Immunodeficiency virus; HR: Hazard Ratio; MRCZ: Medical Research Council of Zimbabwe; SAP: System Application Product; UKZN: University of KwaZulu-Natal.

Declarations

Disclaimer

Opinions expressed in this paper are those of the authors and do not necessarily reflect the views of their respective institutions.

Ethical approval and consent to participate

We obtained ethics approval to conduct the study from Medical Research Council of Zimbabwe (A/2352) and Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE613/18). Gatekeepers' permission was sought from Chitungwiza Hospital as well as Ministry of Health and Child Care, Zimbabwe.

Competing interests

None

Funding

This study received funding from the OAK foundation and UKZN College of Health Sciences to ensure that the PN was able to do field data collection and analysis of data. PN is an OAK Foundation fellow.

Consent for publication

Not applicable

Authors' contributions

PN and MJC conceived the idea. PN with the assistance of MJM designed the protocol and revisions were done by MJC and ENS. PN designed the protocol. PN wrote the first draft of the manuscript and all authors (PN, MJC and ENS) reviewed changes. All authors read and approved the manuscript for submission to the journal.

Acknowledgements

The authors would like to thank the UKZN and OAK foundation who have supported the PN throughout this study. I would like to acknowledge Dr Chester Kalinda and Tafadzwa Madanhire for assisting with designing the sample size and data analysis.

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Figures

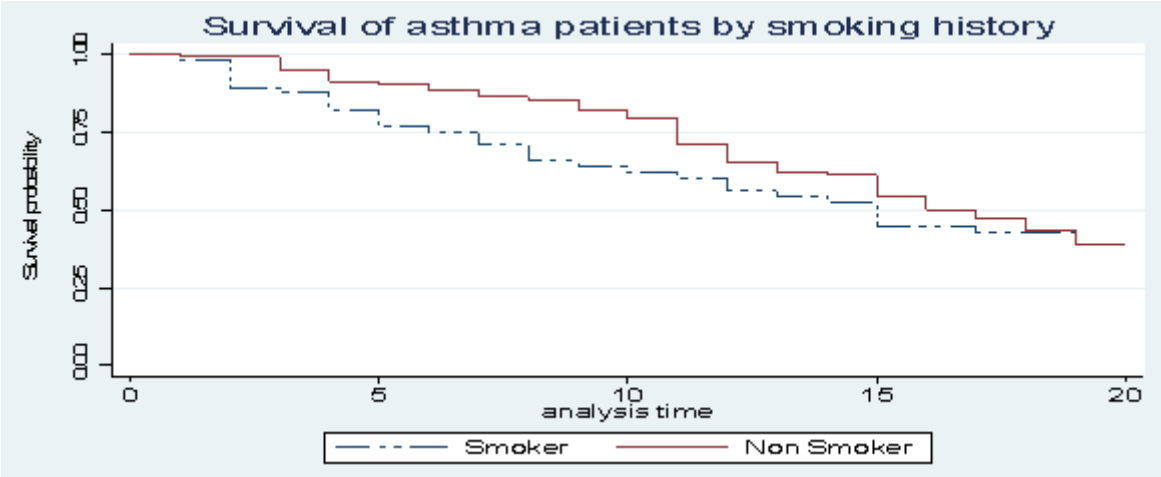

Figure 1

Kaplan Meier survival curves for asthma patients by smoking history.

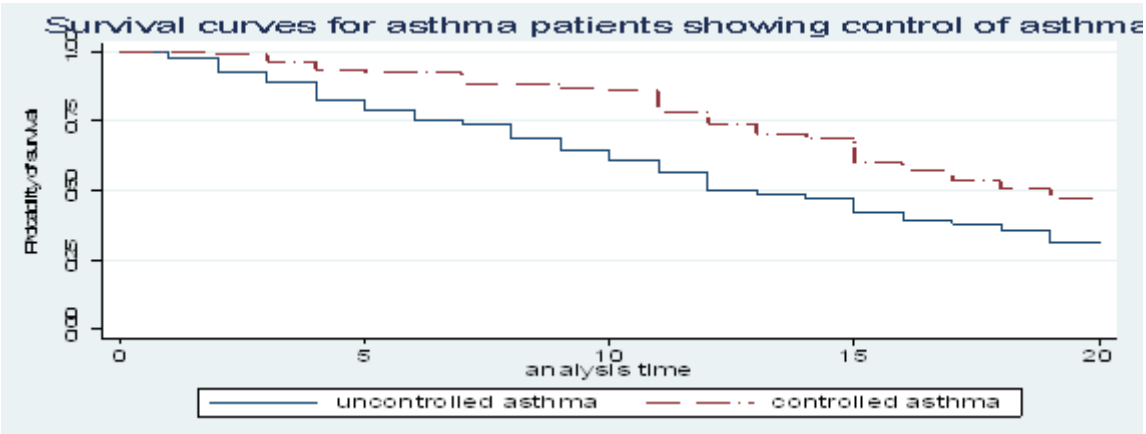

Figure 2

Kaplan Meier Survival curves for asthma patients showing control of asthma

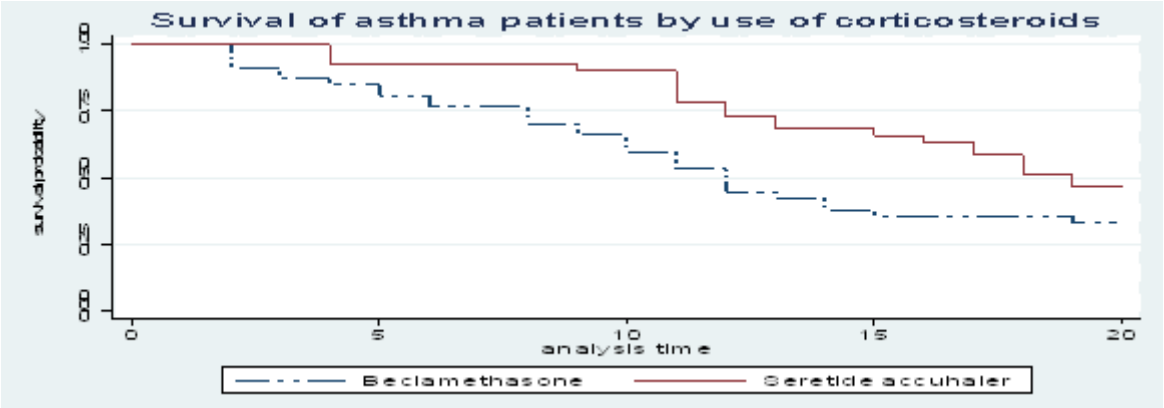

Figure 3

Kaplan Meier Survival curves for asthma patient by use of corticosteroids inhalers

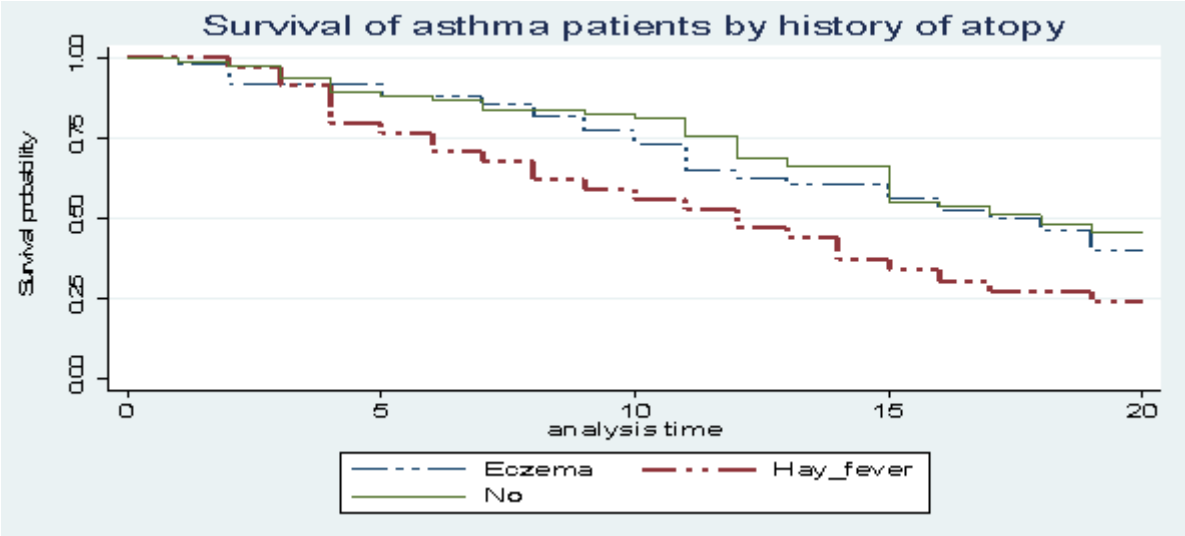

Figure 4

Kaplan Meier survival curves for asthma patients by history of atopy.

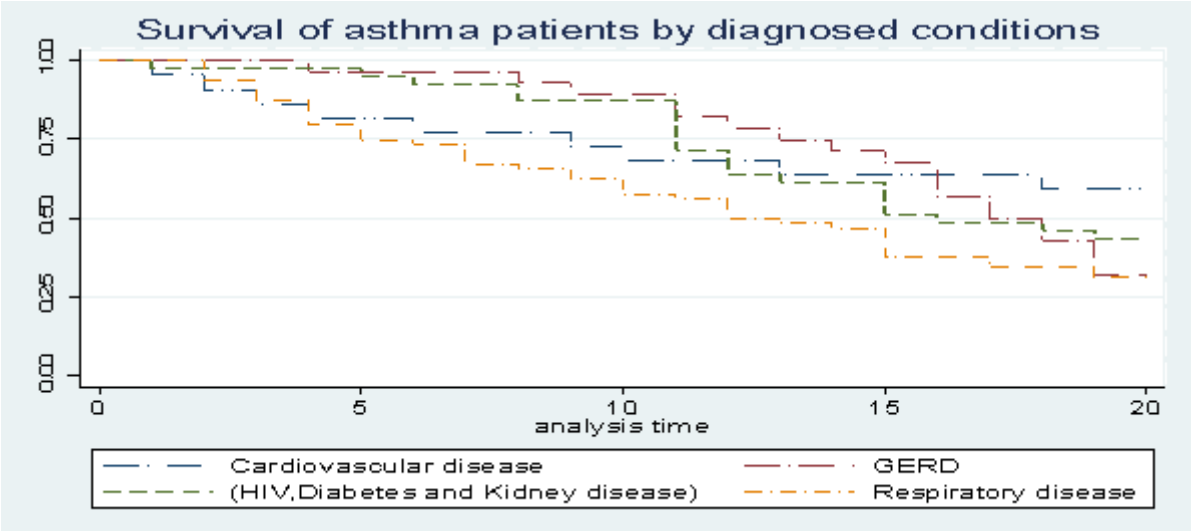

Figure 5

Survival of asthma patients by diagnosed conditions.

Supplementary Files

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- Formula1.jpg