Abstract and Keywords

Objectives: Epistaxis is the second most common referral to the Ear nose and throat (ENT) department. Frailty, a marker for biological vulnerability, has been shown to increase the risk of haemorrhage, but its impact in epistaxis patients is unknown. We aim to establish the impact of Clinical Frailty score, as well as other established risk factors for epistaxis, on the likelihood of admission in patients presenting to secondary care with epistaxis.

Design: Retrospective cohort study

Setting: University hospital Otolaryngology department

Participants: Adult patients presenting to hospital with epistaxis between March 2019 and March 2020.

Main outcome measures: We compare the clinical frailty score of patients admitted with epistaxis to those patients seen and treated same day.

Results: 299 epistaxis presentations were identified, of which 122 (30.8%) required admission for further management. Clinical frailty score of ≥4 had an increased odds for admission (OR 3.15 (95% CI:1.94 – 5.16), p<0.001). In the majority of presentations (66.2%), patients were taking either an antiplatelet, anticoagulant or a combination of them. Of these presentations, the use of an anticoagulant (OR: 2.00 (95% CI: 1.20-1.92), p:0.10) and dual antiplatelet (OR: 2.82 (95% CI: 1.02-7.86), p:0.10, p:0.07) demonstrated increased odds of admission.

Conclusions: We have shown that frailty increases the risk of admission in adult patients presenting with epistaxis. Frailty is becoming an increasingly apparent independent cause for haemorrhage in the elderly population. Careful consideration of bleeding risks, particularly in frail patients, needs addressing due to the morbidity associated with epistaxis.

Key Points

- Epistaxis is a common referral to otolaryngology teams and most of these (59.2%) presentations were seen, treated and discharged on the same day.

- Clinical frailty score ≥ 4 increases the odds of admission by 3 times for those presented with epistaxis.

- Those on monotreatment antiplatelet only, have a risk for admission after presentation with epistaxis.

- Treatment with a dual anti-platelet therapy or an anti-coagulant with or without an anti-platelet increases the odds of admission in adult patients presenting with epistaxis.

- Careful consideration in starting or continuing anticoagulant and/or antiplatelet therapy in frail patients due to increasing evidence of haemorrhage risk in this patient group.

Introduction

Epistaxis, behind sore throat, is the second most common referral to the ear nose and throat department and accounts for 33% of Ear, Nose and Throat (ENT) admissions in Scotland. (1) Despite a lifetime prevalence of 60%, the vast majority of patients will experience minor epistaxis, which can be managed in the community with first aid measures alone.(2) Epistaxis is known to follow a bi-modal age distribution with peak incidence occurring in the 1st and 8th decades. Severe epistaxis requiring secondary care treatment most commonly occurs in elderly patients.(3) The highest proportion of patients attending the emergency department with epistaxis are between the ages of 70 and 79.(3) As well as age, male gender and socioeconomic deprivation have also been shown to increase the likelihood admission to hospital with epistaxis.(4)

Anti-platelet and anti-coagulant medications are used to reduce the risk of myocardial infarction, stroke and thromboembolic complications of atrial fibrillation, deep vein thromboses and mechanical heart valves.(5) Anti-platelet and anti-coagulant medications are commonly prescribed, with the likelihood of taking one of these medications increasing with age.(5) Bleeding is a well-documented complication of anti-platelet and anti-coagulant medications. The incidence of bleeding with classical oral anti-coagulants, such as warfarin, is 10-17%, with 2-5% of patients experiencing severe bleeding. (5,6) A recent retrospective review of 600 epistaxis presentations in Germany found that around 65% of patients admitted with epistaxis take an anti-coagulant. However, they did not reach statistical significance when assessing anti-coagulant or anti-platelet medications as independent risk factors for admission with epistaxis.(7) A small subset of patients will take more than one anti-platelet or anticoagulant medication.(8) This is primarily due to cardiovascular diseases, such as

coronary artery disease, atrial fibrillation and peripheral arterial disease.(8,9) An increased risk of bleeding has been previously shown in patients taking more than one anti-platelet or anti-coagulant medication,(10) however there have been no studies in the UK to show how this impacts patients attending hospital with epistaxis, and their likelihood of being admitted. Patients with multiple medical comorbidities are known to be at an increased risk of bleeding. Hypertension, ischaemic heart disease, peripheral vascular disease and congestive cardiac failure have all previously been demonstrated to increase the likelihood of hospital presentation and re-presentation with epistaxis.(11) Frailty increases with age and has been shown to be an independent risk factor for negative health outcomes, morbidity and mortality.(12) Specifically, frailty has been demonstrated to increase the risk of major bleeding in patients following acute coronary syndrome.(13) Little is known about how frailty influences the risk of severe epistaxis requiring hospital admission.

As the age of our population increases, we will see an increase in the number of elderly patients attending Emergency Departments (ED) with epistaxis. Poly-pharmacy, multi-comorbidity and frailty are all well-documented challenges for clinicians managing elderly patients. Here, we explore the impact of Clinical Frailty score on the likelihood of admission in patients presenting to secondary care with epistaxis and also how other established risk factors, such as anticoagulation, antiplatelet therapy, comorbidities and seasonal variation increase the odds of admission in our cohort.

Materials and Methods

Approval was obtained from our local Caldicot guardian for accessing patient records. Ethics approval was not required as this study data collection was undertaken as part of a local

quality improvement project to integrate CFS into our risk stratification process at our unit for epistaxis during COVID-19. Study design and reporting adheres to STROCCS guidelines.

All presentations of epistaxis over a one-year period (1st March 2019 – 1st March 2020) to secondary care in the Ayrshire and Arran Health Board were obtained from the registry office. Patients under the age of 18 were excluded. Relevant demographic, medical and drug histories, laboratory investigations and treatment information were extracted from patients' electronic record. Comorbidities were reclassified based on the current definition,(14) meanwhile meteorological seasons definitions from the Meteorological Office were used. (15)

Data were analysed based on the epistaxis hospital attendance episodes. Welch t-test was used for unpaired normally distributed data and Mann-Whitney test for unpaired non-normally distributed data. Categorical data was assessed using the Pearson's chi-squared, Fisher's Exact Test or the Monte-Carlo Method. Effect size are presented as odd ratio and risk ratio. Haldane correction by a factor of 1 was also performed to enable effect size calculation. Binomial logistic regression modelling for adjusted odds ratio was performed to enable confounding adjustment based on the clinical variables which the authors perceived to impact hospital presentation. The R version 4.0.0 (2020-04-24) with R Studio version 1.2.5042 were used to performed the data analysis.(16–19)

Results

Admission Event demographics

In total, 299 epistaxis presentations were identified (Table 1). The majority of presentations (59.2%) were seen and treated by ED or ENT physicians and discharged without admission.

The overall distribution between sexes were similar (Female 49.2% vs Male 50.8%, p: 0.553), with female preponderance for admission requirement (51.6% vs male 48.4%, p: 0.553). Sex, however, was not associated with admission status (Adjusted OR 0.66, RR 0.91, p: 0.480, Table 2). The median age for the admission was 76 years [67.0;83.0] and 75 years [66.0;82.0] for non-admissions. Age $\geq$ 76 had lower odds but increase risk for admission requirement (Adjusted OR 0.59, RR 1.10, p:0.507, Table 2).

The median CFS for episodes requiring admissions was 4 [2;6], whilst the non-admissions 3 [1;5]. The majority (63.3%) of admission events had a CFS of $\geq$4, whilst in the non-admission events had a CFS of $\leq$3 (64.7%). A CFS $\geq$4 was associated with an increased odds and risk for admission even on the multivariate logistic regression analysis (Adjusted OR 3.09, RR 1.96, p<0.001, Table 2). Comorbidities were analysed and revealed no statistically significant difference between admission events status (Table 1). Seasonal variation in epistaxis presentations were seen in our cohort with most admission events occur in autumn (40.2%, p:0.011, Table 1). Nevertheless, the odds and risk for admissions were comparable between autumn and winter (Adjusted OR 1.27, RR 1.24 vs Adjusted OR 1.26, RR 1.17, Table 2) when compared to the summer months (Table 1). However, only the spring season has significant statistical impact on the multivariate logistic regression analysis (p:0.05, Table 1)

Antiplatelet and Anticoagulation Profile

In all presentations of epistaxis, 198 episodes (66.2%) identified patients were on an antiplatelet or an anticoagulant or on a combination of treatments (Table 3). Of those admitted, most were on single modality therapy with either an antiplatelet (23.8%) or an anticoagulant (36.9%, p <0.001, Table 3). Aspirin was the most commonly (17.4%) used

antiplatelet followed by Clopidogrel and Dual antiplatelet therapy (Table 3, p = 0.094). Novel oral anticoagulants (NOAC) were the most common anticoagulant (19.7%) followed by warfarin and heparin (Table 3, p < 0.001). Statistically significant risk and odds for admission requirement were noted in the anticoagulant and antiplatelet + anticoagulant treatment group on univariate analysis (p:0.010 vs p:0.009, Table 2) but only dual antiplatelet (p:0.05) and single anticoagulant (p:0.01) were significant on multivariate analysis (Table 2).

Treatment

Of the patients admitted, median length of stay was 2.0 [1.00; 3.00] days (Table 4, p < 0.001). Nasal packing was performed in the majority of admissions (84.4%). A small number of presentations (n = 10) had nasal packing performed in the ED, which was subsequently removed once reviewed by ENT and underwent definitive management without the need for admission. Unilateral nasal packing took placed in 68.1% of the presentations, with a median packing duration of 2.0 [1.0;3.0]. Surgical intervention was required in 3 presentation events which involved 3 different patients (2 sphenopalatine ligations and 1 bipolar diathermy). Blood transfusion was required in 16 (13.1%) presentations (p < 0.001).

Discussion

In keeping with previous studies, our patient cohort showed a male predominance in all patients presenting with epistaxis and those not requiring admission. In the admission group, however the predominance was reversed with a male:female ratio of 1:1.06 which has been identified previously.(20) The median age of patients admitted was 76 years, similar to other UK based studies demonstrating that the second peak of epistaxis appears in the 8th decade of life. (4,20–22)

Of recent times, frailty is becoming a more important indicator of a patient's biological vulnerability than age. Clinical frailty index is a marker of homeostatic reserve and a high CFS is associated with poor clinical outcomes in general.(12) There are currently no studies investigating the impact of frailty on epistaxis and part of our study investigated this effect on admission outcomes through the CFS. Using the median scores for each outcome group, we categorised the data into ≥4 and ≤3. Through multivariate analysis, we identified that a CFS ≥ 4 is independently associated with a statistically significant increased risk of admission with epistaxis (p < 0.001). The distinction between a CFS 3 versus 4 is interesting in that it is between these two points that a patient's symptoms of their health comorbidities begins to impact and limit their physical activity.(23) This is an unexpected finding in that our local policy is to admit patients requiring nasal packing and further illuminates the impact of frailty in bleeding and epistaxis. Additionally, frailty has been reported as an independent predictor of major haemorrhage in acute coronary syndrome patients, irrespective of patient age.(13) Although there are some obvious differences in our cohort, similarities can still be drawn. For example, 67.7% of our patients had a history of cardiovascular disease and will therefore have similar risk factor profile to those patients in the aforementioned study.

We expected comorbidities to impact admission outcomes in our epistaxis cohort. Particularly in patients with haematological conditions and liver disease as their coagulation can be impaired and also in patients with cardiovascular disease who are frequently on anticoagulant or antiplatelet therapy. While comorbidities were more frequently seen in the non-admission group and cardiovascular disease was the most common comorbidity in both groups, nonetheless it did not reach statistical significance. One study has identified congestive cardiac failure, hypertension and diabetes mellitus as risk factors in recurrent epistaxis, but only captures readmission data, and therefore represents a reduced cohort.(24)

There was seasonal variation in our study, with the highest season for admissions in autumn, followed by winter, spring and summer. Summer months have previously been noted in Scotland to have the lowest number admissions for epistaxis, an effect hypothesised to be due to meteorological variations in barometric pressure, humidity and temperature on nasal vasculature.(1) The odds and risk of admission, however, was not increased in the three other seasons in comparison to summer (Table 2).

Anti-coagulant and/or antiplatelet therapy is expected to increase the severity of epistaxis and therefore requirement for nasal packing and admission. In our cohort, patients who were admitted were more commonly on an anticoagulant with or without antiplatelet or dual antiplatelet therapy has a higher odds for admission on multi-variate analysis. Meanwhile, those not admitted were more likely to be on antiplatelet monotherapy, partly in concordance with Buchberger et. al. The use of antiplatelet monotherapy has less of an impact on admission requirement, which may be related to the dose effect of platelet aggregate inhibitors.(25)

Similar to previous UK studies, 122 patients of our cohort (40.8 %) required admission, with a median duration of admission of 2 days.(4,21) 113 patients (37.8%) had nasal packs used in their management, with the literature showing a wide range of nasal pack use (24 – 67%). (7,21) This variability is likely to be impacted by local practice, equipment availability, expertise and to some degree severity of epistaxis. With this in mind, requirement for nasal packing is not a good predictor of admission. Additionally, with new advice and guidelines for the outpatient management of patients who have nasal packing in situ, this point is not as significant as it once was.

Conclusion

Epistaxis is a common cause of ENT presentations to secondary care. This study has shown the clinical frailty and anticoagulant/antiplatelet use are independent risk factors for admission with epistaxis. Therefore, careful consideration should be given to starting or continuing anticoagulant and/or antiplatelet therapy in frail patients due to increasing evidence of haemorrhage risk in this patient group.

Acknowledgements

None

Data Availability Statement

The data that support the findings of this study are available from the corresponding author

upon reasonable request.

Conflict of interest

None to declare

References

1.   Walker TWM, MacFarlane T V., McGarry GW. The epidemiology and chronobiology of epistaxis: An investigation of Scottish hospital admissions 1995-2004. Clin Otolaryngol. 2007;

2.   Viehweg TL, Roberson JB, Hudson JW. Epistaxis: Diagnosis and treatment. J Oral Maxillofac Surg. 2006;

3.   Kasperek ZA, Pollock GF. Epistaxis: An Overview. Emergency Medicine Clinics of North America. 2013.

4.   Douglas CM, Tikka T, Broadbent B, Calder N, Montgomery J. Patterns of hospital admission in 54 501 patients with epistaxis over a 20-year period in Scotland, UK. Clin Otolaryngol. 2018;43(6):1465–70.

5.   Rubboli A. Incidence, clinical impact and risk of bleeding during oral anticoagulation therapy. World J Cardiol. 2011;

6.   Suzuki S, Otsuka T, Sagara K, Semba H, Kano H, Matsuno S, et al. Nine-year trend of anticoagulation use, thromboembolic events, and major bleeding in patients with non-valvular atrial fibrillation shinken database analysis. Circ J. 2016;

7.   Buchberger AMS, Baumann A, Johnson F, Peters N, Piontek G, Storck K, et al. The role of oral anticoagulants in epistaxis. Eur Arch Oto-Rhino-Laryngology. 2018;

8.   Asencio LA, Huang JJ, Alpert JS. Combining antiplatelet and antithrombotic therapy (triple therapy): What are the risks and benefits? American Journal of Medicine. 2014.

9.   Anand S, Yusuf S, Xie C, Pogue J, Eikelboom J, Budaj A, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007;

10.   Shireman TI, Howard PA, Kresowik TF, Ellerbeck EF. Combined anticoagulant-antiplatelet use and major bleeding events in elderly atrial fibrillation patients. Stroke. 2004;

11. Côrte FC, Orfao T, Dias CC, Moura CP, Santos M. Risk factors for the occurrence of epistaxis: Prospective study. Auris Nasus Larynx. 2018;

12. Cesari M, Calvani R, Marzetti E. Frailty in Older Persons. Clinics in Geriatric Medicine. 2017.

13. Alonso Salinas GL, Sanmartín Fernández M, Pascual Izco M, Marco del Castillo Á, Rincón Díaz LM, Lozano Granero C, et al. Frailty predicts major bleeding within 30 days in elderly patients with Acute Coronary Syndrome. Int J Cardiol. 2016;

14. Public Health Scotland. Scottish Intensive Care Society Audit Group report on COVID-19. 2020.

15. MetOffice. When does spring start? Weather & Climate. 2019.

16. Team R. Core. R: A language and environment for statistical computing. Ind Commer Train. 2019;

17. Subirana I, Sanz H, Vila J. Building Bivariate tables: The compareGroups package for R. J Stat Softw. 2014;

18. Stevenson M, Nunes T, Heuer C, Marshall J, Sanchez J, Thorn- R, et al. epiR: Tools for the Analysis of Epidemiological Data. R Packag version 09-79. 2019;

19. Wickham H. Elegant Graphics for Data Analysis. In: Elegant Graphics for Data Analysis. 2016.

20. Tomkinson A, Roblin DG, Flanagan P, Quine SM, Backhouse S. Patterns of hospital attendance with epistaxis. Rhinology. 1997;35(3):129–31.

21. Smith J, Siddiq S, Dyer C, Rainsbury J, Kim D. Epistaxis in patients taking oral anticoagulant and antiplatelet medication: Prospective cohort study. J Laryngol Otol. 2011;

22. Hardman J, Smith ME, Ellis M, Williams R, Hopkins C. Epistaxis and mortality. J Laryngol Otol [Internet]. 2018 Dec 1 [cited 2020 Jul 3];132(12):1061–6. Available

from: /core/journals/journal-of-laryngology-and-otology/article/epistaxis-and-mortality/5C78CDF8E8A34BBF4674A96CFEA1F6B8/core-reader

23.   Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;

24.   Abrich V, Brozek A, Boyle TR, Chyou PH, Yale SH. Risk factors for recurrent spontaneous epistaxis. Mayo Clin Proc [Internet]. 2014;89(12):1636–43. Available from: http://dx.doi.org/10.1016/j.mayocp.2014.09.009

25.   Steinhubl SR, Bhatt DL, Brennan DM, Montalescot G, Hankey GJ, Eikelboom JW, et al. Aspirin to prevent cardiovascular disease: The association of aspirin dose and clopidogrel with thrombosis and bleeding. Ann Intern Med. 2009;

Tables

Summary descriptives table by groups of `Admission Status'. Table 1. Demographic Data

	[ALL] N=299	No N=177	Yes N=122	p.overall
Sex:				0.553
Female	147 (49.2%)	84 (47.5%)	63 (51.6%)	
Male	152 (50.8%)	93 (52.5%)	59 (48.4%)	
Age	75.0 [66.5;83.0]	75.0 [66.0;82.0]	76.0 [67.0;83.0]	0.179
CFS:				<0.001
≤3	154 (53.1%)	110 (64.7%)	44 (36.7%)	
≥4	136 (46.9%)	60 (35.3%)	76 (63.3%)	
Cardiovascular Disease:				0.075
Yes	202 (67.6%)	112 (63.3%)	90 (73.8%)	
No	97 (32.4%)	65 (36.7%)	32 (26.2%)	
Diabetes Mellitus:				0.329
Yes	50 (16.7%)	26 (14.7%)	24 (19.7%)	
No	249 (83.3%)	151 (85.3%)	98 (80.3%)	
Respiratory Condition:				0.030
Yes	44 (14.7%)	19 (10.7%)	25 (20.5%)	
No	255 (85.3%)	158 (89.3%)	97 (79.5%)	
Haematological Condition:				0.583
Yes	32 (10.7%)	17 (9.60%)	15 (12.3%)	
No	267 (89.3%)	160 (90.4%)	107 (87.7%)	
Haematological Malignancy:				1.000
Yes	9 (3.01%)	5 (2.82%)	4 (3.28%)	
No	290 (97.0%)	172 (97.2%)	118 (96.7%)	
Chronic Renal Disease:				0.176
Yes	32 (10.7%)	23 (13.0%)	9 (7.38%)	
No	267 (89.3%)	154 (87.0%)	113 (92.6%)	
Liver Disease:				0.536
Yes	10 (3.34%)	7 (3.95%)	3 (2.46%)	
No	289 (96.7%)	170 (96.0%)	119 (97.5%)	
Seasons:				0.011
Summer	58 (19.4%)	23 (18.9%)	35 (19.8%)	
Autumn	100 (33.4%)	49 (40.2%)	51 (28.8%)	
Spring	72 (24.1%)	18 (14.8%)	54 (30.5%)	
Winter	69 (23.1%)	32 (26.2%)	37 (20.9%)	

Summary descriptives table by groups of `Admission Status'. Table 2. Antiplatelet and Anticoagulant Profile

	[ALL] *N=299*	Yes *N=122*	No *N=177*	p.overall
Combined Treatment:				<0.001
Anticoagulant	85 (28.4%)	45 (36.9%)	40 (22.6%)	
Antiplatelet	86 (28.8%)	29 (23.8%)	57 (32.2%)	
Antiplatelet + Anticoagulant	6 (2.01%)	6 (4.92%)	0 (0.00%)	
Dual antiplatelet	17 (5.69%)	11 (9.02%)	6 (3.39%)	
Dual antiplatelet + Anticoagulant	4 (1.34%)	3 (2.46%)	1 (0.56%)	
None	101 (33.8%)	28 (23.0%)	73 (41.2%)	
Type of Antiplatelet:				0.094
Aspirin	52 (17.4%)	19 (15.6%)	33 (18.6%)	
Clopidogrel	40 (13.4%)	16 (13.1%)	24 (13.6%)	
Dual antiplatelet	21 (7.02%)	14 (11.5%)	7 (3.95%)	
None	186 (62.2%)	73 (59.8%)	113 (63.8%)	
Type of Anticoagulant:				<0.001
Heparin	3 (1.00%)	3 (2.46%)	0 (0.00%)	
NOAC	59 (19.7%)	36 (29.5%)	23 (13.0%)	
Warfarin	33 (11.0%)	15 (12.3%)	18 (10.2%)	
None	204 (68.2%)	68 (55.7%)	136 (76.8%)	

Summary descriptives table by groups of `Admission Status'. Table 3. Outcomes

	[ALL] N=299	No N=177	Yes N=122	p.overall
Admission Duration	0.00 [0.00;1.00]	0.00 [0.00;0.00]	2.00 [1.00;3.00]	<0.001
Nasal Packing Performed:				<0.001
Yes	113 (37.8%)	10 (5.65%)	103 (84.4%)	
No	186 (62.2%)	167 (94.4%)	19 (15.6%)	
Type of Nasal Packing:				0.165
Unilateral	77 (68.1%)	9 (90.0%)	68 (66.0%)	
Bilateral	36 (31.9%)	1 (10.0%)	35 (34.0%)	
Duration of Nasal Packing	2.00 [1.00;3.00]	0.00 [0.00;0.00]	2.00 [1.00;3.00]	<0.001
Surgical Intervention Requirement:				0.067
Yes	3 (1.00%)	0 (0.00%)	3 (2.46%)	
No	296 (99.0%)	177 (100%)	119 (97.5%)	
Blood Transfusion Required:				<0.001
Yes	16 (5.35%)	0 (0.00%)	16 (13.1%)	
No	283 (94.6%)	177 (100%)	106 (86.9%)	

Summary descriptives table by groups of `Admission Status'. Table 4. Adjusted Odd Ratio Modelling

	Adjusted OR (95% CI)	OR (95% CI)	RR (95% CI)	p.ratio	p.overall
Age Category:					0.582
≥76 vs ≤75	0.59 [0.32;1.08]	1.17 [0.74;1.86]	1.10 [0.84;1.44]	0.507	
Sex:					0.553
Male vs Female	0.66 [0.39;1.12]	0.85 [0.53;1.34]	0.91 [0.69;1.19]	0.480	
CFS:					<0.001
≥4 vs ≤3	3.09 [1.77;5.50]	3.15 [1.94;5.16]	1.96 [1.46;2.62]	<0.001	
Combined Treatment:					<0.001
Anticoagulant vs None	2.96 [1.45;6.15]	2.00 [1.20;1.92]	1.47 [1.12;1.92]	0.010	
Antiplatelet vs None	1.37 [0.68;2.78]	0.66 [0.39;1.11]	0.77 [0.55;1.08]	0.146	
Antiplatelet + Anticoagulant vs None **	-	10.65 [1.29;87.69]	2.21 [1.64;2.97]	0.009	
Dual antiplatelet vs None	4.01 [1.31;13.31]	2.82 [1.02;7.86]	1.64 [1.12;2.40]	0.070	
Dual antiplatelet + Anticoagulant vs None	7.12 [0.74;161.50]	4.44 [0.46;43.17]	1.86 [1.04;3.33]	0.308	
Seasons:					0.011
Autumn vs Summer	1.27 [0.62;2.64]	1.46 [0.76;2.84]	1.24 [0.85;1.80]	0.262	

	Adjusted OR (95% CI)	OR (95% CI)	RR (95% CI)	p.ratio	p.overall
Spring vs Summer	0.40 [0.17;0.91]	0.51 [0.24;1.08]	0.63 [0.38;1.05]	0.079	
Winter vs Summer	1.26 [0.58;2.80]	1.31 [0.65;2.69]	1.17 [0.78;1.76]	0.454	

**Haldane correction by a factor of 1 for Odd Ratio calculation