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ORIGINAL ARTICLE

Hemoptysis in 93 Cases during COVID-19: A Suspected Link of Rodent Borne Hemorrhagic Infections.

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Abstract

Background: The global Coronavirus disease 2019 (COVID-19) pandemic has caused severe impact on healthcare systems. Hemoptysis was observed to be a rare symptom in COVID-19 infection. The purpose of this study is to evaluate data based on gender, age group, symptoms, associated comorbidities, seasons, geographical location to understand the distribution of hemoptysis. **Methods:** A total of 16,876 SARS-CoV-2 samples were tested from July 2020 to July 2021. Nasopharyngeal and oropharyngeal swabs were collected for RT-PCR test and data used for the study was obtained from Specimen Referral form (SRF). Data were analysed using SPSS software version 28.0.1.0. **Results:** Of 16,876 samples tested for SARS-CoV-2 infection, 93 (0.55%) exhibited hemoptysis; 56 of the 93 (60%) were tested negative. Majority of the hemoptysis cases were reported to be in males 59% (33 of 56) and in age group of 31 to 45 years i.e., 17 of 56 (30.4%) with a median age of 37 years. 21 out of 56 individuals (37.5 %) had other underlying health issues. Maximum individuals suffered hypertension (n=12; 21.4%). The highest case rates were in the month of September (n=15; 26.8%) thus stating that the maximum cases were seen in monsoon season (n=33; 59 %). **Conclusion:** Atypical manifestation such as hemoptysis was reported as a rare symptom of COVID-19 infection which may also occur because of other causes i.e., underlying comorbidities, seasonal variations and changing lifestyle. The highest case rates were in the monsoon season. Evidently, rodent borne hemorrhagic infections are at peak in these months due to increasing probability of rodent-human contact. Thus, a wise approach would be to rule out the other possible etiological agents of rodent borne infections to have efficient treatment and management of patients.

Keywords: COVID-19, SARS-CoV-2, hemoptysis, rodent borne hemorrhagic infections.

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Introduction

The novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first discovered on December 31, 2019, in Wuhan city, China. On January 30, 2020, the World Health Organization (WHO) announced a Public Health Emergency of International Concern (PHEIC), and a worldwide pandemic on March 11, 2020, due to worldwide spread of the disease [1]. As of 24 January 2022, there have been 39,543,328 confirmed cases with 489,848 deaths in India [2]. Although most common symptoms include fever, cough, breathlessness, body aches, chest pain, sore throat, runny nose, vomiting, diarrhea, evidence reveal that some cases may present atypical symptoms such as hemoptysis [3].

Hemoptysis is a rare symptom associated with SARS-CoV-2 infection [4].Bleeding in the lungs may initiate from bronchiolar pulmonary arteries and bronchial or alveolar capillaries. Bronchial arteries are the frequent site of bleeding being involved in 90% of the cases approximately [5]. Bronchitis (26%), lung cancer (23%), pneumonia (10%), and tuberculosis (8%) were the prevalent causes [6]. Table 1 presents different probable causes of hemoptysis [6-9]. Along with them are four families of Viral hemorrhagic fevers (VHFs)- Bunyaviridae, Arenaviridae, Filoviridae and Flaviviridae that may cause hemoptysis [10]. Hemoptysis may lead to clinical implications like respiratory failure due to airway blockage and thus is regarded as life-threatening [4]. Also the pathogens causing rodent-borne hemorrhagic fever are part of a significant category of zoonotic nature that leads to severe illnesses all over the globe. Our aim was to understand the distribution of hemoptysis in SARS-CoV-2 positive and negative cases based on gender, age group, symptoms, associated comorbidities, seasons, geographical location and majorly focusing on its possible causes.

Materials and Methods

Diagnostic Facility

The diagnosis was performed at the Central Research Facility of

Table 1: Causes of Hemoptysis

Infection based:	**Drugs based:**
Bronchitis, Chronic bronchitis	Glycoprotein inhibitors -II b and III a
Bronchiectasis, Broncholithiasis	"Crack" cocaine
Fungal Infection: Aspergillosis	Trimetallic anhydride
Bacterial Infection: Tuberculosis	Penicillamine
Viral Haemorrhagic Fever: Ebola	Nitrofurantoin
Rodent Borne: Leptospirosis	Isocyanates
Cardiovascular based:	**Autoimmune based:**
Aortic aneurysm, Bronchovascular fistula	Wegener's granulomatosis
Pulmonary embolism, Hypertension	Goodpasture's syndrome
Vasculitis	Systemic lupus erythematosus
Neoplasm based:	**Others:**
Lung cancer	Foreign body
Lung metastases	Lung biopsy
Bronchial adenoma	Thrombolysis, Thrombocytopenia
Bronchogenic carcinoma	Trauma/ Lung contusion
Endobronchial metastasis	Coagulopathy

our institute that has been accredited by National Accreditation Board for Testing and Calibration Laboratories based on ISO15189:2012 for COVID-19 by RT-PCR. Also, this laboratory has obtained 100% concordance result for its active participation in WHO-EQAS and ICMR-EQAS. Sustainable quality standards of the laboratory yielded approval by DAIDS, NIH, USA for multisite studies.

Procedure

Confirmed cases of COVID-19 were defined by real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay. As per guidelines of COVID-19 given by ICMR, the nasopharyngeal and oropharyngeal swabs were collected in viral transport media, received in a biohazard safe packaging from collection centre [11]. The testing protocol included RNA extraction by different kits (Bio flux and TRUPCR), followed by qualitative detection of genetic targets namely envelope, RNA dependent RNA Polymerase and RNase P using SARS-CoV-2 RT-qPCR Kit (TRUPCR) using Quant Studio 12K Flex RT-PCR machine by applied biosystems. The sigmoid shape of curves with Ct below 35 and above 35 was interpreted as positive and negative respectively.

Data Collection

The data used in this study was over a period of one year between July 2020 to July 2021. The demographic and clinical data of each collected sample was obtained from the specimen referral form (SRF) prescribed by ICMR. In this study the data included age, gender, location, the symptoms and comorbidities. All individuals were provided unique sample identification number (SID) to maintain their confidentiality.

Statistical Analysis

The study analysed and evaluated the data of 93 cases exhibiting hemoptysis using SPSS software (version 28.0.1.0). We expressed the continuous variable as median and calculated the percentages of patients in each category for categorical variables. We used QGIS software (version 3.22.1) to plot the number of cases of hemoptysis with the help of coordinates on a map [12] and Microsoft excel for graphs.

Results

Of the 16,876 samples tested for SARS-CoV-2, 93 (0.55%) individuals presented hemoptysis as a clinical manifestation. Overall, 37 (40%) positive and 56 (60%) were negative from 93 cases. Table 2 represents demographic and clinical characteristics. Of 93 cases, the study population was male dominant (n=56; 60.2%) and subservient in females (n=37; 39.8%). As per age group the distribution of hemoptysis was observed to be: below 1 year (n=2; 2.15%), 1-15 years (n=2; 2.15%), 16 to 30 years (n= 29; 31.2 %), 31 to 45 years (n=23; 24.7%), 46 to 60 years (n=20; 21.5%), above 60 years (n=17; 18.3%) with a median age of 37 years. Cough was present in 63.4 % (n=59) cases followed by breathlessness (n=43; 46.2%), fever (n=27; 29%), abdominal pain (n=10; 10.75%) and chest pain (n=9; 9.7%) that lead to hemoptysis. 34 of 93 individuals (36.5 %) had at least one coexisting health issues. Maximum individuals suffered from hypertension (n=16; 17.2 %) followed by diabetes (n =10; 10.75 %), chronic lung disease (n=5; 5.4%), chronic renal disease (n=3; 3.2%), chronic liver disease and malignancy (n=2; 2.15 % each). (Note: An individual may present one or more symptoms and comorbidities at a time). Table 3 shows the month and season wise distribution of hemoptysis. The highest and lowest cases were observed in the month of September (n=22; 23.6%) and May (n=1, 1.07%) respectively. Rise in number of cases was observed in monsoon season (n=51; 54.8%) followed by summer (n=25; 26.8%) and winter (n=17; 18.3%). The geographical distribution of individuals presenting hemoptysis is shown in (figure 1). Two clusters were observed in the Pimpri (n=32) and Bhosari (n=12) whereas rest were scattered (n=49).

Discussion

In our study 0.55% (93 of 16876) individuals exhibited hemoptysis as a clinical manifestation. Large studies of COVID-19 conducted in China and Paris have reported very low rates of hemoptysis ranging from 0.9–5% [13-15].

The common symptoms accompanying hemoptysis include fever, breathlessness, chest pain and cough. In our study, 9.7% (n=9) cases of chest pain were observed. Extreme chest pain in cases of hemoptysis occurred due to spread of tumor mass to the periphery of right lung leading to infiltration of the right chest wall [16].

Table 2: Clinical Characteristics of haemoptysis presenting cases in SARS-CoV-2 tested individuals. An individual may exhibit one or more symptoms and coexisting illness at a time Values are expressed as numbers (%) unless stated otherwise.

	Total (n=93)	Positive (n=37)	Negative (n=56)
		Gender	
Male	56 (60.2)	23 (62.2)	33 (59)
Female	37 (39.8)	14 (37.8)	23 (41)
Median age (years)	37	38	37
		Age	
< 1	2 (2.15)	0	2 (3.6)
1 to 15 y	2 (2.15)	0	2 (3.6)
16 to 30 y	29 (31.2)	13 (35.1)	16 (28.6)
31 to 45 y	23 (24.7)	6 (16.2)	17 (30.4)
40 to 60 y	20 (21.5)	8 (21.6)	12 (21.4)
> 60	17 (18.3)	10 (27)	7 (12.5)
		Symptoms Associated with Haemoptysis	
Cough	59 (63.4)	30 (81)	29 (51.79)
Breathlessness	43 (46.2)	18 (48.7)	25 (44.64)
Fever	27 (29)	13 (35.1)	14(25)
Chest Pain	9 (9.7)	2 (5.4)	7 (12.5)
Abdominal Pain	10 (10.75)	4 (10.8)	6 (10.71)
		Co-existing Illness	
Hypertension	16 (17.2)	4 (10.8)	12 (21.4)
Diabetes	10 (10.75)	3 (8.1)	7 (12.5)
Chronic renal disease	3 (3.2)	0	3 (5.4)
Chronic lung disease	5 (5.4)	3 (8.1)	2 (3.6)
Chronic liver disease	2 (2.15)	0	2 (3.6)
Malignancy	2 (2.15)	0	2 (3.6)

Table 3 : Month and season -wise distribution of haemoptysis presenting cases in SARS-CoV-2 tested individuals. Values are expressed as numbers (%) unless stated otherwise.

Year & Months	Total (n=93)	Positive (n=37)	Negative (n=56)
		2020	
July	13 (13.9)	7 (18.9)	6 (10.7)
August	7 (7.5)	3 (8.1)	4 (7.1)
September	22 (23.6)	7 (18.9)	15 (26.8)
October	9 (9.7)	1 (2.7)	8 (14.3)
November	5 (5.5)	0	5 (8.9)
December	2 (2.15)	1 (2.7)	1 (1.8)
		2021	
January	4 (4.3)	1 (2.7)	3 (5.4)
February	6 (6.45)	3 (8.1)	3 (5.4)
March	13 (13.9)	4 (10.8)	9 (16.1)
April	11 (11.8)	9 (24.3)	2 (3.6)
May	1 (1.07)	1 (2.7)	0
		Seasons	
Monsoon	51 (54.8)	18 (48.6)	33 (58.9)
Winter	17 (18.3)	5 (13.5)	12 (21.4)
Summer	25 (26.8)	14 (37.8)	11 (19.6)

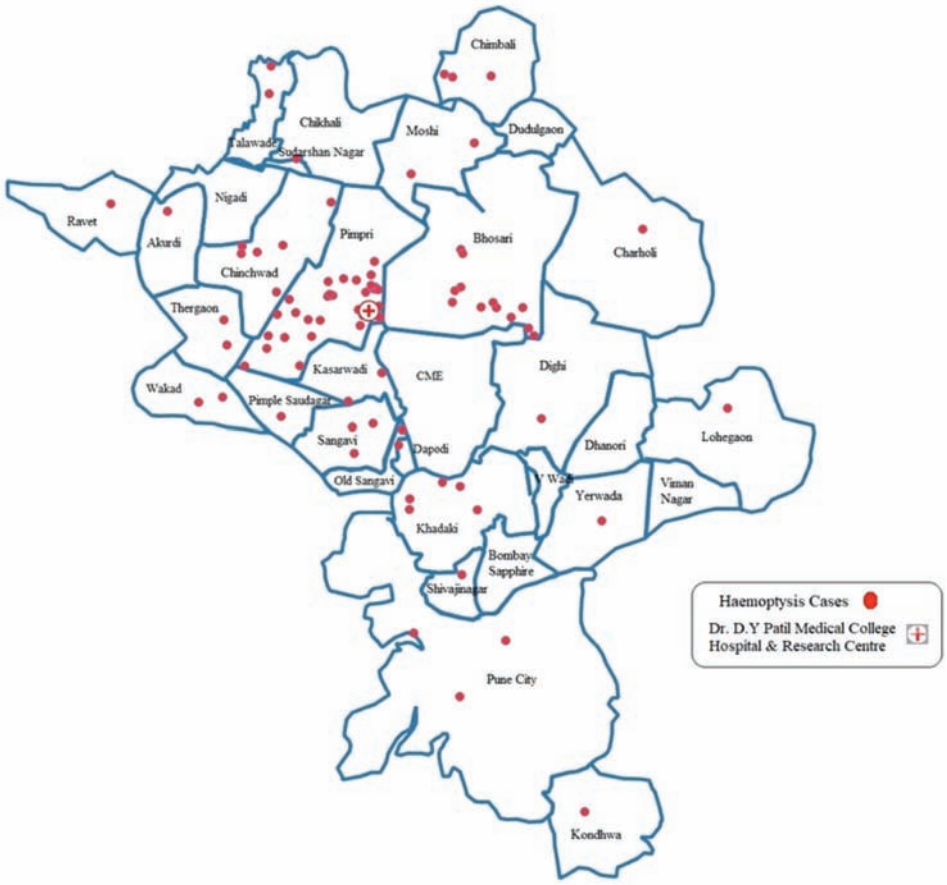

Figure 1: The geographical distribution of haemoptysis cases

Comorbidities play an important role in clinical presentation [17]. A total of 34 individuals (36.5%) had at least one coexisting health issues. Hemoptysis was present in 10.75% of our study's diabetic patients. Hyperglycemia can contribute to complex lung infections like tuberculosis, fungal and mycobacterial infections, which can cause massive hemoptysis [18]. In this study 5.4% of the cases with hemoptysis showed chronic lung disease. Earlier study reports cases of chronic lung disease with active bleeding range from 3.6% to 10.8% [19]. In Srinagarind Hospital, Thailand, 10.9% of the patients with hemoptysis showed malignancy [20] whereas it was (n=2) 2.15% in this study.

In individuals tested for SARS-CoV-2, majority of the hemoptysis cases were male dominant with occurrence of 60.2 % (n=56) in the present study. Previous studies indicates majority of adults experiencing hemoptysis are typically around 62 years old, with a male: female ratio of 2:1. Children were rarely affected when compared to adults in most cases [21]. Similar result was obtained, as hemoptysis was most prevalent in the age group of 16 to 30 years (n=29; 31.2%) followed by 31 to 45 years (n=23; 24.7%) and rarely among the children (n=2; 2.15%). As the testing laboratory is situated in Pimpri, maximum samples received for SARS-CoV-2 testing were from places nearby, thus the two clusters were observed in Pimpri and Bhosari area.

Hemoptysis is highly influenced by weather factors. According to a 5-year research using data from the French national hospital database, incidence of hemoptysis peaked in March (9.5%) and decreased in August (6.7%) [21]. Findings of a study in Pakistan showed that hemoptysis was observed maximum throughout spring (March-May) [22]. Conversely, our results indicate peak in September (n=22; 23.6%) and dropped during May (n=1, 1.07%). This was due to the variability in the number of suspected samples tested for SARS-CoV-2 infection.

The maximum occurrence of hemoptysis was observed in monsoon (n=51; 54.8%) in our study. Temperature conditions and rain are important determining factors of rodent population abundance and distribution [23]. Evidently, rodent borne diseases are at peak during monsoon months i.e., August-October [24] and risk of infection is frequent in areas with rainfall, flooding, and stagnant water pools [25]. Other studies have linked flooding in Orissa with outbreaks of leptospirosis [26]. Also there have been incidences of leptospirosis in Mumbai, where patients presented fever, hemoptysis, and breathlessness [27]. Similarly, hantavirus outbreaks are preceded by heavy rainfall and temperatures, which increases rodent numbers and viral transmission [28]. Excess rainfall may compel rodent vectors to seek refuge in human dwellings thus, leading the increased exposure of rodent-human contact [29].

COVID-19 pandemic has devastating effects on public health globally, causing a decrease in epidemiological control for a number of infectious diseases, including zoonotic diseases [30]. Infectious hemorrhagic fevers have become a severe challenge owing to increased international travelling to areas where diseases may spread easily. A crucial section of these hemorrhagic fevers emerges from

rodents [24]. Initially, the clinical profile of the hemorrhagic fevers is non-specific, thus testing with syndromic panel to overcome misdiagnosis and possible co-infections [24,31].

Our current study does have a few limitations. Firstly, as ICMR frequently makes amendments in its Specimen Referral Form (SRF), hemoptysis as a clinical symptom was only included until May 2021 whereas our survey comprises data from July 2020 to July 2021. Secondly, any diagnostic information specific to occurrence of hemoptysis and its outcome was unavailable.

Conclusion

Patients with COVID-19 may not always present the frequent symptoms but atypical presentations such as hemoptysis. It may be a result of COVID-19 infection in those who have tested positive for the virus, whereas in negative individuals it may occur as a consequence of underlying health comorbidities or other etiological agents. It would be a wise approach to rule out etiologies of infections like hantaviruses and arenaviruses responsible for hemorrhagic manifestations to have timely case management efficiently.

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