

## Research article

# Systematic identification and characterization of clinical and socio-economical correlates of granulomatous nasal and para-nasal sinuses: A large-scale study among patients of Odisha, India



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## ABSTRACT

Granulomatous formation in the nose and paranasal sinuses still presents an unmet clinical challenge as it affects both the physical health and personality of patients, and the lack of a systematic diagnostic and disease management approach has further complicated the scenario. Occurrence of granulomatous nasal disorder in the rural Indian population is associated with several factors such as lack of proper medical care, lack of hygienic and clean working and living conditions, and limited financial abilities to access the already overburdened primary healthcare system. This study aims to understand the correlation disease incidence, manifestation of signs and symptoms and associated socio-epidemiological parameters for 104,000 patients over a period of 23 months in Odisha. Primarily the study used socio-epidemiological surveys collected, annotated, and curated independently for granulomatous nasal disorder patients and compared this with their clinical records for signs & symptoms and performed several statistical analyses to better understand the disease incidence correlation with age, socio-economic and gender based parameters. Overall results suggest that males from low socio-economic background living in rural areas are the most vulnerable population and commonly affected with granulomatous nasal disorder (commonly Rhinosporidiosis sub-type) with common origin of the disease reported at the nasal septum and floor. We also highlight that change in the mass of nose followed by bleeds on touch, nasal discharge and hanging mass in throat are the most common manifestations presented by patients with granulomatous nasal disorders. Together, this research work identifies and characterise clinical and socio-economic factors that lead to and exacerbate the incidence of granulomatous nasal disorders.

## 1. Introduction

The nose is a prominent pyramidal structure with an apex at the tip and base attaching the forehead (Kern, 1975). The principal physiological functions of the nose are to facilitate respiration, entry of warm and humidified inspired air, smell perception and primary immune defense against pathogens, impurities, and dirt particulates (Bluestone et al., 2014; Kern, 1975). Paranasal sinuses are small cavities or hollow spaces in the nasal cavity that have been implicated in entry of warm and humidified inspired air, conferring a lighter feeling to the weight of the head, resonance of voice and as a cushion or crumple zone that protects

the vital nasal structures from nasal injuries or traumas (Yazici, 2019). Anatomically, the nose is located at the central position of the face in the front view and projects outwards of the face in the lateral view (Moon and Han, 2018). Furthermore, nose has been long considered as an aesthetic and important component of one's personality and contributes to beauty and attractive physical appearance (Kern, 1975; Moon and Han, 2018). Taken together, these factors contribute to the physiological and aesthetic important of nose and the associated paranasal sinuses and have been a matter of concern for patients suffering from different nasal abnormalities such as sinusitis, allergic rhinitis and nasal polyps (Bloching, 2007).

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Although many diseases affect the nose, most of them are granulomatous—a condition associated with granuloma formation (a collection of histiocytes made up of modified macrophages/epithelioid cells), often surrounded by T-lymphocytes, multinucleated giant cells & sometimes associated with central necrosis (Vail et al., 2019). Granuloma is formed, when the immune system fails to eliminate foreign bodies and attempts to wall off these substances (Wheeler and Woroniecki, 2001). Some of the primary reasons behind granuloma formation include (a) exposure to keratin and suture fragments, and (b) infectious conditions like bacterial and fungal infections (Muller et al., 2021). Specifically, syphilis, yaws (spirochetes), tuberculosis, leprosy (mycobacteria), rhinoscleroma (rhinoscleromatis), fungal granuloma (aspergillosis), inflammatory conditions like Wegener granulomatosis, sarcoidosis, Churg Strauss syndrome, and midline lethal granuloma are some of the well-known granulomatous disorders of nose & paranasal sinuses (Muller et al., 2021). Granulomatous nasal diseases present with nonspecific sinonasal symptoms like nasal discharge, stuffy nose, nasal obstruction, nasal deformity, epistaxis, crusting, ulceration, or mass. These conditions may progress rapidly to involve contiguous structure such as palate, orbit, and skull base (Cereceda-Monteoliva et al., 2021). Granulomatous lesions are associated pathological presentations like that of neoplastic disorder, malformation, and degenerative lesions of nose (Muller et al., 2021). Undoubtedly, a thorough observation of clinical parameters and careful investigation such as biopsy of the lesions is not only essential for diagnosis and disease-management, but also helps in the exclusion of malignant neoplasms (if any), thereby saving the life of patients (Das, 2020). Although the current treatment regime involves routine as well as thorough diagnostic work up including endoscopic, radiologic, histopathologic, and serologic testing—these approaches have several inherent limitations and challenges that have been reviewed elsewhere. Furthermore, routine use of vast number of antibiotics, corticosteroid, radioisotopes, and radiotherapy have resulted in emergence of new infective organisms, rise in cases of bacterial resistance, heterogeneity in disease presentation and absence of definite protocol, all of which have complicated the clinical management of these diseases. Altogether, these conditions present a significant clinical challenge for timely diagnosis and disease-management. Therefore, there is an urgent need to improve our diagnostic approaches and plan optimal medical & surgical treatment options for detecting and timely treatment of the granulomatous conditions of nasal and paranasal sinuses.

Therefore, this study aimed to improve our understanding and clinical management of granulomatous nasal and paranasal sinuses by (a) systematic identification and characterization of the typical clinical profile including histologic, endoscopic and radiological findings, (b) establishing clinical criteria that can distinguish it from other neoplastic conditions, (c) developing management strategy based on topical and systemic treatments in sinonasal surgery, and (d) understanding the socio-demographic correlation of patients with the occurrence and severity of the disease.

## 2. Methods

This study involved 104,000 patients, conducted in the Department of Otorhinolaryngology (ENT), VIMSAR Medical College, Burla, Sambalpur, Odisha, Eastern State in India, for a period of 23 months (between November 2017–October 2019). All ethics approvals were obtained through the institutional research and ethics committee VIMSAR (No.2017/I-F-CT-01-018) and informed consent was obtained from all patients/participants for the experiments. The study was conducted as a part of the postgraduate in medicine program (ENT) at VIMSAR.

### 2.1. Inclusion criteria

Patients between 5-60 years, both sexes (biological male and female) manifesting symptoms such as (a) nasal obstruction-difficulty in respiration through nasal cavity due to nasal lesion, (b) nasal discharge-nasal

mucopurulent secretion from nasal cavity, (c) epistaxis-discharge of blood from nasal cavity, (d) crusting-dryness and formation of a hard layer over mucosa of nasal cavity, (e) ulceration-disruption in the mucosal layer of nasal cavity and/or (f) mass-abnormal growth inside nasal cavity who were attending either the out-patient department (OPD) or admitted in the otolaryngology in-patient wards (IPD) were selected for this study. These patients were either suspected of or clinically diagnosed to be suffering from granulomatous nose and paranasal sinuses.

### 2.2. Exclusion criteria

Patients below 5 years and above 60 years and/or those unwilling for clinical examination and relevant investigations were excluded from this study. Suspected and/or proven cases of malignancy of nose and paranasal sinuses and cases of primary atrophic rhinitis were also excluded from the study.

### 2.3. Clinical history record-keeping and examination

Each patient was asked to fill a proforma providing their (a) demographic information like age, sex, address and, (b) clinical information including primary clinical complaints, duration of symptoms and previous history of any treatment(s) and, (c) other medical history like diabetes mellitus, hypertension, and tuberculosis (*see supplementary information*).

### 2.4. Statistical analyses

Wherever required, multivariable data were analysed using simple linear regression analysis (95% confidence interval) and multivariable linear regression analysis plotted as normalised quantile-quantile (Q-Q) plots (99% confidence interval) as mentioned in the figure legends using Graph Pad prism v9.0 for windows (GraphPad Software, San Diego, California USA).

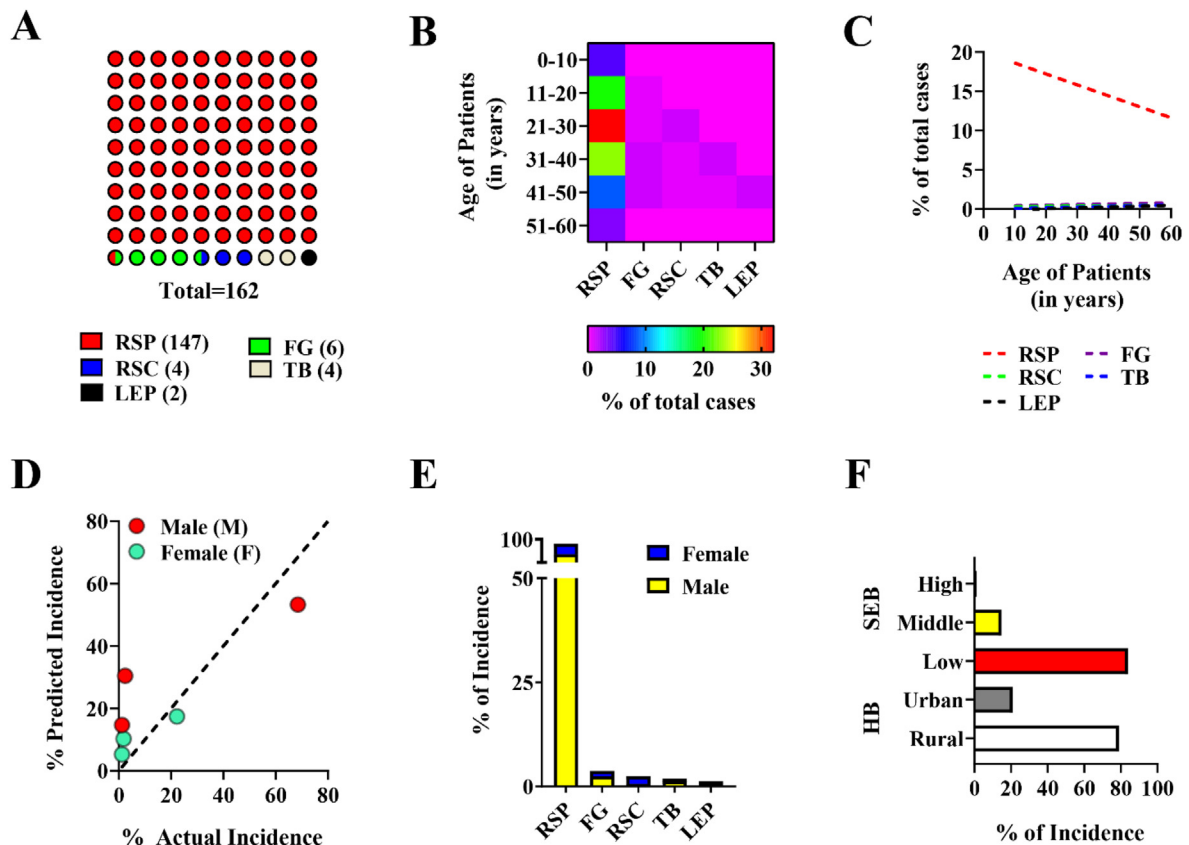
## 3. Result

This longitudinal study involved 104,000 patients who attended ENT OPD at VIMSAR Medical College, of whom 10,578 patients (10.17% of the total) presented various nasal symptoms like nasal discharge, obstruction, epistaxis, crusting, ulceration, or presence of mass suspected. Of these, only 162 patients (1.53%) presented with symptoms of the granulomatous conditions of nose (Table 1). Specifically, Rhinosporidiosis (RSP) had the highest incidence with almost 90.74% positive cases followed by cases of Fungal Granuloma (FG, 3.70%), Rhinoscleroma (RSC, 2.46%), Tuberculosis (TB, 1.85%) and Leprosy (LEP, 1.23%) (Table 1, Figure 1A).

To study the correlation of age of patients and the percent incidence of various forms of granulomatous disorders of nose, we analyzed the age of patients categorized into six age groups between 10-60 years (0-10, 11-20, 21-30, 31-40, 41-50, 51-60 years old) (Table 2). The results suggested that granulomatous disorders of nose were most prevalent (63.57% of total) among young to mid-aged adults (between 20-40 years) (Table 2, Figure 1B). Specifically, RSP cases (most prevalent

**Table 1.** Relative incidence of granulomatous nasal disorders.

| Granuloma Type | No. of Patients | Relative Incidence (%) |
|----------------|-----------------|------------------------|
| RSP            | 147             | 90.74                  |
| FG             | 6               | 3.70                   |
| RSC            | 4               | 2.46                   |
| TB             | 3               | 1.85                   |
| LEP            | 2               | 1.23                   |



**Figure 1.** Epidemiological analysis of granulomatous nasal disorder cases identified at VIMSAR medical College, Odisha. Different forms of granulomatose nasal disorders analysed include Rhinosporidiosis (RSP), Fungal Granuloma (FG), Rhinoscleroma (RSC), Tuberculosis (TB) and Leprosy (LEP). (A) Relative Incidence of different granulomatous nasal disorders. Incidence rate (expressed in % of total) for each type of granulomatous disorder is shown as percentage of total confirmed granulomatous cases (n = 162). Each dot in the grid represents 1% of the total no. of granulomatous nasal disorders. (B) Heat-map depicting correlation of age and disease incidence in granulomatous nasal disorder patients. Results showed variable incidence rates in patients of different age groups (expressed in years). All patients (n = 162), included in the study were between 10-60 years, divided into 6 different age groups each spanning a decade. Color-scheme depicting percentages of total cases (between 0-30%, 30 being the highest incidence percentage) is depicted on the bottom. (C) Simple linear regression analysis of percentage (%) of disease incidence (y-axis) vs age of patient in years (x-axis) for different forms of granulomatous nasal disorders. (D) Normalised Q-Q plot analysis of % predicted incidence vs % actual incidence of granulomatous nasal disorders for male and female patients. (E) Percent incidence of granulomatous nasal disorders identified in males and females (total n = 162). Percentages are expressed for different forms of granulomatous nasal disorders. (F) Percent incidence of granulomatous nasal disorders in patients (n = 162) belonging to different habitats (HB), i.e. rural and urban and different socio-economic background (SEB), i.e. low, middle and high earning families.

granulomatous disorder of nose) showed a peak incidence in the third and fourth decade of life, although its incidence can be observed in patients in all age groups under study (10–60 years) (Table 2, Figure 1B). Furthermore, incidence of FG peaked in patients in their fourth and fifth decade (30–50 years) and RSC peaked in patients in their third decade (20–30 years) of life (Table 2, Figure 1B). Both TB and LEP type of granulomas showed a preferential incidence towards the aged population, patients in their fourth-fifth or fifth decades of life, respectively (Table 2, Figure 1B). Furthermore, linear regression analysis of percent

incidence of various granulomatous nasal disorders vs age of patient (in years) showed a strong negative correlation between the two parameters with maximum likelihood of disease incidence among 10–30 years old patients (Figure 1C), in congruence with the heat-map analysis of the same (Figure 1B). Overall, this suggests a preferential onset of granulomatous nasal disorders in young and mid-aged patients, specifically the most prevalent RSP sub-types were observed in all age groups between 10-60 years with a significant likelihood of detection in patients between 21-40 years (Table 2, Figure 1A-C).

**Table 2.** Correlation of patient's age and incidence of granulomatous nasal disorder.

| Type of granulomatous lesion | <10 yr       |                  | 11–20 yr     |                  | 21–30 yr     |                  | 31–40 yr     |                  | 41–50 yr     |                  | 51–60 yr     |                  |
|------------------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|------------------|--------------|------------------|
|                              | No. of cases | % of total cases | No. of cases | % of total cases | No. of cases | % of total cases | No. of cases | % of total cases | No. of cases | % of total cases | No. of cases | % of total cases |
| RSP                          | 7            | 4.32             | 32           | 19.75            | 52           | 32.09            | 37           | 22.84            | 14           | 8.64             | 5            | 3.08             |
| FG                           | -            | -                | 1            | 0.62             | 1            | 0.62             | 2            | 1.23             | 2            | 1.23             | -            | -                |
| RSC                          | -            | -                | -            | -                | 2            | 1.23             | 1            | 0.62             | 1            | 0.62             | -            | -                |
| TB                           | -            | -                | -            | -                | -            | -                | 2            | 1.23             | 1            | 0.62             | -            | -                |
| LEP                          | -            | -                | -            | -                | -            | -                | -            | -                | 2            | 1.23             | -            | -                |
| <b>Total</b>                 | <b>7</b>     | <b>4.32</b>      | <b>28</b>    | <b>17.28</b>     | <b>61</b>    | <b>37.65</b>     | <b>42</b>    | <b>25.92</b>     | <b>17</b>    | <b>10.5</b>      | <b>5</b>     | <b>3.08</b>      |

**Note:** Dash indicates zero incidence of granulomatous disorder in a particular age-group.

Another aspect of our demographic study of granulomatous nasal disorder was to evaluate the prevalence of the disease in males (M) and females (F). Statistical analysis using normalised Q-Q plot showed that for all forms of granulomatous nasal disorders studied in this report, males had a moderate-severe disease incidence rates, in comparison with females suffering from the same granulomatous nasal disorders (Figure 1D). Specifically, our results suggest that overall, there is an increased incidence of the disease in males (73.46%) in comparison with females (26.54%). Specifically, RSP (M-68.52% vs F-22.22%) FG (M-2.46% vs F-1.23%), and TB (M-1.23% vs F-0.62%) had higher incidence in males in comparison with females (Table 3, Figure 1E). Interestingly, RSC showed higher incidence for females (1.85%) vs males (0.62%) and LEP showed similar incidence percentages in both males (0.62%) and females (0.62%) (Table 3, Figure 1E). It is important to note that due to very low cases of RSC, TB and LEP among the total cases of granulomatous diseases, the significance of these results may not be statistically significant and further study with large case numbers will be useful to substantiate these findings.

Furthermore, patients from rural areas (79.01%) showed higher prevalence of granulomatous nasal disorders as compared with those from urban areas (20.98%) (Table 4, Figure 1F). Previous studies have suggested rural population mostly identifies themselves as low-middle income families and therefore we evaluated demographic data to see if the habitat of patients had any correlation with their economic backgrounds. Interestingly, the data from socio-economic background of these patients suggested a plausible agreement to the patient's habitat preference, as persons from low-(83.95%) and middle (14.81%)-income background were mostly suffering from granulomatous nasal disorders (98.76% of total cases of the disease) (Table 4, Figure 1F).

In addition to analysis of epidemiological parameters associated with granulomatous nasal disorders, this study also tried to analyze different clinical parameters like manifestation of symptoms and signs in patients suspected or confirmed with different forms of granulomatous nasal disorder. Overall, irrespective of the type of granulomatous nasal disorders, patients often presented with symptoms like nasal discharge followed by mass in nose and epistaxis (Table 5, Figure 2A). Specifically, patients with RSP, commonly presented symptoms such as mass in nose (86.4%), nasal obstruction (78.2%), epistaxis (73.4%) and nasal discharge (62.6%). The less common symptoms in these patients included hanging mass in throat (21.8%), change in voice (16.3%), dysphagia (2%) (Table 5, Figure 2A). FG patients mostly presented mass in nose and nasal discharge in almost all cases, with 66.7% patients presenting nasal obstruction and 16.7% presenting a change in voice. Among all the different forms of granulomatous nasal disorder, FG showed highest symptomatic incidence of mass in nose and nasal discharge (Table 5, Figure 2A). Furthermore, RSC patients often (75% of cases) presented a mass in the nose and nasal obstruction followed by 50% of cases presenting symptoms like epistaxis, nasal discharge, and a change in voice (Table 5, Figure 2A). Furthermore, in the less frequently detected cases of granulomatous nasal disorders like TB and LEP, epistaxis (TB-66%, LEP-50%) and nasal discharge (TB-33%, LEP-50%) were commonly presented symptoms (Table 5, Figure 2A).

Apart from the subjective observations like symptoms, we also focused at analyzing measurable signs in these patients. Overall, patients

**Table 3.** Differential incidence of granulomatous nasal disorders in males and females.

| Type of lesion | Male (M)     |            | Female (F)   |            |
|----------------|--------------|------------|--------------|------------|
|                | No. of cases | % of total | No. of cases | % of total |
| RSP            | 111          | 68.52      | 36           | 22.22      |
| FG             | 4            | 2.46       | 2            | 1.23       |
| RSC            | 1            | 0.62       | 3            | 1.85       |
| TB             | 2            | 1.23       | 1            | 0.62       |
| LEP            | 1            | 0.62       | 1            | 0.62       |

**Table 4.** Habitat and economic background of granulomatous nose disorder patients.

| Habitat | % of incidence | Socio-economic status | % of incidence |
|---------|----------------|-----------------------|----------------|
| Rural   | 79.01          | Low                   | 83.95          |
| Urban   | 20.98          | Middle                | 14.81          |
| -       | -              | High                  | 1.23           |

with granulomatous nasal disorders frequently presented signs like mass in nose, nasal discharge, and few cases of bleeds on touch (Table 5, Figure 2B). Specifically, RSP patients often presented signs like mass in nose (100%), bleeds on touch (100%) followed by cases of nasal discharge (70.6%) and hanging mass in throat (25.9%) (Table 5, Figure 2B). FG patients frequently presented signs like mass in nose (100%) and/or nasal discharge (100%). Furthermore, RSC patients often presented signs like mass in nose (100%), nasal discharge (50%) and bleeds on touch (25%) (Table 5, Figure 2B). In contrary, less frequent cases like TB and LEP, are often associated with crusting (66.7%) and septal perforation (66.7%) in TB patients and nasal discharge (50%) and septal perforation (50%) in LEP patients (Table 5, Figure 2B).

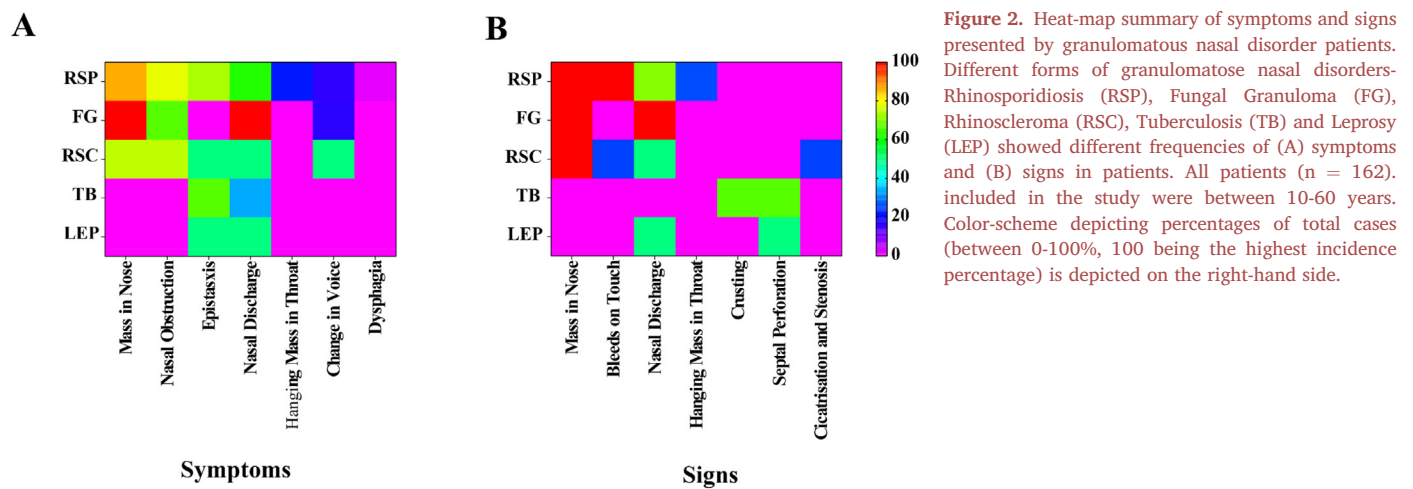
To further characterise RSP infections, we studied the disease incidence and socio-epidemiological parameters of RSP infections. Linear regression analysis of percent of disease incidence vs age of patients (in years) showed a strong negative correlation (i.e., younger (10–30 years old) males are more likely to be infected with RSP) whereas a weaker positive correlation (i.e., older (40–60 years old) females are more likely to be infected with RSP) (Table 6, Figure 3A). Furthermore, since RSP was the most frequently reported type of granulomatous nasal disorder, we aimed to characterize the clinical and epidemiological features of RSP in the patient samples used in this study. RSP is often detected in males (75.71%) in comparison with females (24.49%) (Table 6, Figure 3B). The peak incidence of RSP is seen in patients in their third or fourth decade of life (Table 6, Figure 3B). In-depth analysis of the occupational status of these RSP patients showed that most patients were farmers and their dependents with a rate of 50.34% & 23.13%, respectively, followed by housewives (17.01%) (Table 6, Figure 3C). Interestingly as shown previously that rural population mostly suffers from granulomatous nasal disorders, we questioned whether daily activities like source of bathing water was associated with increased incidence of the disease. Indeed, most of the RSP patients used pond for bathing (91.83%), followed by river water (4.76%), well (2.04%) and tap-water (1.36%) (Table 6, Figure 3D). Furthermore, septum was the most common site (46.26%) of origin of RSP, followed by floor (20.41%), inferior meatus (11.56%), nasopharynx (12.24%), inferior turbinate (6.12%), roof (1.36%), vestibule (1.36%), middle turbinate (0.68%) (Table 7, Figure 3E). The maximum rate of recurrence was associated with nasopharynx (9.52%), followed by inferior meatus (6.12%), floor (4.76%), septum (3.4%) and inferior turbinate (1.36%) (Table 7, Figure 3E). Lastly, RSP patients often presented signs and symptoms like mass in nose (86.19%), nasal obstruction (78.23%), epistaxis (73.47%), and nasal discharge (62.6%) (Table 7, Figure 3F). Some of the least common signs and symptoms associated with RSP were mass hanging in throat (21.77%), change in voice (16.33%) and dysphagia (2.04%) (Table 7, Figure 3F).

#### 4. Discussion

Granulomatous diseases of the nose and paranasal sinuses represent an uncommon but clinically important and potentially lethal group of disorders encountered in otolaryngologic practice (Muller et al., 2021; Vail et al., 2019). There is a pressing need for a knowledge-driven approach that can facilitate high index of suspicion with timely diagnosis, followed by medical and surgical management to avoid any destruction to the nose, paranasal sinuses, orbit and even the central nervous system. Some of the major bottlenecks in the field of granulomatous nasal disorders are (a) poor identification of clinical and

**Table 5.** Clinical manifestation of symptoms and signs in granulomatous nasal disorder patients.

|                 |     | Mass in Nose | Nasal Obstruction | Epistaxis       | Nasal Discharge        | Hanging Mass in Throat | Change in Voice    | Dysphagia                  |
|-----------------|-----|--------------|-------------------|-----------------|------------------------|------------------------|--------------------|----------------------------|
| <b>Symptoms</b> | RSP | 86.4         | 78.2              | 73.4            | 62.6                   | 21.8                   | 16.3               | 2.0                        |
|                 | FG  | 100.0        | 66.6              | 0.0             | 100.0                  | 0.0                    | 16.7               | 0.0                        |
|                 | RSC | 75.0         | 75.0              | 50.0            | 50.0                   | 0.0                    | 50.0               | 0.0                        |
|                 | TB  | 0.0          | 0.0               | 66.6            | 33.3                   | 0.0                    | 0.0                | 0.0                        |
|                 | LEP | 0.0          | 0.0               | 50.0            | 50.0                   | 0.0                    | 0.0                | 0.0                        |
|                 |     | Mass in Nose | Bleeds on Touch   | Nasal Discharge | Hanging Mass in Throat | Crusting               | Septal Perforation | Cicatrisation and Stenosis |
| <b>Signs</b>    | RSP | 100.0        | 100.0             | 70.6            | 25.9                   | 0.0                    | 0.0                | 0.0                        |
|                 | FG  | 100.0        | 0.0               | 100.0           | 0.0                    | 0.0                    | 0.0                | 0.0                        |
|                 | RSC | 100.0        | 25.0              | 50.0            | 0.0                    | 0.0                    | 0.0                | 25.0                       |
|                 | TB  | 0.0          | 0.0               | 0.0             | 0.0                    | 66.7                   | 66.7               | 0.0                        |
|                 | LEP | 0.0          | 0.0               | 50.0            | 0.0                    | 0.0                    | 50.0               | 0.0                        |



**Figure 2.** Heat-map summary of symptoms and signs presented by granulomatous nasal disorder patients. Different forms of granulomatose nasal disorders- Rhinosporidiosis (RSP), Fungal Granuloma (FG), Rhinoscleroma (RSC), Tuberculosis (TB) and Leprosy (LEP) showed different frequencies of (A) symptoms and (B) signs in patients. All patients (n = 162). included in the study were between 10-60 years. Color-scheme depicting percentages of total cases (between 0-100%, 100 being the highest incidence percentage) is depicted on the right-hand side.

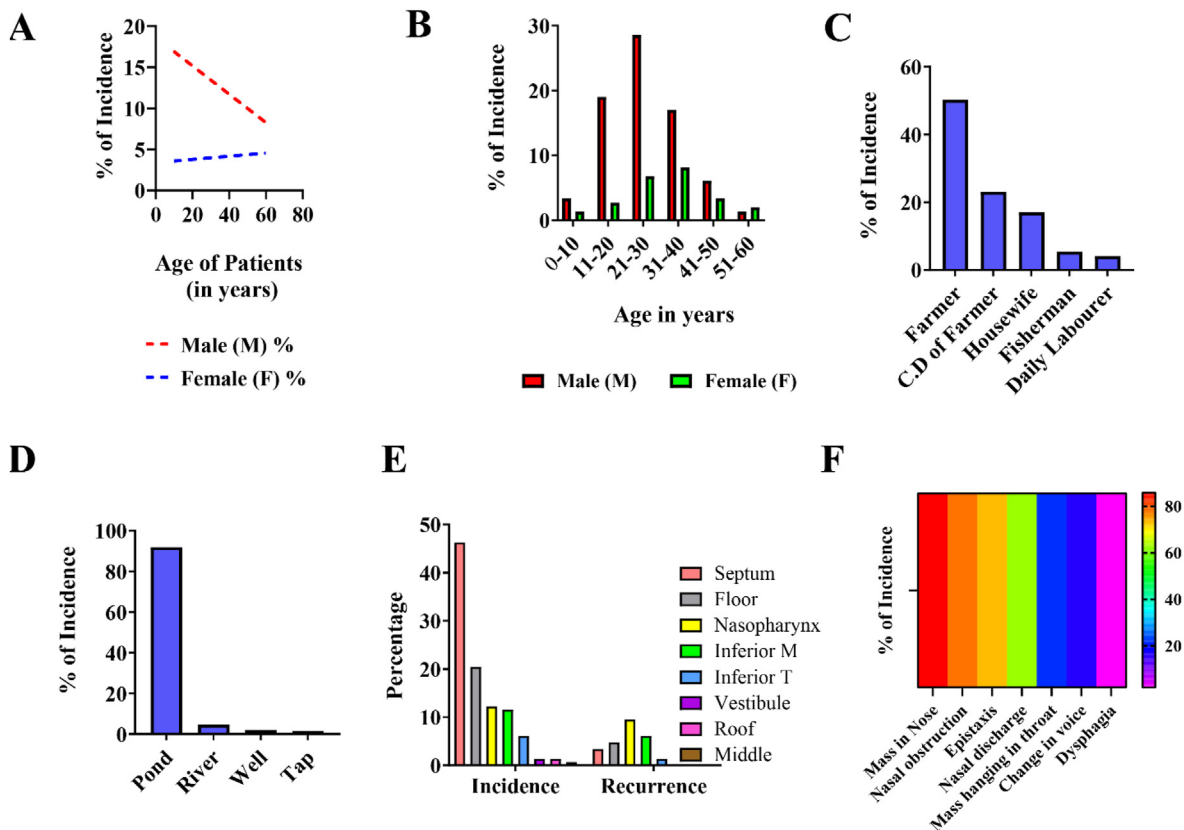
socio-economic factors that contribute to and are positively associated with the occurrence and severity of the disease and (b) the lack of systematic histopathological study for characterisation of the signs and symptoms associated with onset & progression of the disease.

This longitudinal study involving 104, 000 patients and conducted over a period of ~2 years is the largest systematic study for the identification of clinical and socio-economic factors contributing to and associated with the severity of nasal and paranasal sinuses. The results show that RSP is the most prevalent forms of granulomatous nasal and paranasal sinuses, accounting for ~91% of the total cases (Table 1, Figure 1A) and our findings agree with previous report from Das et al., who had

**Table 6.** Epidemiological analysis of RSP patients: Correlation of onset-age, gender, occupation, and bathing habit with incidence of disease.

| Age in yrs | Male (M) % | Female (F) % | Occupation                | % Of Incidence | Bathing Habit | % Of Incidence |
|------------|------------|--------------|---------------------------|----------------|---------------|----------------|
| <10        | 3.4        | 1.36         | Farmer                    | 50.34          | Pond          | 91.83          |
| 11–20      | 19.04      | 2.72         | Child Dependent of Farmer | 23.13          | River         | 4.76           |
| 21–30      | 28.57      | 6.8          | Housewife                 | 17.01          | Well          | 2.04           |
| 31–40      | 17.01      | 8.16         | Fisherman                 | 5.44           | Tap Water     | 1.36           |
| 41–50      | 6.12       | 3.4          | Daily Labourer            | 4.08           |               |                |
| 51–60      | 1.36       | 2.04         |                           |                |               |                |

reported an incidence rate of ~90–95% (Das, 2020). Furthermore, the results presented in this paper show that mid-aged people between 20-40s (~55.2%) are more affected with granulomatous nasal disorder than those younger or older to this age group (Table 2, Figure 1 B&C). Among people of this age group, males in comparison with their female counterparts are more likely (~3 folds higher) to suffer from granulomatous nasal conditions (Table 3, Figure 1D). Especially, in comparison with people living in urban areas, those living in rural areas frequently test positive for granulomatous nasal disorders (~3.8 folds higher) (Table 4, Figure 1E), and those with low socioeconomic background (83.95%) (Table 4, Figure 1F). Finally, our results implicate the role of lifestyle factors such as daily life-routine in the prevalence of RSP, with young-mid aged males commonly using communal bathing spaces in villages such as ponds (~55% in people pf 21–40 years with a 3.08:1 male: female incidence ratio and ~92% of people used ponds for bathing) mostly testing positive for RSP (Tables 1, 2, 3, and 4, Figure 1A &D). A detailed analysis of RSP cases suggest that most patients were farmers (50.34%) and their dependent (23.13%) (Table 6, Figure 3A-D), respectively, possibly because these groups of people are frequently exposed to cow dungs, domestic animals and pond bathing habits. RSP and other forms of granulomatous nasal disorders are associated with infectious diseases often resulting in local tissue inflammation and tissue destruction (Das, 2020). Majority of middle-aged Indian population (20–40 years old), especially those in eastern India live in rural and socio-economically underprivileged areas challenged by low literacy rates, lack of hygienic lifestyle and surroundings and limited accessibility to sanitary water and proper health care (Muhammad et al., 2022).



**Figure 3.** Correlation of epidemiological and clinical parameters associated with RSP infections. (A) Linear regression analysis of percentage (%) of incidence of granulomatous nasal disorder (y-axis) vs age of patient in years (x-axis) for male (M) and female (F) patients. (B) Percentage (%) incidence of RSP infections with gender and age of patient (in years), (C) occupation, and (D) source of bathing water expressed as percent incidence of total number of patients with granulomatous nasal disorders (n = 162). In panel C, C.D of farmer refers to dependent child of farmers. (E) Association of disease symptoms with percent incidence and recurrence among RSP patients (n = 162). Inferior M and T refer to inferior meatus and inferior turbinate, respectively. (F) Heat-map depicting correlation of signs and symptoms associated with incidence of RSP infections expressed as percent incidence of total RSP infections (n = 162). Color-scheme depicting percentages of total cases (between 0-87%, 87 being the highest incidence percentage) is depicted on the right-hand side.

Several studies have shown that these group of people frequently encounter unhygienic settings at workplace, shared public toilets and market areas (Das, 2020; Yadava et al., 1997). Furthermore, owing to the prevalent socio-cultural bias, working population in rural areas is largely dominated by males with very little representation of females, especially those that venture out of home or local village area in search of job or pleasure (Srivastava and Srivastava, 2010). Agarwal et al. and Thami et al. had also previously shown that people living in rural areas are frequently detected with granulomatous nasal disorders and the authors

had identified similar reasons to the ones highlighted above (Agrawal et al., 1959; Thami et al., 1995).

Our results also indicate that among the cases studied, the most common origin of RSP occurs at the nose (87.75% including nasal floor and septum), followed by nasopharynx (12.24%) and most common symptoms included mass in nose (86.4%), nasal obstruction (78.23%) epistaxis (73.47%) and nasal discharge (62.6%) (Table 7, Figure 3E & F). Lastly, although the overall recurrence rate for RSP is relatively low (only ~25% of the total cases), recurrence is often observed in nasopharynx, followed by inferior meatus as both these sites are hard to access for surgical interventions. Similar findings have been previously reported by at least 6 independent research studies conducted among Asian and Caucasian populations (Arseculeratne et al., 2010; Arseculeratne, 2005; Das et al., 2011; Mirakhur et al., 1983; Rao et al., 1976; Sudarshan et al., 2007). These findings can be explained by the fact that floor and nasal septum are known to facilitate the entry of water into nose and are often associated with nasal trauma caused by manual abrasion or scratches caused by fingers (Koh et al., 2016). Therefore, infections originating at the nose (floor and septum) can be identified as the primary source of the disease with primary clinical manifestation featuring changes in mass/-shape of the nose followed by nasal fluid-discharge and often associated with disease recurrence at the nasopharynx (Helliwell, 2010).

FG is the second most common granulomatous nasal disorder (3.7%). The socio-economic correlates of FG are similar to the RSP cases including frequent association of the disease with mid-aged males (~67%) observed in patients in their 30–40s (Tables 1, 2, and 3, Figure 1A & D). Furthermore, most FG cases showed striking similarity

**Table 7.** Common origin site(s) of RSP infection of nose and paranasal sinuses in patients.

| Site of Origin     | % Of Incidence | % Of Recurrence | Signs and Symptoms     | % Of Incidence |
|--------------------|----------------|-----------------|------------------------|----------------|
| Septum             | 46.26          | 3.4             | Mass in Unilateral     | 73.47          |
| Floor              | 20.41          | 4.76            | nose Bilateral         | 12.92          |
| Nasopharynx        | 12.24          | 9.52            | Nasal obstruction      | 78.23          |
| Inferior Meatus    | 11.56          | 6.12            | Epistaxis              | 73.47          |
| Inferior Turbinate | 6.12           | 1.36            | Nasal discharge        | 62.6           |
| Vestibule          | 1.36           | 0               | Mass hanging in throat | 21.77          |
| Roof               | 1.36           | 0               | Change in voice        | 16.33          |
| Middle Turbinate   | 0.68           | 0               | Dysphagia              | 2.04           |

with RSP cases as supported by similarities in the site of disease onset and primary clinical manifestations. Most of the FG cases presented chronic nasal discharge (100%), nasal mass (100%) and nasal obstruction in (66.67%) of cases (Table 5, Figure 2A). Both FG and RSP share several similarities including (a) common pathogenic origin of infection-a fungus (Guarner and Brandt, 2011), (b) overlapping prevalence of fungal infection in rural areas and (c) probable exposure of mid-aged males to these fungi (Gupta et al., 2020). In contrary, unlike RSP cases where the fungus infects immunocompromised hosts only, FG cases have been reported both in immune-competent & compromised hosts (Montone, 2007). Overall, it can be concluded that among the cases studied in this paper, the two most prevalent forms of granulomatous nasal disorders (RSP and FG) share several overlapping features of socio-economic correlations and disease onset/manifestation with few differences in the hosts they affect resulting in observed differences in the incidence rate of these nasal granulomas.

Following RSP and FG, RSC is the third-most prevalent granulomatous nasal disorder mostly seen in females (75%) in their 20–40s (80%) with low socio-economic status (Table 5, Figure 2B). This is a divergence from RSP and FG cases, where middle-aged males and not females (of any age group) were frequently reported positive for the disease. Contrary to RSP and FG, RSC is a bacterial infection and the low prevalence of the causative pathogen (*Klebsiella ozaenae*) in India (more prevalent in western countries like USA & Canada, and south Asian countries like Taiwan) (Botelho-Nevers et al., 2007) are likely to be the main factors for the relatively lesser incidence rates of RSC in rural populations. However, the exact reason of the frequent association of RSC with mid-aged females, is not completely known and future studies should aim to answer this question. Previous studies on RSC have suggested that this disease occurs in all sorts of climate, but more prevalent in tropical countries like West Indies, India, and China (Antony, 2014). However clinical manifestation RSC showed several similarities with RSP and FG cases as most patients present with nasal mass (100%) & nasal obstruction (100%) followed by epistaxis (50%), nasal discharge (50%) and change in voice (50%) (Table 5, Figure 2 A & B).

The occurrence of TB and LEP granulomatous nasal disorders was the least among patients in this study with incidence rate between ~1-2% only (Table 1, Figure 1A), mostly reported in females of low-socioeconomic background, similar to that of RSC cases. Such a low prevalence of TB and LEP granulomatous nasal disorder have been reported previously in different Asian and Caucasian populations and therefore we have not subsequently focussed on these forms of granulomas (Foxen, 1979; Hassan and Goh, 2012; Kim et al., 2021; Kulkarni, 2011). Lastly, frequent occurrence of RSC, TB and LEP cases in middle-aged females (in comparison with age-matched males) suggest that the responsible pathogen for these cases is likely to be widely present in home or local community spaces in rural areas and lack of social and female hygiene could also play an important role (Cabral et al., 2022; Guarner, 2012; Pagan and Ramakrishnan, 2014; Ploemacher et al., 2020). Future studies need to specifically address these differences in the socio-economic correlated of RSP/FG vs RSC/TB/LEP granulomatous nasal disorders.

## 5. Conclusion

Taken together, our findings suggest that males living in rural areas with low socio-economic background are the most vulnerable and largest group of people that are affected by granulomatous nasal disorders due to multiple lifestyle and sanitation factors including but not limited to malnutrition, poor general health, ill ventilated house, unhygienic and pond bathing habits. Furthermore, most forms of granulomatous nasal disorders originate at the nasal septum and floor followed by nasopharynx and inferior meatus. Since nasal floor and septum are more vulnerable to outside conditions, this possibly explains the strong correlation of poor and unhygienic lifestyle of people from low economic background with that of disease incidence and progression. Lastly, the

high proportion of males being affected by granulomatous nasal disorder can be representative of Indian social and cultural fabric in the rural areas, where males are more commonly involved in manual work or activities outside their homes and therefore exposed to harsh and unhygienic conditions.

## Declarations

### Author contribution statement

Arunima Kar: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Sandeep Satapathy: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Kamalini Bepari; Sujata Panda; Arundhati Kar: Conceived and designed the experiments; Wrote the paper.

Sambeet Satapathy: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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### Data availability statement

Data included in article/supp. material/referenced in article.

### Declaration of interest's statement

The authors declare no conflict of interest.

### Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2022.e10741>.

### Supplementary Information.

Proforma for recording patient's clinical history, disease-associated symptoms, and investigative disease markers.

History.

- **General Data**
  - Name and Address
  - Age and Sex
  - Religion
  - Occupation
  - OPD No
  - IPD No
- **Chief Complain**
- **History of Present Illness**
- **History of Past Illness**
- **Family History**
- **Personal History**
- **Socio-economic Status**
- **Bathing Habits**
- **Personal Hygiene**
- **Environment of House**
- **Food Habits**
- **Habits of Addiction**

Examination.

General Examination.

- Body Built
- Anaemia
- Jaundice
- Cyanosis
- Clubbing
- Blood Pressure
- Pulse Rate
- Respiratory Rate
- Temperature
- Lymphadenopathy

#### Systemic Examination.

- Cardiovascular System (C.V.S)
- Respiratory System (Resp)
- Gastrointestinal System (G.I)
- Central Nervous System (C.N.S)

#### Examination of Head and Neck.

- Face
  - Nasolabial Fold
  - Mouth
- Neck
  - Anterior Neck
  - Posterior Neck

#### Ear, Nose, and Throat Examination.

- Nose, PNS and Nasopharynx
  - External Examination of Nose: size, shape, any deformity, for any secretion or growth.
  - Functional Examination: patency of nasal airway by cold spatula test and sense of smell.
  - Vestibule: examined gently by elevating the tip of the nose for any deformity, growth, or infection.
  - Anterior Rhinoscopy: general appearance of the nasal mucous membrane like pale, infected, hypertrophied, and atrophic and presence of any secretions and its character-mucoid, mucopurulent, purulent, sanguineous, and presence of crust.
  - Posterior Rhinoscopy: examination of nasopharynx, posterior nasal aperture and posterior end of the septum, middle turbinate & inferior turbinate with the help of posterior nasal mirror.
  - Examination of Turbinates and Meatii
  - Examination of Septum: for any deviation or presence of any spur or growth
  - Description of lesion in the Nasal Cavity: site, number, size, shape, colour, consistency, bleeding on touch, fluctuation, tenderness, and reducibility.
- Ear
  - External appearance
  - Examination of external auditory canal, tympanic membrane, and middle ear.
- Throat
  - Oropharynx
  - Indirect laryngoscopy.
- Orbit
  - Examination of the orbit and eyeball was done for any abnormality like proptosis, epiphora and erosion of bony orbital wall.

#### Investigations.

- Blood
  - Hemoglobin (Hb) %

*Differential Count (DC)* – measures the level of different white blood cells in the blood expressed as Neutrophil (N) %, Erythrocyte (E) %, Leukocyte (L) %, Monocyte (M) %, Basophil (B)%.

*Total Leukocyte Count (TLC)*- measures the level of total leukocytes in the blood.

*Erythrocyte Sedimentation Rate (ESR)* expressed in mm/1st hour-indirect measurement of the level of inflammation present in the body.

*Venereal Disease Research Laboratory (VDRL) test* – examines for the presence of antibodies for syphilis and other non-venereal treponematoses (diseases caused by *Treponema* bacteria).

*Random Blood Sugar (RBS) test*-measures glucose level in the blood taken at a random time of the day.

*Fasting Blood Sugar (FBS) test*-measures glucose level in the blood taken after 8 hours of intermittent fasting.

*Postprandial Blood Sugar (PPBS) test*-measures glucose level in the blood after a meal (usually measured 2–3 hours after meal).

*Haemoglobin A1c (HbA1c) test*-measures the level of sugar-linked (glycated) form of haemoglobin.

#### • Urine

*Albumin*-measures the concentration of albumin in urine expressed in mg/g of urine.

*Sugar*-measures the concentration of glucose in urine expressed in mmol/L of urine.

*Microscopy*-to visualize the presence of different solid objects in urine like cells (blood and tumor cells), crystals, and pathogens (bacteria and parasites).

#### • Radiological Investigations

*X-ray Paranasal Sinuses (PNS) Water's View*-to visualize the air-filled spaces surrounding the nasal cavity and the soft-tissues surrounding it.

*X-ray Chest Posterior-Anterior (P-A) View*-to examine the anatomy of chest wall including collar bone, breastbone, shoulder blade and muscles surrounding it.

*CT scan of Paranasal Sinuses (PNS)*- diagnostic procedure based on cross-sectional imaging of PNS to examine sinusitis or post-nasal drip.

- Nasal Smear for Acid-Fast Bacillus (AFB) test-a stain-based test for the presence of Mycobacteria performed on patient's sputum or phlegm.
- Mantoux Test-a tuberculin skin test for measuring infection of Mycobacterium Tuberculosis (TB).
- Biopsy and Histopathology of Nasal Lesion-to distinguish between different granulomatous disease of nose.

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