# Can Granulomatosis with polyangiitis be diagnosed earlier in primary care? – A case-control study.


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**Running Header:** Granulomatosis with polyangiitis prior to diagnosis

## Abstract

**Background:** People with granulomatosis with polyangiitis (GPA) commonly describe long delays before diagnosis.

**Aim:** To study the natural history of GPA prior to diagnosis using primary care data, and determine whether clinical features could be identified to help earlier diagnosis.

**Design:** Case-control study using the Clinical Practice Research Datalink.

**Methods:** We compared primary care activity and clinical features between cases and 10 matched controls.

**Results:** We identified 757 cases and matched 7,546 controls. Compared to controls, cases had more GP consultations and overall healthcare activity in the five years prior to their diagnosis, with a marked increase in the year before diagnosis, and particularly in the last 3 months. However, consultations were mostly for symptoms that were not specifically related to GPA. In the year prior to diagnosis, the most frequent and strongly predictive clinical features of GPA were Ear Nose and Throat (ENT) symptoms (34.5% of cases, odds ratio (OR) 10.5, 95% confidence intervals (CI) 8.6-12.7), and general (constitutional) symptoms (21.5% of cases, OR 9.0, 95% CI 7.1-11.3). In the year before diagnosis a larger number of cases attended secondary care (382, 50.5%) than had records of clinical features of GPA.

**Conclusions:** After discussing our findings, we conclude it would be difficult to identify cases of GPA earlier in primary care. Our results support a need for heightened awareness of this condition among secondary care clinicians, especially those assessing emergency admissions, and in the clinics which were most frequently attended by cases 3-12 months prior to diagnosis.

## Introduction

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's Granulomatosis is the commonest life-threatening vasculitis in adults(1). It most commonly presents from the 6th decade onwards with ENT, lung, and/or renal involvement. In 80% of cases it is associated with finding anti-neutrophil cytoplasmic antibodies in serum. 20% of people die within one year of diagnosis, 20% of survivors require renal replacement therapy, and the extent of organ involvement at diagnosis is an important predictor of long-term outcome(2,3).

A survey of members of the patient support group Vasculitis UK reported diagnostic delay of >1 year in 22.9% of patients, the frustration of repeated primary care consultations and a "pinball" experience of attending several secondary care specialties before the condition was finally recognised(4). Shortening this diagnostic odyssey may lead to earlier treatment with potentially better outcomes.

Routinely collected primary care data in the UK provides an opportunity to study healthcare activity prior to a diagnosis of GPA. We used the Clinical Practice Research Datalink (CPRD), to study the natural history of GPA prior to diagnosis using primary care data, and determine whether clinical features could be identified to help earlier diagnosis.

## Methods

### Source of data

We used data from the Clinical Practice Research Datalink (CPRD), which is one of the largest databases of longitudinal medical records from primary care. It contains anonymized healthcare records from more than 13 million people and represents 8% of the UK population. CPRD participants are representative of the UK general population in terms of age, sex and ethnicity(5). CPRD records contain diagnostic and clinical information coded using Read codes (6), as well as prescriptions, and details of specialist referrals . We followed the CPRD's recommendations for selecting research quality patient records and periods of quality data recording by including people contributing acceptable quality data in

up to standard practices. We used data from all 684 general practices contributing data to CPRD up to January 2015.

### Study participants and study design.

We included all incident cases of GPA diagnosed between 1 Jan 1990 and 31 Dec 2014, identified as previously described (7). Briefly, cases were included if they had a first diagnosis of GPA coded in the CPRD or linked Hospital Episode Statistics records; and at least one year of disease-free active follow up in the CPRD prior to their first code for GPA or vasculitis to exclude prevalent cases. Up to ten controls were randomly selected for each case, matched on GP practice, sex and within 5-years of age. All controls had to be alive and contributing data to the CPRD continuously for at least one year up to the diagnosis date of their matched case. The diagnosis date of cases, and the diagnosis date of the matched controls for each is the index date.

### Exposures

#### *Quantification of healthcare activity*

We counted the number of records of healthcare activity recorded for cases and controls in the 5 years prior to the index date. This included records of health promotion and administration (e.g. BP measurement, administration, and medication review), GP delivering healthcare (e.g. consultations, investigations and medication requests) and secondary care activity recorded in primary care (e.g. letters from secondary care, and records of attendance at hospital clinics). In addition we counted separately records of GP consultations, records of secondary care activity (hospital clinic appointments, A&E attendances and hospital admissions) and records of attendance at each hospital specialty clinic. If a patient had more than one consultation record in primary care or secondary care on the same day, we assumed this represented only one activity in order to reduce the chance of duplicate records(8). We excluded records on the index date, to exclude the appointment or hospital admission when the diagnosis was made. For secondary care activity, we conducted a sensitivity analysis excluding the last 3 months before the index date, to exclude secondary care activity directly linked with the diagnostic episode, because of reported delays of up to 3 months for diagnoses made in secondary care being recorded in CPRD (9,10).

### *Clinical Features*

We counted the number of times cases and controls consulted their GP with clinical features that we considered suggestive of GPA before the index date. We included seven groups as shown in table 1. General (constitutional) symptoms, cutaneous, eye, ear nose and throat (ENT), renal, and 'other' clinical features were selected from the American College of Rheumatology (ACR) classification criteria for GPA (11), and version 3 of the Birmingham vasculitis activity score (BVAS) (12). We additionally included a respiratory group of cough and shortness of breath, rather than the specific imaging results included in the ACR classification criteria or BVAS score, because these imaging results were not available in our dataset. We included one control event, road traffic accident, which we expected to be recorded with similar frequency between cases and controls.

### *Code lists*

Lists of Read codes for each clinical feature, and secondary care activity were compiled by searching the description fields of the Read code dictionary using a list of keywords and synonyms and excluding irrelevant codes, using a method described by Dave and Petersen(13). Where possible the resulting code lists were cross-referenced with published code lists available at an online clinical codes repository(14). Full lists of codes are available on request.

## Descriptive and statistical analysis of clinical features and healthcare activity

Firstly, we plotted frequency histograms of the total number of GP consultations, records of healthcare activity, and consultations for each clinical feature in 5 years before the index date for cases and 1 randomly selected control. Consultations increased markedly in the year before cases were diagnosed, therefore the following quantitative analysis reports the year before the index date.

We grouped the number of GP and secondary care consultations/admissions, and all records of healthcare activity into exposure categories, and compared these between cases and all controls using conditional logistic regression. We also compared attendance at hospital specialty clinics, A&E and hospital admissions by calculating a ratio of frequency of attendance in cases and controls. We compared cases and controls who had at least one record for each

clinical feature, and calculated odds ratios (ORs) using conditional logistic regression. Statistical analysis was performed using Stata version 14 (Statacorp, College Station, TX, USA).

### Ethics

Independent Scientific Advisory Committee (ISAC) for MHRA Database Research approval was obtained for this study (protocol 15_150R).

### Reporting guidelines

This study is reported following the RECORD guidelines(15), which are an extension of STROBE(16), designed specifically for reporting studies conducted using observational routinely collected healthcare data.

## Results

We identified 757 cases of GPA and matched 7,546 controls. The baseline characteristics of cases and controls were similar: median age (interquartile range) at the index date was 61 (50-70) years in cases and 61 (50-71) years in controls, and 44.7% of both cases and controls were female.

### Quantification of healthcare activity

Cases had a greater number of GP consultations and overall healthcare activity throughout the 5 years prior to diagnosis, with a marked increase in the 1 year prior to their index date (figure 1 & supplementary figure 1). In the year before the index date, twenty or more GP consultations were recorded in 157 (20.7%) of cases and 435 (5.8%) of controls; 30 or more records of healthcare activity were recorded in 314 (41.5%) of cases compared to 1,144 (15.2%) of controls (table 2). The greatest risks were conferred by ≥30 records of healthcare activity (OR 46.3, 95% CI 31.9-67.2), ≥20 GP consultations (OR 32.1, 95% CI 23.4-44.1), and attending ≥4 different specialty clinics (OR 22.6, 95% CI 13.4-38.0). Cases were 3 times more likely than controls to have records of hospital clinic attendances, with Rheumatology, ENT, Ophthalmology, Respiratory and Renal being the 5 most frequently-attended specialties by cases in the year before the index date. ENT, Ophthalmology, Rheumatology, Gastroenterology and Urology were the most frequently attended specialties when the last 3 months before the index date were excluded (table 3). 35% of cases had a record of ≥1 hospital clinic appointment. 382 (50.5%) of cases had ≥1 contact with secondary care (twice as likely as controls), and were 3 times more likely to attend A&E and 4 times more likely to have an inpatient admission (table 3). Excluding secondary care activity in the 3 months before diagnosis, the ratios were reduced but cases remained more likely than controls to have each type of contact with secondary care (table 3).

### Clinical features recorded before diagnosis

The number of consultations for the ENT, respiratory, and general (constitutional) groups of clinical features were elevated in cases compared to controls throughout the five years prior to their index date, with a notable increase in the final year (figure 1). Consultations for the other groups of clinical features also visibly increased in cases in the final year (supplementary data for

review). In the year before their index date, both the percentage of people affected by each clinical feature, and OR were elevated for cases compared to controls in all clinical features, however each clinical feature was recorded in a minority of cases (table 4). Of the individual clinical features, vasculitic rash conferred the highest risk of diagnosis of GPA (OR 30.3, 95% CI 3.1-288.4), but affected only 0.4% of cases. The groups of ENT and general (constitutional) symptoms were both the most frequent features occurring in 34.5% and 21.5% of cases respectively and conferred the second and third highest increased risk of future development of GPA, (OR 10.5, 95% CI 8.6-12.7 and OR 9.0, 95% CI 7.1-11.3 respectively). There was no increase in risk of road traffic accident (our control code) among cases compared to controls (OR 0.9, 95% CI 0.5-1.8).

## Discussion

### Summary of results and interpretation

This is the first study to provide evidence of increased GP and secondary care consultations in the pre-diagnostic period of GPA. Consultations among cases increased markedly in the year before diagnosis, and particularly in the final 3 months, but they were frequently for non-specific symptoms. The strongest predictor of a diagnosis of GPA was an increase in healthcare activity: ≥30 records of healthcare activity within a year, including records about health promotion and administration, GPs delivering healthcare, and secondary care activity recorded in primary care.

### Strengths and limitations

The main strengths of this study are that it was performed in the largest available database of primary care records, and included a large number of 757 people prior to their diagnosis with GPA. Another strength is that using a prospectively collected database minimises recall bias. The main limitations of this study are common to all observational studies in healthcare databases. The quality of outcome data is likely to be incomplete for coding of symptoms and secondary care activity. This would affect both cases and controls non-differentially, meaning our estimates are likely to be conservative. We attempted to quantify the impact of ascertainment bias in our study by use of a control code, and found no evidence for it, in that our control code of road traffic accident was marginally less common in cases than in controls. It would have been interesting to replicate the study in the other main sub-type of ANCA-associated vasculitis, microscopic polyangiitis. However, this is a more recently defined disease, and under the Read code system was not coded as a specific subtype of vasculitis until 2009, and at this time there were not enough cases to study.

### How our results fit in with the literature

There are few previous studies of the pre-diagnostic period in GPA, and our report is the first to our knowledge of pre-diagnostic consultations. However, length of delay between onset of symptoms and diagnosis has previously been reported. Delay between first symptoms of ANCA-associated vasculitis and diagnosis was found to be median 2.6 (interquartile range 1.2-5.2) months from

retrospective case note review in a multi-region audit including 130 patients newly diagnosed with ANCA-associated vasculitis in 2013-2014(17). This is similar to the diagnostic delay of median 2 months reported in Sweden 1997-2006 (18) and median 4 months in Finland 1996-2000(19). These studies used data collected from doctor's notes which may be limited by selective recording. The Vasculitis UK member's survey of 314 respondents with GPA, reported longer diagnostic delay. 35.7% reported delay between symptom onset and diagnosis of more than 6 months, and 22.9% reported delay of greater than 1 year (4). This study was retrospective, with the limitation of recall bias, however the results are more in keeping with our study's findings.

Our study shows evidence of increased health-seeking behaviour recorded in the primary care record for several years before diagnosis, supporting the odyssey of being unwell for a long time without a diagnosis. And our study shows that attendance at ≥4 different specialist clinics is strongly associated with a diagnosis of GPA, and that the 5 most commonly attended clinics were ENT, Ophthalmology, Rheumatology, Gastroenterology and Urology. This supports the description made by patient charities of delays before recognition of the diagnosis after contact with secondary care and the "pinball" experience of some people who attend multiple medical specialities before receiving a diagnosis.

### Clinical implications

Because electronic algorithms to alert GPs to consider rare disease diagnoses are an aspiration of the UK Strategy for Rare Diseases (20), we considered whether to develop a predictive tool to aid earlier diagnosis in GPA. Predictive models have been recommended by the National Institute for Health and Care Excellence (NICE) for use in UK primary care to predict risk of cardiovascular disease(21) and fragility fractures(22), and have been incorporated into one primary care software system to predict risk of cancer(23).

However, the crucial consideration in prediction of rare disease is that the prevalence of the disease in the population being tested affects the predictive value of a model or test. The rarer the disease the lower the positive predictive value (PPV) of a test (i.e. the probability that an individual actually has the disease if the prediction tool flags them as 'at risk'). The conditions in which risk prediction tools are currently used are much more common than GPA:

cardiovascular disease affects ~3% of the population(24), osteoporosis ~2%(22) and cancers ~0.9%(25), compared to and 0.0013% for GPA(7). If we compare simple predictive models (that flag people as 'high risk' or not), that all have a sensitivity of 100% and a specificity of 90%, they would have different PPVs in different diseases. For cardiovascular disease 31% of people flagged as 'at risk' would have cardiovascular disease, for osteoporosis 20% of people flagged as 'at risk' would have osteoporosis, for cancers 8.6% of people flagged as 'at risk' would have cancer, and for GPA only 1 of every 10,000 people flagged as 'at risk' would have GPA. This would create a large number of well people who would be flagged as 'at risk' in GPA.

In addition, due to the low prevalence of any predictive features in cases of GPA, the combinations needed to build a model with a specificity as high as 90% would reduce the sensitivity, and such a model would only identify a small proportion of cases. We therefore decided that it would not be worthwhile to develop a risk prediction score.

### Conclusion

Our study shows that people who are diagnosed with GPA had increased health seeking behaviour for several years before diagnosis, however it was difficult to identify them earlier in primary care data. Our results support a need for speedier diagnosis of this condition among secondary care clinicians, particularly amongst unselected acute medical admissions, and in the clinics which were the most frequently attended specialty clinics in the 3-12 months prior to diagnosis.

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## Conflict of interest statement

The authors declare no conflicts of interest.

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**Table 1: Clinical features included in the study**

| Clinical feature group | Specific clinical features included | Source |
|---|---|---|
| **General** | Fever / sweats (fevers, pyrexia, rigors or night sweats without specified cause) | *BVAS* |
| | Myalgia (aching muscles, muscle pain, muscular rheumatism without specified cause) | *BVAS* |
| | Arthritis (arthritis or arthralgia without specified cause e.g. septic, rheumatoid) | *BVAS* |
| | Weight loss (documented weight loss regardless of cause) | *BVAS* |
| **Cutaneous** | Rash (any rash or purpura without specified cause) | |
| | Specific rash (non-blanching rash or purpura only) | *BVAS* |
| **Eye** | Eye (scleritis, episcleritis, uveitis, conjunctivitis, blepharitis, keratitis, or significant proptosis without specified cause e.g. infection) | *BVAS* |
| **ENT** | Deafness (hearing difficulty, deafness, blocked ear, deteriorating hearing without specified cause) | *BVAS* |
| | Ear (Otitis media, mastoiditis, earache, ear discharge unless malignant or congenital) | *BVAS* |
| | Purulent or bloody nasal discharge or ulceration (nose bleed, epistaxis, nasal symptoms, nose symptoms, nasal discharge, nasal obstruction, nasal congestion) | *BVAS & ACR* |
| | Hoarseness | *BVAS* |
| | Subglottic stenosis | *BVAS* |
| | Sinusitis (blocked sinuses, sinus pain, sinus infection) | *BVAS* |
| **Chest** | Breathlessness | |
| | Cough | |
| **Renal** | Renal impairment (renal impairment, CKD, rise in creatinine without specified cause) | *BVAS* |
| | Haemoproteinuria (haematuria or proteinuria without specified cause) | *BVAS & ACR* |
| **'Other'** | Fatigue (fatigue, lethargy, malaise, asthenia, lassitude, tiredness, exhaustion, general weakness without specified cause, and excluding chronic fatigue) | *BVAS* |
| **Control code** | Road traffic accident | |

ACR: American College of Rheumatology 1990 classification criteria for granulomatosis with polyangiitis, BVAS: Birmingham vasculitis activity score (version 3).

**Table 2: Records of consultations and healthcare activity in the year before the index date**

| Type of consultation / Healthcare activity | Category | All cases and controls Cases, n (%) N=757 | Controls, n (%) N=7,546 | Odds ratio (95% CI) | P value |
|---|---|---|---|---|---|
| **No. of GP consultations** | **0-4** | 103 (13.6%) | 3,976 (52.7%) | 1 | |
| | **5-9** | 211 (27.9%) | 1,874 (24.8%) | 6.3 (4.8-8.1) | <0.001 |
| | **10-14** | 168 (22.2%) | 872 (11.6%) | 12.5 (9.4-16.6) | <0.001 |
| | **15-19** | 118 (16.6%) | 389 (5.2%) | 23.9 (17.3-33.0) | <0.001 |
| | **20+** | 157 (20.7%) | 435 (5.8%) | 32.1 (23.4-44.1) | <0.001 |
| **No. of records of healthcare activity** | **0-4** | 51 (6.7%) | 2,611 (34.6%) | 1 | |
| | **5-9** | 62 (8.2%) | 1,275 (16.9%) | 3.5 (2.4-5.2) | <0.001 |
| | **10-14** | 85 (11.2%) | 931 (12.3%) | 8.3 (5.6-12.3) | <0.001 |
| | **15-19** | 80 (10.6%) | 688 (9.1%) | 12.7 (8.5-18.9) | <0.001 |
| | **20-24** | 94 (12.4%) | 521 (6.9%) | 21.5 (14.4-32.1) | <0.001 |
| | **25-29** | 71 (9.4%) | 376 (5.0%) | 24.8 (16.2-38.0) | <0.001 |
| | **30+** | 314 (41.5%) | 1,144 (15.2%) | 46.3 (31.9-67.2) | <0.001 |
| **A&E attendances** | **0** | 622 (82.2%) | 7,152 (94.8%) | 1 | |
| | **1** | 76 (10.0%) | 289 (3.8%) | 3.8 (2.9-5.1) | <0.001 |
| | **≥2** | 59 (7.8%) | 105 (1.4%) | 8.7 (6.0-12.5) | <0.001 |
| **Hospital admissions** | **0** | 538 (71.1%) | 7,031 (93.2%) | 1 | |
| | **1** | 110 (14.5%) | 326 (4.3%) | 6.2 (4.8-8.0) | <0.001 |
| | **≥2** | 109 (14.4%) | 189 (2.5%) | 12.8 (9.4-17.4) | <0.001 |
| **Hospital clinic appointments** | **0** | 490 (64.7%) | 6,341 (84.1%) | 1 | |
| | **1** | 59 (7.8%) | 484 (6.4%) | 3.1 (2.2-4.2) | <0.001 |
| | **≥2** | 208 (27.5%) | 718 (9.5%) | 8.6 (6.6-11.2) | <0.001 |
| **Number of different hospital specialty clinics attended** | **0** | 490 (64.7%) | 6,346 (84.1%) | 1 | |
| | **1** | 116 (15.3%) | 784 (10.4%) | 3.9 (3.0-5.1) | <0.001 |
| | **2** | 76 (10.0%) | 261 (3.5%) | 8.9 (6.3-12.5) | <0.001 |
| | **3** | 43 (5.7%) | 105 (1.4%) | 13.5 (8.8-20.7) | <0.001 |
| | **≥4** | 32 (4.2%) | 50 (0.7%) | 22.6 (13.4-38.0) | <0.001 |

**Table 3: Secondary care activity in the year before the index date**

| Type of secondary care activity | Patients attending in the 1 year before diagnosis | | | Sensitivity analysis: 3-12 months before diagnosis | | |
|---|---|---|---|---|---|---|
| | Cases (n=757) | Controls (n=7,546) | Ratio | Cases (n=757) | Controls (n=7,546) | Ratio |
| **≥ 1 clinic appointment** | **267 (35.3%)** | **1,205 (16.0%)** | 2 | **179 (23.7%)** | **1,003 (13.3%)** | 2 |
| Rheumatology clinic | 73 (9.6%) | 62 (0.8%) | 12 | 24 (3.2%) | 50 (0.7%) | 5 |
| ENT clinic | 70 (9.2%) | 102 (1.4%) | 7 | 33 (4.4%) | 79 (1.0%) | 4 |
| Respiratory clinic | 51 (6.7%) | 66 (0.9%) | 8 | 12 (1.6%) | 39 (0.5%) | 3 |
| Ophthalmology clinic | 51 (6.7%) | 202 (2.7%) | 3 | 29 (3.8%) | 151 (2.0%) | 2 |
| Renal clinic | 38 (5.0%) | 20 (0.3%) | 19 | 13 (1.7%) | 15 (0.2%) | 9 |
| General medical clinic | 28 (3.8%) | 56 (0.7%) | 5 | 11 (1.5%) | 34 (0.5%) | 3 |
| Gastroenterology clinic | 24 (3.2%) | 93 (1.2%) | 3 | 17 (2.2%) | 65 (0.9%) | 3 |
| Cardiac clinic | 20 (2.6%) | 112 (1.5%) | 2 | 12 (1.6%) | 84 (1.1%) | 1 |
| Orthopaedic clinic | 18 (2.4%) | 224 (3.0%) | 1 | 13 (1.7%) | 172 (2.3%) | 1 |
| General surgery clinic | 17 (2.2%) | 118 (1.6%) | 1 | 11 (1.5%) | 80 (1.1%) | 1 |
| Urology clinic | 17 (2.2%) | 126 (1.7%) | 1 | 14 (1.8%) | 89 (1.2%) | 2 |
| Dermatology clinic | 14 (1.8%) | 103 (1.4%) | 1 | 10 (1.3%) | 78 (1.0%) | 1 |
| Haematology clinic | 14 (1.8%) | 31 (0.4%) | 5 | 6 (0.8%) | 21 (0.3%) | 3 |
| Neurology clinic | 12 (1.6%) | 45 (0.6%) | 3 | 8 (1.1%) | 31 (0.3%) | 3 |
| Gynaecology clinic | 11 (1.5%) | 57 (0.8%) | 2 | 5 (0.7%) | 30 (0.4%) | 2 |
| Oncology clinic | 8 (1.1%) | 67 (0.9%) | 1 | 4 (0.5%) | 45 (0.6%) | 1 |
| Other clinics attended by <1% of cases | 73 (9.6%) | 376 (5.0%) | 2 | 36 (4.8%) | 271 (3.6%) | 1 |
| **≥ 1 A&E attendance** | **135 (17.8%)** | **394 (5.2%)** | **3** | **71 (9.4%)** | **303 (4.0%)** | **2** |
| **≥ 1 Hospital admission** | **219 (28.9%)** | **515 (6.8%)** | **4** | **102 (13.5%)** | **387 (5.1%)** | **3** |
| **≥ 1 secondary care contact** | **382 (50.5%)** | **1,566 (20.8%)** | **2** | **243 (32.1%)** | **1,309 (17.4%)** | **2** |

**Table 4: Clinical features of vasculitis documented in the year before the index date**

| Clinical Feature | All cases and controls | | | |
|---|---|---|---|---|
| | Cases, n (%) N=757 | Controls, n (%) N=7,546 | Odds ratio (95% CI) | P value |
| **Respiratory** | **221 (29.2%)** | **827 (11.0%)** | **3.6 (3.0-4.3)** | **<0.0001** |
| **Cough** | 165 (21.8%) | 638 (8.5%) | 3.1 (2.6-3.8) | <0.0001 |
| **Breathlessness** | 81 (10.7%) | 279 (3.7) | 3.5 (2.6-4.5) | <0.0001 |
| **Renal** | **81 (10.7%)** | **136 (1.8%)** | **8.7 (6.3-12.0)** | **<0.0001** |
| **Renal impairment** | 65 (8.6%) | 93 (1.2%) | 10.8 (7.3-15.8) | <0.0001 |
| **Haem/proteinuria** | 22 (2.9%) | 45 (0.6%) | 5.2 (3.1-8.9) | <0.0001 |
| **ENT** | **261 (34.5%)** | **381 (5.1%)** | **10.5 (8.6-12.7)** | **<0.0001** |
| **Sinus symptoms** | 127 (16.8%) | 132 (1.8%) | 11.5 (8.8-14.9) | <0.0001 |
| **Nasal bleeding / crusting** | 93 (12.3%) | 63 (0.8%) | 17.0 (12.1-23.9) | <0.0001 |
| **Deafness** | 45 (5.9%) | 109 (1.4%) | 4.4 (3.0-6.2) | <0.0001 |
| **Ear symptoms** | 70 (9.3%) | 69 (0.9%) | 12.0 (8.4-17.1) | <0.0001 |
| **Hoarseness / SGS** | 11 (1.5%) | 28 (0.4%) | 4.0. (2.0-8.0) | 0.0006 |
| **Eye (Red eye)** | **73 (9.6%)** | **159 (2.1%)** | **5.1 (3.8-6.8)** | **<0.0001** |
| **General** | **163 (21.5%)** | **248 (3.3%)** | **9.0 (7.1-11.3)** | **<0.0001** |
| **Arthritis** | 100 (13.2%) | 147 (2.0%) | 8.4 (6.3-11.1) | <0.0001 |
| **Fever** | 22 (2.9%) | 29 (0.4%) | 8.6 (4.8-15.5) | <0.0001 |
| **Myalgia** | 33 (4.4%) | 49 (0.7%) | 7.4 (4.6-11.7) | <0.0001 |
| **Weight loss** | 22 (2.9%)) | 33 (0.4%) | 7.0 (4.0-12.2) | <0.0001 |
| **Other (Fatigue)** | **57 (7.5%)** | **147 (2.0%)** | **4.2 (3.1-5.8)** | **<0.0001** |
| **Cutaneous (Rash)** | **44 (5.8%)** | **231 (3.1%)** | **2.0 (1.4-2.8)** | **0.0002** |
| **Vasculitic rash** | 3 (0.4%) | 1 (0.01%) | 30.0 (3.1-288.4) | 0.0015 |
| **RTA (control)** | 10 (1.3%) | 109 (1.4%) | 0.9 (0.5-1.8) | 0.7856 |

SGS = subglottic stenosis RTA=road traffic accident