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Original Article

Internal Medicine Section

Clinical Profile of Post-COVID-19 Patients with Persistent Chest Pain: A Cross-sectional Study

SIBARAM PANDA[1], SUNIL KUMAR SHARMA[2], JAGANNATH HATI[3], BRAJA BIHARI PANDA[4]

ABSTRACT

Introduction: Chest pain in post-COVID-19 patients can be due to serious alarming post-COVID-19 sequelae, such as Coronary Artery Disease (CAD), pulmonary embolism, myocarditis, etc. Approximately one-fifth of patients attending clinical Outpatient Department (OPD) following COVID-19 recovery present with persistent chest pain. There is limited knowledge about the clinical profile of patients experiencing persistent post-COVID-19 chest pain.

Aim: To describe the clinical profile of such patients to fill the knowledge gap and acquire new insights into patients with post-COVID-19 persistent chest pain.

Materials and Methods: A cross-sectional study was conducted, enrolling a total of 259 patients with persistent chest pain (i.e., chest pain lasting more than 24 weeks after COVID-19 diagnosis). After detailed history-taking and clinical and laboratory examinations, observed data were collected, compiled, evaluated, and analysed to achieve the study objectives.

Results: Out of 259 patients, 133 (51.4%) had cardiac {85 (32.8%)} or pulmonary {48 (18.5%)} abnormalities. Among patients with cardiac abnormalities, CAD, arrhythmia, myocarditis/cardiomyopathy, pericarditis, and PAH were detected in 38 (14.6%), 18 (6.9%), 7 (2.7%), 11 (4.2%), and 11 (4.2%), respectively. Meanwhile, among patients with pulmonary abnormalities, 36 (13.9%) patients had organic residual lesions in the lung parenchyma, 7 (2.7%) had pleuritis, and 28 (10.8%) had pulmonary function abnormalities. The remaining 126 (48.6%) patients experienced chest pain due to non cardiopulmonary aetiologies like gastrointestinal {45 (17.3%)}, musculoskeletal {38 (14.6%)}, psychomotor {35 (13.5%)}, autonomic {8 (3.3%)}, etc.

Conclusion: This study found that chest pain in post-COVID-19 patients arises due to multisystemic aetiologies such as cardiac, pulmonary, visceral, autonomic, psychomotor, musculoskeletal, etc. A wide spectrum of serious cardiac abnormalities (such as CAD, arrhythmia, myocarditis, pericarditis, PAH, etc.) contributes to about 1/3rd of cases of persistent chest pain in post-COVID-19 patients.

Keywords: Chestpain, Multisystemic, Sequele

INTRODUCTION

Approximately, 643 million people have become victims, and 6.6 million have died as a result of the lethal COVID-19. However, it has been noted that a significant proportion of patients who survived COVID-19 are presenting with post-COVID-19 syndrome with persistent clinical symptoms, even months after a mild COVID-19 infection [1]. Therefore, the WHO has raised the utmost concern to prioritise post-COVID-19 care facilities [2]. Approximately, one-fifth of patients attending clinical OPDs following COVID-19 recovery present with persistent chest pain [3]. Chest pain is an alarming symptom that may indicate serious cardiopulmonary diseases like CAD, myocarditis, chronic pulmonary embolism, etc., [4-6], requiring immediate attention. However, to date, no study has been conducted exclusively for patients with post-COVID-19 chest pain. Most of the related existing literature was limited to either case reports or case series [7-12] or studies including post-COVID-19 cardiopulmonary symptoms like dyspnoea, fatigue, etc., [13-16]. Therefore, there is limited knowledge about the clinical profile of patients experiencing persistent post-COVID-19 chest pain. The present study was conducted to describe the clinical profile of patients with post-COVID-19 chest pain.

MATERIALS AND METHODS

A cross-sectional study was conducted at the Department of Cardiology, VIMSAR, Sambalpur, Odisha, India, between October 2020 and October 2022 after ethical approval from the Institutional Ethical Committee (IEC) (IEC no.150/2022/I.F.O-18).

Inclusion criteria: A total of 278 OPD patients attending the cardiology OPD with chief complaints of persistent post-COVID-19 chest pain (i.e., symptoms lasting for more than 24 weeks after COVID-19 infection) [17] were included in the study.

Exclusion criteria: 19 patients with a prior documented history of chronic cardiopulmonary disease, chest pain prior to COVID-19 infection, and patients with a history of clinical COVID-19 but without microbiologically confirmed reports were excluded from the study.

Sample size: A convenient purposive (non probability) sampling method was utilised to identify further participants from our initial sample. Taking into account the prevalence of chest pain in post-COVID patients from the previous study as 21.3% [3], the sample size was calculated as 257 using the formula $N=(Z)^2 P (100-P)/L^2$ {where Z=1.96 at the 95% confidence interval, P (prevalence)=21.3, L (precision error)=5}.

A total of 259 patients complaining of persistent chest pain were finally enrolled as study participants. Different characteristics of chest pain and associated symptoms were derived after detailed clinical history from patients. Patients underwent detailed clinical generalised and systemic examinations. Electrocardiography (ECG) and chest X-rays were done as needed. All patients with abnormal cardiac signs and an ECG or chest X-ray suggestive of underlying cardiac disease underwent echocardiography. Patients were investigated for LV dysfunction, wall motion abnormalities, Pulmonary Artery Hypertension (PAH), RV dysfunction, pericardial effusion, etc. Patients with typical angina and atypical angina with a high-risk heart score [18] underwent a treadmill test. Patients with recent-onset crescendo-type chest pain (suggestive of ACS), LV dysfunction, and wall motion abnormalities were excluded from the treadmill test and recommended for coronary angiography. Patients with clinical signs and symptoms suggestive of a disease other than cardiac disease were consulted in other disciplines, such as pulmonary medicine, psychiatry, orthopaedics, etc., as per the associated symptoms.

Patients with abnormal clinical and X-ray chest signs suggesting underlying pulmonary disease underwent High Resolution Computed Tomography (HRCT) thorax and spirometry as per their indications. Different patterns of post-COVID-19 lung parenchymal abnormalities, like ground glass, reticular, mosaic patterns, or parenchymal bands, etc., detected during HRCT thorax, were duly noted. Patients with abnormal spirometry findings (like restrictive or obstructive patterns, etc.) were duly noted. Patients with clinical, radiologic, and echocardiographic signs of PAH underwent CT pulmonary angiography for further evaluation.

Written consent was obtained before enrolling patients in the study. Confidentiality and anonymity were maintained throughout the study. Observed data were collected, compiled, evaluated, and analysed to achieve the study objectives.

STATISTICAL ANALYSIS

Categorical variables were reported as frequencies and percentages using Epi-info software. The mean and standard deviation were used to express continuous variables. Clinical and demographic variables were reported using the mean±SD or the median when appropriate.

RESULTS

Among 259 patients, 123 (47.5%) were males and 136 (52.5%) were females. The patients' average age was 48.4±17.2 years. Co-morbidities such as diabetes, hypertension, dyslipidaemia, and obesity were observed in 46 (17.7%), 52 (20.0%), 41 (15.8%), and 32 (12.3%) patients, respectively.

During the preliminary stage (while eliciting the clinical history of chest pain), as depicted in [Table/Fig-1], typical angina was noted in only 38 (14.7%) patients. Only 79 (30.5%) of patients reported that their only symptom was chest pain. A total of 180 (69.5%) patients were found to have associated symptoms as described below.

During the general and systemic clinical examination, different clinical signs were noted as depicted in [Table/Fig-2].

Type of chest pain and symptom	Number of patient (%)
Characteristic of chest pain	
Typical angina	38 (14.7)
Musculoskeltal	38 (14.7)
Pericardial	11 (4.2)
Pleuritic	7 (2.7)
Non characterised	165 (63.7)
Associated symptoms	
Abdominal	45 (17.3)
Autonomic	8 (3.0)
Psychomotor	35 (13.5)
Palpitation	23 (8.0)
Dyspnoea	56 (21.6)
Fatigue	13 (5.0)
No associated symptoms	79 (30.5)

[Table/Fig-1]: Frequency of different types of chest pain and associated symptoms among study participants.

As depicted in [Table/Fig-3], a spectrum of abnormal ECG presentations, such as ST-T changes, abnormal Q waves, bundle branch blocks, etc., were detected in 49 (18.9%) patients during electrocardiographic evaluation. Out of 11 patients with pericardial-type chest pain, five (1.9%) patients each had one of the ECG abnormalities (suggestive of pericarditis) like diffuse ST elevation [Table/Fig-4] and PR depression, respectively, and one (0.4%) had both ECG abnormalities. Besides, arrhythmias were detected in 18 (6.9%) patients during ECG evaluation. Premature Ventricular

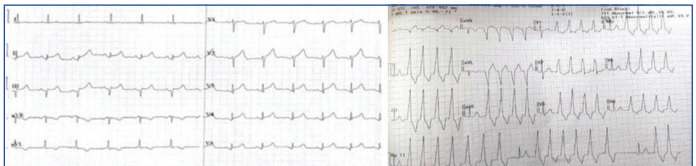
Clinical findings	n (%)
Pedal oedema	13 (5.0)
Irregularly irregular pulse	16 (6.1)
Postural hypotension	6 (2.3)
Raised JVP	9 (3.4)
Cardiomegaly	14 (5.4)
Parasternal lift	6 (2.3)
loud P2	9 (3.4)
LV s3	14 (5.4)
RV s3	8 (3.0)
Pericardial rub	8 (3.0)
Coarse crepitation	32 (12.3)
Rhonchi	16 (6.1)
Bronchial breath sound	13 (5.0)
Pleural rub	5 (1.9)

[Table/Fig-2]: Clinical findings among post-COVID-19 patients with persistent chest pain.

Complexes (PVCs) were the most frequent type of arrhythmia detected in 13 patients, and most of them were polymorphic, i.e., in 11 (84.6%) of cases, while the rest were monomorphic (n=2, 0.7%). Two patients out of 13 patients with PVCs also had non sustained Ventricular Tachycardia (VT) [Table/Fig-5]. Out of the remaining five

Laboratory procedures	Abnormalities	Number of patients (%)
Electrocardiography	ST depression	9 (3.4)
	T wave inversion	6 (2.3)
	ST elevation (contiguous leads)	9 (3.4)
	ST elevation (diffuse)	6 (2.3)
	Q wave	13 (5.0)
	PR depression	6 (2.3)
	Bundle branch block	3 (1.1)
	Arrhythmia	18 (6.9)
Chest X-ray	Cardiomegaly	14 (5.4)
	Right ventricular enlargement	5 (1.9)
	Right atrial enlargement	4 (1.56)
	Dilated pulmonary artery	11 (4.2)
	Residual lesions	36 (13.9)
Echocardiography	LV dysfunction	22 (8.4)
	Pericardial effusion	4 (1.54)
	PAH	11 (4.2)
	RV dysfunction	5 (1.9)
HRCT thorax	Ground glass opacity	23 (8.9)
	Parenchymal band	6 (2.3)
	Reticular opacity	3 (1.1)
	Mosaic pattern	4 (1.56)
Pulmonary function abnormality	Restrictive	11 (39.2)
	Obstructive	17 (60.7)

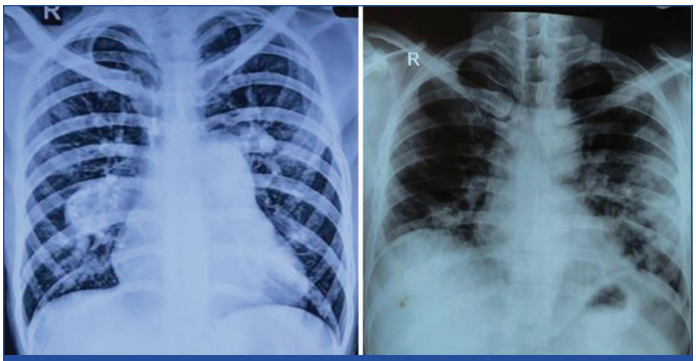
[Table/Fig-3]: Laboratory findings among post-COVID-19 patients with persistent chest pain.



[Table/Fig-4]: ECG image of a patient showing diffuse ST coving suggestive of pericarditis.
[Table/Fig-5]: ECG image of a patient showing non sutained Ventricular Tachycardia (VT). (Images from left to right)

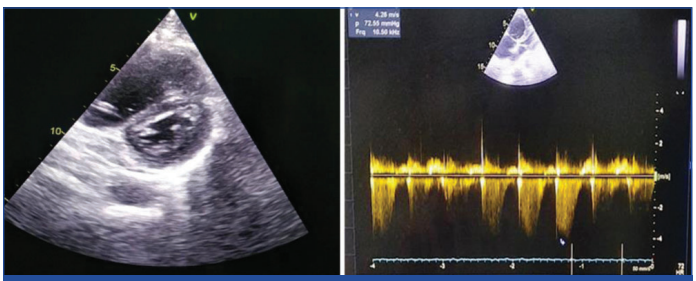
patients with arrhythmias, three (1.1%) patients had atrial fibrillation and two (0.7%) patients had severe sinus bradycardia (HR <40/minute). Five (1.9%) patients had persistent sinus tachycardia detected during holter monitoring. During a Holter examination, a patient who complained of intermittent chest pain and palpitations was found to have supra VT.

During X-ray chest evaluation, radiological signs suggestive of cardiopulmonary disease, such as cardiomegaly, right atrial enlargement, right ventricular enlargement, dilated pulmonary artery [Table/Fig-6], residual lesions [Table/Fig-7], were observed in 14 (5.4%), 4 (1.56%), 5 (1.9%), 11 (4.2%), and 36 (13.9%) patients, respectively.



[Table/Fig-6]: X-ray chest image of a patient showing right ventricular and right atrial enlargement and pulmonary artery dilatation.
[Table/Fig-7]: X-ray chest image of a patients showing residual lesion in left middle and lower lobe. (Images from left to right)

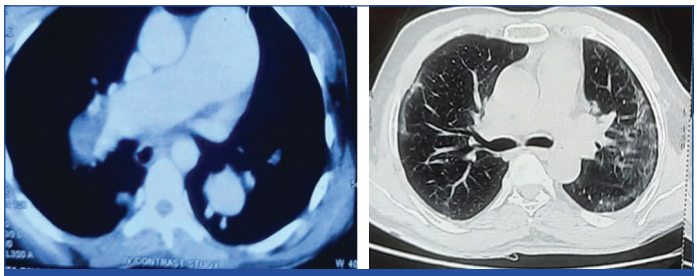
All patients with abnormal cardiac signs, ECG, and chest X-ray suggestive of underlying cardiac disease underwent echocardiography. As depicted in [Table/Fig-3], left ventricular dysfunction was observed in 22 (8.4%) patients. Eleven (4.2%) patients had LV dysfunction with regional wall motion abnormalities suggesting CAD, whereas two (0.77%) and nine (3.4%) patients had LV dysfunction with non-regional wall motion abnormalities and global hypokinesia, suggestive of myocarditis. Eight (36.3%) patients out of 22 patients with LV dysfunction were found to have elevated troponin. PAH was found in 11 (4.2%) patients, with 5 (1.9%) of them also having associated RV dysfunction [Table/Fig-3,8,9]. Two (0.7%) patients with PAH were found to have chronic pulmonary embolism during further evaluation, i.e., CT pulmonary angiography [Table/Fig-10]. Eleven (4.2%) patients with pericardial pain were confirmed to have pericarditis having either a clinical sign (like pericardial rub), an ECG sign (like diffuse ST elevation and PR depression), or an echocardiographic sign (pericardial effusion). Pericardial effusion was detected in 4 (1.54%) patients during echocardiography. All of them were mild.



[Table/Fig-8]: Echocardiographic image showing dilated RV compressing LV in short axis view suggestive of severe PAH.
[Table/Fig-9]: Doppler echocardiographic image showing peak tricuspid gradient suggestive of severe PAH. (Images from left to right)

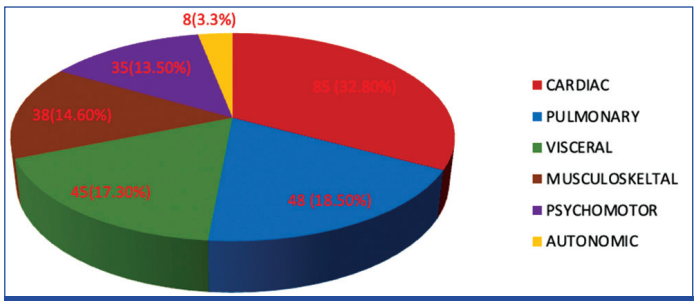
A total of 38 (19.6%) patients with typical angina, abnormal ECG, X-ray, or echocardiographic findings, or treadmill test findings suggesting underlying CAD underwent coronary angiography. Out of the 38 patients with typical angina, 29 (11.1%) were found to have obstructive CAD during angiography. The remaining nine (3.4%) patients had normal or non obstructive findings during angiography despite typical angina and a positive treadmill test, suggesting microvascular CAD.

Additionally, a total of 48 patients with abnormal clinical and X-ray chest signs suggesting underlying pulmonary abnormalities underwent HRCT thorax and spirometry. As depicted in [Table/Fig-3], 36 (13.9%) patients were found to have different anatomical patterns of residual abnormalities on the HRCT thorax [Table/Fig-11]. Furthermore, 28 (10.8%) patients were found to have various types of pulmonary function abnormalities, all of which were mild to moderate. Twelve patients exhibited both anatomical and functional pulmonary abnormalities.



[Table/Fig-10]: CECT pulmonary angiographic image showing filling defect in right pulmonary artery suggestive of pulmonary embolism.
[Table/Fig-11]: HRCT image showing ground glass opacity in left lung. (Images from left to right)

After a complete evaluation of study participants [Table/Fig-12], cardiac abnormalities were detected in 85 (32.8%) patients, while pulmonary abnormalities were found in 48 (18.5%) patients. Among the 126 patients with chest pain of non cardiopulmonary origin, 45 (17.3%) were diagnosed with chest pain due to visceral causes such as gastro-oesophageal reflux disease, which was detected during an upper GI endoscopy. Additionally, 38 (14.6%) patients had localised musculoskeletal chest pain along with local tenderness. Chest pain was determined to be functional (i.e., psychomotor) in 35 (13.5%) patients. Eight (3.0%) patients experienced chest pain due to autonomic causes, with two (0.7%) meeting the criteria for Postural Tachycardia Syndrome (POTS) and six (2.3%) having orthostatic hypotension.



[Table/Fig-12]: Showing frequency distribution of aetiologies of persistent chest pain in post-COVID-19 patients.

DISCUSSION

In the current study, during evaluation, patients were detected to have abnormalities involving multiple systems of the body. Cardiac abnormalities were observed in 85 (32.8%) patients, with CAD being the most commonly detected abnormality in 38 (19.6%) cases. This included 29 (11.1%) cases of obstructive CAD and 9 (3.4%) cases of microvascular CAD. Major contributing factors to the development of macro and microvascular CAD in post-COVID-19 cases include plaque destabilisation, endothelial dysfunction, microvascular inflammation, and persistent COVID-19 inflammation [19-21].

In addition to CAD, pericarditis and myocarditis were detected in 11 (4.2%) patients each in the current study. These conditions can persist even months after COVID-19 recovery due to chronic or recurrent inflammation [22,23]. Chronic recurrent myocarditis and associated scarring create vulnerable substrates and make the

myocardium more susceptible (1.7 times) to developing arrhythmias [24], as reported in 18 (6.9%) patients in the current study.

Furthermore, eleven (4.2%) and five (1.9%) patients were detected to have Pulmonary Arterial Hypertension (PAH) and Right Ventricular (RV) dysfunction, respectively [Table/Fig-3]. Endothelial dysfunction, lung coagulopathy, and ultimately secondary haemodynamic changes in the pulmonary vasculature lead to PAH and RV dysfunction [25,26]. Two (0.7%) patients were detected to have chronic pulmonary embolism along with associated features of PAH and RV dysfunction in the current study. COVID-19 patients are 30 times more likely to develop pulmonary embolism than age, gender, and risk factor-matched non-COVID patients due to their hypercoagulable state [27], and this abnormality may persist unresolved for a long time.

In addition to cardiac abnormalities, patients with chest pain were detected to have a wide spectrum of pulmonary abnormalities, such as organising pneumonia, pleuritis, and pulmonary function abnormalities, in around 48 (18.5%) cases. Among these cases, the most common finding was that 36 (13.8%) patients were detected to have different morphologic patterns of residual organising pneumonia on HRCT thorax in the current study. This was due to the persistence of post-pneumonic inflammation for a prolonged period, unlike other viral infections [28]. Since these residual lesions are often located subpleurally, post-COVID patients are at risk of pleuritis, which was detected in seven (2.7%) patients in the current study. In addition to organic residual lesions, inflammation of the bronchioles, alveoli, and interstitial tissue can result in both obstructive and restrictive types of Pulmonary Function Test (PFT) abnormalities [29], which were detected in 28 (10.8%) patients in the current study.

Aside from cardiopulmonary abnormalities, post-COVID-19 chest pain can arise due to non cardiopulmonary abnormalities, such as autonomic, psychological, musculoskeletal, gastrointestinal issues, etc., detected in around half of the cases in the current study. Out of these cases, 38 (14.7%) patients presented with chest pain associated with local musculoskeletal abnormalities, such as tenderness, which may arise due to the persistence of COVID-19 inflammation [7]. Additionally, 45 (17.3%) patients were found to have chest pain due to gastrointestinal abnormalities, which may be a consequence of autoimmunogenic intestinal mucosal injury and dysbiosis due to persistent and aberrant COVID-19 inflammation [30]. Furthermore, 35 (13.5%) patients were discovered to have psychological chest symptoms in the current study, which may result from immune and inflammatory dysregulation, subsequent impairment of neurotransmission, and dysfunction of the Hypothalami-Pituitary-Adrenal (HPA) axis [31]. Eight (3.0%) patients experienced chest pain along with autonomic symptoms like palpitations, excessive sweating, etc., due to pathophysiological mechanisms such as autoimmunity (e.g., autoantibodies against adrenergic receptors) and impairment of baroreflex and sympathetic autonomic activities (during prolonged bed rest) [32].

In summary, persistent chest pain after COVID-19 is contributed to by multisystemic and multifactorial pathophysiology. Although post-COVID-19 chest pain is often presumed to be cardiopulmonary due to the virus's predilection for the Angiotensin Converting Enzyme (ACE)-II receptor, around half of the cases of post-COVID-19 chest pain result from non cardiopulmonary causes. Moreover, cardiac abnormalities, which together contribute to about one-third of cases, include serious life-threatening abnormalities such as CAD, arrhythmia, myocarditis, pericarditis, PAH, etc. The future outcomes of these groups of patients are either unknown or unclear. Further studies may be needed to establish the aetiology and unfold the long-term outcomes of patients with persistent chest pain after COVID-19.

Limitation(s)

The current study was conducted on a limited number of patients. A multicentre study involving a larger number of patients could have provided a better idea about the same. The present study was a cross-sectional study, whereas long-term follow-up of patients could have provided more valuable information. Present study results can only be applicable to patients tested as COVID-19 positive with persistent chest pain, whereas a good number of patients with clinical COVID-19 and persistent chest pain without previous confirmatory positive COVID-19 reports were not included. Most patients in the latter part of the study were partially or completely vaccinated. The effects of vaccines on outcomes among individuals with existing post-COVID-19 chest pain could not be validated.

CONCLUSION(S)

Chest pain in post-COVID-19 patients arises due to multisystemic aetiologies such as cardiac, pulmonary, visceral, autonomic, psychomotor, musculoskeletal issues, etc. A wide spectrum of cardiac abnormalities (such as CAD, arrhythmia, myocarditis, pericarditis, PAH, etc.) together contribute to about one-third of cases of persistent chest pain in post-COVID-19 patients. Patients with such abnormalities are prone to developing life-threatening complications like acute coronary syndrome, heart failure, ventricular tachycardia or fibrillation, pulmonary embolism, etc., due to sustained inflammation and hypercoagulability. Early detection and treatment can prevent the progression of the disease at an early stage.

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PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Cardiology, VIMSAR, Sambalpur, Odisha, India.
2. Professor and Head, Department of Cardiology, VIMSAR, Sambalpur, Odisha, India.
3. Assistant Professor, Department of General Medicine, VIMSAR, Sambalpur, Odisha, India.
4. Professor and Head, Department of Radiology, VIMSAR, Sambalpur, Odisha, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Sibaram Panda,
Doctor Colony, Burla, Sambalpur-768017, Odisha, India.
E-mail: drsibaram@gmail.com

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